



HAL
open science

Biological time and extended critical transitions: Towards an objectivization of the living state of matter

Maël Montévil

► To cite this version:

Maël Montévil. Biological time and extended critical transitions: Towards an objectivization of the living state of matter. History, Philosophy and Sociology of Sciences. Université Paris 5 descartes, 2011. English. NNT: 2011PA05T020 . tel-04514335

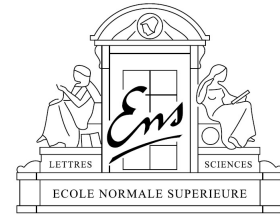
HAL Id: tel-04514335

<https://hal.science/tel-04514335v1>

Submitted on 21 Mar 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



UNIVERSITÉ DE PARIS V – RENÉ DESCARTES
ÉCOLE DOCTORALE 474 – FRONTIÈRES DU VIVANT

THÈSE

pour obtenir le titre de DOCTEUR ÈS SCIENCES
Spécialité : FRONTIÈRES INTERDISCIPLINAIRES DU VIVANT

TEMPS BIOLOGIQUE ET TRANSITIONS CRITIQUES ÉTENDUES

Vers une objectivation de l'état vivant de la matière

Présentée et soutenue par

Maël MONTÉVIL

soutenue le 7 octobre 2011

Thèse dirigée par Giuseppe LONGO

préparée au LIENS, École Normale Supérieure de Paris

| | | | |
|-------|---------------------|----------------------|-----------------------|
| Jury: | <i>Directeur:</i> | Giuseppe LONGO | – CNRS, ENS |
| | <i>Rapporteurs:</i> | Alessandro SARTI | – CNRS, Polytechnique |
| | | Carlos SONNENSCHNEIN | – Tufts University |
| | <i>Examineurs:</i> | Stéphane DOUADY | – CNRS, Paris VII |
| | | Paul-Antoine MIQUEL | – Université de Nice |
| | | Rémy MOSSERI | – CNRS, Paris VI |
| | | Denis NOBLE | – Oxford University |
| | Nadine PEYRIÉRAS | – CNRS | |

A la mémoire de Francis Bailly.

Temps biologique et transitions critiques étendues

Vers une objectivation de l'état vivant de la matière

RÉSUMÉ

Cette thèse se place dans le contexte d'une démarche théorique en biologie, s'inspirant, sans toutefois s'y réduire, des méthodes d'objectivation utilisées en physique. Pour cela, nous rapportons les possibles symétries et invariants biologiques sous forme de "lois d'échelles" empiriques (allométrie et fractales en particulier), ainsi que la variabilité associée. Nous abordons ensuite plusieurs aspects du temps biologique. Nous considérons une dimension temporelle supplémentaire, correspondant à l'autonomie de certains rythmes biologiques. Nous développons aussi une approche de la protension, comme principe d'organisation locale de la temporalité biologique.

La notion de symétrie ayant un statut fondamental pour les théories physiques, nous interrogeons ensuite leur rôles en biologie. Partant de la notion de criticité étendue, nous proposons que la dynamique du vivant soit régie par une omniprésence des changements de symétries, constituant dès lors une historicité irréductible et conférant un statut théorique particulier à l'objet et à la mesure en biologie. Nous appréhendons aussi la notion d'anti-entropie comme mesure d'un potentiel de variabilité.

Nous nous intéressons ensuite à la question des niveaux d'organisation, par deux voies complémentaires. Nous l'abordons dans un premier temps par la notion de clôture organisationnelle. Ensuite nous la considérons comme associée à des singularités fortes, telles que dans les situations critiques. Enfin, nous esquissons un schème opératoire de l'unité de l'organisme, qui combine un grand nombre des aspects préalablement exposés.

Mots clés : criticité, symétries, historicité biologique, variabilité, temps biologique, organisme, mesure, renormalisation

Biological time and extended critical transitions

Towards an objectivization of the living state of matter

ABSTRACT

This work takes place in the context of a theoretical approach in biology which uses the examples of objectivation in physical theories without reducing biological phenomenologies to them. We begin by investigating the empirical biological scaling relationships found in the literature (allometric relationships, fractals, ...), including their variability. We will then consider two different aspects of biological time. First, we will develop the notions of protension and retention as an account of local organization of biological time. Then we consider a supplementary temporal dimension to accommodate proper biological rhythms.

Since the notion of symmetry plays a foundational role in physics, we investigate its possible role in biology. In relation with the notion of extended critical transitions, we propose the hypothesis that organisms and evolution can be understood as characterized by ubiquitous symmetry changes. This transforms the status of biological objects, provides an approach of their historicity and leads to propositions on the theoretical nature of biological measurement. We also discuss anti-entropy as a measurement of a potential of variability.

We focus then on the notion of level of organization. We start from the notion of organizational closure, which is considered as a core biological invariant by many theoretical biologists. Then, we will approach levels of organization by the paradigm of criticality, which will allow to define them in a strong theoretical way. Finally, we sketch an operatorial scheme of the coherence of organisms, which combines most of the above mentioned approaches.

Keywords: criticality, symmetries, biological historicity, variability, biological time, organism, measurement, renormalization

Préface

L'UNE des idées à l'origine de cette thèse est une certaine insatisfaction vis-à-vis des approches mathématisées du vivant. S'il est clair qu'elles apportent généralement une contribution unique à l'intelligibilité des phénomènes, il me semble en effet qu'elles manquent en générale l'originalité des phénomènes vivants, en les traitant, *in fine*, comme des objets de type physique.

Pendant mon Master 2 de sciences cognitives, cet aspect des choses m'a particulièrement frappé, lors des cours de Jean Petitot sur l'approche géométrique du cortex visuel primaire. Cette modélisation est lumineuse, elle donne sens à la structure du cortex et s'articule à bon nombre d'observations expérimentales : sa contribution à l'intelligibilité de la situation biologique est indéniable (et élégante). Pourtant, la compréhension qu'elle propose des phénomènes me semblait particulièrement éloignée de l'appréhension propre que les neurobiologistes, participant à la même série de cours, pouvaient avoir. Cette appréhension insistait en effet sur la diversité, l'ambiguïté en un sens, des situations biologiques ainsi que sur l'intégration, de VI ici, dans un cadre plus vaste (par les rétroactions diverses entre parties du cerveau, à toutes les échelles). Cette situation de "dissonance cognitive" se retrouvait dans d'autres situations, telle que l'approche par des méthodes physiques de la dynamique des microtubules, dont j'ai eu le plaisir de pouvoir discuter avec Éric Karsenti.

Les recherches de Francis Bailly et Giuseppe Longo touchaient justement à cette question, en interrogeant les structures de l'intelligibilité mathématique et physique, et en proposant l'idée de la singularité physique du vivant. Cette thèse est, dans cette filiation, en partie une tentative d'intelligibilité constructive de ce problème.

REMARKS ON THE TECHNICAL ASPECTS OF THIS THESIS

This thesis is at the crossroads of (theoretical) physics and biology. As a consequence, certain passages will appeal to mathematical techniques that can confuse the non-mathematically trained reader. However, the main mathematical tools used in this thesis will remain simple and we will try to explain them both conceptually and intuitively in the text. Similarly, we will refer to numerous physical concepts that we will explain qualitatively (and for some of them, quantitatively). The prevalence of physical concepts will be especially marked in the chapter 5, where some concepts used will have been explained in other chapters. Anyway, the technical reading of this chapter is not necessary to the intelligibility of the thesis.

Also, it is worth mentioning that despite formal and conceptual links between the chapters, most chapters retains a certain level of autonomy and can be read independently.

REMERCIEMENTS

J'aimerais tout particulièrement remercier d'abord mon directeur de thèse, Giuseppe Longo. Non seulement pour sa grande disponibilité et gentillesse mais aussi pour la recherche que nous avons fait (et allons faire) ensemble. Cette recherche ne s'est pas tant faite sur le mode d'une direction que sur le mode d'une collaboration, ce qui est rare et précieux. J'éprouve aussi une immense gratitude envers Francis Bailly, qui fut mon second directeur de thèse officieux jusqu'à son décès. Sa créativité, sa gentillesse et son enthousiasme ont donné (et en un sens donnent toujours) lieu à de fabuleux moments de recherche. Je remercie aussi sa femme, Danielle, pour m'avoir procuré de nombreux textes de Francis et pour ses encouragements amicaux. Francis et Giuseppe ont construit les fondations sur lesquelles s'appuie cette thèse. Je les remercie à la fois pour ce qu'il m'ont enseigné sur le plan scientifique et sur le plan philosophique ; sans cette dernière dimension aussi, cette thèse n'aurait pu voir le jour.

Je tiens aussi à exprimer ma gratitude envers Alessandro Sarti, Carlos Sonnenschein, Stéphane Douady, Paul-Antoine Miquel, Rémy Mosseri, Denis Noble et Nadine Peyriéras pour avoir accepté de participer à mon jury. En particulier, je remercie les rapporteurs Alessandro et Carlos.

Cette thèse doit beaucoup aux personnes avec qui j'ai pu travailler et discuter. En particulier, Ana Soto et Carlos Sonnenschein, qui m'ont beaucoup appris en biologie et font preuve de persévérance dans le dialogue constructif entre nos approches et origines disciplinaires respectives. Je les remercie aussi pour le courageux travail d'édition qu'il ont fait sur l'un des articles dont je suis co-auteur. Je remercie aussi Paul-Antoine Miquel, qui fait partie du même groupe de recherche, et qui a contribué tant par son enthousiasme et sa bonne humeur que par ses éclairages philosophiques.

Je tiens à remercier également Stéphane Douady et les autres membres du club flux pour nos discussions très stimulantes. Je garderai aussi un excellent souvenir du cours de Stéphane sur Naruto.

Je remercie aussi vivement et chaleureusement Arnaud Pocheville pour son écoute attentive, bienveillante et critique, de mes propositions théoriques et autres, par delà le chapitre qui est explicitement le fruit de notre collaboration. La réalisation intellectuelle, pratique et logistique de cette thèse lui doit beaucoup.

La collaboration avec Matteo Mossio, a été à la fois fructueuse et animée d'une amitié ensoleillée par ses accents australiens (y compris sur la plage de San Sebastian).

Travailler avec les membres de l'équipe Complexité et Information Morphologique fut un réel plaisir. Je tiens à remercier en particulier Nicole Perret, Giulia Frezza et Paul Villoutreix pour les moments de recherche, de détente et de discussions politiques passés ensemble.

Evelyn Fox Keller a été une grande source d'inspiration, notamment lors de nos discussions aux meetings FdV et au workshop "Self-organization in biology : scope and limits", organisé par Paul-Antoine et Matteo.

Je ne suis pas prêt d'oublier les moments scientifiques, amicaux et gastronomiques passés en compagnie de Thierry Paul.

Je remercie Philippe Huneman, qui, bien que penchant dangereusement du côté de la philosophie analytique, a toujours été d'un commerce agréable achalandé de conseils fructueux. Je le remercie en particulier de m'avoir permis de participer aux colloques de l'IHPST en philosophie de la biologie ainsi qu'à l'école de printemps de Cargèse.

Je remercie aussi vivement les professeurs invités à l'ENS avec qui j'ai eu d'intenses discussions, Wilson Poon, Christian Calude et Kurt Saetzler, à qui je dois beaucoup. J'espère en retour les avoir initiés convenablement aux cafés parisiens.

Je remercie aussi pour les des échanges que j'ai eu avec eux : Éric Karsenti, Stuart Kauffman, François Taddei, Julia Roberts, Jean Lassègue, Claude Debru, Paul Bourguine, Andrée Weydert, Bernard Hénion, Sophie Heinrich, Annick Lesne, Thomas Seiller et les autres.

Hugh Kingston m'a très gentiment aidé pendant mon stage de biologie expérimentale de M2 AIV ; nous avons par la suite continué à échanger sur nos activités scientifiques avec un plaisir toujours renouvelé.

Pendant cette thèse, j'ai pu compter sur le soutien sans faille de ma famille et de mes proches notamment, Régis, Jérémie, Deborah, Bruno et Arnaud. Je remercient aussi Nicolas Legrand et Arnaud Pocheville pour leur relectures orthographique et grammaticales, sans qui cette thèse seraient probablement à l'image de sept phrases.

Enfin, cette thèse n'aurait pas pu être effectuée dans une autre école doctorale que l'ED Frontières du Vivant (474) dont je tiens à remercier ici vivement les fondateurs en particulier François Taddéi, Samuel Bottani, Ariel Lindler, ainsi que les secrétaires Laura Ciriani, Céline Garrigues et Véronique Waquet, les représentants des étudiants, ainsi que la Fondation Bettencourt-Schueller pour son soutien financier.

Short contents

| | |
|--|------|
| PRÉFACE | v |
| SHORT CONTENTS | ix |
| CONTENTS | xi |
| LIST OF FIGURES | xvii |
| LIST OF TABLES | xix |
| 1 INTRODUCTION | i |
| 2 SCALING IN BIOLOGICAL SYSTEMS | ii |
| 3 A 2-DIMENSIONAL GEOMETRY FOR BIOLOGICAL TIME | 67 |
| 4 PROTENTION AND RETENTION IN BIOLOGICAL SYSTEMS | 89 |
| 5 SOME CRUCIAL PHYSICAL ASPECTS OF SYMMETRY & SYMMETRY BREAKINGS | iii |
| 6 FROM PHYSICS TO BIOLOGY BY EXTENDING CRITICALITY AND SYMMETRY BREAKINGS | 139 |
| 7 BIOLOGICAL MEASUREMENT & EXTENDED CRITICAL TRANSITIONS | 157 |
| 8 BIOLOGICAL ORDER AS A CONSEQUENCE OF RANDOMNESS : ANTI-ENTROPY AND SYMMETRY CHANGES | 181 |
| 9 THE IDEA OF CLOSURE IN BIOLOGICAL SYSTEMS | 209 |
| 10 LEVELS OF ORGANIZATION, SINGULARITIES AND REDUCTIONISM | 227 |
| 11 TOWARDS A BIOLOGICAL RENORMALIZATION | 247 |
| 12 CONCLUSION | 271 |
| A LISTINGS | 277 |

Contents

| | |
|--|-------------|
| Résumé | iii |
| Abstract | iv |
| PRÉFACE | v |
| Remarks on the technical aspects of this thesis | v |
| Remerciements | vi |
| SHORT CONTENTS | ix |
| CONTENTS | xi |
| LIST OF FIGURES | xvii |
| LIST OF TABLES | xix |
| 1 INTRODUCTION | I |
| 1.1 Introduction | I |
| 1.2 Objectivization and Theories | 3 |
| 1.3 Some preliminary aspects of our approach to biological phenomena | 6 |
| 1.4 Map of this thesis | 8 |
| 2 SCALING IN BIOLOGICAL SYSTEMS | 11 |
| 2.1 Introduction | 13 |
| 2.1.1 Power laws | 13 |
| 2.2 Allometry | 16 |
| 2.2.1 Principles | 16 |
| 2.2.2 Metabolism | 18 |
| 2.2.2.1 Interspecific metabolic allometry | 18 |
| 2.2.2.2 Intraspecific metabolic allometry | 20 |
| 2.2.2.3 A word on temperature | 21 |
| 2.2.3 Rhythms and rates | 22 |
| 2.2.4 Cell and organ allometry | 23 |
| 2.2.4.1 Cell allometry | 24 |
| 2.2.4.2 Organ allometry | 25 |

| | | |
|---------|---|----|
| 2.2.5 | Conclusion | 26 |
| 2.3 | Morphological fractal-like structures | 27 |
| 2.3.1 | Principles | 27 |
| 2.3.1.1 | Scale symmetry for sets | 28 |
| 2.3.1.2 | Fractal dimension | 30 |
| 2.3.1.3 | Definition of fractals | 32 |
| 2.3.2 | Cellular and intracellular membranes | 33 |
| 2.3.3 | Branching trees | 34 |
| 2.3.3.1 | Lungs | 35 |
| 2.3.3.2 | Vascular system | 36 |
| 2.3.3.3 | Further aspects for these organs | 38 |
| 2.3.4 | Some other morphological fractal analyses | 38 |
| 2.3.5 | Conclusion | 39 |
| 2.4 | Elementary yet complex biological dynamics | 39 |
| 2.4.1 | Principles | 40 |
| 2.4.2 | A non-exhaustive list of biological dynamics | 45 |
| 2.4.3 | The case of cardiac rhythm | 47 |
| 2.4.3.1 | Structure of cardiac rhythm | 47 |
| 2.4.3.2 | Some factors associated with the cardiac rhythm structure | 48 |
| 2.4.4 | Conclusion | 49 |
| 2.5 | Space-time structures | 50 |
| 2.5.1 | Anomalous diffusion | 50 |
| 2.5.1.1 | Principle | 51 |
| 2.5.1.2 | Examples from cellular biology | 53 |
| 2.5.2 | Biological systems “poised” at criticality | 53 |
| 2.5.2.1 | Principle | 54 |
| 2.5.2.2 | Some examples | 55 |
| 2.5.3 | Other forms of Criticality | 57 |
| 2.5.3.1 | Self-organized criticality | 57 |
| 2.5.3.2 | Self-tuned Criticality | 58 |
| 2.5.3.3 | “Attached” criticality | 58 |
| 2.5.4 | Conclusion | 59 |
| 2.6 | Networks | 60 |
| 2.6.1 | Structures | 60 |
| 2.6.2 | Dynamics | 62 |
| 2.6.3 | Conclusion | 63 |
| 2.7 | Conclusion | 63 |
| 3 | A 2-DIMENSIONAL GEOMETRY FOR BIOLOGICAL TIME | 67 |
| 3.1 | Introduction | 68 |
| 3.1.1 | Methodological remarks | 69 |
| 3.2 | An abstract schema for biological temporality. | 70 |
| 3.2.1 | Premise: Rhythms | 70 |
| 3.2.2 | External and internal rhythms | 70 |

| | | |
|---------|---|------------|
| 3.3 | Mathematical description | 73 |
| 3.3.1 | Qualitative drawings of our schemata | 73 |
| 3.3.2 | Quantitative scheme of biological time | 76 |
| 3.4 | Analysis of the model | 77 |
| 3.4.1 | Physical periodicity of compacified time | 77 |
| 3.4.2 | Biological irreversibility | 78 |
| 3.4.3 | Allometry and physical rhythms | 79 |
| 3.4.4 | Rate Variability | 80 |
| 3.4.4.1 | Renormalization | 80 |
| 3.4.4.2 | Rate Variability | 81 |
| 3.5 | More discussion on the general schema 3.1. | 84 |
| 3.5.1 | The evolutionary axis (τ), its angles with the horizontal $\phi(t)$ and its gradients $\tan(\phi(t))$ | 84 |
| 3.5.2 | The “helicoidal” cylinder of revolution \mathcal{C}_e : its thread p_e , its radius R_i | 85 |
| 3.5.3 | The circular helix \mathcal{C}_i on the cylinder and its thread p_i | 85 |
| 3.5.4 | On the interpretation of the ordinate t' | 86 |
| 4 | PROTECTION AND RETENTION IN BIOLOGICAL SYSTEMS | 89 |
| 4.1 | Introduction | 90 |
| 4.1.1 | Methodological remarks | 91 |
| 4.2 | Characteristic time and correlation lengths | 93 |
| 4.2.1 | Critical states and correlation length | 94 |
| 4.3 | Retention and protention. | 94 |
| 4.3.1 | Principles | 94 |
| 4.3.2 | Specifications | 95 |
| 4.3.3 | Comments | 96 |
| 4.3.4 | Global protention | 98 |
| 4.4 | Biological inertia | 99 |
| 4.4.1 | Analysis | 100 |
| 4.5 | References and more justifications for biological inertia | 102 |
| 4.6 | Some complementary remarks | 104 |
| 4.6.1 | Blurred Protention | 104 |
| 4.6.2 | Power laws and exponentials | 105 |
| 4.6.3 | Causality and analyticity | 106 |
| 4.7 | Towards human cognition. From trajectory to space: The continuity of the cognitive phenomena | 107 |
| 5 | SOME CRUCIAL PHYSICAL ASPECTS OF SYMMETRY & SYMMETRY BREAKINGS | 111 |
| 5.1 | Introduction | 112 |
| 5.2 | Noether’s theorem | 112 |
| 5.2.1 | Classical mechanics version (Lagrangian) | 113 |
| 5.2.1.1 | Variational principle | 113 |
| 5.2.1.2 | Noether’s theorem | 114 |
| 5.2.2 | Field theoretic point of view | 116 |

| | | |
|---------|---|-----|
| 5.2.3 | Conclusion | 117 |
| 5.3 | Typology of symmetry breakings | 118 |
| 5.4 | Criticality, renormalization & scale symmetry. | 120 |
| 5.4.1 | Landau theory | 121 |
| 5.4.1.1 | Statistical mechanics | 121 |
| 5.4.1.2 | Some general remarks on phase transitions | 123 |
| 5.4.1.3 | Landau theory | 124 |
| 5.4.1.4 | First approximation of the fluctuations | 126 |
| 5.4.1.5 | Ginzburg criterion | 127 |
| 5.4.2 | Some aspect of renormalization | 128 |
| 5.4.2.1 | Principle of renormalization | 130 |
| 5.4.3 | Critical slowing-down | 133 |
| 5.4.4 | Self-tuned criticality | 135 |
| 5.4.5 | Goldstone theorem | 136 |
| 5.5 | Conclusion | 138 |
| 6 | FROM PHYSICS TO BIOLOGY BY EXTENDING CRITICALITY AND SYMMETRY BREAKINGS | 139 |
| 6.1 | Introduction and summary | 140 |
| 6.1.1 | Hidden variables in biology? | 141 |
| 6.2 | Symmetry and objectivation in physics | 143 |
| 6.3 | Symmetry breakings and criticality in physics | 146 |
| 6.4 | Symmetry breaking and the biological object: extended criticality | 148 |
| 6.5 | Additional characteristics of extended criticality | 152 |
| 6.6 | Conclusion | 154 |
| 7 | BIOLOGICAL MEASUREMENT & EXTENDED CRITICAL TRANSITIONS | 157 |
| 7.1 | Introduction | 158 |
| 7.2 | Physical measurement | 159 |
| 7.2.1 | Classical measurement | 159 |
| 7.2.2 | Reference frame | 160 |
| 7.2.3 | Quantum measurement | 161 |
| 7.2.4 | Conclusion | 162 |
| 7.3 | Biological measurement as a restricted symmetrization | 162 |
| 7.3.1 | Phylogeny | 163 |
| 7.3.2 | Controlled history | 164 |
| 7.3.3 | Irreducibility of symmetry changes | 166 |
| 7.3.4 | Recapitulation | 166 |
| 7.4 | Allometry and symmetry breaking | 168 |
| 7.4.1 | Variability versus fluctuations | 168 |
| 7.4.2 | Systematic application of our framework | 169 |
| 7.4.3 | A mathematical frame for biological allometry | 170 |
| 7.4.3.1 | Mathematical background | 170 |
| 7.4.3.2 | Biological framework | 171 |

| | | |
|-----------|--|------------|
| 7.4.3.3 | Further aspects of this framework | 172 |
| 7.5 | Compacified time and autonomy | 174 |
| 7.5.1 | Simple harmonic oscillators in physics | 175 |
| 7.5.1.1 | Classical oscillator | 175 |
| 7.5.1.2 | Quantum oscillator | 175 |
| 7.5.1.3 | Conclusion | 176 |
| 7.5.2 | Symmetries and compacified time | 176 |
| 7.5.3 | Conclusion | 177 |
| 7.6 | Observing symmetry changes? | 178 |
| 7.6.1 | From a measured trajectory to specific symmetries | 178 |
| 7.6.2 | Global aspect of extended critical transitions | 179 |
| 7.7 | Conclusion | 179 |
| 8 | BIOLOGICAL ORDER AS A CONSEQUENCE OF RANDOMNESS : ANTI-ENTROPY AND SYMMETRY CHANGES | 181 |
| 8.1 | Introduction. | 182 |
| 8.2 | Entropy in ontogenesis. | 183 |
| 8.3 | Randomness and Complexification in Evolution. | 185 |
| 8.4 | (Anti-)Entropy in Evolution. | 188 |
| 8.5 | Organizational regeneration | 193 |
| 8.6 | Interpretation of anti-entropy as a measure of symmetry changes | 199 |
| 8.7 | Theoretical consequences of this interpretation | 204 |
| 9 | THE IDEA OF CLOSURE IN BIOLOGICAL SYSTEMS | 209 |
| 9.1 | Introduction | 210 |
| 9.2 | Biological determination as self-constriction | 212 |
| 9.3 | Constraints and processes | 214 |
| 9.3.1 | Some biophysical examples | 216 |
| 9.4 | Dependence | 218 |
| 9.5 | Closure | 219 |
| 9.5.1 | The case of scale separation | 220 |
| 9.5.1.1 | Definitions | 221 |
| 9.5.1.2 | Collapse of the multi-scale dynamic | 222 |
| 9.5.2 | Interpretation | 224 |
| 9.6 | Conclusion | 226 |
| 10 | LEVELS OF ORGANIZATION, SINGULARITIES AND REDUCTIONISM | 227 |
| 10.1 | Introduction | 228 |
| 10.2 | Critical phenomena and reductionism | 229 |
| 10.2.1 | Reductionism | 229 |
| 10.2.2 | Interscale reductionism in physics | 230 |
| 10.2.2.1 | A paradigmatic case: the reduction of thermodynamics to statistical mechanics | 230 |
| 10.2.2.2 | When means fail: critical phase transitions | 231 |

| | | |
|----------|--|-----|
| 10.2.2.3 | Reductionism vs renormalization | 232 |
| 10.2.3 | Consequences for biology | 236 |
| 10.2.3.1 | Criticality and living matter | 236 |
| 10.2.3.2 | Circular couplings | 237 |
| 10.2.3.3 | Conclusion on the consequences for biology | 237 |
| 10.2.4 | Conclusion | 238 |
| 10.3 | Levels of organizations | 238 |
| 10.3.1 | Complexification within a level | 239 |
| 10.3.2 | Two types of infinity | 240 |
| 10.3.3 | Transition between two levels | 241 |
| 10.3.4 | Criteria of transition | 241 |
| 10.4 | Application to biology | 242 |
| 10.4.1 | Biological levels of organization as an hypothesis | 242 |
| 10.4.2 | Fractals and functions | 242 |
| 10.4.3 | Non genericity of parts | 243 |
| 10.5 | Conclusion | 244 |
| 11 | TOWARDS A BIOLOGICAL RENORMALIZATION | 247 |
| 11.1 | Introduction | 248 |
| 11.2 | Orgons and biolons | 249 |
| 11.2.1 | Intermezzo: theoretical <i>tuteurs</i> | 250 |
| 11.3 | Where are up and down? | 252 |
| 11.3.1 | Intuitive approach of the singular directions | 252 |
| 11.3.2 | Singular directions and their interactions | 253 |
| 11.3.3 | Where are up and down? | 256 |
| 11.3.4 | Recapitulation and precision | 258 |
| 11.4 | A scheme of the organization of a metazoan | 260 |
| 11.4.1 | Reintroduction of the compacified time | 260 |
| 11.4.2 | Orgonic operators | 261 |
| 11.4.3 | Cellular level | 263 |
| 11.4.4 | Symmetries and singularities | 264 |
| 11.4.5 | Some further remarks | 265 |
| 11.5 | Conclusion | 270 |
| 12 | CONCLUSION | 271 |
| 12.1 | Recapitulation | 271 |
| 12.2 | Perspectives | 274 |
| A | LISTINGS | 277 |
| A.1 | Cran R Programms for chapter 3. | 277 |
| A.2 | C program to simulate Ising model in chapter 5. | 280 |

List of Figures

| | | |
|------|---|-----|
| 1.1 | A scheme of the relation between physics and biology, from a diachronic point of view | 7 |
| 2.1 | Allometry for a cube | 17 |
| 2.2 | Illustration of the interspecific and intraspecific allometry of organs sizes . . . | 26 |
| 2.3 | Example of a strictly self-similar fractal, obtained by a simple iterative procedure: the Sierpiński triangle | 28 |
| 2.4 | Principle of the evaluation of the box-counting dimension illustrated on the Sierpiński triangle | 31 |
| 2.5 | Illustration of topological dimension | 31 |
| 2.6 | A binary tree | 34 |
| 2.7 | A sample of beat-to-beat intervals in human. | 41 |
| 2.8 | Some fractal dynamics | 44 |
| 2.9 | Different forms of diffusion | 52 |
| 2.10 | Example of random and scale-free graphs | 60 |
| 3.1 | Qualitative illustration of our geometric scheme, as a 2-dimensional manifold | 74 |
| 3.2 | Qualitative Illustration of the first components of our model | 75 |
| 3.3 | Illustration of the three scenari | 78 |
| 3.4 | Renormalization and principles of variability representation | 81 |
| 3.5 | Comparison of the situations during sleep and wake | 82 |
| 3.6 | Comparison between a healthy situation and cases of sudden cardiac arrest . . | 83 |
| 4.1 | Illustration of the basic quantities we define: virtual protention, retention and protention | 97 |
| 4.2 | Protention for various values of the parameters | 97 |
| 4.3 | Global protention | 101 |
| 4.4 | Biological inertia | 101 |
| 4.5 | Blured Protention | 105 |
| 5.1 | Mexican hat and (weak) spontaneous symmetry breaking | 119 |
| 5.2 | Simulation of the Ising Model | 129 |
| 5.3 | Bifurcation and critical slowdown | 134 |

LIST OF FIGURES

| | | |
|------|--|-----|
| 5.4 | Goldstone modes | 137 |
| 7.1 | Fluctuation vs variability in allometry | 168 |
| 8.1 | Passive and driven trends | 187 |
| 8.2 | Evolution of complexity as understood by Gould | 188 |
| 8.3 | Time evolution of mass repartition over anti-entropy | 192 |
| 8.4 | Diagram of an elementary loss of anti-entropy | 198 |
| 8.5 | Other schema of entropy/anti-entropy interactions | 198 |
| 9.1 | Logistic case: closure and “failed” closure | 224 |
| 10.1 | Principle of renormalization | 235 |
| 11.1 | A vine pole | 251 |
| 11.2 | Two objects interactions in our framework | 254 |
| 11.3 | A diagonal organ and the supplementary direction corresponding to the composition/behaviour of one of its part | 255 |
| 11.4 | Two organs are related to the rest of the organism via a third organ | 255 |
| 11.5 | Orgonic operator and anti-entropy, the case of the vascular system | 266 |
| 11.6 | Blood vessels and randomness | 267 |

List of Tables

| | | |
|-----|---|----|
| 2.1 | Allometry of biological rhythms in mammals | 22 |
| 2.2 | Allometry of cell types | 24 |
| 2.3 | Allometry of organs | 25 |
| 2.4 | Evaluations of fractal dimensions for vascular networks | 37 |
| 2.5 | Blood cells fluctuations | 45 |
| 2.6 | Heart rate variability at various ages | 49 |
| 2.7 | Statistical properties of some biological networks. | 61 |

Introduction 1

To know the history of science is to recognize the mortality of any claim to universal truth.

E. Fox Keller

CONTENTS

| | | |
|-----|--|---|
| 1.1 | Introduction | 1 |
| 1.2 | Objectivization and Theories | 3 |
| 1.3 | Some preliminary aspects of our approach to biological phenomena | 6 |
| 1.4 | Map of this thesis | 8 |

1.1 INTRODUCTION

CURRENT biology is a discipline where most research activities are (highly demanding) experimentations. For a natural science, this situation may not seem to be an issue; however, it is often associated with the belief that experiments and theoretical thinking can be decoupled. In this context, “concrete” experimentations are conceived as almost autonomous with respect to theoretical considerations, which would be in the abstract. This point of view is particularly prevalent at the molecular level, where researches are related to the finding of hypothesized molecular manipulations (often, molecules) which would allow to solve medical or other socially relevant problem.

However, this point of view is declining and is challenged in different ways. We can informally describe them as the following. First, there are empirical, theoretical and conceptual *instabilities*. This can be exemplified by the notion of gene and its various meanings (Fox Keller 2002), or the dynamic of research fields in molecular biology (Lazebnik 2002). In both cases, the reliability of researches is of course at risk. Another issue is that the molecular level does not allow to approach phenomena that occur typically at *other levels of organization*,

for example, microtubules (Karsenti 2008), cancer at the level of tissues (Sonnenschein & Soto 2000), or the heart at its different levels (Noble 2010). Some authors also emphasize the historical and conceptual shifts that have led to the current methodological and theoretical situation of molecular biology, which is, therefore, misinterpreted (Amzallag 2002; Stewart 2004). In general, even if we start from the molecular level, the problem not only arises from the difficulty to understand the composition of a great variety of molecular phenomena, but also from the fact that a single molecular phenomenon is biologically irrelevant *per se*, and needs to be related to other levels of description if we want to understand its biological significance.

From the point of view of theories, the situation is also not particularly satisfying. Theoretical approaches in biology are numerous and extremely diverse, in comparison, say with the situation in theoretical physics where theorizing has a deep methodological unity (Bailey & Longo 2011). Biological theories range from physical approaches of biological systems to unmathematized conceptual framework. The most prominent ones, in the latter category, are the theory of common descent (all current organisms are the descendants of one or a few simple organisms), Darwin's approach to evolution (death allows to understand — partially — the dynamics of phylogenesis) and cell theory (all organisms have a single cell life stage and are cells, or are composed, among other things, of cells). The crucial issue is, from our point of view, that there are currently no satisfactory theory of biological organization, and in particular of the organism. Darwin's approach (and even more neodarwinian approach), for example, tries to avoid as much as possible this question. Darwin uses the duality between life and death to understand why certain biological forms are observed and other are not. In the modern synthesis and already in Spencer's approach to Darwinian evolution (Stiegler 2001), the determination (fitness) of the organism is understood as predetermined and well defined (by genetics), and, again, the structure of determination of organisms is understood as theoretically unnecessary and is not approached.

In physiology or developmental biology the question of the structure of the determination of the system is often qualitatively approached, but the mathematized approaches are usually limited to specific aspects of organs or tissues, in (relatively) usual physical frameworks. In cellular biology, the equivalent situation leads to (bio)physical approaches of specific structure such as the microtubules, the membrane, On the contrary, the mathematized theories which aim to understand the proper structure of determination of organisms, are mostly based on ideas such as autonomy, see for example Rosen (2005). However, they usually have a crucial weakness: they do not have a normalized connection with experimental biology and current organisms and focus on the questions of the definition of life and its possible origin. Moreover, their relationship with the aforementioned biophysical approaches is tenuous at best.

In this context, physiology and developmental biology (and the study of related pathological situations) are in a particularly interesting situation since these fields are directly confronted with the complexity of biological phenomena. The related research program corresponds to a methodological change which is usually described as systems biology. This change consists, briefly, in focusing on the systemic properties of biological objects instead of trying to understand their components, see Noble (2006, 2011); Sonnenschein & Soto

(1999) and in particular Noble (2008). In the latter, the last principle proposed for systems biology is the following:

There are many more to be discovered; a genuine ‘theory of biology’ does not yet exist. Noble (2008)

This approach is indeed very recent (but corresponds also to a long tradition, according to Noble). The aim of this thesis can be understood as a theoretical contribution to this research program. More precisely, we aim to contribute to a possible general theory of biology (Kauffman 2002). However, if we want to try to provide such an account, there are numerous pitfalls one should avoid. In particular, the relation with the powerful physical theories is a recurring issue. In order to clarify the relationship between theoretical physics, mathematics and biology, a critical and reflexive approach of physical theories (and mathematics) is most helpful if not necessary (Bailly & Longo 2011, 2006). We will provide, in this introduction, a brief, general account on our philosophical background, and the subsequent methodology, which we will follow in the rest of this text.

We will also provide some elements of comparison with other theoretical approaches and then present a commented account of the plan we will follow.

1.2 OBJECTIVIZATION AND THEORIES

Theories are conceptual and sometimes — almost always in physics — mathematized frameworks that provide accounts of natural phenomena.

The strength of these accounts, and their cultural, including religious, background has led to understand them as an intrinsic description of the very essence of nature. For example, for Galileo, “the book of nature is written in the language of mathematics”, which is of course an analogy with the sacred book of revealed religions. Similarly, Descartes writes:

Par la nature considérée en général, je n’entends maintenant autre chose que Dieu même, ou bien l’ordre et la disposition que Dieu a établie dans les choses créées. Descartes (1724)

Besides, in Descartes (1724), it is, *in fine*, the existence of God and its attributes (he should not be deceitful) that legitimate theoretical accounts on the world; on the ground that observations are truthful. In this context, the theory is thus an account of the thing in itself (das Ding an sich, in Kant’s vocabulary). The validity and the existence of such an account are understood mainly by the mediation of a deity, in relation with the perfection encountered in mathematics.

Kant, however, introduced another approach (Kant 1781). Kant’s philosophy is based on the notion of transcendental. In the context of the question of knowledge, the notion of transcendental describes the knowledge on the *a priori* conditions of possibility of knowledge. For example, objects cannot be represented outside space, which are, therefore, the *a priori* conditions of their representation. By this methodology, in particular, the thing in itself is no longer knowable, and the accounts on phenomena are given, in particular, through the *a*

priori form of the sensibility which are space and time. Following this line, mathematics are mostly understood as *a priori* synthetic judgments: it is a form of knowledge that does not depend on experience (it is based on the condition of possibility of experience) but is neither based on the simple analysis of concepts (for example, $2 + 3 = 5$ is neither in the concept of 2 nor in the concept of 3 for Kant).

The transcendental approach of Kant has, however, strong limitations, highlighted by Hegel and later Nietzsche. The limitation highlighted by Hegel is the question of the status of the knowledge of these *a priori* conditions, which he aims to understand dialectically, by the historicity of reason and more precisely by the unfolding of its contradictions. Similarly, with a different background, Nietzsche criticizes also the validity of this transcendental knowledge.

Wie sind synthetische Urtheile *a priori* möglich? fragte sich Kant, — und
was antwortete er eigentlich? Vermöge eines Vermögens [...]

(How are *a priori* synthetic judgments possible?" Kant asks himself — and
what is really his answer? By means of a means (faculty) [...])

Nietzsche (1886)

For Nietzsche, it is essential, in particular, to understand the genesis of such a “faculty” (or behaviour) by its root in the body and the embodiment of the subject (Stiegler 2001).

Recent accounts particularly emphasize the *praxis* underlying scientific theorizing, and mathematical reasoning (Bailly & Longo 2006, 2011), and the cognitive resources mobilized (but also refined in the process). From this perspective, mathematized theories, in particular, are the result of — or are constituted fundamentally by — human activity. It is, therefore, prioritarily the nature of the methodology (the practice) that allows to constitute the objectivity of such theories. As a result, the constitution of such theories is at the same time a process of objectivization. This process constitutes the object of study in a way that simultaneously allows its intelligibility. In this perspective, then, the objects are defined by the theorizing (and they allow the intelligibility), and the validity of the theory (the proof in a sense) is given by experiments. In particular, measurement has a particular status in general, since it is not only the access to an object that would be there beyond the measurement, but is in general a constitution of the object measured and this can be intrinsic in some theories such as quantum mechanics, see chapter 7.

This approach is also valid for the question of the foundations of mathematics. The hallmark of this understanding of mathematics and physics is the relevance of negative results. For mathematics, such results takes the form of incompleteness, where a logical system (a set of rules allowing to prove theorems) does not allow to prove nor disprove certain statements, but nevertheless allows to prove that these statements can neither be proved nor disproved (and mathematically relevant such statements can be found). In physics, this corresponds typically to the results of Poincaré on deterministic unpredictability, and later chaos theory. See Bailly & Longo (2011); Longo (2011) for more details on incompleteness.

Following this line of reasoning, we will approach biological theorizing as the search of ways to constitute theoretical accounts of biological phenomena “directly”. In other words, the research program we follow (see Bailly & Longo 2011) for a theoretical biology

aims at finding manners to constitute theoretically biological objects and objectivize their behaviour. Possible links with other theories¹ can be understood later. In this context, thus, a certain number of problems in the philosophy of biology are not methodological barriers, in principle. We will in the following provide a very brief account of such problems, that will not constitute principle issues for our approach.

PHYSICALISM In the epistemic sense (i.e. with respect to knowledge), physicalism can be crudely stated as follows:

Life can be explained on the basis of the existing laws of Physics .
Perutz (1987)

Even though a wide range of phenomena can be accommodated in the main existing physical theories (classical mechanics, thermodynamics, statistical mechanics, quantum mechanics, general relativity, ...), as soon as the situation we want to understand differs radically, new theoretical approaches are required, also within physics itself. For example, the understanding of criticality requires the introduction of a new structure of determination, and the focusing on original observables (the critical exponents). Similarly, going from macrophysics (classical mechanics) to microscopic phenomena (atoms) necessitates the loss of determinism, and, on the opposite, the understanding of gravity leads to a radical transformation of the classical structure of space-time (and both accounts are not yet compatible). Another example is the link between heat and motion, which requires the introduction of a new quantity (entropy). The latter allows to describe, in particular, the irreversibility of time, which is incompatible with a finite combination of Newtonian particles. Notice also that the current physical understanding of general, far from thermodynamical equilibrium systems is seriously limited (see for example Vilar & Rubí 2001), whilst biological systems, if considered as physical systems, would probably fall in this category.

VITALISM For similar reasons, the question and the debates around the notion of vitalism lead to a flawed approach of biological system. From the theoretical point of view, what matters is simply to find ways to objectivize the phenomena we want to study. Since it hinders original approaches, the fear of negatively connoted vitalist interpretations leads to blind spots in the understanding of biological phenomena.

REDUCTIONISM (SCALE) The methodological assumption that we should understand phenomena beginning at the small scales is, again, at odds with the history of physics. Thermodynamic, for example, started at macroscopic scales and its full mathematical understanding, in relation with microscopic classical mechanics behaviours is recent and limited to demanding assumptions. What is worse, in spite of almost century long researches, microscopic (quantum) gravity is not (yet) understood in a suitable framework. Notice that the hope for “theory of everything” is just meant to overcome

¹The “adjacent” fields are, following Bailly (1991a), physical theories in one direction and human sciences in another.

this difficulty, there is no *a priori* reason why it would help, for example, in the understanding of non-equilibrium thermodynamics (except possibly in the case of black holes thermodynamics).

Moreover, and this point is crucial, the current understanding of microscopic interactions, in the standard model, does not involve a fundamental, small scale; on the contrary it “hangs” between scales (by renormalization methods):

QFT [Quantum Field Theory] is not required to be physically consistent at very short distance where it is no longer a valid approximation and where it can be rendered finite by a modification that is, to a large extent, arbitrary. Zinn-Justin (2007)

We will discuss the question of reductionism in chapter 10 by the use of a conceptual framework which is *in fine* in relation with empiry.

The conclusion of this section is that we understand biological theorizing as a process of constitution of objectivity. Although we mentioned that the above points are not philosophical prerequisites for a genuine intelligibility of biological phenomena, the technical aspects leading to their validity or not (and in what sense) can be insightful. This is typically the meaning of the notion of “the physical singularity of life phenomena” developed in Bailly & Longo (2006, 2011). Another example is the question of (scale) reductionism, which is approached by Soto, Sonnenschein & Miquel (2008). In the latter, the key role of time, with respect to biological levels of organization, is evidenced. As we mentioned above, in chapter 10, we will approach this question in a complementary way, on smaller time scales — but not without time. More generally, we will widely use insights from physical theories, but this use will mainly be a methodological and conceptual reference, and will therefore not be rooted in epistemic physicalism. Indeed, our approach will lead almost to the opposite: we will use the examples of physical theorizing as insights on the way to constitute objectivity, but this will also lead us to contrast biological situations with the very basis of physical theories (in chapter 6 in particular).

Further relations with physical theories will be developed progressively in our text, when needed for our theoretical developments in biology.

1.3 SOME PRELIMINARY ASPECTS OF OUR APPROACH TO BIOLOGICAL PHENOMENA

A methodological point that we first want to emphasize is that we will focus on current organisms. Indeed, numerous theoretical researches are performed on the question of the origin of life. This allows them to use physical or almost physical paradigms, but it comes at the price of neglecting crucial aspects of current biological phenomena. What is worse, most of this research work is mostly separated from possible applications to the understanding of current biological phenomena. On the opposite, biophysics usually allows to approach actual organisms, but this approach is limited to some of their specific aspects and does not allow

to understand the global organization of organisms themselves. The situation is illustrated in figure 1.1.

More precisely, the current paradigm in biophysics usually consists in the transformation of a part of an organism (more generally a living system) into a physical system, separated from the organism. This methodology clearly allows a further understanding of the biological situation. For example, the modelization of microtubules allows to approach their self-organization properties, but it corresponds to an *in vitro* situation, and their relation with the cell is not understood in the physics but requires an interpretation external to the structure of determination at play. Notice that there are often a minimal trace of the organism in such modelization; is the often non-generic² situations which are biologically relevant (Lesne & Victor 2006).

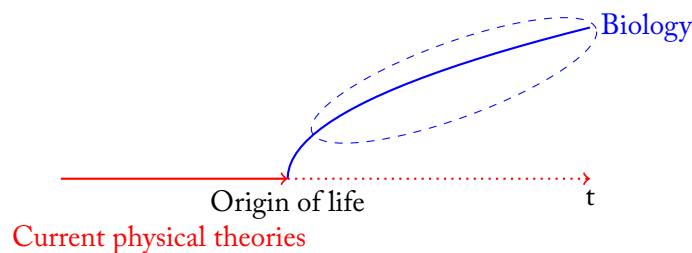


Figure 1.1: *A scheme of the relation between physics and biology, from a diachronic point of view.* Theoretical approaches that focus on the origin of life usually follow the physical line and try to approach the “bifurcation” point. The latter is not well defined since there is no proper theory for the biological domain. Usually, goals such as the necessary ingredients for Darwinian evolution are used. Biophysics, on the contrary, “projects” aspects of the biological domain on physical structure of determination. From our perspective, a proper understanding of biological phenomena need to focus directly, at least as a first (huge) step, on the biological domain. Notice that approaches in terms of shape are relevant for both domains, (Douady, Manning & Hennion 2009).

The general strategy we use is to approach the biological phenomena by different concepts, each of them focusing on different aspects of biological organization and forming germs of more or less mathematized theoretical understanding. This strategy allows us to obtain relatively autonomous progresses on the corresponding different aspects of living systems. An essential difficulty is that, *in fine*, these concepts are fully meaningful in the interaction with each other, that is to say in a unified framework (which we are contributing to establish). In this sense, then, we are generally making progresses by revolving around this not yet existing framework, browsing these different concepts in the process.

The solution to make progress in one of these specific approaches can often be found from a different angle. As a result, we will combine in this thesis a relatively important variety of such approaches, the principal common underlying organizing concepts that we will nevertheless follow in each of these approaches are the question of biological time, on one side, and of extended criticality on the other. The main concepts or conceptual issues

²This means intuitively that they have 0 probability in some sense.

that we will either follow directly or that will make recurrent appearance in this text are the following:

BIOLOGICAL TEMPORAL ORGANIZATION The idea is that, more than space or energy, biological time is the crucial leverage to understand biological organization (which does not mean that these other aspects are irrelevant). The reason for this will be explained progressively in this thesis. Our approach in terms of symmetry changes, which we develop in chapter 6, provides a radical argument for this point of view. Intuitively, the idea is that what matters in biological systems is the organization of organisms, whilst the energetic level (say between mammals of different sizes) is relatively contingent. Other preliminary arguments are the role of time (entropy production) in dissipative structures Nicolis & Prigogine (1977) and the non-ergodicity of the molecular phase space, argued in Kauffman (2002).

EXTENDED CRITICAL TRANSITIONS A good part of our work will use the notion of extended critical transition (Bailly 1991a; Bailly & Longo 2006, 2008) to understand biological systems. This notion is relatively complex, in particular because of its physical prerequisites, and we will also explain it progressively in this text. Notice that it gives a precise meaning to the idea of the physical singularity of life phenomena.

ANTI-ENTROPY This allows to describe an “amount of biological complexity” Bailly & Longo (2003, 2009) and is conceptually an irreducible opposite of entropy. It also determines at least some temporal aspects of biological organization.

BIOLOGICAL RANDOMNESS The notion of randomness is related to entropy and to the irreversibility of time in thermodynamics and statistical mechanics. As a result we expect a proper notion of biological randomness to be related to anti-entropy (at least in part, see also Buiatti & Longo (2011)).

LEVELS OF ORGANIZATION The notion of levels of organization and of their relationships is crucial in biology (Noble 2008; Soto, Sonnenschein & Miquel 2008). We will distinguish two different theoretical kinds of levels of organization (in the last chapter), namely biolons (roughly organisms) and orgons (organs, organelles, ...). This aspects combine with the question of scales (typically a mouse and an elephant are at the same level of organization but not at the same scale).

1.4 MAP OF THIS THESIS

In order to understand biological systems, one first need to consider empirical results. Therefore, in chapter 2, we will review the different forms of scaling that have been observed in biological situations. The choice of such results is motivated by their relative robustness and the theoretical role that they will play latter. We will in particular try to assess their experimental reliability and the variability that is observed. This step is crucial since we will use these results (including variability) both technically and conceptually in the rest of this thesis.

Since biological rhythms are associated to relatively reliable symmetries, we will consider the question of biological temporal organization directly, first by the question of rhythms, in chapter 3. We propose a bidimensional frame for biological time. This frame will allow to take scaling behaviours of different nature into account. Then, we will approach the local structure of biological time, through the notions of protention and retention, in chapter 4, and provide an elementary mathematical approach of the notion of “extended present”.

Chapter 5 provides a technical interlude on some aspects of symmetries and symmetry breakings, which provides some technical background and examples to set the subsequent developments.

In chapter 6, we will approach theoretical structures of determination by the notion of theoretical symmetries. This will allow us to contrast the status of the biological object with the status of the physical objects since for the latter, the theoretical symmetries are stable. We will characterize biological situations as situations undergoing ubiquitous symmetry changes. This will allow us to provide a proper notion of variability and of biological historicity (as a cascade of symmetry changes).

Since this determines a fundamental instability of biological objects, our theoretical proposal “destabilize” the physical approach to objectivation. We will therefore consider the consequences of this situation on the nature of biological measurement, in chapter 7. This will raise the question of a possible global consequence of biological symmetry changes.

To provide some elements of answer to this question, we will, in chapter 8, recall different aspects of a quantified approach of biological complexity introduced in Bailly & Longo (2009) and develop an analysis of anti-entropy in terms of symmetry and symmetry changes, on one side, and approach regenerative aspects of biological organization on the other side. We will also discuss the question of the associated proper randomness.

A proper account of biological complexity requires to take into account the question of the levels of organization and of their relationship. We will first approach this question in chapter 9, in relation with the concept of closure, which is widely used in theoretical biology. We will approach this notion from a different perspective in chapter 10, on the bases, in particular, of criticality (following the line of reasoning of Bailly (1991b)). Finally, in chapter 11, this notion will be further specified, in relation with the accounts of Bailly, Gaill & Mosseri (1993); Bailly & Longo (2003, 2008). In this last chapter, we will combine a large part of the approaches previously discussed in a single, tentative scheme of the structure of coherence of a metazoan.

Scaling in biological systems 2

Observations always involve theory.

E. Hubble

CONTENTS

| | | |
|---------|---|----|
| 2.1 | Introduction | 13 |
| 2.1.1 | Power laws | 13 |
| 2.2 | Allometry | 16 |
| 2.2.1 | Principles | 16 |
| 2.2.2 | Metabolism | 18 |
| 2.2.2.1 | Interspecific metabolic allometry | 18 |
| 2.2.2.2 | Intraspecific metabolic allometry | 20 |
| 2.2.2.3 | A word on temperature | 21 |
| 2.2.3 | Rhythms and rates | 22 |
| 2.2.4 | Cell and organ allometry | 23 |
| 2.2.4.1 | Cell allometry | 24 |
| 2.2.4.2 | Organ allometry | 25 |
| 2.2.5 | Conclusion | 26 |
| 2.3 | Morphological fractal-like structures | 27 |
| 2.3.1 | Principles | 27 |
| 2.3.1.1 | Scale symmetry for sets | 28 |
| 2.3.1.2 | Fractal dimension | 30 |
| 2.3.1.3 | Definition of fractals | 32 |
| 2.3.2 | Cellular and intracellular membranes | 33 |
| 2.3.3 | Branching trees | 34 |
| 2.3.3.1 | Lungs | 35 |
| 2.3.3.2 | Vascular system | 36 |
| 2.3.3.3 | Further aspects for these organs | 38 |
| 2.3.4 | Some other morphological fractal analyses | 38 |

| | | |
|---------|---|----|
| 2.3.5 | Conclusion | 39 |
| 2.4 | Elementary yet complex biological dynamics | 39 |
| 2.4.1 | Principles | 40 |
| 2.4.2 | A non-exhaustive list of biological dynamics | 45 |
| 2.4.3 | The case of cardiac rhythm | 47 |
| 2.4.3.1 | Structure of cardiac rhythm | 47 |
| 2.4.3.2 | Some factors associated with the cardiac rhythm structure | 48 |
| 2.4.4 | Conclusion | 49 |
| 2.5 | Space-time structures | 50 |
| 2.5.1 | Anomalous diffusion | 50 |
| 2.5.1.1 | Principle | 51 |
| 2.5.1.2 | Examples from cellular biology | 53 |
| 2.5.2 | Biological systems “poised” at criticality | 53 |
| 2.5.2.1 | Principle | 54 |
| 2.5.2.2 | Some examples | 55 |
| 2.5.3 | Other forms of Criticality | 57 |
| 2.5.3.1 | Self-organized criticality | 57 |
| 2.5.3.2 | Self-tuned Criticality | 58 |
| 2.5.3.3 | “Attached” criticality | 58 |
| 2.5.4 | Conclusion | 59 |
| 2.6 | Networks | 60 |
| 2.6.1 | Structures | 60 |
| 2.6.2 | Dynamics | 62 |
| 2.6.3 | Conclusion | 63 |
| 2.7 | Conclusion | 63 |

ABSTRACT:

This chapter reviews experimental results showing scaling in biology. The minimal concepts and mathematics needed to understand them is progressively introduced, followed by a discussion of the main experimental findings (either through special cases or more general results). We will in particular give attention systematically to the robustness of these empirical findings and the potential corresponding variability.

More explicitly, we discuss allometry, which is the transformation of quantitative biological observables engendered by considering organisms of different sizes. Then, we discuss anatomical fractal-like structures, the latter being ubiquitous in organs shape (but with a fair amount of variability). We report also observed temporal fractal-like structures in biological time series. Finally, we will provide some examples of space-time situations and then of network configurations and dynamics.

Keywords: Scaling, variability, allometry, fractals, regulation, criticality.

2.1 INTRODUCTION

WE propose, in this text, to provide a picture of the empirical findings showing scaling in organisms and cells. Although these findings mainly revolve around the notion of scale symmetry, they can take various forms. Therefore, we will provide brief accounts of the conceptual and mathematical basis leading to these empirical inquiries. Such accounts are also needed because they define the quantities that are tentatively constituted to be robust and biology relevant.

The first remark we want to make is that there is a strong difference between the allometric relationships and the scaling *inside* a definite system.

- In the allometric methodology, the idea is to compare properties of organisms with different sizes. More precisely the core idea is that, we can bring out fundamental aspects of biological organization by looking how quantities (various rates, sizes of components, ...) change with respect to a degree of freedom (the organism mass usually) and more precisely its scale. This degree of freedom is not *per se* relevant (as a degree of freedom) to the organism.
- The second methodology aims at finding scaling relationships as a property of a system observed at different scales (especially spatial and temporal). Hence, this second approach aims at describing complex geometrical organization, usually by introducing a dependency of observed quantities on the resolution of observation, finding significant results by looking how objects change, depending on this resolution (instead of “seeing all the object at once”).

An extensive review of the second methodology, in the case of neuronal structures and activities, has been done in Werner (2010), see also Werner (2007); Ribeiro et al. (2010). As a result and because scaling and criticality are already well established as useful for neuronal activities, we will have a bias and avoid neuronal examples. In general, we will focus on the basic physiology of cells and organisms.

We are going first to look at allometric properties in biological systems. Then, we will consider the morphological fractal-like properties, their validity and basic properties. These properties concern the space organization of biological systems. Following these aspects, we will consider the temporal organization of biological systems, in the observation of biological time series. Then, we will discuss some space-time cases and biological networks architectures and dynamics.

Before entering this discussion, we will present the basic mathematical form that describe the simplest case of scaling, namely the renowned power laws, and the reason why it describes scaling. More complex definitions of scaling usually have such forms as a mathematical building block.

2.1.1 POWER LAWS

As we said, power laws are met almost everywhere when scaling is discussed. We will show in this section that there is a straightforward mathematical reason that justifies this

situation. We will first present it informally and then with more technical details and generality (only the basic outline of the demonstration will be of importance latter, and will also be crucial for chapter 7). Let us consider a real function f of one variable and suppose that f has a property of scale invariance, by which we mean that f is the same, modulo a factor, when the variable is observed at different scales. Formally this condition can be written as $f(\lambda x) = g(\lambda)f(x)$, where λ characterize the change of scale. This condition can also be seen in terms of symmetries, as an invariance by dilatation: $f \circ D_\lambda = D_{g(\lambda)} \circ f$. We will now show semi-informally that under this conditions, and the assumption that f is continuous, we have $f(x) = f(1)x^\alpha$.

- In this special case, we have $f(x1) = g(x)f(1)$, meaning that f and g are proportional. We will in the following take an arbitrary value, a , as the starting point of transformations. The aim is now to relate quantities $f(x)$ for any value of the variable x , to $f(a)$. The later indeed allows to define α by $f(a) = a^\alpha$.
- Considering an integer n , we have $f(a^n) = g(a^n)f(1)$ and $f(a^n) = f(aa^{n-1}) = g(a)f(a^{n-1}) = \dots = g(a)^n f(1)$. Hence, $g(a^n) = g(a)^n$.
- If p and q are integers, $f(a^{qp/q}) = f(a^p) = g(a)^p f(1)$ and $f(a^{qp/q}) = f((a^{p/q})^q) = g(a^{p/q})^q f(1)$. So we conclude that $f(a^{p/q}) = g(a)^{p/q} f(1)$ and $g(a^{p/q}) = g(a)^{p/q}$.
- This is not sufficient to obtain the value $f(x) = f(a^y)$ for every *real* number y , because there is no *finite* algebraic transformation from the rationals to all real numbers. Nevertheless, since every *real* is the limit of rational numbers and since we assumed that f is continuous, we can conclude that $f(a^y) = g(a)^y f(1)$.
- Writing $g(a) = a^\alpha$ (i.e. $\alpha = \frac{\ln(g(a))}{\ln(a)}$) we have then $f(x) = f(a^y) = g(a)^y f(1) = a^{\alpha y} f(1) = x^\alpha f(1)$.

By contrast with the situation of scale symmetry, the paradigmatic situation involving a characteristic scale is of the form $\exp(-x/x_0)$. Since $\exp(-\lambda x/x_0) = \exp(-x/x_0)^{\lambda-1} \exp(-x/x_0)$: the analog to g depends then crucially on x . From a more conceptual point of view, the nature of the exponential is to describe the decay (or growth) of a quantity which changes in proportion to its magnitude for a given translation of the variable. The magnitude of the translation needed to obtain a decay of a factor e defines then a particular scale.

We will now consider the mathematical situation with more generality than above (the understanding of the demonstration bellow is not necessary to understand the rest of our discussion):

2.1 THEOREM (SCALING) :

Let us consider a function $f : A \rightarrow \mathbb{R}$ and a group $G = \{\mathcal{D}_\lambda | \lambda \in \mathbb{S}\}$ acting on A , where \mathbb{S} is a subgroup of $(\mathbb{R}^{*+}, \times)$ and $\lambda \rightarrow \mathcal{D}_\lambda$. We suppose that $\lambda \rightarrow f \circ \mathcal{D}_\lambda$ is continuous¹ and that there exist g such that $\forall \lambda \in \mathbb{S}, f \circ \mathcal{D}_\lambda = g(\lambda)f$.

Then, there exists α such that $\forall \lambda, g(\lambda) = \lambda^\alpha$. ◇

¹This condition is always met if $\ln(\mathbb{S})$ is proportional to \mathbb{Z} .

PROOF : If $f = 0$, then any α fulfill the conditions of the theorem. Let us consider now $f \neq 0$ and G according to the hypothesis of the theorem. We will proceed by considering sets of increasing size.

[1] $f \circ \mathfrak{D}_1 = g(1)f$ and $f \circ \mathfrak{D}_1 = f$ so $g(1) = 1$.

[\mathbb{N}] Let us consider $a \in \mathbb{S}$, $a \neq 1$ and $n \in \mathbb{N}^*$. We have $f(\mathfrak{D}_{a^n}(x)) = g(a^n)f(x)$ and $f(\mathfrak{D}_{a^n}(x)) = f(\mathfrak{D}_a \circ \mathfrak{D}_{a^{n-1}}(x)) = g(a)f(\mathfrak{D}_{a^{n-1}}(x)) = g(a)g(a^{n-1})f(x)$ and then, $g(a^n) = g(a)g(a^{n-1})$. Finally, we obtain by recurrence $\forall n \in \mathbb{N}$, $g(a^n) = g(a)^n$.

[\mathbb{Z}] Let us take $n \in \mathbb{N}$. We have $g(a^n a^{-n}) = g(1) = 1$ and $f(\mathfrak{D}_{a^n a^{-n}}(x)) = f(\mathfrak{D}_{a^n} \circ \mathfrak{D}_{a^{-n}}(x)) = g(a^n)f(\mathfrak{D}_{a^{-n}}(x)) = g(a^n)g(a^{-n})f(x)$, as a result $g(a^{-n}) = g(a)^{-n}$. We have shown that, $\forall n \in \mathbb{Z}$, $g(a^n) = g(a)^n$.

If $\ln(\mathbb{S})$ is proportional to \mathbb{Z} , there exists a such that $\mathbb{S} = \{a^n \mid n \in \mathbb{Z}\}$. As a result for all $\lambda \in \mathbb{S}$, we have $\ln(\lambda)/\ln(a) \in \mathbb{Z}$. Thus $g(\lambda) = g(a)^{\ln(\lambda)/\ln(a)} = \lambda^{\ln(g(a))/\ln(a)}$, so $\alpha = \ln(g(a))/\ln(a)$ answers the question. In the following step, we will on the contrary assume that \mathbb{S} is dense² in \mathbb{R} .

[\mathbb{S}] We will show that $\alpha = \ln(g(a))/\ln(a)$ fits the expected conditions.

Let us consider $\lambda \in \mathbb{S}$ and $p_k = \lambda^{n_k} a^{-m_k}$ where $\forall k$, $(n_k, m_k) \in \mathbb{N}^{*2}$ and (p_k) tends to 1. This last condition means that (m_k/n_k) tends to $\ln(\lambda)/\ln(a)$.

We have $f(\mathfrak{D}_{p_k}(x)) = g(p_k)f(x)$ which tends to $f(x)$ since $s \rightarrow f \circ \mathfrak{D}_s$ is continuous and (p_k) tends to 1, so $(g(p_k))$ tends to 1. Now, $g(p_k) = \frac{g(\lambda)^{n_k}}{g(a)^{m_k}}$ so $g(p_k)^{1/n_k} = \frac{g(\lambda)}{g(a)^{m_k/n_k}}$ tends to $\frac{g(\lambda)}{g(a)^{\ln(\lambda)/\ln(a)}}$ and to 1. As a result $g(\lambda) = g(a)^{\ln(\lambda)/\ln(a)} = \lambda^\alpha$.

In all cases, we thus have found α such that $g(\lambda) = \lambda^\alpha$. ■

2.1.1 REMARK : If $\ln(\mathbb{S})$ is proportional to \mathbb{Q} , we do not need the continuity hypothesis. Indeed, consider $p \in \mathbb{N}$ and $q \in \mathbb{N}^*$. We have $g(a^p) = g(a)^p$ and $g(a^p) = g((a^{p/q})^q) = g((a^{p/q})^q)$. As a result $g(a^{p/q}) = g(a)^{p/q}$. *

2.1.2 REMARK : The continuity hypothesis is crucial in general. Let us for example decompose \mathbb{R} , as a \mathbb{Q} -vectorial space, as a linear sum of two non-trivial subspaces: $\mathbb{R} = A \oplus B$. We can then define $f : \mathbb{R}^+ \rightarrow \mathbb{R}^+$, so that for $x = \exp(a + b) \in \mathbb{R}$, with $a \in A$ and $b \in B$ we get $f(x) = \exp(2a + 3b)$. f is well defined because the decomposition is unique. For $\lambda = \exp(a_2 + b_2)$, we have $f(\lambda x) = f(\exp(a_2 + b_2 + a + b)) = \exp(2a + 2a_2 + 3b + 3b_2) = f(s)f(x)$. Thus the condition of scale symmetry is met, but not the continuity and neither is the existence of an α valid for all transformations. *

2.2 COROLLARY :

A function $f(x_1, \dots, x_n) : \mathbb{R}^{*n}$ which meet the criteria of theorem 2.1 for the n groups, copies of $(\mathbb{R}^{*+}, \times)$ acting respectively on each x_i by the usual multiplication can be written as:

$$f(x_1, \dots, x_n) = f(1, \dots, 1) \prod x_i^{\alpha_i} \tag{2.1}$$

²We recall that the subgroups of $(\mathbb{R}, +)$ are either proportional to \mathbb{Z} or dense, which leads to the subgroups of $(\mathbb{R}^{*+}, \times)$ either having a logarithm proportional to \mathbb{Z} or being dense.

We understand now that scale-symmetry leads directly to power laws. It is noteworthy that such situations lead to the determination of two kinds of quantities: a coefficient, here $f(1, \dots, 1)$, and one or more exponents, α_i . This two kinds of quantities will be the at the core of empirical results we will discuss in this chapter. Notice, moreover that the exponent is a dimensionless quantity associated to the changing of scale itself, it determines the dilatation D_{λ^α} of the observable, associated to the dilatation D_λ of the variables. The coefficient $f(1, \dots, 1)$ is associated to the choice of units (of what 1 is, for the variables and the observable). Another aspect of this coefficient, in a given choice of units, is that it can be different for different sets of objects that still share the same symmetry by dilatation. In this case, they are not on the same orbit for these transformations: they have the same symmetry but are not symmetric for this transformation (they cannot be changed into each other by this symmetry (see below for an elementary example in the case of allometry)).

2.2 ALLOMETRY

The very first approach of allometry can be found in the theoretical work of Galileo. In his early studies on Dante's *Inferno* and in particular on the size of the Devil (here we have a "biological" bias since; architectural aspects are also relevant) Galileo did not take into account the effect of size on materials resistance (but he did take some of them into account for architectural aspects). In particular the physical implications of the ratio between surfaces and volumes was unclear. This mistake lead to a theoretical accounts on the strength of materials in Galileo (1638).

2.2.1 PRINCIPLES

The idea of allometry is to look at quantitative properties of objects of the same "nature" (i.e. symmetric) but of different sizes. Consider, for example, a cube of side length l , and a dilatation of all axes by a factor λ . If L is the length of the edges, S its surface and V its volume, we have:

$$\begin{array}{rcl} L = l & & \lambda L \\ S = l^2 & \longrightarrow & \lambda^2 S \\ V = l^3 & & \lambda^3 V \end{array}$$

Therefore, we have obtained quantities which have the form al^α , where α characterizes the nature of the quantity observed (a length, a surface or a volume). As we said before, the exponent α defines the scale symmetry associated to the considered quantity, whilst the coefficient a determines a class of objects which are symmetric, with respect to the quantity observed. For example, the set \mathcal{C} of cubes of side length l and the set of spheres \mathcal{S} of radii l share the same symmetries by dilatation for the surface (with exponent 2) and the volume (with exponent 3), but they have different coefficients (fully determined by the value at a given scale, say for $l = 1$).

More generally, the idea of allometry is to postulate that a class of objects, understood as parameterized in particular by their size (for example their mass, W), share a quantitative property $A(W, \dots)$, and that this objects are similar in their constitution. The latter is

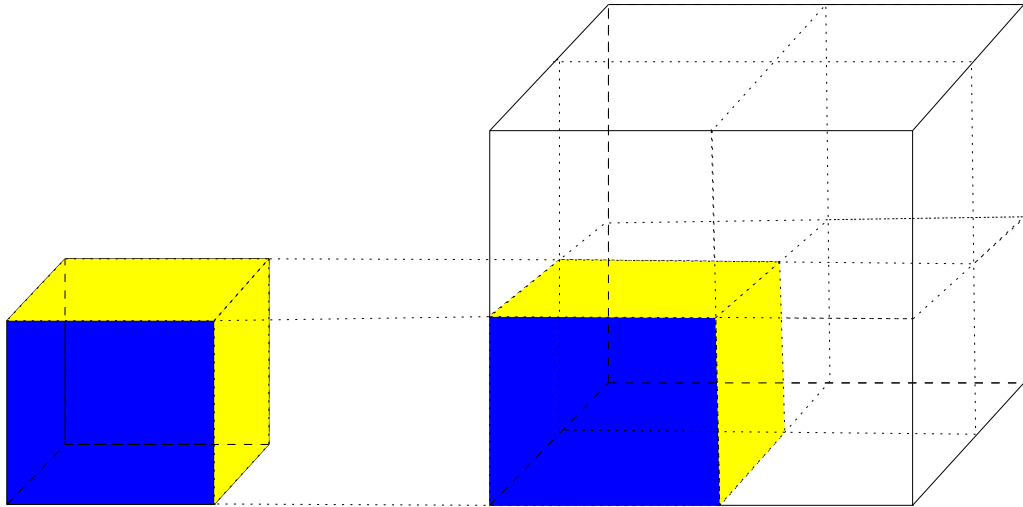


Figure 2.1: *Allometry for a cube*: Doubling the lengths leads to a multiplication by 2^2 of the surfaces and a multiplication by 2^3 of the volume. The corresponding exponents, 2 and 3, characterize in a very general way the geometrical nature of the objects and functions considered.

formulated by saying that A verifies, at least approximately, a symmetry by dilatation with respect to the parameter W . As a result, the expected relationship, when everything else remains constant, is $A(W) \simeq aW^\alpha$. The latter relation describes the scale symmetry associated to the considered objects, then understood as different versions of the same organization for different sizes.

We should notice that this kind of dependency is extremely fundamental and for “simple” systems does not lead to a plethora of situations. For example, in classical thermodynamic³ there are two kinds of quantities: the intensive quantities, with $\alpha = 0$ (for example temperature, pressure, concentrations, ...) and the extensive quantities, with $\alpha = 1$ (volume, energy, entropy, ...).

In order to show allometry experimentally, the simplest methodology consists in representing the observable as a function of its parameter in log-log coordinates. In such a graph, the allometric relation correspond to a straight line, because of the relationship $\log A(W) \simeq \log(a) + \alpha \log(W)$. This relation also shows that the exponent appears as the slope of this line. In order to test such a relationship, a broad set of orders of magnitude is required, because multiplying $\log W$ by n requires measuring a weight W^n (from another point of view, the derivative of \log tends to 0 when the variable tends to infinity). There are mainly two situations in biology that meets this criteria and which correspond to the two main types of allometry: the *intraspecific* or ontogenetic allometry (we observe organisms during their development) and the *interspecific* allometry (we observe adults of species encompassing a wide range of adult masses). From a biological point of view, an essential

³The non-extensive thermodynamic approaches try to construct a framework where the situation is richer, starting from this point of view. See Tsallis & Tirnakli (2010) for a review.

difficulty is to define A in such a way that A can be expected to be similar for organisms with various phylogenetic and ontogenetic histories and widely different sizes.

2.2.2 METABOLISM

From the point of view of allometry, metabolism is a compelling quantity since it is clearly a global quantity, involving the activity level of the whole organism. Besides, it is a quantity that can be measured for a wide class of organisms, in a similar way. Since the work of Rubner (1883) and Kleiber (1932), a considerable amount of studies has been performed focusing on metabolic allometry, also for historical reasons (see below).

In order to compare the metabolism of different organisms, it is necessary to consider them at comparable levels of activity. As a result, levels of activity considered must be broadly defined, and should not exhibit too much specific effects, due to ontogenetic or phylogenetic individuation. The main levels of activity used are:

BASAL METABOLIC RATE (BMR). The BMR is the most used level of activity for allometry.

It corresponds intuitively to a situation of an animal doing nothing in particular but being awoken. More precisely the animal is at rest in a conscious post-absorbative state in a thermo-neutral environment and in the inactive phase of the circadian cycle. We should notice here, that this imply some difficulties for ruminants, which are almost always in an absorbative state. This level is defined for homeothermic animals, and its analog for poikilothermic animals is the Standard Metabolic Rate. However, the distinction between the two terms is sometimes fuzzy in the literature.

MAXIMUM METABOLIC RATE (MMR). The MMR corresponds to a situation at the maximum level of sustainable exercise.

FIELD METABOLIC RATE (FMR). The FMR is measured on animals in the wild. As a result it needs specific measurement methodology, in order to not hinder animals activity. Notice that, by definition, it may depend on the field considered, and on animals habits.

In order to observe quantitatively metabolic activity, the simplest method is the measurement of the O_2 consumption rate, provided that for aerobic organisms this rate is assumed to be proportional to respiration, and the latter is assumed to be proportional to metabolism. For plants, where the metabolic activity consume and produce oxygen, the observed quantity is the increase of mass (dry matter). A less frequently used methodology consists in a calorimetric approach, allowing to directly observe the energy dispersed by organisms in heat form. Notice that Glazier (2005) is an extensive survey on metabolic allometry.

2.2.2.1 *Interspecific metabolic allometry*

Allometry of the BMR and metabolic allometry in general has been first tested experimentally in biology by Rubner (1883); and this experimental approach was initially motivated by a theoretical insight. The idea Rubner followed is that the metabolism R (measured by O_2 consumption rate) was proportional to heat transfers with the environment. The latter is

then assumed to be proportional to the surface of the body, leading to $R \propto S \propto l^2$, where l is a typical length. The mass is also assumed to be proportional to the volume, so we have $W \propto V \propto l^3$ and $l \propto W^{1/3}$. As a result, the expected relationship between metabolism and mass was $R \propto (W^{1/3})^2 = W^{2/3}$. This relationship has been tested experimentally and seemed confirmed on dogs.

Nevertheless, the work of Kleiber (1932) leads to a largely different BMR allometric relationship for adult mammals, with an exponent of 3/4. This relation seems to hold for interspecific allometry, for the observation of O_2 consumption rate among animals (Kleiber 1961; Schmidt-Nielsen 1984; Savage et al. 2004), but with different coefficients R_0 for mammals, birds or reptiles (where $R \approx R_0 W^{3/4}$). For example, this coefficient is roughly 10 times bigger for mammals than for reptiles, which comes as no surprise considering the deep physiological differences between the two phylogenetic groups. The remarkable fact is the finding of similar allometric exponent. In the case of plants, for the observation of dry matter production, the same relation was also found in Niklas & Enquist (2001), with the same coefficient over 20 order of magnitude⁴. Nevertheless, notice that, in all cases, the variability remains high, in spite of the high regularizing effect of the allometric form. For example, in Niklas & Enquist (2001) the 95 % confidence interval has a width of a factor 10 (for the metabolism).

A part of this results, however, is challenged by some authors. To understand the roots of the controversies, we must recall that any statistical analysis is based on an assumption of independence or controlled dependence between points, which will lead to the weight given for various measurement⁵. Savage et al. (2004) takes averages on a per species basis, then gave equal statistical weights for equal $\log(W)$ intervals. The underlying idea is to give equal weight to all masses, which is the straightforward way to follow the form of allometric equation. This allows to deal with the fact that there are more small species than large species. It also indirectly compensate for phylogenetic correlations, since related species tends to have similar masses⁶. White & Seymour (2003), on the contrary focuses, on the question of phylogenetic dependence, but do not take into account the small size over-representation, and even accentuated it by ruling out species, usually big, where the post absorptive state was not clearly achieved⁷. These considerations lead the two studies to find different, statistically incompatible exponents ... by working on the same data set, see Agutter & Wheatley (2004) for a relatively balanced review on this question.

One should note that temperature plays a key role for the metabolic rate. A rule, derived by theoretical arguments, on a thermodynamic basis, as been proposed and tested by Gillooly et al. (2001): $R \propto \exp(\frac{E}{kT})$. This rule is confirmed by empirical data, but seems far more scattered than the mass dependence, see §2.2.2.3.

⁴This article is especially seen as compelling since one of its author was skeptical about the wide range validity of such a relationship.

⁵We will analyze the situation more precisely in chapter 7.

⁶This approach is related to the theoretical justification of 3/4 BMR allometric exponent proposed in West, Brown & Enquist (1997, 1999), which emphasize the scale symmetry aspects as a broad tendency.

⁷As we mentioned earlier, it is indeed extremely difficult, if even possible, to put animals like ruminants in a post-absorptive state.

Maximum metabolic rate, however, seem to have a higher exponent. For mammals, this exponent has been found to be of 0.87 in Weibel et al. (2004) and of 0.83 in Savage et al. (2004); among mammals and birds, Bishop (1999) found an exponent of 0.88. Even if the exponent is not stable in the literature, the fact that it is higher than the *bmr* exponent is well established. We emphasize that it is obvious that the coefficient R_0 for MMR is higher than that of BMR (because in the case where the mass is one, $R_{Max} = R_{0,Max} > R_{Basal} = R_{0,Basal}$); however the two situations could *a priori* lead to similar exponents (like in the comparison of reptiles and mammals). There is, however, a simple mathematical reason, which is not discussed in the literature, why the exponent for MMR cannot be smaller than that of BMR: if it were the case, small animals would have a higher BMR than the MMR. A more theoretical argument is that the MMR is attracted by the inertial mass (for the animal to move), which has an allometric exponent of 1.

The field metabolic rate depends on the habits of animals. As a result, the possible scale symmetry is more broken than for other metabolism values, see Nagy (2005). The exponent found is roughly 0.8, but the importance of the temperature of the environment is emphasized (which comes as no surprise, since it leads to a greater contribution of the external surface/volume ratio).

In the special case of hibernation, the exponent seems to be 1, see Singer et al. (1995). If this result is confirmed — which may prove to be difficult because of the limited availability of hibernating species —, it means that the metabolic rate is an extensive quantity in this very peculiar situation. Hence, the organism behave like a sum of its part and biological integration is weak.

2.2.2.2 *Intraspecific metabolic allometry*

We want to first emphasize that intraspecific allometry actually means ontogenetic allometric, since the size variability among adults is not quite sufficient to perform allometric studies, at least when there is an adult mass, provided that organisms like fishes' have a lifelong growth. Some pathological cases, such as obesity, dwarfism, ..., could also provide mass variability, but in very special circumstances.

Intraspecific allometry seems far less stable than interspecific allometry. A number of study has been performed, especially among fishes, where the intraspecific allometric exponents were found to vary, depending on the species, see for example Bokma (2004). We have to mention, however, that this study does not distinguish field metabolic rate and standard metabolic rate, and use highly heterogeneous data.

The observation of intraspecific allometry allows to obtain results for single species⁸, and, as a result, to examine the potential changes of organization in development through a shift of allometric exponent, or a curve in log-log space. A study of Giguere, Cote & St-Pierre (1988), for example, find that the routine metabolic rate of Atlantic mackerel, *Scomber scombrus* scale isometrically (exponent 1) for fishes at a larval stage, whilst the juveniles and adults have an exponent of 0.8. Another study (Moran & Wells 2007) on the yellowtail kingfish, *Seriola lalandi*, leads to an exponent of 0.90. According to the authors, the situation

⁸As a matter of fact results for single individuals could also be obtained, but such studies have not been performed to our knowledge.

is possibly better described by a quadratic curve in the log-log space (instead of a linear one), comforting the idea of possible changes of exponent during ontogeny. A general study, among five different phyla, Glazier (2006), found in particular that the exponent is higher for pelagic animals in comparison with benthic ones — including a shift when the considered species has a larval, pelagic lifestyle followed by a benthic adult stage. Such a shift occurs in the case of mussels, *Mytilus edulis*, from an exponent 0.9 to 0.7.

The conclusions we can draw from this results is that aquatic intraspecific allometry is correlated to the ecological lifestyle. Beyond this correlation, we want to emphasize that the variability is dominant; and allows to have extreme variations in allometric exponents, including for animals with related ecological statuses.

For terrestrial animals too, the situation is not particularly stable. For example, exponents from 0.62 to 0.68 have been found for different snakes species (Dmi'el 1970). A more extensive study of ectotherms, Glazier (2009), found an average basal metabolic rate exponent of 0.83 ± 0.10 , where the high scattering of this exponent distribution is especially noteworthy. Similarly to the interspecific situation, the active metabolic rate exponent is found to be higher 0.92. A collection of specific results can be found in Glazier (2005, appendix).

2.2.2.3 A word on temperature

Temperature has a direct effect on the rate of chemical reactions, and as a result, can be assumed directly to affect the metabolism of organisms. This effect is expected to especially large when the body temperatures can be significantly different, for poikilotherms⁹. Gillooly et al. (2001, 2006) propose to consider that the effect of temperature on metabolism can be deduced, at least as a tendency, from thermodynamics. Arrhenius equation provides the following relation between the kinetic constant, k , of a chemical reaction, and its activation energy E_i . In particular, the latter is assumed to be constant by the authors (independent of temperature and constant in a given group of organisms) because of the stability of the elementary reactions involved in respiration:

$$k = A \exp\left(-\frac{E_i}{k_b T}\right) \quad (2.2)$$

where k_b is Boltzmann constant and T is the temperature in Kelvin. This leads to a completed metabolic equation:

$$R = R_0 W^{3/4} \exp\left(-\frac{E_i}{k_b T}\right) \quad (2.3)$$

and if we take a reference temperature T_0

$$R(W, T) = R(1, T_0) W^{3/4} \exp\left(\frac{E_i(T - T_0)}{k_b T T_0}\right) \quad (2.4)$$

The results obtained in Gillooly et al. (2001) is $E_i = 0.41$ eV to 0.74 eV, with variations depending in particular on the organisms group, with an overall mean of 0.62 eV. However,

⁹As a matter of fact, one can also change importantly the temperature of homeotherms, but this leads to a major global organizational change, namely hypothermia.

Table 2.1: *Allometry of biological rhythms in mammals*, this table is established using results from Lindstedt & Calder III (1981) and represents $\tau_i = \tau_0 W^\alpha$ where W is in kg and τ_0 in min.

| | log τ_0 | exponent α |
|---|--------------|-------------------|
| Life span in captivity | 6.8 | 0.20 |
| 98 % growth time | 5.8 | 0.26 |
| Time for population doubling | 5.5 | 0.26 |
| Time to reproductive maturity | 5.5 | 0.18 |
| 50 % growth time | 5.3 | 0.25 |
| Gestation period | 5.0 | 0.25 |
| Time to metabolize fat stores (0.1 % body mass) | 2.2 | 0.26 |
| Drug half life (methotrexate) | 1.8 | 0.19 |
| Plasma clearance, inulin | 0.8 | 0.27 |
| Blood circulation time | -0.5 | 0.21 |
| Gut beat duration | -1.3 | 0.31 |
| Respiratory cycle | -1.7 | 0.26 |
| Cardiac Cycle | -2.4 | 0.25 |
| Twitch contraction time, soleus | -3.0 | 0.39 |
| Twitch contraction time, extensor digi- torum longus | -3.5 | 0.21 |

the variability of the data is quite high, including in a phylogenetic group. Still, most allometric study in relation with the level of activity has to take the effect of temperature variations into account, when one has to compare organisms having different optimal temperatures.

However, this account is based on the assumption of a symmetry of the molecular (thermodynamic) activities at different temperature, which is not necessarily met in biological situations. This is true to the point that even the intraspecific exponents (for mass allometry) can depend on temperature. In Glazier (2005), for example, the Arthropoda *Asellus aquaticus* has an exponent of ~ 0.8 for 10 to 20 and of ~ 0.4 for 25 to 30 whilst *Euphausia pacifica* has an exponent that remains approximately constant. We can interpret the situation by saying that temperature changes can lead to an organizational change. Therefore, we have, here, a complete departure from the above developed analysis, see chapter 7 for a further theoretical discussion on this topic.

Notice also that the temperature of the body is not well defined for some species, meaning that it is far from homogeneous with organized temperature differences of 12 to 15 in the example of tuna (see for example Kay 1998).

2.2.3 RHYTHMS AND RATES

Rhythmic processes are another aspect of biological phenomena that allometry can participate to describe. The idea here is to look at processes that occur in similar ways for a great variety

of organisms, and to measure the time τ_i needed for these processes to take place. Such times are, for example, the beat-to-beat interval of the heart or the entire lifespan.

The results in the literature, see Lindstedt & Calder III (1981); Savage et al. (2004); Günther & Morgado (2005), is that $\tau_i \propto W^{1/4}$ for interspecific allometry of mammals and birds. One should notice that we can deduce from this relation that the metabolic rate should scale approximately like $W^{3/4}$. Indeed, the metabolic rate has the physical dimensionality of an energy over a time. We can approximate that energy is proportional to the mass which then leads to $R \propto \frac{W}{\tau_i} \propto W^{3/4}$.

The metabolic rate is unique for an organism (in a given measure), whilst there is at the same time a broad variety of rhythms taking place in an organism. Moreover, characteristic times of non-rhythmic phenomena can also be observed. Hence, a variety of allometric exponents can be observed for the same class of organisms, which makes temporal allometry especially interesting, *a priori*. Their theoretical value is confirmed *a posteriori* by the approximate stability of the obtained allometric exponents, see table 2.1. A consequence of this stability is that the average ratio of two such times does not depend on the mass of the organisms, and then seems to be an invariant quantity. Especially relevant is then the average number of iterations of a given rhythm during the entire life span of an organism, which remains approximately constant among mammals, for example. The drawback of this kind of approach is that observables, such as the cardiac rhythm, become undefined for organisms ... without a heart (and in particular unicellular).

It is usually argued that the maximum spiking rate of neurons does not depend on the mass of organism, because it is determined by the parameters of Hodgkin-Huxley's equation, and this parameters are mostly determined by ion channels which remains symmetric for animals of different masses. In Hempleman et al. (2005), it thus in the neural spiking pattern that allometry is found, for intrapulmonary chemoreceptors, with exponents of 0.22 to 0.26 among birds.

Plants have less relevant rhythms than animals in the allometric perspective. Nevertheless, Marbà, Duarte & Agustí (2007) considered the demographic parameters on a wide collection of plants (from phytoplankton to trees) and found that the times characterizing the mortality rate has an allometric exponent of 0.22 and that the exponent for birth characteristic time is 0.27. As a result, both of them are close to the usual value of 1/4. Partial results on fishes support also comparable exponents (Gerkema 2002).

Interestingly, these aspects directly impact the molecular level. For example, Gillooly et al. (2005) found that the nucleotides substitution rates are associated to exponents of 0.21 to 0.23, depending on the precise phenomenon observed. As a result, the "molecular clock", if any, depends directly on the body size (and temperature) of the organisms involved. Temporal allometry also has direct consequences on the effect of drugs on an organism, see Boxenbaum & DiLea (1995); Kirman et al. (2003) and the discussion in the conclusion.

2.2.4 CELL AND ORGAN ALLOMETRY

If we consider constituents of an organism (cells or organs, typically), looking at the allometry of their properties (with respect to the mass of the organism) provides original and compelling insights on their biological meaning. It indeed directly and quantitatively gives a

Table 2.2: *Allometry of cell types*, this table is established using results from Savage et al. (2007). α_V is the allometric exponent associated to the cells volume and α_N is the exponent associated to the estimated cell number.

| Cell type | α_V | α_N |
|-------------------------------------|--------------------------|----------------------|
| Expected 1 | 0 | 1 |
| Expected 2 | $1 - \alpha \simeq 0.25$ | $\alpha \simeq 0.75$ |
| Alveolar macrophages | 0.08 | 0.96 |
| Erythrocytes | 0 | |
| Fibroblasts | 0 | |
| Fibrocytes | 0.05 | |
| Glomerular epithelium | 0.05 | |
| Goblet cells | 0.07 | |
| Henle loop cells | 0.01 | |
| Hepatocytes | -0.03 | |
| Lung endothelial cells | 0 | 1.00 |
| Lung interstitial cells | 0.06 | 1.08 |
| Lung type I cells | 0.05 | 0.95 |
| Lung type II cells | 0 | 0.98 |
| Proximal convoluted tubules | 0.04 | |
| Sebaceous gland cells | 0.05 | |
| Adipocytes (dorsal wall of abdomen) | 0.13 | 0.80 |
| Adipocytes (skin) | 0.17 | |
| Cerebellar granule neurons | 0.14 | |
| Cerebellar Purkinje neurons | 0.18 | |
| Superior cervical ganglion neurons | | 0.68 |

relation between the part and the whole. Here, we will review some anatomic and metabolic allometric relationship that are especially compelling.

2.2.4.1 Cell allometry

Let us suppose that an organism of mass W is constituted by a number of cell $N(W)$ and has a metabolism of $R = R_0 W^\alpha$ (understood here as a respiration rate). We will first consider two opposite organizational possibilities, as described in Savage et al. (2007). This description will allow to clarify what the logic of the situation is. We will first remark that a principle of conservation (provided that there is no production of O_2 in the organism and that metabolism occurs in cells) leads to $R = \sum R_i$, where R_i is the metabolism of the cell i . In other words, the oxygen consumption of the organism is the sum of the oxygen consumption of the cells¹⁰.

¹⁰The hypothesis of conservation is crucial (and also not very problematic): it is this hypothesis which leads to an additive structure for the oxygen consumption. The same argument is used for the mass.

1. If we assume that the mean cell size does not depend of the size of the organism ($m_c \propto W^0$), then we have $N(W) = \frac{W}{m_c} \propto W$, where m_c is the mean of the cells masses and N is the number of cells. However, in this case, the mean metabolic rate per cell, R_c , is $R_c = \frac{R(W)}{N(W)} = R_0 m_c W^{\alpha-1}$. As a result, if the cells sizes are independent of the size of the organism, their metabolism gets lower when we consider organisms of greater sizes.
2. On the contrary, if we consider that the mean cell metabolic rate stays invariant, we obtain that $N(W) = \frac{R(W)}{R_c} = \frac{R_0}{R_c} W^\alpha \propto W^\alpha$. Then the mean mass of cells become $m_c = \frac{W}{N(W)} = \frac{R_c}{R_0} W^{1-\alpha} \propto W^{1-\alpha}$. As a result, the cells gets bigger when we consider bigger organisms.

This two straightforward organizational possibilities have been proposed and empirically explored by Savage et al. (2007), in an interspecific comparison among mammals, and for the basal metabolic rate. We reproduce their findings in the table 2.2, where m_c is approached by the cellular volume. These results show that the two theoretical organizational tendencies seems to have biological relevance.

2.2.4.2 Organ allometry

Table 2.3: *Allometry of organs* intraspecific after Trieb, Pappritz & Lützen (1976) and interspecific Schmidt-Nielsen (1984); Z. Wang et al. (2001).

| Organs | Male rata | Female rata | Interspecific exponent |
|-------------|-----------|-------------|---------------------------------------|
| Body weight | 1 | 1 | 1 |
| Prostate | 2.13 | ND | |
| Testes | 1.02 | ND | |
| Ovaries | ND | 0.68 | |
| Liver | 0.73 | 0.48 | 0.87 ^c |
| Heart | 0.67 | 0.65 | 0.98 ^c |
| Kidney | 0.67 | 0.57 | 0.85 ^c |
| Thyroid | 0.55 | 0.35 | |
| Adrenal | 0.55 | 1.01 | |
| Pituitary | 0.53 | 0.53 | |
| Lungs | 0.47 | 0.40 | 0.99 ^c |
| Spleen | 0.47 | 0.47 | |
| Brain | 0.16 | 0.18 | 0.76 ^b ; 0.70 ^c |

^a Result from Trieb, Pappritz & Lützen (1976)

^b Results from Z. Wang et al. (2001)

^c Results from Schmidt-Nielsen (1984)

The interspecific allometry of organs weight is not trivial; it involves different exponents for different organs, see table 2.3. As a result, the relative weight of organs depends crucially on the adult mass of the organism considered. This approach provides a limited

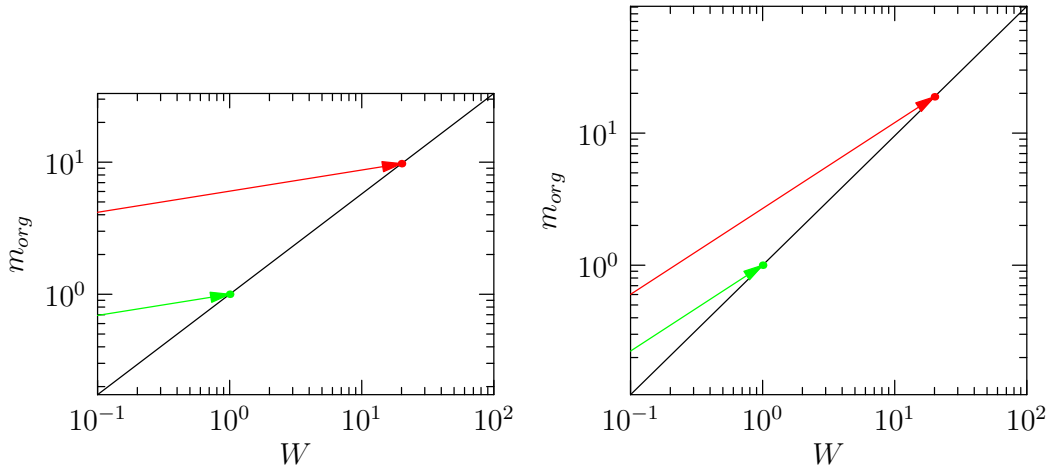


Figure 2.2: *Illustration of the interspecific and intraspecific allometry of organs sizes.* Here, we consider the allometry of brain size (LEFT) and heart (RIGHT), see table 2.3. The black line corresponds to interspecific allometry while the colored line correspond to developmental trajectories for two different species (with different adult masses), however, we still assumed they have the same allometric exponent — qualitatively, we assumed that they have the same kind of developmental trajectory.

but general way to characterize organs functions, through the analysis by size dependence (Schmidt-Nielsen 1984).

The intraspecific approach provides a size-dependency of organs weights, which differs widely from interspecific allometry. The growth of an organism is indeed neither isometric nor following interspecific relationships (a small dog is deeply anatomically distinct from an adult rat of the same weight). On the contrary, developmental organization leads usually to an early growth of vital organs, providing specific proportions to immature organisms, see table 2.3 and figure 2.2. Notice that this differences allows in particular the paleontological identification of juvenile and adults, when the adult size is *a priori* unknown.

2.2.5 CONCLUSION

From a practical point of view, the question of allometry can be crucially found in the problem of pharmaceutical dosage, when no specific study has been performed before (in a veterinary context but also when going from animal models to humans). The naive approach of providing a dosage proportional to the mass of the organism can lead to catastrophic results. The expected dosage depends, among other, of the nature of the toxicity involved, and on the mode of administration, the usual allometric exponents relevant are 0.75 and 1 (Boxenbaum & DiLea 1995; Kirman et al. 2003).

Now, from a more theoretical perspective, we saw that *interspecific* allometry, and the corresponding scale symmetry, is supported by solid empirical data. The 3/4 exponent for BMR is not only supported by a study on plants over 20 orders of magnitude, but also by converging results from the study of biological rhythms and rates. However, this exponent

can only be understood as a broad tendency and, even in the interspecific case, variability is relatively high.

For *intraspecific* allometry, however, the situation is far more scattered, phylogenetic individuation prevails; and specific exponents (or even exponent shifts) arise.

The differences between interspecific and intraspecific allometry are particularly compelling. They show clearly that a developing animal is not equivalent to an adult, even under these broad organizational tendencies that allometry allows to show. From this perspective, the organizational difference between adults and juveniles seems in particular characterized by oversized organs.

Notice also that the general consequence of the complex allometry relationships encountered in biology is that most biological quantities depend in a nontrivial way on the size of the organism considered. This is also relevant, even when no particular organizational changes are involved (for example, the mass repartition among organs depend on the adult size for mammals).

2.3 MORPHOLOGICAL FRACTAL-LIKE STRUCTURES

In this section, we will focus on the geometry of anatomical structures; inasmuch scale symmetries are involved. Structures exhibiting this kind of symmetries, at least approximately, are widespread in biology and consequently we will limit ourselves to important examples. We will first introduce the elementary notion of fractal and fractal dimension; then we will mostly discuss the cases of cellular membranes and tree-like organs.

2.3.1 PRINCIPLES

The term fractal was coined by Mandelbrot (Mandelbrot 1983) for rugged geometric structures, usually exhibiting scale symmetry. The fundamental idea of fractals come from an aspect of usual geometries (based on differential manifold typically) that has been found to be a limitation. These geometries are based on smooth structures, with possibly pointwise singularities (punctually undefined or infinite derivatives). As a result, when zooming, this structures invariably lead to a straight line (in arbitrary dimension, to a linear, flat, structure). However, many situations, let it be natural phenomena or mathematical construct, does not seem to have such properties. On the contrary, when zooming this second type of structure display more and more details and does not converge towards a linear object.

We should notice that this kind of ideas originated first in pure mathematics, in particular in relation with the issues of conceptual instability that 19th century analysis encountered. It was in particular thought that any infinite sum of “usual” functions should be differentiable; however, Weierstrass constructed the counter-example of a “monstrous” nowhere differentiable function, constructed by summing cosine functions. Latter, using the powerful and brand new set theoretic framework, Cantor constructed numerous strange functions and sets, such as a function of one variable filling the plane and Cantor dust which has the power of the continuum (a cardinality property) and is closed but is nowhere dense (see, for example, Edgar (1993) for a collection of historical papers on fractals).

We will now define some of the major kinds of scale symmetric sets that can be encountered, see, for example, Le Méhauté, Nigmatullin & Nivanen (1998); Falconer & Wiley (2003) for complete presentations.

2.3.1.1 Scale symmetry for sets

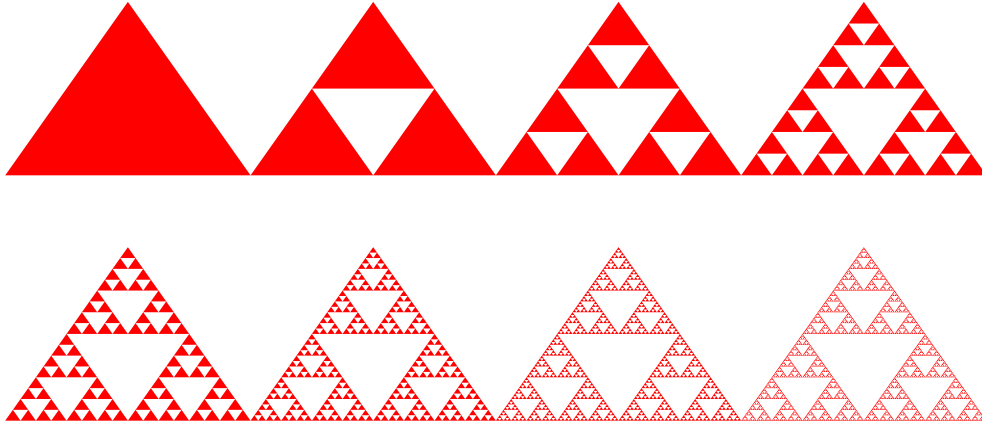


Figure 2.3: *Example of a strictly self-similar fractal, obtained by a simple iterative procedure: the Sierpiński triangle.* Here, the fractal object is encountered at the limit, when the number of iterations tends to infinity. Notice that the figure become more pale when the number of iterations increases, which can be easily explained by the fact that the fractal structure itself has a null measure (for the natural measure of the embedding space, here a surface), so that the convergence to a fractal structure leads to the vanishing of color with iteration.

To approach scale symmetric sets, we first have to define an *iterated function system* (IFS). Let D be an open subset of \mathbb{R}^n . A *contraction* is an application $S : D \rightarrow D$ such that there exists $c \in]0, 1[$, with $\forall(x, y) \in D^2$, $\|S(x) - S(y)\| \leq c\|x - y\|$ (the case of equality defines the notion of *similarity*¹¹). A finite family of contractions $(S_i)_{i \in \llbracket 1, n \rrbracket}$ acts on a non-empty compact¹² set $F \subset D$ by

$$\mathcal{S}(F) = \bigcup_{i \in \llbracket 1, n \rrbracket} S_i(F) \quad (2.5)$$

With these definitions, there exists a unique F , which is called the *attractor* of the IFS and is a fixed point of \mathcal{S} , so that:

$$F = \mathcal{S}(F) \quad (2.6)$$

Indeed, F can (and should) be seen as an attractive fixed point by iteration of \mathcal{S} since F can be equivalently defined as:

$$F = \bigcap_{k=0}^{\infty} \mathcal{S}^k(E) \quad (2.7)$$

¹¹In this case, the distance between points is conserved, modulo a constant factor, see also below.

¹²Here, the compact sets are bounded set stable for taking the limit of converging sequences.

Now, given these preliminary definitions, we can provide definitions of sets exhibiting scale symmetry, by increasing order of generality (meaning that the symmetry we will consider will be more and more loose). These scale symmetric sets correspond to intuitive and for a part of them, constructive notions of fractal.

SELF-SIMILAR SETS. Strictly speaking, a self-similar set is the attractor of an IFS with contractions which are similarities. Similarities conserve all distances (modulo a global factor) and, as a result, are proportional to euclidean transformations, the transformation preserving usual geometric shape. The result of a similarity is (here) a reduced version of the object (which can be translated, rotated and reflected). However, the name of self-similar fractal is sometimes loosely used for fractal defined by an IFS, whatever the nature of the contractions involved is.

SELF-AFFINE SETS. This case corresponds to attractors of an IFS composed of contractions which are affine transformations (the composition of a linear transformation and a translation). This means in particular that these transformations can deform proportions of object (linearly).

QUASI-SELF-SIMILAR SETS. This notion describe situations where the above symmetries are not verified, but are approximately so. A set F is k -quasi-self-similar if there exists $r_0 > 0$ such that for any subset $U \subset F$, with $\|U\| = r \leq r_0$, there is an application $\varphi : U \rightarrow F$, called a k -quasi-similarity such that:

$$\frac{1}{k}\|x - y\| \leq \frac{r}{r_0}\|\varphi(x) - \varphi(y)\| \leq k\|x - y\| \quad (\forall x, y \in U) \quad (2.8)$$

This definition means that a part of the set has approximately the same shape that the whole. We should notice that this kind of approximation concerns all subsets of F at the same time, with a definite level of approximation, and is thus different from usual analytic approximations, which tries to obtain an arbitrarily precise control on the object by considering increasingly small neighborhoods “successively”.

STATISTICAL SELF-SIMILAR SETS. Such a set only has a statistical regularity between scales. This regularity is described by the existence of a fractal dimension (see next section).

MULTI-FRACTAL SETS. Such a set is similar to a statistical self-similar set; however, the fractal dimension is not well defined. Instead, different points have different local scaling behaviour; and we have a spectrum of fractal dimensions. Notice also that the multi-fractal approach is more precise that the fractal one. For example, when one consider a fractal structure near a ball of the embedding space one only obtain the dimension of the embedding space, from a strictly fractal point of view.

We mentioned fractal dimension in the above definitions; so we will now describe this notion with more details.

2.3.1.2 Fractal dimension

The fractal dimension(s) is a way to evaluate how convoluted an object is, or more technically, how densely it occupies space. The classical dimensions are integers: 1 for a line, 2 for a surface 3 for a volume, 4 for a space-time block, However, fractal objects, like the Sierpiński triangle in figure 2.3, do not fit in this category. If we measure the length of Sierpiński triangle's internal frontier, we get (modulo a factor $3l$ where l is the length of the side of the first triangle):

$$L = \frac{1}{2} \times 1 + \left(\frac{1}{2}\right)^2 \times 3 + \left(\frac{1}{2}\right)^3 \times 3^2 + \dots \propto \left(\frac{3}{2}\right)^n \quad (2.9)$$

This length tends to infinity, in spite of the finite extent of the figure. However at each iteration we remove $1/4$ of the surface, so after n iteration the surface is $S_0 \left(\frac{3}{4}\right)^n$, thus the final surface is 0, as physically illustrated by the vanishing of the color's intensity in figure 2.3. We understand then, that both points of view, the 1-dimensional and 2-dimensional measures fail to provide an account of the situation; and that it is related to exponential drifts (either towards 0 or infinity).

Let us consider a cover of a line of length l with cubes of length r we need approximately $l/r \propto 1/r$ cubes. Now, if we want to cover a surface, each cube having a surface r^2 , then we need approximately $l^2/r^2 \propto 1/r^2$ cubes. In the case of Sierpiński triangle, see also figure 2.4, we see that we need one cube for each triangle of the same size. After one iteration, we get 3 times more triangles with half size, so for cubes of size $r = l/2^n$ (which corresponds to $n = -\log(r)/\log(2)$) we need 3^n cubes; thus we obtain that the number of cubes is of the form $3^n = 3^{-\log(r)/\log(2)} = 1/r^{\log(3)/\log(2)}$. We can then intuitively identify the dimension of the fractal shape with $\log(3)/\log(2)$.

More generally the box-counting dimension, or Minkowski-Bouligand dimension of a subset F of a *metric* space is:

$$D(F) = \lim_{r \rightarrow 0} \frac{\log(N(F, r))}{\log(1/\varepsilon)} \quad (2.10)$$

where $N(F, r)$ is the number of balls of radius r needed to cover the set F . This formula performs just the transformation needed to make the number appear, which we “manually” identified above. However, because it is defined as a limit, we see that this dimension has no particular reason to be well defined in all case. When it is not well defined, that is when the sequence does not converge to a single value; we still have bounds for the asymptotic values it can take. As a result, the situation can be characterized by an infimum and a supremum. They define a lower dimension (the infimum) and an upper dimension (the supremum). in such cases, the scaling properties of the objects are oscillating (not necessarily in a regular way) when we are zooming. There is a variety of different definitions of fractal dimensions (Falconer & Wiley 2003; Le Méhauté, Nigmatullin & Nivanen 1998), which generally coincide in the case of self-similar fractals, but do not in some complex cases. The box-counting dimension is not the best from a mathematical point of view. For example, the rationals have dimension 1; whereas they form a countable set, that does not consequently occupies space. A better mathematical notion of dimension than the box-counting dimension

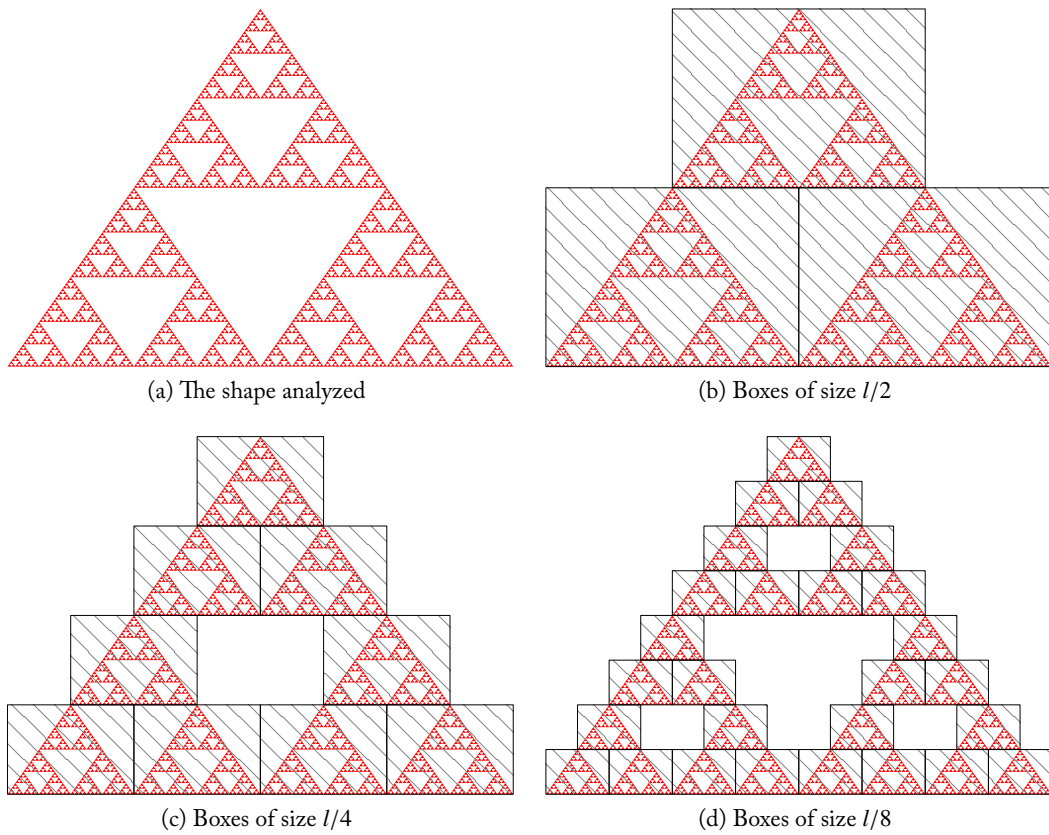


Figure 2.4: Principle of the evaluation of the box-counting dimension illustrated on the Sierpiński triangle. The finer the resolution becomes, the more holes due to fractality appear. As a result, the shape is not “full” enough to have the dimension of a surface.

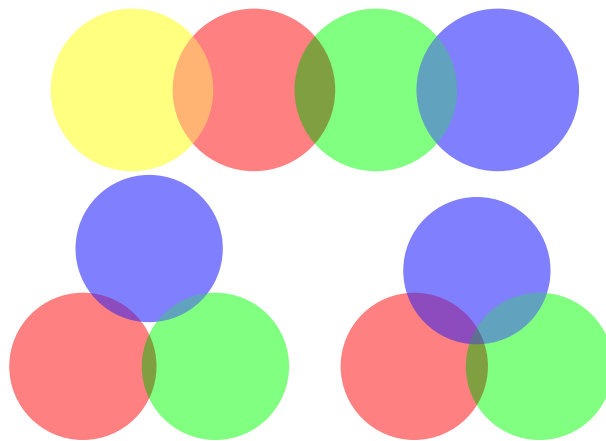


Figure 2.5: Illustration of topological dimension. TOP, a line can be covered with open balls with points that are covered 1 or 2 times. BOTTOM, LEFT, there are missing points if we try to do the same thing in order to cover a surface. BOTTOM, RIGHT, to cover the surface some points are present in 3 balls.

is the Hausdorff dimension. It is based on a parameterized family of measures (in the sense of measure theory); then the Hausdorff dimension is the critical value of the parameter which yields neither infinite nor 0 weight to the characteristic function of the set under study. Notice that in this case, the fractal dimension is a notion associated to measurability theory. In the case of rationals, the Hausdorff dimension is thus 0, which corresponds better to the intuition. However, box-counting dimension is particularly useful since it is used to study empirical cases (with its numerous methodological sophistications). For a recent account of the methodology used to evaluate the properties of experimentally observed structures, including the various forms of fractal dimensions and the image analysis used, see Lopes & Betrouni (2009).

In estimating fractal dimension of natural phenomena, we generally have access to a limited range of scale. This range should be large enough to allow genuinely to claim the validity of a fractal description; however, the term fractal is also used by experimenters in physics when this condition is not met, see Avnir et al. (1998) for a critical discussion¹³.

2.3.1.3 Definition of fractals

So we have sets with scale symmetry and a notion of fractal dimension. What is the definition of a fractal then? The situation is not obvious. We could say that it is a set corresponding to one of the criteria for scale symmetry above. However, flat structures like a segment or a piece of a plane meet these criteria, and worse meet all of them (we see exactly the same thing when zooming in on a flat structure). Reciprocally, we could approach the notion of fractal by the notion of fractal dimension, and associate fractality with non-integer dimensions. However, there exists structure such as Peano curve that have a convoluted structure; but are nevertheless space-filling, so have an integer dimension (roughly this criterion is better, though).

We need a more precise criteria to grasp the concept of fractal. To formulate it, we need to introduce another concept, the concept of topological dimension. The definition of this notion is the following:

DEFINITION 2.1 (TOPOLOGICAL DIMENSION (LEBESGUE)). Let us consider a topological space X . The topological dimension is the integer n , such that for any finite *open* cover of X , a finite refinement of this cover can be found where each point of X is in at most $n + 1$ open sets of the refined cover. ♣

The idea behind this definition is relatively straightforward. We are considering open sets, which are intuitively sets without their frontier, for example an interval $]a, b[$ without a and b . As a result, overlaps are needed to avoid gaps, see figure 2.5. However, if points are missing in the structure of X (gaps), then there is no need of overlap. As a result, the overlaps are engendered by the local, *gapless*, degrees of freedom on X . Of course, this dimension, in general, can be infinite (when there is no finite n which meets the criteria, but this can only happen in an infinite dimensional space, in the context of linear algebra).

¹³The case of critical transition, however, display sharp fractality, associated to a sound theoretical background.

We understand then that there is a conceptual tension between fractal dimension (Hausdorff dimension, a metrical notion) and topological dimension (a topological notion). Mandelbrot then defines fractals as structures where these notions do not coincide, meaning that they do not lead to the same dimensions:

DEFINITION 2.2 (FRACTALS). A fractal is a set F with $\dim_H F \neq \dim_{topo} F$ ♣

Notice that the fractal dimension is not always defined. When it is defined, the fractal is also called monofractal to emphasize the unicity of the dimension (for a given definition) and contrast the situation with more complex structures. When the dimension is not defined, as we said earlier, we nevertheless have an infimum and a supremum for it, which correspond, for example, to an oscillation when looking at smaller scales. Alternatively, multifractals correspond to a situation where the fractal dimension is not the same when zooming to look at different points.

Since natural objects studied, when fractality is found to be relevant, are limited to a range of scales they are usually called prefractal to emphasize this limitation. However, and anticipating on the following of the rest of this thesis, biological cases usually do not have the same level of invariance than physical cases where fractality is theoretically justified (which is far from being all reported cases of fractality Avnir et al. (1998)). As a result, here, we will prefer the terminology of *fractal-like* situation.

2.3.2 CELLULAR AND INTRACELLULAR MEMBRANES

The need to use fractal geometry, instead of notions using euclidean geometry, historically came, in morphology, from very practical considerations. A nice historical example of the difficulties that lead to this paradigm shift is provided in Weibel (1994). In the 70', two different teams tried to evaluate the surface density of the endoplasmic reticulum in the liver. However, these teams surprisingly reported different results: $5.7 \text{ m}^2/\text{cm}^3$ and $10.9 \text{ m}^2/\text{cm}^3$. This puzzling situation was clarified by the notion of fractal: if considered fractal, the evaluated surfaces depend on the scale of observation (and tends to infinity with increasing magnification, in principle). This approach has been tested (Paumgartner, Losa & Weibel 1981) and lead to an estimate of the fractal dimension of 2.7 for endoplasmic reticulum's surface and of 2.54 for mitochondrial inner membranes. This results were found for data over 2 order of magnitude (which is a limited range, but nevertheless substantial¹⁴).

Comparison of fractal-like properties of cell membranes has been investigated to discriminate between different relevant biological situations. Such investigations have especially been done with respect to cancer cells, also in order to contribute to cell type or cells activity classification. In Smith, Lange & Marks (1996), for example, the fractal dimension reported for Purkinje neurons is 1.89 whilst the dimension for Spinal cord neurons is 1.62, see also Losa (2006) for other examples. In De Vico, Peretti & Losa (2009), fractal analysis of cellular (internal and external) membranes was performed to analyze feline oocytes. Statistical self-similarity has been found over 2 orders of magnitude. An interesting point in this study is that the methodology followed by the authors involved different image analysis (basically

¹⁴Whether it is sufficient to talk about fractality or not depends on authors.

different thresholds) in order to focus on different aspects of cellular morphology, and lead to different fractal dimensions. They remark also that in general, active states (including cancerous cells) display a higher fractal dimension than inactivated ones, with some exceptions. One of the exceptions is found in Losa, Baumann & Nonnenmacher (1992), where the fractal dimensions observed for the pericellular membranes of leukocytes is of ≈ 1.2 in the normal case and ≈ 1.1 in the case of lymphoblastic leukemia.

2.3.3 BRANCHING TREES

A branching tree is constituted by a starting branch and an iteration pattern: a branch splits in n sub-branches. The number of sub-branches can be fixed, in which case the *topology*¹⁵ of the tree is uniquely determined. However, n can also be random, uniformly or depending on the number of iterations.

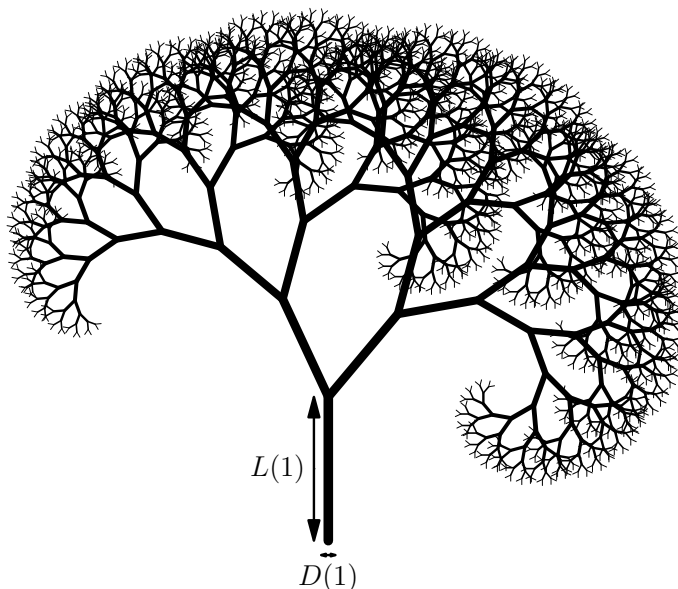


Figure 2.6: *A binary tree.* Here, the branching order stay a constant, 2, and the tree is generated deterministically by iterating the pattern encountered in the first branching. More precisely there is in general some remaining choice when we have just the first branching, corresponding to different possible symmetries, see Le Méhauté, Nigmatullin & Nivanen (1998) for more details on this question.

The biologically relevant situations are usually cases of branches having tubular structures, embedded in the usual 3-dimensional space. For some observational methodologies or some cases, the tree is looked at in 2 dimensions, for example when using classical microscopy or the morphological observation of the vascular tree of retina. Biological structures have also *metrical* properties. The quantities typically considered are the lengths of branches, L , and their diameters, D . The angles between branches are also commonly studied.

¹⁵Here, by topology we mean properties that are invariant under smooth transformation.

The natural question then arises as to what is the evolution of these lengths with the branch order, z (the number of branching from the first branch to the considered branch). These quantities and the aim of morphological measurement will depend in particular on the model used to understand the shape encountered. In particular, Gabrys, Rybaczuk & Kedzia (2005) compares symmetrical and asymmetrical models of vascular morphology. This aspect is especially relevant because the scale range of analysis (and of potential fractality) is limited and because other structures, associated to scale dependent morphogenic principles, can exhibit similar features for a limited range of scales, leading to wrong estimations of fractality.

Generally speaking, there are different methodologies to observe such structures. The main constraint on the methodologies used is that they need to be able to observe a geometrical shape in a similar way for a wide range of scales. The main methodologies are: working on silicone casts of the studied structure (for lower resolution studies), performing microscopy or photography observations (leading to 2-dimensional projection, but which can be performed *in vivo*), tomography, ... The shape can be observed as a 2-dimensional projection or directly in 3-dimensions, as mentioned before. It is noteworthy that in general, the branching structure is embedded in the (smooth) geometrical structure of organs or tissues; for example the vascularization of the retina takes places approximately in a curved 2-dimensional structure (Masters 2004), and the curvature introduce a particular scale (which disappears in local analysis).

2.3.3.1 Lungs

Lungs form highly convoluted structures, allowing fast bi-directional gas exchanges. Their structure vary among phylogenetic classes, but in the case of mammals¹⁶, their topological shape is that of a branching tree. This binary branching allows (for humans), to go from a single trachea to an observed number of alveoli¹⁷ of 274×10^6 to 790×10^6 (Ochs et al. 2004), meaning that the number of branching, from the trachea to an alveola has a mean of approximately 29.

The first approaches to the understanding of the morphological properties of the lung assumed that a length S (diameter, length of the branch, ...) decreases exponentially with the branch order, i.e. $S(z+1) = qS(z)$ (as reported in Bassingthwaite, Liebovitch & West 1994). This assumption fits the empirical results for approximately 10 branching levels; but the observed quantities depart clearly from this equation for smaller scales. In West, Bhargava & Goldberger (1986), it is argued that there is variability in the distribution of branch sizes of the same order z (instead of the basic factor q), and that this variability should be scale-free (at least for high values of z). Moreover, the authors argue the branches should have sizes of the form q^n (see also Bassingthwaite, Liebovitch & West (1994)).

This approach leads to describe the mean evolution of a metric quantity S with the branch order z with the form: $S(z) \simeq z^{-\alpha} \left(A_0 + A_1 \cos \left(2\pi \frac{\ln(z)}{\ln(q)} + \varphi \right) \right)$. This description coincides well with empirical results (Nelson, West & Goldberger 1990). Interestingly, for the four

¹⁶Amphibian, for example, have simpler, more or less convoluted bag-like lungs.

¹⁷This study has been performed on 6 individuals, notice that the variability is high. However, the size of alveoli has been found to be stable in this study.

species studied (rat, dog, hamster and human), the exponents α_D (for the diameters) and α_L , are similar among species (for the branches lengths), even if the lung sizes are very different. However, the phase, φ , distinguishes human from other the other species (among these four species). These findings correspond to a number of branching of ~ 22 , spanning ~ 2 orders of magnitude for the lengths.

Interestingly, Canals et al. (2000) argue that the fractal dimension of lungs is higher in the case of juveniles (1.626 ± 0.157 for males) than for adults (1.547 ± 0.012 for males) in *Rattus norvegicus*. This result, however, is based on a limited difference and would need confirmation.

Another study (Boser et al. 2005) shows a significantly reduced fractal dimension of lungs in the case of asthma; it is also noteworthy that this reduction is higher in the case of a lethal asthma condition.

It is interesting to mention that the alveolar perimeters also have fractal-like properties (Witten et al. 1997). The fractal dimensions found are small; however, they are noteworthy in particular because they are correlated with the age of the subjects (and significant changes are found in diseases). Numerically, for the less than 16 year old subjects, the mean fractal dimension found is 1.047 ± 0.010 ; and for older subjects it is 1.093 ± 0.013 . Note also that this supplementary structure is conceptually interesting because it shows the “concatenation” of the lungs tree structure and the alveolar rugged structure.

2.3.3.2 *Vascular system*

The vascular system is composed of structures with sizes ranging from the scale of cm to a few μm . It is composed of the arterial tree, going from the heart to organs and of the venous tree, from organs to the heart. It’s function is to transport mater to organs (especially oxygen and nutrient) and from them (especially carbon dioxide and wastes but also hormones). It forms a (mostly) closed system, where exchanges arise at the level of capillaries, between arteries and veins.

A considerable amount of research has been performed to evaluate the geometrical properties of the vascular system. In Masters (2004), the methodological difficulties are discussed in the case of the retina, and some stability of the fractal dimension is found in this case around for a value of 1.7. In table 2.4, we report other results compiled in Lorthois & Cassot (2010). The crucial point is that low resolution measurements support a fractal-like structure with variable fractal dimension, but usually not very far from 2.7 (1.7 if projected). However, the studies looking at capillaries found a space filling structure, with dimension estimates comparable to the embedding space.

A study (Risser et al. 2006), important because of the technical breakthrough mobilized (3 orders of magnitude observed in 3 dimensions), lead to unexpected results. The vascular system has been found to be fractal-like at small (capillary) scales and homogeneous at bigger scale. These findings were highly unexpected because of the results in table 2.4. However, the situation was clarified by Lorthois & Cassot (2010) by using considerations on the vascular development. The latter is indeed dominated by two different processes: the formation of a mesh-like structure (capillaries), homogeneous and space filling above a certain scale,

Table 2.4: *Evaluations of fractal dimensions for vascular networks*. The values reported here are after Lorthois & Cassot (2010). Notice the sharp differences between the situations where capillaries are not considered and when they are considered (low and high resolutions). We do not report, here, the other methodological differences involved in these measurements (which come from different studies, in different laboratories). CAM stands for chorioallantoic membrane (this membrane plays a crucial exchange role during development for oxygen, calcium, ...); and ID stands for incubation days. The scale range of these studies is mostly around or below 2 order of magnitudes.

| Resolution | System studied | evaluated fractal dimension |
|-----------------|------------------------------|---------------------------------|
| Low resolution | Subcutaneous AV | 1.70 ± 0.03 |
| | Developing CAM (ID 15) | $1.42 \pm 0.05 - 1.49 \pm 0.04$ |
| | Developing CAM (ID 13–ID 18) | 1.1–1.8 |
| | Developing CAM (ID 13) | 1.26 ± 0.03 |
| | Developing CAM (ID 3–ID 6) | 1.3–1.68 |
| | Developing CAM (ID 6–ID 12) | $1.37 \pm 0.01 - 1.54 \pm 0.03$ |
| | Placenta’s arterial a | 1.86 |
| | Pial vasculature | 1.31 ± 0.03 |
| High resolution | Retinal vasculature | 1.70 ± 0.02 |
| | Subcutaneous capillary | 1.99 ± 0.01 |
| | Epifoveal vessels | 2.00 |
| | Developing CAM (ID 14) | 1.86 ± 0.01 |
| | Hepatic sinusoidal network | 2.01 ± 0.01 |

^a The dimension in 2d embedding space is estimated from a 3d result for comparative purposes.

followed by the growth of a fractal-like structure in this capillary mesh¹⁸. They showed that simulated models presenting these features can lead to the results of Risser et al. (2006) and that an analysis of cortical vasculature adapted to this structure seems to confirm it.

In order to discuss the situation further, it is noteworthy to mention that the vascular structure has been hypothesized, for optimality reasons, to follow the Murray law:

$$d_0^x = d_1^x + d_2^x \quad (2.11)$$

where d_0 is the diameter of the mother branch and d_1 and d_2 are the diameters of the daughter branches. The initial formulation was for $x = 3$ and corresponded to an optimization principle taking into account the energy needed to transport the blood and the energy needed to confine it. However, the experimental results do not really back this relation up, especially since the data are highly scattered. As a result, it was proposed to extended this relation for values of x between 1 and 4. Even in these cases the variability remains high so that multi-fractal analysis should also be performed. This position is defended in

¹⁸More precisely, this growth is understood as equivalent to diffusion-limited aggregation, driven by the blood pressure field in the homogeneous capillary mesh.

Zamir (2001), based on results on the vascular structure of the heart, where multi-fractal analysis (whose criteria seems approximately met) seems useful. This leads to an architectural variability of scaling in the vascular system, even in the case of a single organ.

2.3.3.3 *Further aspects for these organs*

Following the above discussed properties, we can raise the question of the possible geometrical relationship between different tree-shaped organs. In Maina & van Gils (2001), silicon casts have been obtained for the airway, venous and arterial systems of the lung, for a specimen of domestic pig, *Sus scropha*. This study focuses on the relation between these structures and shows that they have statistical correlations in their geometrical properties (diameter depending on the branching order for example). These structures obviously meet at the alveolar level (which is not directly observed by silicon casts), but their geometrical relationship is not limited to it. The three structures (except the venous system in some regions) follow each other closely, both with respect to their branching pattern and spatial positions. Since a physical fractal growth usually require some kind of randomness (because of its singular nature), these spatial and structural correlations at all scales indicate a correlated growth of these hierarchical structures, observable by abnormal similarities between them.

We therefore have a kind of “geometrical entanglement” that seems needed to understand the pulmonary structure. More results would be needed to formulate and characterize precisely the scope of this developmental “entanglement”, let us note, however, that it seems to fall in the conceptual framework in Soto, Sonnenschein & Miquel (2008), where the ontogenetic historicity is argued to be a crucial and irreducible part of biological structure of determination.

The question of the heritability of vascular structure has been studied in Glennly et al. (2007) for armadillos¹⁹. The results, obtained by microsphere deposition, showed that correlations exists between being from the same litter and the fractal dimension of blood flow distribution. However, the degree of variability in a litter was still very high, especially in studied muscles. Interestingly, this study show that correlations are particularly high between the heart and the lung.

One can also raise the question of the effects of activity levels on the vascular fractal dimension. A study (Sinclair et al. 2000), using microsphere deposition methods, establishes a change of blood flow spatial structure in lungs for horses. More precisely, for the fractal dimension of this structure, they found high variability among individuals at rest and a change with the level of exercise. This change consisted in a reduction of the variability among individuals and a progressive reduction of the fractal dimension from trot to canter to gallop. This study was performed at low resolutions on four horses.

2.3.4 SOME OTHER MORPHOLOGICAL FRACTAL ANALYSES

The frontier of tumor growth has been reported as a tool for estimating the nature of the corresponding tumor, see Baish & Jain (2000). It has also been shown that, at least in a

¹⁹The fact that armadillos have clonal offspring in a litter make it particularly useful for studies on clonal variability in complex metazoans.

specific case, a high fractal dimension for carcinoma was correlated to bad prognosis (Delides et al. 2005).

Another interesting kind of morphological fractal-like structure (even though a dynamical description is better) is the case of protein. The fractality by itself does not come as a surprise in this case, since a crude statistical mechanics description of them is a self-avoiding walk. However, proteins have variations with respect to their fractal dimension; and exhibit also specific, local, structures Lewis & Rees (1985). As a result, fractality is biologically relevant in this context too.

Chromatin has also been reported to have a fractal-like structure (Bancaud et al. 2009), allowing to discriminate euchromatin, which has an estimated fractal dimension of 2.2 and heterochromatin, with 2.6. We will discuss this situation further in the paragraph 2.5.1, on anomalous diffusion.

2.3.5 CONCLUSION

We have seen various aspects and cases of biological structures showing fractal-like properties in space. This review is, of course, by no means exhaustive; however, we can point out certain interesting and general aspects. First, the number of magnitudes involved rarely reaches 3, which means that the fractality is limited. As a result, one should be cautious when we are discussing it as a scale symmetry, with respect to metrical properties. Moreover, the determination of the fractal dimension is not fully stable: even with a constant methodology (and as Masters (2004) interestingly points out, with the same experimenter) the evaluation of fractal dimensions leads to a high level of variability.

We can also now draw significant, positive conclusions. First, the space structure we have seen are clearly highly fractured. Moreover, they also display measure anomalies: lengths and surfaces should be considered scale dependent and do not seem to stabilize toward a finite value when observed with increasing precision. Thus, these hierarchical (non-homogeneous) and rugged structures are, in a loose, but nevertheless etymologically sound, sense fractals. In this loose sense, fractals are present in an organism from the scales of proteins to the scales of organs.

It is sometimes argued that the geometry of nature in general and of biological phenomena in particular is predominantly fractal. Putting aside the difficulties we discussed, there is a difficulty, in this point of view, which is that the fractal-like structures in an organism are widely heterogeneous in their (fractal) dimensions, geometrical structures, This point is sufficient to lead to a non-obvious situation (from a geometrical but also physical point of view). Indeed, most theoretical approaches depend on a unique parameter, roughly corresponding to the fractal scaling properties (for example: Tsallis entropy, fractional derivatives and analysis, analysis on fractal structures, ...). Notice also that these physical and mathematical accounts are recent and remains somewhat unstable with respect to physical applications.

In Werner (2010), examples are also provided from the neuronal system. These examples include the neuronal dendritic tree, of the white matter repartition, ...

Beyond these cases, we will see more fractal structures involving space in section 2.5, on the spatiotemporal situations.

2.4 ELEMENTARY YET COMPLEX BIOLOGICAL DYNAMICS

Fractal or fractal-like structures are not only encountered in space, but also in the temporal behaviour of biological systems. The specificity of fractal-like dynamics is that they lead to nonstandard statistical situations: instead of the usual reduction of variance with an increase in statistical power, quantities like the statistical mean or the statistical variance diverge (they tend to infinity with the increase of samples). This situation is relatively counter-intuitive with respect to the classical notion of homeostasis, which is usually understood as a stabilization around a fixed mean. However, as we will see, it is still the fractal-like dynamics which are ubiquitous in biology, and in particular when the situation is associated with physiological regulation.

In order to describe specific examples one first need to provide some elementary methodological and mathematical background. Then, we will report various examples of such biological situations. Last, we will focus on the specific example of cardiac rhythm, and its various properties since this case constitutes half the available literature on biological fractal dynamics according to Eke et al. (2002), and thus allows us to provide a finer grained account of the variability and the statistical structure of biological dynamics.

2.4.1 PRINCIPLES

The first point we should emphasize is that there are two elementary kinds of temporal structures observed (with respect to the physical time). The first one, commonly called time series, correspond to a quantity observed at different time points, usually regularly spaced. The second one is generated by a sequence of equivalent events, which thus leads to the observation of the time of their occurrence. Of course, the second category can be mathematically transformed into the first one by considering $s = \sum_i \delta_{t_i}$ (where δ_{t_i} is a pulse of magnitude 1 at time t_i). The time series, obtained by this procedure, is then $\int_{t_0}^t s(t)dt$. However, from a theoretical point of view there is still an associated particularity of the second situation, since such series can also be expressed as Δt_i with $t = t_0 + \sum_i \Delta t_i$. In other words, this form of time series is a purely temporal structure, and there is no other dimensional quantity involved in its description than time.

In order to obtain an intuitive apprehension of the situation, and before describing the analytic tools used to apprehend experimental data, it is useful to look at the historical example of the Weierstrass function (Edgar 1993).

$$f(x) = \sum_n a^n \cos(\pi b^n x) \quad (2.12)$$

For $|a| < 1$, since $|\cos(\pi b^n x)| \leq 1$, the sum converge uniformly, thus f is continuous. However, if we look at the derivative of its terms we get $-\pi(ab)^n \sin(\pi b^n x)$, thus, if $ab > 1$, we see that the derivative correspond to a divergent sum at all points (this is a heuristic argument not a rigorous proof, for the latter see for example Edgar (1993)). Even though this function has been introduced as a mathematical counter-example, it has a physically meaningful form: it is a sum of periodic functions with pulsations $\omega_n = 2b^{-n}$ and corresponding weights

$\omega_n^{-\log(a)/\log(2b)}$. We then recognize a power-law in the decomposition of f . As a result, such a process possesses a form of scale symmetry.

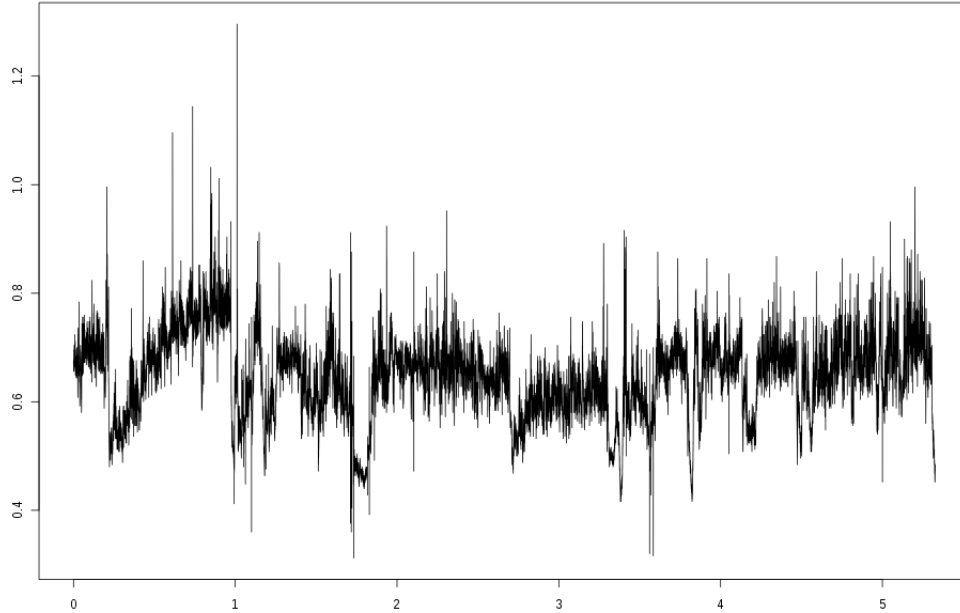


Figure 2.7: *A sample of beat-to-beat intervals in human.* The beat-to-beat interval is given in minutes, and the time of each beat, in abscissa, is given in hours. Notice the significant variations in this rhythm, which are in particular characterized by its long-range temporal correlations. The result of such a situation is that evaluating the beat-to-beat interval at different times, even with a prolonged measurement, will not lead to a stable result. The data come from the Long-Term ST Database, (Goldberger et al. 2000), notice that some unusually long beat-to-beat intervals can be erroneous (typically a heartbeat is not detected, which leads to an interval of approximately double length).

To understand another aspect of fractal dynamic, we can consider a classical example of a situation with infinite mean: the St. Petersburg game. In this game, the player tosses a coin as long as he obtains tails. When he finally gets heads he wins 2^n \$, where n is the number of tails obtained before. The mean gain is then $2^{-1}2^1 + \dots + 2^{-n}2^n + \dots = 1 + \dots + 1 + \dots = \infty$ (Bassingthwaite, Liebovitch & West 1994). Experimentally, this means that the more one plays such a game, the more the statistical means increases. A similar situation occurs when considering the classical Brownian motion, which has mean 0 but a variance which diverges (proportionally to n).

With more generality, Eke et al. (2002) insist on the distinction between two forms of (fractal) processes. The *stationary* processes, on one side, for which the statistical description is stable along time evolution and the *non-stationary* processes, on the other side, which simply do not have this property. They propose as a paradigmatic stationary example, the case of the fractional Gaussian noise, and the fractional Gaussian motion as a non-stationary dynamic. The latter can be easily obtained by the summation over time of a fractional Gaussian noise. Reciprocally, the difference between two consecutive time points of a

fractional Gaussian motion is a fractional Gaussian noise. This comes as no surprise because when one considers the simplest case of Brownian motion, the spatial displacement traveled at each time step has a constant probability distribution. In the notions Gaussian noise and motion, the word Gaussian refers to the unstructured distribution of the values of the time series, when the temporal structure is no longer taken into account (that is to say when we consider properties invariant by data shuffling). We will mostly not discuss these distributions since we are primarily interested in the temporal structures of the empirical time series that we will discuss.

We will now give the definition and discuss some statistical quantities characterizing fractal-like time series. Remark that, in general, the validity of the approach of a process by such quantities depends of the stationarity or not of the process, see Eke et al. (2002). In the following, we will consider a time series $f(t)$.

POWER SPECTRUM This approach of biological, temporal structures is based on the classical concepts of Fourier analysis. It consists in describing the time series $f(t)$, originally given in the time domain, by its Fourier transform $\hat{f}(\omega)$, in the frequency domain. Then, the power spectrum corresponds to the squared weight of each frequency.

$$S(\omega) = \left| \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} f(t)e^{-i\omega t} dt \right|^2 = \frac{1}{2\pi} \hat{f}(\omega) \bar{\hat{f}}(\omega) \quad (2.13)$$

The fractal situation is characterized by a behaviour $S(\omega) \simeq b\omega^{-\beta}$ for large ω . It is then a behaviour associated to scale-free contributions of the various frequencies.

The auto-correlation function is the Fourier transform of the power spectrum. In the case of a power law for the power spectrum, the auto-correlation function decays like $C(0) - C(h) \simeq h^{\beta-1}$ (for small h). The fractal dimension of the graph of the signal is in this case $\frac{1}{2}(5 - \beta)$ for $1 < \beta < 3$, see Falconer & Wiley (2003).

In practice, finite time series are used, and the power spectrum is found by FFT (fast Fourier transform). However, a lot of care is needed in the use of this approach. In particular, a preliminary interpolation is generally required, and the high frequencies contributions should be neglected (Eke et al. 2002).

The more qualitative meaning of β is that it describes the repartition of “energy” among the various frequencies. When all frequencies have the same weight, we have $\beta = 0$ (white noise, see below). Notice that in finite cases, $\beta < 1$ is also possible and corresponds to an anti-correlation between different time points. $-1 < \beta < 1$ corresponds to a domination of high frequencies (the weight of high frequencies is infinite at the limit). This situation corresponds roughly to a case of stationarity because the large period behaviours are not relevant. Reciprocally $1 < \beta < 3$ correspond to a situation where the low frequencies (large period) are the dominating contributions (and the infinite case converges) which leads also to a non-stationary situation. In general, a smaller β means a more noisy time series and a bigger β leads to a more regular time series.

DETRENDED FLUCTUATION ANALYSIS (DFA) This method has been introduced specifically for non-stationary biological series, initially to study DNA structure and heart rates variability (C. Peng et al. 1995). In order to perform such an analysis, one first has to center the time series around its mean, and then to integrate it. The point of this procedure is to obtain an unbounded time series g with 0 average increase. Indeed, the local variations of rates (heart rate for example) are usually bounded by the viability domain; however, the accumulated distance from the mean (the distance of the number of heartbeat during a given time to the mean number of heartbeat during such a time) increase is not necessarily so. Then, the standard deviation of g with respect to local (linear) trends at various resolution, n , is computed. In other words, we evaluate the quadratic distance of g to g_n , the piecewise (best) linear approximation of g where the segments are of length n :

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [g(k) - g_n(k)]^2} \quad (2.14)$$

Then, in scale-free cases $F(n) \simeq n^\alpha$. Moreover, we have the relation $\beta = 2\alpha - 1$ for infinite sequences. The interpretation of α can therefore be transferred from our discussion of the power spectrum and of its exponent β .

A crucial motivation for the introduction of this approach and its widespread use in biology is that it allows to study both stationary and non-stationary time series. Its drawback, however, is that it is usually less precise than more specialized approaches (Eke et al. 2002).

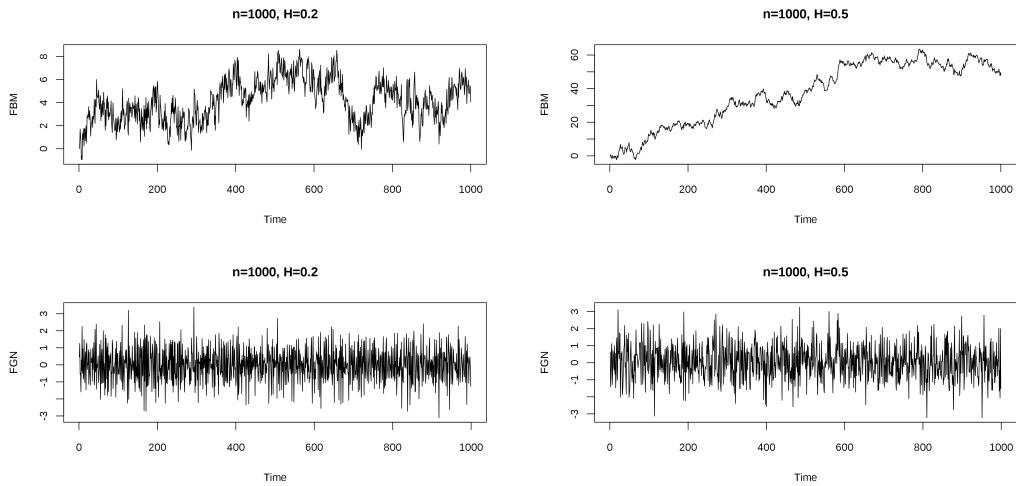
RELATIVE DISPERSIONAL ANALYSIS (RDA) Relative dispersion is the ratio of standard deviation by the mean, thus leading to a dimensionless quantity. In the context of fractal time series, RDA consists in evaluating relative dispersion as a function of the level of coarse graining applied to the time series. Notice that it can only be applied to stationary processes.

The exponents α and β are usually noted in the literature with the same letters than in this text, however there are some exceptions.

There is three main kind of random time series that are used for comparative purposes, which are named after colors. Let us recall that these designations correspond to the *temporal structure* of time series (and not for the unstructured distribution of their values).

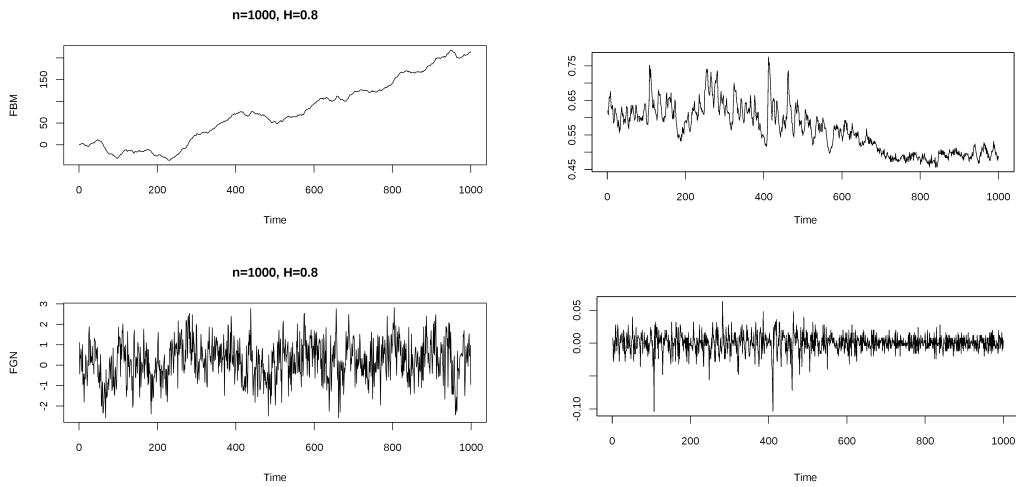
WHITE NOISE. This case roughly corresponds to a situation where the time points are not related to each other. This can, for example, be defined by saying that the expected value of a process is 0, and the expected correlation between two different time points is also 0. White noise leads to $\beta = 0$, meaning that energy is equally distributed among all frequencies. This situation also leads to $\alpha = 0.5$. This case is illustrated in figure 2.8c, BOTTOM.

2. SCALING IN BIOLOGICAL SYSTEMS



(a) Fractal Gaussian motion (UP) with anti-correlated increment (DOWN).

(b) Brown noise (UP) and white noise (DOWN).



(c) Fractal Gaussian motion (UP) and noise (DOWN). (d) Beat-to-beat interval (UP) and its increment (DOWN).

Figure 2.8: *Some fractal dynamics.* In each computer generated case, we represent the Gaussian motion up and the corresponding noise downs. The last case corresponds to empirical data of the cardiac dynamic. Notice that the increment does not seem completely stationary.

Table 2.5: *Blood cells fluctuations of two sheep*. We report, here, the exponents obtained by detrended fluctuation analysis, α , and for the power spectrum β . Let us recall that a scale free situation leads to $\beta = 3 - 2\alpha$. For comparison, a (standard) random walk leads to $\alpha = 0.5$ and white noise leads to $\alpha = 1.5$, the lowest value of correlation coefficient is 0.995 for 200 days (2 orders of magnitudes).

| Cell categories | Sheep 1, α | Sheep 2, α | Sheep 1, β | Sheep 2, β |
|-------------------|-------------------|-------------------|------------------|------------------|
| Red blood cell | 0.98 | 1.00 | 0.97 | 0.91 |
| Platelets | 1.24 | 1.11 | 0.65 | 0.70 |
| White blood cells | 0.83 | 0.83 | 1.14 | 1.16 |

BROWN NOISE. This case is equivalent to Brownian motion, where $X_{t+\Delta t} = X_t + Y$, where Y has mean 0 (and is stationary). From another point of view, brown noise is obtained by integrating white noise. Brown noise leads to $\beta = 2$, so lower frequencies have more energy than higher frequency. This qualitative aspect is logical for a random motion, were the random contribution at each time point is added to the already existing displacement. We also have $\alpha = 1.5$. Figure 2.8c, TOP, corresponds to this case.

PINK NOISE. This case is intermediary between the preceding situations, quantitatively it corresponds to $\beta = 1$. As a result, this situation corresponds to an equal repartition of energy per octave. We also have $\alpha = 1$ in this case. In a looser sense, situations with $0 < \beta < 2$ are also called pink noise.

The dynamics, which corresponds to scale-free behaviours with respect to one of these analyses, are usually called fractional dynamics or fractal dynamics.

2.4.2 A NON-EXHAUSTIVE LIST OF BIOLOGICAL DYNAMICS

In this section, we will provide examples of biological dynamic with long-range behaviours. This list is far from exhaustive; nevertheless we took examples at various levels of organization, and corresponding to a wide variety of phenomena.

Blood cell number. In a study (Perazzo et al. 2000), the blood of two sheep has been sampled each day, for 1000 days, and the number of cells for different cell categories has been estimated. To the authors surprise, the observed time series are remarkably different from the main hypothesized structures, namely a random walk or white noise fluctuations around a mean value. Indeed they computed detrended fluctuations and found scale-free behaviour of exponents α near 1, see table 2.5 (let us recall that 0.5 is expected for white noise and 1.5 for a random walk). A power spectrum analysis shows also that these long-range correlations take the form of anti-correlations ($\beta < 1$), except in the case of white blood cell which are correlated. Notice that the variability on the considered exponents is low (in the sense of a stability with respect to their evaluation at different times).

Cellular respiration. In Aon et al. (2008), time series associated to cellular respiration are analyzed. The two situations under study are a yeast culture and the mitochondrial network of cardiomyocytes.

For yeast cultures (*Saccharomyces cerevisiae* under controlled constant conditions), the time series under consideration are the concentration levels of dissolved O_2 and CO_2 . The measurements were performed with a 12 s resolution, and span 118 h. The cultures seem dominated by a cycles of ≈ 13 h (with a periodicity that is, however, unstable). The analysis of these time series provided a constant relative dispersion among scales in both cases, and a power spectrum exponent $\beta = 1.95$ for O_2 . These results hold in spite of the aforementioned seemingly predominant cycle (which still generates some subharmonic bumps), and have been also tested by cutting of above its scale (looking at the behaviours at time scales smaller than this particular scale). This means that the long-range behaviours are not caused by this cycle. For CO_2 , however, the situation was somewhat more complicated since only small (time) scale behaviour (< 1 min) is associated with scale-free behaviour $\beta = 1.45$, while larger scale are dominated by white noise. Notice also that considering a given, specific part of the ≈ 13 h cycle leads nevertheless to multi-scale behaviour at large scales (beyond the 1 min limit).

Let us recall that cardiomyocytes, the cells of the cardiac muscle, rely heavily on oxygen supply for their intense biological activity. Respiration occurs via mitochondria, which are in a particularly high number in each cell. The observed quantities are the mitochondrial membrane potential $\Delta\Psi_m$ (observed by two photon microscopy associated to a potentiometric fluorescent dye) and the amount of reactive oxygen species (ROS). The time resolution is 110 ms while the duration is 7 min. The corresponding time series have a scale-free behaviour, associated to a power spectrum exponent of $\beta = 1.79$. This behaviour is also confirmed by RDA. Interestingly, an isolated mitochondria only display such a behaviour for a range of scales much more limited than in a collective situation: the fractional dynamic occur only at the shorter time scales. Accordingly, the power spectrum shifts towards a white noise behaviour at larger scales and the RDA shows a loss of correlations across scales.

Lung respiration. A variety of different quantities associated with lungs respiration can be measured. The two quantities which have been mainly studied are the inter-breath interval and the tidal volume. Results of DFA for these two quantities are reported in Thamrin, Stern & Frey (2010). In all cases, the mean exponents α are below 1 and, except in one case, above 0.5, so between white and pink noises. The exception is the tidal volume in non-REM sleep. Indeed, in the decomposition of sleep in different phases, the first partition criterion is whether rapid-eye movements (REM) are observed or not. This two situations are physiologically very distinct (in terms of activity), which is confirmed here by an exponent of 0.8 for REM sleep and 0.5 for non-REM sleep, in Thamrin, Stern & Frey (2010). For inter-breath intervals (C. Peng et al. 2002), results are of 0.68 ± 0.07 for young men and of 0.60 ± 0.08 for elderly men. The measurement was performed for 2 h (roughly 2000 respiratory cycles), in an inactive awake state. Here, we see that the tendency is a decrease of the exponents with aging. This tendency is also reported for the women group, but is somewhat smaller. This result qualitatively means that the inter-breath intervals tend to be more random with increased age (closer to white noise) and have less correlations.

Body temperature. The structure of temperature variations follows also such a behaviour. In Stern et al. (2009), using DFA the authors find exponents of $\alpha \approx 1.5$ for rectal temperature fluctuations, with an increase of this exponent in correlation with age, from 1.42 at 4 weeks to 1.58 at 20 weeks. This tendency is valid both in the mean population and for individual trajectories of same subjects at different age. This growth, however, goes with variability, meaning that the exponent decreases for some infants. Another noteworthy aspect is the absence of correlation of α with room temperature, the mean body temperature or immunization. The exponent has been also evaluated for adults in Varela, Jimenez & Fariña (2003), but with a different methodology (skin temperature). The authors found $\alpha \approx 1.3$. A positive correlation between the exponent and age was also noted (from 18 to 83 years).

Some other cases. In Labra, Marquet & Bozinovic (2007), the fluctuations of O_2 consumption log increment ($r = \log(VO_2(t + \Delta t)/VO_2(t))$) has been studied. The shape of the distribution found, depending on initial conditions, is a double exponential also known as the Laplace function. This leads to a characteristic “tent” shape when the log of the probabilities is plotted. The allometric exponent found for the standard deviation is -0.241 ± 0.103 , which is consistent with a temporal allometry following the exponent 1/4 for times. This structure corresponds to a power law distribution for the fluctuations, which has a structure compatible with allometric relationships.

Other cases showing this kind of fluctuations are the blood pressure (Wagner, Nafz & Persson 1996), the colonic pressure (Yan et al. 2008), the exploratory behaviour of rats (Yadav, Verma & Ghosh 2010), the gait dynamic and the gut dynamics (West 2006), Interestingly, in the case of ocular cascades and fixations, using literate and illiterate subjects, Shinde, Mehta & Mishra (2011) show that the scale-free dynamic is broken in association with attentional behaviour.

2.4.3 THE CASE OF CARDIAC RHYTHM

The cardiac rhythm is probably the most studied case of biological time series. One of the reason for this is that this time series have obvious medical implications. Accordingly, a crucial motivation in the analysis of beat-to-beat time series is to find properties that have diagnosis applications. However, the study of such time series is also highly relevant for understanding healthy physiology, aging, ... Usually, the beat-to-beat interval is more precisely defined as the interval between two R wave, in an electrocardiogram. These intervals are the easiest to use considering their short duration and strong magnitude, resembling a Dirac function.

2.4.3.1 Structure of cardiac rhythm

The study of the beat-to-beat interval *increment* (C.-K. Peng et al. 1993), which is the discrete derivative of the beat-to-beat interval²⁰, has shown anti-correlations, with an exponent of

²⁰This series was studied instead of the beat-to-beat interval because it is roughly stationary whilst the beat-to-beat interval is not (and DFA was not available yet). Notice that, under regularity hypothesis, the corresponding exponent for the beat-to-beat interval is $\beta = \beta' + 2$.

$\beta' \simeq -1.01 \pm 0.16$ in healthy cases and $\beta' \simeq -0.54 \pm 0.25$ in diseased cases. This results are obtained for over 10^5 heartbeats, on time series obtained for routine behaviour.

An interesting point is raised in C. Peng et al. (1995), using DFA on time series recorded with an ambulatory monitor. This feature called crossover phenomena, is that a shift of the exponent is observed between α_1 for the short time scale (< 10 beats) and α_2 for the longer time scales. This shift is different in the healthy situations and in some pathological cases. In the healthy cases, we have $\alpha_1 > \alpha_2$ ($\alpha_1 = 1.20 \pm 0.18$ and $\alpha_2 = 1.00 \pm 0.13$), which means that the short time scale evolution is more regular than the dynamic at larger time scales. This aspect is interpreted by the authors as a regularization, at short time scales, by the interactions with the respiratory rhythm. However, for patients with congestive heart failure, the exponents found are such that $\alpha_1 < \alpha_2$ ($\alpha_1 = 0.80 \pm 0.26$ and $\alpha_2 = 1.13 \pm 0.22$). This differences are argued to be able to distinguish the healthy and pathological cases (which means that the overlap of the two behaviours is limited). The authors remark, however, that the shift in exponents is not observed for certain subjects.

A study (Pilgram & Kaplan 1999), using data from C. Peng et al. (1995) over 24 h, focused on the power spectrum and its repartition when analyzed locally (in time). Their findings show that there is an instability of the exponent β for time windows of the same sizes, but at different temporal positions. This can be understood as a non-stationarity of the power spectrum, which goes beyond a possible bimodal distribution (for wake and non-REM sleep). This result is confirmed by multifractal analysis (Ivanov et al. 2001). A larger singularity spectrum is found in the healthy case, leading to a greater complexity of healthy heart rhythm, beyond the sole value of the exponent described above. Compatible results are also found in Makowiec et al. (2006), where healthy aging is also studied and lead to a decreased complexity in the above sense.

In Kiyono et al. (2004), the authors focused on the fine structure of the (detrended) *distribution* of the time increment corresponding to n heartbeats. This structure and especially its dependence with the scale n allows to discriminate between models that have been proposed to understand the variability of the heart rate. These models are turbulence-like models, called multiplicative cascade, and models based on criticality. The authors have found non-Gaussian scale invariance for these distributions, with a shape that is also incompatible with the cascade turbulence like models, but is, however, a general feature of critical behaviours. These results have been found for both constant routine protocol and normal daily life, for measurements spanning 24 h.

2.4.3.2 *Some factors associated with the cardiac rhythm structure*

Age is correlated with a decrease of heart rate complexity or, from another point of view, a more regular heart rate (Pikkujamsa et al. 1999), see figure 2.6. However, as before, the variability, observed by the variations of exponents, remains high among different individuals. These measurements have been done among subjects with no observed heart disease. Notice that the criterion for a healthy condition given above, $\alpha_1 > \alpha_2$, is also met for these results, and this at all ages. It is also noteworthy that the mean difference between these exponents is low for the elderly group. These results are not isolated and are confirmed by several other studies, such as Iyengar et al. (1996).

Table 2.6: *Heart rate variability at various ages.* The results are from Pikkujamsa et al. (1999), on 24 h measurements on healthy humans. Notice the increase of regularity (loss of complexity) with age. It is also relevant to emphasize the high level of variability of the measured exponents, which is given here by the standard deviation.

| Quantity | Children < 15 year | Young Adults 15 yearto39 year | Middle-Aged 40 yearto60 year | Elderly > 60 year |
|------------|-----------------------|----------------------------------|---------------------------------|----------------------|
| β | 1.15 ± 0.18 | 1.12 ± 0.19 | 1.32 ± 0.14 | 1.38 ± 0.17 |
| α_1 | 1.06 ± 0.11 | 1.19 ± 0.14 | 1.19 ± 0.16 | 1.15 ± 0.16 |
| α_2 | 0.98 ± 0.06 | 1.00 ± 0.08 | 1.07 ± 0.07 | 1.14 ± 0.07 |

In Wilson, Hart & Parcell (2009), the DFA approach lead to significant differences between a group of healthy subjects having long term sedentary habits ($\alpha_1 = 1.20 \pm 0.16$) and another group doing regular aerobic exercise ($\alpha_1 = 1.02 \pm 0.20$). The evaluation of habits, in this study, is obtained by self-report. The criterion for the sedentary group is the reporting of less than 1 half an hour seance of exercises intense enough to break a sweat per month; the members of the active group have had 3 to 4 such seances per week. Both regimes have to be sustained for at least a year in order to be valid. This study is not based on a large statistical sample but is still interesting. Another relevant point is that the classical linear statistical analyses do not allow to show a significant difference between the two groups. This tendency has been confirmed by different studies, see Carter, Banister & Blaber (2003) for a review.

An approach of heart rate variability during sleep (Bunde et al. 2000) leads to DFA exponents of ~ 0.5 for both light and deep sleep, with less variability for the observed exponents when the sleep is artificial. Exponents of ~ 0.85 have been reported for REM sleep (Rapid eye movement sleep), with, again, a lower variability of the exponents when the sleep is artificial than when it is spontaneous.

In Esen, Özbeit & Esen (2001), the heart dynamics of young habitual smokers have been found to exhibit different characteristics than the control group. At rest, in the supine position, the mean exponents found are $\beta = 1.42 \pm 0.36$ for smokers and 0.96 ± 0.16 for non-smokers. By contrast, in a standing position, the exponents observed are 1.47 ± 0.25 and 1.27 ± 0.12 respectively. A noteworthy point is that the dynamic of the heart for smokers is characterized, in particular, by remarkably limited changes of exponents associated to the postural differences (in comparison with the healthy situation).

Notice also that long-range variations in heart rate are found to be correlated to body movements, and both of them are also correlated to circadian rhythms (Aoyagi et al. 2000). It has also been shown in Song & Lehrer (2003) that heart rate variability is changed when breathing rate is modified, which is obtained on humans by conscious control. More precisely, slower respiratory rate lead to a higher heart rate variability.

To sum this paragraph up, we have seen that all the following factors change the heart rate scaling properties: age, diseases, the activity habits, sleep stages, smoking, circadian rhythms, body movements,

2.4.4 CONCLUSION

We have seen that a wide class of biological time series has particular forms, that can be described as fractal-like and display long-range correlations. These characteristics lead to a change of perspective from the usual mathematical interpretation of homeostasis. The latter understands the biological regulation as a relaxation towards a mean and corresponding fluctuations as having a Gaussian shape. In West (2006), this point is especially emphasized and is argued to lead to paradigm change for the understanding of biological regulation. In particular, this analysis leads to a further argument, added, for example, to the point of view of autopoiesis (Varela 1979), leading to understand biological systems as processes.

Notice, however, that the relevance of the means, in physiology, has been criticized before such dynamics have been discovered, primarily with respect to the point of view of the organism. For example, in Canguilhem (1972), physiology is understood as “la science des fonctions et des allures stabilisées de la vie” (the science of stabilized functions and styles of life). This perspective is not at odd with the more recent accounts provided in this section.

From the point of view of scale symmetries, we have seen that the exponents found experimentally are usually associated with an important amount of variability. In particular we have seen that aging and serious diseases lead in most cases to more regular time series (see also Goldberger et al. 2002; Goldberger, Peng & Lipsitz 2002). In the case of the cardiac rhythm, we have seen that there is a variety of factors which influence the variability of the observed exponents. In particular, the long-term habits have a relevant effect on them (smoking and exercising), but other factors are also relevant such as circadian rhythms, body movements, This variability is also found in the study of the variation of the exponent over time.

To provide a short conclusion to this section, we can safely say that a great variety of biological time series exhibit (time) scale symmetry and consequently long-range correlations (which is why these processes are also said to exhibit memory). However, in spite of the universality usually found in this context, in physics, we found that the experimentally observed exponents are associated with a high degree of variability, which can, in part, be associated to various observable factors.

2.5 SPACE-TIME STRUCTURES

The case of structures in space-time is more complex than the situations we discussed earlier. The reason for this is that the mathematical account of an object in space and time is very close to a description in a phase space, by which we mean that it is very close to physical structures of determination. As a result, such accounts are usually described almost directly with respect to full-fledged physical models. Hence, we will not provide, in this section, a general introduction to the nature of the (hopefully) observed exponents, which depends on these models.

2.5.1 ANOMALOUS DIFFUSION

Anomalous diffusion, as the name of diffusion implies, corresponds to a macroscopic description the dispersion, by time flow, of the spacial repartition of some entities. Microscopically,

diffusion corresponds in general to random movements in space. Anomalous diffusion correspond to a situation where the macroscopic description does not correspond to the usual one.

2.5.1.1 Principle

Classical diffusion is a diffusion based on a homogeneous space and time and with homogeneous probabilities of movement (in space and time). From a microscopic point of view, the probabilities of movement are the same at each point and in each direction and are equally distributed over time, on a euclidean space. In this situation, the macroscopic equation describing the evolution of a density ρ subject to diffusion (without sources, or in other words with a conservation principle) is the following:

$$\frac{\partial \rho}{\partial t} = D \sum \frac{\partial^2 \rho}{\partial x_i^2} \quad (2.15)$$

where D is the diffusion coefficient and the x_i are the 3 space directions. Since the expectation of the distance traveled is 0, only the mean squared distance traveled is interesting. It has the form:

$$\langle (\Delta x)^2 \rangle = D \Delta t \quad (2.16)$$

However, these homogeneity conditions are not always met. In particular, when the diffusion occurs in a “crowded” medium, space homogeneity can be lost (because of the space taken by other particles). Another relevant situation is the case where space has a fractal structure. Similarly, in an interacting medium, time homogeneity can be lost, the interactions “gluing” temporarily the traveling particle, which is particularly relevant when the times of these stops have a power law distribution. Another aspect that can disrupt classical diffusion is active transports.

The simplest form allowing to describe such situations is the following:

$$\langle (\Delta x)^2 \rangle = \Gamma (\Delta t)^\alpha \quad (2.17)$$

where Γ is called the generalized diffusion coefficient. The crucial quantity, here and as usual, is the exponent α , which determines the precise nature of the observed phenomenon.

$0 < \alpha < 1$ defines *subdiffusion*. This situation corresponds in particular to a diffusion in a crowded environment. Somewhat reciprocally, for inactive molecules, the properties of subdiffusion can be used as a measure of the crowding of an environment (Weiss et al. 2004). A recent review, Berry & Chaté (2011), argue that subdiffusion is better obtained by time trapping (with power law escape probabilities) than by homogeneous obstacles. Notice also that diffusion on fractals (Renner, Schütz & Vojta 2005) can lead to this situation, with an exponent that is not given by the spatial fractal dimension alone. This situation is associated with a greater confinement of particles for long-ranges, see figure 2.9.

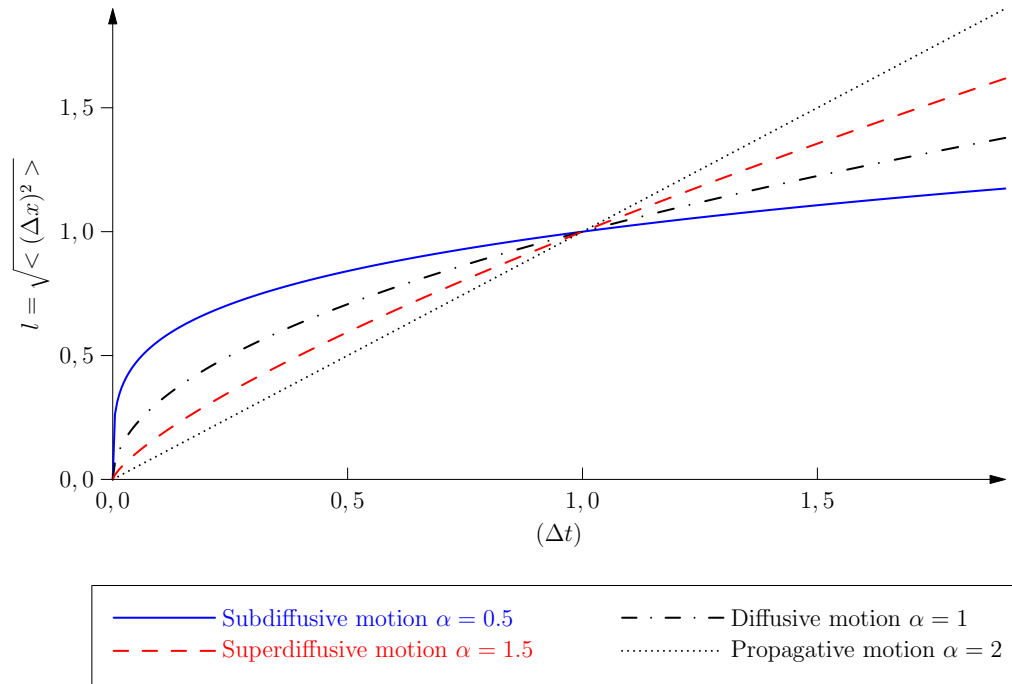


Figure 2.9: *Different forms of diffusion.* Here, we represent the standard deviation of the distance to the initial position as a function of the time interval of diffusion. Notice that the long time behaviour correspond to a greater confinement for small α . However, for short time scales a small α correspond to a faster dispersion.

$\alpha = 1$ corresponds to classical diffusion.

$1 < \alpha < 2$ defines *superdiffusion*. In this case the transport is faster for long distances than in the case of classical diffusion. Such a situation is analyzed as active transport, where energy is used to organize (order) the motion of particles. In the cell, this situation typically corresponds to the effect of molecular motors moving on the cytoskeleton.

$\alpha = 2$ corresponds to the case of classical transport. It is not really a case of diffusion, and there is a macroscopic velocity associated to this behaviour, corresponding to a collective oriented movement.

When α is not an integer, diffusion is called *anomalous* since it corresponds to situations where the spatiotemporal structure is non-homogeneous. However, the deeper reason for this name is the singular nature of the situation, leading to a description in terms of fractional derivation (West 2010).

Such behaviours can be empirically studied by single particle tracking (for example molecules with fluorescent labels). Somewhat reciprocally the spatial structure of the cytoplasm can be assessed by evaluating the form of the diffusion, for inactive molecules of various sizes.

From a theoretical point of view, anomalous diffusion utterly changes the probabilities of chemical reactions (Aon, O'Rourke & Cortassa 2004) or from a different perspective, changes

their kinetics. This is particularly straightforward, since, in particular, subdiffusion leads to more compartmentalization than classical diffusion. As a result, for example, molecules that are produced in the same region have a higher probabilities of interaction. This is in particular valid in the case of the structure of DNA (Bancaud et al. 2009).

2.5.1.2 Examples from cellular biology

The nature of diffusion in the bacterial cytoplasm has been recently studied, thanks to the recent progresses in single particle tracking with high spatiotemporal resolution. In Golding & Cox (2006), the motion of individual fluorescently labeled mRNA is studied in *Escherichia coli*. The observed motion of such a molecule in the bacterial cytoplasm looks confined for periods and time ended by major jumps, which is a qualitative description of the behaviour of anomalous diffusion. Indeed, the evaluation of the corresponding anomalous exponent lead to $\alpha \simeq 0.7$, which describes a subdiffusive behaviour. This exponent is relatively stable, and robust with respect to the study of different situations, when, for example, considering mutated cells, with altered cytoskeletons. This result is confirmed by a power spectrum analysis of the space trajectories of molecules. This analysis leads to an indirect estimation of α , which is 0.77. The coefficient Γ , however, has a strong dependence on the specific molecule and cell involved, leading to a lot of variability. Notice that in such an approach, based on the diffusion of mRNA, the source of anomalous diffusion is not known since, in particular, this approach cannot identify the relative contributions of the space crowding on one side and of interactions on the other.

On the other side, Weiss et al. (2004) uses the property of subdiffusion, measured for inactive molecules of various sizes, to evaluate the structure of the cytoplasm in HeLa cells²¹. In a similar way than for bacteria, anomalous subdiffusion has been observed, with α from 0.59 to 0.84, depending on the sizes of tracer molecules. Again, these results are robust with respect to the disruption of the cytoskeleton (actin filaments and microtubuli). For particles of bigger sizes, spontaneously appearing lipid granules have been studied in yeasts (Tolić-Nørrelykke et al. 2004), leading to a comparable exponent of ~ 0.75 over a wide range of time scales (10^{-4} s to 100 s).

Diffusion occurs also in plasma membranes. In Smith et al. (1999), the properties of the diffusion of major histocompatibility complex molecules in the membrane have been studied. The result is a coefficient $\alpha = 0.49 \pm 0.16$, with, thus, a large variability.

In the case of eukaryotic nuclei, the anomalous diffusion correspond also to an exponent of ~ 0.79 for euchromatin and ~ 0.75 for heterochromatin (Bancaud et al. 2009). In both cases, these exponents were found to be independent of the size of the molecules observed. However, when chromatin is not the main component of nuclei, this independence is no longer met. Here, we then have anomalous diffusion associated to a structure with a further symmetry of the anomaly, for different sizes of particles, associate to the fractality of the structure of DNA.

²¹HeLa cells are cells from a human, immortal cell line from cervical cancer cells taken from Henrietta Lacks.

2.5.2 BIOLOGICAL SYSTEMS “POISED” AT CRITICALITY

The title of this section refers to a recent survey (Mora & Bialek 2011), which emphasizes the prevalence of criticality²² in biological systems. The term poised stands for the fact that criticality is typically a non-generic behaviour and describes pointwise transitions, found on points when the parameter is one-dimensional. As a result, this situation is not observed spontaneously (in its classical form), the surprising result is then that criticality is observed, as if the system was poised at such special points. Criticality, here, is obtained experimentally by an original methodology, that we will describe before providing some biological examples.

2.5.2.1 Principle

Usually, statistical mechanics is used to determine macroscopic behaviours (thermodynamic equations) by knowing the symmetries of the interactions of elementary components (or in other words the microscopic Hamiltonian). Let us recall that, in the case of critical phenomena, the macroscopic behaviour is not thoroughly described by classical thermodynamics and is better described as a scale symmetry (or more generally a conformal symmetry), in particular determined by the critical exponents and is obtained by renormalization in the asymptotic limit of large scales.

Here, however, the strategy is different. Since the “microscopic” objects are usually bigger than in physics (cells, birds, ...) and are in a more limited number, their individual trajectory can be observed. From this observation, the statistical structure of a collective phenomenon can then be inferred, and, from the latter, a technical transfer in terms of statistical mechanics can then be performed. From this transfer, an abstract “Hamiltonian” and “temperature” are defined. These objects, here, have only a statistical meaning, in particular there is no *a priori* reason for them to have the same physical dimensionality than their usual physical counterparts. In particular, heat transfers cannot be performed in the usual sense, so that this temperature is not measurable with a thermometer. The formal and mathematical meaning of these objects is, however, corresponding to their statistical mechanical sense.

The mathematics, behind what we have just described, are the following simple equations, for a microscopic state σ :

$$P(\sigma) = \frac{1}{Z} \exp\left(-\frac{\mathcal{H}(\sigma)}{kT}\right) \quad Z = \sum_{\sigma} \exp\left(-\frac{\mathcal{H}(\sigma)}{kT}\right) \quad (2.18)$$

Thus, assuming that the measurement is performed at a fixed temperature, defining k so that $kT = 1$, and conventionally²³ assuming $Z = 1$, we get:

$$\mathcal{H}(\sigma) = -\log(P(\sigma)) \quad (2.19)$$

Of course, additional assumptions are required actually to determine a Hamiltonian from data. These assumptions essentially concern the symmetries of this functional and

²²Some introductory theoretical aspects of criticality are provided in section 5.4.

²³All these assumptions, except the first one, do not lead to a loss of generality because the situation is not related to physical dimensionalities.

depend of the specific features of the system under study. General assumptions, however, are that \mathcal{H} is stationary (does not change with time) and that only means and pairwise contributions should be taken into account in the Hamiltonian. These symmetries allow then to go from the data to an estimated Hamiltonian.

With such a Hamiltonian and the equations 2.18, a “natural” macroscopic degree of freedom is then the “temperature”. The theoretical collective behaviour can then be mathematically analyzed, depending on this parameter, and quantities such as susceptibilities can be evaluated. Finally, the *observed* statistical distributions can be localized in the parameter space. It is then in this sense that biological systems are surprisingly found at or near critical points, “poised” at criticality in the words of Mora & Bialek (2011).

Other aspects of criticality are of course observable, such as the effect of a perturbation, the spatial distribution of states (or better of energy in the above sense), ...

2.5.2.2 Some examples

We will now describe some biological situations, where this methodology has been applied. These examples correspond to recent studies because the simultaneous observation of a large number of states is required, and such a feat has been only recently made possible.

Flocks of birds. The collective behaviour in flocks of birds and similar systems such as schools of fish have recently raised considerable interest. Indeed, such situations are not dominated by the behaviour of a single individual but are nevertheless able swiftly to adapt to environmental conditions, such as the presence of a predator. This interest originates also from the recent finding, in Cavagna et al. (2010), of signs of criticality in their spatiotemporal statistical structure.

This kind of system is understood as corresponding to states which are the position and velocities of each bird, in 3d. The statistical mechanical interpretation of the situation is that birds tend to mimic their neighbours speed, in a way similar to the tendency of elementary magnets to align with their neighbours in an Ising spin glass²⁴ (because of the magnetic field). In this sense, the “temperature”, as described above, is the propensity of birds to mimic their neighbours.

In Cavagna et al. (2010), it is mainly the correlations of birds velocities that are studied. More precisely, both the correlations of the absolute values of speed and the orientations are evaluated, in function of the spatial distance of birds. Two important results are to be mentioned:

- First, there are strong correlations at small distances and anti-correlations at longer distances. Let us recall that anti-correlations are not the contrary of correlations (which is uncorrelated behaviour or in other words independence). Anti-correlation is the opposite of correlation in the mathematical sense; but also implies a high level of coherence. In the case of birds, it intuitively means that if a large *spatially structured*

²⁴This situation is, however, somewhat more complicated than spin lattices, because the collective structure concerns velocities, so that it changes the positions of the objects in space, whilst in spin lattices these positions are fixed, and only the fields vary.

subgroup has its velocities that varies coherently (with respect to the group) in a direction, then an other spatially structured subgroup has a variation in the opposite direction (these considerations are not limited to combinations of two subgroups; we have considered this case for illustrative purposes).

- The other key result of this study is that the correlation functions, for both speeds and orientations, follow power laws, so that $C(r) \propto r^\gamma$ in the infinite size limit. However, in this case, the situation is even more remarkable than usual scale-free behaviours, since the evaluation of γ is remarkably close to 0. This means that there is almost no decrease of correlations with distance. From another perspective, the correlation function does not depend (much) on the size of the flock if written in the form $C(\frac{r}{\xi})$. In this equation, ξ is the characteristic length and is found to be proportional to L , which is the size of the flock. This relation holds for both orientations and magnitudes of the velocities.

These results are found for flocks of sizes spanning approximately one order of magnitudes, which is limited; however, as we said, the situation has very strong signatures of criticality in this range. These results strongly suggest that the system should be considered critical.

Neural network of the retina. We will not discuss this situation with many details, but we will nevertheless provide a basic description of its properties, following Mora & Bialek (2011). The (salamander) retina is used as a paradigmatic case since it allows the recording of a relatively high number of neurons ($\simeq 40$ neurons in current experiments) during an important interval of time. The basic modelization of the situation is then the following. The activity of each neuron, i is recorded, so that its state σ_i for time windows of a given length $\Delta\tau$, is defined to be either 1 if a spike (or more) is recorded or -1 if no spike is recorded.

The collective, statistical behaviour of the system is then approached as equivalent to the Ising model, which allows to fit the means and the two points correlation functions of the model on the observed data.

$$\mathcal{H}(\sigma) = - \sum_i h_i \sigma_i - \sum_{i < j} J_{i,j} \sigma_i \sigma_j \quad (2.20)$$

The observed results exhibit a peak for the susceptibility with respect to the “temperature” parameter. This maximum converge towards the temperature of the observed data (conventionally set to 1), when considering systems of greater sizes. This support the hypothesis that the system is poised at criticality. Another aspect of the situation which is consistent with criticality, is the distribution of probability of global activity, which follows approximately a power law (with an exponent 1). The empirical results are closer to this relationship when the number of neuron observed is larger.

Percolation in myofibril mitochondria. In Aon et al. (2003) and Aon, Cortassa & O’Rourke (2004), the state (depolarization and ROS²⁵ concentrations) of mitochondria in a

²⁵Reactive Oxygen Species, we mentioned these observables earlier, in subsection 2.4.2.

myofibril of a cardiomyocyte is understood as, and found experimentally to be, approximately equivalent to the physical situation of percolation. A clarification, here, is needed; these studies consider a limited depolarization, and, as a result, do not involve the permeability transition pores or intracellular C_a^{2+} overload (Aon et al. 2003). This point is crucial since it means that we are not considering transitions, usually not reversible, towards a state close to cellular death. Instead, these processes are understood as “regenerative” by the authors, inasmuch they allow to control excessive ROS leaks by decreasing mitochondria activity by depolarization.

Now, the mitochondrial system of a myofibril is approached as an approximately bi-dimensional lattice, where each square of the lattice is occupied by one or two mitochondria. The evaluated quantities are then the ratio of depolarized mitochondria, their spatial distribution, the effect of a perturbations (by a local increase of ROS concentration), and particularly characteristic times. When global depolarization occurs, these observed aspects are consistent with the physical universality class of 2d percolation transition (which thus leaves fractal like clusters of polarized mitochondria, as in percolation). In Aon, Cortassa & O’Rourke (2004), these features are argued to explain oscillations of mitochondria depolarization observed in Aon et al. (2003) and discussed also in section 2.4.2.

2.5.3 OTHER FORMS OF CRITICALITY

In the literature, there are other forms of criticality that are argued to be relevant in the study of biological systems, and used to describe particular spatiotemporal situations. They usually more or less revolve around the idea of a stabilization with respect the punctual nature of criticality.

2.5.3.1 *Self-organized criticality*

The basic idea behind self-organized criticality is that the critical point is understood as an attractor of the dynamic of the system (Jensen 1998). The paradigmatic, first example of this kind of situations is the sandpile model (Bak, Tang & Wiesenfeld 1988), which is an automaton. This model is defined by the following basic rules: when there is too much difference between adjacent grains heights, the grain that is too high falls, and the grains are added slowly so that the system has sufficient time to relax between two perturbations. This system spontaneously converge towards a critical situation, where the size of the avalanches follows a power law distribution. Notice that, for large systems, this behaviour means that the input has to be infinitely slow.

The pitfall of this approach is that the criticality obtained this way remains valid only for a point. This fact is, for example, “hidden” by the association of this point with a conservation property. In this sense, then, the critical behaviour remains specific and can be mathematically analyzed as a standard form of criticality (Sornette, Johansen & Dornic 1995). In this analysis, the suitable parameter is associated to a feedback mechanism, based on the value of the order parameter. This reasoning also explains why the system needs to have a slow input in order to exhibit criticality.

From an empirical point of view, which, here, is ours, the concept of self-organized criticality leads to focus on the observation of avalanches. We will now provide some

biological examples, where self-organized criticality is crucial for the analysis of the situation.

The first example is the detailed analysis of respiration, and of the flow of oxygen in the lungs. During exhalation, peripheral airways, in the lungs, tend to close up. Re-inflation then leads to the progressive reopening of these airways. The resulting phenomenon is then a succession of jumps, corresponding to these re-openings, which are caused by the pressure differences. This dynamic can be observed by measuring the airway resistance. The two observed distributions, in Suki et al. (1994), are then the time intervals between jumps and the magnitude of the jumps. Both of them, according to the results of this study, follow power laws over 2 orders of magnitudes, with exponents 2.5 ± 0.2 and 1.8 ± 0.2 , respectively. This dynamic is argued to correspond to a situation where the openings occurs in bursts, the opening of one branch being followed by an avalanche of successive opening. In particular, by modeling the situation, the authors also show that this situation leads also to a power law for the air volume increase of the lungs, which corresponds to an exponent 1.1 ± 0.2 . The size of the volume freed by an avalanche can therefore be extremely large.

In Phillips (2009a, 2009b), some aspects of protein folding are shown to be equivalent to self-organized systems. In particular, this approach allows to focus on long-range interactions and to understand their consequences on the structure and physical properties of proteins, such as hydrophobicity. Another quantity associated with scaling is the solvent-accessible surface area which follows statistically power laws, depending on the amino acids involved.

2.5.3.2 *Self-tuned Criticality*

The sensibility of hair cells to stimuli of the order of magnitude of thermal noise can be understood by the proximity of the system to a Hopf bifurcation. However, this situation is not generic; the authors thus introduce a second dynamical system, which determines the behaviour of the parameter and leads to a convergence of the first system towards its bifurcation point (Camalet et al. 1999; Balakrishnan & Ashok 2010).

In this situation, the gain is highly non-linear, and diverges for small inputs. It has the following form:

$$r = \frac{|x_1|}{|f_1|} \sim |f_1|^{-\frac{2}{3}} \quad (2.21)$$

where f_1 is the first coefficient of the input (by Fourier analysis) and x_1 is the corresponding coefficient of the output, the spatial displacement of the “hairs”. We provide more details on the mathematics involved in section 5.4.4.

This amplification occurs for the critical frequency, which depends on the precise values of the parameters. These parameters differ from cell to cell, so that the cochlea is globally able to react to a wide class of sound frequencies. However, the value of the parameter of the first system at bifurcation point is not a parameter of the second system, so that the self-tuning of the system is generic.

2.5.3.3 *“Attached” criticality*

A particularly interesting theoretical and empirical situation is analyzed in Machta et al. (2011). Plasma membranes fluctuates in relation with a critical point observed at a temperature of 22, on giant plasma membrane vesicles, which are separated from living cells. In

the context of a living cell, the membrane has relatively large heterogeneities in particular in the form of lipid rafts, associated to proteins, receptors, and disordered lipid structures The third element that comes into play is the cytoskeleton, which is attached to the plasma membrane and seems necessary to observe these heterogeneous structures.

The question then arises as to how these large heterogeneities are sustained. A related aspect is that temperatures below the critical point, in isolated membranes, lead to a phase separation, between the liquid ordered and liquid disordered phases. This transition is not observed in the context of the cell. The idea developed in Machta et al. (2011), is then that these peculiar, relatively large scale structures are explained by the features of the critical point and the interaction of the critical fluctuations with the cytoskeleton. Indeed, even though the system is not at the critical point, it remains not far from it in physiological temperature, 37 (one should recall that the physically relevant quantities are in K). At these temperatures, the critical fluctuations have ranges consistent with observations (for isolated membranes). The cytoskeleton comes into play by forcing the behaviour of determined points of the plasma membrane. Below the critical temperature, this prevents the system from undergoing the phase transition by limiting the size of homogeneous clusters, whilst at physiological temperatures it stabilizes the fluctuations, and bestows them a larger lifetime. This also leads to an explanation of the confinement observed in the diffusion of the lipid rafts and allows at the same time interactions over large distances. Both features are possible because of the formation of a pavement of the membrane by relatively thin frontiers (allowing fast diffusion) and bounded surfaces where the lipid rafts are confined.

2.5.4 CONCLUSION

We have seen some examples of situations involving space-time scaling. Notice that the case of anomalous diffusion has made significant progress recently, thanks to the development of single molecule tracking methods. These behaviours have compelling consequences on the understanding of the molecular level. In particular, subdiffusion leads to a partial compartmentalization, beyond the classical connectivity loss associated with membranes. This behaviour thus introduces a homogeneously heterogeneous spatial organization in the cell, as a crucial determinant of chemical reactions in the cell.

When considering biological criticality, the amount of studies is also limited for practical reasons. The number of units that one needs to observe is indeed approximately $(L/l)^d \times T/\tau$, where L is the spatial extent of the object, d is the dimension of space (1, 2 or 3) and l is the spatial resolution, T is the duration of the measurement and τ the temporal resolution. This should be put in contrast with the fact that an empirical evidence of scaling requires large objects, precisely because of the collective and multi-scale nature of such structures (when discussing criticality). These difficulties prevent us from actually discussing the question of variability in general. Notice that the latter is not relevant from a physical perspective because of the notion of universality but this point is not obvious in biology.

Nevertheless, the results we have reported are compelling. They show in particular that collective behaviours occur in biology, which are comparable to the physical situation of criticality. In a sense, this logic is reinforced by the very limitation of these approaches. Indeed, such approaches require a certain homogeneity of the objects considered (birds,

Table 2.7: *Statistical properties of some biological networks.* These results are from Almaas, Vázquez & Barabási (2007). Notice that the variance remains high.

| | Transcription | | Metabolic | | Protein Interaction |
|----------|----------------|----------------------|----------------|----------------------|----------------------|
| | <i>E. coli</i> | <i>S. cerevisiae</i> | <i>E. coli</i> | <i>S. cerevisiae</i> | <i>S. cerevisiae</i> |
| γ | 2.1 ± 0.3 | 2.0 ± 0.2 | 2.0 ± 0.4 | 2.0 ± 0.1 | 2.4 ± 0.4 |
| α | 1.0 ± 0.2 | 1.0 ± 0.2 | 0.8 ± 0.3 | 0.7 ± 0.3 | 1.3 ± 0.5 |

neurons, membrane, mitochondria ...), but, even in these cases of relative homogeneity of the constituents, the biological cases exhibit criticality, whereas the physical situations corresponding to strongly collective behaviours are usually met only on a single point of the parameter space (with a one-dimensional parameter).

2.6 NETWORKS

Approaches in the conceptual and mathematical frame of networks allow to consider situations with a large number of entities, represented by nodes, having specific interactions among them, represented by edges, which can be considered as oriented or not, depending on the nature of the interactions. Corresponding to this description, both the structure of the networks and the question of their dynamics can be raised, and approached experimentally.

2.6.1 STRUCTURES

The subject of networks is an important and extremely active field of research, both theoretically and experimentally. We will restrict ourselves to very basic aspects of their description and empirical analysis. See, for example, Lesne (2006) for more theoretical details.

The structure of a network can typically be approached by the statistical properties of its number of edge per node. A scale-free network is then a network which has a statistic of the form $k^{-\gamma}$ for the number of edges, k , for each node. Resulting from this form, the sub-graphs of a scale-free network have the same statistical properties than the whole network. There is a wide variety of processes (iterated network transformations typically) that can generate such networks. One of the simplest such processes is a growth with preferential attachment of the new nodes one nodes having already many connections. As a result, and since various network structures can lead to the same statistics, the validity of such accounts should not be theoretically overemphasized, as it is not an evidence of common causal mechanisms (Fox Keller 2005).

Another statistically interesting quantity is the clustering coefficient and its scaling properties. The local clustering coefficient C_i for a node i is the ratio of the number of edges among its neighbours N_i with the maximum possible number of such edges.

$$C_i = \frac{2N_i}{k_i(k_i - 1)} \quad (2.22)$$

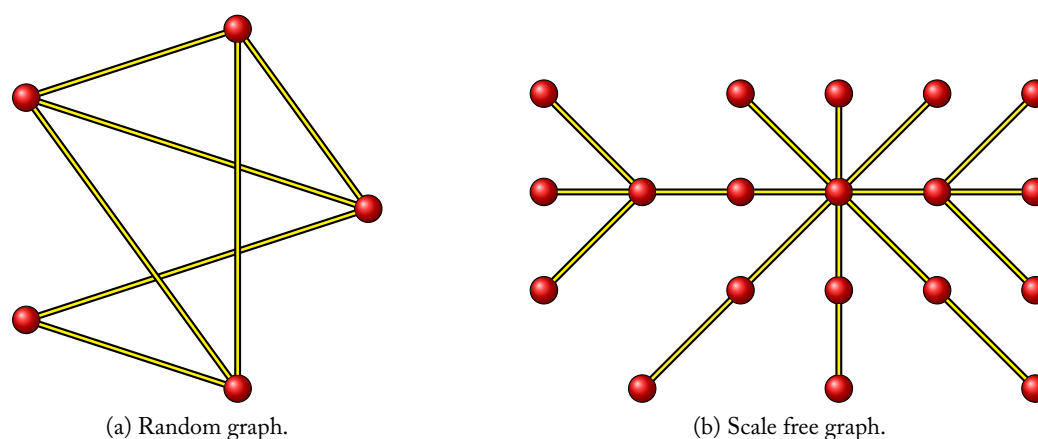


Figure 2.10: *Example of random and scale-free graphs.* In the random graph, in the sense of Erdős-Rényi, the probability of each edge to be present remains independent of the rest of the graph. In the scale-free case, however, the nodes that have more edges tend to have even more edges, during the graphs growth (this is only one of many ways to illustrate the statistical properties associated to the situation).

This quantity thus evaluate the local connectivity, around nodes. Then, in a scale-free situation we have a distribution of the clustering which is expected to follow a power law: $C(k) \propto k^{-\alpha}$.

We present some empirical evaluations of α and γ in table 2.7, for different biological networks which are found approximately to be scale-free. The networks are evaluated by high-throughput techniques, and usually have a high degree of imprecision, which can have different forms depending on the technique used (with false positives or not and more or less prone to miss some links). The approaches used are generally technically based more or less completely on nucleic acids screening techniques. For example, the metabolic networks, which represent the chemical reactions, are estimated by a combination of genetics and biochemical results (Jeong et al. 2000). The protein interaction networks are in particular evaluated by screening for protein complexes, which means that only complexes stable enough to last throughout the manipulation process can be seen. Transcription networks are estimates of the mutual interactions between gene transcriptions.

It is noteworthy that all these networks represent, in general, relatively arbitrary slices on the networks of molecular interactions (inasmuch this object is well defined). In particular, all these networks interact with each other, but they also miss wide classes of interactions. For example, mRNA are usually not taken into account, and this example still remains close to DNA.... The regularity of the statistical properties evaluated is also challenged by some authors, on the basis of alternative statistical methods to assess them. In Khanin & Wit (2006), for example, scale-free behaviour are found to be valid only for a restricted range of scales, whilst this study is based on data that have been previously claimed to correspond to scale-free networks.

Notice also that the theoretical validity of such networks can be problematic, since these theoretical objects are not necessarily well defined. In particular, a theoretical reason to

challenge their definition is the dependence of chemical reactions on spatial organization, as described in our section on anomalous diffusion. This means that the ability of molecules to interact in a cell does not only depend on the structural ability of these molecules to interact, even in a given cellular compartment (in the sense of membranes).

A recent study, Rossberg et al. (2011), has found scaling in the structure of the trophic links of marine animals (fish and squid). The approach of this study is, however, substantially different of what we have already discussed, since it is based on *weighted* links. Indeed, the considered function is, for a consumer specie, the number of preys Z_c , which have, in its diet partition, a weight that is stronger than f ($0 < f < 1$). These quantities are evaluated by the study of stomachs contents, meaning that the exceedingly rare preys cannot be taken into account. Since f is bounded, a change of parameter is used in favor of the diet ratio, $r = f/(1 - f)$, which tends to infinity when f tends to 1 (This change of variable does not change much the situation for small f). Then, the empirical results obtained follow approximately a power law, $Z_c \propto r^{-\alpha}$, with a mean exponent of 0.54. This exponent is consistent with the community average of Z_c for all data sets studied except one. The variability for the diet partition function of individual consumer species is, however, high (this is a community regularity property, not a specie property).

2.6.2 DYNAMICS

The dynamic of such networks has been extensively studied theoretically, especially in the line of the work of Kauffman. The question is typically that of the nature of the effect a perturbation. The classification of the situation depends on whether a perturbation leads to a return to the previous situation (stable situation) or whether it leads to a further departure from the initial situation (chaotic dynamic). Between these two cases, a critical situation occurs, where complex dynamics arise (Kauffman 1993, 2001; Nykter, Price, Larjo, et al. 2008).

Since it is technically difficult to assess directly the networks dynamics over time, an alternative way to show that there is an underlying critical dynamic, in the above sense, is to look at the time series of the states of the nodes of the network.

The structure of such time series is, however, somewhat difficult to study. Such a study indeed requires to consider high dimensional states, where the metric (the notion of distance) is not obvious, and one ignores the structure of the network, which defines normally how close two states are. For example, in (Shmulevich, Kauffman & Aldana 2005; Nykter, Price, Aldana, et al. 2008), the system considered is the transcriptome, observed by microarrays time course experiments. In particular, this means that we are not considering individual trajectories (since the cell considered is destroyed in the process). The trajectories considered are thus collective behaviours, associated in particular to external perturbations, antigens for macrophages. The state is then represented by a vector, which corresponds, at a given time point, to the presence (1) or absence (0) of each RNA. The distance the authors use, the normalized compression distance, is based on an estimation of the algorithmic complexity (by the compressibility). More precisely, for boolean vectors x and y , this distance is:

$$NCD(x, y) = \frac{C(xy) - \min\{C(x), C(y)\}}{\max\{C(x), C(y)\}} \quad (2.23)$$

where $C(u)$ is the compressed size of u and xy is the concatenation of the vectors x and y . It is noteworthy to remark that the algorithmic complexity *stricto sensu* (Kolmogorov complexity) is not computable. Let us recall that this complexity is the size of the shortest program generating the sequence studied. If Kolmogorov complexity were computable, then we could write a finite program which would generate sequences of any Kolmogorov complexity, by screening all strings by increasing sizes until finding one with the right complexity (this is a contradiction). Another point of view is that, when trying to implement a program which would compute Kolmogorov complexity, one stumbles quite straightforwardly on the halting problem. Indeed, not being able to compute the stopping of a program, implies that one cannot, in general, compute if it returns (or not) the expected string. The result of this situation is that an approximation is used, usually Lempel-Ziv algorithm. It is the latter which is the method used in the papers we are discussing.

Now, the idea used in these articles is to compare the distance between time points t and $t + \Delta t$ and the distance between the time points $t + \Delta t$ and $t + 2\Delta t$. If this distance shrinks, it means that we have a form of relaxation, or in other words stability. On the contrary if it grows, it means that we have a chaotic situation and that the perturbation gets amplified. If it stays roughly constant, then we should be in a critical situation (the validity of this classification and the validity of the approximation is tested by the authors on data generated by simulation of known network dynamics). The authors finally find that macrophages exposed to different antigens have a critical dynamic at the level of their transcriptome.

A wider study (Balleza et al. 2008) shows similar results for specimen in four biological kingdoms: bacteria *E. coli* and *B. subtilis*, fungi *S. cerevisiae*, animal *D. melanogaster* and plant *A. thaliana*. The method to show critical behaviour, here, differs from above, and is based on simulation of the result of perturbations, on the basis of the known topology and dynamic of the graphs. Two kinds of situations are studied: either small well-known networks or larger network with heuristically estimated dynamics. *In fine*, the dynamics are found to be consistent with criticality.

2.6.3 CONCLUSION

In this brief description of scale-free networks and critical network dynamics, we have reported very interesting results, based on techniques which allow in particular to assess global properties in situations that can be described as collections of discrete entities with heterogeneous natures. As a result, these accounts tend to be a huge progress with respect to the methodologies that focus on the properties of elementary components only.

There are, however, limitations in the validity of these results, corresponding to both empirical (statistical) discussions and theoretical interpretations. Overall, this research field is recent; study of “natural” scale-free networks is only approximately 10 years old, whilst the empirical analysis of networks dynamics is only in its infancy. The results obtained are nevertheless interesting, when considered in a cautious perspective.

Let us finally remark that the quantitative relation between the different network that are usually studied in cells is not straightforward. Indeed, a recent study (Taniguchi et al. 2010) has shown that the number of mRNA and of the corresponding protein are not correlated at the level of a single cell.

2.7 CONCLUSION

This survey of scale symmetries in biological, empirical results has led us to discuss a variety of techniques and empirical situations. Generally speaking, we have seen that a wide variety of biological situation is relatively well described by scale symmetries. By the latter, however, we mean that the situation is better described as scale symmetric than with a characteristic scale. This distinction is needed because we want to emphasize that almost all cases where the studies are sufficiently comprehensive, important (intraindividual, interindividual or interspecific) variability in the scaling exponents has been found. As a result, the scale symmetries under question should be taken cautiously.

Among these approaches, allometry is somewhat particular, in the sense that it does not describe (directly) the scaling relations inside an object but compares objects of different sizes. With this approach, we have seen that globally, most times scale approximately with an exponent of $1/4$, which is a nontrivial situation. Accordingly the masses scale globally with an exponent close to $3/4$. However, the variability of species with respect to such relations remains high and can correspond to ten fold variations in the case of the metabolism. Different approaches of the statistical situation lead also some authors to argue that other exponents are relevant. Moreover, if one consider intraspecific allometry, associated with the development, we see that a wide range of allometric relations can be described, including symmetry shifts (change of exponent). The relevance of the $1/4$ allometry is, however, still high (in interspecific cases), since it is approximately observed for a wide class of rhythms and rates.

We have then considered morphological fractality, in organisms. Again the situation is approximately described by a (statistical) scale symmetry, which typically corresponds to the definition of the fractal dimension. The reliability and stability of such results is, however, far from perfect, with respect to both interindividual variability and the intrastructural variations in scaling properties. However, as we have pointed out, the structures involved are highly discontinuous and intricate; thus, they loosely correspond to fractal situations. Moreover, their structure clearly leads to an instability, with respect to the resolution, of the measurement of euclidean notions such as lengths, surfaces, As a result, the fractal description is still a considerable progress, but it leads to results that should be taken cautiously.

The dynamics we have considered lead to similar lessons. Multi-scale dynamic are ubiquitous, and long-range correlations should be taken as the default assumption, which has profound consequences on the theoretical nature of biological regulation. From the point of view of the measurement, these results are crucial; they typically mean that the heart rate or the blood cell count change spontaneously and importantly, even when the measurement is performed and averaged on large time scales. There, again, variability of exponents is found both between individuals and inside a given dynamic.

It is noteworthy that, for both morphological fractal-like structures and biological fractional dynamics, the exponents found can be experimentally shown as correlated to specific factors. In particular, the age is relevant in both cases. For dynamics, aging is generally related to a more regular dynamic. Other relevant factors are the activity habits, diseases, Again we should recall that all these correlations, which are sometimes remarkably clear tendencies, are found on a general background characterized by an important variability. It

is also noteworthy that, in some cases, other factors do not influence the observed exponents, whilst one would have expected they would have.

The two last sections, on space-time structures and on networks, correspond to recent advances. The technical availability of the necessary data has indeed only been recently achieved and is still limiting the analysis of the situation. The results available are nevertheless promising, and criticality has been shown to correspond to a variety of situations. However, the technical limitation does not allow, for example, to apprehend the possible variability in the scaling structures.

As a final statement, we can say that the situations discussed in this chapter are relatively subtle. Scale symmetries are relevant; they provide a unique grasp on biological phenomena and allow to exhibit instabilities of more classical measurement. However, they do not match exactly the empirical situation. Variability is clearly shown almost ubiquitously, where the data available are sufficient. This variability can be put in relation with various factors, corresponding in particular to the history of the object considered.

In the following chapter, we will use a part of the regularities discussed here. More precisely we will use temporal allometries to propose a geometrical account of biological time. This will also allow us, among other aspects, to propose an original approach of the multi-scale structure of biological time series, as described here in section 2.4.

A 2-dimensional geometry for biological time 3

This chapter is a slightly revised version of:

F. Bailly, G. Longo & M. Montévil. 2011. A 2-dimensional geometry for biological time. *Progress in Biophysics and Molecular Biology* 106 (3): 474–484. ISSN: 0079-6107, doi:10.1016/j.pbiomolbio.2011.02.001

CONTENTS

| | | |
|---------|--|----|
| 3.1 | Introduction | 68 |
| 3.1.1 | Methodological remarks | 69 |
| 3.2 | An abstract schema for biological temporality. | 70 |
| 3.2.1 | Premise: Rhythms | 70 |
| 3.2.2 | External and internal rhythms | 70 |
| 3.3 | Mathematical description | 73 |
| 3.3.1 | Qualitative drawings of our schemata | 73 |
| 3.3.2 | Quantitative scheme of biological time | 76 |
| 3.4 | Analysis of the model | 77 |
| 3.4.1 | Physical periodicity of compactified time | 77 |
| 3.4.2 | Biological irreversibility | 78 |
| 3.4.3 | Allometry and physical rhythms | 79 |
| 3.4.4 | Rate Variability | 80 |
| 3.4.4.1 | Renormalization | 80 |
| 3.4.4.2 | Rate Variability | 81 |
| 3.5 | More discussion on the general schema 3.1. | 84 |
| 3.5.1 | The evolutionary axis (τ), its angles with the horizontal $\phi(t)$ and its gradients $\tan(\phi(t))$ | 84 |
| 3.5.2 | The “helical” cylinder of revolution \mathcal{C}_e : its thread p_e , its radius R_i | 85 |
| 3.5.3 | The circular helix \mathcal{C}_i on the cylinder and its thread p_i | 85 |
| 3.5.4 | On the interpretation of the ordinate t' | 86 |

ABSTRACT:

This chapter proposes an abstract mathematical frame for describing some features of biological time. The key point is that usual physical (linear) representation of time is insufficient, in our view, for the understanding key phenomena of life, such as rhythms, both physical (circadian, seasonal, ...) and properly biological (heart beating, respiration, metabolic, ...). In particular, the role of biological rhythms do not seem to have any counterpart in mathematical formalization of physical clocks, which are based on frequencies along the usual (possibly thermodynamical, thus oriented) time. We then suggest a functional representation of biological time by a 2-dimensional manifold as a mathematical frame for accommodating autonomous biological rhythms. The “visual” representation of rhythms so obtained, in particular heart beatings, will provide, by a few examples, hints towards possible applications of our approach to the understanding of interspecific differences or intraspecific pathologies. The 3-dimensional embedding space, needed for purely mathematical reasons, allows to introduce a suitable extra-dimension for “representation time”, with a cognitive significance.

Further aspects of the compactified time will be analyzed in the chapter 7, where we will associate this approach to extended critical transitions.

Keywords: biological rhythms, allometry, circadian rhythms, heartbeats, rate variability.

3.1 INTRODUCTION

LIVING phenomena displays rather characteristic and specific traits; among these, manifestations of temporality and of its role are particularly remarkable: development, variegated biological rhythms, metabolic evolution, aging, This is why we believe that any attempt at conceptualizing life phenomena — be it only partially — cannot avoid addressing such temporal aspects that are specific to it. In that which follows, we will examine this question from different angles in view of providing a first attempt at synthesis.

The intuitive “geometry of time” in physics was (and often still is) based, first, on the absolute Newtonian straight time line. This was later enriched by the order structure of Cantor type real numbers, an ordered set of points, topologically complete (dense and without gaps). Thermodynamics and the theories of irreversible dynamics (phase transitions, bifurcations, passing into chaos, ...) have imposed an “arrow” upon classical time, by adding an orientation to the topological and metric structure. But it is with relativity and quantum physics that the theorization of time has led to rather audacious reflections. In the first case, to give only one example from a very rich debate which goes so far as to introduce a circular time (proposed by Gödel as a possible solution to Einstein’s equations) to Minkowski space: by means of its famous causality cone, this space explains, within the framework of a unified geometry of space-time, the structure of any possible correlation between physical objects, in special relativity.

In quantum physics the situation is maybe even more complex or, in any event, less stable. We go from essentially classical frameworks to a sometimes two-dimensional time (in accordance with the structure of the field of complex numbers with regard to which

Hilbert spaces are defined, the theoretical loci of quantum description), up to the audacity of Feynman’s temporal “zigzags” (Feynman & Gleick 1967). This latter approach is a very interesting example of intelligibility by means of a “geometric” restructuring of time: the creation of antimatter would cause within the *CPT* symmetry (charge, parity, time) a symmetry breaking in terms of charge, while leaving parity unchanged. Global symmetry is then achieved by locally inverting the arrow of time. Another approach, with similar motivations, is that of the fractal geometry of space-time, specific to the “scale relativity” proposed by Nottale (1993): in it, time is reorganized upon a “broken” line (a fractal), which is continuous but non-derivable. Further interesting reflections, along similar lines, may be found in Le Méhauté, Nigmatullin & Nivanen (1998).

Physics however will remain but a methodological reference for our work, because the analysis of the physical singularity of living phenomena (Bailly & Longo 2006, 2011) requires a significant enrichment of the conceptual and mathematical spaces by which we make inert matter intelligible. One of the new features which we introduce consists in the usage that we will make of the “compactification” of a temporal straight line: in short, we will try to *mathematically understand rhythms and biological cycles by means of the addition of “fibers” (a precise mathematical notion, introduced summarily below) which are orthogonal to a physical time that remains a one-dimensional straight line.* From our standpoint, a living being is a true “organizer” of time; by its autonomy and action, it confers it a more complex structure than the algebraic order of real numbers, but also more than any organization one could propose for the time of inert matter. In short, the time of a living organism, by its specific rhythms, intimately articulates itself with that of physics all the while preserving its autonomy. We would therefore like to contribute to making the *morphological complexity* of biological time intelligible, by presenting a possible geometry of its structure, as a two dimensional manifold.

The first section will introduce the theme of biological rhythms. One consequence of our approach is the possibility of mathematically giving what we hope to be more precise and relevant meaning to notions that are usually treated in a rather informal fashion and unrelated between one another, such as those of representation time, physical time vs. biological rhythms, ... and this within a rigorous mathematical frame.

3.1.1 METHODOLOGICAL REMARKS

Let us recall that physics, in its history, was constituted according to major dimensional constants (gravitation, the speed of light, Planck’s constant — with dimensions, respectively: acceleration, speed, action). What is striking, in biology, is the presence of a few major invariants *with no dimension*, those that are specified in the rhythms of which we will speak below. The mathematization of physics concentrated on invariants, among which the above constants, but also those of “objective determinations”, which has been addressed in length in Bailly & Longo (2006, 2011). We suggest here to start with these rare invariants, these constants and rhythms which are to be found in biology, because, beyond the physico-chemical, the *structural stability* of living phenomena is not “invariant”, physically speaking: it is profoundly imbued with *variability*.

Observe also that in physics, time is mostly described as a parameter of the state functions describing a system. The phenomena encountered in biology, however, seem to trigger

the need of other theoretical strategies and this at many different temporal levels of organization (physiology, ontogenesis, phylogenesis, ...). We will provide a geometrical scheme of biological time that stresses the crucial role of time in life and allow to understand some of the above features mainly through the use of two theoretical concepts.

The first one, which we will discuss in depth latter, is the ubiquity of rhythms in biological temporal organization. There is indeed few features that are ubiquitous in biology but the iteration of similar processes seems to be one of them. We will however make a clear distinction between two type of cyclicity encountered in living systems.

The second concept is a way to understand the constitution and maintenance of biological organization, both in phylogenesis and embryogenesis, that has been formalized by the notion of anti-entropy in Bailly & Longo (2009), see also chapter 8, see also chapter 6. That approach allows the addition of a new theoretical aspect of time irreversibility in biological systems, that completes and adds up to the thermodynamical irreversibility driven by the notion of entropy. At the level both of evolution and embryogenesis, this irreversibility manifests itself by the increase of complexity of the organism (number of cells, number of cell types, cell networks — neural typically, geometrical complexity of the organs, constitution of interacting yet differentiated levels of organization, ...).

Methodologically, by a duality with physics, in Bailly & Longo (2009) time is understood as an operator (like energy in Quantum Physics), not as a parameter. This makes time a fundamental observable of biology (like energy in physics) and it gives meaning to its key role in “biological organization”, since rhythms organize life.

3.2 AN ABSTRACT SCHEMA FOR BIOLOGICAL TEMPORALITY.

3.2.1 PREMISE : RHYTHMS

We will introduce a second dimension of time¹, associated to the endogenous internal rhythms of organisms as defined bellow, a dimension of time which we will represent as compactified (\mathcal{S}_1 topology²).

We denote this compactified time as θ , which we can represent as a sort of “circle” with a “radius” R_i (where R_i is the proper biological time): this circle expresses the temporal circularity, the iterative component, that is specific to internal rhythms.

3.2.2 EXTERNAL AND INTERNAL RHYTHMS

We will distinguish two types of rhythms associated with biological organization, each referring to a distinct temporal dimension (below, we will note them as t and θ , respectively):

(EXT) “external” rhythms, *directed by* phenomena that are exterior to the organism, with a physical or physico-chemical origin and which physically impose themselves upon the organism. So these rhythms are the same for many species, independently of their

¹In chapters 7 and 11, we will provide further arguments which justify the introduction of a supplementary time-dimension.

²The circle is the *compactification* of the real number straight line, by the addition of a point and its folding.

size. They express themselves in terms of physical, hence dimensional, periods or frequencies (s, Hz) and the invariants are dimensional; they are described with regard to the dimension of physical time (in $\exp(i\omega t)$). Examples: seasonal rhythms, the 24 hours-cycle and all their harmonics and sub-harmonics, the rhythms of chemical reactions which oscillate at a given temperature, etc.

- (INT) “internal” rhythms, of an endogenous origin, *specific to physiological functions* of the organism, depend on purely biological functional specifications. These rhythms are characterized by periods which scale as the power 1/4 of the organism’s mass and, when related to the life span of the organism which scales in the same way, they are expressed as pure numbers (they have no physical dimensionality). Invariants are therefore numeric. We propose to describe them with regard to a new compactified “temporal” dimension θ , with a non-null radius, the numeric values then corresponding to a “number of turns”, independently of the effective physical temporal extension (we have mentioned some examples: heartbeats, breathings, cerebral frequencies, etc.).

We will now, even if we must be somewhat repetitive, describe further how these rhythms take place in biological organization, which is precisely what we would like to provide account for:

- The external rhythms (Ext) are to be identified with physical time (typically measured by a clock) determined universally — their temporal features does not depend of the biological system we consider. Key examples include circadian, circannual or tidal cycles. The effects or the relevancy of these cycles depend of course on the organism that we consider (with possible sexual dimorphism). For example, diurnal and nocturnal animals are in phase opposition, whereas tides are mainly relevant for marine organisms, and especially in the foreshore. Whatever organism we consider, the period and the phase of these rhythms are the same as they are dependent on external physical events. In order to be a little more precise, this rhythms are generally associated with a double process: the physical process, outside the living system (and which can be very precisely predicted) and its “shadow” inside the system which is kept synchronized by so-called “Zeitgeber” (light for circadian cycle for example). This distinction leads in particular to a specific inertia, encountered for example in the “jet lags” phenomenon.

Simple chemical oscillations inside an organism will fall in this category too, since their period is determined by physical principles, however their phase depends on a specific organism (a specific trajectory) since it is the organism which constructs this chemical system.

As a result, this kind of rhythms, and their subharmonics, can be considered in the usual physical way and represented by terms like $e^{i\omega t}$.

- The second kind of rhythms, the endogenous biological cycles in (Int), do not depend directly on external physical rhythms. They could be called autonomous or eigen rhythms and scale with the size of the organism (frequencies brought to a power $-1/4$

of the mass, periods brought to a power $1/4$), which is not the case with constraining external rhythms which impose themselves upon all (circadian rhythms, for example). Such rhythms are encountered when we consider the heart rate, the respiratory rate, the mean life span, ..., see chapter 2, section 2.2 or, for example, Savage et al. (2004) or Lindstedt & Calder III (1981). These rhythms are naturally associated with the number of their iterations (they can be seen as dual variables), and these numbers provide a natural way of speaking of the age of a biological system, yet different of the time measured by a clock. The distinction between replicative and chronological aging for yeasts, is a clear example of this situation, see Fabrizio et al. (2004).

It is worth noting that this kind of rhythms leads to the use and the study of pure numbers instead of quantities with a physical dimensionality (such as intervals of physical time). Moreover these numbers seem, at least in certain cases, to have invariant³ properties, a clear and impressive example of this is the mean number of heartbeat (or respiration) during life which is almost invariant among mammals.

In summary, endogenous biological rhythms:

- are determined by pure numbers (number of breathings or heart beats over a lifetime, for example) and not, in general, by dimensional magnitudes as is the case in physics (seconds, Hertz, ...);
- depend on the adult mass of the organism that we consider, by following the allometric law $\tau_i \propto W_f^{1/4}$ (for heterotherms, the temperature is involved too);
- in our approach, they are analyzed and put into relation to each other by adding an additional compactified “temporal” dimension (an angle, actually, like in a clock), in contrast to the usual physical dimension of time, a line, non-compactified and endowed with dimensionality.

Since these endogenous rhythms co-exist with physical time, we consider a temporality of a topological dimension equal to 2 formed by the *direct product* of the non-compactified part, the real straight line of the variable t (the physical time parameter) and, as a fiber upon the latter, the compactified part, a circle S_1 , of which the variable is θ . Since we consider a two-dimensional time, with a second dimension associated with specific biological invariants, our approach is very different of the usual approach of biological time in terms of dynamical systems, which allows to tackle different kind of questions, like synchronization or stability (see for example the noteworthy book of Winfree (2001)), but do not deal with these invariants.

The idea of using supplementary compactified dimensions in theoretical physics has been introduced by Kaluza and Klein (Overduin & Wesson 1997), and is still widely used in unification theories (string, superstring, M-theory, ...). There are of course major differences between these uses of compactified dimensions and ours. First they concern mostly

³There is still some variability, but this variability appears “naked” when considering these numbers, whereas the mass and temperature effects come first when considering dimensional quantities.

the addition of *space*-dimensions; second these dimensions are not observable in physics, whereas they are clearly observable in biology. In our approach, the projection of this second dimension on physical time leads to quantities that have the dimension of a time; their mean follows the allometric law, as such they are parametrized by a mass (or, equivalently, by an energy; here one may see again the dual role of energy vs. time as parameter vs. operator, the duality w. r. to Quantum Physics we mentioned and that have been extensively used in Bailly & Longo (2009)).

We insist that the endogenous rhythmicities and cyclicities are not physical temporal rhythms or cycles as such, as they are *iterations* of which the total number is set independently from the empirical (temporally physical) life span. As we said, they are pure numbers, a few rare constants (invariants) in biology. Our aim is that of a geometric organization of biological time which, by the generativity specific to mathematical structures, would also enable us to *derive* meaning and to *mathematically correlate* diverse notions. The text itself constitutes the commentary and the specification of the following schemata, which are meant to “visualize” the two-dimensionality which we propose for the time specific to living phenomena.

3.3 MATHEMATICAL DESCRIPTION

We first consider both external and internal rhythms; later, we will mainly focus on internal rhythms of organisms (we can take as a paradigmatic example the heart rate of mammals). We begin by providing a qualitative draft of our scheme to show its geometrical structure in figure 3.1, then we will quantify its parameters and explain more precisely their meaning.

3.3.1 QUALITATIVE DRAWINGS OF OUR SCHEMATA

Following the aforementioned ideas, biological time is a (curved) surface: thus, it will be described in 3-dimensions (the embedding space). Note that, if we were considering only biological rhythms, our 2-dimensional manifold would be a cylinder: the (oriented) line of physical time *times* the extra compactified dimension. The situation is more complicated, in view of the further, physical rhythms we want to take into account. They do not require an extra dimension, but they “bend” the cylinder, by imposing global (external) rhythms. Thus, a proper biological rhythm is represented by what we may call a “second order helix”, that is, a helix that is obtained (is winding) over a cylinder, \mathcal{C}_i , which, in turn, is winding around a bigger cylinder, \mathcal{C}_e , of which the axis is the line (τ). As basic reference, we choose orthogonal Cartesian coordinates. Physical time, which is oriented by thermodynamic principles of irreversibility and is measured by a clock as in classical or relativistic physic, will be the first axis (t) of our reference system and will enable the characterization of instants and the measurement of durations. The second axis, (t'), will be associated with the proper irreversibility of biological time (for example the irreversibility of embryogenesis or, just, of “living”, see 3.5). As such, it will represent the *biological age*, or the internal irreversible clock of the organism we consider. The (t) and (t') axis are oriented in the usual way (t) towards the right and (t') pointing upwards). The third axis, (z), (see 3.1) is generated by

the mathematical need of a 3-dimensional embedding space; yet, we claim that it has a biological meaning that will become clear later, in section 3.3.2.

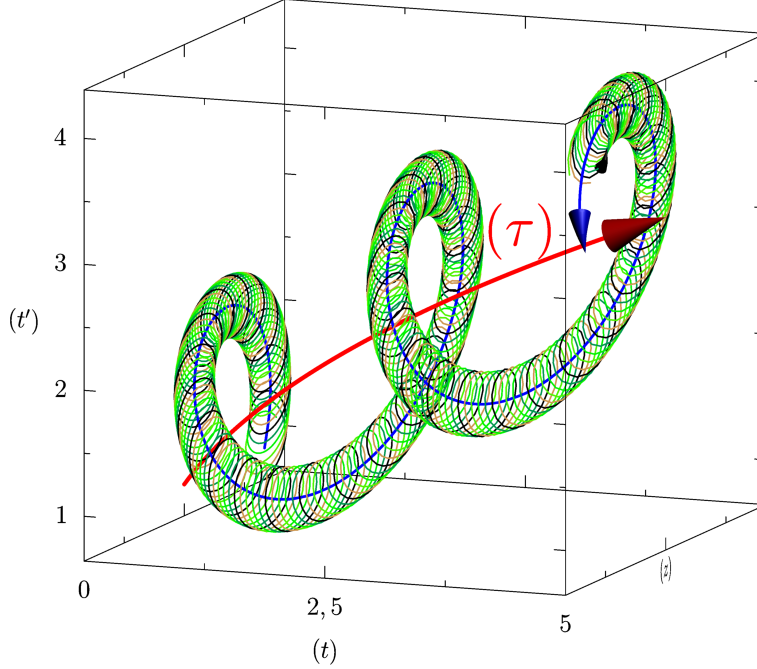


Figure 3.1: *Qualitative illustration of our geometric scheme, as a 2-dimensional manifold.* In red, the global age of the organism, in blue its modulation by the physical rhythm. Here the surface is suggested by varying values of θ .

We consider the surface of the cylinder \mathcal{C}_i as parametrized by t (the physical time) and $\theta \in [0, 2\pi]$ (the compactified time).

Let's then take a further step by gradually making explicit the functional dependencies.

- The average progression with respect to (t') will be represented by a function $\tau\left(\frac{t-t_b}{\tau_i}\right)$. τ is a growing function due to the irreversibility of biological time, and has a decreasing derivative due to the decrease of activity during development and aging. t_b is the physical time of a biological event of reference (time of fecundation for example). τ_i is a characteristic time of the biological activity of the adult: for example, the mean “beat to beat” interval under standardized conditions (other reference systems can be chosen such as the mean time taken to attain 98 % of adult mass, life expectancy, respiratory interval, ...). This value represents, as a function of physical time, the age of the system inasmuch this age is biologically relevant (see figure 3.2a: the graph of τ lies on the $(t \times t')$ plane). Set then:

$$\vec{\mathfrak{F}}_{\tau_i}(t, \theta) = \begin{pmatrix} t \\ \tau\left(\frac{t-t_b}{\tau_i}\right) \\ 0 \end{pmatrix} \quad (3.1)$$

- We next consider a physical (external) rhythm of period τ_e (its pulsation is then $\omega_e = \frac{2\pi}{\tau_e}$) that affects the activity rate of the organism — the circadian rhythm, for example, leads to $\tau_e = 24$ hours. This produces a winding spiral or helix, \mathcal{C}_e (see figure 3.2b: here we need the third dimension (z) for the embedding space of our manifold). In the definition of $\vec{\mathcal{G}}_{\tau_i}(t, \theta)$, R_e represents the impact of this physical rhythm on biological activity:

$$\vec{\mathcal{G}}_{\tau_i}(t, \theta) = \vec{\mathcal{F}}_{\tau_i}(t, \theta) + \begin{pmatrix} 0 \\ \frac{R_e}{\omega_e \tau_i} \cos(\omega_e t) \\ \frac{R_e}{\omega_e \tau_i} \sin(\omega_e t) \end{pmatrix} \quad (3.2)$$

The term $\frac{1}{\omega_e \tau_i}$ is proportional to the number of iterations of the compactified time during one period of the physical rhythm, as such it can be considered as the temporal weight of this rhythm for an organism (mean number of heartbeat during a day, for example), it allows to understand that a year is more important for a mouse and for an elephant. As a consequence the radius of \mathcal{C}_e is proportional to both the impact R_e of this rhythm on biological activity, and on the weight of this rhythm in terms of number of iteration of the endogenous rhythm considered during one period of the physical rhythm.

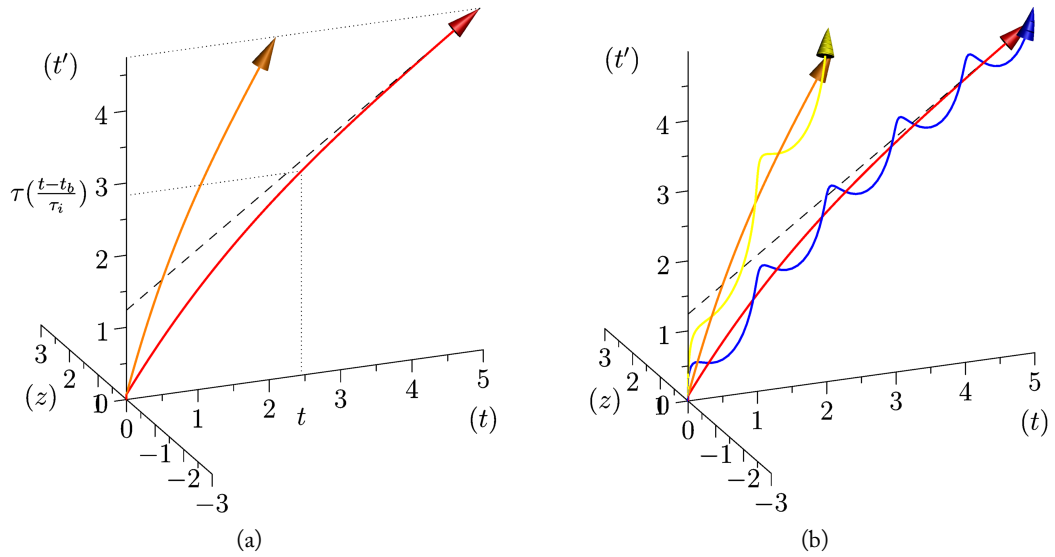


Figure 3.2: *Qualitative Illustration of the first components of our model.* LEFT, the function $\tau\left(\frac{t-t_b}{\tau_i}\right)$, which represents the global age of an organism: this age increases at a greater pace during development and slows down progressively, see section 3.5. In orange a small mammal (a mouse for example) and in red a bigger one (an elephant). The life span of the first is shorter than one of the second. RIGHT, in blue (and yellow), a physical rhythm has been added (this rhythm is very slow for illustrative purposes). Notice that this physical rhythm has the same period for both animals, but one of its iteration has a greater weight for the smaller animal.

- We can finally add a biological (internal) rhythm, which depends on an increasing function $s_{\tau_i}(t)$ (see figure 3.3). $s_{\tau_i}(t)$ has a proper biological meaning: for example, if we impose $s_{\tau_i}(t_b) = 0$, with $t = t_b$ when the heart begins to beat⁴, $s_{\tau_i}(t)$ is the number of heartbeats of the organism at time t , and thus the mean maximum of s , obtained when death occurs, does not depend on the organism we consider (among mammals, typically). Set then, for $\vec{\mathfrak{G}}_{\tau_i}(t, \theta)$ as in equation 3.2:

$$\vec{\mathfrak{I}}_{\tau_i}(t, \theta) = \vec{\mathfrak{G}}_{\tau_i}(t, \theta) + \begin{pmatrix} 0 \\ R_i \cos(2\pi s_{\tau_i}(t) + \theta) \\ R_i \sin(2\pi s_{\tau_i}(t) + \theta) \end{pmatrix} \quad (3.3)$$

3.3.2 QUANTITATIVE SCHEME OF BIOLOGICAL TIME

Now, one of the simplest way to define more precisely s is to use $\vec{\mathfrak{G}}_{\tau_i}$ and more precisely the length of the curve defined by $\vec{\mathfrak{G}}_{\tau_i}$. We obtain then for the instantaneous pulsation, where τ' is the derivative of τ (thus $\frac{d}{dt}\tau\left(\frac{t-t_b}{\tau_i}\right) = \frac{1}{\tau_i}\tau'\left(\frac{t-t_b}{\tau_i}\right)$) and the other components are the derivative of the remaining coordinates in equation 3.3:

$$\frac{ds_{\tau_i}(t)}{dt} = \alpha^2 \times 1^2 + \left(\frac{\tau'\left(\frac{t-t_b}{\tau_i}\right)}{\tau_i} - \frac{R_e}{\tau_i} \sin(\omega_e t) \right)^2 + \left(\frac{R_e}{\tau_i} \right)^2 \cos^2(\omega_e t) \quad (3.4)$$

The term α is here for (physical) dimensionality reasons: since our metric has the dimension of a frequency, and $\frac{dt}{dt} = 1$, the derivative of the first component of the vector in equation 3.2, has no dimension, then we need to introduce this coefficient whose dimension is a frequency⁵.

When $\alpha = 0$ we can simplify 3.4 to:

$$\frac{ds_{\tau_i}(t)}{dt} = \left(\frac{\tau'\left(\frac{t-t_b}{\tau_i}\right)}{\tau_i} \right)^2 + \left(\frac{R_e}{\tau_i} \right)^2 - 2 \frac{R_e \tau'\left(\frac{t-t_b}{\tau_i}\right)}{\tau_i^2} \sin(\omega_e t) \quad (3.5)$$

Now, if we consider hibernating animals, or frozen organisms, we have situations where the physical time flows normally but where the biological time almost stops or even totally stops. For $\alpha \neq 0$, even in the frozen case, biological time would flow with $\frac{d}{dt}s_{\tau_i}(t) \geq \alpha$. It seems then natural to suggest that $\alpha = 0$. Moreover, for $\alpha = 0$, we go back to allometric

⁴Let's remark that, unlike in physics — classical, relativistic or quantum— biological time has an origin, whatever level of organization we consider. As a result there is no time-symmetry for translations, a fundamental property, in (relativistic) physics for the constitution of invariants, e.g. energy conservation.

⁵This kind of reasoning is commonplace in physics.

relations, since, in this case, $\frac{d}{dt}s_{\tau_i}(t)$ is proportional to $\frac{1}{\tau_i}$. Now, τ_i is proportional to $W_f^{1/4}$, by allometry, and, thus, $\frac{d}{dt}s_{\tau_i}(t)$, which is a frequency, to $W_f^{-1/4}$, as it should be.

Another way to express this is to say that physical time *per se* does not make biological organization get older: it is only when there is a biological activity (which in return is of course always associated with physical time) that aging appears.

We can now even give a meaning to the third, (z), axis: since $\tau\left(\frac{t-t_b}{\tau_i}\right)$ is on the $(t \times t')$ plane, a positive (z) corresponds to a positive $\sin(\omega_e t)$, by equation 3.3, and it is associated with a slowdown of biological activity (sleep, for example), whereas the negative values are associated to a faster pace (wake for example).

As a fundamental feature of the model that we will analyze next, we assume that the speed of rotation with respect to the compacified time is constant, which leads to a radius $R_i = \text{Cst}$.

$$\left\| \frac{\partial \vec{\mathfrak{X}}_{\tau_i}(t, \theta)}{\partial \theta} \right\| = R_i(t, \theta) = \text{Cst} \quad (3.6)$$

This assumption “geometrizes” time even further: acceleration and slow-down will be *seen* as contraction and enlargement of a cylinder in §3.4.4.2. In that section, as an application, we will develop a geometrical analysis of biological rate variability, and, as an example, we will consider heart rate. Note that this radius R_i is the dimension accommodating the biological rhythms, thus it is not a physical dimension (it is a pure number). Our assumption is consistent with the idea that each iteration along the compacified time contributes equally to aging.

3.4 ANALYSIS OF THE MODEL

In this section we will explore the various biological aspects our approach allows to put together, mainly on the questions of interspecific and intraspecific allometry and on (heart) rate variability.

3.4.1 PHYSICAL PERIODICITY OF COMPACIFIED TIME

Since $\frac{d}{dt}s_{\tau_i}(t)$ provides the frequency of the biological rhythm, it is interesting to look for a simple analytical expression of the period associated. To do so, we perform a Taylor development (under the hypothesis $\tau'\left(\frac{t-t_b}{\tau_i}\right) \gg R_e$) of the inverse of equation 3.5, and as a result we obtain an approximation of the physical time associated with an iteration of the compacified time (the time between two heartbeats for example):

$$\frac{1}{\frac{ds_{\tau_i}(t)}{dt}} \simeq \tau_i \left(\frac{1}{\tau'\left(\frac{t-t_b}{\tau_i}\right)} + \frac{R_e}{\tau'\left(\frac{t-t_b}{\tau_i}\right)^2} \sin(\omega_e t) \right) \quad (3.7)$$

We can observe several things here. First, for adults (i.e. : $\tau'\left(\frac{t-t_b}{\tau_i}\right) \simeq \text{Cst}$ and it does not depend on the size of the organism we consider) the result has the form $\tau_i(a + b \sin(\omega_e t))$. As a consequence, when we take different species, there is no variation of the ratio $\left(\frac{\tau_i b}{\tau_i a}\right)$

between the continuous and the period components of the biological rates. Alternatively the ratio between the rates of the biological rhythm during the slow period of the physical rhythm (sleep for example) and during the fast period (wake) does not depend of the species either. This result holds experimentally (see for example Savage et al. (2004) and Mortola & Lanthier (2004)).

On the other side, the relationship between this two rates is not linear in intraspecific variations (i.e.: when τ' is not constant, mainly during development), and the variation of the coefficient of the rhythmic component $R_e \tau' \left(\frac{t-t_b}{\tau_i}\right)^{-2}$ is far greater than that of the steady (continuous) component $\tau' \left(\frac{t-t_b}{\tau_i}\right)^{-1}$. This mathematical deduction agrees with experimental results, since Massin et al. (2000), for example, find that the continuous component varies like $t^{0.16}$ while the sinusoidal part (associated with the circadian rhythm) varies like $t^{0.75}$ for humans (between 2 months and 15 years).

3.4.2 BIOLOGICAL IRREVERSIBILITY

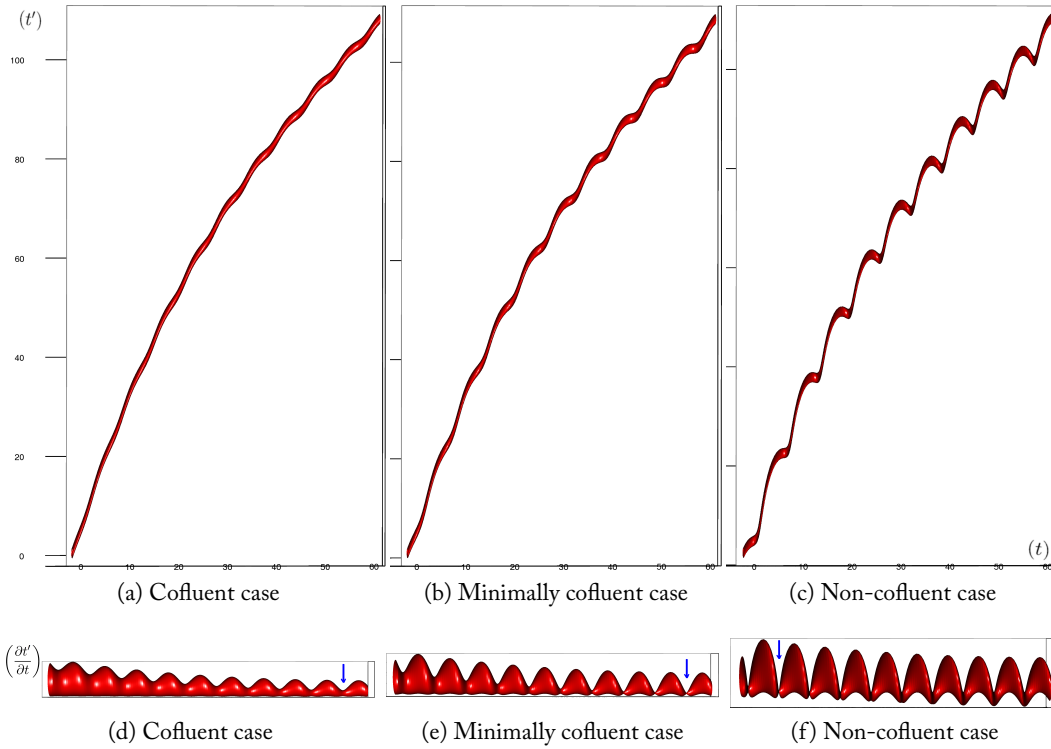


Figure 3.3: *Illustration of the three scenari.* TOP: the scheme $\vec{\mathfrak{X}}_{\tau_i}(t, \theta)$ and BOTTOM its time derivative $\frac{\partial \vec{\mathfrak{X}}_{\tau_i}(t, \theta)}{\partial t}$. FROM LEFT TO RIGHT: Cofluent case, minimally cofluent case and non-cofluent case. Since the radius of the compactified time is proportional to its physical rate when looking at $\frac{\partial \vec{\mathfrak{X}}_{\tau_i}(t, \theta)}{\partial t}$ (see §3.4.4.1), the bottom pictures allows to see when the slowest rate occurs (i.e.: when the radius is the smallest, blue arrow. Here respectively: for adults in figure 3.3d and 3.3e and for infants in 3.3f).

We can now look more precisely at the second axis, (t'), of our reference system. Since this aspect of biological time is irreversible and flows in the same direction than physical time ($\tau(t)$ is an increasing function of t), $\vec{\mathbb{G}}_{\tau_i}$ in equation 3.2 should increase with respect to this direction. When this condition is met, we will say that these times are “*cofluent*”. This can be easily mathematized by looking at the partial derivative of the (t') component of $\vec{\mathbb{G}}_{\tau_i}$ (obtained with the dot product by the unitary vector $\vec{e}_{t'}$) with respect to t :

$$\frac{\partial \vec{\mathbb{G}}_{\tau_i}(t, \theta)}{\partial t} \cdot \vec{e}_{t'} = \frac{1}{\tau_i} f' \left(\frac{t - t_b}{\tau_i} \right) - \frac{R_e}{\tau_i} \sin(\omega_e t) \quad (3.8)$$

We obtain then three different scenari, assuming that $\tau' \left(\frac{t - t_b}{\tau_i} \right)$ tends to be a constant for adults (and seniors), written $\tau' \left(\frac{t_{\infty}}{\tau_i} \right)$. We then use equation 3.5 to derive their *observable* consequences:

$\tau' \left(\frac{t_{\infty}}{\tau_i} \right) > R_e$. In this case, biological age and the physical clock are confluent, and the minimum rate is achieved during adult sleep (figure 3.3a and 3.3d).

$\tau' \left(\frac{t_{\infty}}{\tau_i} \right) \simeq R_e$. In this case, they are minimally confluent, the derivative tends to zero (during night or winter) when the organism grows older, that is the rate of the biological rhythm tends to 0 during the (physical) time of little biological activity. It seems to be particularly relevant for hibernation (figure 3.3b and 3.3e)....

$\tau' \left(\frac{t_{\infty}}{\tau_i} \right) < R_e$. in this case they are no longer confluent, the nullification of the biological rate would appear during development, and, as a result, the slowest biological rhythm would appear during sleep of young individuals (figure 3.3c and 3.3f).

This case analysis has an actual correspondence with empirical data for the first two cases (see for example Hellbrugge et al. (1964); Cranford (1983)). We believe that theoretically biological time should be always confluent so that the third case should never be realized. Indeed, the existing data, which are mostly given for humans, confirm that case 3 does not hold (young individuals have slow rhythms, during sleep typically, which are faster than adults slow rhythms).

It would be nice that our theoretical deduction, excluding, like in physical reasoning, the third mathematical possibility as meaningless, were empirically confirmed in large phyla. Conversely it would be also interesting if this theoretical derivation leads to the discovery of species where also the third case is realized.

3.4.3 ALLOMETRY AND PHYSICAL RHYTHMS

When we consider organisms with different adult masses (W_f), we obtain a variation of τ_i according to the scaling relationships ($\tau_i \propto W_f^{1/4}$), whereas ω_e does not change. As a result, this change corresponds to a dilatation of the (t) axis (as far as f is concerned) whereas the physical rhythm modifies the geometry of biological time because the variations it triggers are anchored to the physical value ω_e (see figures 3.2a, without physical rhythm, and 3.2b, with physical rhythms.).

Then, it is the interplay between physical rhythms and biological ones that breaks the symmetry (by dilatation) between organisms of different (adult) masses that have the same temporal invariants (most mammals for example). As a result, in this situation, the physical conditions can be seen as constraints or frictions on biological temporal organization. Our point of view can be compared to the dimensionless time in West & Brown (2005), but they only consider the autonomous aspect of biological time, thus not considering this important interplay.

An other way to illustrate these aspects is to count the lifelong number of iterations of cycles: for biological cycles, this number does not vary much when considering different species, whereas it is strictly proportional to life span for physical ones.

3.4.4 RATE VARIABILITY

Let us first introduce informally the applications we will hint to in this section, where the data are obtained from the medical references in place. Our approach to biological time leads naturally, as we will further specify, to a representation by a cylinder whose radius is proportional to the cardiac *rate*. If we assume that n heartbeats yield a complete rotation around the cylinder, then a faster heart rate would appear as a circular outgrowth (a sudden increase in the radius). In this representation, a healthy individual has a complex cardiac dynamics during the day, with frequent rhythms' accelerations of varying length (from seconds to many hours). This shows up in the figures by the many circular outgrowths of different radii. On the contrary, an individual with an artificially regulated pace (with a pacemaker, say) gives a relatively smooth cylinder. The last figure below corresponds to a sudden cardiac death, without particular symptoms.

Of course we do not provide a *theoretical determination* of spontaneous biological rates variability, but just a *geometrical representation*. As a matter of fact in our framework, it is quite straightforward to explore the *structure* of biological rhythms and of their variations. More precisely, we can easily and effectively represent raw datas (for example the series of "beat to beat" interval over time). As a result, we obtain more than a qualitative schema: it is a theoretical grounded representation of the "anatomy" (and pathological anatomy) of biological time. First we need to see how we can use scales in our framework.

3.4.4.1 Renormalization

If we want to consider n iterations of the compactified time θ as an iteration of an other compactified time $\tilde{\theta}$ we obtain $\tilde{\theta} = \frac{\theta}{n}$ and $\tilde{s}_{\tau_i} = \frac{s_{\tau_i}}{n}$, then by some sort of renormalization using the principle of constant speed for the compactified time, one has:

$$\left\| \frac{\partial \vec{\mathfrak{X}}_{\tau_i}(t, \theta)}{\partial \theta} \right\| = \frac{\tilde{R}_i}{n} = \text{Cst} \quad (3.9)$$

So $\tilde{R}_i = R_i n$. This result is exactly (modulo a global dilatation of the (t') and (z) axis by a factor $\frac{1}{n}$) what we obtain if we construct directly our system at the level of n iterations.

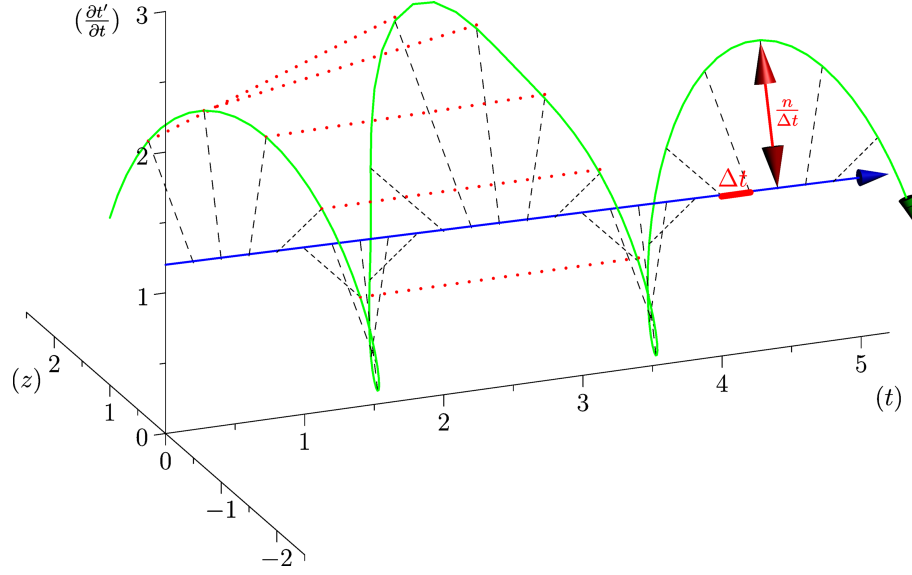


Figure 3.4: *Renormalization and principles of variability representation.* Here, we consider $\frac{\partial \vec{\mathfrak{Z}}_{\tau_i}(t, \theta)}{\partial t}$ and we renormalize the compacified time by $n = 10$. A change of speed for the iteration m of the original compacified time appears as a sharp contrast between this iteration and its neighbors: iteration $m - 1, m + 1, m - 10, m + 10$. As a result, if there is a coherence for 10 successive iterations, we obtain a fully circular outgrowth or contraction (for an acceleration or a slowdown respectively).

3.4.4.2 Rate Variability

If we look at the function obtained by taking the derivative of $\vec{\mathfrak{Z}}_{\tau_i}(t, \theta)$ with respect to t , we obtain:

$$\frac{\partial \vec{\mathfrak{Z}}_{\tau_i}(t, \theta)}{\partial t} = \begin{pmatrix} t \\ \frac{1}{\tau_i} \tau' \left(\frac{t-t_b}{\tau_i} \right) - \frac{R_e}{\tau_i} \sin(\omega_e t) - 2\pi R_i s'_{\tau_i}(t) \sin(2\pi s_{\tau_i}(t) + \theta) \\ \frac{R_e}{\tau_i} \cos(\omega_e t) + 2\pi R_i s'_{\tau_i}(t) \cos(2\pi s_{\tau_i}(t) + \theta) \end{pmatrix} \quad (3.10)$$

Here, instantaneous heart rate, $2\pi s'_{\tau_i}(t)$, appears directly as the radius of compacified time, (which has the physical dimension of a frequency now).

If the experimental time of each heartbeat is given in a list $(t(m))_{1 \leq m \leq M}$, we obtain a discrete empirical version of $\frac{\partial \vec{\mathfrak{Z}}_{\tau_i}(t, \theta)}{\partial t}$, renormalized by n :

$$\frac{\partial \vec{\mathfrak{Z}}_{\tau_i}(m)}{\partial t} = \begin{pmatrix} t(m) \\ \hat{A} - \hat{R} \sin(\omega_e t(m)) - 2\pi \frac{n}{t(m+1)-t(m)} \sin\left(\frac{2\pi m}{n}\right) \\ \hat{R} \cos(\omega_e t(m)) + 2\pi \frac{n}{t(m+1)-t(m)} \cos\left(\frac{2\pi m}{n}\right) \end{pmatrix} \quad (3.11)$$

where \hat{A} is an estimation of $\frac{n}{\tau_i} \tau' \left(\frac{t-t_b}{\tau_i} \right)$ which may be soundly considered constant during the few days of the measure. \hat{R} is an estimation of $n \frac{R_e}{\tau_i}$. Both of these values are estimated by using equation 3.5 and $(t(m))_{1 \leq m \leq M}$. We obtain a 2-dimensional structure by using triangles

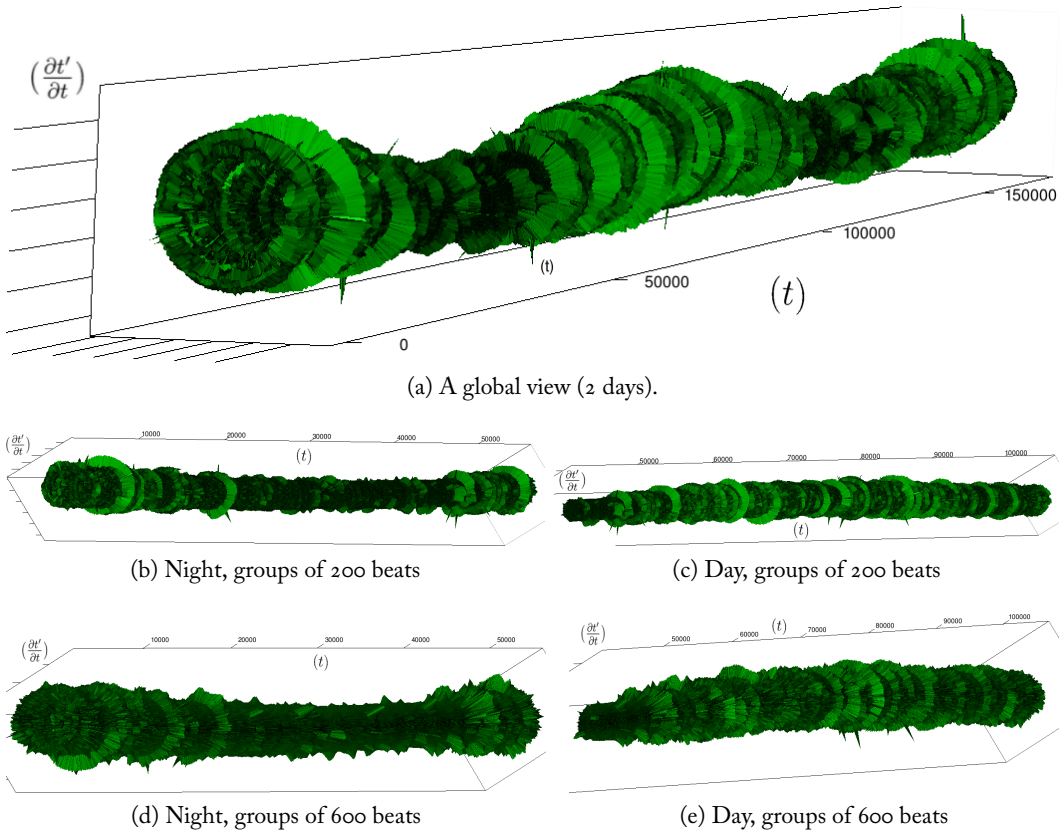


Figure 3.5: *Comparison of the situations during sleep and wake.* The point to notice here, is that the structure tends to become a regular cylinder during night at high scales, whereas the wake is always complex. (Sample s200111 from The Long-Term ST Database, Goldberger et al. (2000)). The series of beat to beat intervals provided by this database is used directly, in our framework, to estimate the few parameters we need and more importantly to provide the radii involved (each heartbeat is represented).

between adjacent points, that is to say for $m \leq M - n - 1$, the triangles $(m, m + 1, m + n)$ and $(m, m + n, m + n + 1)$. It is worth mentioning that this approach allows to obtain an empirical version of $\vec{\mathfrak{X}}_{\tau_i}(t, \theta)$ too.

The renormalization by n allows to observe directly the correlations between n consecutive heartbeats (a full circle) and the contrasts between a group and its neighbors (see figure 3.4), thus discriminating easily between the sleep situation (no correlations wider than ≈ 100 heart beat) and the healthy wake state (correlations at each scale). The latter is indeed characterized by a succession of randomly spaced outer circle (see figure 3.5).

Moreover this representation may be useful to study cases of heart diseases and even aging, since this situations are characterized by an alteration of heart rate variability. We illustrate this alteration in cases of sudden cardiac death in figure 3.6 computed with datas from the The Sudden Cardiac Death Holter Database, see Goldberger et al. (2000). This

figure evidentiates the anatomy and the pathological anatomy of heart rhythms and suggests the extension of this approach to other biological rhythms which are less explored.

- Figure 3.6a is an example of a healthy case, which is characterized by a complex temporality during wake.
- In figure 3.6b, (intermittent) pacing leads to an excessively regular cylinder, with few heart rate variability.
- Atrial fibrillation in the figure 3.6c (a kind of arrhythmia, see comments in figure 3.6) leads to an “hairy” structure, which represents a strong short term randomness (few correlations between successive heartbeats).
- Last but not least the figure 3.6d is not associated with a specific diagnosis (put aside sudden cardiac death at time 9000) but it clearly shows a very simpler structure than the healthy case.

Our approach allows to discriminate all these various cases by rather striking geometrical differences. Wavelet analysis is often used for the same purpose, but this approach is based on a massive reorganization of datas, through a decomposition in various components, whereas we only perform a geometrical and synthetic composition of them.

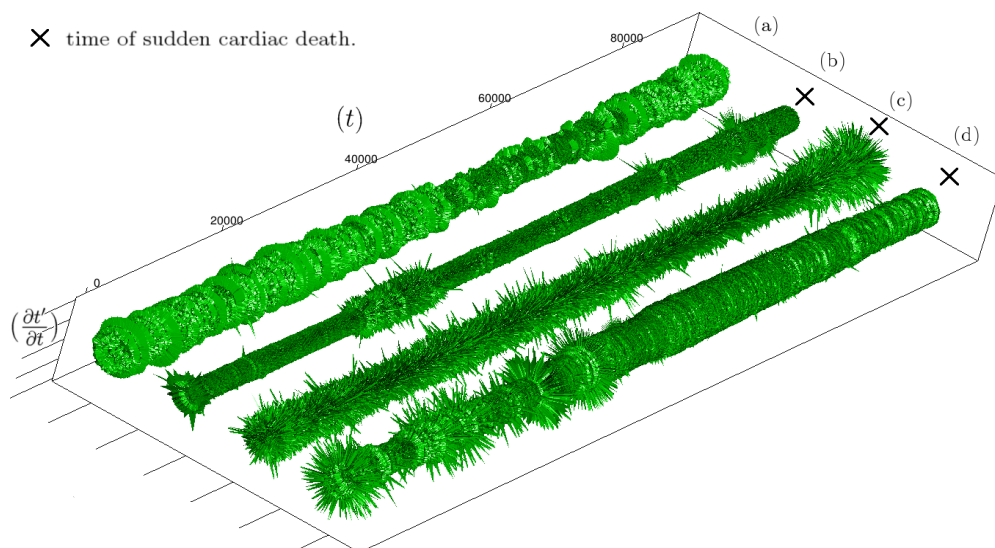


Figure 3.6: *Comparison between a healthy situation and cases of sudden cardiac arrest.* (a) Healthy case, cf figure 3.5. (b) Female aged 67 with sinus rhythm and intermittent pacing. (c) Female, 72, with atrial fibrillation. (d) Male, 43, with sinus rhythm. (The data are from samples 51, 35 and 30 from The Sudden Cardiac Death Holter Database, see Goldberger et al. (2000)).

3.5 MORE DISCUSSION ON THE GENERAL SCHEMA 3.1.

3.5.1 THE EVOLUTIONARY AXIS (τ), ITS ANGLES WITH THE HORIZONTAL $\phi(t)$ AND ITS GRADIENTS $\tan(\phi(t))$

The central line (τ), see figure 3.1, is the “result” of the various components (physical time, external and internal rhythms) and it is supposed to refer to a “physiological” time associated to the evolution of the organism over the course of its life. In order to better understand the different chronological parts of life, this “axis” may be decomposed in distinct segments, each being characterized by their angle, ϕ , with regard to the abscissas (the ϕ angle under consideration then becomes that of the tangent), connected by zones with a fast curvature around specific times (t_0, t_1, t_2, \dots). We will in particular distinguish five parts (with unequal lengths).

- I Around t_{00} (which would correspond to the fertilization of the egg that will form the organism or to a mutation which generates a new species), a new segment begins with a very large angle (80° for example) and consequently with a very high gradient. This segment will correspond to *embryogenesis*.
- II Around t_0 , there occurs a first curvature of the axis in order to initiate a segment of which the angle (and the gradient) still remains high (at 60° , for example). Time t_0 would correspond to birth⁶ and the following segment to *growth* (development).
- III Around t_1 , we would have a new curvature generating a medium sized angle (45° for example) with a gradient approaching 1; t_1 would correspond to the apparition of the reproductive faculty (age of puberty⁷) and to the entering into the phase of *adult maturity*.
- IV Around t_2 , we would have another curvature generating a small angle segment (30° for example) with a weak gradient; t_2 would correspond to the period of loss of fecundity (menopause, eventual andropause)⁸ and to the beginning of *aging* as such.
- V Around t_3 the axis becomes horizontal ($\phi = 0, \tan(\phi) = 0$) and is definitely broken; t_3 represents the moment of *death*.

Concerning the various durations (namely that of the life span $t_3 - t_0$), we know by the above mentioned laws of scaling generally encountered in biology, that these durations scale according to the organism approximately by $W_f^{1/4}$, where W_f is the mass of the adult organism.

If we now consider $v_t = \tan(\phi(t))$ as being the “speed” of evolution of the physiological time (τ) with regard to the physical time t , we would make the following remarks which motivate the various gradients of (τ):

⁶At germination, for plants.

⁷At the moment of flowering or of fruit-bearing, for plants.

⁸At the end of production, for plants.

- between t_{00} and t_0 this speed is very high: initial cell divisions, morphogenesis, setting in of the first functionalities;
- between t_0 and t_1 , the speed remains high; it corresponds to growth, to development, to the completion of the setting in of functionalities, to a high metabolism;
- between t_1 and t_2 the speed is moderate; it corresponds to the regularity of the metabolic reactions, of cellular renewal, etc., that are characteristic of adult age;
- between t_2 and t_3 , the speed is low: lowering of the metabolic rate, of cellular regeneration, of activity; this corresponds to aging;
- after t_3 the speed is null: it is the death of the organism.

3.5.2 THE “HELICOIDAL” CYLINDER OF REVOLUTION \mathcal{C}_e : ITS THREAD p_e , ITS RADIUS R_i

In our qualitative analysis (see 3.1) we have a cylinder of revolution \mathcal{C}_e , with a radius R_i , which is winded as a helix having a thread of p_e around the (τ) axis, without touching this axis but faithfully following its changes of direction.

The thread p_e of this helicoidal cylinder can be assimilated to a period; it corresponds to the *external* cyclical rhythms imposed upon the organism by its environment (annual, lunar, circadian cycles, for instance, see §.3.2.2(EXT)), which are independent physico-chemical rhythms that we have taken into account in the first paragraph; they are essentially of a physical origin and are imposed upon all organisms exposed to them. The $R_i = 0$ case will be evoked below.

3.5.3 THE CIRCULAR HELIX \mathcal{C}_i ON THE CYLINDER AND ITS THREAD p_i

This circular helix \mathcal{C}_i , with a thread p_i , is winded around the surface of the cylinder \mathcal{C}_e (it is a “second order” helix because the winding cylinder is also helicoidal). We consider the thread of this helix (which is also a period) to refer to the compactified time θ (the circle which generates this cylinder) introduced here and associated to the *internal* biological cycles of the organism which are also independent (or almost) from the environment; this is the case, let’s recall, for example, of cardiac and respiratory rhythms, of the rhythms of biochemical cascades, etc. (see §.3.2.2(Int)). Let us also recall that the period associated to these cycles also scale by $W_f^{1/4}$, at least from t_1 (and also practically from t_0).

To summarize, we thus have, from a biological standpoint, in addition to the objective physical time t (evidently still present and relevant):

- a general temporality of biological evolution (τ) (the axis);
- a temporality associated to the external rhythms (the helicoidal cylinder winded around this axis from a distance) that are characterized by the thread p_e ;
- a temporality associated to the internal rhythms involving a compactification of time: the helix with a p_i thread at the surface of the cylinder.

We should also note that if the radius R_i of the helicoidal cylinder becomes null, it will be reduced to a helix wound around (τ) and the internal cyclicity will tend to disappear as such (there remains only the external rhythms that are physical). If we may consider the general schema we have presented to concern mainly the properties of the animal world, this last case, where $R_i = 0$, mainly concerns plant. In this sense, the non nullity of R_i , that is, the two-dimensionality of the cylindrical surface, should be associated to the greater autonomy — the rhythms of the central systems, typically — and to the autonomous motor capacity which the animal enjoys comparatively to vegetal organisms, the two being obviously correlated. Actually, the rhythms (metabolic, chlorophyllian, of action — activation of organs...) of plants are often completely subordinated to the physical external rhythms.

Of course, there is no clear-cut transition, no well-defined boundary between animal and plant life forms in particular in the marine flora/fauna. For this reason, we find the representation of the passing from the one to another in the form of a continuum to be adequate: the continuous contraction of the helicoidal cylinder which tends towards being a helix, which is a line (the time of plants). The non observability of the difference between animal and plant, in some “transitional” cases, would correspond to an interval of biologically possible measurement, with no phase transition (of the type of life form) that is clear or discontinuous. Once the limit, the helicoidal line, is reached, even the three-dimensional embedding space can be collapsed onto the two dimensions: the rhythm becomes the oscillation of one measurement (of chlorophyllian activity, for example) with regard to the axis of oriented physical time (the spiral is flattened into a sine, for example) as is the case in many periodic physical processes.

3.5.4 ON THE INTERPRETATION OF THE ORDINATE t'

Let us return now to our questioning regarding the interpretation we can give to the ordinate t' . In a certain sense, it is *generated* by the compaction of the fiber of the temporal rhythms specific to living phenomena. More specifically, it is mathematically necessary as a component of the three-dimensional embedding space of helices produced by the direct production of the physical time t and of the compactified time θ , which are, according to our hypothesis, two independent dimensions. We already hinted to a possible biological meaning of the (z) coordinate. Then, what could the ordinate t' correspond to, from a biological standpoint?

If we define a speed for the passing of time τ comparatively to t' in a way that is similar to the definition of $v_t = \tan(\phi(t))$, we will have $v_{t'} = \cotan(\phi(t))$; at the inverse of v_t (we have $v_t v_{t'} = 1$), this velocity is small at first but continues to grow when t (or τ) grows.

In the case where the organism under consideration is the human being, an interpretation promptly comes to mind. The velocity $v_{t'}$ would correspond to the *subjective perception* of the speed of the passing of the “specific” or physiological time τ : at first very slow, and then increasingly rapid with aging. In such case, t' would be the equivalent of a *subjective time*. One will notice that, from the quantitative standpoint, if between t_1 and t_2 (the area of the adult phase) we confer ϕ with the value of 45° approximately, as we have already indicated above, the speed of the passing of time τ with regard to objective physical time (v_t) coincides more or less with the subjective perception of the passing of this time ($v_{t'}$) (in fact, $\tan(\phi) \simeq \tan \phi \simeq 1$).

As it is matter, here, of human cognitive judgment of the time flow, we are aware of its historical contingency. The remarks below, thus, are just informal preliminaries to forthcoming reflections, where the historicity of young vs. old age perception of time, for example, should be relativized to specific historical cultures and social frames. We then leave the reader to have any reflection regarding the subjective perception of time during youth and old age. We can imagine that such thoughts will coincide with ours, if we belong to the same “culture” (time which passes slowly while young and, later, very quickly...).

In what concerns organisms other than human beings, of which we do not know if they have a subjective perception of the speed of the passing of physiological time τ , it is more difficult to assign a clear status to this dimension of t' (although certain relatively evolved species seem likely to express impatience, for example, or to construct an abstract temporal representation by exerting faculties of retention and especially of protention). So would this dimension not begin to acquire a concrete reality only with the apparition and development of an evolved nervous system (central nervous system, brain)? But then what of the bacterium, the amoeba, the paramecium...?

Actually, it may be possible to somewhat objectivize the approach by advancing a plausible hypothesis regarding the general character of t' : we could consider that it is a question of a “temporality” that is associated to the “representational” dimension. Let us explain.

Since living organisms are endowed with more or less capacity for retention and *protention* (possibly pre-conscious “expectation”), we propose (temporarily, this is ongoing work) to base ourselves on the following qualitative argument: the element of physiological time $d\tau$ is associated to the element of physical time dt and to dt' by the evident relation $d\tau^2 = dt^2 + dt'^2$; it stems from this that dt'^2 can be written as $dt'^2 = d\tau^2 - dt^2$ or as

$$dt'^2 = (d\tau - dt)(d\tau + dt)$$

It is then tempting to see in the first factor the minimal expression of an element of “retention” (for physiological time, relatively to physical time) and in the second the corresponding expression of an element of “protention”. The product of the two would generate the temporality component of a “representation” which borrows from the “past” and from the “future”, as constitutive of the flow of biological time. As all living organisms appear to be endowed with both a capacity for retention — as rudimentary as it may be — and with a protentional faculty (even more rudimentary maybe), the generality of the dimension t' would be preserved and the “representational” capacity (at least in this elementary sense) appears as being a property of living phenomena. We will develop this idea, of protentional and retentional capacity of living organisms in the following chapter (Longo & Montévil 2011b). This property, for conscious thought, could even be extended to subjectivity in accordance, in the specific case of the human being, with the phenomenological analysis with which we began: dt'^2 would be a form, as elementary as infinitesimal, of the “extended present”, in the Husserlian tradition, described by other analyzes, such as the coupling of oscillators in Varela (1999).

Finally, it would be the two-dimensionality $t \times t'$ — (physical time) \times (representation time) — which would enable to *mark out* the temporality of living phenomena, which may be represented in the geometrical way as we have described in this chapter.

Protention and retention in biological systems 4

Husserl uses the terms protentions and retentions for the intentionalities which anchor me to an environment. They do not run from a central I, but from my perceptual field itself, so to speak, which draws along in its wake its own horizon of retentions, and bites into the future with its protentions. I do not pass through a series of instances of now, the images of which I preserve and which, placed end to end, make a line. With the arrival of every moment, its predecessor undergoes a change: I still have it in hand and it is still there, but already it is sinking away below the level of presents; in order to retain it, I need to reach through a thin layer of time.

M. Merleau-Ponty

This chapter is a slightly revised version of:

G. Longo & M. Montévil. 2011b. Protention and retention in biological systems. *Theory in Biosciences* 130 (2): 107–117. ISSN: 1431-7613, doi:10.1007/s12064-010-0116-6

CONTENTS

| | | |
|-------|---|-----|
| 4.1 | Introduction | 90 |
| 4.1.1 | Methodological remarks | 91 |
| 4.2 | Characteristic time and correlation lengths | 93 |
| 4.2.1 | Critical states and correlation length | 94 |
| 4.3 | Retention and protention. | 94 |
| 4.3.1 | Principles | 94 |
| 4.3.2 | Specifications | 95 |
| 4.3.3 | Comments | 96 |
| 4.3.4 | Global protention | 98 |
| 4.4 | Biological inertia | 99 |
| 4.4.1 | Analysis | 100 |
| 4.5 | References and more justifications for biological inertia | 102 |
| 4.6 | Some complementary remarks | 104 |

| | | |
|-------|--|-----|
| 4.6.1 | Blured Protention | 104 |
| 4.6.2 | Power laws and exponentials | 105 |
| 4.6.3 | Causality and analyticity | 106 |
| 4.7 | Towards human cognition. From trajectory to space: The continuity of the cognitive phenomena | 107 |

ABSTRACT

This chapter proposes an abstract mathematical frame for describing some features of cognitive and biological time. We focus here on the so called “extended present” as a result of protentional and retentional activities (memory and anticipation). Memory, as retention, is treated in some physical theories (relaxation phenomena, which will inspire our approach), while protention (or anticipation) seems outside the scope of physics. We then suggest a simple functional representation of biological protention. This allows us to introduce the abstract notion of “biological inertia”.

Keywords: Memory, Cognition, protention, retention and biological time.

4.1 INTRODUCTION

THE notions of “memory” and “anticipation” are analyzed and formalized here from a temporal perspective. By this, we propose a simple mathematical approach to *retention* and *protention* that are apparently shared by all organisms, albeit rudimentarily. Moreover, in life phenomena, memory is essential to learning and it is oriented towards action, the grounding of protention. Our approach will allow to address the issue of what we call “biological inertia”, a form of “continuation” of ongoing action, derived from the notions above. The frame is purely mathematical and abstract: only practitioners will be able to give values to our coefficients and develop, possibly, concrete applications of the approach, from cell biology to human cognition. Our aim is to give a precise and relevant meaning to notions that are usually treated in a rather informal fashion and unrelated between one another, such as those of time of representation, time of retention and time of protention.

A long phenomenological tradition introduces an important distinction between memory and retention, on the one hand, and anticipation and protention on the other. In short, the common meaning of “memory” seems to essentially refer to a “conscious reconstruction” of something that was experienced (very well put by Edelman & Tononi (2001) as a “brain which sets itself back into a previously experienced state”). Anticipation would be its temporal opposite — the awareness of an expectation, of a possible future situation. Memory and anticipation do not, a priori, have a biological *characteristic time*, a notion which is essential to our analysis. In our approach, instead, possibly pre-conscious retention is to be seen as an extension of the present; it is the present which is “retained”, during a brief interval of time (related to what will be called its characteristic time) for the objective of the action (and of perception), it is a form of extension of the immediate past into the present. For example,

when listening to a word or a phrase, we retain the part which has already occurred for a certain (characteristic) duration of time. The mental duration of a phrase, particularly of a musical “phrase”, is needed for grasping meaning or a melody (see for example Perfetti & Goldman (1976); Nicolas (2006)): it is the present which leaves a trace the time necessary for action or, possibly, for subsequent awareness. But protention (as preconscious anticipation) is essential to appreciate a melody or understand a phrase. When reading, the analysis of saccadic eye movements demonstrates that we first look at least at half of the word following the one we are reading, see Wildman & Kling (1978). This protentional behaviour participates in the reconstruction of meaning: we appear to make sure of the meaning of the word we are reading by making a partial guess upon the following word.

Technically, protention will be given by a temporal mirror image, as it extends retention forwards into time. Protention is, above all, the *tropism* inherent to action performed by any life form. This point is at the center of our approach: we call retention and protention these particular aspects of memory and of anticipation that are specific to all life forms — a sort of present which is extended in both directions. Thus we do not limit our analysis to the phenomenological use of these words, inasmuch it limits their meaning to situations that can be examined through conscious activities. We believe that this extension to pre-conscious activities remains compatible with (and helps to understand) its classical usage, particularly such as described by Van Gelder (1999) and Varela (1999) who develop the concepts of intentionality, retention and of protention, introduced and discussed in length by Husserl in his analysis of human consciousness.

In this chapter, it is then a question of trying to propose an elementary modelization of these inevitably fuzzy notions, one which is as rudimentary as possible, but one that can nevertheless support discussions regarding their precise conceptualization and their increasingly thorough mathematization. The introduction of the notions of “biological inertia” and “global protention” are, typically, a consequence of the generative power of mathematics.

To our aim, we will define some basic principles and more specific notions, after some methodological preliminaries.

4.1.1 METHODOLOGICAL REMARKS

Let us recall that in our general approach, also presented and followed in Bailly & Longo (2011, 2008, 2009); Bailly, Longo & Montévil (2011), our attempted aim is not to reconstruct the physico-mathematical complexity of some aspects of biology, but to propose firstly and above all a proper biological perspective. We believe that the *theoretical differentiation* between theories of inert and of living phenomena requires, among other things, a change in the relevant *parameters* and *observables*.

As long as the actions of living organisms, including their cognitive performances which occur the moment that life appears (in this sense, we speak of protention and of retention in the amoeba or the paramecium), are analyzed within physical space-time, the physico-mathematical takes precedent over the specificity of the biological. For example, the formidable mathematics of morphogenesis, from phyllotaxy to the analysis of the fractal structures of organs, organize the results of friction in the growth of living organisms accord-

ing to physical geodesics. This friction is nevertheless shaped within physical space-time (fractality optimizes the occupation of physical space, the exchange of energy by a surface within a volume, ...). In all of these cases, the spatio-temporal and energetic parameters and observables enable a very interesting and often technically very difficult analysis. This is an approach of the *physical complexity* of living phenomena and of its material structures. We could also say the same of analyses of networks of cells, of which the most complex are neural networks. Informational interaction, often a gradient of energy, enables to develop a theory, now very rich from the mathematical standpoint, of these formal networks of which increasingly important applications are being considered for the construction of machines that are somewhat intelligent (at last).

In this chapter, our mathematics will not go beyond a few equations which could be presented to high school students. What matters in our view is approaching biological time according to its own specificity, by starting with some invariants which appear to be *exclusively* specific to living phenomena, as it has been done in Bailly & Longo (2011), or with properties that are not treated by current physical theories, as protention here. In chapter 3 (Bailly, Longo & Montévil 2011), we proposed a two dimensional representation of biological time as a mathematical frame to accommodate the autonomous (internal) biological rhythms (cardiac, respiratory, metabolic rhythms, ...). In the perspective of this chapter, one may understand the expectation or anticipation of a rhythm to iterate, as a minimal form of protention: once rhythms are installed, the organism is “tuned” to (and “expects”) their iteration.

Before developing a further geometrization of biological-time, we will face yet another taboo of physicalism in biology: the inverted causality specific to protention. We will not present a physical theory of teleonomy, but will use as data and principle the evidence of protentional behaviours that may be observed in any life form. When the paramecium, encircled by a ring of salt, tries after many attempts to break through the obstacle, risking its own life and possibly even succeeding (Misslin 2003), we can take note of the retention/memory-learning of what we see and of the ensuing teleonomic gesture (a protention) and develop an adequate theory (see also Saigusa et al. (2008)). Likewise, when we hear that the brain, prior to a saccadic eye movement, in an obvious anticipation, prepares the corresponding primary cortex which is apt to receive the new signal (see Berthoz (2002)), we can say that there is certainly an underlying physico-chemical mechanism which will one day enable to grasp the phenomenon by means of physical causality, a causality which may need to be invented.

For the moment, let us consider these phenomena as a form of protention to be analyzed (correlated, formalized, ...) by a theory specific to living phenomena, even if it has no correspondence or meaning within current physical theories. Then, the unification with the physico-chemical theories may be better considered, in order to evidentiate the physico-chemical components which underlie these phenomena. As a matter of fact, unification will be possible only when we will have *two* theories to compare to one another, both theories being as mathematized as possible. We are talking about *unification* and not *reduction*, since physicists aim to unify the relativistic and quantum fields and not perform a reduction of the one *theory* to the other: string theory and non-commutative geometry aims the construction

of a new unified frame which presents a new perspective for both theories. The mathematics to be found in the following pages will give us the advantage of formalization: it forces to specify concepts and to stabilize them as much as possible (this is what mathematics is first about). Maybe that which follows is false, but it should then be possible to say so in relation to a precise formulation.

4.2 CHARACTERISTIC TIME AND CORRELATION LENGTHS

The notion of “characteristic time”, which we inherit here from physics, appears to be very important in biology as well: it concerns the unity of the living individual because, for example, fluxes and their transport entail lengths and, therefore, relevant transport times. We will also speak of characteristic times for retention and protention.

For example, according to the size of the organism, there appears to be two sorts of transport processes. For large organisms, it would be of a “propagational” type (v_p velocity, along networks and “channels”) with a typical correlation length of $L_p = v_p \tau$, where τ represents the characteristic time. For smaller organisms (cells, for example), it would rather be of a “diffusional” type (diffusion coefficient D , due to molecular diffusion processes) and the typical correlation length would be $L_d = (D\tau)^{1/2}$.

We stress the difference regarding dependency in function of time: linear in one case, as a power of 1/2 in the other¹.

Two complementary remarks:

- The size of the organism also affects structures determining the mode of transport, for example the respiratory function (oxygen transport): in the case of small organisms (insects, for example) the transport is performed by *tracheas* (or even pores), multitudes of little cylinders where the air diffuses in order to reach the cells. In the case of large organisms (fish, mammals), transportation and exchanges are performed by means of *gills* or of *lungs*, centralized anatomic structures which present the fractal geometries we evoked above and which enable to conciliate difficultly compatible constraints (efficiency, steric limitation, homogeneity), and then by various sorts of vascular systems. Transportation, in this last case, is also much more of a “propagational” type (even if diffusion does play a role, namely in bronchioles).
- These considerations essentially apply to various *structural* aspects responding to identical functions. The *functional* aspect responds for its part very generally to common scaling laws (the metabolism which corresponds particularly to oxygen intake, the variegated rhythmicities, the relaxation times, ...). It therefore appears that the modes of transport associated to identical functions can be different and can correspond to different anatomic structures (tracheas, gills, bronchial trees/lungs). This is the well-known phenomenon of analogy of structures in evolutionary biology.

¹Notice that anomalous diffusion can also occur, see section 2.5.1, which leads to different exponents, usually smaller (subdiffusion) and sometimes bigger when energy is used.

Finally, account taken of these remarks, since the characteristic times τ mostly scale as $W_f^{1/4}$, where W_f is the mass of the intended adult organism (see chapter 2, section 2.2 or Lindstedt & Calder III (1981); Savage et al. (2004)), it is necessary to expect the correlation lengths to scale differently according to the mode of transport: respectively L_p in $W_f^{1/4}$ and L_d in $W_f^{1/8}$, following the definitions of L_p and L_d .

In the sequel, our characteristic times will more precisely refer to “relaxation times”, still in analogy to physics (see next footnote), yet in properly biological frame, in relation to retention and protention.

4.2.1 CRITICAL STATES AND CORRELATION LENGTH

The physics of criticality and self-organized systems has massively entered the domain of biology since early ideas by Nicolis & Prigogine (1977); Bak, Tang & Wiesenfeld (1988); Kauffman (1993); We further extended this approach, in direct reference to far from equilibrium systems in the sense of Prigogine, by considering living entities as being in an “extended critical situation”, beyond the pointwise analysis of critical transitions proper to physical theories, see Bailly & Longo (2008).

It is interesting now to consider that physical criticality is associated with a so-called critical slowdown (see for example Suzuki, Kaneko & Takesue (1982) or section 5.4.3 for a brief introduction): the relaxation time of a system tends to infinity when it goes near the critical point. The qualitative meaning of these situations in biology is that the effect of a stimuli would take a long time to stabilize (or, more generally, the organism would take a long time to “react” or “adjust”), if one views life as close or in an (extended) critical state. In particular, criticality would lead to very slow cognitive reactions if reaction needs a stabilization.

More generally, also in an information theoretic perspective, the elaboration/reaction time is necessarily slow in an organism with long correlations in space and slow characteristic time of the individual components of the system. However organisms and especially metazoans must often react quickly and are able to do so. Consequently, biological organization provides a solution to this paradox. This solution is to compensate this slowness by preparing the organism to a forthcoming stimulus *in advance*. We will try to provide a simple framework to tackle these properties, by an analysis of protention and biological inertia. Of course, in this context, perception itself is co-determined by this protentional activity.

4.3 RETENTION AND PROTENTION.

4.3.1 PRINCIPLES

We therefore consider *retention* R by specifying it under the form:

$$R_k(t_0, t) \text{ at an instant } t \text{ of an anterior “event” } e \text{ of nature } k \text{ at time } t_0,$$

For short and if needed, we will pose that $e_0^k = e^k(t_0)$ (where $t_0 \leq t$).

Virtual protention, of an event of the same nature $e_1^k = e_{t_1}^k$ at moment t of an ulterior instant t_1 ($t \leq t_1$) will be noted $V_{Pk}(t, t_1)$. However, (actual) protention will be considered as a function also of retention R_k because, and this is an essential principle of our approach, in *the absence of the retention of an event of nature k there will be no possible protention for an event of such nature*. We will therefore have $P_k(R_k, t, t_1) = 0$, for $R_k = 0$. For the sake of simplicity, we described this dependence of protention on retention as a linear dependence and our (actual) protention, $P_k = R_k V_{Pk}(t, t_1)$, will express this². Moreover, in conformity with our previous analyses, we will pose that this protention is a monotonous increasing function of the retention in question, that is $\frac{\partial P_k}{\partial R_k} \geq 0$.

4.3.2 SPECIFICATIONS

On the basis of the distinction made above, we have thus introduced the notions of retention and of virtual protention, as “immediate” and “passive” memory and anticipation in order to express the fact that what we have are phenomena that do not stem from the intentionality related to a conscious activity of a subject (generally endowed with a more or less elaborate nervous system), but to simple processes of biological reaction/stimuli/response, of which many primitive organisms in relationship to their environment are the locus. To the end of developing this point of view, we now introduce distinct concepts with effects which we propose to represent by means of simple functions, mainly *relaxation functions* and their combinations³.

More specifically, we will first define the retention function:

$$R(t_0, t) = a_R \exp\left(\frac{t_0 - t}{\tau_R}\right) \quad (4.1)$$

t_0 is the time of occurrence of an event which is the object of the retention, t is the present moment ($t > t_0$); τ_R is the characteristic time associated to the decrease of the retention as we move away from the occurrence of the event. Notice that when τ_R tends to 0, $R(t_0, t)$ tends to 0. a_R is a coefficient which can be associated to an individual or to a species, for example, in comparison to others of which such faculties are more or less developed.

We propose to use relaxation functions, because the loss of retention, by moving away from the moment of the beginning of a phrase or, more generally, from the beginning of any action (including listening), can be considered as a sort of “return to equilibrium”. A necessary return if we want to grasp the meaning of the ensuing phrase or action. This, obviously, does not preclude us from maintaining a memory of a more long-term past

² After reading a draft of this text, L. Manning gave us references to fMRI data confirming the neurophysiological and neuroimaging evidence for protention and the dependence of protention on retention: Szpunar, Watson & McDermott (2007); Botzung, Denkova & Manning (2008). Further, more specific experiments would be required in order to quantify the coefficients we introduce here and check/adjust the linearity of this dependence.

³Relaxation functions are among the simplest decreasing functions enabling to define a characteristic time τ in physics, they often represent the basic model for the return to the equilibrium of a system that was initially brought out of equilibrium, with the speed at which the system returns to the equilibrium f_e of the system's f function, $\left(\frac{df}{dt}\right)$ remaining proportional to this interval $\frac{df}{dt} = -\frac{|f-f_e|}{\tau}$.

(the initial part of a discourse, for instance): we limit ourselves to an analysis of the local, pre-conscious effect which contributes to the extended present of an ongoing activity.

How may we now formally define virtual protention, a property which belongs only to living phenomena? We propose to make it mathematically intelligible by means of a *temporal symmetry* with regard to R (time t will change sign). So we define, by a symmetry adjusted by two new parameters, a_P and τ_P , a *virtual* protention. Now, time t_1 is the time of the event to be anticipated and which is in the future of the present instant t ($t_1 > t$), in the form of the function:

$$V_P(t, t_1) = a_P \exp\left(\frac{t - t_1}{\tau_P}\right) \quad (4.2)$$

Where the different parameters, a_P and τ_P , play the same *mutatis mutandis* role as those which intervene in R (cf fig. A). In particular, $\tau_P = 0$ leads to $V_P(t, t_1) = 0$.

Finally, we define *protention* $P(t, t_0, t_1)$ by the product RV_P :

$$P(t, t_0, t_1) = R(t_0, t)V_P(t, t_1) = a_P a_R \exp\left(\frac{t_0 - t}{\tau_R}\right) \exp\left(\frac{t - t_1}{\tau_P}\right) \quad (4.3)$$

The (linear) dependence of P on R , according to the principles stated above, emphasizes that such a capacity can only exist, phenomenologically speaking, if there exists in one form or another a sort of “memory” R (retention) relative to the event of which the reiteration or something resembling it is to be anticipated (we are aware that we are making a strong but empirically plausible hypothesis here, see footnote 2). In our view, the specific traits of this “expectation” of an unknown future, protention, is not exactly symmetrical with regard to the retention of a known past. And this by the fact that protention depends on retention — and not conversely — and that, by its nature, it remains “potential” (it is the expectation of a “possible” event).

In the case where $R = 0$ (complete absence of retention), the protention is cancelled out by the fact that there no longer exists any referent enabling to anticipate the expected event.

Still from the phenomenological standpoint, we will expect that in general $\tau_P \ll \tau_R$, that is, that the characteristic time of retention be greater than that associated to protention P (in order to “anticipate”, it is first necessary to “remember”, as stressed above). So the contribution of V_P in the definition of P (the second exponential in τ_P^{-1}), evolves more rapidly than that of retention for a same concerned duration. And we will always have $P \leq a_P R$, as a function of time t , and this for any values of τ_P and τ_R ($P = a_P R$ being achieved only in the very moment that the time to be anticipated is the actual present, that is for $t = t_1$ and hence $\exp\left(\frac{t-t_1}{\tau_P}\right) = 1$).

To make the role of the parameter t more explicit, with regard to the interval (t_0, t_1) and to the characteristic times τ_P , τ_R , some simple algebraic manipulations enable to put the expression P in the form of the product of a function of t and of two coefficients solely dependent on t_0 and t_1 , that is:

$$P(t) = a_R a_P \exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P}(t - t_0)\right) \exp\left(\frac{t_0 - t_1}{\tau_R}\right) \exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P}(t_0 - t_1)\right) \quad (4.4)$$

4.3.3 COMMENTS

First, we should notice that $\frac{\tau_R \tau_P}{\tau_R - \tau_P}$ is an interesting quantity: it has the dimension of a time and is the characteristic time of $P(t)$.

When τ_P tends toward τ_R , this characteristic time tends to infinity, and respectively $\frac{\tau_R - \tau_P}{\tau_R \tau_P}$ tends to 0. This means that when τ_P is close to τ_R , $P(t)$ is almost stationary as a function of t .

On the contrary, when $\tau_R \gg \tau_P$, minor changes in time strongly affect $P(t)$. More precisely, $P(t)$ is small when far from t_1 (and close to t_0), while it is very sensitive to (small) changes of t , when t is close to t_1 . This means that, in this condition, the vicinity of the virtual event is where the effect of protention is important, see figure 4.2.

It is crucial, however, to understand that protention, for example in the case of a cognitive situation, is not empirically associated with a change of behaviour, but with the *speed* of this change of behaviour. This suggests a way to approach these quantities empirically by a comparison of the reaction time between situations where the event associated with retention (at time t_0) occurs and when it *does not*: in the first case, a more sudden change is then to be expected close to the the expectation time t_1 .

Alternatively, the situation when the event at time t_0 occurs but where the event (at time t_1) does not occur allow to evidenciate the presence of protention and to see a part of its effects. It is in particular the case of amoeba in Saigusa et al. (2008). However, in many situations, the effect of protentional action will consist in a “sensibilization” to the virtual stimuli with the preparation of a response. This may lead to no behavioural change when the virtual stimuli does not happen, but leads to a change of organization associated with the preparation of the response (including at the sensory level) and possibly to a greater sensitivity to noise.

4.3.4 GLOBAL PROTENTION

One may wonder when protention is maximal for a given individual. In our approach, the first possible answer is given by looking at the diagram in figure 4.2: this quantity is maximal close to t_1 . However, we can refine the question (and the answer) by looking at the global amount of protention along the intended interval $[t_0, t_1]$. As protention is both variant and contravariant in the size of $[t_0, t_1]$ (see definition 4.3), this question has a non-obvious answer.

For this purpose, we define the notion of *global protention*, which is the sum (the integral) of protention over time, between t_0 and t_1 .

$$G_P(t_1 - t_0) = \int_{-\infty}^{\infty} P(t) dt \quad (4.5)$$

$$= \int_{t_0}^{t_1} P(t) dt \quad (4.6)$$

Following our specification of protention we can compute the global protention, which has

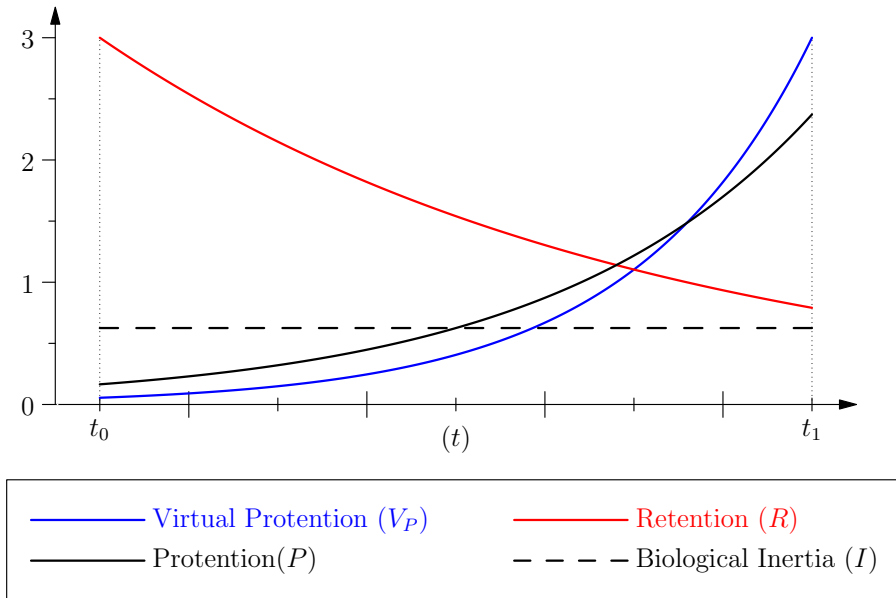


Figure 4.1: *Illustration of the basic quantities we define.* Notice that protention is a growing function of time.

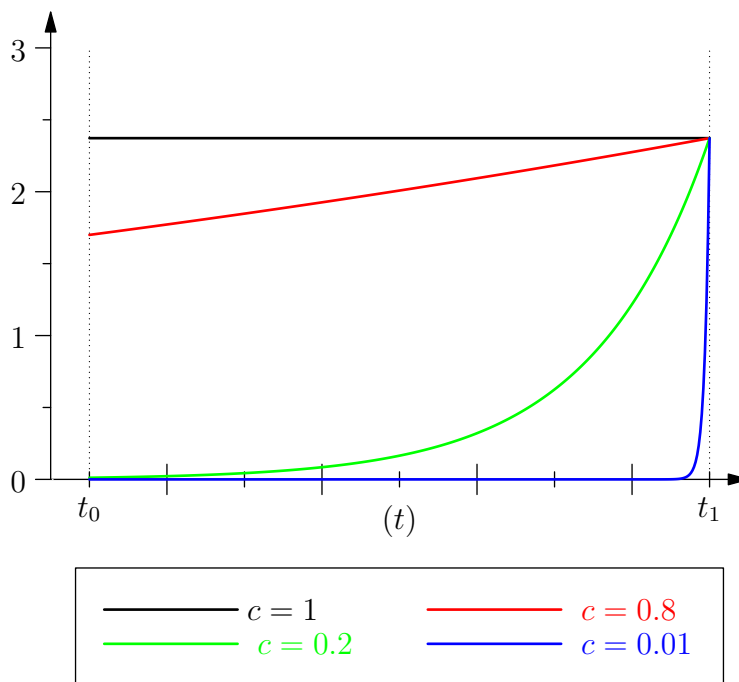


Figure 4.2: *Protention* for various values of the ratio $c = \frac{t_P}{t_R}$. We observe that small value of c leads to a sharp curve near t_1 whereas value close to 1 are flat in the interval. We will discuss the biological meaning of this case in section 4.4.

the following form:

$$G_P(t_1 - t_0) = \int_{t_0}^{t_1} P(t) dt \quad (4.7)$$

$$= \frac{a_R a_P \tau_R \tau_P}{\tau_R - \tau_P} \exp\left(\frac{t_0 \tau_P - t_1 \tau_R}{\tau_R \tau_P}\right) \times \left[\exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P} t_1\right) - \exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P} t_0\right) \right] \quad (4.8)$$

$$= \frac{a_R a_P \tau_R \tau_P}{\tau_R - \tau_P} \left[\exp\left(\frac{t_0 - t_1}{\tau_R}\right) - \exp\left(\frac{t_0 - t_1}{\tau_P}\right) \right] \quad (4.9)$$

This quantity has a maximum for:

$$t_1 - t_0 = \frac{\tau_P \tau_R}{\tau_R - \tau_P} \ln\left(\frac{\tau_R}{\tau_P}\right) \quad (4.10)$$

This maximum is a compromise between the need to give the protention time to have effect (covariant dependence on the size of $[t_0, t_1]$) and the need to have instants in $[t_0, t_1]$ that are close *both* to t_0 and t_1 (contravariance). This result means that there is a specific duration between the past event and the future event which optimize the protentional effects. This seems to be consistent with the results in Saigusa et al. (2008), since these authors found that a specific value of the delay $t_1 - t_0$ (in our notation) leads to a greater protentional effect, that is the functional dependency on this interval of time has a maximum (a non-obvious fact). In section 4.4 we will go back to the relevant ratio $c = \frac{\tau_P}{\tau_R}$.

4.4 BIOLOGICAL INERTIA

Consider now a relaxation phenomenon in physics. It will typically be given by $\Phi(t) = d \exp\left(\frac{t_0 - t}{\tau_R}\right)$. If time $t_1 > t_0$ is given, one may decompose $\Phi(t)$ as

$$\Phi(t) = d \exp\left(\frac{t_0 - t_1}{\tau_R}\right) \exp\left(\frac{t_1 - t}{\tau_R}\right) \quad (4.11)$$

The coefficient, not depending on t , that is $d \exp\left(\frac{t_0 - t_1}{\tau_R}\right)$, is the “residual” at time t_1 and it may be understood as a form of “inertia” of the intended relaxed quantity (for example, it corresponds to “what remains” at time t_1 of a compound which decay with characteristic time τ_R). This coefficient is constant in the interval and decreases for increasing t_1 .

In eq. (4.4) one has the following factors that do not depend on t :

$$a_R a_P \exp\left(\frac{t_0 - t_1}{\tau_R}\right) \exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P} (t_0 - t_1)\right) \quad (4.12)$$

The first exponential term corresponds to a physical inertia, let us call it $I_\phi(t_0, t_1)$. Then, we can consider that the other coefficient of protention represents a *biological inertia*, in the interval $[t_0, t_1]$, depending on the biological constants a_R , a_P , τ_R and τ_P :

$$I(t_0, t_1) = a_R a_P \exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P} (t_0 - t_1)\right) \quad (4.13)$$

In other words, protention in eq. (4.4) may be considered as a product of a function of time t , $\exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P}(t - t_0)\right)$, modulated by constants and characteristic times, of a physical inertia $I_\phi(t_0, t_1)$ and of a “biological inertia” $I(t_0, t_1)$. This last coefficient is also independent of t , but depends on the specific organism by the various indexed constants.

The physical inertia represents the “passive” decay of a physical relaxation phenomena, which makes a perturbation disappear during the return to equilibrium. On the contrary, the biological inertia coefficient is to be understood as a capacity to “carry over” the protensive effect. Their names are freely inspired by the inertial mass as a coefficient of acceleration (thus and very informally, biological inertia would be the biologically pertinent coefficient of protention). In section 4.5, by references and a discussion, we will say more about this new concept. First a few technicalities.

We have to check whether our definitions depend on the specific reference we choose. That is to say if a time origin change:

$$t_0 \leftarrow \tilde{t}_0 = t_0 + \Delta t \quad t_1 \leftarrow \tilde{t}_1 = t_1 + \Delta t \quad t \leftarrow \tilde{t} = t + \Delta t \quad (4.14)$$

changes the way we split P in three parts, in equation 4.4. It is then straightforward to see that:

$$\exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P}(t - t_0)\right) = \exp\left(\frac{\tau_R - \tau_P}{\tau_R \tau_P}(\tilde{t} - \tilde{t}_0)\right) \quad (4.15)$$

$$\exp\left(\frac{t_0 - t_1}{\tau_R}\right) = \exp\left(\frac{\tilde{t}_0 - \tilde{t}_1}{\tau_R}\right) \quad (4.16)$$

$$a_R a_P \exp\left(\frac{(\tau_R - \tau_P)}{\tau_R \tau_P}(t_0 - t_1)\right) = a_R a_P \exp\left(\frac{(\tau_R - \tau_P)}{\tau_R \tau_P}(\tilde{t}_0 - \tilde{t}_1)\right) \quad (4.17)$$

This means that each of these quantities has a sound biological meaning.

Inertia introduces a coefficient which is independent of t and is, in general, much smaller than $a_R a_P$ (and always smaller than $a_R a_P$). This coefficient contributes to the dependence of P in function of t . In particular, it contributes in an essential manner to the decrease of the protention according to the temporal distance.

4.4.1 ANALYSIS

In order to better understand the sense we attribute to this “inertia” of living phenomena, given our preceding remark regarding orders of magnitude respective of characteristic times, we may focus on the ratio c of figure 4.3, that is on c such that $\tau_P = c\tau_R$. We consider $0 \leq c \leq 1$ and rewrite I in the equivalent form:

$$I(t_1 - t_0) = a_R a_P \exp\left(\frac{1 - c}{c\tau_R}(t_0 - t_1)\right) \quad (4.18)$$

$$= a_R a_P \exp\left(\frac{1}{\alpha_R(c)\tau_R}(t_0 - t_1)\right) \quad \text{with } \alpha_R(c) = \frac{c}{(1 - c)} \quad (4.19)$$

Then I has the form of a “long term retention” if $c > 0.5$ or a “short term retention” if $c < 0.5$. Conversely, and maybe even more intuitively, inertia can be also interpreted (by writing $\tau_R = \frac{\tau_P}{c}$ and eliminating this time τ_R) as a “long term virtual protention”:

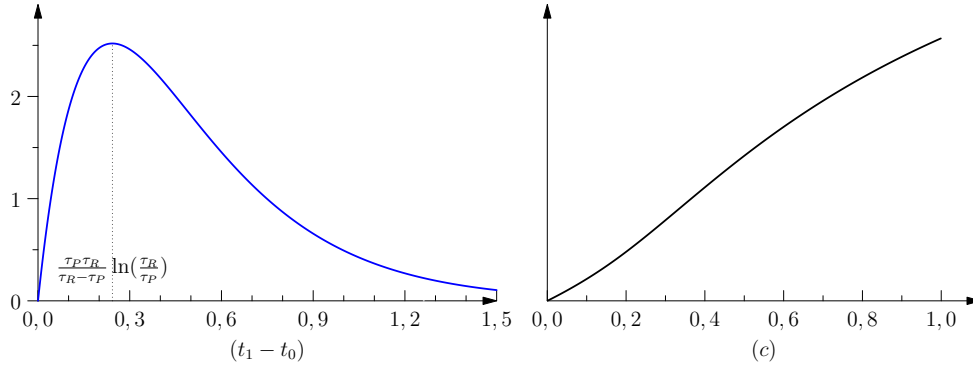


Figure 4.3: *Global protention*. When considered as a function of the length of the time interval (LEFT), there is a maximum which corresponds to the greater effect of the couple Protention/Retention. RIGHT, we see the global protention as a function of $c = \frac{\tau_P}{\tau_R}$.

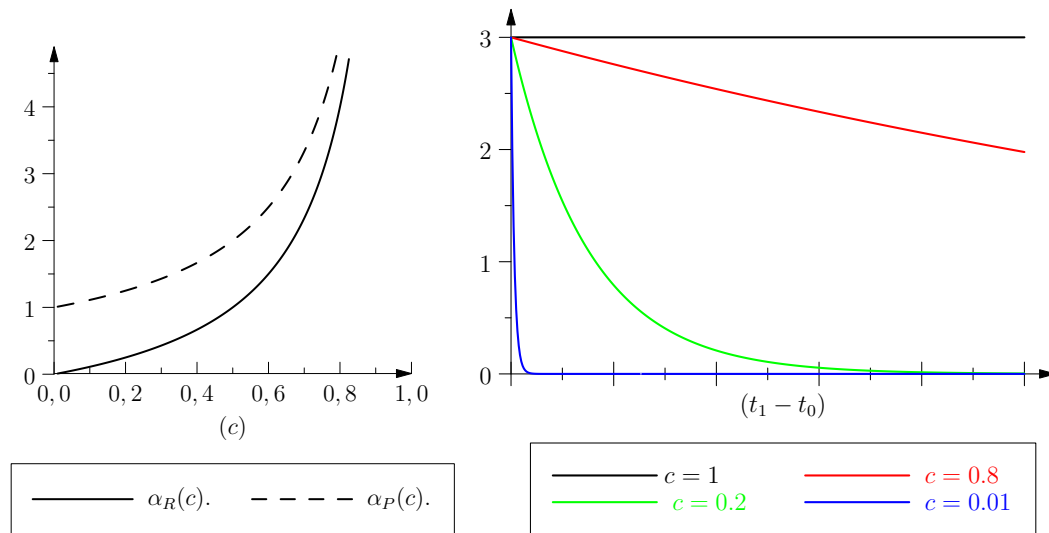


Figure 4.4: *Biological inertia*. LEFT: we plot the factor of the characteristic time of biological inertia seen as protention (or retention). RIGHT: biological inertia as a function of the length of the time interval for various values of c .

$$I(t_1 - t_0) = a_R a_P \exp\left(\frac{1 - c}{\tau_P}(t_0 - t_1)\right) \quad (4.20)$$

$$= a_R a_P \exp\left(\frac{1}{\alpha_P(c)\tau_P}(t_0 - t_1)\right) \quad (4.21)$$

$$\text{with } \alpha_P(c) = \frac{1}{(1 - c)} \quad (4.22)$$

Biological inertia would then be both an extended retention, eq. (4.18), and a virtual protention, eq. (4.20), which are both *independent* of the time t of the action: in fact, it depends only on the instants that are relevant to the event retained and occurring in t_0 or which is the object of an expectation (protention towards t_1). It is therefore an inertia which “carries over” the life form from t_0 towards t_1 , by the preservation of its own structure and its relationship with the environment (see section 4.5).

The $\tau_R = \tau_P$ case

It can be observed that in the case where the characteristic retention and virtual protention times are equal ($\tau_R = \tau_P = \tau$ where the c from the equation above is equal to 1), the protention P becomes $a_R a_P \exp\left(\frac{t_0 - t_1}{\tau}\right)$ and is therefore independent of the present observation time t . This, of course, within the interval between the moment of the occurrence of the event in question and the moment t_1 where it is mobilized again (since we still have $t_0 < t < t_1$). But then, according still to hypothesis $c = 1$, one has $P = a_R a_P \exp\left(\frac{t_0 - t_1}{\tau}\right)$, with $I(t_0, t_1) = a_R a_P$. Thus, when ($\tau_R = \tau_P$), only inertia is present in protention.

We can also note this situation by considering that if the observation time t is close to the instant t_0 of the occurrence of the event (recent retention), then the temporal interval for a virtual protention, $(t - t_1) \simeq (t_0 - t_1)$, increases; conversely, if time t is far from t_0 (remote retention), the temporal interval involved in this virtual protention and within which the latter plays its role (the future of the observation moment t) diminishes in importance, given of course that the protention P as such remains independent of t , in this case.

These remarks are meant to highlight the fact that, in the latter case, the *intensity* P of the protention remains invariant, whereas the duration upon which virtual protention takes place — the future of t — can change in size: $t_1 - t$.

4.5 REFERENCES AND MORE JUSTIFICATIONS FOR BIOLOGICAL INERTIA

We have come to propose a mathematical notion of biological inertia through an apparently arbitrary play of symmetries and calculations, of which we would now like to better explain the meaning and the objectives. To emphasize the importance of the concept, but without wanting to make excessive and uncontrolled analogies with immensely illustrious precedents,

let us note that modern physics started off with a good analysis of inertia, as a “pursuing a state” without aim nor teleology: Galilean inertia⁴.

In biology, this notion can already be found, although rarely, under various forms. For Vaz & Varela (1978) “the lymphoid system has an *inertia*, which resists attempts to induce sudden and profound deviations in the course of events”. So this is a weak notion of inertia, close to the “persistence” of structural stability. Likewise, we could talk about inertia in the case of the notion of “dynamic core” presented in Edelman & Tononi (2000), because it also refers to the continuity/persistence of individuation (see also Le Van Quyen (2003)). This theme is also used by Varela (1997), where the term of inertia appears also in the attempt to grasp the “force”, specific to any organism, enabling its “bringing forth of an identity”.

In our approach, which is inspired by the methods of physics without identifying with it, we firstly define retention by a relaxation function, which is a physical notion — which can even be considered as adequate to describe the “memory” to which some often refer in relation to certain physico-chemical activities. Virtual protention is given then by a temporal symmetry, *modulo* some adjustment coefficients; this notion, which has no analogy in physics, is by this, and at least, the “projective” reflection of retention. Protention follows, as a linear combination of these two values, in function of time. Then, by a simple algebraic device, we separate the part containing the temporal variable from the functional definition: what remains is a constant, a function of all other parameters (characteristic times, specific constants, interval range), which we called biological inertia. As we pointed out, when retention and protention have the same characteristic times ($\tau_R = \tau_P$), inertia coincides with protention. We would then say that this is the simplest situations from a cognitive viewpoint: the organism can only anticipate by means of inertia. In any case, the proposed notion of inertia appears to clearly specify the informal idea of “bringing forth of an identity”, with the reference to retention and to protention, at the minimal cognitive level.

But why would this inertia not simply correspond to the fact of following a geodesic trajectory, like in physics? Some will say that the amoeba, the paramecium, etc., follow a gradient in the same way that a physical object follows the trajectory dictated by the Hamiltonian (through the principle of least action). It may appear that such is the case in *in vitro* experiments where, within a highly purified environment, the unicellular organism is exposed to one or two very specific gradients (chemical, thermal, ...). On the other hand, in an *in vivo* situation, in the ecosystems preferred by such animalcules (and which are very polluted, from our standpoint) they must “arbitrate” between qualitatively different stimuli: several physico-chemical gradients, an edible and close bacterium that is not too large, another smaller one, etc. Now the paramecium, say, appears to “learn” (see Misslin (2003)), that is, it enjoys at least retention, which contributes to protention (and, after reading Mislin and references, one could posit for it $\tau_R > \tau_P$, or even $\tau_R \gg \tau_P$)⁵. And it

⁴Without forgetting Giordano Bruno who had an informal yet quite relevant notion of inertia, a few years prior to Galileo. It then became possible to understand planetary movements without God being required to push the planets around at all times. We similarly aim at a concept of inertia for living phenomena with no reference to “vital impetus” or divine thrust.

⁵A paramecium manages the movements of about 2,000 cilia during highly complex swimming activities; some of its cilia also serve to direct food towards a “mouth” (opening upon the membrane), by means of very articulate movements.

is difficult to conceive of learning without error, or without several attempts and without the memory of these attempts (retention), even if such memory is extremely rudimentary. The subsequent action is therefore one among many possible ones, from the standpoint of the ecosystem, because it also depends on the specificity of individual retention (experience). Among these many possible trajectories, the one it follows has only to be *compatible* with the ecosystem. No gradient or physical geodesic is adequate to describe this plurality of possibilities of evolution, phylogenesis, ontogenesis and of action, which also depends on the specificity, hence on the history, of the species or of the individual (retention and biological inertia). Our modest inertial attempt tries to do this, in a way that is as preliminary as mathematically simple.

We can interpret the growth of $(\tau_R - \tau_P) \geq 0$ as a greater cognitive “complexity”. It appears that the protention, when $\tau_R \gg \tau_P$, must account for more “experience” in order to achieve the objective of the action; it depends upon a greater amount of lived and retained history, and hence on a greater specificity (individuality) of the living object. So it better participates to the incessant process of individuation, which is a play between the richness of retention and the diversity of possible future trajectories.

Another way to associate a growth of complexity to the growth of $(\tau_R - \tau_P) \geq 0$, is to consider cases where the *global* protention is constant. Then the increase of $(\tau_R - \tau_P) \geq 0$ means that protention is more localized near t_1 , with the same global effect. Then this situation is more “complex”, since the preparation to the virtual event occurs when it is closer (and the organism must be “quickly ready”). In this case, it is easier for it to protend another event t'_1 , with t'_1 between t_0 and t_1 , since the organism is not yet fully focused on t_1 (the P grows very slowly “for long” and fastly increases only close to t_1). This situation allows the organism to have longer times of correlation: during the early part of these extended protentional activities, it may prepare also for other events .

4.6 SOME COMPLEMENTARY REMARKS

In this section⁶ we will discuss other aspects associated to protention and retention. This aspect constitute mostly open issues, which could lead to further investigations.

4.6.1 BLURED PROTENTION

Here, we will analyze the situation corresponding to an event with uncertain time of occurrence.

We can indeed consider cases when the organisms bet on an event with an uncertainty upon when it will happen. For example, we can take a Gaussian repartition with a mean t_1 for this event. When t is approximately outside the Gaussian, the situation is equivalent to a punctual event, but the half of the Gaussian which is closer to t has a greater weight, so

⁶This section is not included in the published version.

the time of the equivalent event is before t_1 . More precisely:

$$\int_t^{+\infty} e^{\frac{t-t'}{\tau_p}} e^{-\frac{(t'-t_1)^2}{2\tau^2}} \frac{dt'}{\tau\sqrt{2\pi}} = e^{\frac{t-(t_1-\frac{\tau^2}{2\tau_p})}{\tau_p}} \int_t^{+\infty} e^{-\frac{(t'-(t_1-\frac{\tau^2}{2\tau_p}))^2}{2\tau^2}} \frac{dt'}{\tau\sqrt{2\pi}} \quad (4.23)$$

There is *a priori* two very different situations for this virtual events that can occur at an uncertain time. This situations are different in the way protention change when time flows and the event does not occur:

- If the organism's bet is that the event will occur, then it seems relevant to renormalize probability of it to happen, in order for this event to always have probability 1 of occurring (If we consider an unicellular organism, this situation may be relevant for the event "cell division").
- On the contrary, when the virtual event may or may not occur, for cognitive events for example, the fact that it is not occurring (when it could occur) means that its chance of occurring gets smaller, thus no renormalization is needed, in contrast to the previous case.

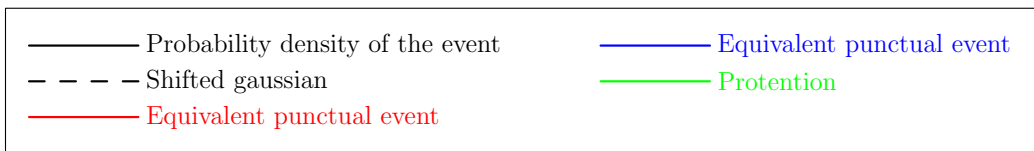
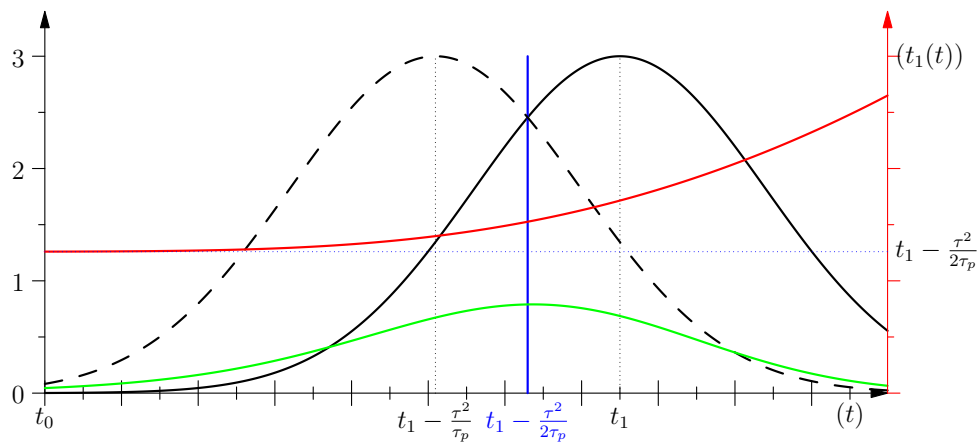


Figure 4.5: *Blured Protention*. Protention appears to be focused on a time before the the mean of the Gaussian distribution of the expected event. This effect is caused by the fact that closer expected events have a bigger protentional weight. The shifted Gaussian corresponds to the new Gaussian generated by the effect of protention on the Gaussian representing the probability of occurring of the event.

4.6.2 POWER LAWS AND EXPONENTIALS

We have chosen here to approach protention and retention by relaxation function, which are crucially associated to a particular scale.

In contrast, some aspects of biological “memory” are associated to power laws, which define typically scale-free situations, see for example Werner (2010) for cognitive aspects or chapter 2 for other aspects.

This question will allow us to describe four typically relevant aspects, which will allow us to analyze the situation more precisely.

- The decay of memory, measured in psycho-physics, can take power laws forms, see Werner (2010). We should notice that this behaviour is associated to relatively long term tendencies; it describe the tail of distributions and not the short term behaviour. In general, such distribution have a small scale cutoff, which also allows integration, and in this chapter we are mostly interested in short term effects. Interestingly, Shinde, Mehta & Mishra (2011) experimentally find that the attentional behaviour are typically associated with a specific time scale, whilst situation typically not associated to attention are scale free (these results are found by observing saccadic eye movements). In all cases, our approach is therefore not at odds with these empirical results.
- However, the various results on the scale free fluctuations of biological time intervals can lead us to propose that the time constants (τ_R and τ_P) can have non-stationary behaviour, and fluctuate in a scale free manner (as the heart’s rhythm). In this case we would have local (in time) scale dependant behaviour, with temporal properties that vary with time.
- Last but not least, the allometric behaviour of this temporal quantities is a crucial question. When associated with usual “physiological” rhythm, protention and retention logically should follow allometric scaling with exponent 1/4. However, when associated to neuronal activities the situation can be more difficult to analyze, see section 2.2.

In fine, our default assumption is that at least a part of protentional activity is naturally associated to the temporal structure described in chapter 3. This is also consistent with the idea that the minimal protensive behaviour is associated with the iteration of internal rhythms, as a bet of the organism on its own physiological stability.

4.6.3 CAUSALITY AND ANALYTICITY

This subsection is a preliminary analysis, which shows a potential line for future research.

Under certain conditions, we can formalize strict causality as the following situation. We consider an input $I(t)$ and an output $G(t)$, and, under assumptions, in particular, of time translation invariance of the response kernel and of superposition of the answer, we obtain that the relation between them is of the form:

$$G(t) = \int_{-\infty}^{\infty} I(t')K(t-t')dt' \quad (4.24)$$

Then, strict causality is the following condition $t' > t \Rightarrow K(t - t') = 0$, which simply means that the future does not influence the output at a given time. This condition can be simplified by simply saying that $\tau < 0 \Rightarrow K(\tau) = 0$

Under this assumption, one can show that we can derive properties of analyticity of the transfer function in Fourier space (Toll 1956; Bros & Iagolnitzer 1973). More precisely we have:

$$I(t) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \hat{I}(\omega) e^{i\omega t} d\omega \quad (4.25)$$

$$G(t) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \hat{K}(\omega) \hat{I}(\omega) e^{i\omega t} d\omega \quad (4.26)$$

Then, $\hat{K}(\omega)$ is the real boundary of an analytic function of the strict upper half plane (with $\Im(\tilde{\omega}) > 0$, $\hat{K}(\tilde{\omega})$ is analytic). More precisely, for $\tilde{\omega} = \omega_r + i\omega_i$,

$$\hat{K}(\tilde{\omega}) = \hat{K}(\omega_r + i\omega_i) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} K(\tau) e^{i\omega_r \tau} e^{-\omega_i \tau} d\tau \quad (4.27)$$

The analyticity is then associated to the exponential decrease allowed by the cancellation of $K(\tau)$, for negative τ and the corresponding decrease of $e^{-\omega_i \tau}$ in the upper half-plane, where $\omega_i > 0$.

Physically, this corresponds to the frequency point of view, and Fourier transform, for ω_r , and to Laplace transform and decay point of view, for ω_i (the combination is usually called a generalized Laplace transform). Analyticity allows to derive the Kramers–Krönig relation between the real and imaginary part of a response function (see for example Sethna 2006, section 10.9).

The most straightforward analogy with protention and retention is in the form of a quadratic response (where protention is considered as exact, which is conceptually incorrect):

$$\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} P(t, t_0, t_1) I(t_0) I(t_1) dt_0 dt_1 \quad (4.28)$$

$$= \int_{-\infty}^t \int_t^{\infty} a_R I(t_0) \exp\left(-\frac{t-t_0}{\tau_R}\right) a_P \exp\left(-\frac{t_1-t}{\tau_P}\right) I(t_1) dt_1 dt_0 \quad (4.29)$$

This interpretation correspond to a situation where the values taken at different time points lead to distinct protentional activities. Another interpretation is, however, that it is whole quantity I that is relevant, which leads to:

$$\int_{-\infty}^t R(t, t_0) I(t_0) dt_0 \times \int_t^{\infty} P_v(t, t_1) I(t_1) dt_1 \quad (4.30)$$

In which case, we have a causal and an anti-causal transfer function, which correspond to analyticity and non-analyticity in different complex half-plane for the transfer functions. If we consider that the product should be a sum (which would be the cumulative effect of retention and protention), then we should have singularities of an unique transfer function in both half planes.

4.7 TOWARDS HUMAN COGNITION. FROM TRAJECTORY TO SPACE : THE CONTINUITY OF THE COGNITIVE PHENOMENA

The continuity of space-time, which the mathematics of continua proposes and structures in a remarkable way, from Euclid to Cantor, follows — and does not precede — the continuity of a figure, of a contour or of a trajectory. Euclidean geometry is not a geometry of space, it is a geometry of figures, with continuous edges, constructed by means of ruler and compass and submitted to translations and to rotations. It is much later, with Descartes, that geometry finds its constitutive environment in an abstract space, underlying and independent from the figures which evolve within. The analytical reconstruction of Euclidean geometry will follow, by means of this ideal framework, an algebraico-geometrical continuum, organized in Cartesian coordinates. Then, since Cantor, we have a fantastic reconstruction of the underlying continuum, a possible one, though (see Bell (1998) for an alternative topos-theoretic approach, with no points).

Let us now try to grasp a possible constitutive path or even a cognitive foundation of this *phenomenal* continuum which is the privileged conceptual and mathematical tool for the intelligibility of space, on the basis of our analysis of retention and of protention.

The recent analysis of the primary cortex (see Petitot (2008) for a survey) highlight the role of intracortical synaptic linkages in the perceptual construction of edges and of trajectories. Neurons correlate themselves locally, along “association fields” (Field 1987; Field, Hayes & Hess 1993) composed of smooth (differentiable) curves that “are grouped together only when alignment fails along particular axes” (Field, Hayes & Hess 1993). These neurons are sensitive to “directions”: that is, they activate when detecting a direction, along a tangent. Then they (pre-)activate other neurons in the association field (they prepare in advance the spike which is not yet fired). This preactivation of associated neurons is, in our view, a component of the protensive activity. Then, neuronal activation follows a specific direction which (re-)constructs the pertinent line (Petitot 2008).

Thus, the continuity of an edge or of a trajectory is constructed by “gluing” together fragments of the world, in the precise geometrical (differential) sense of gluing. In other words, we force *by continuity* the unity of an edge by relating neurons which are pre-associated and are, locally, along particular axes.

This phenomenon participates in the retention and the protention of a *non-existing* line, a trajectory say, by “integrating”, in the mathematical sense, the tangents that are locally associated in the field. The related inertial phenomena of the activation/deactivation of neurons may be one of its constitutive elements, with inertia as a coefficient of protention. The retention of ocular movements or saccades which follow a moving body, an edge, should also be quoted: this retentive/protensive phenomenon originates in the muscles enabling the saccades or in the neurons managing them. As for the case of protention, in particular, there are protentional displacements in the receptor field of the cortical neurons that *precede* the saccades (Berthoz 2002). The brain prepares itself and anticipates a moving object, of which the movement is perceived following an ocular saccade, or of which the trajectory or

edge is perceived by running the eye along or over it. This is, in our view, the keystone of a fundamental protentional activity.

Now, we propose the following conjecture. First, the World is not continuous, nor discrete: it is what it is. Since Newton and Cantor, by continuous tools, or, now, in Quantum theories and Topos Theoretic approaches, we mathematically organized it in various ways, possibly over different “backgrounds”. In our view, the phenomenal continuity of trajectories, of an edge, is due to the *retention* of that trajectory, edge, scanned by the eye, which is “glued” with the *protention* by the very unit of the cerebral and global physiological activity (the vestibular system, for example, has its own retention and inertia).

In the case of contours, the specific saccades along the direction of movement or towards the extreme of a reconstructed segment (for example in Kanizsa triangles, see Petitot (2008)) stimulates a specific activation in the association field (a specific connection between neurons in the field).

It would then be this “gluing” — a mathematically solid concept (at the center of differential geometry, of which Riemannian geometry is a special case) — that entails the cognitive effect which *imposes* continuity upon the world: the image of the object and of its past position is reassembled (glued by the conjunction of protention and retention) with that of the object and of its expected position or a contour is made continuous even when non existing (as in Kanizsa illusions). We could indeed imagine that an animal with no fovea (the part of the eye which enables a follow up of a target by a continuous focus), a frog for example, and which takes spaced out snapshots of an object in movement would not have the impression of a continuous movement in the way in which we, the primates, “see” it.

By measuring relaxation and (pre-)activation times of associated neurons it should be possible to quantify our coefficients in these specific phenomena. Inertial coefficients in particular would yield different values according to the different protentional capacities in different species (frogs for example may have no inertia w.r. to these phenomena, if our understanding above is correct).

So the continuity of a trajectory or of an edge is, in our opinion, the result of a spatio-temporal reassembling of the retentions and protentions that are managed by global neural activity in the presence of a plurality of activities of such type (muscles, vestibular system, ... but also the differentiable continuity of the movement or gesture participates by means of its own play of retention/protention). In short, by a cognitive process of glueing, we attribute continuity to phenomena which are what they are (and which a frog surely sees quite differently). Then, by a remarkable conceptual and mathematical effort having required centuries, we have even come to theorize, as abstract lines, surfaces and their edges, first, and then even the continuity of envioning space, as the background of these structures. And this is the consequence, we believe, not the cause of the cognitive/perceptive continuity of the movement and of the gesture, which is instead grounded on the unity of protention and retention (note that, in this perspective, the continuity of an edge would also be the continuity of a movement: the movement of the saccade or of the hand caressing it, both retained and protended).

Let us note that, in our attempt towards spatialization of time for living phenomena, in this chapter and in chapter 3 (Bailly, Longo & Montévil 2011), — a spatialization which,

although schematic, should contribute to its intelligibility — we have proceeded, in this section, along the opposite approach: a sort of temporalization of space. Its apparent continuity would be the result of a cognitive activity *on* time, the extended present obtained by retention and protention.

We have seen, in the precedent chapter and in this chapter, two different, original aspects of biological time. The first is associated with rhythms, physical and internal; the second concerns the abnormal local structure of biological time.

In the following chapter, we will provide some more background on symmetries and symmetry breaking in physics, which will be a technical introduction to the subsequent chapters. In chapter 6, we will return to biology and, from the point of view of biological time, we will undertake the question of biological historicity and give a specific meaning to it. This will provide us a deeper insight on the biological general structure of determination.

Acknowledgements: We would like to thank the anonymous referee for his/her critical comments and suggestions.

Some crucial physical aspects of symmetry & symmetry breakings 5

CONTENTS

| | | |
|---------|--|-----|
| 5.1 | Introduction | 112 |
| 5.2 | Noether's theorem | 112 |
| 5.2.1 | Classical mechanics version (Lagrangian) | 113 |
| 5.2.1.1 | Variational principle | 113 |
| 5.2.1.2 | Noether's theorem | 114 |
| 5.2.2 | Field theoretic point of view | 116 |
| 5.2.3 | Conclusion | 117 |
| 5.3 | Typology of symmetry breakings | 118 |
| 5.4 | Criticality, renormalization & scale symmetry. | 120 |
| 5.4.1 | Landau theory | 121 |
| 5.4.1.1 | Statistical mechanics | 121 |
| 5.4.1.2 | Some general remarks on phase transitions | 123 |
| 5.4.1.3 | Landau theory | 124 |
| 5.4.1.4 | First approximation of the fluctuations | 126 |
| 5.4.1.5 | Ginzburg criterion | 127 |
| 5.4.2 | Some aspect of renormalization | 128 |
| 5.4.2.1 | Principle of renormalization | 130 |
| 5.4.3 | Critical slowing-down | 133 |
| 5.4.4 | Self-tuned criticality | 135 |
| 5.4.5 | Goldstone theorem | 136 |
| 5.5 | Conclusion | 138 |

ABSTRACT:

In this chapter, we present some mathematical results and approaches relevant for the role of symmetries and symmetry breaking in physics. More precisely, we provide an account of Noether's theorem, which relates invariant quantities and symmetries, here in a Lagrangian context. Then we give a short, general classification of symmetry breaking in physics. Then, we will describe some aspects of spontaneous symmetry breaking, in particular associated with criticality.

This brief overview allow us to draw some general conclusions, in particular concerning the distinctive consequences associated to continuous symmetries and discrete symmetries. We will also understand, at least partially, why symmetry breaking is associated to specific features, such as singularities, and the loss of "standard" behaviours, such as exponential relaxations.

Keywords: symmetry, invariant, symmetry breaking, criticality, fluctuations

5.1 INTRODUCTION

IN this chapter, we will review some conceptual and technical aspects of symmetries and symmetry breaking in physics. Of course, we do not aim at an exhaustive review, but we want nevertheless to provide a minimally technical account of fundamental physico-mathematical results which have global consequences in physics. As a consequence, this chapter illustrates some aspects of the discussion in chapter 6 (Longo & Montévil 2011a) and is a preparation further to develop the possible consequences of extended critical transitions. We will also provide some background on models used in other chapters, which are related to symmetry breaking.

We will not develop, here, an analysis of the foundation of physical theories, which can, for example, be found in Bailly & Longo (2006, 2011), but we will discuss, with diverse levels of details, some interesting, technical aspects relevant for our general discussion in the following chapter. This chapter is therefore not original research, but it provides some technical background on results used elsewhere in this thesis.

5.2 NOETHER'S THEOREM

Noether's theorem (Noether 1918) has been first formulated to explain why energy, which is conserved in classical mechanics, is not locally conserved in general relativity (see Byers 1999 for a historical account of the problem). In order to do so, the theorem shows a relationship between *continuous* symmetries (with a finite number of infinitesimal generators) and invariants. The relevance of this relation is far more general in theoretical physics than this particular yet fundamental situation. Indeed, this approach has been adapted to various frameworks, and, as a result, is one of the standard tools used in theoretical physics, both in order to understand the consequences of original theoretical propositions and to investigate specific phenomena.

We will first give and prove the theorem in the framework of classical Lagrangian mechanics, and then we provide this result in the (Lagrangian) field theoretic settings.

5.2.1 CLASSICAL MECHANICS VERSION (LAGRANGIAN)

We provide, here, a proof of Noether's theorem in the framework of Lagrangian mechanics. In order to start from first principles, we will as a first step derive the equations of motions from the variational principle, since this equations are used in the proof. The derivation of this equation exemplifies our discussion of the specificity of physical trajectories in chapter 6 (Longo & Montévil 2011a).

5.2.1.1 Variational principle

Let us consider a classical system, governed by its Lagrangian $\mathcal{L}(t, q_1, \dot{q}_1, \dots, q_n, \dot{q}_n)$, where $\dot{q}_i = \frac{dq_i}{dt}$. The state is then described as a $2n$ dimensional vector, we will write such a state as $\bar{q}(t)$. In order to simplify the notations, we will write in the following:

$$\mathcal{L}(t, q_1, \dot{q}_1, \dots, q_n, \dot{q}_n) = \mathcal{L}(t, q_i, \dot{q}_i)$$

The variational principle, also called Hamilton's principle, states that the trajectory between two points in phase space is stationary with respect to the *action*:

$$\mathcal{S} = \int_{t_1}^{t_2} \mathcal{L}(t, q_i(t), \dot{q}_i(t)) dt \quad (5.1)$$

We can then derive the *Euler-Lagrange equations*, which are the equations of motion in a Lagrangian point of view. Let us consider a stationary trajectory in phase space $\bar{q}(t)$ and a small perturbation $\bar{\varepsilon}(t)$, with $\bar{\varepsilon}(t_1) = \bar{\varepsilon}(t_2) = 0$. We then have a corresponding change of the action:

$$\delta\mathcal{S} = \int_{t_1}^{t_2} \mathcal{L}(t, q_i(t) + \varepsilon_i(t), \dot{q}_i(t) + \dot{\varepsilon}_i(t)) - \mathcal{L}(t, q_i(t), \dot{q}_i(t)) dt \quad (5.2)$$

We will use from here on the Einstein summation convention, meaning that silent indexes that appear twice, one in an up position and one in a down position implies a summation over all possible values. Here, the concerned index is α which is thus associated to an implicit sum. The above gives at the first order:

$$\simeq \int_{t_1}^{t_2} \varepsilon_\alpha(t) \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial q_\alpha}(t) + \dot{\varepsilon}_\alpha(t) \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial \dot{q}_\alpha}(t) dt \quad (5.3)$$

With a partial integration, we obtain:

$$= \left[\varepsilon_\alpha(t) \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial \dot{q}_\alpha}(t) \right]_{t_1}^{t_2} + \int_{t_1}^{t_2} \varepsilon_\alpha(t) \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial q_\alpha}(t) - \varepsilon_\alpha(t) \frac{d}{dt} \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial \dot{q}_\alpha}(t) dt \quad (5.4)$$

On one side, the first term is null because $\bar{\varepsilon}(t_1) = \bar{\varepsilon}(t_2) = 0$, by definition. On the other side, $\delta\mathcal{S} = 0$ at the first order because $\bar{q}(t)$ is a stationary point of the Lagrangian. As a result, we obtain for every $\bar{\varepsilon}(t)$

$$0 = \int_{t_1}^{t_2} \varepsilon_\alpha(t) \frac{\partial \mathcal{L}(q_i, \dot{q}_i)}{\partial q_\alpha}(t) - \varepsilon_\alpha(t) \frac{d}{dt} \frac{\partial \mathcal{L}(q_i, \dot{q}_i)}{\partial \dot{q}_\alpha}(t) dt \quad (5.5)$$

And the latter proves the *Euler-Lagrange equations*:

$$0 = \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial q_\alpha} - \frac{d}{dt} \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial \dot{q}_\alpha} \quad (5.6)$$

This equations corresponds to the fundamental principle of dynamics with the momenta $p_\alpha = \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial \dot{q}_\alpha}(t)$ and the forces $F_\alpha = \frac{\partial \mathcal{L}(t, q_i, \dot{q}_i)}{\partial q_\alpha}(t)$.

This short derivation shows that the Lagrangian formalism is equivalent to the Newtonian point of view. Another classical and powerful point of view is Hamiltonian mechanics. These different formalisms have different efficiency, depending on the problem considered.

5.2.1.2 Noether's theorem

We will formulate Noether's theorem in this context and prove it.

5.1 THEOREM (NOETHER, CLASSICAL LAGRANGIAN MECHANICS) :

For the above Lagrangian, let us suppose that \mathcal{S} is preserved under the action of a one parameter continuous group \mathfrak{G} with infinitesimal generator¹ $v = \tau \frac{\partial}{\partial t} + \varphi_\alpha \frac{\partial}{\partial q_\alpha} + \psi_\alpha \frac{\partial}{\partial \dot{q}_\alpha}$. Then, the quantity:

$$C = \tau \mathcal{L} + \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} (\varphi_\alpha - \dot{q}_\alpha \tau) \quad (5.7)$$

is an invariant of the dynamic (meaning a quantity with a null derivative with respect to time). \diamond

PROOF : In order to show that this quantity is conserved, we will consider its time derivative which we will prove to be 0.

EFFECT OF THE TRANSFORMATION Let us consider $g \in \mathfrak{G}$, we will note for every variable $g.x = \tilde{x}$.

$$\tilde{\mathcal{S}} = \int_{\tilde{t}_1}^{\tilde{t}_2} \mathcal{L}(\tilde{t}, \tilde{q}_i, \dot{\tilde{q}}_i) d\tilde{t} = \int_{t_1}^{t_2} \mathcal{L}(\tilde{t}, \tilde{q}_i, \dot{\tilde{q}}_i) \frac{d\tilde{t}}{dt} dt \quad (5.8)$$

Since, by hypothesis, the action is conserved, we have:

$$\tilde{\mathcal{S}} = \mathcal{S} \quad (5.9)$$

$$\int_{t_1}^{t_2} \mathcal{L}(\tilde{t}, \tilde{q}_i, \dot{\tilde{q}}_i) \frac{d\tilde{t}}{dt} dt = \int_{t_1}^{t_2} \mathcal{L}(t, q_i(t), \dot{q}_i(t)) dt \quad (5.10)$$

This equation is true for all t_1 and t_2 so:

$$\mathcal{L}(\tilde{t}, \tilde{q}_i, \dot{\tilde{q}}_i) \frac{d\tilde{t}}{dt} = \mathcal{L}(t, q_i(t), \dot{q}_i(t)) \quad (5.11)$$

¹We cannot choose freely all the parameters of the generator, more precisely we will show in the proof that the ψ parameters is determined by the others (for example).

Thus, at first order:

$$0 = \tau \frac{\partial \mathcal{L}}{\partial t} + \varphi_\alpha \frac{\partial \mathcal{L}}{\partial q_\alpha} + \psi_\alpha \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} + \mathcal{L} \frac{d\tau}{dt} \quad (5.12)$$

Notice that the last term is due to the changed scope of integration, the other terms come from the variation of the Lagrangian generated by the transformation.

RELATION BETWEEN THE PARAMETERS OF THE GROUP. At first order in ε , the following relation holds:

$$\dot{q}_\alpha(\tilde{t}) - \dot{q}_\alpha(t) = \psi_\alpha \varepsilon \quad (5.13)$$

$$= \frac{d}{d\tilde{t}} (q_\alpha(\tilde{t} - \varepsilon\tau) + \varepsilon\varphi_\alpha) - \frac{d}{dt} q_\alpha(t) \quad (5.14)$$

$$= \varepsilon \left(\frac{d\varphi_\alpha}{dt} - \frac{d\tau}{dt} \dot{q}_\alpha(t) \right) \quad (5.15)$$

This leads to:

$$\psi_\alpha = \frac{d\varphi_\alpha}{dt} - \frac{d\tau}{dt} \dot{q}_\alpha(t) \quad (5.16)$$

REMAINING OF THE PROOF Let us start from equation 5.12

$$0 = \tau \frac{\partial \mathcal{L}}{\partial t} + \varphi_\alpha \frac{\partial \mathcal{L}}{\partial q_\alpha} + \psi_\alpha \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} + \mathcal{L} \frac{d\tau}{dt} \quad (5.17)$$

$$= \frac{d}{dt} (\tau \mathcal{L}) - \tau \dot{q}_\alpha \frac{\partial \mathcal{L}}{\partial q_\alpha} - \tau \ddot{q}_\alpha \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} + \varphi_\alpha \frac{\partial \mathcal{L}}{\partial q_\alpha} + \psi_\alpha \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \quad (5.18)$$

We use equation 5.16

$$= \frac{d}{dt} (\tau \mathcal{L}) - \tau \dot{q}_\alpha \frac{\partial \mathcal{L}}{\partial q_\alpha} - \tau \ddot{q}_\alpha \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} + \varphi_\alpha \frac{\partial \mathcal{L}}{\partial q_\alpha} + \left(\frac{d\varphi_\alpha}{dt} - \frac{d\tau}{dt} \dot{q}_\alpha(t) \right) \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \quad (5.19)$$

$$= \frac{d}{dt} (\tau \mathcal{L}) + \frac{\partial \mathcal{L}}{\partial q_\alpha} (\varphi_\alpha - \tau \dot{q}_\alpha) + \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \frac{d}{dt} (\varphi_\alpha - \tau \dot{q}_\alpha) \quad (5.20)$$

We remark that:

$$\frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} (\varphi_\alpha - \tau \dot{q}_\alpha) \right) = \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \frac{d}{dt} (\varphi_\alpha - \tau \dot{q}_\alpha) + \frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) (\varphi_\alpha - \tau \dot{q}_\alpha) \quad (5.21)$$

$$\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \frac{d}{dt} (\varphi_\alpha - \tau \dot{q}_\alpha) = \frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} (\varphi_\alpha - \tau \dot{q}_\alpha) \right) - \frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) (\varphi_\alpha - \tau \dot{q}_\alpha) \quad (5.22)$$

We thus obtain, combining equations 5.20 and 5.22:

$$0 = \frac{d}{dt} (\tau \mathcal{L}) + \frac{\partial \mathcal{L}}{\partial q_\alpha} (\varphi_\alpha - \tau \dot{q}_\alpha) + \frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} (\varphi_\alpha - \tau \dot{q}_\alpha) \right) - \frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) (\varphi_\alpha - \tau \dot{q}_\alpha) \quad (5.23)$$

$$= \left(\frac{\partial \mathcal{L}}{\partial q_\alpha} - \frac{d}{dt} \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) (\varphi_\alpha - \tau \dot{q}_\alpha) + \frac{d}{dt} (\tau \mathcal{L}) + \frac{d}{dt} \left(\frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} (\varphi_\alpha - \tau \dot{q}_\alpha) \right) \quad (5.24)$$

We recognize the Euler-Lagrange equations (5.6) in the first term, which is thus null, so

$$0 = \frac{d}{dt}(\tau\mathcal{L}) + \frac{d}{dt}\left(\frac{\partial\mathcal{L}}{\partial\dot{q}_\alpha}(\varphi_\alpha - \tau\dot{q}_\alpha)\right) = \frac{dC}{dt} \quad (5.25)$$

Thus C is an invariant of the dynamic. ■

5.1.1 EXAMPLE (SPACE TRANSLATIONS) We consider space translations along vector u : $x \mapsto x + \varepsilon u$. For now, we have left the spacial structure of the system implicit (it was handled by the possible structure of the Lagrangian). To show the effect of space translations, we will assume that space has 3 dimensions and that the coordinates are ordered in the following way: q_1, q_2, q_3 are the three coordinates of a material point, then q_4, q_5, q_6 is the coordinate of a second point, etc. We will then write ji ($j = 1, 2$ or 3) the various coordinates that correspond to the j direction. Reciprocally, for any coordinate α , the corresponding direction is $j = \alpha[i]$ (α modulo i)

The generator of the group is then $v = 0\frac{\partial}{\partial t} + u_{\alpha[3]}\frac{\partial}{\partial q_\alpha} + 0\frac{\partial}{\partial \dot{q}_\alpha}$. Applying Noether's theorem, we get the following conserved quantity:

$$C = 0\mathcal{L} + \frac{\partial\mathcal{L}}{\partial\dot{q}_\alpha}(u_{\alpha[3]} - \dot{q}_\alpha 0) = u_{\alpha[3]}p_\alpha \quad (5.26)$$

Thus, the symmetry of space translations along vector u lead to the conservation of the momentum in the u direction.

Then, it is straightforward, by taking a basis of \mathbb{R}^3 , that the invariance of the Lagrangian by space translations leads to the conservation of momenta. *

5.1.2 EXAMPLE (TIME TRANSLATION) We consider time translations $t \mapsto t + \varepsilon$. The generator is then $v = 1\frac{\partial}{\partial t} + 0\frac{\partial}{\partial q_\alpha} + 0\frac{\partial}{\partial \dot{q}_\alpha}$. Applying Noether's theorem, we get the following conserved quantity:

$$C = 1\mathcal{L} + \frac{\partial\mathcal{L}}{\partial\dot{q}_\alpha}(0 - \dot{q}_\alpha 1) = \mathcal{L} - \dot{q}_\alpha\frac{\partial\mathcal{L}}{\partial\dot{q}_\alpha} = -\mathcal{H} \quad (5.27)$$

Thus, the symmetry by time translations lead to the conservation of energy². *

5.2.2 FIELD THEORETIC POINT OF VIEW

We will consider now a relativistic field theoretic version. The interesting aspects involved is the notion of *current* that the theorem allows to define and the shift to a space-time point of view instead of the specific role played by time in the classical point of view. See for example for a general introduction to field theories Altland & Simons (2006).

²Let us recall that, if the energy of a system is $\mathcal{H} = \frac{1}{2}p_\alpha\dot{q}_\alpha + V(q_i)$ then the Lagrangian is $\mathcal{L} = \frac{1}{2}p_\alpha\dot{q}_\alpha - V(q_i)$

5.2 THEOREM (NOETHER, FIELD THEORY) :

For continuous and differentiable fields Φ_i on space-time (whose coordinates are noted X^μ , $\mu = 0, \dots, 3$) consider the action:

$$\mathcal{S} = \int_{\Omega} \mathcal{L} \left(\Phi_i, \frac{\partial \Phi_i}{\partial X_\mu}, X^\mu \right) d^4 X \quad (5.28)$$

Let us suppose that \mathcal{S} is preserved under the action of a continuous group \mathfrak{G} with a finite number of parameters (index by r). Let us note its infinitesimal generators³ as $v = x_{\mu,r} \frac{\partial}{\partial X_\mu} + \varphi_{\alpha,r} \frac{\partial}{\partial \Phi_\alpha} + \psi_{\alpha,\mu,r} \frac{\partial}{\partial \left(\frac{\partial \Phi_\alpha}{\partial X_\mu} \right)}$. Then, we define the Noether current densities:

$$j_{\mu,r} = - \frac{\partial \mathcal{L}}{\partial \left(\frac{\partial \Phi_\beta}{\partial X_\mu} \right)} \varphi_{\alpha,r} + \left[\frac{\partial \mathcal{L}}{\partial \left(\frac{\partial \Phi_\alpha}{\partial X_\mu} \right)} \frac{\partial \Phi_\alpha}{\partial X_\nu} - \mathcal{L} \delta_{\mu,\nu} \right] x_{\nu,r} \quad (5.29)$$

(where $\delta_{\mu,\nu}$ is the Kronecker symbol: 1 iff its parameter are equal, else 0). This currents verify:

$$\text{Div } j_r = \frac{\partial j_{\mu,r}}{\partial X_\mu} = 0 \quad (5.30)$$

This equality means, through the Gauss–Ostrogradsky theorem⁴, that the quantity associated to j_r (its integral over a space-time volume Ω) equals its flow through the boundaries of Ω . As a result, the currents can be seen as currents of quantities, called charge, which are conserved⁵. \diamond

5.2.1 REMARK : Here we have considered a 4-dimensional space-time, but this choice is mathematically arbitrary and only motivated by the usual physical applications. *

5.2.2 REMARK : Noether's theorem, in its classical mechanics version, is a special case of this field version. Indeed, if we consider spacial coordinates as a 3-dimensional field over a 1-dimensional space-time (only a time dimension), then we fall back to the version provided by Lagrangian mechanics. *

5.2.3 CONCLUSION

There is a couple of remarks that we can make now. First the continuity of the group under consideration is crucial. Indeed, it is this continuity that allows to preserve, infinitesimal step by infinitesimal step, the conserved quantity that we obtain as a result of the theorem. Notice also that the boundary conditions are crucial in this context: it is with respect to these boundary conditions that the quantities are conserved. In the Lagrangian classical mechanics, this corresponds typically to the initial conditions.

³As in the classical case, the ψ parameters are defined by the other parameters.

⁴This theorem, also known as divergence theorem, states that for sufficiently regular volume and field the integral of the field on the volume is equal to its fluxes across the boundaries. Intuitively: Sources – Sink = fluxes in – fluxes out. As a result, a null divergence leads to: fluxes in = fluxes out.

⁵Note that the definition of Noether's current is up to a solenoidal vector field (aka, a field with null divergence).

From a theoretical perspective, the classical Lagrangian (or other formalisms) is not sufficient *per se*. The further description of the Lagrangian, besides the symmetries of space and time, is in general given by other symmetries, which are the symmetries of the fields handling the interactions. The field theoretic version allows to handle such fields (here, without quantization). The quantum field theory's analog of Noether's theorem, the Ward–Takahashi identity, shows also that quantities such as the electric charge (in quantum electrodynamics) are associated to symmetries by Noether's theorem. It is noteworthy then to understand that this approach captures an intuitive aspect of the fuzzy notion of matter (consistent with the notion of charge in the field theoretic version): the conservation property, which leads to flows of the quantities considered and is allowed by the continuity of the transformations.

Notice also that, in spite of the wide generality of Lagrangian formalism, the situation described above is associated to specific symmetries, which correspond here to the symplectic nature of the geometry of the phase space. It appears, for example, in equation 5.16 and leads to nontrivial relationships.

5.3 TYPOLOGY OF SYMMETRY BREAKINGS

We will present in this section some details on the main different types of symmetry breaking encountered in physics. We will provide a classification depending on the way in which a symmetry is broken, which is based on Holstein (2000) and precised by considerations in Strocchi (2005).

EFFECTIVE SYMMETRY BREAKING. It corresponds to a situation where the symmetry considered is, in fact, approximated and where there are relevant perturbations. As a result, in particular, the corresponding Noether charges are not exactly conserved (they have a divergence corresponding to the perturbation). A slightly different version is also called explicit symmetry breaking. It corresponds to a situation where terms are added (external fields for example), which explicitly breaks the symmetries of the Lagrangian. In both point of view, the ground state is changed because of the change of Lagrangian (or Hamiltonian) symmetries.

SPONTANEOUS SYMMETRY BREAKING (WEAK VERSION). This situation, also called degenerate ground state, occurs when a problem (typically the potential or the Hamiltonian) has a symmetry that the state cannot have, because the symmetric state does not minimize the potential, for example. The resulting state then breaks this symmetry.

A typical example of such situations is the Mexican hat potential $V(\varphi) = 2a|\varphi|^2 + |\varphi|^4$, illustrated in figure 5.1. This potential indeed has a rotational symmetry, since it only depends of the absolute value of φ . Its minimums obey the necessary condition $a|\varphi| + |\varphi|^3 = 0$, which yields $|\varphi| = 0$ or $|\varphi| = \sqrt{-a}$ when $a < 0$. As a result, when $a < 0$, the minimums correspond to the second equation, $|\varphi| = \sqrt{-a}$. In this case, all minimums are generated by the rotations of an arbitrarily chosen minimum. For example, in dimension 1 we have two states $\varphi_0 = \sqrt{-a}$ and $\varphi_0 = -\sqrt{-a}$; in dimension

2, we obtain a circle of radius $\sqrt{-a}$, as illustrated in figure 5.1; in dimension 3, we obtain a sphere; ...

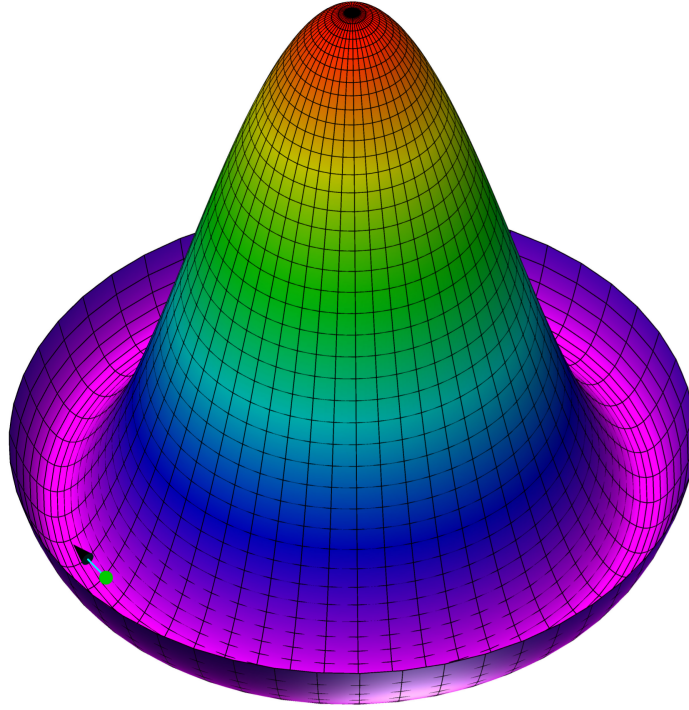


Figure 5.1: *Mexican hat and (weak) spontaneous symmetry breaking.* The Mexican hat potential is a classic example of a spontaneous breaking of a continuous symmetry. The potential has a rotational symmetry; however, its minimum is not at the center but at a distance, thus on a circle because of the rotational symmetry. As result, minimizing the potential leads to breaking the symmetry (green point), but energetically free fluctuations can occur (cyan arrow). In particular, if the system is subject to additive Gaussian noise and has also some dissipation, then the system will follow an additive Gaussian Brownian motion along the symmetric circle.

SPONTANEOUS SYMMETRY BREAKING (STRONG VERSION). In Strocchi (2005), a sharp distinction is made between two kinds of spontaneous symmetry breaking, in the above sense. Indeed, depending on the situation, the different states corresponding to a broken symmetry can be *physically* changed into each other or not. The latter case will be qualified as a (strong) spontaneous symmetry breaking. This case is obtained in particular when there are an infinite number of degrees of freedom. In this context, the breaking of the symmetry can lead to different behaviours, which live in different domains of the phase space. These domains are formalized as Hilbert space sectors in Strocchi (2005), which are in particular stable with respect to the time evolution.

The line of reasoning behind this notion is that of physically possible transformations are essentially localized so that different configuration at infinity cannot be physically

interchanged. They can, however, be unstable with respect to symmetry transformations (which can be a symmetry of the Hamiltonian), which is then spontaneously broken. In particular this situation leads to an alternative version of Noether theorem, where the continuous group involved has to be a symmetry of a given sector (if it is not the case, the symmetry cannot generate the conserved quantity). We will briefly discuss it below in terms of ergodicity breaking associated a symmetry breaking phase transition.

ANOMALOUS SYMMETRY BREAKING This case corresponds, in the framework of quantum field theory, to a situation where there is a symmetry of the classical action that the quantum field does not manage to maintain after any regularization. Depending on the nature of the symmetry considered, it can be theoretically acceptable (chiral anomaly for example) or not (gauge anomaly). More generally, the terminology is used when breaking a symmetry but making this breaking (for example, the order parameter) tend toward zero does not lead again to the symmetric situation. In other word, situations when tending to the limit is not the same than at the limit, the latter is then not continuous.

In the following, we will focus on spontaneous symmetry breaking.

5.4 CRITICALITY, RENORMALIZATION & SCALE SYMMETRY.

In this section, we will approach criticality in association with spontaneous symmetry breaking. In this case, we have a group of transformations G , which is a symmetry of the first situation, the disordered situation, and not of the second, the ordered one. Here, order precisely means that a specific direction has been “chosen” with respect to this symmetry. The symmetry of the second is restricted to a subgroup G_2 of G_1 . In general, then, defining the macroscopic state requires the introduction of a supplementary variable, called the order parameter, and which defines the strength and direction of the symmetry breaking. This parameter thus uniformly takes the value 0 in the disordered phase and is different of 0 in the ordered phase.

For example, we can consider an Ising spin lattice, in which case the field value of each element of the lattice, Φ_i , can either be 1 or -1 . We assume that the Hamiltonian is symmetric by the *global* permutation of these two directions (namely by the transformation g , with $g(1) = -1$ and $g(-1) = 1$). Physically, this assumption also means that this two signs, at least at this scale, are arbitrary labels (the resulting algebraic structure, however, is not arbitrary). Thus, if the system is disordered, it has in particular the symmetry group⁶ $\mathcal{O}(1)$, which corresponds to this permutation and identity. However, if this symmetry is broken for the global system, we have a macroscopic distinction between these two orientations. This distinction can be taken into account by the order parameter $\Phi = \langle \Phi_i \rangle$, the mean of the spins. When $\Phi = 0$, the symmetry is macroscopically respected. However, when $\Phi \neq 0$, Φ is either positive or negative, and the symmetry is broken by the state of the system, and replaced by the trivial subgroup only containing the identity $\{1\}$.

⁶ $\mathcal{O}(n)$ is the group of symmetry of the sphere in dimension n .

In this case, we have considered a discrete symmetry. The simplest extension to a continuous symmetry is the $\mathbb{O}(2)$ symmetry, which leads to an order parameter that can be written in the form $\rho e^{i\theta}$. In this case, the Hamiltonian does not depend on a global multiplication by a phase factor $e^{i\theta}$. In general, the cases of $\mathbb{O}(n)$ symmetries are especially widely studied. Their breaking corresponds to the usual “choice” of an oriented direction in an n dimensional real space, and correspond, for example, to the magnetization of magnets. We can, however, easily provide alternative examples. The liquid crystals in LCD screens are nematic, which leads to the determination of a direction but not of an orientation (a direction but no poles).

5.4.1 LANDAU THEORY

Landau theory is a remarkably straightforward approach of second order phase transitions that allows nevertheless to provide information on the basic properties of such situations. In particular, Landau theory allows a first account of the relation between symmetry breaking and phase transitions and gives a first account, valid only in certain cases, of the singular behaviour at the critical point.

5.4.1.1 *Statistical mechanics*

We will first recall basic aspects of statistical mechanics. The point here is mainly to show the general relation between fluctuations, on the one side, and susceptibilities and heat capacities on the other side.

The key function that governs a systems behaviour is the partition function (see for example Sethna 2006):

$$Z = \sum_{s \in \text{states}} \exp(-\beta E_s) \quad (5.31)$$

where E_s is the energy of the state s , and β is the inverse of the temperature: $\beta = \frac{1}{k_b T}$. The probability to obtain a state s is then:

$$P(s) = \frac{\exp(-\beta E_s)}{Z} \quad (5.32)$$

The theoretical crucial point, here, is that the states with the same energy have the same probabilities (they are symmetric from a statistical perspective). This is usually justified by an assumption of ergodicity of the microscopic trajectories. As a result, statistical mechanics is related to the geometry of the phase space in high dimensions.

Notice that, here, the temperature just “tunes” the impact of energy on the probabilities distribution. At ∞ temperature ($\beta = 0$), all states have the same probability which amounts to ignore the consequences of the energy of the different states. On the contrary, when tending to 0 temperature ($\beta \rightarrow \infty$), only the minimum energy states are possible (the probability of the other states vanish), so that energy directly determines the possible states. At and near 0 temperature (but not exclusively), other approaches are needed because fluctuations in energy are engendered by quantum uncertainty; this leads to quantum phase transitions, which are an extraordinarily active and promising research field. We will not describe them here, see for example Belitz, Kirkpatrick & Vojta (2005).

The equivalent to the usual thermodynamic functions are then obtained straightforwardly as follows. We provide, here, the *extensive* version of these quantities; however, at the thermodynamic limit, it is their intensive version that are actually relevant. They can be obtained by dividing the results by n , the number of elementary objects or in an experimentally more practical way, by V the volume or a mass m .

ENERGY. The mean energy is obtained as follows:

$$-\frac{\partial \ln Z}{\partial \beta} = -\frac{\partial Z}{\partial \beta} \frac{1}{Z} \quad (5.33)$$

$$= -\sum_{s \in \text{states}} -E_s \exp(-\beta E_s) \frac{1}{Z} \quad (5.34)$$

$$= \sum_{s \in \text{states}} P(s) E_s \quad (5.35)$$

$$= \langle E \rangle \quad (5.36)$$

ENERGY FLUCTUATIONS. A similar reasoning leads to:

$$\langle (\Delta E)^2 \rangle = \langle (E - \langle E \rangle)^2 \rangle = -\frac{\partial^2 \ln Z}{\partial \beta^2} \quad (5.37)$$

HEAT CAPACITY. Heat capacity is the energy needed to increase the temperature of the system.

$$C = \frac{\partial \langle E \rangle}{\partial T} = \frac{1}{k_B T^2} \langle (\Delta E)^2 \rangle \quad (5.38)$$

This relation is particularly interesting; it relates the heat capacity to the energy fluctuations.

HELMOLTZ FREE ENERGY.

$$\mathcal{F} = -\frac{\ln Z}{\beta} (= \langle E \rangle - TS) \quad (5.39)$$

ENTROPY.

$$S = -\frac{\partial \mathcal{F}}{\partial T} \quad (5.40)$$

If one introduces another parameter B (which can be a vector), for example associated to an external field, then a similar reasoning allows to define the corresponding susceptibility. This can be introduced by $E_s = -\sum_i B \cdot \Phi_{s,i} + E'_s$.

MAGNETIZATION. We consider the magnetization along the u direction of the field ($u \cdot B$ denotes the scalar product along direction u); the reasoning is then the same than the one for the mean energy:

$$\langle \Phi \cdot u \rangle (\beta, B) = -\frac{\partial \mathcal{F}}{\partial (B \cdot u)} \quad (5.41)$$

SUSCEPTIBILITY. The susceptibility corresponds to the ability of an external field to change the internal field of the object.

$$\chi_i(\beta) = \frac{\partial \langle \Phi \cdot u \rangle}{\partial (B \cdot u)} = - \frac{\partial^2 \mathcal{F}}{\partial (B \cdot u)^2} \quad (5.42)$$

FIELD FLUCTUATIONS. In this case we will detail the calculus which relates the susceptibility to the fluctuations.

$$- \frac{\partial^2 \mathcal{F}}{\partial (B \cdot u)^2} = \frac{1}{\beta} \sum_{s \in \text{states}} \beta \sum_i u \cdot \Phi_{s,i} \frac{\partial \exp(-\beta(E_s - \sum_i B \cdot \Phi_{s,i}))/Z}{\partial (B \cdot u)} \quad (5.43)$$

$$= \sum_{s \in \text{states}} \beta \left(\sum_i u \cdot \Phi_{s,i} \right)^2 \frac{\exp(-\beta(E_s - \sum_i B \cdot \Phi_{s,i}))}{Z} \quad (5.44)$$

$$- \sum_{r, s \in \text{states}} \beta \left(\sum_i u \cdot \Phi_{s,i} \right) \left(\sum_i u \cdot \Phi_{r,i} \right) \frac{\exp(-\beta(E_s - \sum_i B \cdot \Phi_{s,i} + E_r - \sum_i B \cdot \Phi_{r,i}))}{Z^2} \quad (5.45)$$

$$= \beta \sum_{s \in \text{states}} \left(\sum_i u \cdot \Phi_{s,i} \right)^2 P(s) - \sum_{s \in \text{states}} \sum_{r \in \text{states}} \left(\sum_i u \cdot \Phi_{s,i} \right) P(s) \left(\sum_i u \cdot \Phi_{r,i} \right) P(r) \quad (5.46)$$

$$= \beta \left\langle \left(\sum_i u \cdot \Phi_{s,i} \right)^2 \right\rangle - \beta \left\langle \sum_i u \cdot \Phi_{s,i} \right\rangle^2 \quad (5.47)$$

$$\chi_u(\beta, B) = \beta \left\langle \left(\Delta \sum_i u \cdot \Phi_{s,i} \right)^2 \right\rangle \quad (5.48)$$

5.4.1.2 Some general remarks on phase transitions

A very classical example for the study of phase transition is the Ising model, which is described by the Hamiltonian:

$$E_s = \sum_{i < j} 2J_{ij} \varphi_i \varphi_j + \sum B_j \varphi_j \quad (5.49)$$

where $\Phi = \pm 1$. Simulations of this model with coupling constant of 1 for neighbours in 2 dimension are given in figure 5.2. This model is particularly important because exact solutions are known in dimension 1 and 2 (without external field).

It is straightforward that the partition function is *analytic* when there is a finite number of spin, in the Ising model. More generally, this result also holds directly, even when an infinite number of states, with a finite number of elementary objects, is generated by a symmetry of the Hamiltonian. The general point is then that finite-size systems have analytic partition function, and thus all the above (pre-)thermodynamic functions are analytic (the only “dangerous” operation is the application of the logarithm, but it is applied on a finite sum of exponentials with the same positive coefficient). By contrast, the order parameter, typically one of the $\Phi \cdot u$, has a non-analytic behaviour, since it is not the zero function (it is

different from 0 in the ordered phase), and has non-isolated zero (the whole ordered phase). As a result, *no phase transition occurs in finite-size systems, and the transition occurs only at the thermodynamic limit*⁷.

In general, the partition function (and all thermodynamic functions) are analytic except at the critical point. When prolonged to the whole complex plane (complex temperatures), the non-analyticity propagates to a set of non-isolated, dense zeros, which touches the real line at the critical point. This structure is a vertical line for isotropic Ising model (Lee-Yang approach), but can be far more complex in the case of anisotropic magnets (van Saarloos & Kurtze 1984). This point of view can be used to characterize finite-size phase transition (in the isotropic case), by the density of complex zeros.

Another crucial aspect is that a spontaneous symmetry breaking, in this context, leads to an *ergodicity breaking*. Indeed, without entering in many details, Boltzmann approach to entropy states that the most probable states are those that have a maximum entropy (with given constraints); however, the symmetry breaking confines the system in a given direction of the order parameter, whilst other states are symmetric in particular with respect to their entropy (following the above description). This confinement of the microscopic phase space is precisely the situation that we called strong symmetry breaking, and that is described by Strocchi (2005). The description in terms of ergodicity breaking means that the mean time evolution (which follows a given breaking of the symmetry) is not equivalent to the mean on the phase space (which do not follow it).

5.4.1.3 Landau theory

Landau theory allows to straightforwardly approach phase transitions, from their thermodynamic description. This approach is based on an almost self-contradictory point of view, since it assumes that a limited development makes sense whilst the considered function is typically non-analytic at the critical point. We will further discuss this question bellow. Another limitation is analyzed in Sen (2010), which tries to distinguish the situation where this approach can be used even as a heuristic and when it cannot, depending on the properties of the symmetry breaking.

We will suppose that the system depends only of the temperature T and the external field B . We will first assume that $B = 0$. We will also suppose that the thermodynamic functions are symmetric with respect to the change of sign of Φ , so that the thermodynamic potential verifies $\mathcal{F}(-\Phi) = \mathcal{F}(\Phi)$ ($\mathbb{C}(1)$ symmetry). In the following, all quantities are considered intensive. Considering this symmetry, the limited expansion in Φ , near $\Phi = 0$, of the thermodynamic potential only has even terms (the odd terms would break the symmetry):

$$\mathcal{F} = \mathcal{F}_0 + \frac{1}{2}a_T t \Phi^2 + \frac{1}{4}c_T \Phi^4 \quad a_T = a \quad t = \frac{T - T_c}{T_c} \quad c_T = c > 0 \quad (5.50)$$

The equilibrium state Φ_0 of the system minimize the thermodynamic potential \mathcal{F} , we consider then:

⁷At least in the usual sense. For finite-size systems, which are practically relatively small size system for this limitation to be relevant, other definitions can be used. This field is an active research topic

$$\left(\frac{\partial \mathcal{F}}{\partial \Phi}\right)_{\Phi_0} = at\Phi_0 + c\Phi_0^3 = 0 \quad (5.51)$$

This yields:

$$\Phi_0 = \pm \sqrt{\frac{a}{c}}(-t)^{1/2} \quad T < T_c \quad (5.52)$$

$$\Phi_0 = 0 \quad T > T_c \quad (5.53)$$

We will now consider that an external field can be present, which will allow us to compute the zero field susceptibility, and therefore the fluctuations of the order parameter.

$$\mathcal{F} = \mathcal{F}_0 - B\Phi + \frac{1}{2}at\Phi^2 + \frac{1}{4}c\Phi^4 \quad (5.54)$$

Thus we have at equilibrium:

$$\left(\frac{\partial \mathcal{F}}{\partial \Phi}\right)_{\Phi_0} = -B + at\Phi_0 + c\Phi_0^3 = 0 \quad (5.55)$$

We differentiate this equality with respect to B at zero external field.

$$0 = -1 + at\frac{\partial \Phi_0}{\partial B} + 3c\frac{\partial \Phi_0}{\partial B}\Phi_0^2 \quad (5.56)$$

$$\frac{\partial \Phi_0}{\partial B} = \frac{1}{at + 3c\Phi_0^2} \quad (5.57)$$

This leads to:

$$\chi(T, 0) = \beta \langle \Phi^2 \rangle - \beta \langle \Phi \rangle^2 = \frac{1}{2a}(-t)^{-1} \quad T < T_c \\ \frac{1}{a}(t)^{-1} \quad T > T_c \quad (5.58)$$

Thus, the susceptibility and the fluctuations diverge when we are getting closer to the critical point.

These results, the divergence of the derivative of the order parameter and of the fluctuations, are at odd with the hypotheses of regularity that we assumed in order to perform the limited expansion, at the first step of this model. Physically, this corresponds also to the issue of only approaching the system by its macroscopic properties, namely by the macroscopic value of the order parameter. Moreover, it is also not obvious that the dependencies on T of the different functions, in particular \mathcal{F}_0 , are regular (because of the fluctuations at the critical point).

This approach is related to the microscopic description by the mean field theory, which simply consists in considering that the interaction of one element with a second one, say Φ_i can be considered as an interaction with the mean value of this quantity $\langle \Phi_i \rangle$. This

approach, by elementary means (*in fine* a consistency equation), allows to predict possible phase transitions from the definition of the Hamiltonian, and then to show their property. However, the arguments we developed above are relevant; this approach does not allow to take the contribution of the fluctuations into account. As a result, its validity is limited and incorrect predictions occurs, such as missing phase transitions or wrong behaviour near critical points.

5.4.1.4 First approximation of the fluctuations

In order to take the fluctuations into account, we consider that Φ is a function of the position r , which is simply written $\Phi(r)$ but leads also to the consideration of a free energy density \mathcal{F}' . Then, we have by limiting ourselves to the second derivatives and by considering the symmetries of the the system:

$$\mathcal{F}' = \mathcal{F}'_0 - B(r)\Phi(r) + \frac{1}{2}a\Phi^2(r) + \frac{1}{4}c\Phi^4(r) + g\left(\frac{\partial\Phi(r)}{\partial r}\right)^2 \quad (5.59)$$

Here, we have assumed that the mixed partial derivatives are irrelevant and that the system is isotropic. Moreover, $g > 0$, so that the situation without fluctuations is favored.

As usual, we look at the derivative of the free energy with respect to Φ , which is now a function, at the equilibrium point:

$$\left(\frac{\partial\mathcal{F}'}{\partial\Phi}\right)_{\Phi_0} = -B(r) + a\Phi(r) + c\Phi^3(r) + 2g\nabla^2\Phi(r) = 0 \quad (5.60)$$

Then we differentiate it with respect to the value of the external field at another position $B(r')$. We use the generalized susceptibility $\chi_T(r, r') = \frac{\delta\Phi(r)}{\delta B(r')}$

$$-\delta(r - r') + (a + c3\Phi^2(r) + 2g\nabla^2)\chi_T(r, r') = 0 \quad (5.61)$$

The generalized susceptibility is proportional to the correlation function (the computation is similar to the one for the susceptibility and its relation with fluctuations), and we assume translational invariance so that:

$$(a + c3\Phi^2(r) + 2g\nabla^2)G(r - r') = k_bT\delta(r - r') \quad (5.62)$$

Assuming $\Phi(r) \simeq \Phi_0$, we obtain:

$$\left(\frac{1}{\xi^2(t)} - \nabla^2\right)G(r - r') = \frac{k_bT}{2g}\delta(r - r') \quad (5.63)$$

with:

$$\xi(t) = \begin{cases} \sqrt{\frac{g}{2a}}(-t)^{-1/2} & T < T_c \\ \sqrt{\frac{g}{a}}t^{-1/2} & T > T_c \end{cases} \quad (5.64)$$

We can solve the latter by Fourier transform. It leads to:

$$G(\|r\|) \propto \frac{e^{-\frac{\|r\|}{\xi(t)}}}{\|r\|^{d-2}} \quad (5.65)$$

The quantity $\xi(t)$ is thus the correlation length of the system. As expected, it diverges at the critical point. More details on this derivation can be found in Altland & Simons (2006); Schulte-Frohlinde & Kleinert (2001). Technically, this derivation is the first perturbative correction to the Landau theory. Notice, that the Φ^4 terms is not taken into account in the fluctuation (except through the equilibrium value)

5.4.1.5 Ginzburg criterion

The Ginzburg criterion tests the consistency of the Landau theory by verifying that the fluctuations determined in this framework are not strong enough to break its validity. We will follow the reasoning in Als-Nielsen & Birgeneau (1977), a more extensive discussion can be found in Schulte-Frohlinde & Kleinert (2001), both in the Landau Framework and in the renormalization framework, which allows to provide a better determination of these fluctuations.

The criterion is proposed as a domination of the value of Φ over the magnitude of the fluctuations, in an appropriate volume Ω .

$$(\delta\Phi)_{\Omega}^2 \ll \Phi_{\Omega}^2 \quad (5.66)$$

In order to assess the strength of the fluctuations, the correct volume is given by the characteristic length $\xi(t)$, so that $\Omega = \omega_{\xi}$. This region is indeed the region where the spins are correlated, so that we have a local order. We will in the following write $t = \frac{T-T_c}{T_c}$

$$(\delta\Phi)_{\Omega_{\xi}}^2 \ll \Phi_{\Omega_{\xi}}^2 \quad (5.67)$$

$$N(\Omega_{\xi(t)})\chi(t)k_bT \ll N(\Omega_{\xi})^2\Phi_0^2(t) \quad (5.68)$$

$$\chi(t)k_bT \ll N(\Omega_{\xi})\Phi_0^2(t) \quad (5.69)$$

we use d , the dimension of space

$$\chi(t)k_bT \ll \xi(t)^d\Phi_0(t)^2 \quad (5.70)$$

We use equations 5.64, 5.58 and 5.52 so that:

$$\frac{1}{ta}k_bT \ll \left(\frac{g}{a}(t)^{-1}\right)^{d/2} \frac{a}{c}(-t) \quad (5.71)$$

We are only interested by the behaviour at the critical point so for small t

$$1 \ll t^{\frac{4-d}{2}} \quad (5.72)$$

We thus observe that the criterion is met for $d > 4$ and not met for $d < 4$. $d = 4$ is thus called the critical dimension. For $d > 4$, the Landau approach is thus consistent, whilst it is inconsistent for $d < 4$. Notice that we have done important assumptions, in particular on the isotropy of the system, anisotropy can change the situation importantly (Als-Nielsen & Birgeneau 1977). We want to emphasize that the consistency of Landau theory is a limited result; on the opposite its inconsistency for $d < 4$ is a definitive answer (modulo the other hypothesis on the system).

A qualitative and heuristic approach can also be done by dimensional analysis, on the basis of equation 5.59.

$$\int \frac{1}{2}at\Phi^2(r) + \frac{1}{4}c\Phi^4(r) + g\left(\frac{\partial\Phi(r)}{\partial r}\right)^2 dr \quad (5.73)$$

To show the internal structure of this object, we divide by g

$$\int a't\Phi^2(r) + c'\Phi^4(r) + \left(\frac{\partial\Phi(r)}{\partial r}\right)^2 dr \quad (5.74)$$

We can now perform a dimensional analysis with respect to space, assuming this quantity has no spatial dimension.

$$\int \left(\frac{\partial\Phi(r)}{\partial r}\right)^2 dr \rightarrow [\Phi] = L^{\frac{2-d}{2}} \quad (5.75)$$

$$\int a't\Phi^2(r)dr \rightarrow [a't] = L^{-2} \quad (5.76)$$

$$\int c'\Phi^4(r)dr \rightarrow [c'] = L^{d-4} \quad (5.77)$$

- If we set $a't = 0$ and $c' = 0$, we have what is called a free massless field. In this case, the equation is *space-scale invariant*, in association with the exponent $\frac{2-d}{2}$.
- With $a' \neq 0$ and $c' = 0$, we have a free massive field. The above scale invariance is broken by the Φ^2 term. We get then that the characteristic length of the system is proportional to $\sqrt{\frac{1}{a't}}$, which is consistent with the result in equation 5.64. The term $a't$, however, vanishes at the critical point, and the corresponding length diverges.

Looking the system from a greater distance means that the lengths shrink. We thus see that the “mass” term a' gets larger in the process. This means simply that when we are looking at the system from a large distance, the correlations vanishes (except at the critical point).

- With $a' \neq 0$ and $c' \neq 0$, the Φ^4 term also breaks the (naive) scale invariance, when $d \neq 4$.

Using the same reasoning than above, the coupling “constant” c' gets larger when $d < 4$. Which means that it is not limited to local interactions. On the contrary, when, $d > 4$, this coupling constant vanishes at large scales, which justifies the fact that this term (and the corresponding fluctuations) can be neglected at large scales. This also means that the system does not generate more and more relevant interactions.

We understand also that, for $d < 4$, there is an instability of the behaviour of the system associated to the Φ^4 term (at the critical point), since this term grows exponentially with the scale.

As a general conclusion, we can say that the crucial point for the Ginzburg criterion is the interplay between the local terms (derivation) and global terms (integration). The latter leads to the dependency on the spatial dimension of the system.

5.4.2 SOME ASPECT OF RENORMALIZATION

In order to go beyond the Landau theory and the perturbative approach that can be used to estimate the fluctuations, an original approach is needed. This approach is called renormalization and, from a certain point of view, is a (highly) refined and quantitative version of the dimensional analysis we have just performed.

The basic idea behind renormalization is that, when more and more interactions are relevant (typically when $d < 4$ in the above case) and when the system fluctuates strongly, we can nevertheless understand its behaviour by looking how its equational description (the Hamiltonian, or the partition function, but it can also be an evolution function, over time) changes when we integrate a part of the contributions to this description. This could be seen as a reduction of the number of degree of freedom of the system, but this alone would be pointless because the number of degree of freedom is infinite. The point is then more rigorously to observe the change of the equational form, its stability, and crucially its parameters (the coupling constants typically).

Renormalization then succeeds when this operation allows to obtain an equational stability with vanishing quantities (coupling constants), which are then irrelevant, and non-vanishing quantities, which are relevant and correspond to the scaling behaviour of the system. Here, we will focus on statistical mechanics, but renormalization is also crucial in quantum field theory. In the latter, divergences occur in particular with respect to small space-scales (equivalently high energy). The conceptual question is then how can “long” range interactions be approached whilst we cannot build them (integrate them) on small length scales. Renormalization allows to answer this question by saying that the equational forms stay the same when we integrate the couplings over a larger set of scales, and we almost only need to change the coupling constants by doing so (this is of course a highly simplified discussion). Renormalizability of a quantum field theory is then crucial because its failure leads to the appearance of new parameters when we extended the scale domain of integration. The result is then that we need to know at which scale we should start (and what happens at this scale). A crucial example to this issue is quantum gravitation, which typically leads to non-renormalizable theories (Zinn-Justin 2007), and leads to an attempt to a theoretization at a fundamental scale, namely string theory. The other three fundamental interactions have, however, been formalized as renormalizable theory in the standard model.

We will now describe the principle of renormalization in the statistical mechanics context. One should notice that there are different versions of this method. Typically, the renormalization can be performed in real space or in momentum space (after a Fourier transform). Moreover, it can start from the upper critical dimension, where the mean field approximation

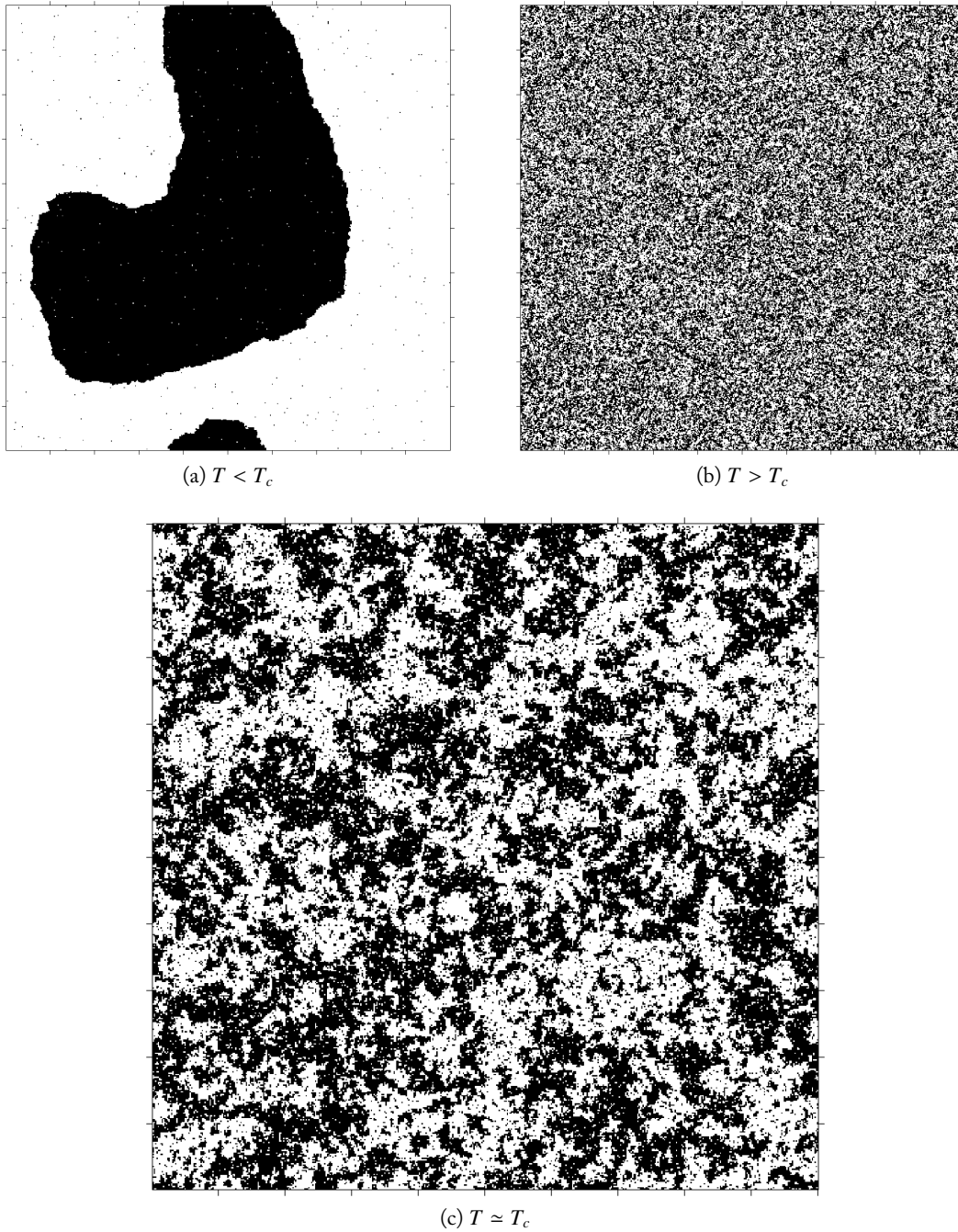


Figure 5.2: *Simulation of the Ising Model.* From a large distance, we have an homogeneous gray block for $T > T_c$. For $T < T_c$, here, the white spins dominate the system, and the system is ordered. Near the critical point, we have, for all sizes, clusters where the different signs of spin dominate, leading to a fractal distribution. The program to perform the simulations is given in annex, section A.2. Notice that the simulation near the critical point needs an important amount of iterations because the relaxation time is diverge.

is valid (4, in the situation discussed above) and approach the other dimensions $4 - \varepsilon$ as expansion over ε , or be performed more directly, in an exact way or not,

5.4.2.1 Principle of renormalization

Here, we will follow the presentation of the basic steps of the method which is given in Lesne (2003). Another general account can be found in Fisher (1998), and a more technical presentation is given in Zinn-Justin (2007), for example.

We first consider a small scale a , corresponding, for example, to the resolution of the measurement apparatus or to an estimated minimal scale of the system (when such a scale is known). This scale corresponds to the *microscopic* description of the system. We will also consider a *macroscopic* scale of observation, L . We will work on a family of models \mathcal{M} , indexed by the scale at which they describe the same physical system \mathcal{S} . These models have a subjective flavor, since they usually are highly simplified versions of the physical situation⁸, for example, in the case of the Ising model of magnets, the magnetic interactions are only local, and the states have only binary possibilities.

The scale a determines the sub-systems of \mathcal{S} that we regard as simple and, therefore, that can be described by a small number of quantities, noted s . These elementary sub-systems typically have a linear extension of magnitude a and will be modeled as points in the model \mathcal{M}_a . In this model, the state of \mathcal{S} will be described by a *configuration* $\bar{s} \equiv (s_1, \dots, s_N)$, which provides the states of all elementary components. In the example of lattice that we described above, $s_i = \Phi_i$. Typically, $N = \left(\frac{L}{a}\right)^d$ in dimension d . We can then define for a model \mathcal{M}_a :

- *The phase space* $\mathcal{E} = \{\bar{s}\}$, which is the set of possible configurations (and thus depend on a and N).
- *The evolution or structure function* describing the system (depending on the static or dynamic nature of the problem): $F(\bar{s})$. It is thus a function on \mathcal{E} , which determines the behaviour of the system (statistical weights in the static case, evolution rules in the non-equilibrium case, probability transitions, ...). $F \in \mathcal{F}$ depends on the scale. In the usual statistical mechanics framework, F is usually a partition function (and thus indirectly the Hamiltonian).

Renormalization method is based on three basic operations: a decimation, scale changes and parameter transformations. The principle of renormalization is then to iterate a correct combination of these operations. This combination is called the *transformation of renormalization*. The core idea is then to analyze the effect of this transformation and more precisely of its iterations in the space of models.

- *The decimation* is a procedure which handles the effects of a change of resolution $a \rightarrow ka$ on the configurations $\bar{s} \in \mathcal{E}$. This operation is performed by grouping the

⁸In the case of quantum field theory, the precise description at a smallest scale is not even available. It is generally thought that such a description is epistemologically necessary. However, such a description is not technically necessary, precisely because of the renormalization method which we are exposing, in the context of statistical mechanics. See, for example, Zinn-Justin (2007).

elementary constituents of scale a (*coarse-graining*) and is represented formally by a function $\bar{s}' = T_k(\bar{s})$.

This operation allows to reduce the number of degrees of freedom of the system by a factor k^d in dimension d (or equivalently, with a constant N , to increase linearly the scope of observation by a factor k). By doing this transformation, we lose all information on scales smaller than ka . Since T_k is chosen partly arbitrarily, one should try to keep as much information on the smaller scales as possible. This can be obtained by focusing on the elements that can be considered qualitatively as crucial.

- *The scale changes* do not change the minimal scales of the model, the aim of this operation is to keep the same phase space and to highlight the properties of self-similarity. In order to do so, one determines a family (usually unique) $(k, k^{\alpha_2}, \dots, k^{\alpha_n})_{k \geq 1}$, which verifies the following property: when multiplied to the parameters of the models (including the spatial scale) they lead to a nontrivial limit when $k \rightarrow \infty$.

These exponents can be chosen *a posteriori* in certain cases.

- *The effective parameters* are used to replace the former parameter in order to describe the same physical system in spite of the former transformations. We transform then F in $R_k(F)$ so that $R_k(F)$ describe the statistics or the evolution of $T_k(\bar{s})$. R_k is called the *renormalization operator* and acts on the \mathcal{F} . It is crucial here that (a part of) the structure of the interactions is taken into account in this step.

The notion of *covariance* is then essential, because it refers to the conditions on the transformations of the various aspects of the model for it to describe the same physical object. It comes into play, for instance, with respect to the consideration of the systems symmetries.

A particularly strong notion is then the notion of *invariance by renormalization*, which can be written as: $R_k(F^*) = F^*$. It corresponds, therefore, to a fixed point by renormalization, and to an exact scale invariance (asymptotically): the system has a property of *self-similarity*. This notion is compelling because of the following reasons:

- All models which converge towards the same fixed point by renormalization have the same properties for large scales. This consideration leads to the notion of *universality class*.
- The characteristic scale ξ^* , associated to a fixed point is either 0 or infinite because $k\xi^* = \xi^*$. In the first case, the fixed point corresponds to an asymptotic situation, where there is no coupling between the (sufficiently renormalized) components of the system seen at large scales. In the second case, we have a critical situation.
- In the case of a critical phenomenon, the analysis of R_k near the fixed point F^* determines the asymptotic scaling laws of the different situations which converge towards this fixed point. The critical exponents are, in particular, determined by the eigen values provided by the linearization of R_k in the neighbourhood of F^* .

The latter point leads to the notion of *class of universality*, which regroup models having the same behaviour by renormalization. This allows to distinguish among variants of a model, what changes lead to *relevant* or *irrelevant* contributions.

An elementary example is the (nearest neighbour) Ising model. We will not develop the corresponding calculation (which are not particularly difficult in dimension 1 or 2). Then, the assumption of a scale invariant law of F leads to a unique parameter $K(k)$ with $K(a) = \beta J$. Then, we obtain two degenerate fixed point: $K_0^* = 0$ and $K_1^* = \infty$. They can be interpreted straightforwardly: the first fixed point corresponds to a situation with $\beta = 0$ ($T = \infty$) and, therefore, to no coupling between the different elements of the system. On the contrary, the second fixed point corresponds to $T = 0$, and, therefore, to an ordered situation. Physically, this means that since in both cases the correlations have a limited range, corresponding to the different temperatures; the large scale equational form is not concerned with these scale limited aspects, and the situation collapses to one of these fixed points. In dimension 2, we have a critical point at a finite temperature, which separate the basin of attraction of the two aforementioned fixed points.

5.4.3 CRITICAL SLOWING-DOWN

We will illustrate the phenomenon of critical slowing-down with an elementary example, following the idea of the presentation in Scheffer et al. (2009), in the context of bifurcation theory. Let us consider a dynamical system with a pitchfork bifurcation:

$$\frac{dx}{dt} = -x(\alpha + x^2) \quad (5.78)$$

When $\alpha < 0$, the system straightforwardly has three equilibrium points: $x_0 = 0$ and $x_{\pm 1} = \pm \sqrt{-\alpha}$. Otherwise, it has only one equilibrium point: $x_0 = 0$. We can obtain the stability of the system by looking at its second derivative:

$$\frac{d^2x}{dt^2} = -\frac{dx}{dt} ((\alpha + x^2) + 2x^2) \quad (5.79)$$

Thus, at the point x_0 , we have $\frac{d^2x}{dt^2} = -\frac{dx}{dt} \alpha$; therefore, a perturbation is amplified when $\alpha < 0$ and stabilized when $\alpha > 0$. At the point x_1 , when defined, we have similarly $\frac{d^2x}{dt^2} = \frac{dx}{dt} 2\alpha$, so that x_1 is stable when $\alpha < 0$. When $\alpha > 0$ it is anyway not defined. The same analysis applies, *mutadis mutandis*, for x_{-1} . As a result, when x_0 is stable, the other points are not defined, and when they are defined $x_{\pm 1}$ are stable and x_0 is unstable.

Assuming that x_i is stable and that we are near the equilibrium, we can write $x(t) = x_i + \varepsilon(t)$ where ε remains small. In general, a linearization near the equilibrium leads to:

$$\frac{dx_i + \varepsilon}{dt} = f(x_i + \varepsilon) \quad (5.80)$$

$$\frac{d\varepsilon}{dt} = f(x_i) + \varepsilon \frac{\partial f}{\partial x}(x_i) \quad (5.81)$$

which in our example yields (we have $b - a > 0$):

$$\frac{d\varepsilon_0}{dt} = -\alpha\varepsilon_0 \quad \frac{\varepsilon_{\pm 1}}{dt} = 2\alpha\varepsilon_{\pm 1} \quad (5.82)$$

The latter equations defines exponential decreases of ε over time, characterizing a fast return to equilibrium.

When approaching the critical point, however, the characteristic times of recovery, $\frac{1}{\alpha}$ and $\frac{1}{2\alpha}$ tend to ∞ . At the bifurcation point we have:

$$\frac{dx}{dt} = -x^3 \quad (5.83)$$

So that the dynamic starting from a perturbation a at time $t = 0$ is

$$\frac{2}{x^2} - \frac{2}{a^2} = t \quad (5.84)$$

Thus, we get a relaxation of the form $t^{-1/2}$ and the return to the equilibrium follow a power law, which is slower than any exponential decrease.

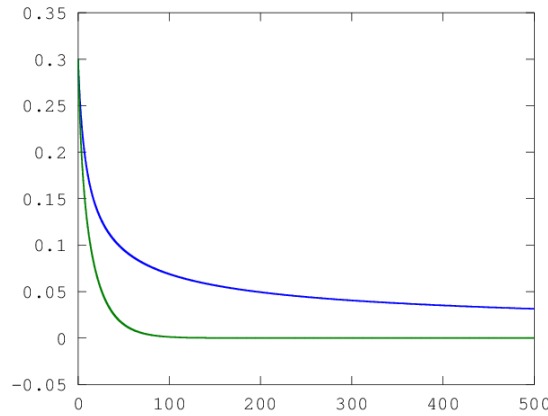


Figure 5.3: *Bifurcation and critical slowdown*. In green (bellow), the relaxation of the system discussed at a generic point. In blue (above), we represent the relaxation at the bifurcation point.

We will now consider, as an example, that this dynamical system is subject to additive noise (which leads to Langevin equation). We will show that the slowdown has dramatic consequences. We rewrite the dynamic:

$$\frac{dx}{dt} = -x(\alpha + x^2) + \zeta(t) \quad (5.85)$$

Then, we get near “normal” stable equilibrium, for $x = x_i + \varepsilon$

$$\frac{dx_i + \varepsilon}{dt} = \frac{\partial f}{\partial x}(x_i)\varepsilon + \zeta(t) \quad (5.86)$$

We write $-\frac{1}{\tau_i} = \frac{\partial f}{\partial x}(x_i)$. This yields:

$$\frac{d\varepsilon}{dt} = -\frac{1}{\tau_i}\varepsilon + \zeta(t) \quad (5.87)$$

$$\varepsilon(t) = \exp\left(-\frac{t}{\tau_i}\right) \left[\int_{-\infty}^t \zeta(t') \exp\left(\frac{t'}{\tau_i}\right) dt' \right] \quad (5.88)$$

$$\varepsilon(t) = \int_{-\infty}^t \zeta(t') \exp\left(\frac{t'-t}{\tau_i}\right) dt' \quad (5.89)$$

We assume that ζ is in fact a random process, following a white Gaussian noise distribution with standard deviation σ :

$$\varepsilon(t)^2 = \int_{-\infty}^t \int_{-\infty}^t \zeta(t') \zeta(t'') \exp\left(\frac{t'-t}{\tau_i}\right) \exp\left(\frac{t''-t}{\tau_i}\right) dt' dt'' \quad (5.90)$$

$$\langle \varepsilon(t)^2 \rangle = \int_{-\infty}^t \int_{-\infty}^t \langle \zeta(t') \zeta(t'') \rangle \exp\left(\frac{t'-t}{\tau_i}\right) \exp\left(\frac{t''-t}{\tau_i}\right) dt' dt'' \quad (5.91)$$

Our white noise assumption leads to no correlation between different time points

$$\langle \varepsilon(t)^2 \rangle = \int_{-\infty}^t \langle \zeta(t')^2 \rangle \exp\left(2\frac{t'-t}{\tau_i}\right) dt' \quad (5.92)$$

$$\langle \varepsilon(t)^2 \rangle = \tau_i \frac{\sigma^2}{2} \quad (5.93)$$

Thus, the variance of ε is proportional to τ_i . It thus therefore tends towards ∞ when $\frac{1}{\tau_i}$ tends to 0 (that is to say when the parameter tends to the bifurcation point).

Critical slowing-down is a fundamental property; it renders the convergence of straightforward Monte-Carlo simulations⁹ of critical phenomena exceedingly slow. Moreover, Scheffer et al. (2009) argue that the slow decay of the effect of perturbation can be used to detect the vicinity of a critical point in a complex system. Qualitatively, in statistical physics, this corresponds to the global determination of the system so that the relaxation involve the destabilization and restabilization at long ranges.

Notice also that self-organized criticality usually relies (implicitly) on a feedback equation, based on the value of the order parameter (Sornette, Johansen & Dornic 1995). The critical slowing-down, therefore, justifies the necessary slow input needed for criticality to be observed.

5.4.4 SELF-TUNED CRITICALITY

A situation that illustrates well the high level of sensibility of a critical system is the model of hair cells described by Camalet et al. (1999). The basic idea is that the hair bundles of this cells oscillates spontaneously because their dynamic is close to a Hopf bifurcation. This situation, however, cannot be understood as spontaneously appearing (it is a point in the parameter space) so a second dynamical system is needed which tunes the system to the bifurcation point.

⁹i.e. using pseudo randomness and the probabilities given by the partition function.

Let us consider a dynamical system $x(t)$ controlled by a parameter C . When $C > C_c$ the system has a stable fixed point, however for $C < C_c$ the system oscillates spontaneously. We are interested in the systems output with respect to a stimulus which has a frequency $\nu = \frac{\omega}{2\pi}$. Therefore, we will consider the Fourier decomposition of the output: $x(t) = \sum x_n e^{in\omega t}$. Near the Hopf bifurcation, the mode $n = \pm 1$ is prevalent. We can then write, for a stimulus $f(t) = f_1 e^{i\omega t} + f_{-1} e^{-i\omega t}$:

$$f_1 = \mathcal{A}(\omega, C)x_1 + \mathcal{B}(\omega, C)|x_1|^2 x_1 + \dots \quad (5.94)$$

where $\mathcal{A}(\omega, C)$ and $\mathcal{B}(\omega, C)$ are functions with complex values.

For $C < C_c$, the system oscillates spontaneously with an amplitude $|x_1|^2 \simeq \Delta^2 \frac{(C_c - C)}{C_c}$ where Δ is a characteristic magnitude. Moreover, we have $\mathcal{A}(\omega_c, C_c) = 0$, for $C = C_c$ and $\omega = \omega_c$, the form of the output is then:

$$|x_1| \simeq |\mathcal{B}|^{-\frac{1}{3}} |f_1|^{\frac{1}{3}} \quad (5.95)$$

The gain is then:

$$r = \frac{|x_1|}{|f_1|} \sim |f_1|^{-\frac{2}{3}} \quad (5.96)$$

The gain become then arbitrary large for small stimuli. The output has thus a linear component $\mathcal{A}(\omega, C_c) \simeq A_1(\omega - \omega_c)$, at first order. It, however, remains predominantly non-linear when the linear component remains small with respect to the cubic component.

When this situation is not verified, that is when:

$$|\omega - \omega_c| \gg |f_1|^{\frac{2}{3}} \frac{|\mathcal{B}|^{\frac{1}{3}}}{|A_1|} \quad (5.97)$$

The output has the form:

$$|x_1| \simeq \frac{|f_1|}{|(\omega - \omega_c)A_1|} \quad (5.98)$$

and the gain no longer depend of f .

A system near a Hopf bifurcation behaves thus as a highly selective filter with an important gain for weak stimuli. For stronger stimuli, the system is less selective but has also a weaker gain.

We introduce now a second equation in order to maintain C near C_c , but without an explicit dependence on the latter (because C_c depend of the critical frequencies and thus is different for different cells):

$$\frac{1}{C} \frac{\partial C}{\partial t} = \frac{1}{\tau} \left(\frac{x^2}{\delta^2} - 1 \right), \text{ where } \delta \text{ is a typical amplitude} \quad (5.99)$$

When no external force is applied, this equation leads to C_δ , where the system oscillates spontaneously with an amplitude $|x_1| \simeq \delta$. If δ is small in comparison with Δ , we are near the bifurcation since:

$$\frac{C_\delta - C_c}{C_c} \simeq \left(\frac{\delta}{\Delta} \right)^2 \quad (5.100)$$

As a result there is two kinds of responses: for short stimuli in comparison with τ , the system stays at C_δ and leads to the above discussed non-linear response. For long stimuli, it maintains $|x_1| \simeq \delta$.

5.4.5 GOLDSTONE THEOREM

Here, we will present a result that shows that a spontaneously broken continuous symmetry leads to long-range fluctuations (in the language of condensed matter physics), called Goldstone modes. In the language of particle physics, this result shows that we obtain massless particles called Goldstone bosons.

The basic idea behind this result can be explained quite simply. Let us consider a system with a continuous symmetry group G . For example, a lattice where the state of each spin is described by an angle θ_i , in which case G is the set of rotations changing all the θ_i simultaneously by the same angle. Since the transformations of G are symmetries, they do not change the energy of any part of the system. The symmetry breaking means that the state of the system does not have this symmetry (there is a privileged direction θ_b). Then, a small variation following the (former) symmetry group (an infinitesimal rotation of all the spins in our example) do not need energy at the first order, because of the corresponding symmetry of the potential. In particle physics, one say that this kind of field structure constitute a massless particle, because there is no energetic “resistance” to it (the Φ^2 term vanishes).

Such fluctuations are peculiar: they almost involve the whole system (in our example, all spins are *simultaneously* rotated) which also correspond to the lack of an Hamiltonian term which would impose a particular length (see the dimensional analysis in 5.4.1.5). Conceptually, this kind of situation describe a form of stiffness: in a fluctuation, almost all the system is transformed simultaneously and in the same way. The most practical example is the case of a crystal; the Goldstone explains its mechanical rigidity, see for instance Sethna (2006) for more illustrations.

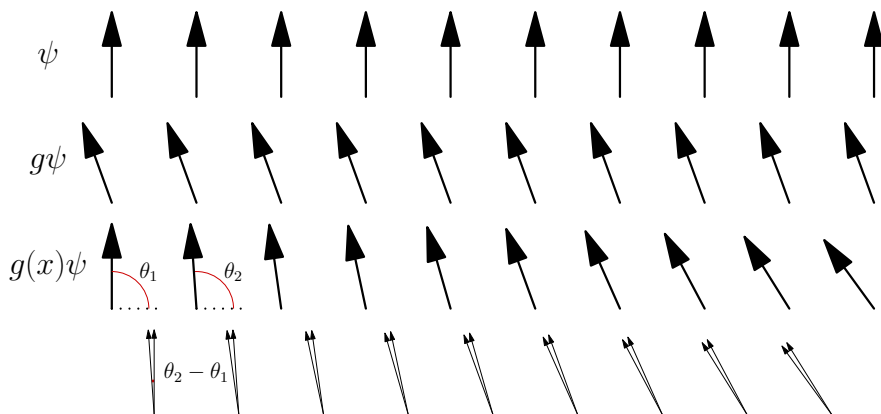


Figure 5.4: *Goldstone modes*. The states ψ and $g\psi$ are symmetric and thus have the same energy. A long-range fluctuation $g(x)\psi$ which leads to very small local angle discrepancies needs a small amount of energy. As a result, at the limit, an infinite size fluctuation cost no energy. Typical examples are the vibration of a crystal, spin waves in a magnet,

This result is somewhat more difficult than Noether theorem because it applies to situation with an infinite number of degree of freedom. Moreover the theorem has specific hypothesis, which are not met in certain physically very relevant situations.

We use the classical version given in Strocchi (2005). As discussed briefly in section 5.3, we are in a situation of strong spontaneous symmetry breaking, where a distinction should be made between different physically valid sectors of the phase space. These sectors, called Hilbert Space Sectors, are stable with respect to additive finite perturbations and the time evolution.

5.3 THEOREM :

Goldstone Let us consider G a finite continuous group of symmetries of a model. We suppose that this symmetry group is spontaneously broken to G_{Φ_0} , by a solution Φ_0 which is an absolute minimum of the potential. Let us write H_{Φ_0} the sector of this solution. Then for any infinitesimal generator v^α of G_{Φ_0} with $v^\alpha \neq 0$ we have:

- scattering configurations (behaviour for infinite time) associated to solutions in H_{Φ_0} , which are solutions of the free wave equation (they are the Goldstone modes).
- solutions in H_{Φ_0} which in arbitrary large finite volume (in space and time) behave like free waves (Goldstone-like solutions). \diamond

Beyond its predictive aspect, this very general result allows to hypothesize an underlying spontaneous symmetry breaking when long wavelength modes are observed. This result is however scarcely used in biology.

5.5 CONCLUSION

We have seen that symmetry and symmetry breaking have fundamental consequences on the determination of the behaviour of objects. Theoretical symmetries (of the Lagrangian, here) correspond to conserved quantities, which are the properties of physical objects and allow their theoretical determination.

On the contrary, at a spontaneous symmetry breaking critical point, the loss of the determination of *both* phases behaviour leads to a particular behaviour, which is associated to the non-analyticity of the partition function. More precisely, the critical point constitutes a singularity in the determination of the system because it is (infinitely) close to two different behaviours, characterized by different relevant macroscopic phase spaces.

The strength of these singularities can be of different levels; this point is taken into account, here, by the Ginzburg criterion. This qualitatively corresponds to the bigger averaging nature of models in higher spatial dimensions. When this averaging is insufficient, renormalization methods are necessary to take into account the global structure of determination of the system that results from the coupling between fluctuations and the local averages.

As a general comment, we see that (finite) continuous symmetries are particular. They allow, by continuity, to propagate invariant quantities (Noether's theorem) and generate massless fluctuations (Goldstone theorem).

In the following chapter, we will return to biology and consider the question of the role played by symmetries in our theoretical proposal for understanding the phenomena that occur in this field.

From physics to biology by extending criticality and symmetry breakings 6

Since the beginning of physics, symmetry considerations have provided us with an extremely powerful and useful tool in our effort to understand nature. Gradually they have become the backbone of our theoretical formulation of physical laws.

Tsung-Dao Lee

The artificial products do not have any molecular dissymmetry; and I could not indicate the existence of a more profound separation between the products born under the influence of life and all the others.

L. Pasteur

This chapter is a slightly revised version of:

G. Longo & M. Montévil. 2011a. From physics to biology by extending criticality and symmetry breakings. *Systems Biology and Cancer, Progress in Biophysics and Molecular Biology* 106 (2): 340–347. ISSN: 0079-6107, doi:10.1016/j.pbiomolbio.2011.03.005

CONTENTS

| | | |
|-------|---|-----|
| 6.1 | Introduction and summary | 140 |
| 6.1.1 | Hidden variables in biology? | 141 |
| 6.2 | Symmetry and objectivation in physics | 143 |
| 6.3 | Symmetry breakings and criticality in physics | 146 |
| 6.4 | Symmetry breaking and the biological object: extended criticality | 148 |
| 6.5 | Additional characteristics of extended criticality | 152 |
| 6.6 | Conclusion | 154 |

ABSTRACT

Symmetries play a major role in physics, in particular since the work by E. Noether and H. Weyl in the first half of last century. Herein, we briefly review their role by recalling how symmetry changes allow to conceptually move from classical to relativistic and quantum physics. We then introduce our ongoing theoretical analysis in biology and show that symmetries play a radically different role in this discipline, when compared to those in current physics. By this comparison, we stress that symmetries must be understood in relation to conservation and stability properties, as represented in the *theories*. We posit that the dynamics of biological organisms, in their various levels of organization, are not “just” processes, but permanent (extended, in our terminology) critical transitions and, thus, symmetry changes. Within the limits of a relative structural stability (or interval of viability), variability is at the core of these transitions.

Keywords: symmetries, systems biology, critical transitions, levels of organization, hidden variables, coherent structures, downward causation.

6.1 INTRODUCTION AND SUMMARY

A synthetic understanding of the notion of organism requires drawing strong correlations between different levels of organization as well as between the global structure and the local phenomena within the organism. These issues should govern any systemic view on biology. Here, we sketch an approach in which the living state of matter is interpreted as a permanent “transition”, conceived as an ongoing or *extended* and *critical* transition. A large amount of very relevant work pertaining to the Theories of Criticality in physics has been successfully applied to biology (see below). The mathematical core of these theories rests upon the idea that a “phase transition,” which can be either critical or not, may be described as a *point* along the line where the intended control parameter runs. For example, the ferromagnetic / paramagnetic transition takes place for a precise value of the temperature, the Curie temperature. Mathematically, this is expressed by the “pointwise” value of this temperature, i.e., one mathematical point in this parameter’s space. When the temperature

decreases and passes through that point, the magnetic orientation organizes along one direction and magnetism appears. When the temperature increases through that point, disorder prevails and magnetism disappears. A (phase) transition is critical when some observables, or their first or second derivatives, diverge. This corresponds to the appearance of a “coherent structure”, that is to say space and/or time correlations at all scales, which at the transition point give a “global” aspect to the new physical object. These ideas are relevant to the analysis of biological organisms.

In contrast to known critical transitions in physics, biological entities should not be analyzed just as transient over a point of a phase change; instead, they permanently sustain criticality over a non-zero interval and this with respect to many control parameters (time, temperature, pressure). This represents a crucial change of perspective. First, the mathematical tools used in physics for the analysis of criticality, i.e. the renormalization methods, essentially use the pointwise nature of the critical transitions. Secondly, *symmetries* and *symmetry breakings* radically change when enlarging the mathematical locus of criticality from one point to a non-zero interval. These symmetry changes make a key theoretical difference with respect to the few cases in physics where the transition seems extended (see footnote 10, below). Our approach may be seen as a move from physics to biology by an analysis of the radically different symmetries and symmetry breakings at play in their respective theoretical frames. Thus, we will mostly focus on physical vs biological criticality in terms of symmetries and then apply this method to the analysis of the difference between physical and biological “objects” as well as of physical vs biological “trajectories”.

Living entities are not “just” processes, but something more: they are lasting, *extended critical transitions*, always transient toward a continually renewed structure. In general, physical processes do not change fundamental symmetries: to the contrary, they are mostly meant to preserve them. Typically, conservation properties (of energy, of momentum) are symmetries in the equations of movement. Critical transitions are an exception to the preservation of symmetries in physics; their “extension” radically changes the understanding of what biological processes are. This perspective also proposes a possible way of overcoming a key issue in the analysis of the complexity of the living state of matter. As for the construction of physico-mathematical or computational models, it is difficult to take the global structure of an organism into consideration, with its correlations between all levels of organization and in all lengths, including the many forms of integration and regulation. Thus, the complexity of the living unity is often modeled by the stacking of many but *simple* elementary processes. Typically, these formal systems deal with many observables and parameters. Since the framework is classical in a physical sense, these variables are local, i.e. they depend on pointwise values of the intended phase space. Instead, conceptual and mathematical dependencies in biology should be dealt with as “global” ones, where variables may depend on systemic or *non-local* effects. In physics, these dependencies are a relevant aspect of critical transitions, and they are even more so in biology, where criticality is extended.

6.1.1 HIDDEN VARIABLES IN BIOLOGY?

In classical and relativistic physics, once the suitable “phase space” and the equations that mathematically determine the system are given, the knowledge of the pointwise position-

momentum of the intended object of analysis allows to describe *in principle* the subsequent dynamics. This is “in principle” since physical measurement, which is always approximated, may produce the phenomenon of *deterministic unpredictability*, in particular in the presence of non-linear mathematical determination¹. Moreover, not all “forces” in the game may be known and there may be “hidden variables” (like the frictions along the trajectory of bouncing dice). Yet, these theories are deterministic and, once all pertinent variables and forces are assumed to be known, it is the *epistemic* lack of knowledge which yields classical randomness. *Per se*, a dice follows a “geodesic”. This is a unique, optimal and “critical” path, completely determined by the Hamiltonian and may be computed as an optimum of a Lagrangian functional.² This very beautiful paradigm, which may be summarized as the “geodesic principle”, may be further grounded on *symmetries* by an analysis of conservation principles (see Bailly & Longo (2011) for a recent synthesis and references).

In order to compare this situation with other fields of physics and subsequently to biology, we refer to the pointwise or local nature of the mathematical variables. Cantorian (and Euclidian) points are *limit* conceptual constructions; that is, they are the limit of a physical access to space and time by an always approximated measurement, i.e., an “arbitrarily small” interval. Yet, their perfect theoretical “locality” makes all classical dynamics intelligible (in principle). So, if something is unknown, one expects that by adding enough observables and/or more variables with definite values at any given time, one could increase knowledge, since the values of these observables are intrinsic and independent of the context.

The situation is rather different in Quantum Mechanics. The simultaneous, perfect, pointwise knowledge of position *and* momentum (or energy *and* time) are, in principle, forbidden because indeterminacy is intrinsic to the theory. Moreover, suppose that two quanta interact and form one system and that they later separate in space. Then acquiring knowledge regarding an observable quantity by performing a measurement on one of these quanta produces an instantaneous knowledge of the value of the measurement made on the other, i.e., the two quanta are “entangled” (Einstein, Podolsky & Rosen 1935). These features of the theory have several consequences: for instance, variables cannot always be associated to separated points and quantum randomness is intrinsic (under the form of Schrödinger equation, the “determination” gives the *probability* to obtain a value by measurement). Within this theoretical framework, quantum randomness differs from the classical one: two interacting dice which later separate obeying independent statistics, while the probability values of an observable of two previously interacting quanta are correlated. This is the so called “violation of Bell inequalities”, which has been empirically verified repeatedly since the experiments described in Aspect, Grangier & Roger (1982). Quantum entanglement requires considering some phenomena as being “non-local” and unseparable by any physical measurement (“non-separability”).

Since the '30s, some have found this situation unsatisfactory and have searched for

¹ More generally, unpredictability may appear when the dynamics is determined by an evolution function or equations that mathematically represent “rich” interactions. Non-linearity is a possible mathematical way to express them.

² These are mathematical operators, that is, functions acting on functions that contain all known physical information concerning the energy state of the system.

“hidden variables” like in the epistemic approach to randomness and determination of classical and relativistic physics. The idea is that these hidden variables corresponding to quantum mechanical observables have definite (pointwise/local) values at any given time, and that the values of those variables are intrinsic and independent of the device used to measure them. A robust result has instead shown that these assumptions contradict the fundamental fact that quantum mechanical observables need not be commutative (Kochen & Specker 1967). Moreover, even when assuming the existence of, or the need for, hidden variables, these would be “non-local” and thus, far from the pointwise/local dependence of set-theoretic variables.

The difference between the classical and quantum frameworks has the following consequence: quantum systems may have a proper systemic unity for at least two reasons. Conjugated observables (position and momentum) are “linked” by joint indetermination. Entangled quanta remain a “system”, in the sense of their non-separability by measurement³.

Can this perspective help us in biology? On technical grounds, surely not, or rather not yet. Perhaps, “entangled molecular phenomena” or “tunnel effects ... in the brain” may clarify fundamental issues in the future. However, theoretical ideas in Quantum Mechanics may at least inspire our attempts in system biology, in particular by considering the methodological role of symmetries and symmetry breakings in this area of physics.

A living organism is a system. And entanglement, non locality, non-separability, superposition, whatever these concepts may mean in biology, may present themselves both at each specific level of organization and in the interactions between levels of organization. Physiological interactions among molecules, cells, tissues, organs do not simply sum each other up: they are “entangled”, “non-local”, “non-separable” ... they are “superposed” (see examples described by Noble (2006); Soto, Sonnenschein & Miquel (2008)). Thus, the theoretical and mathematical approaches to biology cannot be based only on a continual enrichment of “local” views: mathematical models cannot work just by assuming the need for more and more variables (possibly hidden to the previous models). A global view of the system and of its symmetries is required. In this context, the differences in symmetries and their breakings will help in clarifying and facilitating the passage from physics to biology.

6.2 SYMMETRY AND OBJECTIVATION IN PHYSICS

In Physics, objectivity is obtained by the co-constitutive use of experiments and mathematized theories. So far, however, there is little mathematics for a “theory of the biological organisms” despite the large amount of data collected and of theories proposed within specific levels of organization. These include the geometric analysis of the fractal structures of lungs, of vascular systems, of various plant organs, of networks of neural cells, of tumor shapes, to name but a few. To make further progress towards mathematizing theories in biology, in particular towards theories of the “living object” or of the organism as a system, it would help first to understand how such a feat was achieved in physics. Physical theories have very general characteristics in their constitution of objectivity, and in particular in their

³ Superposition should also be mentioned, see Silverman (2008).

relationship with mathematics. In order to define space and time, as well as to describe physical objects, physicists ultimately use the notion of symmetry. Physical symmetries are the transformations that do not change the intended physical aspects of a system in a theory. As we shall see, they allow to define these aspects in a non-arbitrary way.

Galileo's theory provides a simple and historical example of this role of symmetries. For scholastic physics, the speed at which a body falls is proportional to the space traveled. Galileo instead proposed that it is proportional to the time of the fall and that it is independent of the nature (including the mass) of the empirical object considered (Galileo's law of gravitation). This idea together with the "principle of inertia" has been a starting point for the constitution of *space* and *time* in classical physics. More precisely, as a consequence of the analysis of inertia and gravitation, the geometry of space and time was later described by the Galilean group⁴.

A change of this symmetry group, for example by adopting the Poincaré group⁵, can lead to a very different physical situation, that of special relativity involving massive conceptual and physical changes. The "principle of relativity" states that the fundamental laws of physics do not depend on the reference system; they are actually obtained as invariants with respect to the change of reference system. A specific speed (the speed of light in the void) appears in the equations of electromagnetism. Einstein modified Galileo's group in order to transform this speed into an invariant of mechanics, which turned time-simultaneity into a relative notion.

As a result of the role and implications of symmetries, most contemporary physical challenges lead to the search for the right symmetries and symmetry changes, such as the work aiming at the unification of relativistic and quantum theories. In moving from physics to biology we suggest here to apply a similar approach (symmetry changes).

Since the 1920s, due to Noether's theorems, symmetries lead to the mathematical intelligibility of key physical invariant quantities. For example, symmetries by time translations are associated with energy-conservation, and symmetries by space rotations are associated with the conservation of angular momentum. Thus, conservation laws and symmetries are in a profound mathematical relation (see chapter 5, section 5.2 for technical details). Consequently, the various *properties* that define an object (mass, charge, etc.) or its *states* (energy, momentum, angular momentum, etc.) are associated to specific symmetries which allow these quantities to be defined. Depending on the theory adopted, this conceptualization allowed to understand why certain quantities are conserved or not: for example, there is no local energy conservation in general relativity. This explicit reference to the theory adopted is required in order to produce "scientific objectivity", *independently* of the arbitrary choices made by the observer, such as, the choice of time origin, the unit of measurement,

⁴ Symmetries form a set of transformations that have a group structure; that is, two symmetries applied successively yield a symmetry and a symmetry can be inverted. Galileo's group is the group of transformations that allows to transform a Galilean space-time reference system into another. It is interesting to notice that Galileo measured time by heartbeat, a biological rhythm; the subsequent theoretical and more "physical" measurement of time were precisely provided by classical mechanics, his invention.

⁵ The symmetry group of a Euclidean space is the Euclidean group of automorphisms, while Poincaré's group corresponds to the automorphisms defining Minkowski's spaces.

etc, but *relatively* to the intended theory. Thus, we say that symmetries provide “objective determinations” in physics (Bailly & Longo 2011).

The symmetries that define physical properties allow us to understand the physical object as *generic*, which means that any two objects that have the same properties can be considered as physically *identical*; in a sense, they are symmetric or invariant (interchangeable) in experiments and in pertinent mathematical framework (typically, the equations describing movement). For example, for Galileo, all objects behave the same way in the case of free fall, regardless of their nature. Moreover, symmetries allow the use of the *geodesic principle*, whereby the local determination of trajectories leads to the determination of the full trajectory of physical objects through conservation laws. For example, the local conservation of the “tangent” (the momentum) of movement, typically yields the global “optimal” behavior of the moving object; that is, it goes along a geodesic. Thus, in classical or relativistic mechanics, a trajectory is unique and fully deterministic (formally determined). In quantum mechanics the evolution of the state or wave function (roughly, a *probability distribution*) is fully deterministic as well – and determined by Schrödinger’s equation – while measurement follows this probability distribution (and here appears the indeterministic nature of quantum mechanics). In conclusion, by symmetries, the trajectory of a generic classical or quantum physical “object” corresponds to a critical path: physical trajectories are *specific*.

To better understand the problem of *general* mathematical theorizing in biology, let’s further analyze how, in physics, a concrete problem is turned into robust models and mathematics. To begin with, physicists try to choose the right theoretical framework and the relevant physical quantities (properties and states) which are constituted by proper symmetries. As a result, typically, a mathematical framework is obtained, where one can consider a generic object; in classical mechanics, a pointwise object of mass m , speed v and position x , where these quantities are generic. Now, a generic object will follow a specific trajectory determined by its invariants obtained by calculus. A measurement is then made on the experimental object to determine the quantities necessary to specify where this object is in this mathematical framework, namely, what is its mass, initial position and speed. And finally, what specific trajectory will the object follow ... at least approximately. In classical or relativistic physics, to a specific measurement will correspond generic objects localized near the measurement due to the limited precision of this measurement. This value may have, in principle, an arbitrary high precision. In quantum mechanics, as we recalled above, the equational determination (Schrödinger’s equation) yields the dynamics of a probability law⁶.

In classical dynamics, we face a well-known problem: the specific trajectories can either stay close or diverge very rapidly. The linear situation corresponds to the first case, whereas the second situation is called “sensitive to initial conditions” (or chaotic, according to various definitions). Note that even the latter situation leads to the definition of new invariants associated to the dynamics: in other words, the attractors that have a precise geometrical structure. In both cases, these trajectories have robust properties with respect to the mea-

⁶In quantum physics, “objects” do not follow trajectories in ordinary space-time, but they do it in a suitable, very abstract space, a Hilbert space (a space of mathematical functions); what “evolves” is a probability distribution.

surement. In quantum physics, the situation is more complex because the measurement is not deterministic. Yet, when approximations on the state function are performed, it leads to usually stable, robust statistics. In all cases, “robust” means invariant or approximately invariant in a definite mathematical sense, as concerns the measurement of states and properties of generic objects along specific trajectories. Thus, we can finally say that generic objects, which lead to a specific measurement, *behave* in the same way or approximately so. Notice that this property of robustness, allowed by the genericity of the object, is mandatory for the whole framework to be relevant. We insist that both genericity for objects and specificity for trajectories (geodesics) are mathematically understood in terms of symmetries.

In conclusion, in the broadest sense, symmetries are at the foundation of physics, allowing objective definitions of space and time and the constitution of objects and trajectories. In their genericity, these objects follow specific trajectories associated with invariants that are robust with respect to measurement.

6.3 SYMMETRY BREAKINGS AND CRITICALITY IN PHYSICS

The physics of criticality is a relatively novel discipline which analyzes, typically by the renormalization techniques, some peculiar phase transitions, i.e., state changes (see Toulouse, Pfeuty & Barton (1977); Binney et al. (1992), and also chapter 5, section 5.4 for a partial technical account). This theoretical framework has also been applied to a possible understanding of life phenomena (see for example, Bak, Tang & Wiesenfeld (1988); Jensen (1998), as for “self-organized criticality”; or, Kauffman (1993), as for criticality in networks). We will next move towards biology through a different insight into the symmetries in criticality.

Since symmetries are at the core of the definition of the physical objects by their properties and states, a *symmetry change* (that is, the breaking of some symmetries and the formation of new ones) means a qualitative change of the object considered, or a change of physical object, understood as co-constituted by theory and empiricity. For example, a research project in cosmology is to consider a single force to have existed in the universe right after the big bang. Then, the four fundamental forces may have appeared by successive symmetry breakings, whereby some transformations, which were symmetries⁷, did not preserve the object invariance anymore. In other words, with the cooling of the universe, the system moved to a smaller symmetry group. Closer to the scale of biology, materials like water or iron were able to show different properties in different situations. Depending on the temperature and pressure, water may be a solid, a liquid, or a gas. When liquid, there is no privileged direction (the system is isotropic, that is to say symmetric by rotations), whereas ice has a crystalline structure with spatially periodic patterns. This implies that the system is no longer symmetric by continuous rotations: it has a few privileged directions determined by its crystalline structure and a smaller symmetry group. Similarly, iron can have paramagnetic behavior (the system is not) or ferromagnetic behavior (it is magnetized). In most cases, one can distinguish a more disordered phase at high temperature, where entropy dominates, and

⁷The Higgs mechanism is an example of this phenomenon; in this case, the symmetry breaking in the abstract electroweak space leads in particular to different masses of bosons and as a consequence to a very short range for weak interaction and a long range for electromagnetism.

a more ordered phase, where energy dominates. These situations can be characterized by an *order parameter* which is 0 in the disordered phase and different from 0 in the ordered phase⁸.

Now, in physics, the change of state, or *phase transition*, occurs always mathematically at a point of the parameters' space. This point, called the *critical point*, is intuitively associated with a sudden change of behaviour due to a change of symmetry, and ultimately to singularities of the state functions (for example, the order parameter is non-analytical because it goes from a *constant* 0 to a finite quantity, *by a finite change*). More technically, the *critical point* represents a singularity in the partition function describing the system⁹. In the case of iron's paramagnetic-ferromagnetic transition, this allows to deduce the divergence of some physical observables, such as magnetic susceptibility. It should be remembered that this notion of *singularity*, which is associated with infinite quantities at the critical *point*, is a core notion for physical criticality.

This peculiar situation leads to a very characteristic behaviour at the critical point (Jensen 1998):

1. Correlation length tends to infinity, and follow a power law, as for continuous phase transitions (i.e., for a vector x and an observable N , if we note by $\langle \cdot \rangle_r$ the average over point r in space, then $\langle N(r+x)N(r) \rangle_r - \langle N(r) \rangle_r^2 \sim \|x\|^\alpha$. This is associated with fluctuations at all scales leading in particular to the failure of mean field approaches. Following this approach, the value of an observable at a point is given by the mean value in its neighbourhood or, more precisely, its mathematical distribution is uniform.
2. Critical slow down: the time of return to equilibrium of the system after a perturbation tends to infinity (Suzuki, Kaneko & Takesue 1982; Tredicce et al. 2004).
3. Scale invariance: the system has the same behavior at each scale. This property leads to fractal geometry and means that the system has a specific symmetry (scale invariance itself).
4. The determination of the system is global and no longer local.

These properties are the key motivations for the biological interest of this part of physics. The global “coherence structure” that is often formed at critical transitions provides a possible understanding, or at least, an analogy for the unity of an organism (in current terminology, its “global determination or causation”). Also, power laws, so frequent in biology, are ubiquitous in critical phenomena. They are mathematically well-behaved functions (e. g. $f(x) = x^\alpha$) with respect to the change of scale [typically, λ is the scale change in $f(\lambda x) = \lambda^\alpha f(x) = \lambda^\alpha x^\alpha$, a power law in α], and they yield *scale symmetries*. In our example, scale change just multiplies the function f by a constant λ^α . Now, a power law depends on a quantity without physical dimension (α in the notation above). These quantities involved in critical transitions are

⁸ Here, order means low entropy (or less symmetries) and disorder means high entropy (and more symmetries, when symmetries are computed in terms of “microstates”).

⁹ This function is non-analytical at the critical point, which means that the usual Taylor expansions, linearizations or higher order approximations do not actually provide an increasing approximation.

called *critical exponents* and describe how the change of scale occurs. In our terminology, they describe the properties due to the objective determination of a phase transition because they are the invariants associated with the scale symmetry.

Specific analytical methods, called renormalization methods, are used to find these quantities (Delamotte 2004). These methods consist in analyzing how scale changes transform a model representing the system, and this analysis is made “asymptotically” toward large scales. One may deduce the critical exponents from the mathematical operator representing the change of scale. The key point is that a variety of models ultimately lead to the same quantities, which means that they have the same behavior at macroscopic scales. Thus, they can be grouped in so-called *universality classes*. This analytical feature is confirmed empirically, both by the robustness of its results for a given critical point and more stunningly by the fact that very different physical systems happen to undergo the same sort of phase transitions; that is, they are associated with the same critical exponents, thus with the same symmetries. Finally, there exist fluctuations at all scales, which means, in particular, that small perturbations can lead to very large fluctuations.

To conclude, the transition through a specific point of the parameters’ space, i.e., a transition between two very different kinds of behavior is associated in physics to a change of symmetries. At this point, the system has very peculiar properties and symmetries. Symmetries by dilation (by a coefficient λ as above) yield a scale invariance. This latter invariance is associated to a global determination of the system and the formation of a “structure of coherence”. As observed above, this allows to describe a global determination of local phenomena and a unity that by-passes the idea of understanding the global complexity as the sum of many local behaviors by adding more and more local, possibly hidden, variables. For some physical phenomena this theoretical framework presents peculiar and very relevant forms of “systemic unity”.

6.4 SYMMETRY BREAKING AND THE BIOLOGICAL OBJECT : EXTENDED CRITICALITY

We have presented a picture of the situation in physics, but what about biology? We need to propose one or several specific frameworks relevant to the unity and coherence of biological entities, because, to our knowledge, there are no formalized theories of the “organism”. To do so, it may be worthwhile to look at the symmetries which may be involved in biological theorizing. Here, the concept of symmetry is used in a more fundamental context than when used, for example, for “bauplans”, the latter being the main biological research subject where the concept is explicitly applied. In physics, one mostly deals with *fundamental* or *theoretical* symmetries as typically given by the equations. For example, the already mentioned fundamental principle of energy conservation corresponds to a time translation symmetry in the equations of movement. This use of symmetries also justifies the soundness of empirical results: Galilean inertia is a special case of conservation of energy and it may be empirically verified. In biology, as in any science, a missing analysis of invariants may give unreliable results and data. For example, early measurements of membrane surfaces gave very different results, since their measure is not a scale invariant property: as in fractal structures,

it depends on the scale of observation¹⁰. In other words, in physics, both the generality of equations and the very objectivity of measures depend on theoretical symmetries and their breakings, such as scale invariants and scale dependencies.

As mentioned above, critical transitions in physics are mathematically analyzed as isolated points¹¹. In our approach to biological processes as “*extended* critical transitions”, “extended” means that *every point* of the evolution/development space is near a critical point. More technically, the critical points form a dense¹² subset of the multidimensional space of viability for the biological process. Thus, criticality is extended to the space of all pertinent parameters and observables (or phase space), within the limits of viability (tolerated temperature, pressure and time range, or whatever other parameter, say for a given animal), see Bailly, Gailly & Mosseri (1993); Bailly & Longo (2008, 2011). In terms of symmetries, such a situation implies that biological objects (cells, multicellular organisms, species) are in a *continual transition between different symmetry groups*; that is, they are in transition between different phases, according to the language of condensed matter¹³. These phases swiftly shift between different critical points and between different *physical determinations* through symmetry changes.

Our perspective provides an approach concerning the mathematical nature of biological objects as a *limit* or asymptotic case of physical states: the latter may yield the dense structure we attribute to extended criticality only by an asymptotic accumulation of critical points in a non-trivial interval of viability — a situation not considered by current physical theories. In a sense, it is the very principles grounding physical theories that we are modifying through an “actual” limit. Thus, a biological object is mathematically and fundamentally different from a physical object because it may be characterized in terms of partial but continual changes of symmetry within an interval of viability, as an extended locus of critical transitions. In particular, this mathematical view of “partial preservation through symmetry changes” is a way to characterize the joint dynamics of *structural stability* and *variability* proper to life. We thus consider this characterization as a tool for the mathematical intelligibility of fundamental biological principles: the global/structural stability is crucially associated with variability.

A first consequence of these permanent symmetry changes is that there are very few invariants in biology. Mathematically, invariants depend on stable symmetries. Structural stability in biology, thus, should be understood more in terms of *correlations of symmetries*

¹⁰In Weibel (1994), another “historical” example is given as for the different results that are obtained according to different experimental scales (microscope magnifications). One team evaluated the surface density of the liver’s endoplasmic reticulum at $5.7 \text{ m}^2/\text{cm}^3$ the other at $10.9 \text{ m}^2/\text{cm}^3$ (!). More details on this question are given in chapter 2.

¹¹The Kosterlitz-Thouless transition in statistical physics presents a marginally critical interval; that is, it is a limit case between critical and not critical. It presents correlations at all scales, as critical features, but with no symmetry changes. Thus, this particular situation is not a counter-example to our statement (the essentially pointwise nature of the proper physical transitions), in view of a lack of symmetry changes that are essential to our notion of extended criticality.

¹²Here, dense means that for every small volume of the intended phase space being considered, there is a critical point in such volume.

¹³The dense set of symmetry groups may be potentially infinite, but, of course, an organism (or a species) explores only finitely many of them in its life span, and only viable ones.

within an interval of the extended critical transition, rather than on their identical preservation. It is clear that the *bauplan* and a few more properties may be “identically” preserved. Yet, in biology, theoretical invariants are continually broken by these symmetry changes. A biological object (a cell, a multicellular organism, a species) continually changes symmetries, with respect to all control parameters, including time. Each mitosis is a symmetry change because the two new cells are not identical. This variability, under the mathematical form of symmetry breaking and constitution of new symmetries, is essential both for evolution and embryogenesis. The interval of criticality is then the “space of viability” or locus of the possible structural stability.

The changes of symmetries in the dense interval of criticality, which provide a mathematical understanding of biological variability, are a major challenge for theorizing. As a matter of fact, we are accustomed to the theoretical stability warranted by the mathematical invariants at the core of physics. These invariants are the result of symmetries in the mathematical (equational) determination of the physical object. This lack of invariants and symmetries corresponds to the difficulties in finding equational determinations in biology¹⁴.

As a further consequence of our approach, phylogenetic or ontogenetic trajectories cannot be defined by the geodesic principle, since they are not determined by invariants and their associated symmetries. These latter are continually changing in a relatively minor but extended way.

Biology may be considered to be in an opposite situation with respect to physics: in contrast to physics, in biology, *trajectories* are *generic* whereas *objects* are *specific* (Bailly & Longo 2011). That is, a rat, a monkey or an elephant are the *specific* results of *possible* (generic) evolutionary trajectories of a common mammal ancestor — or each of these individuals is *specific*. They respectively are the result of a unique constitutive history, yet a possible or *generic* one (Bailly, Gaill & Mosseri 1993; Bailly & Longo 2011).

The evolutionary or ontogenetic trajectory of a cell, a multicellular organism or a species is just a *possible* or *compatible* path within the ecosystem. The genericity of the biological trajectories implies that, in contrast to what is common in physics, we cannot mathematically and *a priori* determine the ontogenetic and phylogenetic trajectory of a living entity be it an individual or a species. In other words, in biology, we should consider *generic* trajectories (or possible paths) whose only constraints are to remain compatible with the survival of the intended biological system. Thus, phylogenesis and embryogenesis are *possible* paths subject to various constraints, including of course the inherited structure of the DNA, of the cell and the ecosystem. The *specificity* of the biological object, instead, is the result of critical points and of symmetry *changes* of the system considered *along its past history* (evolutive and ontogenetic). These constitute the specific “properties” of this object, which allow to define it. A rat, a monkey or an elephant or their species are *specific* and cannot be interchanged either as individuals nor as species. A living entity is the result of its history and cannot be defined “generically” in terms of invariants and symmetries as it is done for physical objects.

¹⁴In a rather naive way, some say this by observing that any (mathematized) theory in biology has a “counterexample”. This instability of the determination goes together with the “structural stability” of biological entities. This is largely due to the stabilizing role of integration and regulation effects between different levels of organization. The mathematics of extended criticality and of variants of the renormalization methods are yet to be developed.

This situation has a particular meaning when we consider time translation and time reversal symmetries. In physics, time symmetries correspond to the maintaining of the system's invariant quantities that define the geodesics, as for example, conservation of energy. In biology both symmetries are broken. In particular, evolutionary and ontogenetic paths are both irreversible and non-iteratable; there is no way to identically “rewind” nor “restart” evolution or ontogenesis. This corresponds to the breaking of time translation and reversal symmetries. In particular, this lack of time symmetries is associated with the process of *individuation*, understood here as the specificity of cells, organisms and species (as much as this latter notion is well defined). It is crucial to understand that time plays a key role in this framework, since the *history* of all the changes in symmetry are not reducible to a specific trajectory in a given space of the dynamics. Thus,

The sequence of symmetry changes defines the historical contingency of a living object's phylogenetic or ontogenetic trajectory.

Biological processes are more “history based” than physical processes. Usual physical processes preserve invariants, whereas extended critical transitions are a permanent reconstruction of organization and symmetries, i.e., of invariants. This situation also points to a lack of symmetry by permutation. For example, even in a clonal population of bacteria, different bacteria are not generic, because they are in general not interchangeable, i.e., they cannot be permuted. This allows to understand biological variability in a deeper way than the usual Gaussian (or combination of Gaussians) as random distribution of a set of observables. Now, let us consider organs (and organelles). Some organs have a functional role that can be expressed in a physical framework, particularly as far as energy transfer is concerned. This functional role can lead to restrictions on the variability of the cells that constitute the organ, while the same could be said for individual organisms in populations. At least for certain aspects of their behaviour and on average, these restrictions make cells behave symmetrically. In other words, those cells behave, in part and approximately, like generic objects with specific trajectory (geodesics). They may be interchangeable, like physical objects.

The simple case of cells secreting a protein such as erythropoietin (EPO) under specific conditions indicate that on average, a sufficient amount of the protein must be produced, independently of the individual contribution of each cell (which become “relatively” generic). Since the result of these cells' production is additive (linear), its regulation does not need to be sharp. Even if some cells do not produce EPO there is no functional problem as long as a sufficient quantity of this protein is secreted at the tissue level. However, when cells contribute to a non-linear framework as part of an organ, the regulation may need to be sharper. This is the case, for example, for neuronal networks or for cell proliferation where non-linear effects may be very important. In the latter case, regulation by the tissue and the organism seems to hold back pathological developments, like cancer, see Sonnenschein & Soto (1999). This point of view can possibly be generalized in order to understand the robustness of development.

The role of physical processes in shaping organs is crucial; for example, exchanges of energy (or matter) force/determine the optimal (geodesic) fractal structure of lungs and vascular systems. Organs in an organism may even be replaced by man-made artifacts (as for kidneys, heart, limbs, etc.). As biological entities, organisms and even cells are specific or, at

most, weakly generic given that they can be interchanged only within a given population or tissue and occasionally. In general, they are not generic, and by their specificity they cannot be replaced by an artifact — structurally.

In summary, in critical transitions one may consider variables depending on global processes because of the formation of coherent structures. For example, there may be functional dependencies on a network of interactions, which cannot be split into a sum of many local dependencies (local variables). Thus, the search for more variables would not take into account this fundamental property of biological systems, considered as extended critical transitions. Moreover, symmetries in physics allow to define generic objects which follow specific trajectories (the latter allowing to find invariants in terms of symmetries, which are robust regarding measurement). On the contrary, in biology, the continual symmetry changes lead to generic trajectories that remain compatible with the survival of the system. The generic/specific duality with respect to physics helped us understand this key issue, in relation to extended criticality — which is a form of “relatively stable instability.” In other words, this is stability under changes of symmetries in an interval of viability. In a sense, the biological object is also defined by its symmetries but in a very different way: it is the *specific* result of a history, where its dynamics is punctuated by symmetry changes. This makes it “historical” and *contingent*.

6.5 ADDITIONAL CHARACTERISTICS OF EXTENDED CRITICALITY

In physics, criticality implies more than a pointwise symmetry change; that is, it requires a change on a mathematical point, as it leads to peculiar behaviors that are relevant to biology. The first of these properties is that criticality implies a global determination, instead of a simply local one. More precisely, the singularities involved in criticality lead to a change of the level of organization in a very strong sense. Also in physics, in view of the mathematical divergence of some observables, the singularities break the ability of the “down level” to provide a causal account of the phenomena and they lead to the need for a “top level” to overcome this difficulty. In mathematical physics, this upper level can be found in the renormalization operator (it is the abstract level of *changing scale*). In biology, instead, the upper level is the functional unity of an organism. As a result, the existence of different levels of organization is a component of our notion of extended critical transition. “Downward causation” may find the right frame of analysis in this theoretical context.

The permanent reconstruction of these levels of organization is mathematically represented by the density of the critical points and by the continual change of determination (symmetry change) in the passage between these points within the interval of extended criticality.

The second property is the presence of power laws which seem to be ubiquitous in biology. They appear regularly especially when regulation is concerned, such as in cardiac rhythms (Makowiec et al. 2006; Pikkujamsa et al. 1999), blood cell number regulation (Perazzo et al. 2000), blood pressure (Wagner, Nafz & Persson 1996), in brain activities (Werner 2007), sensory cells (Camalet et al. 1999), mitochondrial networks (Aon, Cortassa & O'Rourke

2004), in ecology (Sole et al. 1999) and gene networks (Shmulevich, Kauffman & Aldana 2005; Nykter, Price, Aldana, et al. 2008). See chapter 2 for a more comprehensive account on this question, and on the limitation of this approximate symmetries.

Extended critical transitions also concern the relevant lengths of local and global exchanges, the temporalities mobilized for such exchanges and biological rhythms. To summarize, the extended critical situation has at least the following characteristics (Bailly & Longo 2008, 2011):

1. A spatial volume enclosed within a semi-permeable membrane;
2. Correlation lengths of the order of magnitude of the greatest length of the above referred volume;
3. A metabolic activity that is far from equilibrium and irreversible, involving exchanges of energy, of matter and of entropy with the environment, as well as the production of entropy due to all these irreversible processes, see Bailly & Longo (2009);
4. An anatomico-functional structuralization into levels of organization that can be autonomous but also coupled to each other. They are “entangled” in the sense defined by Bailly & Longo (2009); Soto, Sonnenschein & Miquel (2008). These levels are likely to be distinguished by the existence of fractal geometries (membranous or arborescent), where the fractal geometries can be considered as the trace (or a “model”) of effective passages to the infinite limit of an intensive magnitude of the system (for example, local exchanges of energy¹⁵). The different levels of organization induce, and are a consequence of, the alternation of “organs” and “organisms”, such as organelles in cells, which, in turn, make up the organs in multicellular organisms. Organisms stay in an extended critical transition, while organs are partially “optimally shaped” by the exchange of physical energy and matter. For example, fractal geometries essentially manifest in organs that are also the privileged loci of endogenous rhythms (see below). Correlation lengths are manifested both *in* and *between* these levels¹⁶. Likewise, the various biological “clocks” are coupled, and in some cases even synchronized, within and between these levels.

With the purpose of providing biological temporality with a structuring of the mathematical type, we will consider two other aspects as being specific to extended criticality.

- The two-dimensionality of time, proposed in chapter 3 (Bailly, Longo & Montévil 2011):

¹⁵The fractal dimension of some organs may be calculated by optimizing the purely physical exchanges within the intended topological dimension (for example, the maximization, within a volume, of surfaces for lungs, or of volumes for the vascular system, West, Brown & Enquist (1997)), and it may be subjected to constraints in terms of stericity and homogeneity, as in the cases mentioned (lung, vascular system, kidney, etc).

¹⁶The term “entanglement” in Soto, Sonnenschein & Miquel (2008) does not correspond, of course, to the physical meaning of “quantum entanglement” as expressed by Schrödinger’s treatment of the state function and the inseparability of quantum measure, yet it may be appropriate because there is no way to isolate one of the organs mentioned above (e.g. put a brain in a flowerpot) and perform any reasonable physiological measure on it.

1. One dimension is classical and is parametrized according to the line of real numbers limited by fertilization on one side, and death on the other. This dimension is linked to the bio-physicochemical evolution of the organism in relation to an environment.
2. The other dimension is compactified, i. e. it is parametrized on a circle. This second dimension is linked to the organism's endogenous physiological rhythm that is manifested through *numeric quantities without dimension* such as the mean total number of heartbeats and respirations during the lifetime of mammals. These are the interesting interspecific invariants and they are "pure" numbers, *not frequencies* (they have no dimension; they are the "total number of ..."). They become frequencies (with the inverse of time as a dimension), according to the average lifespan. The extra dimension is needed exactly because the invariant phenomenon is not defined by a period which has the dimension of time, but by this new invariant observable. For example, on average, the identical (invariant) number of total heartbeats give different frequencies according to the different lifespans of an elephant or of a mouse.

Moreover, the temporality of extended criticality involve protention (i.e. pre-conscious expectation) and retention (i. e. pre-conscious memory) as described in chapter 4 (Longo & Montévil 2011b), which seems to lead to a breaking of conservation of information in cognition.

- The confinement within a volume of a parameter space (such as temperature, pressure, etc) of n dimensions of which 3 are spatial and 2 temporal and whose measure is different from 0 (see above).

6.6 CONCLUSION

Since ancient Greece (Archimedes' principle on equilibria) up to Relativity Theory (Noether's and Weyl's work) and Quantum Mechanics (from Weyl's groups to the time-charge-parity symmetry), symmetries have provided a unified view of the principles of theoretical intelligibility in physics. We claimed here that some major challenges for the proposal of mathematical and theoretical ideas in biology depend, in principle, on the very different roles that symmetries play in biology when compared to physics. The unifying theoretical framework in biology is neither associated to invariants nor to transformations preserving invariants like in (mathematical/theoretical) physics. It focuses, instead, on the permanent change of symmetries that *per se* modify the analysis of the internal and external processes of life, both in ontogenesis and evolution.

In a sense, variability may be considered as the main invariant of the living state of matter. In order to explain it, we proposed to consider the role played by local and global symmetry changes along extended critical transitions. In extended criticality, dynamically changing coherent structures as global entities provide an understanding of variability within a global, extended stability. The coherent structure of critical phenomena also justifies the use of variables depending on non-local effects. Thus, an explicitly systemic approach may help

in avoiding the accumulation of models and previously hidden variables. In conclusion, the notion of extended criticality provides a conceptual framework, to be further mathematized, where the dynamics of symmetries and symmetry breakings provide a new, crucial role for symmetries in biology with respect to physics.

This chapter is a major turning point of our thesis. Its conclusion indeed directly concerns the nature of the mathematical accounts that we can provide on biological organization, given the instability of biological symmetries.

In the following chapter, we will explore the consequences of our analysis on the notion of biological measurement.

Acknowledgement: We warmly thank the editors of the published version of this chapter for several and very close preliminary revisions of this conceptually difficult text.

Biological measurement & extended critical transitions 7

Whether you can observe a thing or not depends on the theory which you use. It is the theory which decides what can be observed.

A. Einstein quoted in Salam (1990).

CONTENTS

| | | |
|---------|---|-----|
| 7.1 | Introduction | 158 |
| 7.2 | Physical measurement | 159 |
| 7.2.1 | Classical measurement | 159 |
| 7.2.2 | Reference frame | 160 |
| 7.2.3 | Quantum measurement | 161 |
| 7.2.4 | Conclusion | 162 |
| 7.3 | Biological measurement as a restricted symmetrization | 162 |
| 7.3.1 | Phylogeny | 163 |
| 7.3.2 | Controlled history | 164 |
| 7.3.3 | Irreducibility of symmetry changes | 166 |
| 7.3.4 | Recapitulation | 166 |
| 7.4 | Allometry and symmetry breaking | 168 |
| 7.4.1 | Variability versus fluctuations | 168 |
| 7.4.2 | Systematic application of our framework | 169 |
| 7.4.3 | A mathematical frame for biological allometry | 170 |
| 7.4.3.1 | Mathematical background | 170 |
| 7.4.3.2 | Biological framework | 171 |
| 7.4.3.3 | Further aspects of this framework | 172 |
| 7.5 | Compacified time and autonomy | 174 |
| 7.5.1 | Simple harmonic oscillators in physics | 175 |

| | | |
|---------|---|-----|
| 7.5.1.1 | Classical oscillator | 175 |
| 7.5.1.2 | Quantum oscillator | 175 |
| 7.5.1.3 | Conclusion | 176 |
| 7.5.2 | Symmetries and compactified time | 176 |
| 7.5.3 | Conclusion | 177 |
| 7.6 | Observing symmetry changes? | 178 |
| 7.6.1 | From a measured trajectory to specific symmetries | 178 |
| 7.6.2 | Global aspect of extended critical transitions | 179 |
| 7.7 | Conclusion | 179 |

ABSTRACT:

In this chapter, we discuss the theoretical nature of biological measurement. Following the idea of extended critical transitions, we propose to understand biological measurement as based on two different strategies. The first concerns an approach focused on symmetrization, or in other words, on the constitution of a restricted genericity of the object. This approach is based on the control of symmetry changes occurring at various time scales (phylogenetic, ontogenetic, cognitive, ...). We will provide a mathematical skeleton corresponding to this analysis and that applies to allometry. The second approach consists in following a biological trajectory, which defines, through its symmetry changes one, or a sequence, of dominating symmetries. This approach will be introduced by our 2-dimensional approach of biological time.

Keywords: Biological measurement, extended critical transitions, symmetry, symmetry breaking, allometry, historicity

7.1 INTRODUCTION

HERE, we will develop some consequences of the conceptual framework of extended critical transitions. We saw in chapter 6 (Longo & Montévil 2011a) that extended critical transitions are associated with ubiquitous symmetry changes. Starting from this premises, we aim at a first proposal for a proper theoretical understanding of biological measurement.

As a general epistemological guideline, we want to emphasize that a mathematized theory (in natural sciences) is not in general a description of an object “by itself”, where the point of view of an omniscient daemon would *exist*¹. On the contrary, such a theory aims to provide objectivation of the studied phenomena. As a result, the question of the nature of measurement in theories is essential in the formulation of theories and is deeply embedded in their mathematical structure.

¹In mathematics, this kind of question is usually one of well-definiteness.

Physical concepts are often used for biological approaches, and measure is no exception. In particular, the classical interpretation of measurement is widely, more or less explicitly used, especially in association with biophysical models. As a result, the question can be raised whether specific aspects of biological measurement should be taken into account, both empirically and theoretically.

In the literature, there is indeed already at least one such account: following the informational metaphor, molecular biology generally consider measure as a kind of classical measure of a *finite discrete* structure. Following such a perspective, the measure is considered “perfect” *in principle*, since knowing such a system with a sufficient *finite* precision means knowing it *exactly*. This point of view is conceptually extraordinarily poor but should be contrasted with the experimental methodologies used in biology which are exquisitely delicate and rich. We will show here that the framework of extended critical transitions allows to understand intrinsically some of their aspects.

We will first discuss briefly how measurement is handled in fundamental physical theories, which will allow us to illustrate the theoretical role played by theoretical accounts of measure in these theories. We will then analyze the biological measure associated with a strategy of symmetrization, which will allow us to propose a first notion of biological measure. The case of allometry will allow us to provide a partial mathematical interpretation of the conceptual frame developed. Then we will consider an other strategy, based on individual trajectories, and see if it leads to radically different theoretical considerations. To do so, we will first present a further justification and discussion of the compactified time dimension, discussed in chapter 3 (Bailly, Longo & Montévil 2011), in order to illustrate the consequences of symmetry breaking on the physical definiteness of biological phenomena. Then, we will discuss this approach with more generality.

7.2 PHYSICAL MEASUREMENT

In order to better understand the theoretical roles of measure, we will show how it is conceptualized in the main physical theories. We will restrict ourselves to the elementary aspects of measurement, understood here as the “obtaining of quantities” in the experiment, and its counterpart in the theory. This counterpart is minimal, which means that the aim is not to cope with specific experimental difficulties but with *principal* issues. As a matter of fact, these accounts are sufficiently abstracted to be valid for *all* measurements in the corresponding theory. In this sense, we can understand them as accounts of generic measurements. In spite of this abstract character, these notions are, however, undoubtedly essential for any practical measurement.

7.2.1 CLASSICAL MEASUREMENT

In classical mechanics, the measure is a *metrical* notion. A system is understood as having some properties², and at a given time, a pointwise state in the phase space. The empirical

²Properties are independent of the specific interactions in the system considered; examples are the mass, the charge, friction coefficient, They correspond to the description of the object independently of it being in a particular system.

access to this state is understood as being approximate, meaning that, in an experiment, we can measure a quantity with a finite precision, ε , which can *in principle* be arbitrarily small. Thus, the state of a system is understood as a point and the result of the measure as an interval and never limited to a point.

As a side remark, we notice that the well-definiteness of this notion of measure implies a property of (metric) completeness of the phase space. Let us recall that this property is one of the main mathematical motivation for going from the rational numbers (which lacks this property) to the real numbers and is sufficient to define the latter as the completion of the first. Let us consider a sequence of intervals measured, (I_{ε_n}) and suppose this sequence verifies: $m > n \Rightarrow (\varepsilon_m < \varepsilon_n) \& (I_{\varepsilon_m} \subset I_{\varepsilon_n})$. This condition is very natural since having the measures I_{ε_1} and I_{ε_2} means that we know the system is in $I_{\varepsilon_1} \cap I_{\varepsilon_2}$. Then the vanishing imprecision ($\varepsilon_n \rightarrow 0$) define at most a point $\cap I_{\varepsilon_n}$. The physical hypothesis that measure should actually capture something (a point, i.e. $\cap I_{\varepsilon_n} = \{x\}$) leads then precisely to the definition of the notion of metrical completeness. Of course, there are other reasons to make this mathematical hypothesis. The main other physically meaningful reason to do so is the use of differential calculus, which is not stable on rational numbers.

Another noteworthy aspect of classical measurement is that, depending on the *dynamic* of the system, measurement may or may not allow to determine (with a reasonable approximation) the subsequent trajectory. The cases where such predictions are not possible correspond to a mathematical property of the dynamic called sensitivity to initial conditions which is in particular a characteristic of chaotic systems. In Bailly & Longo (2011), it is pointed out that such a situation can be understood as a form of incompleteness³ (in analogy with logic). Let us recall that logical incompleteness means that the (logical) theory allows to formulate statements that the theory does not allow to prove or refute. Then, the analogy is that unpredictable dynamics means that the physical theory allows to prove that the future states cannot be proved, because the dynamic escapes what the measurement allows to capture.

A toy example of such a situation is the discrete time system x_n defined by recurrence $x_{n+1} = 10x_n - [10x_n]$ (x_{n+1} is the decimal part of $10x_n$). We conclude then that x_n is roughly the n^{th} decimal of X_0 . As a result, if we know only N decimals of x_0 (because of the limited precision of measurement) we know nothing about the values taken by the system after N iterations.

7.2.2 REFERENCE FRAME

A physical experiment is performed in a specific time and place, or more precisely an experimenter determines its own space-time “point of view” on a physical phenomenon. This aspect is understood in particular by relativity theories (galilean, special and general). These theories allow to understand most observables of a system as relative to a reference frame. These theories allow nevertheless to obtain objectivity by focusing on aspects invariant by changes of reference frame. Let us notice that there is a gradation from Galilean relativity to special relativity and finally to general relativity, which constitutes a growing departing from a possible notion of an absolute time and space (independent from an arbitrary choice of

³The corresponding notion of completeness has no obvious link with the notion of metric completeness in the paragraph above.

reference frame). Indeed, in Galilean relativity, beyond the space coordinate changes, only speed is a relative notion. However in special relativity, length, duration and even simultaneity become relative (to the reference frame). In general relativity, gravitation become also a part of relativity, in particular by the Gedankenexperiment of the elevator: if we are in an elevator, we cannot distinguish *a priori* if it is accelerating or under the effect of a gravitational field.

We should notice that general relativity is a huge step in comparison with the previous formulations: Galilean and special relativity needs the experimenter to be or to relate to a specific kind of reference frame. On the contrary, general relativity describe “laws” of physics that stay the same for *any* reference frame (the corresponding transformations are diffeomorphisms), the other forms of relativity being *local approximations* of the generalized equations.

7.2.3 QUANTUM MEASUREMENT

In quantum mechanics, measurement has a highly distinctive and fascinating role. As we will see, quantum measurement has an *algebraic* (and geometric) nature, which is in sharp contrast with the metric nature of classical measure.

Informally, a quantum state can be decomposed *for a given measurement* as the superposition (the sum) of different states, each of them being associated to obtainable measures which are defined and can be different. However, when we perform a measurement the state corresponds to this measured quantity, so the other states in the initial superposition are lost. A key point is that the decomposition is *not* necessarily the same for different observables. We will now present the situation more formally.

A state is defined in this theory as a vector, ψ , in a Hilbert space, which means in particular that we have a notion of orthogonality (and a generalized dot product). An observable is a Hermitian operator A on this space⁴. The measurement is then the projection of the state vector on one of the eigenvector⁵ of A . The measured value is the corresponding eigenvalue α . Before the measurement, the probability to obtain each possible values α is the size of the orthogonal projection of ψ on the corresponding eigenvector ψ_α .

We should notice first that there is an internal consistency in this notion: performing the same measurement twice in a row will lead to the same result. Indeed, let us assume that we have measured α , the state is then the corresponding eigenvector ψ_α (modulo a phase factor). Because A is Hermitian, we have for every other eigenvector ψ_β , $\langle \psi_\alpha | \psi_\beta \rangle = 0$ (the eigenvectors are orthogonal). As a result, the only eigenvalue with non-zero probability is α which is associated to probability 1, leading again to the measure α .

There is already a powerful consequence of this notion of measure: quantum measure is an *irreversible* process as it leads to the collapse of the state (or wave-function) on an eigenvector, the other components of the state disappearing irremediably. Moreover, quantum measurement has other exotic features. Typically operators representing measurements may not commute, which means that if we measure, say, position and *then* momenta or momenta and *then* position, we will not obtain the same results.

⁴This means in particular that A is linear and “compatible” with the orthogonal structure.

⁵Let us recall that an eigenvector ψ_α is such that $A\psi_\alpha = \alpha\psi_\alpha$.

More precisely, the position operator is \hat{x} with $\hat{x}\psi(x) = x\psi(x)$ and the momentum operator is $\hat{p} = -i\hbar\frac{\partial}{\partial x}$, which leads to:

$$[\hat{p}, \hat{x}] \psi(x) = (\hat{p}\hat{x} - \hat{x}\hat{p}) \psi(x) = -i\hbar\frac{\partial}{\partial x}x\psi(x) + i\hbar x\frac{\partial}{\partial x}\psi(x) \quad (7.1)$$

$$= -i\hbar x\frac{\partial}{\partial x}\psi(x) - i\hbar\psi(x) + i\hbar x\frac{\partial}{\partial x}\psi(x) \quad (7.2)$$

$$= -i\hbar\psi(x) \quad (7.3)$$

This equality leads to Heisenberg uncertainty principle: $\sigma_x\sigma_p \geq \frac{\hbar}{2}$, where σ_X represents the standard deviation of X . In full generality, we have $\sigma_A\sigma_B \geq \frac{1}{2}|\langle[A, B]\rangle|$ (where $[A, B] = AB - BA$ is called the commutator). This result interprets non-commutation (non-simultaneous measurability) through its consequences on dispersion (if an object is localized in position it is dispersed in momenta and reciprocally).

As a last remark, we want to indicate that it can be argued, see Mugur-Schächter (2002), that, for quantum mechanics, a measurement is needed to put the system in its initial state (to define it). The structure of the determination in an experiment is then: measure, time evolution (Schrödinger equation), measure, ...

7.2.4 CONCLUSION

The forms of physical measurement we described are highly heterogeneous. We have seen three main kind of measurements, understood as imprecision, association with an arbitrary reference frame and projection of the state on an eigenstate of a measurement operator.

It is noteworthy that quantum measurement is the only one which is intrinsically a process, and it is even an irreversible process (yet it is a punctual process). The other forms of measurement correspond more to the nature of what is obtained (an interval, quantities relative to a reference frame, ...). It is noteworthy also to remark that quantum measurement has an algebraic nature, whereas classical measurement is a metric notion. It is this algebraic feature that defines how measurement change the state measured.

7.3 BIOLOGICAL MEASUREMENT AS A RESTRICTED SYMMETRIZATION

Following the ideas of extended critical transitions, a specific understanding of biological measurement should be conceptually linked with the symmetry changes occurring spontaneously in biological objects and leading to their specificity. Indeed, in physics, measurement allows to approach phenomena as theoretically generic objects (and allows to reproduce experiments). However, we argued in chapter 6 (Longo & Montévil 2011a) that the biological object (the organism, typically) is specific. As a result, biological measurement cannot have the same status than physical measurement, and, even worse, seems to put the reproducibility of experiments in jeopardy.

In order to (partially) overcome this difficulty, a strategy has been widely used, although implicitly. This strategy consists in trying to control the history of symmetry changes of

the object, in order to obtain a restricted genericity of objects. By the latter, we mean obtaining specific objects, which share nevertheless “a lot of” symmetries (be it individually or collectively⁶).

7.3.1 PHYLOGENY

To obtain such a partial genericity, there is a first, elementary strategy used in biology. It consists in choosing organisms that have a very recent common ancestor, so that the obtained objects share a common phylogenetic history. More precisely, symmetry changes are associated to the progression of biological time, so the more we manage to “freeze” biological time (between two experiments), the less symmetry changes should occur⁷. Practically, this lead, for example, to the methodology in microbiology that consists in sharing strains between laboratories, in order to perform the same or associated experiments, and to keep the samples frozen (the latter operation allowing to essentially stops biological time). We should notice that this methodology is usually mostly interpreted in terms of DNA changes. Even though mutations are obviously crucial, our approach is not limited to them, since, for example, it is not sufficient to understand inheritance (see Youngson & Whitelaw (2008) for a review on the question of epigenetic inheritance and Danchin et al. (2011) for a recent theoretical exposition of the various forms of inheritance. See also Buiatti & Buiatti (2008) for more conceptual approaches on the problem of biological randomness in relation with evolution).

We want to emphasize that this somewhat elementary methodological aspect is in sharp contrast with most physical experiments: physical object do not usually *need* to be shared. Instead, because of their genericity, they just need to have the same symmetry, and can be generated in a generic way (they are sometimes easy to produce, since, for example, Newton’s gravitation applies to anything with a mass⁸). More precisely, the general difficulty in experimental physics (added to the question of measure we already discussed) is to generate a situation “symmetrical” enough to test what we want to study and *in fine* to allow reproducibility. This can be illustrated by purity control of a sample or the approximate Galilean property of a reference frame⁹. It is then an issue of “cleaning up” the unwanted perturbations in the theoretical framework or perturbations of the symmetries of the theoretical framework.

The point here is not that physical objects do not have “memory”, they can very well exhibit some kind of hysteresis or be far from equilibrium (like dunes or rivers). However, their theoretical description remains in a given phase space, allowing experimentally to reproduce (up to a possible randomness) their main features. On the contrary, the role of historicity in biology, understood as a cascade of symmetry changes, leads to changes of phase

⁶By the latter we mean that certain symmetry can only be seen by observing a collection of object, especially when randomness is involved. For example, the symmetries of the 6 faces of a dice are found only statistically as a symmetry of the results.

⁷This intuitive reasoning can be seen as a hypothesis on the relationship between (biological) time and biological symmetry changes. From another point of view, it can even be seen as a definition of biological time

⁸More precisely we need also to relate to an approximate Galilean (also called inertial) reference frame. A terrestrial reference frame is suitable with sufficient precision for a large class of practical purposes.

⁹Notice that impurities, for example, can also play a valuable role to study the underlying symmetries, by the very perturbations they produce.

space and this leads experimentally to look for restricted genericity. The latter is obtained, among other, by a phylogenetic history shared by objects corresponding to a given experiment. This leads, in particular, to the research strategy focusing on model organisms or certain arbitrary cell types, such as the HeLa cells¹⁰, the first laboratory immortal human cell line, which originated from a patient, Henrietta Lacks (who died in 1951). It is also noteworthy to point out that the choice of the experimenter to focus on a specific phylogenetic history is in general arbitrary from a theoretical point of view (motivated by practical purposes or history of by the history of the field).

In order to sum the situation up, a practical consequence of the specificity of the object is the widespread use of objects having the *same* phylogenetic history, allowed by the *proliferative* nature of biological objects. Of course, an application of this method can be more or less fine grained, for example, we can work on a precise strain of bacteria or on members of the class of mammals. More precisely, a measurement is always performed on a specific biological object, having a specific history of symmetry changes, by taking phylogeny into account, up to a certain point, we can therefore have a shared history of symmetry changes and as a result, a restricted genericity of objects, defined by this common symmetry changes.

7.3.2 CONTROLLED HISTORY

We have seen that phylogenetic considerations are relevant; however, the theoretical consequences of the specificity of the object on biological measurement is not limited to the general phylogeny (and practically, for example, the sharing of specimens between labs). On the contrary, the more recent history of an organism is comparably crucial. As a result, beginning right after the choice of a phylogenetic history begins the necessary control of symmetry changes (ontogenetic, physiologic, ...) by two different methods: the control of the environment and the ruling out of specimens with unwanted symmetry changes.

The control of the environment (including the possible control of interactions with other organisms) is used to obtain regularized specimen. For bacteria, this aspect corresponds first to the use of a standardized medium, the control of temperature and crucially the avoiding of contamination. Moreover, it also involves the taking into account of the *time* that bacteria need to adapt themselves to a change of conditions. Notice that the situation can be somewhat more complicated when microscopy or even microfluidic is involved (because of the spatial structuring). However, when we are studying mammals, for example, the situation gets far more complex. The control of ontogeny has to take into account the *specificity* of the development, which is partially conferred a restricted genericity by a controlled environment, with regular temperature and light cycle, abundant (and well chosen) food, controlled interactions between males and females, As a result, when working with such a methodology, an experimenter does not look at an object "as it is", she chooses, as much as possible, a specific object, through reproducible constraints. The aim is then to have, as much as possible, the same symmetry changes in different instances of the same experimental protocol (in which we include the preparation of the specimen), the validity

¹⁰In PubMed, there are more than 60000 references to this cell line. From a heuristic point of view, notice that their very name come from their history, while the name of physical objects correspond to their definition as generic objects, in the suitable theory.

of the results depends then on the limited influences of the remaining random symmetry changes relevant for the observed phenomenon.

These aspects can even be seen at shorter time scales. If we want to perform a measurement, say of heart rate on a rat, we should take into account the retention and protention¹¹ associated with the changing of room, in a lab, and the corresponding scare associated with the use of the measurement apparatus. Indeed, an unprepared animal undergo considerable changes in heart rate in such a situation. If we do not wish to study those changes, we can prevent them by *training* the animal to change its protentional activity associated with this situation — we are then actively changing the behaviour of the organism. However, the situation can even be more subtle. If we want to compare heart rate between different organisms, we have to try to get rid of the various differences in their physiologies that can be relevant for the heart rate. As a result, some kind of symmetrizing level of activity has to be defined which can be understood as common for all the organisms we want to consider. Typical approaches are (see section 2.2 for more examples):

- considering a maximum activity, defined by the inability to have a higher level of activity and which leads to the maximum heart rate. It is an upper boundary of the viability domain.
- considering a level at which the experimenter tries to make every *specific* activities irrelevant (a local reduction of the impact of the different symmetry changes undergone between the two systems, whatever their origin are: phylogenetic, ontogenetic, behavioural, ...). This approach leads to the basal heart rate.

Another comparable situation is the constitution of standardized actions on the specimens, in order to (hopefully) obtain generic responses. Bonnarens & Einhorn (1984) gives an example of this approach. We understand here that, not unlike in the quantum situation, the experimenter has a crucial effect on the object, by constituting objects with a restricted genericity, from specific objects.

As we mentioned in the beginning of this section, the control of symmetry changes is not limited to preventing the organisms of undergoing relevant symmetry changes. The other method consists in ruling out the specimens which have clearly gone through unwanted symmetry changes, or equivalently which have not gone through wanted symmetry changes. This can go from developmental anomalies, mutations, pathologies to an animal that gets frightened during measurement. Even in a microscopy study of bacteria this approach is relevant since, for example, the commonly appearing “spaghetti” (very long bacteria) are usually ruled out.

In order to sum the situation up, we can say that the experimenter constitute the object by trying to constrain the symmetry changes that it can undergo, allowing, at least to a certain point, to provide a restricted genericity to the objects. The complementing approach consists in ruling out the objects exhibiting identified unwanted symmetry changes.

¹¹Presentation of these concepts is done in chapter 4 (Longo & Montévil 2011b).

7.3.3 IRREDUCIBILITY OF SYMMETRY CHANGES

In spite of these different strategies aiming to symmetrize the object, the hypothesis of extended critical transitions implies that there are always remnant symmetry changes, intrinsically driven by the structure of determination of our theoretical framework. Observable symmetry changes can be shown experimentally even for bacteria, for example, through the asymmetry in cellular division (Cai, Friedman & Xie 2006; Stewart et al. 2005; Lindner et al. 2008). Of course, ontogenesis, also leads to a high level of variability — by which we mean the random components of symmetry changes, associated here to, and in contrast with, a certain level of symmetrization in the measurement.

It is crucial that irreducibility of biological objects to a symmetry preserving situation occurs even when comparing an individual with himself. It can be seen, for example, by the non-stationarity of biological time series, that we have described with more details in sections 2.4, 2.5 and in the former section. This feature implies in particular the instability of a straightforward (temporally local) measure of many (if not all) physiological observables.

The point is then, for the symmetrization to be successful, that the symmetry changes spontaneously occurring should have a limited impact on the observed quantity. If it is a scale symmetry which is tested (for example allometry), the impact of variability is limited by the “flattening” effect of the logarithm. Besides, such symmetries are an extremely general characterization of elementary geometrical or mathematical aspects of systems. However, even in this case, variability remains remarkably high. Indeed, when allometry is used to approach developmental trajectories of different species, the scales symmetries and their changes are highly variable (see section 2.2 and Glazier (2005)).

7.3.4 RECAPITULATION

There is a biological notion that seems especially related to this approach of biological measurement. This notion is that of model (in the sense of an experimental model, not in the sense of a mathematical model). While it is virtually absent in physics (except sometimes in the study of complex systems and often in connection with biology), this notion is ubiquitous in biology. The point of such an approach is to focus researches on particular objects (model organisms, cellular constructs, ...) having “nice” experimental properties (for example, a high rate of proliferation for cells or organisms) in order to understand them with a high level of precision. Then the results can be extrapolated and tested in more experimentally difficult situations.

From our theoretical point of view, it seems that the notion of experimental model is related to the specificity of biological objects. We can understand it as a selection of objects having particular symmetries or history of symmetry changes. More precisely, our framework leads us to make a distinction between model organisms and models that are *in vitro*. In the first case, we have the extended critical transitions associated to the organism, but the amount of researches allows to navigate, with more or less accuracy, among the main symmetry changes relevant for these objects. In the second case, however, the integration in the organism is partially replaced by the control parameters of the experiment.

In both cases, the aim is to examine some properties which can have a certain level of genericity *beyond* the specificity of the considered object or the displacement from the context

of the organism. This genericity corresponds to symmetries and, in general, can very well be broken for another specific object¹². Notice that this perspective is not limited to model organisms. For example in Dhimolea et al. (2010), a tissular model is designed to approach the interactions between cells and the collagen matrix. In comparison with the *in vivo* situation, this model consists, in particular, in a symmetrization of the interactions between the tissue model and the rest of the organism (which is replaced by control parameters). One aim of this model is to study the influence, on tissular organization, of physical forces applied to the matrix. In this context, these forces, in particular, become a parameter of the system, controlled by the experimental device, instead of being an observable in the context of an organism. This approach allows then to reveal how various quantities of the control parameters leads to a change in the reorganization of the matrix by the cell and more generally to different morphogenesis.

To sum our theoretical approach up we can propose the following principles for at least a certain kind of biological measurement:

1. The measure is relative to/constituted by a history, understood as a cascade of symmetry changes. This means that it *always* involves a certain kind of control of these symmetry changes. This control is (at least) composed from *all* the following elements:
 - phylogeny — which we understand here as an uncontrolled history but *shared* by different organisms — through the *proliferation* of objects (and not their generation *de novo*).
 - controlled experimental environment/interactions — the (partially) controlled history in the laboratory, including active prevention against unwanted symmetry changes, associated in particular to pathologies and to protention. When possible, this includes also the conditions of *ontogeny*.
 - the *a posteriori* ruling out of situations with strong, unwanted, symmetry changes (pathological cases, unwanted behaviour, ontogenetic or even phylogenetic histories, ...). Notice in particular that since the preceding point is very limited in certain cases (measurement on humans for example is ethically incompatible with a controlled ontogenetic environment), this approach allows to partially compensate. This leads to the methodological substitution of a part of the excepted similar history by a set of controlled symmetry (morphological, physiological, ...).
2. The measure includes (is impacted by) the unavoidable symmetry changes that are not controlled, as a result, when quantitative, it leads to non-vanishing intervals (in contrast with classical measure).

This notion of measurement follows from the idea to consider the object as specific. This is a much more radical notion than what exists in physics, where the fact that we work on *an* object is understood as a choice of possible parameters, reference frame, ..., allowing to

¹²This of course depends of the nature of these properties, of the symmetry changes of the two different objects,

understand the object as generic (with specific values of the various parameters and initial conditions, leading to the specific trajectory). However, biological specificity does not necessarily lead to a *fragmentation* of the theoretical significance of (all) experiments. On the contrary, the *constitution* of observables, for example, the *basal* metabolic rate, allows to evidentiate/constitute symmetries ... and symmetry changes.

7.4 ALLOMETRY AND SYMMETRY BREAKING

We reviewed, in chapter 2, the main empirical aspects of scale symmetries in biology. In particular, allometry, with mass M as a scale parameter, is a powerful tool to study physiology (by relationship of the form $A = bM^\alpha$). We have seen, however, that there are some difficulties associated with this approach, leading to controversies over the validity of the exponents, α (Agutter & Wheatley 2004; West & Brown 2005). Since the question in this topic is on the validity of a biological symmetry, it is an interesting and relevant situation for us to apply our theoretical framework. We do not intend to resolve the situation completely; however, we propose a change of perspective on the question of the nature of such relationships.

7.4.1 VARIABILITY VERSUS FLUCTUATIONS

To begin this analysis, we will first give a sharp distinction between the understanding of a physical experiment and a biological allometric analysis. In a regular (classical) physical experiment, there are fluctuations and imprecision leading to a deviation of the measured quantity from the expected one (or discrepancy between two similar experiments). These fluctuations are random, meaning that they are not reproducible (except through a high number of trials). On the contrary, a deviation from the allometric curve, corresponding to a specie, for example, is (modulo some classical imprecision and intraspecific variability) completely reproducible (see figure 7.1). In other words, the biological variability, here, is robust and can be contrasted with the physical fluctuations, which are understood as contingent.

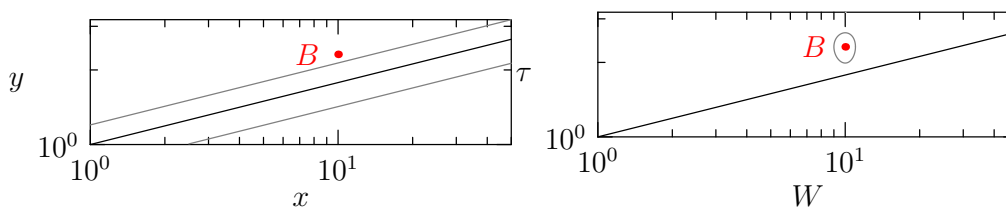


Figure 7.1: *Fluctuation vs variability in allometry*. LEFT, the case of a physical experiment, where B is the result of a measure. The following measurement will not be related to the first one, following the imprecision hinted by the gray lines. RIGHT, the case of biological allometry is represented. Here, a second measure (for objects having approximately the same histories) will lead to the same result (modulo some variability and classical imprecision) and is therefore robust. This situation is hinted by the gray curve.

This situation can be conceptually clarified in our theoretical framework. Let us assume that the allometric relationship is valid among mammals. The measure for a specie is relative

to the choice of a phylogeny (the specie), or, in other words, the specificity of the object allows to understand that this measure escapes robustly from the general “law”, the scale symmetry. We have found again, through this example, that we have a sharp distinction between imprecision, which is due to noise (or fluctuations), and variability, which is due to a cascade of symmetry changes.

We can develop further this distinction. For a classical system, imprecision can be, *in principle* (in the mathematical framework) reduced to an arbitrary small size. If we consider a thermodynamic (not critical) system, fluctuations can be reduced by increasing the size of the system. However, for the biological situation, the departure from the symmetric situation is robust. As a crude example, one can think of the physiological changes between reptiles and mammals — where the different symmetry changes between the two specific objects are numerous. However, relevant symmetry changes can occur at a much smaller time scale. Obesity, for example, takes place at ontogenetic time scales and leads to a very moderately higher heart rate in relation with an importantly higher body mass (Hirsch et al. 1991). This relation is quantitatively and even qualitatively the contrary of what interspecific allometric equations leads to (increased mass leads to lower heart rate). Of course, the non applicability of the standard allometric approach, here, can be easily understood, at least qualitatively, since obesity is a changing of the organization (say, mass repartition among cell types for example). In order to propose a further interpretation, we can say that the usual allometry involves a corresponding transformation of organs, of cells, ... and of their activities, leading to the possibility of a global slowing down with increased mass. However, in the case of obesity the organs sizes are “stuck”, and need to accommodate a larger body weight, which leads to a strain on organs (mostly responded to, in the case of the heart, by an increase in stroke volume, the increase of heart rate is low, see Kopelman (2000)).

In other words, typically, the values of a physical measure are typically distributed symmetrically around mean values, while measures of observable quantities as for species or individuals, are not symmetric. In principle: they are not generic/interchangeable, but correspond to *specific* and *historical* biological organizations. This is so even in the case they are given through symmetrizing measurement such as defined by basal metabolic activity, for example.

7.4.2 SYSTEMATIC APPLICATION OF OUR FRAMEWORK

We will apply systematically our framework to the measurement of an allometric exponent. In this case, the scale symmetry is obtained with respect to the following aspects:

1. Symmetrisation.

- Phylogeny: the measurement is performed with respect to a phylogenetic domain (for example the class of mammals, birds, ...). For intraspecific allometry, it is performed on developing members of a given species.
- controlled experimental environment/interactions: this defines, for example, the basal metabolic rate, the maximum metabolic rate, the field metabolic rate, ...

- The *a posteriori* ruling out of certain situations: pathological cases or species when the above is not obtainable are not taken into account.

2. Robust deviations occur for subclasses or species.

More precisely this version is, what we could call a strict allometric analysis. Some authors, however, propose a different type of measurement associated to the “transfer” of aspects corresponding to the remaining symmetry changes into the symmetrization part (for example taking account subclasses). This corresponds, from our point of view, to a *different* measurement, which allows to show different aspects of biological organization.

We will now propose a mathematical structure that allows to accommodate an important (but incomplete) part of our theoretical analysis.

7.4.3 A MATHEMATICAL FRAME FOR BIOLOGICAL ALLOMETRY

The mathematized approach we will now expose is limited to allometric symmetries, but, as we shall see, will still allow to take into account fundamental aspects of our conceptual framework.

7.4.3.1 *Mathematical background*

We saw in theorem 2.1 that the equational form $f(\mathfrak{D}_\lambda M) = g(\lambda)f(M)$, assuming that f is continuous, leads to the equation $g(\lambda) = \lambda^\alpha$. However, here, we will *not* make this continuity hypothesis. To simplify the situation, we will consider the one dimensional case.

Since it is usually easier to apprehend linear and affine situations, we will work up to an isomorphism and define $F = \ln \circ f \circ \ln$ and $G = \ln \circ g \circ \ln$. This change of variables corresponds to the transformation of a multiplicative structure into an additive structure.

We obtain the following relation:

$$F(x + y) = G(x) + F(Y) \tag{7.4}$$

$$F(x) = G(x) + F(0) \tag{7.5}$$

$$G(x + y) = G(x) + G(y) \tag{7.6}$$

Let us recall the mathematical properties we obtain under this assumptions, through pure algebraic reasoning (without continuity).

- By using recurrence, we can show that for $a \in \mathbb{R}$.and for all $n \in \mathbb{N}$, $G(na) = nG(a)$, because $G(na) = G(a(n-1)) + G(a)$. This result is extended to \mathbb{Z} (because $G(na - na) = G(0)$).
- We then observe that for $r = \frac{p}{q} \in \mathbb{Q}$, $G(ra) = rG(a)$ because $G(\frac{p}{q}qa) = G(pa) = pG(a)$ and $G(\frac{p}{q}qa) = qG(\frac{p}{q}a)$.
- The conclusion is that G is \mathbb{Q} -linear: for $x, y \in \mathbb{R}$ and $r, s \in \mathbb{Q}$, $G(rx + sy) = rG(x) + sG(y)$.

- Reciprocally, every \mathbb{Q} -linear function, G matches our hypothesis, and modulo a choice of $F(0)$, defines uniquely F following equation 7.5.

Since we are going to use \mathbb{Q} -linearity a lot, we will define the common notation $x\mathbb{Q} = \{xr|r \in \mathbb{Q}\}$, which is a vectorial \mathbb{Q} -line, and also $y + x\mathbb{Q}$ which corresponds to an affine \mathbb{Q} -line.

7.4.3.2 Biological framework

Let us now introduce the theoretical use of this mathematical structure. Suppose $f(x)$ is an observable (F is then the corresponding observable in log-log coordinates). For example, $f = \tau$ can be the inter-beat interval of the heart and its parameter $x = m$, the mass of the organism. Then, we will write in log-log coordinate $T(M)$. In particular, the classical (not in our discontinuous framework) allometric relation reads $\tau = bm^{1/4}$, which equivalently leads to $T = B + \frac{1}{4}M$.

The transformations of the (logarithm of the) mass which lead to an observed power law will thus be the following for $r \in \mathbb{Q}$:

$$M_0 \rightarrow M_0 + rM_1 \quad (7.7)$$

$$T(M_0) \rightarrow T(M_0 + rM_1) = T(M_0) + rT(M_1) \quad (7.8)$$

Reciprocally, taking a limit such as $\lim_{n \rightarrow \infty} r_n M_1 = M_2 \notin M_1\mathbb{Q}$ will allow to escape this power law, and thus correspond to a symmetry change. This limit will generate an other power law for the transformations rM_2 , and a class of possible combinations of the two, associated to $r_1 M_1 + r_2 M_2$.

The measurement will then have two basic components:

A METRIC, OR PHYSICAL COMPONENT: this component is associated with the *classical physical* measure that is involved in the biological measure. It defines the magnitude of the (logarithm of) the mass and of the observable (for a specific object). The discontinuous nature of F , however, implies that this measure is not sufficient at all to exhibit symmetries.

AN ALGEBRAIC OR SPECIFIC COMPONENT, which is associated to the *specificity* of the object and of the experimental protocol. This aspect determines the *dominant* direction $M\mathbb{Q}$ in the measurement setup (for example, interspecific allometry of the basal heart among mammals). This algebraic component cannot be obtained by the physical measure alone (because $M\mathbb{Q}$ is dense in \mathbb{R}).

We can now define what we propose to call the *physical form* corresponding to a transformation $M_0 \rightarrow M_0 + rM_1 = M$, in order to clarify the biological and experimental meaning of such a transformation.

This transformation leads to $F(M_0 + rM_1) = F(M_0) + rF(M_1)$, or equivalently $m = \exp(M_0) \exp(rM_1)$ leads to $f(m) = f(\exp(M_0)) \exp(r)^{F(M_1)}$. From the latter we can write:

$$f(m) = f(\exp(M_0)) \exp(-M_0)^{F(M_1)/M_1} \exp(M_0 + rM_1)^{F(M_1)/M_1} \quad (7.9)$$

$$= a(M_0, M_1) m^{F(M_1)/M_1} = am^\alpha \quad (7.10)$$

Thus, the allometric exponent α is given by $\alpha = h(m_1)/m_1$, while the coefficient a depends, in particular, on $f(m_0) = f(\exp(M_0))$. We should emphasize again that this equation is only valid for m of the forms $m = \exp(M_0) \exp(rM_1)$. We will then call the equational form $f(m) = a(M_0, M_1)m^{F(M_1)/M_1} = am^\alpha$ the *physical form* of the equation because it relates two physically measurable quantities, provided that the context of an algebraic measurement is given.

Now, let us look more precisely at the possible symmetry changes. We have seen that taking a limit, $\lim_{n \rightarrow \infty} r_n M_1 = M_2 \notin M_1 \mathbb{Q}$, leads to a symmetry change by generating a change of the algebraic nature of the transformation. In this case, we can then distinguish three different situations:

1. biologically, the degree of freedom $M_1 \mathbb{Q}$ is still valid, but the transformations in $M_2 \mathbb{Q}$ are not. This leads to masses of the form $M_2 + rM_1$. Under this conditions, the allometric exponents associated to M_1 remain the same, but we are looking at a new class of objects (typically we go from mammals to birds, for example). The physical forms indeed are $f(m) = am^\alpha$ and $f(m) = bm^\alpha$. It is a change of classes of objects, but both are invariants for the same symmetry.
2. the degree of freedom $M_2 \mathbb{Q}$ is valid, but not $M_1 \mathbb{Q}$. This situation leads to possible masses of the form rM_2 . Then, we can identify a new corresponding allometric exponent, leading to the physical form bm^β . We can think here of a radical organizational or measurement change, for example, observing maximum heart rate instead of the basal heart rate. It is a complete change of symmetry.
3. Both degrees of freedom are valid, leading to masses $r_1 M_1 + r_2 M_2$. We then have a physical form $a \left(\frac{m}{\rho}\right)^\alpha \rho^\beta$. This is, for example, the case if we consider overweight, where $r_2 M_2$ parameterizes the corresponding organizational change, while $r_1 M_1$ correspond to, say, interspecific allometry. In physical form, $\frac{r}{\rho}$ would be the health weight and ρ is the corresponding overweight ratio. If we assume that overweight does not influence heart rate, for example, we obtain $\beta = 0$.

7.4.3.3 Further aspects of this framework

To sum the situation up, we have defined a framework where measurement has an algebraic aspect and a metrical aspect. The metrical expression is sufficient to determine what happens provided the algebraic component is preserved. This more precisely corresponds, in the log-log space, to a translation along a \mathbb{Q} -line, $M_1 \mathbb{Q}$. This translation correspond to a power law, so it corresponds to a scale symmetry. This leads to an exponent that can be empirically evaluated provided the algebraic structure can be (approximately) followed experimentally (for example the basal heart rate among mammals). When following an other \mathbb{Q} -line, say $M_2 \mathbb{Q}$, an other exponent can be found, for example, by the experimental constitution of an other symmetry (the maximum metabolic rate, say). A punctual shift can also occur, which does not allow to specify a corresponding exponent, because there is no empirical degree of freedom associated to this transformation, so metrical measure is impossible (however, this status can be temporary, if an underlying transformation is found). Nevertheless, such

a shift can be associated to a specific biological phenomena, for example, a change of class (mammals and birds).

Now, there is a mathematical aspect, here, that has a significant biological meaning. To define such a function f completely, one has to choose a base of \mathbb{R} as a \mathbb{Q} -vectorial space. However, such a definition in set theory requires the axiom of choice (via Zorn's lemma). The axiom of choice corresponds to the possibility of defining a function which returns one element per set in any set of sets (Herrlich 2006). The difficulty of this axiom, which lead to a lot of debates in mathematical logic, is that no finite rule can in general define such a function. Notice that in set theory (ZF), both the axiom and its negation lead to the same consistency than ZF .

The biological consequence of this aspect is that f cannot be finitely defined. From a biological perspective, then, it means that there is an intrinsic and irreducible randomness in the determination of the possible symmetry changes (here, among allometric symmetries) that biological systems can undergo. Another consequence of this situation is that only a finite number of such biologically relevant transformations are generally known. From a different point of view, it also means that the f function is only partially defined and that evolution (or possibly ontogenesis) can bring the definition of new symmetry changes, corresponding to new observables.

Notice, however, that the result of a set of experiments, the transformations along a line $M_m\mathbb{Q}$, needs, for the observability of the related exponent, a certain limitation of the quantitative impact of the diverse symmetry changes occurring because of the specificity of biological objects. This limitation is obtained for a good part by the measurement, which selects the specific transformations, along $M_m\mathbb{Q}$. However, the possibility of such a limitation is also associated to a limited magnitude of the random symmetry breaks for a given time scale, in which we also take into account, for example, the phylogenetic driven variability. The resulting transformation is the following:

$$rM_m \rightarrow rM_m + \sum_i r_i M_i = M \quad (7.11)$$

$$F(rM_m) \rightarrow rF(M_m) + \sum_i r_i F(M_i) \quad (7.12)$$

This leads in particular to:

$$F(M) = \left(r + \sum_i r_i \frac{M_i}{M_m} \right) F(M_m) + \sum_i r_i \left(F(M_i) - \frac{F(M_m)M_i}{M_m} \right) \quad (7.13)$$

$$= M \frac{F(M_m)}{M_m} + \sum_i r_i M_i \left(\frac{F(M_i)}{M_i} - \frac{F(M_m)}{M_m} \right) \quad (7.14)$$

This last equation gives us the expected measure as the first term (a power law); its observability through physical measure depends on the possibility of deviations of the second term from being a constant among all elementary measurements. More precisely, if this term differs from a constant, then the expected symmetry encounters variability (which always occurs), with a magnitude corresponding to the deviation. Observability and thus theoretical

validity of the power law thus requires the variation of this term to remain small, which is achieved in particular by biological measurement, following our principles. Notice that the former equation can be written as:

$$F(M) = M \left[\frac{F(M_m)}{M_m} + \sum_i \frac{r_i M_i}{M} \left(\frac{F(M_i)}{M_i} - \frac{F(M_m)}{M_m} \right) \right] \quad (7.15)$$

Which means that the observed deviations from the power law are better evaluated by the second term. We want to emphasize that variability occurs both by variations of r_i (for example through a change of body index) or by the taking place of unknown symmetry changes, since, in particular the various $(M_i, F(M_i))$ are not necessarily the same (and in fact are not all the same) for all the organisms involved in the experiments (or for the same organism at different times).

Another crucial point is that, considering the tendency of biological systems to change their symmetries, the observability of such a biological power law is in general meaningful. This is particularly the case when the control over symmetry changes is limited. For example, when we are considering allometry of mammals, the phylogenetic symmetry changes that can be controlled are extremely limited. The validity of such a law corresponds also to a certain genericity of the control of symmetry changes (through basal or maximal physiology, for example).

Notice that this framework has been described here for a particular one parameter continuous symmetry. This procedure can be generalized at least to certain finite continuous symmetries relatively straightforwardly (for example matrix groups). Notice also that important cases of differential or partial differential equation are associated to Lie groups (which allow to solve them), which also suggest further extensions.

7.5 COMPACIFIED TIME AND AUTONOMY

We will now consider the case of biological rhythms following chapter 3 (Bailly, Longo & Montévil 2011). This case will allow us to apprehend the relationship of biological measure with symmetry changes from a different perspective.

We have seen in chapter 3 that a second temporal dimension, added to the usual physical time, allows to accommodate biological internal rhythms. This dimension is compacified (with the topology of a circle) and is associated with the allometry of biological internal rhythms ($\tau \propto W^{1/4}$). As a result, this supplementary time dimension is (as a first step) justified by an allometric scale symmetry.

This symmetry, however, takes only into account the broad tendencies among species sharing similar physiological traits. From another point of view, we can look at the time series generated by the iterations of the compacified time and parameterized by physical time, for a specific organism. This approach, in our 2-dimensional framework, is in particular described in section 3.4.4. Considering their variability, this kind of precise trajectories, for a given internal rhythm, is not determined by the allometric symmetry alone.

In order further to understand the situation, we will first recall how periodic behaviours are determined in physics and we will then analyze the situation in biology. The core point

that we want to emphasize is the relationship between the periodicity of physical phenomena and energy (and its conservation). The other reason why we provide these examples; is that the form of elementary repetitive phenomena provides paradigmatic insights on the consequences and on the nature of a theoretical framework.

7.5.1 SIMPLE HARMONIC OSCILLATORS IN PHYSICS

Oscillatory behaviours in physics have multiple forms. However, the simplest of them, the simple harmonic oscillator, is usually a key and paradigmatic model since it regularly appears, at least as a first approximation, in a wide range of situations.

A reason, why such behaviours regularly appear, is that it is a general linear approximation of a behaviour near equilibrium, meaning that it is valid near equilibrium as soon as that the latter is well defined and the associated functions are sufficiently regular.

7.5.1.1 Classical oscillator

If we consider a classical conservative system near a local stable equilibrium at $x = 0$, we obtain:

$$m \frac{d^2 x}{dt^2} = f(x) \simeq f(0) + \frac{\partial f}{\partial x}(0)x \quad (7.16)$$

$$\simeq -kx \quad (7.17)$$

Indeed, the condition for stable equilibrium leads to $f(0) = 0$ and to $k > 0$. The general solution for such a system is $x(t) = a \cos(\sqrt{\frac{k}{m}}t + \varphi)$, where a depends on the initial energy of the system and φ depends on the direction in phase space of the initial state. The corresponding energy is

$$E = \mathcal{H} = \frac{1}{2}m \left(\frac{dx}{dt} \right)^2 + \frac{1}{2}kx^2 \quad (7.18)$$

as a result the simple harmonic oscillator is a system which continuously transfers its energy from kinetic energy to potential energy and successively the other way round. The time an iteration takes depends only on the relative “strength” of kinetic energy (the inertial mass, m) and of potential energy (the coefficient k).

7.5.1.2 Quantum oscillator

The quantum harmonic oscillator is somewhat different. Its behavior is still determined by energy; however, the structure of determination and in particular the nature of the objects used is different. The Hamiltonian is:

$$\hat{\mathcal{H}} = \frac{1}{2m} \hat{p}^2 + \frac{1}{2}k\hat{x}^2 \quad (7.19)$$

$$\text{with } \hat{x}\psi(x) = x.\psi(x); \quad \hat{p} = -i\hbar \frac{\partial}{\partial x} \quad (7.20)$$

$$\text{Possible measures verify } \hat{\mathcal{H}}\psi = E\psi \quad (7.21)$$

Solving this system leads to discrete energy levels: $E_n = \hbar \sqrt{\frac{k}{m}} \left(n + \frac{1}{2}\right)$ and correspondingly a set of frequencies $f_n = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \left(n + \frac{1}{2}\right)$. Again, the behaviour of the system is determined by energy, but in this context energy is quantized and has a minimum which is different from zero, meaning that the system is never at the corresponding classical equilibrium point¹³. More generally, quantum physics introduces wave-particle duality, in particular through the De Broglie relation: $f = \frac{E}{h}$.

7.5.1.3 Conclusion

We saw that in both cases, the simple harmonic oscillator is characterized by its symmetric form, for energy, of the momentum and the position contribution. Their respective weight in energy leads to the determination of the period of the phenomenon. This example shows how, in fundamental physics, the “repetitive behaviours” have their properties determined by energy, with its underlying symmetries.

The result of these accounts is that the period of such physical phenomena is determined by the form of energy. More precisely, these periods are determined by the ratio of the coefficients, in the Hamiltonian, corresponding to the contributions of position and momentum. In both cases, the period depends then on parameters characterizing the properties of the objects (the mass and the coefficient k). The consequence of this theoretical origin of the period is that its values are robust and rooted in the properties of objects. The further consequence of this situation is then that these phenomena have an intrinsically regular relationship with physical time (which have been conceptualized and mathematized precisely for this purpose).

Of course, physics is not limited to these cases, which are the most elementary ones. More complex situation can occur, in particular by introducing non-linearities (linearity almost directly leads to a superposition of harmonic oscillators).

7.5.2 SYMMETRIES AND COMPACTIFIED TIME

In the case of biological internal rhythms, however, energy conservation does not seem to be able to determine the trajectory of the iterative process¹⁴ since there is no underlying symmetry corresponding to a possible energetic determination. Let us consider, for example, the case of the heart rhythm. This rhythm is neither *fully* determined by the properties of the heart (insofar they are defined) nor by direct response to a well defined requirement in “energy” of the organism. On the contrary, the determination of the heart rate involves the full complexity of *both* the heart organ and the regulation associated to the behaviour of the whole organism. For example, the various activities of organs, are related to the history of the organism at different time scales. As a result, the determination of the heart rate depends also on the environment of an organism and more precisely depends on its complex relationship to it (including protection and retention, as described in chapter 4 Longo & Montévil (2011b)).

¹³This kind of quantum behaviour leads to quantum fluctuations, even at 0 temperature, see §7.2.3.

¹⁴Understood as a trajectory parameterized by the usual physical time

In other words, the theoretical determination of the trajectory of an organ, such as the heart involves the activity of the whole organism¹⁵. As a result, the symmetry changes of the whole organism breaks any geodetic determination of heart trajectories. This situation leads to the lack of a complete theoretical determination of this trajectory with respect to physical time. From a slightly shifted point of view, the generic trajectories of the organism influence the trajectories of the heart (beat to beat interval, here), breaking possible regularities with respect to physical time. Our point here is not to say that there would be some violation of energy conservation in an organism, but to say that there is no invariant form (symmetry) of the determination of something like a heart rate, at least since this determination requires the organism.

The symmetry we have proposed in chapter 3 (Bailly, Longo & Montévil 2011) to accommodate such a rhythm, beside the question of allometry, is based on the iterative nature of the organ considered (and the pure number of their iteration). We understand then that the strategy we propose to understand this kind of fundamental “biological oscillator”, is based on the introduction of a supplementary temporal structure (generated by the second time dimension), irreducible to the usual physical time precisely because of the lacking energetic determination. Now, this conceptual change, from the physical oscillator to the “biological oscillator” — or in more precise terms, biological iterator — is associated to the peculiar features of heart rate variability. This features lead to an instability of the beat to beat (physical time) interval during wake, instability which can have different forms depending on age, activity, possible pathologies,

As a result, our mathematical approach in chapter 3 should be understood as slightly different from the usual physical approaches. The framework is based on very general tendencies (symmetries), such as allometry and the regularity of the physical, external, rhythms (based on a regularity among mammals, birds, ...), but the engendered mathematical structure does not provide objective, specific trajectories. On the contrary, the observed trajectory of a specific organism can be embedded in our framework in a “natural” way. This operation allows to show the specificity of the object by geometrically emphasizing the qualitative features of a trajectory, which can also be seen as the structure(s) of its variability, or in other words, as the various shapes of its relationship with physical time.

7.5.3 CONCLUSION

The aspects we described provide a supplementary justification to the introduction of a second temporal dimension. Indeed, the points we raised and our more general framework leads to an inadequacy of the theoretical determination of biological trajectories with respect to the physical time.

Moreover, we pointed out the role of a trajectory associated to a specific objects, since our 2-dimensional framework allows to represent and study the complex and diverse relationships between physical time and biological proper rhythms. This kind of trajectory is associated to the individuation of the organism at various time scales; it include both “spontaneous” variations and association with various factors.

¹⁵In general, the precise aspects of the activity of the organism that are directly relevant for a particular organ depend of course on the nature of the organ.

7.6 OBSERVING SYMMETRY CHANGES?

In our previous conceptual analysis of biological measurement, we focused on a notion of biological measurement based on symmetrization. We will, however, look here if the symmetry changes themselves can be used for a specific form of measurement. The case of biological time, and more specifically the analysis of the variability in the relation of the compactified time with physical time leads to consider a biological trajectory and the specific structure it generates.

7.6.1 FROM A MEASURED TRAJECTORY TO SPECIFIC SYMMETRIES

This lead to another point of view, instead of symmetrization, the measure focuses on the observation of the constitution of various temporal structures by a specific biological object. This approach can be considered with more generality, and lead to an alternative account of biological measurement (at least *prima facie*).

Here, we have to make a theoretical assumption on the nature of an observed trajectory. This assumption is precisely that we can observe the trajectory constituted by the organism at the level of an organ (a part of it). In this case, the specific trajectory is the trajectory that has been observed¹⁶. This *a posteriori* trajectory determines then, at least partially, the relevant symmetries for its description, and their changes along the time evolution.

In other words, focusing on a single trajectory, whether it is a physiologic, ontogenetic or phylogenetic one, will lead to the (indirect) observation of various symmetries and symmetry changes. The latter correspond to the variability, intrinsic in biological organization, that acts in this trajectory. In this perspective, then, the observed trajectory determine the theoretical symmetries of the system, and its changes.

We can understand that such a perspective is also used when the biological object under study is pushed towards very peculiar trajectories, or in other words when the empirical strategy consists in exploiting the specificity of biological object as much as possible. For example, in Patterson & Linden (1981), the cognitive abilities of gorillas is not approached by symmetrization but instead by obtaining a highly specific object, in strong interaction with the experimenter, namely a gorilla knowing sign language (up to 2000 symbols). Such trajectories are not necessarily, even approximately, reproducible; however, this point does not compromise the objectivity of their study.

It is noteworthy to point out that the point of view we just described is not as far from the symmetrization approach that one could think *prima facie*. Indeed, the specificity of the object is not overcome in the symmetrization approach, on the contrary this proposal involve the focusing on specific objects sharing symmetries, in particular through the control of their history and of their experimental conditions. Reciprocally, an observed specific trajectory is also dependent on a given history, corresponding to a certain form of stability. From a temporal point of view, a limited amount of time given to a biological system limits the symmetry changes it can undergo. *In fine*, the difference between these two approaches

¹⁶This situation is not unlike the state of a quantum system after measurement which corresponds to the measured value.

is then that the first conceptual frame emphasizes the (restricted) symmetry constitution, whilst the second focuses on the various symmetry changes.

Another feature associated with symmetry changes and with the measurement of a trajectory, is the long-range fluctuations and the scale symmetries associated with symmetry breaking, in a large class of physical situations. As a result, biological symmetry changes can be expected to be associated to such features. This kind of signatures can be observed, almost directly (and are observed, see section 2.4, for example). For example, in Scheffer et al. (2009), the properties of a system before it reached a critical transition are considered in terms of long-range fluctuations. The result of this aspect is that the observation of symmetry changes is especially associated with the observation of particular forms of fluctuations. However, and in spite of the notion of universality involved in the corresponding physical situations, these scale symmetries do not seem to have the robustness encountered in physics, see chapter 2.

7.6.2 GLOBAL ASPECT OF EXTENDED CRITICAL TRANSITIONS

We have seen that the above considerations do not lead to a change of the principles of section 7.3.4, but still to a change of perspective on them. In the mathematical framework that we provided, the consequences of symmetry changes appear through a specific observable, as generating variability with respect to a main symmetry (when there is one). This aspect, however, is confined to a specific observable or a specific combination of observable.

The question that we can raise and to which we will not answer directly, is whether we can observe, in some more or less indirect way, an amount of all symmetry changes occurring in an organism. In chapter 8 we will consider the notion of anti-entropy (Bailly & Longo 2009), which is, in particular a description of biological complexity. This notion can help provide a solution to this question, see chapter 8. Another related aspect, or more precisely a particularly relevant component of anti-entropy, are the potential scaling relationships associated with criticality, which we will analyze in chapter 10 and 11.

7.7 CONCLUSION

We have determined that, in the conceptual framework of extended critical transitions, biological measurement can be understood as having proper features. These features consist in a co-constitution of the symmetries (and their changes) observed by the specific biological objects and the experimental/theoretical action. This does not mean that the results of measurement, or the conclusions drawn from it, are necessarily confined to this co-constitution, but that there is no measure without this kind measurement.

We also provided more justification to our introduction, in chapter 3, of a supplementary time dimension. This justification come from the lack of invariant theoretical determination of the biological proper rhythms with respect to physical time. This aspect is associated with the observation of the various forms of their relationships.

The thing we especially lack in biology is a theoretical determination of the dynamic of symmetry changes. This aspect is what our mathematical theoretical frame lacks to be equivalent in status to physical phase spaces. Notice that such a theoretical determination is not meant to be necessarily deterministic. On the contrary, we pointed out that the

mathematical frame proposed is associated to a function f which cannot be defined in a finite way by the use of observable symmetries (or degrees of freedom, like body index, activity habits, ...). This points to a strong form of randomness in the biological structure of determination.

However, in order to approach the global aspects of symmetry changes in an organism, we need a better account of such a structure of determination. In chapter 8, we will discuss a candidate notion, which can help provide such an account.

Biological order as a consequence of randomness : Anti-entropy and symmetry changes 8

This chapter is a variation of:

G. Longo & M. Montévil. 2012. Randomness increases order in biological evolution. In *LNCSS, proceedings of the colloquium in honor of Christian Calude, Auckland*. Submitted. Springer-Verlag

CONTENTS

| | | |
|-----|---|-----|
| 8.1 | Introduction. | 182 |
| 8.2 | Entropy in ontogenesis. | 183 |
| 8.3 | Randomness and Complexification in Evolution. | 185 |
| 8.4 | (Anti-)Entropy in Evolution. | 188 |
| 8.5 | Organizational regeneration | 193 |
| 8.6 | Interpretation of anti-entropy as a measure of symmetry changes | 199 |
| 8.7 | Theoretical consequences of this interpretation | 204 |

ABSTRACT:

In this text, we revisit part of the analysis of anti-entropy in Bailly & Longo (2009) and develop further theoretical reflections. In particular, we analyze how randomness, an essential component of biological variability, is associated to the growth of biological organization, both in ontogenesis and in evolution. This approach, in particular, will focus on the role of global entropy production and will provide a tool for a mathematical understanding of some fundamental observations by Gould on the increasing phenotypic complexity along evolution. We also propose a preliminary analysis of biological regenerative processes, which allows to associate entropy production of adults to anti-entropy, by considering collisions between entropy and anti-entropy (from the point of view of randomness, a purely mathematical analogy will be made with the “collisions” between particles and antiparticles). Lastly, we

analyze the situation in terms of theoretical symmetries, in order to further specify the biological meaning of anti-entropy as well as its strong correlations to randomness.

Keywords : anti-entropy, entropy production, macroevolution, metabolism, regeneration, variability, randomness

8.1 INTRODUCTION.

NOTIONS of entropy are present in different branches of physics, but also in information theory, biology ... even economics. Sometimes, they are equivalent under suitable transformations from one (more or less mathematized) domain to another. Sometimes, the relation is very mild, or may be at most due to a similar mathematical expression. For example, one often finds formulas describing a linear dependence of entropy from a quantity formalized as $\sum_i p_i \log(p_i)$, where the p_i are a measure of the probability of the system to be in the i -th (micro-)states. Yet, different theoretical frames may give very different physical meanings to these formulas: somehow like a wave equation describing water movement has a similar mathematical formulation as Schrödinger's wave equation (besides some crucial coefficients), yet water waves and quantum state functions have nothing to do with each other.

Another element seems though to be shared by the different meanings given to entropy. The production of entropy is strictly linked to irreversible processes.

But ... what is entropy? The notion originated in thermodynamics. The first law of thermodynamics is a conservation principle for energy. The second law states that the total entropy of a system will not decrease other than by increasing the entropy of some other system. Hence, in a system isolated from its environment, the entropy of that system will tend not to decrease.

More generally, increasing entropy corresponds to *energy dispersion*. And here we have the other element shared by the different views on entropy: in all of its instances, it is linked to randomness, since diffusions, in physics, are based on *random walks*. Thus, energy, while being globally preserved, diffuses, randomly. In particular, heat flows from a hotter body to a colder body, never the inverse. Only the application of work (the imposition of order) may reverse this flow. As a matter of fact, entropy may be locally reversed, by pumping energy. For example, a centrifuge may separate two gazes, which mixed up by diffusion. This separation reduces the ergodicity (the amount of randomness, so to say) of the system, as well as its entropy.

Living beings construct order by absorbing energy. In Schrödinger's audacious little book, *What is life?* (Schrödinger 1944), it is suggested that organisms *also* use order to produce order, which he calls *negentropy*, that is entropy with a negative sign. And this order is produced by using the order of the chromosomes' a-periodic structure (his audacious conjecture) *and* by absorbing organized nutrients (don't we, the animal, eat mostly organized fibers?). Of course, a lot can be said, now, against these tentative theorizations by the great physicist.

But is really entropy the same as disorder? There is a long lasting and sound critique, in physics, of the “myth” of entropy as disorder. F. L. Lambert (see <http://entropysite.oxy.edu/>, especially Lambert (2007)) is a firm advocate of this critical attitude. This is perfectly fair since entropy is “just” energy dispersal in physics, regardless of whether the system is open or closed¹. Yet, as explained in Hayflick (2007), “*in physics, a lowered energy state is not necessarily disorder, because it simply results in the identical molecule with a lowered energy state. The fact that such a molecule might be biologically inactive may not concern the physicist, but it definitely does concern the biologist ...*” In this perspective, it is then sound to relate entropy to disorder in biological dynamics: a lesser activity of a molecule may mean metabolic instability, or, more generally, less coherent chemical activities of all sorts. As a consequence, this may result in less bio-chemical and biological order.

In either case, though, and by definition, entropy has to be related to energy dispersal. As a matter of fact, the analysis of heat diffusion in animals and humans has a long history that dates back to the ‘30s (Hardy 1934). Since then, several approaches tried to bridge the conceptual gap between the purely physical perspective and the biologist’s concern with organization and with its opposite, disorder, in particular when increasing, in aging typically (Aoki 1994; Hayflick 2007; Marineo & Marotta 2005; Pezard et al. 1998).

Let’s now summarize the perspective of this paper in a very synthetic way: Evo/devo processes (Evolution and development or ontogenesis) may be globally understood as the “never identical iteration of a morphogenetic process”. Randomness is at the core of that “*never identical iteration*”. By adding selection and following Gould’s remarkable insight, we will in particular understand below the increasing complexity of organisms along Evolution, as the result of a purely random diffusion in a suitable phase space (and its definition is the crucial issue).

8.2 ENTROPY IN ONTOGENESIS.

In an organism, the internal entropy production has “in primis” a physical nature, related to all thermodynamic processes, that is to the transformation and exchange of matter and energy. Yet, we will add to this a properly biological production for entropy, the production due to all *irreversible* processes, including biological (re-)construction, that is both embryogenesis and cell replacement and repair (ontogenesis, globally).

Observe first that, in a monocellular organism, entropy is mostly released in the exterior environment and there are less signs of increasing disorder within the cell. Yet, changes in proteome and membranes are recorded and may be assimilated to aging, see Lindner et al. (2008); Nyström (2007). In a metazoan, instead, *the entropy produced, under all of its forms, is also and inevitably transferred to the envioning cells, to the tissue, to the organism*, (Bailly & Longo 2009). Thus, besides the internal forms of entropy (or disorder) production, a cell in a tissue, the structure of the tissue itself ... the organism, is affected by this dispersal of energy, as increasing disorder, received from ... the (other) cells composing the tissue (or the organism). Aging, thus, is also or mostly a tissular and organismic process: in an organism, it

¹However, the argument that disorder is an epistemic notion, not suitable to physics, is less convincing, since classical randomness, at the core of entropy, is also epistemic (see above and Bailly & Longo (2007)).

is the network of interactions that is affected and that may have a fall-out also in the cellular activities (metabolism, oxidative stress ... , see below).

Moreover, the effect of the accumulation of entropy during life contributes, mathematically, to its *exponential increase* in time. Thus, with aging, this increase exceeds the reconstructive activities, which oppose global entropy growth in earlier stages of life (this theory, articulated in four major life periods, is proposed in Bailly & Longo (2009)). Now, we insist, entropy production, in all its forms, implies increasing disorganization of cells, tissues, and the organism. This, in turn, may be physically and biologically implemented by increasing metabolic instability, oxidative effects, weakening of the structure and coherence of tissues (matrix, collagen's links, tensegrity) ... and many more forms of progressive disorganization (Demetrius 2004; d'Alessio 2004; Sohal & Weindruch 1996; Olshansky & Rattan 2005). Of course, there may be other causes of aging, but the entropic component should not be disregarded and may also help in proposing a unified understanding of different phenomena.

Our second observation is that entropy production is due to *all irreversible processes*, both the thermodynamic ones and the permanent, irreversible, (re-)construction of the organism itself. This generating and re-generating activity, from embryogenesis to repair and turnover, is typically biological and it has been mathematically defined as "anti-entropy" (see Bailly & Longo (2009) and below²). In other words, irreversibility in biology is not only due to thermodynamic effects, related to the production of energy, typically, but also to all processes that establish and maintain biological organization — that is, it is concomitantly due to entropy production and its biological opposite, anti-entropy production: embryogenesis, for example, is an organizing and highly irreversible process "per se". And it produces entropy not only by the thermodynamic effects due to energy dispersion, but also, in our view, by the very biological constitutive activities. Let's see this more closely.

Cell mitosis is *never an identical "reproduction"*, including the non-identity of proteomes and membranes. Thus, it induces an *unequal diffusion of energy* by largely random effects (typically, the never identical bipartition of the proteome). That is, biological reproduction, as morphogenesis, is *intrinsically joint to variability* and, *thus, it produces entropy also by lack of (perfect) symmetries*. By this, it induces *its proper irreversibility*, beyond (and in addition to) thermodynamics.

As a comparison, consider an industrial construction of computers. The aim is to produce, in the same production chain, identical computers. Any time a computer is doubled, an identical one is produced (identical up to observability) and organization (locally) grows, at the expenses of energy (a computer is a highly complex and structured machine, made out of less complex components). Entropy is then produced, in principle, only by the required use and inevitable dispersal of energy, while the construction "per se" just increases organization,

²The word anti-entropy has already been used, apparently only once and in physics, as the mathematical dual of entropy: its minimum coincides with the entropy maximum at the equilibrium, in mixture of gases at constant temperature and volume (Duffin & Zener 1969). This is a specific and a very different context from ours. Our anti-entropy is a new concept and observable with respect to both negentropy and the mathematical dual of entropy: typically, it does not add to an equal quantity of entropy to give 0 (as negentropy), nor satisfies minimax equations, but it refers to the quantitative approach to "biological organization", as opposing entropy by the various forms of biological morphogenesis, replacement and repair.

along the production chain. Moreover, if, in the construction chain of computers, one destroys the second computer, you are back with one computer and you can iterate identically the production of the second. The process is both reversible (destroy one computer) and iterable (produce again an identical machine), by importing a suitable amount of energy, of course. Imperfection must be (and, for 99% or so of the machines, they are) below observability and functionality: they are errors and “noise”.

As we said, it is instead a fundamental feature of life that a cell is *never* identical to the “mother” cell. This is at the core of biological variability, thus of diversity, along Evolution as well as in embryogenesis (and ontogenesis, as permanent renewal of the organism, never identically). In no epistemic nor objective way this may be considered a result of errors nor noise: variability and diversity are the main “invariants” in biology, jointly to structural stability, which is never identity, and, jointly, they all make life possible.

Thus, while producing new order (anti-entropy), life, as iteration of a never identical and an always *slightly disordered* morphogenetic process, generates also entropy (disorder), by the (somewhat disordered) reproductive process itself. In a metazoan, each mitosis produces two slightly different cells, both different also from the “mother” cell: the asymmetry is a form of disorder and, thus, of entropy growth, within the locally increasing order. And this, of course, in addition to the entropy due to free energy consumption. It is this variability that gives this further, and even more radical, form of irreversibility to all biological dynamics (in Evolution and ontogenesis). There is no way to neither revert nor iterate an evolutionary or embryognetic process: if you kill a cell after mitosis, you are not back to the same original cell and this cell will not iterate its reproduction, *identically*³.

It should be clear that this theoretical frame concerning the overall increase of entropy in biology says nothing about how this disorganization takes place in the various processes, nor anything about its “timetable”. The analyses of the detailed phenomena that implement it in ontogenesis are ongoing research projects. So far, we could apply these principles to an analysis of growing complexity in Evolution, as summarized next. In the following, we also propose a first analysis of organizational regeneration.

8.3 RANDOMNESS AND COMPLEXIFICATION IN EVOLUTION.

Available energy production and consumption are the unavoidable physical processes underlying reproduction and variability. At the origin of life, bacterial reproduction was (relatively) free, as other forms of life did not contrast it. Diversity, even in bacteria, by random differentiation, produced competition and a slow down of the exponential growth (see diagram 8.3). Simultaneously, though, this started the early variety of life, a process never to stop.

Gould, in several papers and in two books (Gould 1989, 1997), uses this idea of random diversification in order to understand a blatant but too often denied fact: the increasing

³The incompetent computationalist (incompetent in Theory of Computation), who would say that also computers are not identical and misses the point: the *theory* of programming is based on identical iteration of software processes on reliable hardware, i.e. functionally equivalent hardware (and it works, even in computer networks, see the analysis of primitive recursion and portability of software in Longo (2009)). Any biological theory, instead, must deal with variability, *by principle*. As recalled above, variability as never identical iteration, in biology, is not an error.

“complexification” of life. The increasing complexity of biological structures has been often denied in order to oppose finalistic and anthropocentric perspectives, which viewed life as *aiming* at *Homo sapiens* as the “highest” result of the (possibly intelligent) evolutionary path.

Yet, it is a fact that, under many reasonable measures, an eukaryotic cell is more “complex” than a bacterium; a metazoan, with its differentiated tissues and its organs, is more “complex” than a cell ... and that, by counting also neurons and connections, cell networks in mammals are more complex than in early triploblast (which have three tissues layers) and these have more complex networks of all sorts than diploblasts (like jellyfish, a very ancient animal). This non-linear increase can be quantified by counting tissue differentiations, networks and more, as hinted by Gould and more precisely proposed in Bailly & Longo (2009), that we will extensively summarize and comment, next. The point is: how to understand this change towards complexity without invoking global aims? Gould provides a remarkable answer based on the analysis of the *asymmetric* random diffusion of life. Asymmetric because, by principle, life cannot be less complex than bacterial life⁴. So, reproduction by variability, along evolutionary time and space, randomly produces, just as *possible paths*, also more complex individuals. Some happen to be compatible with the environment, resist and proliferate (a few even very successfully) and keep going, further and randomly producing *also* more complex forms of life. *Also*, since the random exploration of possibilities may, of course, decrease the complexity, no matter how this is measured. Yet, by principle, *any asymmetric random diffusion propagates, by local interactions, the original symmetry breaking along the diffusion*. Thus there is no need for a global design or aim: the random paths that compose *any* diffusion, also in this case help to understand a random growth of complexity, *on average*. On average, as, of course, there may be local inversion in complexity; yet, the asymmetry randomly forces to the “right”. This is beautifully made visible by figure 8.1, after Gould (1989, 205). The image explains the difference between a random, but oriented development (on the right, 8.1b), and the non-biased, purely random diffusive bouncing of life expansion on the left wall, on the left 8.1a.

Of course, time runs on the vertical axis, but ... what is in the horizontal one? Anything or, more precisely, anywhere the random diffusion takes place or the intended phenomenon “diffuses in”. In particular, the horizontal axis may quantify “biological complexity” whatever this may mean. The point Gould wants to clarify is in the difference between a fully random vs. a random *and* biased evolution. The biased right image does not apply to evolution: bacteria are still on Earth and very successfully. Any finalistic bias would instead separate the average random complexification from the left wall.

Note that, in both cases, complexity may *locally* decrease: tetrapodes may go back to the sea and lose their podia (the number of folding decreases, the overall body structure simplifies). Some cavern fishes may lose their eyes, in their new dark habitat; others, may lose their red blood cells (Ruud 1954). Thus, the local propagation of the original asymmetry may be biologically understood as follows: on average, variation by simplification leads towards a biological niches that has *more chances* to be already occupied. Thus, *global* complexity increases *as a purely random effect of variability* and on the grounds of *local effects*: the greater

⁴Some may prefer to consider viruses as the least form of life. The issue is controversial, but it would not change at all Gould’s and ours perspective: we only need a minimum which differs from inert matter.

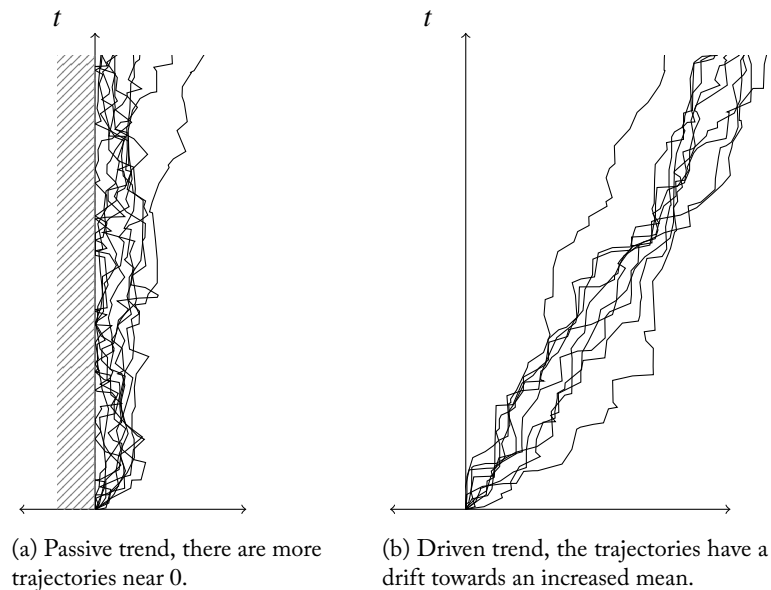


Figure 8.1: *Passive and driven trends*. In one case the boundary condition, materialized by a left wall is the only reason why the mean increase over time (boundary condition), and this increase is slow. In the case of a driven trend, or biased evolution, however, it is the rule of the random walk that leads to an increase of the mean over time (there is an intrinsic trend in evolution). Notice that from the neo-darwinian point of view, a driven trend typically correspond to a selective pressure, here for increased complexity; whilst the passive trend correspond to a neutral theory (Hubbell 2001), with a domain incompatible with life (the left wall of complexity).

chances, for a “simpler” organism, to bump against an already occupied niche. Thus, more complex variants have just slightly more probabilities to survive and reproduce — but this slight difference is enough to produce, in the long run, very complex biological organisms. And, of course, variability and, thus, diversity are grounded on randomness, in biology. No need for finalism nor a priori “global aim” nor “design” at all, just a consequence of an original symmetry breaking in a random diffusion on a very peculiar phase space: biomass times complexity times time (see figure 8.3 for a complete diagram)⁵.

Similarly to embryogenesis, the complexification is a form of local reversal of entropy. The global entropy of the Universe increases (or does not decrease), but locally, by using energy of course, life inverts the entropic trend and creates organization of increasing complexity. Of course, embryogenesis is a more canalized process, while evolution seems to explore all “possible” paths, within the ecosystem-to-be. Most turn out to be incompatible with the environment, thus they are eliminated by selection. In embryogenesis increasing

⁵By our approach, proposed in Bailly & Longo (2009), we provide a theoretical/mathematical justification of the ZFEL principle in McShea & Brandon (2010), at the core of their very interesting biological analysis: “ZFEL (Zero Force Evolutionary Law, general formulation): In any evolutionary system in which there is variation and heredity, there is a tendency for diversity and complexity to increase, one that is always present but may be opposed or augmented by natural selection, other forces, or constraints acting on diversity or complexity.”

complexity seems to follow an expected path and it is partly so. But only in part as failures, in mammals say, reach 50% or more: the constraints imposed, at least, by the inherited DNA and zygote, limit the random exploration due to cell mitosis. Yet, their variability, joint to the many constraints added to development (first, a major one: DNA), is an essential component of cell differentiation. Tissue differentiation is, for our point of view, a form of (strongly) regulated/canalized variability along cell reproduction.

Thus, by different but correlated effects, complexity as organization increases, on average, and reverts, locally, entropy. We called *anti-entropy*, Bailly & Longo (2009), this observable opposing entropy, both in evolution and embryogenesis; its peculiar nature is based on reproduction with random variation, submitted to constraints. As observed in the footnote above, anti-entropy differs from negentropy, which is just entropy with a negative sign, also because, when added to entropy, it never gives 0, but it is realized in a very different singularity (different from 0): extended criticality (Bailly & Longo 2011; Longo & Montévil 2011a). In the next section, we will use this notion to provide a mathematical frame for a further insight by Gould.

8.4 (ANTI-)ENTROPY IN EVOLUTION.

In yet another apparently naïve drawing, Gould proposes a further visualization of the increasing complexity of organisms along Evolution. It is just a qualitative image that the paleontologist draws on the grounds of his experience. It contains though a further remarkable idea: it suggests the “phase space” (the space of observables and parameters) where one can analyze complexification. It is *bio-mass density* that diffuses over *complexity*, that is, figure 8.2 qualitatively describes the diffusion of the frequency of occurrences of individual organisms per unity of complexity.

This is just a mathematically naive, global drawing of the paleontologist on the basis of data. Yet, it poses major mathematical challenges. The diffusion, here, is not along a spatial dimension. Physical observables usually diffuse over space in time; or, within other physical matter (which also amounts to diffusing in space). Here, diffusion takes place over an abstract dimension, “complexity”. But what does biological complexity exactly mean? Hints are given in Gould (1997): the addition of a cellular nucleus (from bacteria to eukaryotes), the formation of metazoa, the increase in body size, the formation of fractal structures (usually — new — organs) and a few more.... In a sense, any added novelty provided by the random “bricolage” of Evolution and at least for some time compatible with the environment, contributes to complexity. Only a few organisms become more complex over time, but, by the original symmetry breaking mentioned above, this is enough to increase the global complexity.

Of course, the figure above is highly unsatisfactory. It gives two slices over time where the second one is somewhat inconsistent: where are dinosaurs at present time? It is just a sketch, but an audacious one, as we said, if analyzed closely. Mathematics though, may help us to consistently add the third missing dimension: time.

A simple form of diffusion equation of a quantity q in time t over space x , goes like:

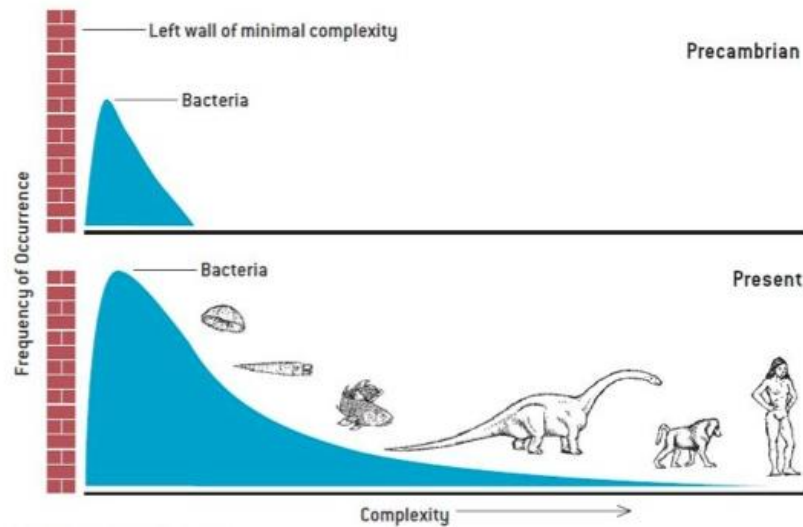


Figure 8.2: *Evolution of complexity as understood by Gould*. This illustration is borrowed from (Gould 1997, 171). This account is provided on the basis of paleontological observations. The core idea is to explain the biological mean increase of complexity by the left wall of minimal complexity.

$$\frac{\partial q}{\partial t} = D \frac{\partial^2 q}{\partial x^2} + Q(t, x) \quad (8.1)$$

where $Q(t, x)$ is a source term describing the situation at the origin of the process. The equation gives the variation of q in time ($\partial q / \partial t$) as a function of the variation ($\partial \dots / \partial x$) of the space gradient ($\partial q / \partial x$).

Yet, in our case, the diffusion of this strange quantity, m , a *bio-mass density*, takes place over an even more unusual “space”, biological complexity, whatever the latter may mean. In Bailly & Longo (2009), we dared to further specify Gould’s hints for biological complexity, as a quantity $K = \alpha K_c + \beta K_m + \gamma K_f$ where α , β , and γ are the respective “weights” of the different types of complexity within the total complexity (we take $\alpha + \beta + \gamma = 1$). We do not get into the details in Bailly & Longo (2009), let’s just summarize the basic ideas. So, K_c (“combinatorial” complexity) corresponds to the possible cellular combinatoric (which includes cellular differentiation); K_m (“morphological” complexity) is associated to the topological forms and structures which arise (connexity and fractal structures); K_f (“functional” complexity) is associated to the relational structures supporting biological functions (metabolic and neuronal relations, interaction networks; references to Edelman and others are provided on place). $K = \alpha K_c + \beta K_m + \gamma K_f$ will be more closely defined in section 8.6.

K is a tentative quantification of complexity as *anti-entropy*, in particular in biological evolution: the increase of each of its components (more cellular differentiation, more or higher dimensional fractal structures, richer networks ... yield a more “complex” individual).

Of course, many more observables and parameters may be taken into account in order to evaluate the complexity of an organism: Bailly & Longo (2009) provides just a mathematical basis and a biological core for a preliminary analysis (an application to ontogenesis as an analysis of *C. Elegans* development is also presented). They suffice though for a qualitative (geometric) reconstruction of Gould’s curve, with a sound extension to the time dimension.

As mentioned above, anti-entropy opposes, locally, to entropy: it has the same dimension, yet it differs from negentropy, since it does not sum up to 0, in presence of an equal quantity of entropy. It differs also from information theoretic frame, where negentropy has been largely used, as negentropy (= information) is *independent from coding and Cartesian dimensions*. This is crucial for Shannon as well as for Kolmogorof-Chaitin information theories. Anti-entropy, instead, as defined above, depends on foldings, singularities, fractality ... it is a *geometric* notion, thus, by definition, it is *sensitive to codings* (and to dimension).

The first step now is to adapt equation 8.1 to these new dimensions. Just use Gould’s observables and parameters, m and K , that we specified some more, and write:

$$\frac{\partial m}{\partial t} = D \frac{\partial^2 m}{\partial K^2} + Q(t, K) \quad (8.2)$$

But what is here $Q(t, K)$, the source term? In order to instantiate Q by a specific function, but also in order to see the biological system from a different perspective (and get to the equation also by a different procedure, an “operatorial approach”), we then gave a central role, as an observable, to the “global entropy production”.

Now, in physics, energy, E , is the “main” observable, since Galileo inertia, a principle of energy conservation, to Noether’s theorems and Schrödinger’s equation. Equilibria, geodetic principles etc directly or indirectly refer to energy and are understood in terms of symmetry principles (see Van Fraassen (1989); Bailly & Longo (2011)). At least since Schrödinger and his equation, in (quantum) physics, one may view energy as an operator and time as a parameter⁶.

As hinted above, in biology, also constitutive processes, such as anti-entropy growth (the construction and reconstruction of organization), *produce entropy*, since they also produce some (new) disorder (recall: at least the proteome, after a mitosis, is non-uniformly and randomly distributed in the new cells). In these far from equilibrium, dissipative (possibly even non-stationary) processes, such as Evolution and ontogenesis, energy turns out to be just one (very important) observable, a parameter to be precise. One eats (and this is essential) and gets fatter: production and maintenance of organization requires energy, but it yields a different observable, one that has a different dimension, tentatively defined by K above, as organization. Typically, in allometric equations, so relevant in biology, energy or mass appear as a parameter. Thus, in our approach, the key observable is organization that is formed or renewed (anti-entropy production).

⁶ In Bailly & Longo (2009) a brief introduction to Schrödinger’s approach is given. In short, Schrödinger transforms an equation with the structure $E = \frac{p^2}{2m} + V(x)$, where $V(x)$ is a potential, by associating E and p to the differential operators $\partial/\partial t$ and $\partial/\partial x$, respectively.

Moreover, *entropy*, as associated to all irreversible processes, from energy flows to anti-entropy production, is the observable which summarizes all ongoing phenomena; by its irreversibility, it is strongly linked (conjugated) to time.

In summary, we proposed to change the conceptual frame and the conceptual priorities: we associated the global entropy production σ to the differential operator given by time, $\partial/\partial t$ (Schrödinger does this for energy, which is conjugated to time, in quantum physics). Thus, our approach allows to consider biological time as an “operator”, both in this technical sense and in the global perspective of attributing to time a key constitutive role in biological phenomena, from evolution to ontogenesis. But how to express this global observable?

In a footnote to Schrödinger (1944), Schrödinger proposes to analyze his notion of negative entropy as a form of Gibbs free energy G . We applied this idea to our anti-entropy S^- , where $S^- = -kK$ (k is a positive dimensional constant and K is the phenotypic complexity). Now, $G = H - TS$, where T is temperature, S is entropy and $H = U + PV$ is the system’s enthalpy (U is the internal energy, P and V are respectively pressure and volume). By definition, the *metabolism* R has the physical dimension of a power and corresponds to the difference between the fluxes of *generalized free energy* G , entering and exiting through the surface Σ :

$$R = \sum [J_G(x) - J_G(x + dx)] = - \sum dx(\text{Div } J_G) \quad (8.3)$$

Take the volume $\sum dx = 1$, then the conservation (or balance) equation is expressed in the general form:

$$R = -\text{Div } J_G = \frac{dG}{dt} + T\sigma \quad (8.4)$$

where σ represents the speed of global production of entropy, that is σ is the entropy produced by *all* irreversible processes, including the production of biological organization or anti-entropy. Thus, the global balance of metabolism for the “system of life” (the biosphere) has the following form, where S^- and S^+ are anti-entropy and entropy, respectively:

$$R = \frac{dH}{dt} - T \left(\frac{dS^-}{dt} + \frac{dS^+}{dt} \right) + T\sigma \quad (8.5)$$

That is,

$$R = a \frac{dM}{dt} - T \left(\frac{dS^-}{dt} + \frac{dS^+}{dt} \right) + T\sigma \quad (8.6)$$

where $H \simeq aM$, for a mass M and a coefficient a , which has the magnitude of a speed squared.

$T\sigma$ is a crucial quantity: it contains our σ , modulo the temperature T , since R is a power. $T\sigma$ corresponds to the product of forces by fluxes (of matter, of energy — chemical energy,

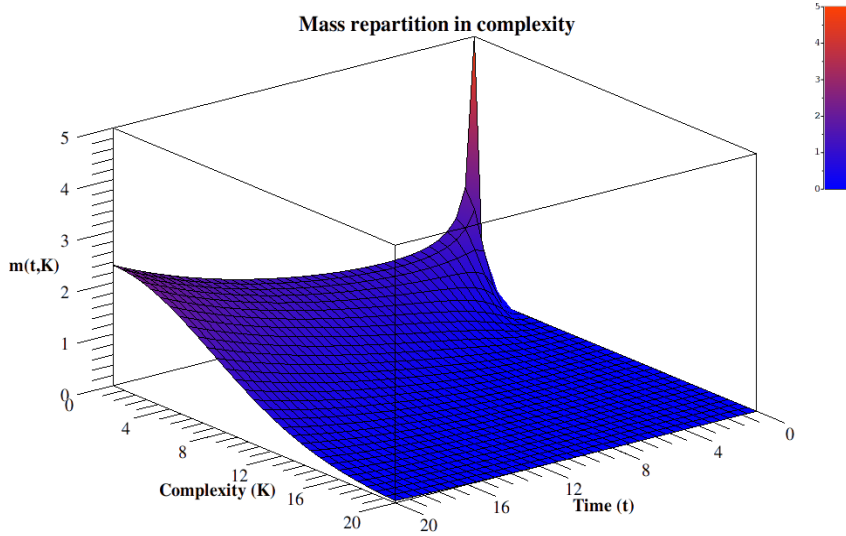


Figure 8.3: *Time evolution of mass repartition over anti-entropy.* The initial condition is a finite mass at almost 0 anti-entropy, thus having the shape of a pulse. The biomass is latter driven by diffusion. The asymmetry of the distribution is given only by the propagation of the effects of the wall of minimum complexity.

for instance — etc.). Now, a flux is proportional to a force, thus to a mass, and hence $T\sigma$ is proportional to a mass squared. It can then be written, up to a coefficient ζ_b and a constant term $T\sigma_0$ as:

$$T\sigma \approx \zeta_b M^2 + T\sigma_0 \quad (8.7)$$

ζ_b is a constant that depends only on the global nature of the biological system under study and it is 0 in absence of living matter.

Without entering into further details, by using as “state function” a *bio-mass diffusion function* over complexity K , that is the bio-mass density $m(t, K)$ in t and K , the operatorial approach applied to equation 8.7 gave us the equation, with a linear source function $\alpha_b m$:

$$\frac{\partial m}{\partial t} = D_b \frac{\partial^2 m}{\partial K^2} + \alpha_b m \quad (8.8)$$

Its solution

$$m(t, K) = \frac{A}{\sqrt{t}} \exp(\alpha t) \exp(-K^2/4Dt) \quad (8.9)$$

yields the diagram in figure 8.3.

In summary, by skipping all the technical details in Bailly & Longo (2009), we could derive, by mathematics and starting from Gould’s informal hints, a general understanding

as well as the behavior of the “Evolution of complexity function” w. r. to time. And this fits data: at the beginning the linear source term gives an exponential growth of free bacteria. Then, they complexify and compete. Of course, this diagram, similarly to Gould’s, is a global one: it only gives a qualitative, geometric, understanding of the process. It is like looking at life on Earth from Sirius and summarizing 4 billions years in 6 centimeters. Analogously to Gould’s diagram, the “punctuated equilibria”, say, and the major extinctions are not visible: the insight is from too far and too synthetic to appreciate them. It only theoretically justifies Gould’s proposal and soundly extends it to time dependence, by mathematically deriving it from general principles: the dynamics of a diffusion by random paths, with an asymmetric origin. Its source is given by a “doubling” at each step (the reproduction of free bacteria), thus beginning by an exponential growth (due to the linear source function, in the differential equation). Life expansion is then bounded, canalized, selected in the interaction with the ever changing, co-constituted ecosystem. The core random complexification persists, while its “tail” exponentially decreases, see equation 9 and figure 8.3. In that tail, some neotenic big primates, with a huge neural network, turn out to be the random complexification of bacteria, a result of variability and of the immense massacres imposed by selection (according to Gould, about 99% of the species that appeared on Earth are extinct).

Another (important) analogy can be made with Schrödinger’s approach (his famous equation, not his book on life) and further justifies the reference to it for the analysis of this (rather ordinary) diffusion equation. Schrödinger dared to describe the deterministic evolution of the wave function in Quantum Mechanics as the *dynamics of a law of probability* (and this gives the intrinsic indetermination of the quantum system). We synthetically represented Biological Evolution as the *dynamics of a potential of variability*, under the left wall constraint. Again, this idea is essentially Gould’s idea in his 1996 book: he sees Evolution just as an asymmetric diffusion of random variability. We just made this point explicit and developed some computations as a consequences of the analogy with the equational determination in Quantum Mechanics and the operatorial approach used by Schrödinger.

8.5 ORGANIZATIONAL REGENERATION

We want first to recall why the biological notion of anti-entropy differs from other approaches, and in particular of the notion of negentropy. As we said earlier, negentropy simply opposes entropy and it is used to understand biological organization as a situation where, in spite of the presence of many energy production/consumption processes, an unusually low entropy (high organization) is maintained and made possible by the openness of the system. Note though that *negative* entropy has no physical meaning *per se* — as a physical observable. Indeed, the third principle of thermodynamic states that the minimum entropy is zero, in the case of pure crystalline states at 0° K. From a statistical point of view, the number of microscopic configuration corresponding to a macrostate cannot be smaller than 1, so entropy cannot be negative. However, negative contributions in the expression of entropy can be found and interpreted, both in physics and biology — see next.

In Bailly & Longo (2009), the theoretical proposition leading to the term of anti-entropy consists in a conceptual symmetry between the relationships of matter and antimatter, on

one side, and of physical entropy and “amount of biological organization”, on the other. We already recalled some basic properties this assumption leads to, and we will now present further considerations along this line. Notice first that the metabolic equation 8.6, by its formulation, can take into account the overall growth of anti-entropy occurring in development, but does not describe, even not “in abstracto”, how biological organization is *sustained* and more precisely *regenerated*. We will use our approach now for a closer analysis of the local interactions of entropy vs anti-entropy production, in comparison with some existing data.

In particle physics (relativistic quantum mechanics and quantum field theories), the collision of a particle and the corresponding antiparticle leads to the annihilation of both particles and the emission of photons, which are a radiative form of energy (corresponding in particular to momentum conservation). Reciprocally, energy leads to the spontaneous production of particle/anti-particle pairs (following the symmetries of the theory). This phenomenon spontaneously occurs in the vacuum because the latter is a state with no “real particles”, but where energy is, nevertheless, not 0 — this can be viewed also through the time/energy uncertainty: their product never goes below Planck’s h . More precisely, in quantum fields theories, the vacuum is generally understood as a extremely complex situation, described by virtual pairs of particles and antiparticles, which spontaneously appear and disappear on short time lengths⁷. Now, can these complex theoretical structures help us in order to obtain a better understanding of biological phenomena?

In the comparison between the physical and the biological concepts we are dealing with, we can highlight some common points and, also, some crucial differences. First, anti-entropy coexists with entropy over an extended period of time — the life of an organism, typically — while particles and anti-particles interact in a (point-wise) singularity. This point is an aspect of our understanding of the *extended* “physical singularity” of life phenomena, that we treated in terms of “extended criticality” (Bailly & Longo 2011; Longo & Montévil 2011a). Moreover, particle/anti-particle pair can spontaneously be produced, whereas anti-entropy necessitates, for its growth, a preceding anti-entropy (“life from life”). There is at least one exception to the latter statement: the origin of life. Nevertheless, even if we think that simple (proto-)organisms may appear spontaneously today, biologically *ex nihilo*, they should usually disappear very quickly, by getting consumed by phylogenetically older organisms. Observe now that, if anti-entropy is unlikely to re-appear spontaneously, then some space-time extension of the coexistence of entropy and anti-entropy is needed in order to observe anti-entropy (an extended singularity — our extended criticality).

Last but not least, the key observables and parameters for particles and antiparticles are energy, momentum, charge, ..., the most crucial one being energy. They all correspond to conserved quantity, whereas, in the context of entropy and anti-entropy, we are considering typically non conservative quantities. The lack of conservation is indeed expressed by the

⁷Notice that this situation usually leads to divergences in physical quantities, especially because the higher the level of energy of an experiment is, the larger the parts of this complex structure become physically relevant. However, finite differences between the coupling constants allow to understand the situation by the renormalization methods. It is also interesting to note that this highly complex situation is due to the quantification of fields (called second quantification), which breaks the classical symmetries at quantum scales. Reciprocally, the classical fields are understood as the result of an infinite number of such interactions, by the renormalization of a linear combination of the possible interactions.

entropy production term σ , which is non-zero when irreversible processes occur in the system⁸.

Let's consider now a possible analog of the matter/anti-matter collisions. In order to better understand the situation, we will first explain what may happen in the simplified situation, not sustainable for long (biologically “instantaneous”), where the fluxes are null. In this case, equation 8.6 reads:

$$0 = -\frac{dS^-}{dt} - \frac{dS^+}{dt} + \sigma \quad (8.10)$$

Since $\sigma > 0$, we have that an organism can, at least in principle, do the following:

1. It can *sustain* its organization ($\frac{dS^-}{dt} = 0$) or even *increase* it ($-\frac{dS^-}{dt} > 0$) if the system can accommodate an accumulation of entropy ($\frac{dS^+}{dt} = -\frac{dS^-}{dt} + \sigma$). In order to do so, a reservoir of highly entropic matter is usually involved, which prevents this high entropic matter to interfere too much with biological organization (and affect or “disorganize” it). A typical example is the structure of the egg: whilst allantois collects high entropic liquids, the yolk sac contains low entropic reserves. Of course, in this case, isolation is not complete because of the gaseous exchanges, but we can nevertheless see such an organizational tendency, with both high $-\frac{dS^-}{dt} > 0$ and $\frac{dS^+}{dt} > 0$ (and $-\frac{dS^-}{dt}$ much higher than $\frac{dS^+}{dt}$).
2. If the organism does not have the possibility to produce entropy and simultaneously maintain its organization, then it can use a part of its anti-entropy to reduce entropy, that is to “absorb” its own entropy production and then sustain it. It is crucial that this process implies a supplementary production of entropy associated with the transition from anti-entropy to negentropy, as lowering of entropy, since this transition is irreversible. Notice that such phenomenon occurs in relatively common situations such as autophagy (Rabinowitz & White 2010). Besides the cases of starvation, it is thus a normal part in the process of organizational renewal. These processes may also contribute to (or be observed in) an actual decrease of organization (i.e. of anti-entropy), for example in degenerative diseases, Pezard et al. 1998, or aging processes, as part, in our views, of the widely acknowledged entropic component of this latter fact of life, (Aoki 1994; Hayflick 2007; Marineo & Marotta 2005).

In order to develop the analogy with (anti-)particles in physics, such a “collision” may be seen as the collision of (a part of) the anti-entropy δS^- and (one of) the entropy δS^+ . Consider a “biologically instantaneous” situation, that is a sufficiently short time so that we can disregard fluxes. Then one has $\delta S^+ = -\delta S^- + \sigma$. This assumption will allow us to propose a preliminary, simplified analysis. Further work is needed in order to have a more stable understanding of the situation.

As a consequence of the assumption on the very short biological time, the collision between entropy and anti-entropy can lead to both situations discussed above, provided that

⁸Recall that σ is a crucial quantity for us exactly because it is associated to all irreversible processes. Moreover, anti-entropy is not 0 — life is possible — only if it is permanently reconstructed, thus only if σ is not 0.

the existence of the *biological* time arrow is equivalent to $\sigma > 0$ ⁹. Case 1 is similar to the production of particle/anti-particle pairs, leading to an increase (in absolute value) of both entropy and anti-entropy. Case 2 is similar to the annihilation of a particle/antiparticle pair and it is a form of transformation of anti-entropy into negentropy, as a negative quantity of entropy, corresponding to a reduction of entropy. In both cases, the collisions involve a production of entropy along time, $\tau\sigma > 0$ (where the time interval τ is extremely small, or even a Dirac function).

The production of entropy limits the number of such collisions that can occur simultaneously, since we have to assume that the sum of all entropy produced at the same time are finite. As a result, as entropy production has a positive sign, only a finite number of collisions of the same nature (producing similar quantities of entropy) can occur in a finite amount of time. This situation is different from quantum field theory, where an infinite number of such collisions can occur and the resulting sum can remain finite, since the relevant quantities do not all have the same sign. Of course, this argument does not prevent the possibility of an infinite number of collisions in a finite duration, but the entropy production contributions has to be summable, which leads to a quantitative hierarchy of vanishing contributions — an infinitary case that may make mathematical sense in physics, but not necessarily in biology.

The paradigmatic and simplest situation following this pattern of entropy/anti-entropy collision is the death of a cell in an organism. In this case, most of the negentropy obtained¹⁰ is not stable as such, which means that the entropy will rapidly increase, or, in other words, that this negentropy will rapidly vanish. Worse, this temporary decrease of entropy will in general lead, after some time, to a greater entropy than the initial entropy. In this context, it is noteworthy that the function of macrophages is typically to increase irreversibly the entropy of the remains of dead cells, in a spatially constrained domain (namely in a vacuole). After the collision (or sometimes before this event), the corresponding cell is replaced, which leads to a growth of anti-entropy (in absolute value) that compensate the loss of anti-entropy associated to the cell death. This growth leads also to a certain amount of entropy production. Notice, however, that this process is not necessarily as stationary as one might think. For example, significant scale free fluctuations in the cell numbers have been observed for blood cells of different categories, for time-scales of 1 to 200 days (Perazzo et al. 2000). Somewhat reciprocally, as we suggested, the replacing cell can be produced *before* the death of the old one, sometimes even leading to the lysis or the release of the preceding cell.

In order to analyze further the possible situations, we will now propose a graphical representation of the interactions between entropy and anti-entropy, very loosely inspired by Feynman's diagrams. This representation will allow us to schematize (mainly) singular

⁹We stress once more that, since σ is associated to all irreversible processes, including the setting up and the maintenance of organization. Mathematically, $\sigma > 0$ represents our fundamental way to understand the strong irreversibility of biological time, which includes thermodynamical irreversibility, of course, but it also includes the properly biological formation and renewal of anti-entropy — in evolution, embryogenesis and ontogenesis. These are totally, deeply irreversible processes, for their proper phenomenology as “life organization constructors”, well beyond thermodynamical irreversibility. As recalled above, in some cases, by using energy, one may reverse physical entropy (separate, say, mixed gases): no way to revert the three processes above.

¹⁰This negentropy corresponds to the low entropic matter associated to the trace of the former biological organization before the cell death.

events associated to the entropy/anti-entropy relations. We will split the representation space in two parts, one for entropy (top) and one for anti-entropy (down). The solid lines will represent the currently non-interacting quantities. Their distance to the central axis corresponds to the corresponding values of these variables, whilst the winding curves will correspond to entropy production and the zigzags correspond to quantities involved in an interaction. The color corresponds to the sign of the involved quantities: positive is red and negative is blue. Figure 8.4 provides an elementary description of what happens in the case of an elementary disorganization.

When summing over diagrams of this kind, we find that the contribution of organizational renewal is *in fine* found in the entropy production, at the core of our mathematical analysis of Gould's diagram. More precisely, there are two typical contributions to entropy production: the entropy following from the destruction, *per se*, of a biological component and the entropy produced in its reconstruction, as mentioned above. Their close analysis is surely very complex and in particular needs to be extended over a substantial period of time. However, a crude macroscopic approximation of the situation can be of the form: $\sigma \simeq -aS^-/\tau_r$, where $0 < a < 1$ is the proportion of anti-entropy that is renewed. The introduction of a seems necessary. For example, even though there is a turnover for all cells in the lung of mammals, there is no destruction/reconstruction of whole lungs for adults. See also the right diagram in 8.5 for a more subtle example. For adults at rest, we expect then that $R \simeq T\sigma \simeq -aTS^-/\tau_r$ ¹¹. Notice that a more subtle approximation would be to assign specific renewal times to the different components of anti-entropy, some of them being infinite (which correspond to no renewal).

Interestingly, McCarthy & Enquist (2005) have roughly found the empirical relation $R = R_0 n^{0.58} M^{3/4}$ among different taxa, where n is the number of cell types. Assuming that $\tau_r \propto M^{1/4}$ (see (Lindstedt & Calder III 1981; Savage et al. 2004)) and $N \propto M$ (which holds for part of the cell types, see Savage et al. (2007)) we get:

$$R \simeq -aT \frac{S^-}{\tau_r} \propto -N \frac{S^-}{NM^{1/4}} \quad (8.11)$$

$$\propto -M^{3/4} \frac{S^-}{N} \quad (8.12)$$

The experimental results then leads to:

$$R \propto M^{3/4} n^{0.58} \quad \text{so} \quad (8.13)$$

$$\frac{-S^-}{N} \propto n^{0.58} \quad (8.14)$$

The latter equation differs strongly from the form of the combinatorial complexity we discussed, but this difference does not come as a surprise. Indeed, the latter result involves all anti-entropy renewal processes, and not only the renewal of the combinatorial component

¹¹The metabolism of adults, normally, is not used to produce new organization. In equation (6) then, at constant mass M and with anti-entropy production (reconstruction) just enough to compensate entropy production, one is left with only $R \simeq T\sigma$, use then $\sigma \simeq -aS^-/\tau_r$ (see in Bailly & Longo (2009) for a closer analysis of the relative weight of the production of S^- and S^+ along individual life time).

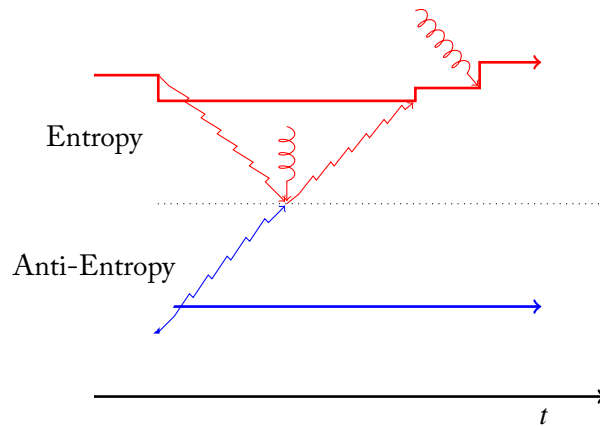


Figure 8.4: *Diagram of an elementary loss of anti-entropy.* A small amount of anti-entropy $-\delta S^- < 0$ “collides” with a corresponding entropy $-\delta S^+ > 0$ and is transformed in an amount of entropy *produced* $-\delta S^- - \delta S^+ + \int \sigma > 0$ (the red, spring-like, winding curve), which adds to the entropy of the system (the zigzag line adding to entropy). Since this leads to an unstable and irreversible result (and since it is purely entropic), there is a subsequent entropy production (the second red winding curve; the time shift is meant to represent the fact that the collision lowers the entropy at first, but usually leads to a higher entropy latter on).

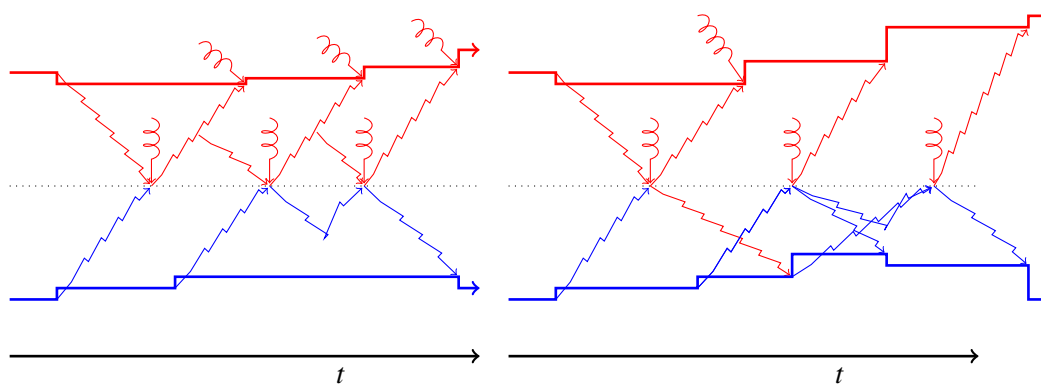


Figure 8.5: *Other schema of entropy/anti-entropy interactions.* LEFT: the diagram represents, in temporal order, the lysis of a cell, the subsequent phagocytosis by a macrophage (involving a small increase of the anti-entropy of the macrophage, at least morphological), then the low entropic content interact with the anti-entropy of the macrophage. RIGHT: a cell is destroyed, but in this case we take into account its functional contribution. This is showed by the emission in the collision of a negative quantity of anti-entropy, which is then transformed into a quantity of anti-entropy in jeopardy. However, here a cell also divide (second collision) leading to a release of two cells (and an important amount of entropy). One of this cells replace the destroyed cell and reestablishes the functional anti-entropy (third collision), however this process is also irreversible, leading to some reorganization and thus produces entropy. In this case the initial and final anti-entropy are the same.

of anti-entropy. This empirical result then shows that anti-entropy and the number of cell types are correlated to a certain degree (beyond the combinatorial part). This results also corroborates our general approach to anti-entropy, which relates organizational complexity to metabolism.

Notice that the general line of reasoning presented here have been made possible and should be further mathematically developed in the terms of a *time operator* formalism. This approach can allow us to understand the situation in the a biologically proper theoretical framework. Indeed, if we consider our observables, anti-entropy, entropy and entropy production, these are difficult to evaluate directly in experiments, as their theoretical determination does not seem classical. On the contrary, their temporal structure is observable (at least in part), and it seems easier to associate to regularities, by loosing the physical specificity of time parameterized trajectories.

8.6 INTERPRETATION OF ANTI-ENTROPY AS A MEASURE OF SYMMETRY CHANGES

In Longo & Montévil (2011a), we proposed to understand biological phenomena, in comparison and contrast with physical theories, as a situation where the theoretical symmetries are “constantly” broken. We will now show that such considerations allows us to interpret anti-entropy, somewhat in the spirit of Boltzmann’s approach of physical entropy. In Bailly & Longo (2009), premises of these aspects are considered from a strictly combinatorial point of view, leading to a “constructive” definition of the three components of anti-entropy, $K = \alpha K_c + \beta K_m + \gamma K_f$, we recalled in section 8.4.

The simpler way to understand how symmetries come into play is to look at these components of anti-entropy and exhibit the underlying symmetries that allow these definitions.

COMBINATORIAL COMPLEXITY, K_c : For a total number of cells N and for a number n_j of cells of cell type j , the combinatorial complexity has been defined as:

$$K_c = \log \left(\frac{N!}{\prod_j n_j!} \right) \quad (8.15)$$

A classical combinatorial point of view consists in saying that it is the number of ways to classify N cells in j categories each of sizes n_j . More precisely, we recognize, inside the logarithm, the cardinal, $N!$, of the symmetry group S_N , that is the group of transformations, called permutations, that exchange the labels of N elements. Similarly, $n_j!$ is the number of permutations among n_j units, which has the biological meaning of permutations of cells within a cell type: in other words, permuting cells *within the same cell type* is a combinatorial invariant of the complexity of an organism. Thus, the group of permutations leaving the cell types invariants is the group $G_{type} = \prod S_{n_j}$, that is the group obtained as direct product of the symmetries corresponding to permutations within each cell type. Formally, this group corresponds to the change of labels in each cell type, which can all be performed independently and conserve the classification by cell types. The cardinal of this group is $\prod_j n_j!$.

Then, the number of cell type configurations is the number of orbits generated by the right action of G_{type} on S_N . In other words, a cell type configuration is first given by a permutation of $\llbracket 1, N \rrbracket$, which gives the random determination for N cells. Moreover, these transformations must be computed modulo any transformation of G_{type} that gives the same configuration (as we said, cells within each cell type are combinatorially equivalent — we will discuss below this hypothesis, in more biological terms). Lagrange theorem then gives the number of remaining transformations $\frac{N!}{\prod_j n_j!}$, which is the number of possible configurations. Clearly, if there were only one cell type, $K_c = \log \frac{N!}{N!} = 0$, that is an organism with just one cell type (typically, a unicellular being) has combinatorial complexity 0.

As a result, this measure of combinatorial complexity depends on the total number N of cells, but is actually *a measure of the symmetry breaking induced by the differentiation in cell types*.

Let's compare the situation with Boltzmann approach of entropy¹². If one has a number of microscopic phase space states Ω having the same energy, the corresponding entropy is defined as $S = k_b \log(\Omega)$. In the case of gases, one considers that the particles are indiscernible (besides their position in phase space, which is already taken into account). This means that one does not count twice situations which differ only by permuting particles. In other words, in thermodynamics, one formally understands the situation by saying that labels attached to particles are arbitrary. As a matter of fact, if Ω_0 were instead defined by fixing labels, one would have more states than needed. Thus, more soundly, S is defined by $S = k_b \log(\Omega_0/N!) = k_b \log(\Omega) - k_b \log(N!) > 0$. By considering this symmetry by permutation, one reduces the size of the microscopic possibility space, and, as a result, one obtains a value of entropy which is lower than the value computed without these symmetry considerations.

In our approach, we have $K_c = \sum_i \log(N!) - \log(n_i!)$ which is greater than 0, as soon as there is more than one cell type. The contribution to anti-entropy is given by $S_c^- = -kK_c$. Thus, the increase of the possibility space (the diversity or the differentiations) increases the complexity (increases the anti-entropy). More precisely, the complexity, as absolute value of anti-entropy, is increased by the added symmetries, quantified by the term $\sum_i \log(n_i!)$. We understand then that anti-entropy can be analyzed, at least in this case, as an account of how many biological symmetries are broken by the cascade of differentiations. Formally, we can sum up the situation by saying that combinatorial complexity and its contribution to anti-entropy are based on a group of transformations, S_N , and a subgroup, G_{type} . The biologically relevant quantity is then the ratio of sizes of the groups S_N and G_{type} . This can be equivalently seen as the number of orbits of S_N under the right action of G_{type} .

MORPHOLOGICAL COMPLEXITY, K_m : This complexity is associated to the geometrical description of biologically relevant shapes. It is computed in particular by counting

¹²This account is based on “microcanonic ensembles”, that is on the hypothesis of a symmetry for the probability distribution in the (microscopic) phase space: the states of equal energy have equal probabilities.

the number of connex areas. Note that this number corresponds to *space symmetry breakings* for motions covering this space — or ergodic motions. Then, one has to consider the number of shape singularities, in the mathematical sense, where singularities are invariants by action of diffeomorphisms. The fractal-like structures are particularly relevant since they correspond to an exponential increase of the number of geometrical singularities with the range of scales involved. Thus, fractal-like structures lead to a linear growth of anti-entropy with the order of magnitudes where fractality is observed (but also the variability in fractal shape should be involved, as scale symmetry changes).

FUNCTIONAL COMPLEXITY, K_f (the last quantity proposed in Bailly & Longo (2009)): This quantity is given by the number of possible graphs of interaction. As a result, the corresponding component of anti-entropy is given by the choice of one graph structure (with distinguished nodes) among the possible graphs. This involves the selection of the structure of possible graphs and, correspondingly, which resulting graphs are considered equivalent. In terms of symmetries, we first have a symmetry among the possible graphs which is reduced to a smaller symmetry, by the equivalence relation. For example, in Bailly & Longo (2009), the case is considered where the number of edges is fixed, so the considered symmetry group is engendered by the transformations which combine the deletion of an edge and the creation of another one. The orbits preserve the total number of edges, so that the orbit of a graph with $\langle k \rangle N$ edges are the graphs with this number of edges. The remaining symmetry was considered to be the identity.

We understand then that anti-entropy, or at least its proposed decomposition in Bailly & Longo (2009), is strictly correlated to the amount of symmetry changes. We will now look more closely at the case of combinatorial complexity since it involves only the groups of permutations and their subgroups, but at the same time will also allow us to express a crucial conceptual and mathematical point.

We indeed encounter a paradox in the case of combinatorial complexity. On one side, we have an assumption that cells of the same cell type are symmetric (interchangeable). On the other, in section 8.2, we stressed that each cell division consists in a symmetry change. This apparent paradox depends on the scale we use to analyze the problem, as well as on the “plasticity” of the cells in a tissue or organ, as the possibility to be interchanged and/or to modify their individual organization. Typically, liver cells function statistically (what matters is their average contribution to the function of the organ), while neurons may have strong specific activities, yet they may also deeply modify their structure (change number, forms and functionality of synaptic connections, for example). Thus, we will next consider the individual contribution of cells to the combinatorial complexity of an organism at different scales.

If we consider an organism with a large number of cells, N , and the proportion q_j of cells of cell type j (assuming that we also have a relatively large number of cells for each cell type) we get two different quantities for the combinatorial complexities *per cell*, K_{c1} and K_{c2} :

$$K_{c1} = \frac{\log(N!)}{N} \quad K_{c2} = \frac{\log\left(\frac{N!}{\prod_j (q_j N)!}\right)}{N} \quad (8.16)$$

$$\simeq \frac{\log\left((N/e)^N\right)}{N} \quad \simeq \frac{\log\left(\frac{(N/e)^N}{\prod_j (q_j N/e)^{q_j N}}\right)}{N} \quad (8.17)$$

$$\simeq \log(N) - 1 \quad \simeq \log(N) - 1 - \sum_j q_j (\log(q_j) - 1 + \log(N)) \quad (8.18)$$

$$\simeq \sum_j q_j \log(1/q_j) \quad (8.19)$$

We propose to understand the situation as follows. Basically, both levels of cellular individuation are valid; but they have to be arranged in the right order. Cellular differentiation is the first and main aspect of the ability of cells to individuate in a metazoan, so we can assume that the main determinant of combinatorial complexity is K_{c2} . It is only after this contribution that the further process of cellular individuation occurs. The latter leads to a mean contribution to the complexity of the organism which is of $\sum_j a_j (q_j \log(q_j N) - 1)$ per cell, where a_j quantifies the ability of each cell type to change their organization and the relevance of this change. It seems reasonable to expect that the a_j are high in the cases, for example, of neurons or of cells of the immune system. On the contrary, the a_j should be especially low for red blood cells. The reason for this is not only their lack of DNA, but also because of their relatively simple and homogeneous cytoplasmic organization. Similarly, liver cells may have statistically irrelevant changes in their individual structure.

Thus, the contribution of cell types to anti-entropy derives first from the formation of new cell types, while considering the ability of cells to reproduce, with changes, within a cell type as a further important (numerically dominant) aspect of their individuation process. Note that this analysis does not suppose that a cell type for a cell is irreversibly determined, but it means that the contribution of cell type changes to anti-entropy are understood as changes of K_{c2} .

We can then provide a refined version of S_c^- , where a_{ct} is the “weight” accorded to the formation of different cell types:

$$\frac{S_c^-}{-Nk_b} = a_{ct} \sum_j q_j \log(1/q_j) + \sum_j a_j (q_j \log(q_j N) - 1) \quad (8.20)$$

$$= \sum_j [q_j (a_{ct} - a_j) \log(1/q_j) + a_j q_j (\log(N) - 1)] \quad (8.21)$$

$$= (a_{ct} - \langle a_j \rangle) \langle \log(1/q_j) \rangle + \langle (\langle a_j \rangle - a_j) \log(1/q_j) \rangle + \langle a_j \rangle (\log(N) - 1) \quad (8.22)$$

where $\langle x \rangle$ is the mean of x among all cells (so that the contribution of each cell type is proportional to its proportion in the organism). Both equations 8.20 and 8.22 are biologically meaningful. The terms in equation 8.20 correspond, by order of appearance, to the contribution of the categorization by cell types and to the contribution of individuation

among a cell type. In equation 8.22, we have obtained terms that can be assimilated to K_{c1} (last term) and to K_{c2} (first term), the latter being positive only if $a_{ct} - \langle a_j \rangle > 0$, meaning that the contribution associated to cell types is positive only if it is greater than the mean cellular individuation. This is logical since cell types make a positive contribution to the complexity only if the amount of cellular diversity they introduce is greater than the one that cellular individuation alone would introduce.

Last but not least, the second term has the sign of an anti-correlation between a_j and $\log(1/q_j)$, meaning that this term is positive when there are many low complexity cell types (given that this leads also to fewer cells per low complexity cell type or cell types with a very low complexity) and few high complexity cell types (with more cells or with a very high complexity). More precisely, using the Cauchy-Schwartz equality case, we get that maximizing (and minimizing) this term (everything else being kept constant), leads to $\langle a_j \rangle - a_j \propto \log(1/q_j) - \langle \log(1/q_j) \rangle$. Then this optimization *a priori* leads to maximizing the second moment of information (in informational terms), at constant entropy (first moment), or in other terms, maximizing its *variance*. The situation gets quite complicated to solve analytically, but this point may be conceptually interesting¹³.

Here, the issue derived from looking with an increasing finer resolution at the individuation potential. However, the reciprocal situation can also occur. Let's consider the functional complexity, understood as the possibility of interactions between cells (here, the paradigmatic example will be neurons). Then, by assuming that there are N neurons with $\langle k \rangle$ average number of synapses for each neuron (where $\langle k \rangle$ is between 10^3 and 10^4 for humans), as presented in Bailly & Longo (2009), we get:

$$N_G = \binom{N}{2} \quad (8.23)$$

$$\frac{K_{f1}}{N} \simeq \langle k \rangle \log(N) \quad (8.24)$$

However, if we postulate that *any* graph of interaction is possible, then we get a total number of possible interactions which corresponds to a choice between interaction or no interaction for each entry of the interaction matrix (N^2 cells). However, the latter is symmetric; and we do not count the self-interactions (because they correspond to the complexity of the cell) so we obtain $N(N - 1)/2$ binary choices, so $2^{n(n-1)/2}$ possibilities:

$$\frac{K_{f2}}{N} \simeq \frac{N}{2} \quad (8.25)$$

There is two main lines of reasoning we can follow to understand the situation. The first is to look at the time structure of symmetry changes. Indeed, the symmetry changes occur as a temporal cascade. As a result, the temporal hierarchy of individuation is crucial.

¹³Notice that this situation is not very different from the statistical mechanics of hard spheres freeze by a correlation entropy term in competition with the configuration entropy term (which corresponds more intuitively to disorder), see Baus (1987).

Here, we can refer to some phenomena concerning the graph of interaction of neurons. A crude description of the formation of neural networks is the following. First, a large number of “disordered” connections take place. Only after, the functional organization really increases by the decay of unused synapses (see for example Luo & O’Leary 2005). Then, the “bigger” symmetry group involved in the description is of the form K_{f1} , with $\langle k \rangle$ mean number of connections; but then this symmetry group is reduced to obtain a smaller symmetry group with $\langle l \rangle$ mean number of connections. This operation can be seen as a change of symmetry groups, from the transformations preserving the number of connections with $\langle k \rangle N$ connections to those preserving $\langle l \rangle N$ connections.

Of course there are many other possible components for a measure of biological complexity. This proposal, defined as anti-entropy, provides just a tentative backbone for transforming the informal notion of “biological organizational complexity” into a mathematical observable, that is into a real valued function defined over a biological phenomenon. It should be clear that, once enriched well beyond the definition and the further details given in Bailly & Longo (2009), this is a proper (and fundamental) biological observable. It radically differs from the rarely quantified, largely informal, always discrete (informally understood as a map from topologically trivial structures to integer numbers) notion of “information”, still dominating in molecular circles, see Longo et al. (2012) for a critique of this latter notion.

8.7 THEORETICAL CONSEQUENCES OF THIS INTERPRETATION

In the section above, we have been focused on technical aspects of the “microscopic” definition of anti-entropy. Using this method, we have seen that anti-entropy can mainly be understood in terms of symmetry changes. We will now consider the theoretical meaning of this situation in a more general way. As we exposed in Longo & Montévil (2011a), we propose to understand biological systems as characterized by a cascade of symmetry changes. Now, our understanding of a “biological trajectory”, a phylogenetic and ontogenetic path, as a cascade of symmetry changes yields a proper form of randomness to be associated to the construction and maintenance of biological organization. This perspective is particularly relevant for us, since it links the two theoretical approaches of the living state of matter that our team has introduced: anti-entropy (Bailly & Longo 2009) and extended criticality (Bailly & Longo 2008; Longo & Montévil 2011a).

More precisely, in phylogenesis, the randomness is associated to the “choice” of different organizational forms, which occurs even when the biological objects are confronted with remarkably similar physical environment and physiological constraints. For example, the lungs of birds and mammals have the same function in similar environments; they also are effectively compatible with a wide common range of body sizes; but they have phylogenetic histories which diverged long ago and, thus, extremely different architectures (Kay 1998).

This example is particularly prone to lead to approximate common symmetries, since it relates to a vital function (respiration and therefore gas exchanges with the environment) shared by a wide class of organisms. It is noteworthy that numerous theoretical studies have analyzed lungs by optimality criteria (Horsfield 1977; West, Brown & Enquist 1997, 1999; Gheorghiu et al. 2005). However, the criteria for optimality are not the same among

all these studies (minimum entropy production, maximum energetic efficiency, maximum surface/volume ratio, ...). Accordingly, even among mammals, structural variability remains high. For example, Nelson, West & Goldberger (1990) describe the differences in the geometrical scaling properties of human lungs on one side, and of rats, dogs and hamsters lungs on the other side. Moreover, Mauroy et al. (2004) show that the criteria of energetic optimality and of robustness for the gas exchanges, with respect to geometric variations, are incompatible. More generally, optimization criteria are not particularly stable. In particular robustness is essential but is nevertheless a relative notion: it depends on the property that we consider as robust as well as on the transformations with respect to which we expect the object of study to be robust (Lesne 2008).

Similarly, the theoretical symmetries constituted in ontogenesis are the result of the interactions with the environment, on one side, and of the developmental trajectory already followed at a given time, on the other. In our perspective, this trajectory must then be understood as a history of symmetry changes. And, of course, the situation at a given moment does not “determine” the symmetry changes that the object will undergo. This is a crucial component of the randomness of the biological dynamics, as we consider that random events are associated to symmetry changes. These events are given by the interplay of the organism with its own physiology (and internal milieu) and with its environment, the latter being partially co-constituted by the theoretical symmetries of the organism, since the relevant aspects of the environment depend also on the organism.

In other terms, the conservation, in biology, is not associated to the biological *proper observables*, the phenotype, and the same (physical) interface (e.g. energy exchange) with the environment may yield very different phenotypes; thus, there is no need to preserve a specific phenotype.

In short, the symmetry changes occurring in an organism can only be analyzed in terms of the previous theoretical symmetries (biology is, first, an historical science) and the differences of the possible changes can be associated to different forms of randomness:

- In the cases of symmetry breakings, the symmetry change corresponds to the passage to a subgroup of the original symmetry group. As a result, the theoretical possibilities are predefinable (as the set of subgroups of the original group). This typically occurs in the case of physical phase transitions, and the result is then a randomness associated to the choice of how the symmetry gets broken, which is usually described by the direction of the order parameter (for example the sign or the direction of a global magnetization, which breaks the symmetry of an Hamiltonian). For example, if an organism has an approximate rotational symmetry, we can say that this symmetry can be broken in a subgroup of this symmetry group, for example by providing a particular oriented direction. We then have a rotational symmetry along an axis. This can again be broken, for example into a discrete subgroup of order 5 (starfish). Another example is the breaking of metabolic allometry, corresponding to physiological changes in ontogeny (Glazier 2005).
- Another form of symmetry change corresponds to the case where the symmetry changes are constituted on the basis of already determined theoretical symmetries

(which can be altered in the process). This can be analyzed as the formation of additional observables (phenotypes) which are attached to or the result of already existing ones. Then these symmetry changes are associated with already determined properties, but their specific form is nevertheless not predetermined. A typical example of this theoretical situation is the case of physically non-generic behaviours that can be found in the theoretical analysis of some biological models. In Lesne & Victor (2006), this kind of situation is argued to be widespread in biophysics. From the point of view of the theoretical structure of determination, it is then a situation where there are predetermined attachment points, prone to lead the biological system to develop its further organization on them. The form of the biological response to these organizational opportunities of complexification is not, however, predetermined and then generates an original form of randomness. This theoretical account is close to the notion of next adjacent niche, proposed in Kauffman (2002); however, we emphasize, here, that the theoretical determination of these next organizational possibilities is only partially determined. For example imagine that a biological dynamic has approximately certain symmetries, which leads to a non-generic singular point, then it is possible (and maybe probable) that this point will be stabilized in evolution, in an unknown way. Another example is the apparition of a new possible niche, but which we can identify as such. Example, are the apparition of swim bladder, following Kauffman (2002), or the apparition of guts, but also external geological factors. In Such cases, we know that the environment will be colonized but we do not know the resulting organizational form of its inhabitants.

- The former case is constituted, in a sense, by a *specific* organizational opportunity. We can, however, consider cases where such opportunities are not theoretical predetermined. In such cases, the constitution of symmetry changes should be understood as having an even more random status, and the associated predictability is extremely low. Gould's most quoted example of "exaptation", the formation of the bones of the internal ear from the double jaw of some tetrapods, some two hundred million years ago, is an example of this highly unpredictable evolutionary dynamics.

We have seen that the symmetry changes lead to a strong form of randomness. This randomness and its iterative accumulation are, however, the very fabric of biological organization. Therefore, we have a theoretical situation where order (biological organization) is a direct consequence of randomness. Its global analysis allowed us to give mathematical sense to Gould's evolutionary complexification along evolution, as a consequence of the random paths of an asymmetric diffusion (sections 8.3 and 8.4). A finer (or local) analysis suggested a way to understand also ontogenetic changes in these terms, that is as a random dynamics of symmetry changes.

This situation should be not confused with the cases of order by fluctuations or statistical stabilization (for example, by the central limit theorem). In our case, indeed, the order is not the result of a statistical regularization of random dynamics into a stable form, which would transform them into a deterministic frame. On the contrary, the random path of a cascade

of symmetry changes yields the theoretical symmetries of the object (its specific phenotypes), which also determine its behaviour.

In this context, the irreversibility of these random processes is taken into account by entropy production. The latter, or more precisely a part of the latter, is then associated to the ability of biological objects to generate variability, thus adaptability. In ontogenesis, this point confirms our analysis of the contribution of anti-entropy regeneration to entropy production, in association with variability, including cellular differentiation. This situation is also consistent with our analysis of anti-entropy as a measure of symmetry changes. Notice that the symmetry changes, considered as relevant with respect to anti-entropy, may be taken into account, for example, in the coefficients corresponding to the individuation capacity of different cell types in our discussion above (see section 8.6).

In the next chapter and the following, we will focus on the notion of levels of organization, which will allow us in the last chapter to provide a first account of their contribution to anti-entropy.

The idea of closure in biological systems 9

This chapter has been written in collaboration with M. Mossio. It has been presented, in the Workshop on Artificial Autonomy, in ECAL 2011.

CONTENTS

| | | |
|---------|---|-----|
| 9.1 | Introduction | 210 |
| 9.2 | Biological determination as self-constriction | 212 |
| 9.3 | Constraints and processes | 214 |
| 9.3.1 | Some biophysical examples | 216 |
| 9.4 | Dependence | 218 |
| 9.5 | Closure | 219 |
| 9.5.1 | The case of scale separation | 220 |
| 9.5.1.1 | Definitions | 221 |
| 9.5.1.2 | Collapse of the multi-scale dynamic | 222 |
| 9.5.2 | Interpretation | 224 |
| 9.6 | Conclusion | 226 |

ABSTRACT:

In this chapter, we provide a general characterization of closure as a distinctive causal regime of biological systems, which cannot be reduced to physicochemical causation without losing relevant information about the system's organization.

Our argument consists in three steps. First, we put an account forward of how different levels of causation can be realized within a biological autonomous system, by making a conceptual and formal distinction, based on the idea of symmetry, between processes and constraints exerted on these processes. Second, we develop the notion of dependence among constraints and, third, we claim that closure is realized as a mutual dependence among a set of entities having the status of constraints within the system. The chapter might then make

a relevant contribution to the elaboration of a conceptual and formal theory of closure, able to overcome some of the weaknesses of previous accounts.

Keywords: closure, time scales, autopoiesis, scale separation, levels of organization

9.1 INTRODUCTION

IN Theoretical Biology, a long-lasting tradition puts strong emphasis on the idea that a distinctive feature of biological systems consists in the fact that they realize closure, i.e. a mutual dependency among its constitutive parts and processes which, hence, exist insofar as the whole organization is maintained. In the philosophical literature, the first explicit formulation of this view is said to go back to Kant who, in the *Critique of Judgement*, writes:

“In such a product of nature each part, at the same time as it exists throughout all the others, is thought as existing with respect to the other parts and the whole, namely as instrument (organ). That is nevertheless not enough (because it could be merely an instrument of art, and represented as possible only as a purpose in general); the part is thought of as an organ producing the other parts (and consequently each part as producing the others reciprocally). Namely, the part cannot be any instrument of art, but only an instrument of nature, which provides the matter to all instruments (and even to those of art). It is then — and for this sole reason — that such a product, as organized and organizing itself, can be called a natural purpose.” (Kant 1790)

After Kant, the scientific and philosophical work on what is initially called biological “self-organization” has been first undertaken by Cybernetics (Von Förster 1960) and then, during the last four decades, by several approaches in Theoretical Biology. Among the most prominent ones, it is worth mentioning the concept of Autopoiesis (Varela 1979), (*M, R*)-Systems (Rosen 2005), the Chemoton (Ganti 2003) and, more recently, autocatalytic sets (Kauffman 1993, 2002), which have given rise to an increasing number of investigations in various directions (Pattee 1982; Chandler & van de Vijver 2000).

According to Varela, for example, (operational or organizational) closure designates an organization of processes such that “(1) the processes are related as a network, so that they recursively depend on each other in the generation and realization of the processes themselves, and (2) they constitute the system as a unity recognizable in the space (domain) in which the processes exist” (Varela 1979, 55). According to the “Closure Thesis”, closure is a necessary requirement for autonomy, to the extent that “every autonomous system is operationally closed” (58).

Although there are relevant differences among these accounts, they all share the general idea that the notion of closure captures one of the central features of biological systems, or at least of systems being somehow “at the edge” of the biological domain. Accordingly, closure would constitute, in this perspective, an emergent and distinctively biological causal regime, in addition to evolution by natural selection. In a slightly different perspective, the notion

of closure is usually considered as one of the central determinations of the autonomy of biological systems.

Yet, in spite of the increasing convergence on the relevance of closure for the understanding of biological organization, existing characterizations of the notion have crucial weaknesses, which prevent its application as a fully operational tool in biological theorizing, modeling and experimentation. In particular, the way one can empirically access this property, directly or more or less indirectly is not well specified. Moreover, no explicit account of the relations between closure and other kinds of causal regimes at work in Physics and Chemistry has been provided so far, so that it is currently unclear whether or not closure is open to reductive interpretations to physicochemical causation.

As a consequence, the status of closure as a distinctive determination of biological systems remains somehow controversial. It might indeed be the case that all accounts of biological organization referring to closure could be reformulated by appealing to causal regimes at work in various categories of physical and chemical systems — and then by no means distinctive of the biological realm — without losing relevant information. If reductive interpretations were possible, then the central assumption of the models appealing to closure would be incorrect, in which case the notion could have, at best, some heuristic value in the biological research, but no explanatory role.

The central objective of this chapter is to provide a characterization of closure on the basis of which its status as a distinctive causal regime of biological organization can be assessed in precise terms. Yet, our approach will consist in considering closure *per se*, which in particular can be compatible with physical theoretical accounts.

As a consequence, we will aim at establishing a theoretical and formal framework in which it could be shown that biological systems realize at the same time several regimes of causation, one of which is the closure, while considering empirical modalities of this realization through the concept of scale. The outcome of the chapter will be an account of closure in which it is possible to distinguish, within an autonomous system, between a causal level of open thermodynamic transformations and a causal level of closed dependence among constraints. In particular, on the basis of the explicit formulation of the requirements that entities must fulfill in order to have the status of constraint, the account makes a relevant contribution to connect in a more straightforward way the theoretical expression with empirical aspects of relevant biological phenomena.

The aim of this chapter, in the context of our thesis, is to investigate the notion of closure in terms of precarious symmetries that are maintained by the activity of the whole. By doing so, we will show that closure may have special consequences in the case of a “highly critical” situation (the technical sense of this notion will become clear latter). It will also allow us to draw links between the theoretical accounts of closure and our approach in terms of extended critical transitions. As such, it is a point of entry to the structure of coherence of organisms.

In our view, one of the reasons why closure might be exposed to reductive interpretations is precisely the fact that existing models do not adequately justify the distinction between levels of causation and, consequently, are unable to specify what kind of entities and processes of a biological system are involved in the realization of closure. Accordingly, it will be our contention in this chapter that a sound characterization of closure requires an explicit

and operational account of how distinct levels of causation may be specified in a general framework. To achieve this aim, we will use the notion of constraint as an “upper” level of causation and provide a precise characterization of it. The resulting proposed closure will then be a notion of closure among constraints. More precisely, the structure of the chapter will be as follows:

In section 9.2, we describe the general approach behind our characterization of closure. In particular, we will put forward an understanding of biological systems in the light of the idea of self-determination as “spatiotemporal localized canalization/constriction” of physical and chemical processes. In section 9.3, we elaborate on the notion of constraint, which we take as the fundamental structure on which the distinction between levels of causation can be adequately established. Crucially, specific criteria for considering a given entity as a constraint will be provided. Section 9.4 will make a further step, by elucidating how the idea of dependency among entities working as constraints is to be conceived, and making the required distinctions with other kinds of causal dependency. Finally, section 9.5 will consider a specific case of dependency among constraints, closure, characterized as the case in which a set of constraints realizes the mutual dependency among them. We will also study closure, as defined before, in the special case of scale separation. In conclusion, we will discuss some central implications of our framework, by focusing in particular on the contribution that it may provide in relations to the existing accounts of closure.

9.2 BIOLOGICAL DETERMINATION AS SELF-CONSTRICTION

The very idea of closure, despite the variety of existing characterizations, refers to the mutual causal dependency among a set of elements, so that the standard, oriented relation between “causes” and “effects” is replaced by a network in which each element is at the same time cause and effect of the others. Yet, the condition in which elements of a system are mutually dependent seems to be by no means distinctive of biological systems. Let us mention an example that is usually mentioned in this kind of debate, i.e. the hydrologic cycle on Earth. In this case, a set of water structures (e.g. clouds, rain, spring, river, sea) generate a cycle of causal relations in which each of them contribute to the maintenance of the whole, and is maintained by the whole. The clouds generate the rain, which (contribute to) generates a spring, which generates a river, which (contribute to) generates a lake, which regenerates clouds, and so on

Arguably, a large number of physical and chemical systems could be described as realizing cycles of this kind or, more generally, some form of mutual dependence between their constitutive processes and reactions¹. As a consequence, a coherent account of closure has to choose between two alternative paths. On the one hand, closure could be conceived as a specific realization of mutual dependence as encountered in Physics and Chemistry, in which case the difference between physicochemical and biological systems would possibly

¹Notice that modern physics is better described as a tissue of interaction (Bailly & Longo 2011), where the theoretical determination is better described by the block of all interactions than by classical causes and effects. However, even in this case one can distinguish, by approximations, the main contributions to the determination, which can then be analyzed as cycles or not.

be quantitative, but not in kind. On the other hand, it might be the case that closure would constitute a causal regime which would be qualitatively irreducible to whatever kind of physical and chemical dependencies or loops, possibly in association with specific mathematical hypothesis.

The approach in this chapter is that *closure* can be shown to be a distinctively biological regime of causation by understanding it as occurring at a different level with respect to usual physical and chemical causation. We will, however, also see that the two levels are related, so that the epistemic validity of closure depends of the nature of the physical processes at play. In particular, we claim that closure consists in a mutual dependence among a set of entities working as constraints in a system.

What are constraints? In a general sense, a constraint can be seen as a reduction of the degrees of freedom of a system, which simplifies or changes its description and contributes to provide an adequate explanation of its behaviour, which would otherwise remain under-determined or wrongly determined. In contrast to physical, fundamental equations, constraints are local and contingent causes, exerted by specific material structures or processes, which usually are taken as asymmetrical relations, in the sense that they contribute to determine the behaviour and dynamics of a system, while being somewhat independent of those dynamics (Pattee 1972, 1973). In order to take a classical example, an inclined plane acts as a constraint on the dynamics of a ball on it, whereas the constrained dynamics do not exert a causal action on the plane.

In describing physical and chemical systems, constraints are usually introduced as external to the interactions described (boundary condition, parameters, restrictions on the configuration space, ...), which means that they are not only independent from the local dynamics on which they act, but also they are independent of the system taken as a whole. In some cases, a system may also contain a causal chain among entities working as constraints, such that some of the constraints are produced within the system. However, those chains remain asymmetrical since each constraint may either act on or be affected by another constraint, but no mutual dependence is realized.

The central claim of the chapter is that one distinctive feature of biological organization consists precisely in the fact that it realizes a closure among constraints, i.e. a set of structures and/or processes, acting locally as constraints, realizes a mutual dependence among them.

What are the intuitions underlying this idea?

- If an adequate characterization of a constraint can be provided, then a closure of constraints should be shown to be different from most if not all physical loop, as in the case of the water cycle.
- In particular, the fact of being closed at the level of constraints and at the level of processes would be independent, which means that a system closed to constraints would not necessarily be closed to "material causation".
- Indeed, our point is that biological systems as a whole cannot be closed to fluxes of matter, energy, or entropy because they are thermodynamically open. Hence, either they are closed with respect to constraints, or with respect to a similar idea, or the whole approach of closure is not valid.

- The fact of realizing a closure among constraints constitutes an approach to the way in which a biological system determines itself. Biological determination is realized through a specific form of self-constriction, which is underspecified by physicochemical symmetries.

In the following section, we will propose a characterization of the notion of constraint, on the basis of which it might be justified to claim constraints constitute a distinct level of causation, on top of usual physical determination.

9.3 CONSTRAINTS AND PROCESSES

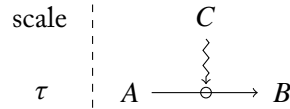
The claim according to which organizational closure is a distinctive causal regime of autonomous (biological) systems requires an account of the specificity of closure with respect to other kinds of causal regimes. In particular, given the dissipative nature of biological systems, which are, therefore, traversed by a flow of matter, energy and entropy through their boundaries, the relations between (thermodynamic) openness and (organizational) closure should be clarified in theoretical and formal terms.

In this chapter, we account for the distinction between levels of causation in terms of the distinction between *processes* and *constraints* (exerted on these processes). Processes refer to the whole set of physicochemical changes (including reactions) occurring in biological systems, which involve the alteration, consumption, and/or production of relevant entities. Constraints, in turn, refer to entities which, while acting upon these processes, can be said to remain unaffected by them, at least under certain conditions or from a certain point of view.

We propose to ground the theoretical and formal distinction between processes and constraints on the concept of symmetry. In full generality, this notion indicates a transformation that does not change the relevant aspects of an object (Weyl 1983; Goodman & Wallach 2009; Bailly & Longo 2011). In particular, given a process $A \rightarrow B$ (getting B from A), C is a constraint on $A \rightarrow B$ at a time scale τ if and only if the following three conditions are fulfilled:

- I/ The situations $A \rightarrow B$ and $A_C \rightarrow B_C$ (the former under the influence of C) are not symmetric by permutation at a time scale τ . They are distinguishable both empirically and theoretically at this time scale, beyond the mere addition of C .
- II/ A temporal symmetry is associated to C with respect to the process $A_C \rightarrow B_C$, at the time scale τ
- III/ The space of possible evolution of $A_C \rightarrow B_C$ is smaller or equal to the space of possible evolution of $A \rightarrow B$, each space being described at the relevant scale.

Conditions I-II-III can be met either directly or after analytic approximations. The situation which fulfills conditions I-II-III will be expressed as $A \xrightarrow{C} B(\tau)$ or, in an expanded form:



Let us discuss these three conditions by explaining the motivation behind them and referring systematically to a concrete example, i.e. the vascular system taken as a constraint on the flow of oxygen in an organism.

- I/ The first condition corresponds to the idea that a constraint is causal for the system constrained. We formalize this point by saying that the situation with or without this system are not symmetric, which simply means that they are different, even when we are not considering the constraint (but just its effects). We need the latter precision because it is always clear that a situation AB (say a cube on a plane) and a situation ACB with a supplementary object (say a second cube near the first one) are always different because of the object we added; however, this addition does not necessarily change something on the objects involved only in the first situation (it depends on whether they interact in a relevant way).

There is an asymmetry associated with the flow of oxygen when considered under the influence of the vascular system ($A_C \rightarrow B_C$) or not ($A \rightarrow B$) since, for instance, $A_C \rightarrow B_C$ occurs as a transport (canalized) to the neighbourhood of each cell, whereas $A \rightarrow B$ has a diffusive form. As a consequence, the situation fits condition I, which means that the vascular system exerts a causal role on the flow of oxygen.

- II/ A constraint is something that changes the way a subsystem behaves but, in a sense, is not changed by this subsystem. For example, the concentration of a catalyst is not changed during a reaction, or the topology of the vascular system is not changed during the blood flow. This aspect leads us to propose the condition that a temporal symmetry is associated to C in the process ACB .

A temporal symmetry is associated to the vascular system C with respect to the transformation $A_C \rightarrow B_C$ since, among other things, the topology of the vascular system remains unaltered during the blood flow. Hence, the situation fits conditions II, which means that C is conserved throughout the process.

- III/ Last but not least, a constraint is something that transforms the behaviour of a system but does not lead to a fundamentally new behaviour. In other words, it changes the relevant behaviour but does not generate new behaviour. We propose to approach this aspect by saying that the constraint does not extend the evolution space. For example, a catalyst does not make an otherwise impossible reaction possible, but it leads to a (far) greater speed of reaction.

The flow of oxygen could reach each cell at an adequate rate even in the form $A \rightarrow B$, i.e. in the absence of the vascular system, from the point of view of statistical mechanics. Hence, the vascular system does not extend the space of possible evolutions of the process $A \rightarrow B$ which means that the situation fulfills condition III. In other terms,

the vascular system is not required, at least in principle, for oxygen to reach the cells at an adequate rate — the probability of the unconstrained situation to occur being, however, very low².

Since the three conditions are fulfilled, the vascular system can be taken as a constraint on the flow of oxygen, and constitutes, we claim, a distinct level of causation.

It is crucial to emphasize that each condition is met *only at the relevant time scales*.

Let us take condition II, in our example. Although the topology of the vascular system does not change for small time scales, it does change on greater time scales. It is the case when, for instance, neovascularization occurs and changes the topology of the system. The same holds for enzymes, which can be shown to fit conditions I-II-III, and then play the role of constraints. But, even though enzymes are not consumed during the process they catalyze, they still decay and can randomly disintegrate at larger scales. Somewhat similarly, at very small time scales, enzymes are not conserved either, since they bind with the substrate, lose or gain hydrogen or electrons, protons, etc.. Yet, there is a relevant scale at which, when the reactive process is achieved, the enzyme is restored, leading to a middle-scale time symmetry.

Note, in addition, that the time scale τ at which conditions I and II must be fulfilled is the same. In turn, for condition III, the relevant scales, at which the space of possible evolutions of $A \rightarrow B$ and $A_C \rightarrow B_C$ can be described, can be very different from τ .

Our approach aims at a general description of biological constraints. In the following, we will give a conceptually interesting example, on the basis of physical models which approach biological situations.

9.3.1 SOME BIOPHYSICAL EXAMPLES

Let us see now how these concepts may apply to biophysics. Biophysics, here, is understood as the use of physical methods in a biological context. As such the determination involved in biophysical models inherits the “flat” causality of physics, the tissue of interactions described by the equations.

We will show that the usual physical requirement, that observed and thus relevant situations are generic (an explanation of this concept follows), is crucially not met in some biophysical situations. In these cases, we will argue that our approach is usually valid and corresponds technically or implicitly to the theoretical argument used by biophysicists in order to understand the situation. As a result, these particular cases are examples of our framework, which corresponds to situations that are not neutral with respect to the mathematical methodology that comes into play in the modelization.

In order to discuss the situation, we can consider, for example, a dynamical system in continuous time:

$$\frac{dx}{dt} = f(x, \alpha) + I(t) \quad (9.1)$$

²This aspect, due to the vanishing weight of certain probabilities, is unstable by the operation that consist in taking limits (making small probabilities equivalent to 0 for example). As a result, its objectivity relies mostly, in general, on the theoretical symmetries determining the possibility space.

A physicist will be interested in its generic trajectories, which are, in particular, trajectories that are physically relevant because they correspond to a non-null measure of the initial conditions and/or parameters space. A classical example of the difference between a generic and a non-generic situation is the description of a ball rolling on the slope of the mountain. The ball will move following the slope of the mountain except if it is put just at the top of it (where the slope does not define a horizontal direction). However, this situation is not physically relevant, in a sense, because it requires an infinite precision of the experimenter setting the initial conditions.

Such a situation also occurs if this dynamical system encounters a bifurcation for $\alpha = \alpha_0$, separating between different kinds of generic trajectories, obtained for intervals below and above this critical value. However, the behavior at this point is non-generic, because it is, again, physically impossible to put the system at a precise point and this point is the only one leading to this precise behavior. In other words, this situation is possible, but it will “almost” never happen, in the sense that, when randomly choosing a real number between 0 and 1, the probability of obtaining say 0.18 is 0.

However, in Camalet et al. (1999), this kind of non-generic behavior is analyzed as biologically relevant and is rendered, in a sense, generic by transforming the system into a system where the parameter becomes a dynamic variable:

$$\begin{cases} dx/dt = f(x, \alpha) + I(t) \\ d\alpha/dt = g(x, \alpha) \end{cases} \quad (9.2)$$

When we consider the attractors, α converges towards α_0 when the stimuli I are short and, the trajectory of x in 9.2 correspond approximately to the non-generic trajectory of 9.1 for $\alpha = \alpha_0$.

This system is an ordinary physical system, but we can compare the system 9.1 and the system 9.2 in our framework. $g(x, \alpha)$ changes α and, as a result, changes (through f) the trajectory of x and the condition I is met. The physical analysis of this system consists in a time scale separation between $I(t)$ and the dynamic of α . The result, and this is mandatory for the understanding of the situation, is that α is still considered locally as a parameter, and *in fine*, as invariant in time (but depends on properties of $I(t)$, namely a transient or a sustained stimuli). As a result, α , paradoxically, is still essentially time symmetric (condition II). Finally, the dynamic of x are locally the same in systems 9.1 and 9.2 (because α is asymptotically considered as a parameter), as a result, condition III is met. We can then conclude that the dynamic of α plays the role of a constraint, transforming a non-generic behavior in a generic one.

Another similar, yet different, scenario that often occurs in biophysics is the case where parameters or properties of objects in a system are found to be “well chosen”. This situation is often more technically described by the fact that different quantities or equational forms are (at least approximately) equal, whereas there is no particular physical reason for these equalities. In this case, a cause, external to the physical modeling, is invoked (mostly evolution), which justifies this physically improbable, yet possible, situation (see Lesne & Victor (2006) for an example where the argument is used and explained). In some cases, the argument of evolution is used mathematically as an optimization principle in the modeling

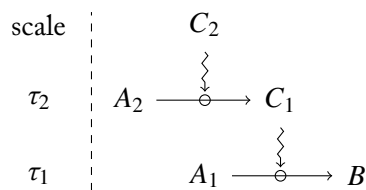
and allows to select a specific subspace of the configuration space (see West, Brown & Enquist (1997, 1999)). In both cases (formalized or not), our framework allows to understand the situation: these causes do not change the physical determination of the processes (the generic physical equations). They change what is observed (the physically improbable situation instead of the generic ones). The new space of possible evolution is a subspace of the former one.

We have seen through these examples that biophysical models often requires a paradigmatic shift from regular physical models. This change is that specific behaviours, which are irrelevant in a physical context, are relevant in biology, which is understood as possible by invoking other level/aspects of causation compatible with our approach of constraints.

9.4 DEPENDENCE

We have defined a level of constraint and a level of processes. The elements of processes do not form closure, *in fine*, because the system is thermodynamically open. We are then left with constraints as candidates for closure, which leaves us with the question of the possible relation that can exist between constraints. The constraints are, however, defined in particular by a time symmetry. As a result, constraints dynamics are not observable at the level where the objects can be seen as constraints, and their possible dependence on another process is also not observable at this scale. It is then, in a sense, a paradoxical situation that we will define here, where the notion of scale will allow us to put together antagonist notions. We will show that entities acting as constraints within an autonomous system may have a relationship of “dependence” among them.

As we mentioned, each constraint C is associated to a time symmetry at the scale of the process that it constrains (τ_1 below), but not necessarily at other scales (τ_2). At the same time, C can itself be the product of a process which, in turn, can be constrained by another constraint. This situation leads to the following diagram of minimal causal dependence among constraints:



More generally, let us consider a constrained process $A_1 \xrightarrow{C_1} B$ (τ_1). Because of condition II, there is a time symmetry at scale τ_1 associated to C_1 . At the same time, C_1 is the product of another constrained process $A_2 \xrightarrow{C_2} C_1$ (τ_2), at a different time scale. At scale τ_2 , C_2 plays the role of constraint, whereas C_1 does not, being the product of the process $A_2 \xrightarrow{C_2} C_1$. In this situation, we claim that there is a *dependence* of constraint C_1 on constraint C_2 .

Following this line of reasoning, we define a relation of *dependence among constraints* as a causal regime in which, given two time scales τ_1 and τ_2 considered jointly, we have:

- There exists an object C_2 which is a constraint at scale τ_2 on a process producing C_1
- C_1 is a constraint at scale τ_1

We will now make a couple of important remarks:

First, dependence among constraints is logically distinct from dependence among processes. In fact, at scales other than τ_2 , where C_2 does not play the role of constraint, there might be no other causal connection among the processes involved.

Second, because of condition III, $A_2 \rightarrow C_1$ does not require C_2 for occurring, at least at the very large scale of its possible evolutions, which implies that dependence can be observed only at the specific scale τ_2 .

Third, there are two basic situations that correspond to a situation of dependence between constraints. These situations are classified by the scales involved: we can either have $\tau_2 > \tau_1$ (left bellow) or $\tau_1 > \tau_2$ (right bellow). We will show that, when discussing closure, these two kind of situations are necessarily encountered.



In one case $\tau_2 > \tau_1$, the second constraint, C_2 , acts as a constraint at a larger time scale than the first one, which also means that it is involved in a slower process. Notice that if the dynamic of C_1 , engendered by the process at scale τ_2 , if smooth, leads straightforwardly to a local time symmetry. This aspect, added to the status of C_1 as a constraint at smaller scales, leads to a global (in the sense of: with respect to all processes) time symmetry of C_1 at scale τ_1 if τ_1 is sufficiently small.

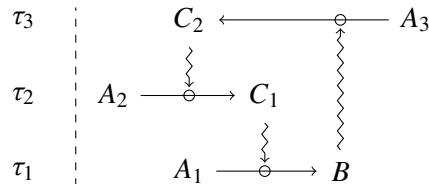
In the second case, $\tau_1 > \tau_2$, the second constraint, C_2 , is involved in a faster process than the process constrained by C_1 . Again, in order to obtain a global time symmetry at scale τ_1 for C_1 , the process constrained by C_2 has to constitute a statistical (or similar) time symmetry at large scale τ_1 .

It is noteworthy that “repair mechanisms” (J. Wang et al. 2009) can be analyzed as dependence among constraints. On the one hand, repairing implies the existence of a subsystem (C_1) which is only marginally altered while the main process occurs (i.e. its alteration is negligible at the relevant scale, τ_1), although it is altered on the long run (τ_2). On the other hand, the maintenance of the system’s organization requires, at a time scale τ_2 , the existence of a second subsystem (C_2) in charge of maintaining C_1 through the adequate canalization of a process $A_2 \xrightarrow{C_2} C_1$.

9.5 CLOSURE

The third step of the chapter will consist in defining closure as a specific case of dependence among constraints such that, given a set of constraints \mathcal{C} , each constraint of \mathcal{C} depends on, and contributes to the maintenance of, (at least) another constraint of \mathcal{C} .

Let us consider a simple example of a system realizing a closure among constraints:



As for whatever relation of dependence, two scales must be considered for each constraint (C) that are subject to closure: a scale ($\tau_s(C)$) at which C is associated to a time symmetry, and a scale ($\tau_d(C)$) at which it is produced and/or maintained. As shown in the diagram, closure requires that at least one constraint for which $\tau_s(C) - \tau_d(C) > 0$ and another constraint for which $\tau_s(C) - \tau_d(C) < 0$.

However, as we will discuss, these requirements do not necessarily lead to complex relations between scales. More precisely, we will distinguish between two possible situations. First, it might be the case that, when the constrained processes are regular enough, the complex “scale structure” of the system leads, in fact, to a *dynamic* that takes place at the upper scale alone (scale separation). Second, the multi-scale dynamic might be sustained as such, which would lead to an irreducibility of the multi-scale *dynamic* (see, for example, West, Bologna & Grigolini 2003).

We will in this chapter mostly discuss the case of scale separation, and analyze the general conceptual consequences that this special situation allows to derive. The case of processes having a singular nature is the object of ongoing work.

9.5.1 THE CASE OF SCALE SEPARATION

In this part, we do not aim at providing an account of closure that could be suitable for biology. On the contrary, we will establish what happens in a relatively straightforward mathematical situation: when the processes, roughly, only see what happens at their scale. By doing so, we will show that closure, even though not trivial in this case, leads to a global dynamic reducible to a particular scale, and closure itself leads to a set of static equations. By contrast, we want to point out the interest, to the conceptual understanding of closure, of looking at the nature of processes and in particular of their possible singularities.

It is useful to mention that even though scale separation could be understood as a somewhat arbitrary assumption, especially with respect to a wide class of biological dynamics (see section 2.4), it is nevertheless a more or less implicit assumption in the analysis of partial aspects of biological organization (in biophysics, for example, but not exclusively). If one consider, for example, the mathematized models of a specific part of an organism, say the model of hairs cells that we discussed above, then there is a considerable amount of constraints

that are not taken into account in the model. This slicing of biological organization can be justified under assumptions of temporal symmetries associated to the constraints out of the scope of the model; however, it also amount to more or less directly replace the possible faster or slower non-stationary dynamics by time symmetric ones.

The study of the case of scale separation is also useful since it leads to a mathematical problem that is easily tractable, and thus allows to study the possible consequences of our framework, with a limited generality, however. In the logical sense of the word, scale separation provides a model of our framework of closure among constraints: it is a mathematical (relatively unsophisticated) situation which is compatible with the (partially) formal definition of our framework but which is not the only one to be compatible. This approach will allow us to provide conceptual clarification on our approach of closure.

9.5.1.1 Definitions

The basic idea we will follow is that a specific but instructive situation is the one where the processes, related to each other but at different scales, have separated dynamics, so that only their mean or their equilibrium values are relevant.

To study the situation more mathematically, we will approach it by the classical notion of dynamical systems, to which we add scale considerations. For a process $A_1 \xrightarrow{C_1} B(\tau_1)$, we will write:

$$\alpha_{\Delta t}^1(A_1(t), B(t), C_1(t)) = (A_1(t + \Delta t), B(t + \Delta t), C_1(t + \Delta t)) \quad (\tau_1) \quad (9.3)$$

where t is the time localization, Δt is a time change at scale τ_1 , C_1 , A_1 and B are the time parameterized values of the involved objects and which may be determined by other processes, at other scales. We do not impose that the observables involved should be deterministically determined; the resulting B can be, for example, a density of probability or any relevant object. The process takes place at scale τ_1 which implies that if $\Delta t \ll \tau_1$, B does not have the time to change and if $\Delta t \gg \tau_1$, the transitory part of the dynamic is irrelevant (for example, the system can be considered as equal to its attractor).

Now, we do not really want to study $\alpha_{\Delta t}^1$ in details. What we want is to study the interscale relationships in this situation. To do that, we will make assumptions on the behaviour of $\alpha_{\Delta t}^1$ (and comparable functions). These assumptions, to be meaningful, need to be homogeneous with the framework we developed.

The key assumption we make is one of scale separation. For the process $A_1 \xrightarrow{C_1} B(\tau_1)$, in a situation where there are other processes, we define *scale separation* as corresponding to the following hypotheses:

1. Following our definition of a constraint we will assume that the relevant aspects of C_1 are not changed by α^1 (at scale τ_1).
2. If B is involved in another process, at scale $\tau_2 > \tau_1$, then only a stabilized aspect of the dynamic of B is relevant for this other process. As a result, at scale $\tau_1 \bowtie \tau_2$ with $\tau_1 \ll \tau_1 \bowtie \tau_2 \ll \tau_2$, the relevant quantity is $\Phi_{\tau_1 \bowtie \tau_2}^{1,2}(\alpha^1)(A_1, B, C_1)(t) \simeq \Phi_{\tau_1 \bowtie \tau_2}^{1,2} B(C_1(t), A_1(t))$. This assumption is in particular verified when the mean of B at scales $\tau_1 \bowtie \tau_2$ is well

defined and only this mean is relevant at scale τ_2 , but it could also very well be that it is the mean oscillations (per unit of time) of B at scale τ_1 that can be relevant (assuming also that it is well defined).

3. If C_1 , for example, is generated by another process at a greater scale τ_2 , then we assume that the relevant aspect of C_1 , $\Phi_{\tau_1 \ll \tau_2}^{2,1} C_1$ can be considered constant with respect to the dynamic that C_1 constrains.

Notice that we used Φ in the above definitions in order to formalize the description of the relevant aspects of an observable, with respect to a specific dynamic and at a given scale. The notation $\tau_1 \ll \tau_2$ represent a time scale large before τ_1 and small before τ_2 and latter we will also use the notations $\tau+$ and $\tau-$ to describe respectively scale large and small with respect to τ . The use of these intermediary scales, comparable to the meso-scales in thermodynamics, at the same time allows to take into account only the large-time behaviour of the fast processes and to use differential calculus and comparable methods.

Notice in particular that this assumption of scale separation means in particular that the system does not have bifurcations (or similar symmetry changes behaviours) or at least can be safely assumed to remain far from them. In these situations, indeed, we have usually an instability of the effect of small perturbation (infinite gain for example in the model of hair cells in Camalet et al. (1999), or infinite susceptibilities in criticality, see also section 5.4).

To clarify the situation, we will provide an elementary example. Let us assume crudely that the number of cell in an organ is B , but is (by a crude approximation) constrained by the available volume for their growth C_1 . We will also assume that the volume taken by a cell is a constant, v_c . Then, we can assume that the dynamic of the number of cells in the organ considered has the form of the logistic equation, which is the classical and simplest form used to describe such situations.

$$\frac{dB(t)}{dt} = \frac{1}{\tau_1} B(t) \left(1 - \frac{B(t)}{v_c C_1} \right) \quad (9.4)$$

$$\alpha_{\Delta t}^1(A_1(t), B(t), C_1(t) + \Delta C_1) \simeq \alpha_{\Delta t}^1(A_1(t), B(t), C_1(t)) + \Delta C_1 \frac{\partial}{\partial C_1} \alpha_{\Delta t}^1(A_1(t), B(t), C_1(t)) \quad (9.5)$$

$$\langle \alpha_{\Delta t}^1(A_1(t), B(t), C_1(t) + \Delta C_1) \rangle \simeq \alpha_{\Delta t}^1(A_1(t), B(t), C_1(t)) \quad (9.6)$$

where $\langle \cdot \rangle$ is the mean over time, for a duration τ , with $\tau_1 \ll \tau \ll \tau_2$. This dynamic converges exponentially towards $B_\infty = v_c C_1$.

In a developmental context, C_1 changes with time, leading to a dynamic $C_1(t)$ at a scale τ_2 . We will assume that this dynamic is slow in comparison with τ_1 . At scale τ_2 , the result of the fast dynamic is therefore just $B(t) = v_c C_1(t)$.

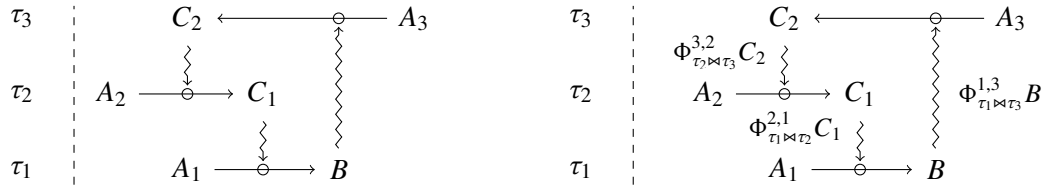
Let us consider that a third process is constrained by this cells number, for example endocrine hormone production at a scale $\tau_3 > \tau_1$. Then one has a hormonal production that can be assumed³ to be $\propto B$, which is also $\propto v_c C_1(t)$.

³Notice that this assumption could be replaced by an allometric relation. However, in the context of our framework, such a relation does not change the theoretical situation much since allometric relations are smooth (except at zero).

A noteworthy, special case is the situation where the slower-scale dynamic only depends on the mean of the faster one. Typically, this can happen when the dynamic of the process is differentiable with respect to its dependence on the faster dynamic.

9.5.1.2 Collapse of the multi-scale dynamic

Now, assuming all processes follow the above hypotheses, what happens in the case of closure? In order to approach this question, we will first consider the above given simple case of closure, which is given by the following diagram:



We have then the following dependencies:

$$\Phi_{\tau_2 \bowtie \tau_3}^{3,2} C_2(B(t), A_3(t)) \quad \Phi_{\tau_1 \bowtie \tau_3}^{1,3} B(C_1(t), A_1(t)) \quad \Phi_{\tau_1 \bowtie \tau_2}^{2,1} C_1(C_2(t), A_2(t)) \quad (9.7)$$

We can then replace the constraints:

$$\Phi_{\tau_2 \bowtie \tau_3}^{3,2} C_2(B(t), A_3(t)) = \Phi_{\tau_2 \bowtie \tau_3}^{3,2} C_2\left(\Phi_{\tau_1 \bowtie \tau_3}^{1,3} B(C_1(t), A_1(t)), A_3(t)\right) \quad (9.8)$$

$$= \Phi_{\tau_2 \bowtie \tau_3}^{3,2} C_2\left(\Phi_{\tau_1 \bowtie \tau_3}^{1,3} B\left(\Phi_{\tau_1 \bowtie \tau_2}^{2,1} C_1(C_2(t), A_2(t)), A_1(t)\right), A_3(t)\right) \quad (9.9)$$

At scale τ_3+ , we thus have:

$$\Phi_{\tau_3+}^{3,2} C_2 = \Phi_{\tau_2 \bowtie \tau_3}^{3,2} C_2\left(\Phi_{\tau_1 \bowtie \tau_3}^{1,3} B\left(\Phi_{\tau_1 \bowtie \tau_2}^{2,1} C_1\left(\Phi_{\tau_3+}^{3,2} C_2, A_2(t)\right), A_1(t)\right), A_3(t)\right) \quad (9.10)$$

We thus obtain a fixed point equation.. To clarify further the situation, we will identify ΦX and X and assume that the A_i remain roughly constant, then we get:

$$C_2 = C_2(B(C_1(C_2))) \quad (9.11)$$

So we see that in this case, we have transformed a theoretical account of a dynamic into a functional equation. If one further assume that the functional dependencies are of the form $X(Y) = a_X Y$ which is for example the case in the situation described by equation 9.4, then we get:

$$C_2 = C_2(B(C_1(C_2))) \quad (9.12)$$

$$C_2 = a_{C_2} a_B a_{C_1} C_2 \quad (9.13)$$

$$1 = a_{C_2} a_B a_{C_1} \quad (9.14)$$

We thus see that the validity of closure corresponds in this case to a condition on the parameters of the system. When this condition is not met, the system is unstable, see figure

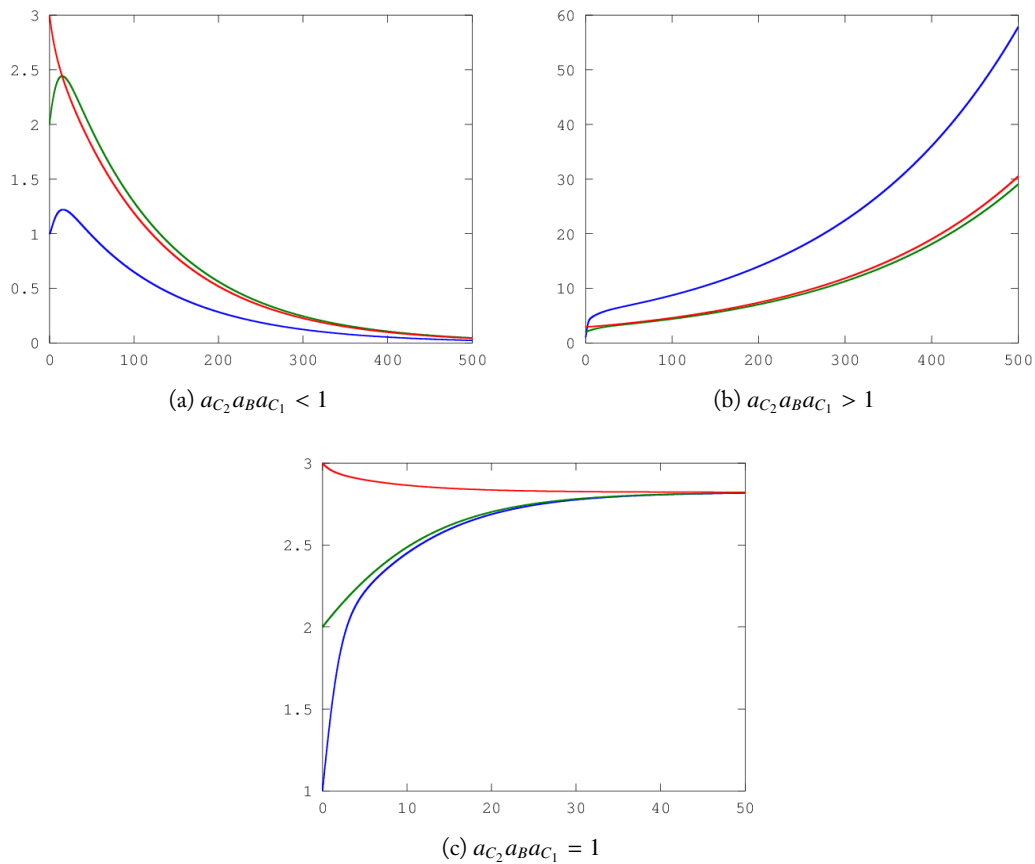


Figure 9.1: *Logistic case: closure and “failed” closure.* By order of speed, from the fastest to the slowest, the curves are colored in blue, green and red. Only when the functional equation is met, is the situation really stable. Notice that the fast curves rapidly follow the slow ones.

9.1. Interestingly this situation is not generic, it corresponds to a specific choice of the parameters. However, if one just relaxes the hypothesis on the form of the functions, we see that the case of closure is not necessarily non-generic. In order to have generic closure in this special case, the mathematical condition is that at least one of the functions has a constant part.

Let us now consider the situation with more generality, in the case where closure is obtained by a *loop* of dependencies among constraints. In a finite graph of relations, there is a smallest time scale. At this smallest scale τ_1 , our hypothesis leads to the determination of the possible effects of B at other time scales by a locally static object instead of a dynamic: $\Phi_{\tau_1+B}(C_1(t), A_1(t))$. Then, the dynamic of B will simply follow the one of C_1 at scale τ_2 , at a greater time scale, because it is fast enough. Then, the dynamic of C_1 will follow a slower one and so on. *In fine*, thus, the whole dynamic is driven by the slowest one in the case of a simple loop. At the scale at which this slowest dynamic stabilizes, we finally obtain a functional equation, corresponding to the stability of the whole system.

This result can also be generalized to any graph topology. The outcome is then a set of equations, corresponding to the topology of the graph. The algorithm to obtain them is to look at the processes which do not depend on a faster process, and replace them at an upper scale by the obtained relevant functional dependencies.

9.5.2 INTERPRETATION

Now that we have obtained this technical results, we need to understand them in a proper way. In order to do so, we will distinguish the level of the (macroscopic) dynamic and the level of the multi-scale analysis.

DYNAMICAL ASPECT. In the case of scale separation, the conclusion we can draw from our analysis is that the multi-scale structure collapses into a dynamic at a single time scale, the slowest one, and even leads to a static equation when considering a scale large in comparison with the latter. In such a situation, the structure of the dynamic is reducible to a dynamical relation that is neither irreducibly a process, since it can be described by static values, nor strongly multi-scale, since the situation can be described, *in fine*, at the upper scale only. From this dynamical point of view, then, scale separated closure cannot lead to a macroscopically observable signature. Notice that this macroscopic system can be stable or not depending on the validity of the equational relation associated with closure; however, from the point of view of the macroscopic observer, this just corresponds to a macroscopic parameter.

MULTI-SCALE RELATION. As we have seen, scale separation allows, however, to derive one or several equational relations associated with closure. These equational relations depend on the specific dynamics of the processes at various scales. As a result, we cannot obtain it by the macroscopic behaviour of the system alone. Notice also that this nontrivial equational relation is only the trace of the analysis in terms of constraints. The latter indeed corresponds to a judgment on the multi-scale structure of the processes involved. In order to objectivize it, an objectivization of the individual processes, at various scales, is needed. Scale separation indeed allows such an objectivization (because they can be studied relatively independently, typically). Thus, the final result, the closure among constraints is in particular not observable at the upper scale alone.

The case of scale separation combines therefore a specific mix of dynamical reducibility, on one side, and of an irreducibility of closure, on the other side. We want to emphasize that the analysis in terms of closure is not limited to the equational result that we can derive from it. Indeed, if one assume that closure among constraints is a key invariant, then its analysis correspond to the analysis of the processes involved. The equation(s) that one can derive from it is then only a consequence of closure, which also needs a multi-scale account of the situation to be derived (even though the resulting dynamic is not multi-scale).

Scale separation consists thus in a *decoupling* between the dynamic and the causal structure, in the sens of closure among constraints.

However, if one considers the negation of these conditions, we obtain a situation where the reduction of the dynamic to a particular scale is not (at least in certain cases) possible.

These situations correspond in particular to non-stationary behaviours and inter-scale relationships associated to singularities. Interestingly, these situations are also what is generally observed in biological behaviours (see chapter 2, and in particular section 2.4).

In the context of extended criticality, we can thus conclude that closure has a particular meaning, since we can conjecture that there is, on the contrary, a *coupling* between closure and the dynamic. In this case we can thus also conjecture that closure become dynamically irreducible, but a proper mathematical treatment is needed to show this point.

9.6 CONCLUSION

The outcome of the chapter is a characterization of organizational closure based on an explicit, formal distinction between two levels of causation (constraints and processes) whose relations, in turn, rely on the identification of symmetries at the relevant (temporal) scales. Accordingly, the chapter could then provide a relevant contribution to the elaboration of a conceptual and formal theory of closure as a distinctive causal regime of autonomous organization, able to overcome some of the weaknesses of previous accounts. Yet, although the specific formulation developed in this chapter is supposed to capture some of the *distinctive* features of organizational closure (with respect to whatever other causal regime), it cannot be taken, *per se*, as a definition of the closure at work in biological autonomous systems. The complexity of biological organization would require more accurate accounts, capturing the additional properties of closure as realized by full-fledged biological systems.

The mathematical analysis of the case of scale separation allows to draw a certain number of conclusion. First, the whole dynamic of the system is mainly driven by the slowest dynamic (under this assumption). When stabilized at the upper scale, closure leads to a static fixed point equation, in the case of a simple loop. More generally, the situation can be described by functional equations. In this case the dynamic is reducible to a macroscopic behaviour. The condition of closure is thus not observable at the macroscopic level and need a proper account, in a multi-scale decomposition. There is thus decoupling of closure among constraints and of the macroscopic behaviour, which is proper to scale separation.

We thus see that there is a sharp distinction between the scale separation situation and the case where the dependence of a phenomena at a lower time scale is typically not smooth, or when the lower scale has a non-stationary behaviour. It is conceptually particularly interesting that the introduction of elementary physical considerations (the notions of symmetries, time, and time scales) leads to a strong distinction concerning the possible consequences of closure, between the decoupling of the macroscopic dynamic with the closure condition, and its possible coupling when singular phenomena are involved.

In the following chapter, we will take another point of view and approach directly the notion of levels of organization by the use of singular behaviours.

Levels of organization, singularities and reductionism

10

This chapter has been written in collaboration with A. Pocheville.

CONTENTS

| | | |
|----------|--|-----|
| 10.1 | Introduction | 228 |
| 10.2 | Critical phenomena and reductionism | 229 |
| 10.2.1 | Reductionism | 229 |
| 10.2.2 | Interscale reductionism in physics | 230 |
| 10.2.2.1 | A paradigmatic case: the reduction of thermodynamics to statistical mechanics | 230 |
| 10.2.2.2 | When means fail: critical phase transitions | 231 |
| 10.2.2.3 | Reductionism vs renormalization | 232 |
| 10.2.3 | Consequences for biology | 236 |
| 10.2.3.1 | Criticality and living matter | 236 |
| 10.2.3.2 | Circular couplings | 237 |
| 10.2.3.3 | Conclusion on the consequences for biology | 237 |
| 10.2.4 | Conclusion | 238 |
| 10.3 | Levels of organizations | 238 |
| 10.3.1 | Complexification within a level | 239 |
| 10.3.2 | Two types of infinity | 240 |
| 10.3.3 | Transition between two levels | 241 |
| 10.3.4 | Criteria of transition | 241 |
| 10.4 | Application to biology | 242 |
| 10.4.1 | Biological levels of organization as an hypothesis | 242 |
| 10.4.2 | Fractals and functions | 242 |
| 10.4.3 | Non genericity of parts | 243 |
| 10.5 | Conclusion | 244 |

ABSTRACT:

The notion of level of organization seems to be crucial to the biological thinking. However it is not clear how levels should be defined, and how they (and the corresponding models or theories) are supposed to relate with each other. In the first part, we will approach this question by investigating the operative modalities of interscale reductionism in some fundamental physical cases. This will lead us to identify several limits to a strong reductionism in physics. We then show that biology is not more prone reduction. In the second part, following Bailly (1991b) we discuss a strong criterium of level transition. The core idea of the criterium is to start from the breaking of the determination of the first level.

Keywords: reductionism, criticality, renormalization, levels of organization

10.1 INTRODUCTION

THE problem we want to tackle, here, is theoretical pluralism in biology with respect to the notion of levels of organization, in particular in the light of critical situations. Theoretical accounts¹ on living systems are diverse, for instance, these accounts crucially depend on the scale and/or level of study the biologist focuses on (think, for instance, to a molecular approach compared to an organismal one). But when different accounts are meant to deal with what is supposed to be the same biological matter, we are faced with the question of pinpointing the relationships between these accounts, and the possible reduction of one scale/level of description to another. This is the question the first part of this chapter deals with. The second part deals with the question of the nature of the levels of organization in living systems, provides a strong definition of the change of level of organization and deals with the implications of the coexistence of several levels of organization in a living system.

First, let us clarify the difference between scales and levels. Scales appear through *quantities* (which can have the dimensionality of e.g. space, time, energy, mass), varying in magnitude between descriptions. By contrast, levels of organization appear through *qualitative* changes between objects that are organized in a hierarchical manner (for examples atoms, molecules, organelles, cells, organs, organisms, etc). As we will see below, the notions of scales and levels of organization are not equivalent, especially in biology. An example of the difference between these two notions is to be found in the allometric relationships, that describe how certain quantities (such as the metabolic rate) change through scales (usually the mass) while keeping the level of organization fixed (usually the level of organisms, see also section 2.2).

In biology, scales are not seen as problematic, since they are usually inherited from physically defined quantities². Contrariwise, the notion of levels of organization, while

¹We purposely avoid the term "theory" here as theoretical accounts in biology are not fully integrated theories (Brigandt & Love 2008).

² A closer analysis of biological measurement, see chapter 7, would more precisely lead to say that the physical measure of biologically relevant quantities involve instabilities, but we will not discuss this point forward here.

widely used, appears to be loosely defined, and its relevance, beyond mere heuristics, remains to be shown (Bailly 1991b; Brigandt & Love 2008). Therefore, in the first part of the chapter, we will remain neutral as to the notion of level of organization and will restrict ourselves to interscale theoretical relationships. We will come back to the question of interlevel theoretical relationships later.

10.2 CRITICAL PHENOMENA AND REDUCTIONISM

10.2.1 REDUCTIONISM

Reductionism is a vast philosophical issue, which, it is fair to say, we will tackle only a small part (see Batterman (2007); Brigandt & Love (2008); Cat (2007) for reviews of reductionism's vastness).

Here we will let aside ontological and methodological issues and will focus on epistemological reductionism, that is, the question of intertheory relations.

Let's start with Nagel's seminal concept of reductionism: T reduces T' if and only if the laws of T' are derivable from those of T (Nagel 1961, Chap. 11). When T' is not directly derivable from T (that is, most of the time), some assumptions (often called bridge laws) have to be made to connect T' and T (for instance, bridge laws can take the form of limit relationships³). Notice that the notion of deducibility is not straightforward, and in particular, the mathematical sense of this notion is different from its logical sense, if one considers the results of "concrete" incompleteness, see Longo (2011). Our aim here, is to question the validity of this scheme in some singular physical and biological situations, with respect to reduction of theories, or theoretical accounts, developed at different scales of a system (that is, we will focus on hierarchical reductions sensu Sarkar (1998)), and will investigate the corresponding mathematical structure of intertheory relationships.

To make the long story short, the simplest way to understand the relationships between different scales (or levels) of description is probably to think of them as being embedded in a linear hierarchy (viz a tree without cycle), where the combination of parts exactly determine the properties of the system at upper scales/levels (see for instance Oppenheim & Putnam (1958)). In this bottom-up hierarchical picture, the basic level of living systems should be at least molecules or atoms, organisms would be reducible to sets of molecules. To this theoretical hierarchy traditionally corresponds a disciplinary hierarchy, which confers a more fundamental role to lower-scale disciplines (e.g. the scales of molecular phenomena in biology).

An opposite way to understand the relationships between scales/levels of description, and their corresponding disciplines, is to think of them as being partially or totally autonomous with respect to lower scales/levels, that is, to hold a so-called holistic position. Thus according to this tenet, organisms are not reducible to sets of molecules, but show emergent properties (that is, properties that do not exist at lower scales/levels). See Cat (2007) for

³When bridge laws are (regular) limit relationships, we obtain reduction in the physicist's sense, sensu Batterman (2007, 2005), who gives credit to Nickles' distinction (Nickles 1973). Ever since, much work has been done by Nagel and others (see e.g. Schaffner (1967)) to discuss and refine this scheme.

a review of anti-reductionist approaches and Looijen (2000, chap.2) for a review of the holism/reductionism debate in biology.

Whatever marked, dichotomies are not necessarily insurmountable. Some authors have called for seeking alternatives to the reductionism/holism dichotomy (Brigandt & Love 2008; Looijen 2000). Without any provincialism, we propose to examine the question of epistemic hierarchical reductionism first in physics, which, by being more formalized, allows to tackle the problem with the constraints and guidance of mathematics. Even in this field, questions appear not to be trivial. Then, we examine how these reflexions can highlight the same questions in biology and possibly lead to a different answer than a strong dichotomy between epistemic holism and reductionism.

10.2.2 INTERSCALE REDUCTIONISM IN PHYSICS

First we will specify in which sense we are taking reductionism here. Let's start with Nagel's concept of reduction applied to hierarchical systems, and substitute Nagel's condition of derivability (that is, logical deduction sensu Nagel) with a more pragmatic condition of mathematical derivability of the upper scale determination from the local interactions. The modalities of this integration of the parts will determine the form of the possible reductionism at play (if any).

10.2.2.1 *A paradigmatic case: the reduction of thermodynamics to statistical mechanics*

The main way to achieve the reduction of an upper scale model to a lower scale model is to use some form of statistical averages over the microscopic properties, provided that the number of lower-scale entities is sufficient. Reduction of thermodynamics to statistical mechanics is one of the most (supposedly) paradigmatic examples of a successful Nagelian reduction and operates this way⁴.

The principle of statistical mechanics are the following (see Sethna (2006) or chapter 5 section 5.4.1.1). We consider elementary objects (microscopic objects), which live in a given phase space and have a state described by this phase space. A microstate is given by the state of all elementary objects. Each one of these elementary objects have a determined energy function, which depends on its state and on the states of other elementary objects (interactions). The sum of all these elementary energetic contributions defines the energy of the microstate considered. The energy as a function of the state is called Hamiltonian. The crucial hypothesis is that all microstates with the same energy have equal probability. Therefore, the macroscopic equilibrium state corresponds to the greatest number of possible microscopic states at fixed energy (microcanonical ensemble). This leads to Boltzmann's interpretation of entropy, where entropy is the logarithm of the number of state at fixed energy. The most probable state is, therefore, the one with the highest entropy. Then, the (inverse) temperature can be introduced as a quantity associated to energy (Lagrange multiplier), and the distribution of states follows by generic optimization principle (for a

⁴This example has been challenged, notably as soon as 1961 by Feyerabend (Feyerabend 1985) see Cat (2007) for a review.

large number of particles). All statistical properties are then given by the partition function $Z = \sum_{s \in \text{microstates}} \exp(\mathcal{H}(s)/k_b T)$. The probability of each state is $\exp(\mathcal{H}(s)/k_b T)/Z$

The point is that the distribution depends only of the Hamiltonian, and the conjugated variable, the temperature (and possible other external parameters when relevant). Moreover, the thermodynamical quantities can be obtained straightforwardly as averages, sums, variance, etc., from this distribution. Mathematically this is elegantly obtained by elementary operations on Z : derivation, application of the logarithm, multiplication by the inverse temperature, etc. For example the macroscopic energy is the expected value of the energy of the microstates $\langle E \rangle = -\frac{\partial \ln Z}{\partial 1/k_b T}$, see section 5.4.1.1 for other examples.

The probability of deviating from the most probable state decreases exponentially, depending on the number of lower-level entities (this result is known as the fluctuation theorem). Thus, reductionism corresponds to the determination of the macrostate by microscopic energies and is in this case mathematically achieved and controlled.

Notice that if one considers classical mechanics, however, the reduction is not straightforward, because certain notions and mathematical manipulations have to be introduced in the classical framework, which are not “natural” in this framework⁵. The main notions involved are ergodicity (that is, roughly speaking, a symmetry assumption between time average and phase space average) and the thermodynamic limit (the assumption of an infinite number of particles leads to a coincidence of averages and macroscopic states), which in particular leads to the time reversal symmetry breaking.

10.2.2.2 *When means fail: critical phase transitions*

There are some cases in physics where approaches of the kind described above fail. This is particularly the case in some second-order phase-transitions, in thermodynamics (Toulouse, Pfeuty & Barton 1977).

An example is as follows: a piece of iron can be considered as composed of a large number of elementary magnets. These elementary magnets tend to be in line with their neighbors (that is the elementary energetic contribution), but thermic agitation tends to break down this alignment. Below a given temperature, the elementary magnets are predominantly aligned and the piece of iron is magnetizable. Above this temperature, the thermic agitation is large enough to prevent the elementary magnets to be collectively aligned. The transition between these two behaviors (order and disorder) does not occur progressively but at a precise temperature, which corresponds to the so-called critical point. When approaching this point, the correlation lengths tend to infinity, which means that the elementary magnets fluctuate in an increasingly ordered manner. At this point, there are fluctuations at every scale, which means that there are magnetic alignments of every size. Moreover, some physical quantities (susceptibility to an external field) which become infinite at the critical point.

But ...can a system with fluctuation of any sizes be effectively described by averages?

⁵Because of the novelty of concepts involved in the reductive process, it is tempting to view this process as a unification rather than a reduction. Another physical example highlights this view: the theoretical methodology to understand quantum phenomena and the general relativity account of gravity is to provide a radically new account of *both* phenomena, for example through a change of object, in string theories. See Cat (2007) for a review of the philosophical positions on unification.

The strategy of Landau theory is the following (see section 5.4.1): let us assume that we can obtain such an account and derive the consequences of this assumption. This leads to a first determination of the mean of considered variables. Then, one can consider the local structure of the fluctuations as a first perturbation of this mean approach⁶, when tending towards the critical point. If the mean dominates, then the approach based on them is valid. However, when these fluctuations dominate the local behaviour, it implies that ...they dominate “local” behaviour of arbitrary sizes, since we are tending toward the critical point, where the length of correlation diverge.

The distinction between these two situations is given by the Ginzburg criterion (a mathematical criterion which depends in particular on the dimension of space), see section 5.4.1.5 or Als-Nielsen & Birgeneau (1977).

A related approach to phase transition is the mean-field theory. The basic idea of this approach is to consider the microscopic interactions and to replace the non-linear (bilinear typically) interactions between particles by interactions with a global parameter representing their mean (e.g. $\sum S_i S_j = \sum S_i S$). This usually leads to consistency equation (given by $S = \langle S_i \rangle$). This approach, initiated by Landau and Ginzburg is also clearly related to the validity of the macroscopic, mean parameter and can be technically related to Landau theory (which is in this sense a mean-field theory)⁷.

Thus for systems undergoing a second-order phase transition, we have a criterion to determine where reduction (here, by the uses of macroscopic means) succeeds. In the preceding section, however, we said that the description by statistical mechanics converges nicely, when the number of elementary objects increases. How comes then that this description is broken here so badly? The point is that the convergence towards the mean is based on a certain independence of the microscopic degrees of freedom, which basically leads to a statistical convergence (central limit). However, when the fluctuations dominates, we have a coherence of the microscopic structure (non-independence). When we approach the critical temperature and the thermodynamic limit simultaneously, we have a systems whose statistical properties are dominated by fluctuations. Mathematically, this correspond to singularities of the partition function at the critical point and thermodynamic limit, which, therefore, gives infinite quantities for certain statistical quantities (variance typically).

Such systems lead us to limit the scope of application of interscale reductionism, since the ability to approach the system when its elementary components are put together is undermined by divergences generated by their combination.

10.2.2.3 *Reductionism vs renormalization*

We now examine how systems at critical point may be studied, to determine in what respect their approach can be considered as reductionistic, holistic, or something quite different.

⁶This means that we are considering the fluctuations from this mean. The approximation signifies that we are not considering how fluctuations can interact with each other and build up even stronger fluctuations.

⁷Paradoxically, it is precisely in order to study criticality that mean field approaches were developed (for example in the Landau theory). They thus play a role in the understanding of phase transitions, as a first, technically simple approach, and are even more useful where they are justified — in our example, in dimensions four and above.

In order to study critical phase transitions, one uses renormalization methods⁸, that we describe as follows. One starts with a system described by a model at a given scale (which can be chosen arbitrarily. For instance, one can choose the scale of the measurement error). This model is composed of a set of parameters and of a function that determines the behaviour of the system (e.g. the Hamiltonian). Instead of solving the model at this scale, as one usually does, one looks at the way the parameters and functions change when the system is described at an upper scale. The way models change with respect to scales is formalized by a mathematical object, the so-called renormalization operator.

In usual cases (like para-ferromagnetic transitions), the renormalization of the model is asymptotically invariant. This means that, when the scales tend to infinity, the models tend to a fixed point through rescaling. Such asymptotic invariance corresponds to scale-invariance properties. In this case the physical properties of the system are determined by the behavior of the operator in the neighbourhood of the fixed point.

The conceptual meaning of renormalization is the following. We cannot mathematically obtain what the combination of elementary constituents leads to because it generates singularities (at the thermodynamic limit), or in other words, because this combination does not converge nicely. In terms of fluctuations, the situation is not tractable because the local behaviour is dominated by fluctuations that occurs also at upper scales. We can nevertheless consider a limited part of the system's interactions, bounded by arbitrary cutoffs. This limited part of interactions is integrated and constitutes the new elementary components of a new model. We cannot know what this new elementary components exactly do, but we can relate them to the rest of the determination of the system. In short, since we cannot consider the whole interactions of the elements of the system, we consider a limited part of these interactions and we mathematically simplify it, in order to produce a new equational determination. This renormalized determination is, however, as complicated as the original one since we have an infinite number of degrees of freedom. In general, the operation is performed in order to *conserve the equational form of the determination*, but with renormalized parameters and variables.

If some of these parameters vanish when we iterate the procedure, then the fixed point is simplified. This procedure can also be applied in the case where the situation is not critical. The result is a simplified determination which justifies the smooth behaviour obtained by Landau theory, for example. On the contrary, in the case of critical phenomena which are of interest to us here, the resulting determination (the fixed point) remains essentially as difficult as the initial one: we do not lose the fluctuations in the process because they dominate the behaviour of the system at all scales, as we said. How come, then, that we have made a huge progress towards the determination of the global behaviour of the system under study? When we are at the fixed point, by definition, the iteration of renormalization does not change the equational determination. This iteration is the taking more interactions into account, as we said earlier. Therefore, when we consider the fixed point, we are considering a stabilized situation with respect to the contribution of supplementary interactions. When

⁸These methods were first used in quantum physics and were successfully transposed in the field of criticality by Wilson, who was awarded the 1982 Nobel Prize in Physics for this feat. This subject is presented, for example, in Toulouse, Pfeuty & Barton (1977), see also chapter 5.

we add interactions to the fixed point (in its renormalization), the corresponding change of parameters and variables cancels this supplementary account of the system's interactions (because we have a fixed point) and are therefore a description of them. In this sense, *all* the large interactions are images (copies) of the interactions that are taken into account in the renormalization of the fixed point. Therefore, we have an *explicit* account of *all the relevant* (large scale) interactions⁹ of the system, even though this account is not given by a description at a single scale.

Finally, it is worth emphasizing that one can consider different models as starting points (possibly at different scales), for if they have the same asymptotic behavior through renormalization, then they lead to the same physical properties and are grouped into a unique class of universality (there is an infinity of models in a class of universality since, among a plethora of other, the renormalized model at any scale can be considered as a starting point).

One can consider renormalization methods as a case of reductionism, given that the study of the system only depends on the starting point, which is the lower-scale model. However, the starting point is also largely contingent, both because one can start from any scale as a minimal scale, and because one can change the starting model as long as it remains in the same class of universality.

On the opposite, a holistic aspect of this approach is that the local situation at the critical point depends upon the global situation, which come from the fact that correlation lengths are infinite. More precisely the system is "so global" that we cannot combine its interactions completely, we can only, but explicitly, find the form of all (large) interactions contributions.

The radically new aspect of renormalization methods is that one does not try to solve a model anymore, but rather to know the behavior of the transition from one model to an upper-scale model when we move through scales. In this respect, the system is studied at the level of a meta-model: what matters is not the inter-model relationship, but the behavior through scales of this inter-model relationship. This metamodel allows to start from a subjective model (shaped by approximations and pragmatic constraints) and to reach, through asymptotic properties, objective knowledge about classes of universality and physical properties of systems.

An interesting situation is also the case of quantum field theories, which also use renormalization methods. The nature of divergences in this domain can be diverse, but we are interested in the going from small scales to large scale here. The point is that, when we are considering more and more microscopic¹⁰ interaction we are faced with divergences (comparable to the one of critical phenomena). This means that the behaviour at a scale cannot be given, in this theory, by the contribution of objects of arbitrarily small space scale (this would blow up the equational structure, by the appearance of infinities). However, we can handle a part of the interactions, and consider the stability and the transformations of the equational forms and "constants" when we are looking at more and more interactions. The possibility

⁹Of course in practice, approximations are usually performed.

¹⁰Notice that small scale, here, is equivalent to large energy. The reason for that is simple: the quantum momentum is the spatial derivation operator (associated with the constant \hbar). A small scale behaviour means a behaviour with a high derivative (e.g. $\frac{d \sin(x/\lambda)}{dx} = \cos(x/\lambda)/\lambda$) so that the energy is high. From the field point of view, the classical potential diverge when we are going towards the punctual source of the field.

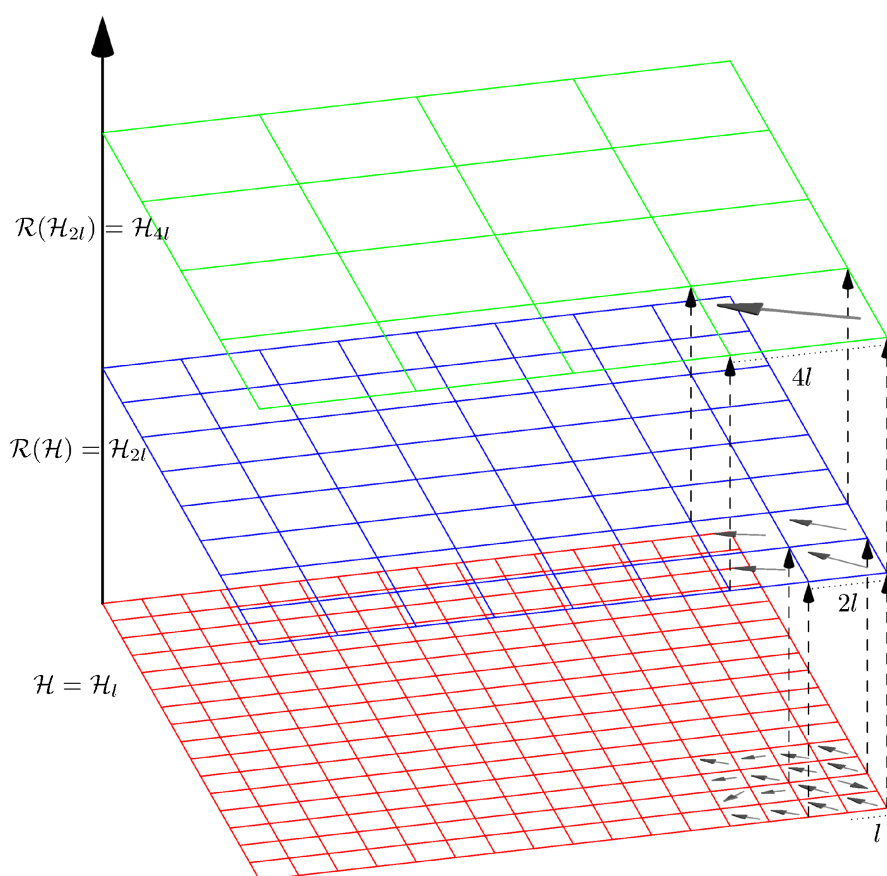


Figure 10.1: *Principle of renormalization.* We start from a model at a given scale. The determination of the system is represented by a Hamiltonian. The latter can be transformed into a Hamiltonian at another by taking into account the small scale interactions. Then, the operation can be iterated and describe a flow of model. When the equational form is stable, this corresponds to a flow of “constants” of the models.

for theories to be renormalized is a condition of their theoretical validity, here. The point we want to emphasize is that the standard model handles three of the four fundamental physical forces in this manner, where there is no objective, predominant small scale. On the contrary, the introduction of a peculiar small scale behaviour is in contradiction with the manner of which this theory understand microscopic phenomena (Zinn-Justin 2007). Of course, this does preclude paradigmatic changes, especially because the introduction of gravity leads to non-renormalizability (more introductions leads to a complexification of the equational form, by the introduction of new variables). In this sense, the current understanding of microscopic phenomena is *bottomless* in terms of small scale.

In short, renormalization allows to provide an explicit (and measurable) account of *all* relevant interactions in a system when the *actual combination* of all relevant interactions is impossible. In other words, from the point of view of the theoretical determination, the whole is not the sum of the parts (the sum diverges) but it can be understood by successive

partial sums of its parts (which become symmetric to all partial sums of parts at large scales). *in fine*, the whole is therefore not understood by the *sum* of its parts but by *sums* of its parts. In the process, the modelization of the microscopic scale appears for a large part contingent and arbitrary (and renormalization allows to study this). For these reasons, we consider renormalization methods at the edge of reductionism and holism. These methods appear as a mean to go beyond reductionism while keeping a relatively reductionistic approach (integration of interactions), though a considerably weakened one¹¹. In particular, renormalization in quantum field theory is associated with a bottomless situation (the small scale behaviour cannot be integrated in the sense of an actual combination).

10.2.3 CONSEQUENCES FOR BIOLOGY

Now, what holds for physics does not necessarily hold for biology. However, physical criticality, by its form of weakened reductionism, implies that a successful physicalism would not even necessarily lead to the understanding of the organism as an *actual* combination of the interactions between its parts (strong reductionism).

10.2.3.1 *Criticality and living matter*

Among common features with physical critical systems, biological systems present a complex structure of interactions involving different scales, both in space and time, see for example the case of the heart (Noble 2002). Moreover, simple collective biological phenomena have experimentally been described as critical in —almost— the physical sense, see section 2.5.2 or Mora & Bialek (2011). If one considers the question of susceptibilities (sensibility to perturbation), biological transcriptome networks (see section 2.6.2 or Shmulevich, Kauffman & Aldana (2005); Nykter, Price, Aldana, et al. (2008)), or hair cells (Camalet et al. 1999) seem to provide such examples. Such a structure of interscale correlations could explain why critical phenomena seem (more and more) pervasive in biology (see for example Bailly & Longo 2006, 2008, 2011; Werner 2010).

A paradoxical example can be provided by molecular biology. Indeed, when we abandon the notion of program (and we have good reason for that Noble (2008); Longo & Tendero (2007)), and when we look naively at the manipulation performed, we observe that highly microscopic manipulations (mutations by substitution for example concern structure measuring 3.3 Å) can lead to dramatic consequences concerning the whole organism (inasmuch it manages to develop). This implies a considerable amplification over space scale of this perturbation.

Thus, the mathematical difficulty found in critical physical states may well be encountered also in an organism, except that the structure of determination in this field is both more heterogeneous and not generally scale-invariant (even though some of its aspects have approximate scale symmetry, see chapter 2). Here by heterogeneity, we mean that different

¹¹Batterman (2007) has expressed a different (but compatible) point of view. To him: "It is fair to say ... that being able to understand such intertheoretic relations via renormalization techniques does not entail the existence of reductive relations between the theories either in the philosophers' or the physicists' sense of the term."

parts of a system might be described by different theoretical objects (e.g., the dynamics of a neural network is different from carcinogenesis).

Another point is that the accounts of biological objects can be different at different scales. This seems to be a crucial difficulty in comparison with the theoretical leverage of scale invariance used for physical critical systems. A pragmatic way to get round this scale dependence is to consider biological systems simultaneously at different scales. This seems indeed to be, de facto, the current approach: biology is a growing field of flourishing subdisciplines Brigandt & Love (2008).

One difficulty if we are to link phenomena occurring at different scales, is their non-homogeneity. This corresponds to the use of different mathematical techniques, see Saetzler, Sonnenschein & Soto (2011). If we could study scale-transitions, it would then appear that the models encountered at different scales would in fact use different kinds of parameters and maybe even different mathematical concepts (e.g. numerical parameters versus functions or geometrical shapes).

10.2.3.2 *Circular couplings*

Another theoretical difficulty with living systems is that they seem to be shaped by circular interdependencies in both space and time. Circular interdependencies occur when not only the upper-level system depends on the lower-level system, but also the reverse.

Darwinian evolution provides such examples of circular coupling between populations of variants at different scales. For instance, selection occurring at the scale of a subgroup of variants can influence the selective fate of a group, while the subgroup can undergo, as a consequence, a selective feedback (see for instance the intra-genomic conflicts, carcinogenesis, the evolution of social insects, and more generally the problem of major transitions in evolution (Maynard-Smith & Szathmary 1997)). A similar example is found in ecology, where a population can modify a whole ecosystem on the long term through the activities of organisms (a process called ecosystem engineering Jones, Lawton & Shachak (1994) or niche construction Odling-Smee, Laland & Feldman (2003)), and undergoes at the same time a selective feedback due to the modified ecosystem (despite similarities with the previous example, it is not clear that the dynamical process at the scale of the ecosystem is a selective process).

Another example is provided in cognitive sciences by the concept of global workspace (Baars 1988; Dehaene & Naccache 2001; Dehaene & Changeux 2005), which is based on this kind of relationships.

For some authors (Rosen 2005), the circular coupling of lower and upper-scales is an essential feature of biological phenomena, and particularly in relation with time (Soto, Sonnenschein & Miquel 2008). See also chapter 9 for an account of such a closure, between time scales.

10.2.3.3 *Conclusion on the consequences for biology*

Because of these very aspects of biological systems, the renormalization method cannot be used directly and requires to be at least adapted to this class of systems. We will further investigate the application of renormalization ideas to biology in chapter 11. Nevertheless,

we can already notice that at least in some cases the biological systems behave like physical critical situations. Thus, it is fair to assume that biological systems cannot be understood through strong reductive relationships between determinations at different scales.

10.2.4 CONCLUSION

In physics, we have shown that interscale reductionism can lead to at least two different situations. The first corresponds to a validity of the approach of the macroscopic system by statistical quantities. The second, however, corresponds to genuinely critical situations, where a system builds up a global structure of coherence. In this case, the direct composition of the interactions occurring in the system leads to divergences (when going to the thermodynamic limit). Therefore, the situation cannot be studied by the composition of the interaction, in a model at a given scale. However, the renormalization method nevertheless allows to understand the *global* structure of the interactions because it handles a partial composition of interactions which are symmetric to other composition of interactions, at larger scale (the sum of all this interactions remains intrinsically divergent). This is also combined with a certain contingency and arbitrariness of the initial model of the interactions (classes of universality).

Interscale reductionism, for these reasons, has a highly counter-intuitive nature in this physical situation. The determination of the system is not given by the *sum* of (the determination of) its parts but by *sums* of its parts (in an iterative way). Because certain biological situations have clear empirical critical signatures, biological interscale reductionism cannot be claimed, in full generality, to be stronger than this weak version.

This, however, does not mean that biology can be understood by this form of reductionism, and an even weaker form, if any, may be required. Indeed, biology seems to imply a finite class of circularly linked scales, which means, under the hypothesis of criticality, that several scales may be fundamentally relevant and that their codetermination may be a fundamental and necessary aspect of biology. We will develop this hypothesis in chapter 11.

10.3 LEVELS OF ORGANIZATIONS

For the moment, we remained neutral as to whether there are levels of organization in biology, and if there are, what the nature of these levels could be. However, the question of reductionism in biology is typically framed in terms of *levels* of organization Brigandt & Love (2008), not only scales. The question of the nature of the levels is of prime importance to the development of a science of systems, as seems to be the aim of the growing field of systems biology.

But, if at first sight the notion of level of organization seems intuitive, it appears that we still lack objective criteria allowing us to determine what should count as a level or not Bailly (1991b); Brigandt & Love (2008). In particular, we would like to be able to distinguish between the complexification within a given level, and the transition between two levels. Indeed, at a given level, we can observe various degrees of complexity, corresponding to an accumulation of objects (see below), or, mathematically, to an accumulation of degree of freedoms or of iterations of a recursive function. This question is crucial theoretically, since,

for example, there is no obvious reason why certain system, argued to have fundamental biological relevance, should have a peculiar structure of determination. For example, Piedrafita et al. (2010) argue that a peculiar chemical system, corresponding to specific circularity criteria, should be a (minimal) model of a fundamental aspect of biological organization. However, since the system is written and theoretically handled by usual reaction kinetic theory, it is not obvious that the system should be theoretically fundamental, and associated to a change of level of organization.

Here, we first aim at objectivizing the notion of level of organization, following mainly the work of Francis Bailly (Bailly, Gaill & Mosseri 1988; Bailly 1991b, 1991a), adapted to our own understanding.

Let us first emphasize that, here, we understand a theoretical level of organization in a very strong sense. A level of organization will be, in the following, a fundamental level of theoretical determination of objects. Typically, in physics, this corresponds to a mathematical frame allowing to provide the specific, theoretical trajectories of given generic objects.

10.3.1 COMPLEXIFICATION WITHIN A LEVEL

Complexification within a level of organization involves the combinatory accumulation of objects defined and determined in this level. Accumulation of objects is made possible by the generativity of the determination at the given level. Indeed, most, if not all, theoretical structures of determination allow to accommodate combinations of arbitrarily large (finite) number of objects.

A fundamental example of such accumulation within a level is the increase in number of degrees of freedom of a system, which leads to an accumulation of terms in a Hamiltonian, both independent or corresponding to interactions¹².

Theoretical frames provide the relationships between finite quantities (number of objects, extensive or intensive values, time, etc). This corresponds to the fundamental commensurability of the quantities which are involved, and which precisely corresponds to the ability of a frame to handle the determination of these quantities. It is crucial here to keep in mind that the frame itself articulates these quantities, so that finite should be understood with respect to it. For example the integration of a function which is singular (infinite) at a given point can be finite.

When some *relevant* quantities become infinite, some fundamental operations can become degenerate (e.g. $\infty + \infty = \infty$) or undefined (e.g. $\infty - \infty = ?$). For example, one usually does not know, by the determination of the system we already have, what a physical system will do after a finite time blow up (a situation where the solution becomes infinite in finite time, and is therefore interpreted as a break down of the determination if there are physical reasons to consider that the considered quantity must remain finite). The crucial point is that, when no relevant infinite quantities are involved, the accumulation of terms does not change the algebraic structure of the theoretical frame. In physical terms, when no infinite

¹²It is noteworthy that such combinations are usually associated to a linear aspect (the addition of terms in the Hamiltonian, the superposition of states in quantum mechanics and the corresponding unitarity of the Hamiltonian operator, ...) and of non-linearity, corresponding to interactions in the Hamiltonian or measurement in quantum mechanics.

quantity is involved, causes and effects remain commensurable (incommensurability would occur typically if the ratio between a cause and an effect got infinite).

10.3.2 TWO TYPES OF INFINITY

It is worth emphasizing that at least two types of infinity are at stake here. The first deals with the extensive observables (sizes or numbers of objects) and occurs through the accumulation of objects within a level. The second deals with the intensive (so to speak “qualitative”) properties of objects and will appear to relate to moving from one level to another. “Intensive” means that the given quantity, in an homogeneous system, is independent from the size of the system, and can therefore be considered to be a local property (we will come back to this point later). In particular, the ratio between two extensive properties is an intensive property. Typical extensive quantities are, in thermodynamics, the volume, the mass, the number of particles, On the contrary, intensive quantities are the temperature, concentrations, volumic masses, volumic thermic capacity,

The extensive and the intensive infinities have very different theoretical meanings. With extensive infinity, the theoretical structure of the components is left unchanged, so the whole remains described by the same interactions between its parts. However, it is worth noticing that extensive infinity can make a probabilistic determination become a deterministic determination, and thus can change the causal regime. In parallel, extensive infinity can lead to the loss of time reversibility. These two modifications of the causal regime (determinism and time irreversibility) are exemplified in physics by the thermodynamical limit.

By contrast, intensive infinity can disrupt relationships between parts and thus changes the structure of the determination (such a disruption typically occurs, in thermodynamics of phase transitions, when the Ginzburg criterion is met). In statistical physics, it is necessary to have extensive infinity for intensive infinity to be obtained (because of the analyticity of the finite size partition function, see chapter 5).

It is also interesting to relate these two types of infinities to the question of the theoretical symmetries of a system. One should first consider that symmetries have, in general, a “conservative” nature: these transformations can be inverted. However, we are not really interested by exact solutions, which preserve all the symmetries of our first hypotheses. We can take first an elementary example to illustrate this point. The classical relaxation equation $\frac{df}{dt} = -\frac{1}{\tau}f$ corresponds to a situation where the function and its derivative are proportional, which is a symmetry. Physically, this corresponds to a decay that is proportional to the magnitude of the quantity, so that all “small pieces” of the corresponding quantity decay independently (think of radioactive disintegration). This symmetry is preserved during the trajectory and never allows the corresponding quantity to disappear completely since the function which verifies this symmetry is the exponential ($f(t) = f(0) \exp\left(-\frac{t}{\tau}\right)$). However, after a time $t \gg \tau$, the corresponding quantity is very small and for most practical purposes it is negligible. By the use of infinite time limit, we can break the symmetry of this decreasing exponential and replace the value of f by its equilibrium value. This allows to take into account the physically relevant behaviour of the system for $t \gg \tau$ since the classical measure has a finite precision (see chapter 7). This kind of reasoning have almost unlimited applications in physics. For example renormalization is based on such considerations (it consists in

separating relevant and irrelevant components, and the latter vanish at large scales, and *in fine*, their objectivity is not guaranteed). A more sophisticated situation is the notion of symmetry breaking *sensu* Strocchi (2005) (named strong symmetry breaking in section 5.3), where infinity is required in order to decidedly, physically separate objects corresponding to the symmetry breaking. Another conceptually interesting example is the breaking of time reversibility of the Newtonian frame at the thermodynamic limit.

Last but not least, infinities should be handled carefully. In particular, when we consider two quantities that goes to infinity, the way we approach this combination of infinities matters in general, and one cannot recklessly take one limit after the other (the limits do not commute with specific hypothesis). In this case, we have usually a discontinuity of the second limit: the behaviour at the limit is not the same and not even close to the behaviours near it. For example, in the case of criticality the number of objects $n \rightarrow \infty$ (thermodynamic limit) and the singularity associated to criticality, for $T \rightarrow T_c$ need to be taken jointly, in a sense, via renormalization methods (Lesne 2003). Qualitatively this is natural: the thermodynamic limit allows to define thermodynamic relationships, between macroscopic observables, but at the critical point fluctuations at all scale dominate the behaviour of the system.

One should notice that infinite time, at least in a number of situations, corresponds to an extensive infinity, see for example Lesne (2003). Qualitatively, we have the same epistemic role of these two limits (they make negligible variations disappear). Statistically, making 1 random experiment on n independent objects, or making n successive experiments on a memoryless objects are equivalent (this is an highly rudimentary version of the ergodic hypothesis). Physically, this can also be understood via the conjugation of energy and time.

10.3.3 TRANSITION BETWEEN TWO LEVELS

For a transition between two levels to occur (and not just a complexification within a level), it is necessary to have a change in the objects (or in their relationships). As we already mentioned, such a change seems to only occur through the apparition of intensive infinity; however, intensive infinity alone is not sufficient to break the determination of a given level.

Thermodynamics of second order phase transition provides a good illustration of when intensive infinity can or cannot lead to a change of level. Landau theory handles critical systems with macroscopic (uniform) variables. This account constitutes a first level of determination, but it necessarily produces a singularity at the critical point. In particular the fluctuations and correlation lengths will diverge. As a result, a first perturbative approach¹³ will discriminate situations where the mean dominates over the divergent fluctuations (in which case there is no change of level), and situations where it is the converse. When divergent fluctuations dominate, the macroscopic relationships blow up, and the theoretician must consider new relevant objects (via the (semi-)group of renormalization). These objects allow to take into account the global structure of coherence associated to the domination of scale-free correlations. The theoretical determination therefore operates at a new level.

¹³That is to say, an approach where we start from the Landau theory but try to precise it by considering fluctuations which do not change the mean behaviour of the system, obtained in Landau theory. See section 5.4.1.

10.3.4 CRITERIA OF TRANSITION

As a conclusion, we will consider that a transition from a level to another occurs when the two following conditions are met (Bailly 1991b):

1. *Transition to infinity*: at least one intensive property that is relevant to the first level should be considered as tending to infinity (relevance here means that the given magnitude contributes to the determination of the objects and of their relationships).
2. *Change in relevant objects*: the fact that the magnitude tends to infinity should make obsolete the empirical and theoretical determinations of the objects, and should introduce new relevant objects in the system's determination, that will be associated to the new level.

We want to emphasize that this criterion has two fundamental strengths. First, it is associated to observable consequences: the divergence of intensive properties. Second, it is based on break down of the theoretical determination of the first level and not on its invalidity for external reasons. Both of this aspects open perspectives to objectivize the notion of level of organization.

10.4 APPLICATION TO BIOLOGY

10.4.1 BIOLOGICAL LEVELS OF ORGANIZATION AS AN HYPOTHESIS

Let's first start with the intuition that there are several levels of organization within an organism (we will discuss this intuition below). Because an organism, in general, experiences rather a range of internal and external conditions than a single point value, the multiplicity of levels associated to the considered organism should obtain within a (supposedly dense) range of viability parameters. In other terms, criticality (understood here as singularities in the determination) should obtain within a dense range of parameters, rather than at a single critical point as in usual physical situations. The intuition of multiple levels thus drives us to the hypothesis of an extended criticality of organisms. In particular, a small effect at a given level can have incommensurable consequences on a upper level (criterion of intensive infinity) within a dense range of a given parameter.

Reciprocally, it is clear that if organisms show *extended* criticality (that is, in the sense of chapter 6, symmetry changes within a dense range of parameters *and* a condition on the strength of the associated fluctuations), the multiplicity of levels of organization obtained in the extended critical transition is robust.

Biological function typically tie the parts together in an integrated whole. This justifies that they can be associated with biological change of levels of organization.

10.4.2 FRACTALS AND FUNCTIONS

Let's consider the hypothesis that levels of organization are associated to biological functions. Bailly, Gaill & Mosseri (1988) defended the thesis that the integration of parts within a

whole is achieved through fractal structures, as fractal structures play a fundamental role in exchanges between different media.

Reviewing several biological cases, they made the following hypothesis:

1. to any vital function defined at a given level within an organism (macromolecule, cell, organism), corresponds one structure (active sites, organites, organs) exhibiting at least one fractal dimension associated to this function
2. reciprocally, to any fractal dimension of a structure, corresponds a vital function, which integrates this structure in a whole
3. moreover, the correspondence between the fractal dimension and the functionality is to be linked with the transition between levels of organization, as fractality enables to make compatible properties that have to be both singular and homogeneous (see below).

Bailly, Gaill & Mosseri (1988) then proposed to explain the occurrence of fractal structures in organisms by the satisfying of three constraints:

TENDENCY TO MAXIMAL PROLIFERATION: for instance, the maximisation of an exchange surface (to enhance efficiency and precision of exchanges). This tendency of unbounded growth can lead to a transition to infinite limit

STERIC CONSTRAINT: the living system is bounded (because of other developmental or evolutionary constraints)

HOMOGENEITY: solution structure should be homogeneous, that is to say that the singularities should not be limited to a point. This constraint excludes theoretical solutions to the two preceding criteria, such as limit point or surface point, where the asymptotic limits would play a particular role. By contrast, fractal solutions are homogeneous (in their singular behaviour).

We provide some examples in chapter 2. Typically surfaces of organs or organelles tend to have fractal shape, with infinite surfaces at the limit. In the context of an organism these shapes are associated to the functionality of the organs, with respect to the organism. In such a situation, we have therefore a change of the relevant object.

10.4.3 NON GENERICITY OF PARTS

It is worth investigating here a fundamental problem of biological theorization. If living systems are organized in levels, then perturbations can propagate through levels in some cases. That is to say, a symmetry breaking occurring at one level can break other symmetries at other levels. Thus, if living systems are in extended critical transitions, it is expected that every levels are impacted by this situation. Therefore, even the lowest levels (say, macromolecules) have not necessarily actual specific trajectories in the system (“effective” trajectories, *in vivo*). As a consequence, parts would possibly not exhibit stable enough effective (i.e. in the system)

symmetries for us to observe these symmetries being broken at the moment of level transition. Moreover, certain parts are themselves in extended critical transitions (cells, typically).

A simple example of this feedback of extended criticality on the effective trajectories of parts (which are stable *in vitro*) is the trajectory of the structure of *dna* of living organisms in evolution.

However, if one first considers a contingent determination at a level to obtain generic parts (the determination would be contingent in that it would be local in time and could be limited to some cellular types for example), for instance if we suppose that the rhythm of symmetry breaking is slow enough, then we would obtain a situation close to criticality with level transitions.

Now, with non-generic parts, it is through the stabilization associated to the organism structure that a relative stability of the structure of determination (that is to say, a relative genericity) of parts can be obtained. For instance, parts are maintained in their viability zones (by preventing ischemia, providing nutrients, etc), their proliferation is tempered (Sonnenschein & Soto (1999)), etc. Of course more complex regulations are also involved, such as the fine tuned ionic concentrations in the brain.

These questions will be further deepened in chapter 11.

10.5 CONCLUSION

We have seen that interscale reductionism, understood as the way the parts combine to form the structure of determination of the whole can have at least two very different forms in physics. The first, which we called strong reductionism, corresponds to the situation where the determination of the whole can be obtained directly by the combination of the contributions of the parts to it. The second, which is a weakened reductionism, corresponds to a situation where the determination of the whole diverges and because of the formation of global coherent structures. In this case the theoretical and mathematical way to understand the situation consists in considering partial combinations of contributions of parts to the change of the equational determination. The global structure is thus found because all the large scale contributions are symmetrical in physical critical phenomena.

As for biology, it seems to us that the notion of level of organization is well grounded only if a transition between levels corresponds to, at best, a weak reductionism between levels. Following Bailly (1991b), we gave a criterion allowing to determine when one can consider that there is a breaking of the determination at one level, which therefore corresponds to a transition between two levels. This criterion is inspired by the theory of critical phenomena, where an intensive value tending towards infinity breaks the structure of the determination. In biology, such singularities are achieved in particular by fractal structures (for instance, the liver has an infinite volumic surface of endoplasmic reticulum). Fractal structures appear to be connective devices (for instance membranes) that link parts together in an integrated whole. Following Bailly (1991b), we can make the hypothesis that such singular structures are the sufficient and necessary signature of vital functions.

We have seen that assuming living systems are organized in levels as understood by Bailly (1991b) naturally leads to consider that living systems are in extended critical situation.

Criticality here means that several levels can coexist so that we have strong singularities (for example, when the Ginzburg criterion tells that the mean field approach fails). This notion of criticality differs from the notion found in chapter 6, where extended criticality is understood as ubiquitous symmetry changes. For instance, in the case where Ginzburg criterion legitimates mean field approaches ($d > 4$), we have a symmetry change without a strong breaking of the structure of the determination. In our view, the two approaches of extended criticality are complementary.

In the chapter 11, we are going to propose a scheme for the understanding of the coherence structure of an organism. This approach will show to be deeply rooted in the notion of level transition that we have described here, and will in particular discuss more precisely how fractal structure are related to biological functions.

Towards a biological renormalization 11

This chapter is a conceptual approach of a work initiated with F. Bailly.

CONTENTS

| | | |
|--------|---|-----|
| II.1 | Introduction | 248 |
| II.2 | Orgons and biolons | 249 |
| II.2.1 | Intermezzo: theoretical <i>tuteurs</i> | 250 |
| II.3 | Where are up and down? | 252 |
| II.3.1 | Intuitive approach of the singular directions | 252 |
| II.3.2 | Singular directions and their interactions | 253 |
| II.3.3 | Where are up and down? | 256 |
| II.3.4 | Recapitulation and precision | 258 |
| II.4 | A scheme of the organization of a metazoan | 260 |
| II.4.1 | Reintroduction of the compacified time | 260 |
| II.4.2 | Orgonic operators | 261 |
| II.4.3 | Cellular level | 263 |
| II.4.4 | Symmetries and singularities | 264 |
| II.4.5 | Some further remarks | 265 |
| II.5 | Conclusion | 270 |

ABSTRACT:

In this chapter, we will provide a tentative scheme of the structure of coherence of the organism. This scheme will use an important part of notions and conceptual approaches discussed in the former chapters. In this conceptual frame, we will propose to understand biological organization via a method inspired by the renormalization used in physics. In our approach, however, the strategy we are sketching involves a renormalization where (compacified) time plays a crucial role, as the scaling parameter, with two anomalies, for 0 (small scale) and $1/2$ (large scale).

The crucial point of our scheme is to try to have a global approach of biological interactions in the organism without the assumption of a perfect knowledge of them, but by focusing on the structure of their relations and transformations. This structure itself is also associated to a proper variability. We finally illustrate this scheme with the entropy of the vascular system, which leads to a further justification for our introduction of anti-entropy.

Keywords: Extended critical transitions, fractals, organism, anti-entropy, biological time.

11.1 INTRODUCTION

THE problem we will undertake in this chapter is that of the *global* structure of coherence of an organism; here, we will consider mammals as a running example.

The structure of determination described theoretically concerns usually, in other approaches, a single organ, a single scale symmetry, or a single observable. It is, for example, the case in the model of metabolism in West, Brown & Enquist (1997, 1999), which is based on the transport system of oxygen and aims to understand metabolic allometric relationships. On the opposite, other approaches, such as the proposals in Rosen (2005), focus on the idea of the organism. However, they are undermined by their lack of association with experiments. They thus lead to studies of minimal models which can be appealing in their own right; but are extremely far from observable biological phenomena. They are also usually either disconnected from natural phenomena or reducible to physicochemical theories. Here, however, we will develop an approach which is focused on “current” organisms (with a bias for mammals, but we will nevertheless keep in mind the physiologic diversity among organisms).

Following the ideas in chapter 10, see also Bailly (1991a); Bailly & Longo (2008), we will focus on singularities, which will be understood as changes of level of organization and will reciprocally allow us to understand them. In order to theoretically build on them, the closest physical theoretical framework is thus renormalization methods (Binney et al. 1992; Fisher 1998; Zinn-Justin 2007), see also chapter 5 and 10. However, this method is only conceived in order to deal with a critical point, whilst we want to study an extended critical situation. From another point of view, the problem that standard renormalization does not allow to understand is the interaction of different heterogeneous fractal-like structures. Renormalization would be immediately useful if we expected an organism to have a monofractal structure; however, and on the contrary, an organism has a variety of approximately scale-free structures, with distinct exponent and spatial repartition.

In order to consider a situation closer to this physical method, and in order also to have a controlled relationship with empirical measurements, we propose to approach the situation by a finite number of singularities. These singularities will nevertheless be understood as able to generate an indefinite number of symmetry changes, from the point of view of the organism’s structure of determination. In more usual biological terms, this finite number of singularities roughly (see below) corresponds to the organs with a more or less unfolded fractal structure. The theoretical problem is then to understand how a finite number of singularities, associated to organs, allows to establish the peculiar structure of determination of the organism, and how, in particular, it can generate the dense structure of symmetry

changes of extended critical transitions. We will however only provide a preliminary analysis with respect to this question.

The problem we want to approach can also be stated as follows. Considering a collection of cells, what is the theoretical structure needed for it to form an organism, in an extended critical transition? We will approach this question by a temporally local, physiologic, point of view, but this restriction is only meant as a temporary step. The question of the development is indeed crucial (Soto, Sonnenschein & Miquel 2008); our approach, as we will see, allows to raise it in an interesting way. The rationale for approaching the situation in this manner, is that it will allow us to approach how symmetry changes are generated. Now, returning to our collection of cells, the question we want to undertake is how these cells form an integrated whole, by the mean of singular structures. The crucial aspect of this integration is its space and time organization, which are the conditions of the possibility for the organism to form such an integrated whole.

Let us assume that there are sufficient symmetries, in an organism, for the following to have a meaning (in particular one would need some scale symmetries and cellular homogeneity). Let us start from cellular, local interactions (which we assume more or less locally defined¹) and progressively zoom out (“renormalize” the interactions). We obtain, in this manner, and by iterations of the procedure, the more and more global structure of coherence of the system. The latter could in particular be fully obtained by considering the changing of scale, if one succeed to obtain a scale symmetry. In this case, we would indeed have apprehended the globality of the interactions in the organism because the limited interactions we can handle simultaneously are symmetric to the other interactions in the systems (and this symmetry would typically be objective). However, we do not have the theoretical leverage to perform this operation! As a result, we shall propose other paths to approach the structure of coherence of the organism, but one should keep in mind that, we are *in fine* interested in the global structure of the interactions and in the way to objectivize it, in the context of extended criticality.

11.2 ORGONS AND BIOLONS

To proceed further, we first have to specify the nature of the theoretical objects we will work with. The terms of biolon and orgon have been coined in Bailly, Gaill & Mosseri (1993). We will here provide a brief discussion of the principles that are mobilized in this paper and that are at the root of the distinction of these theoretical objects, but we will also provide additional arguments to justify their theoretical role.

In Bailly, Gaill & Mosseri (1993), we have the following description of biolons and orgons.

BIOLONS. They correspond, from an intuitive point of view, to objects which have a high level of autonomy. In particular, they have an interior, an exterior and a frontier. They form a whole, which integrates its components; this aspect is precisely the point we shall

¹This typically can be interpreted in terms of our ability to define and measure them *in vitro*, not necessarily in their correct magnitudes, but at least in their correct form.

try to understand better in this chapter. They constitute a proper temporal structure, by (allometrically) synchronized clocks. Moreover, they have the ability to reproduce.

ORGONS. They only exist as a subordinate level of a biolon. In particular, they are not autonomous. In general, they are spatially specified and associated with fractal geometries. Notice that an organon also can, at least in some cases, be replaced by an artificial machinery, whilst preserving the biolonic structure of which it is a part. They are in particular associated with energy transport.

Further characterizations of biolons and orgons, in this paper, are based on quantum analogies. More precisely, biolons are understood as corresponding to bosons, and orgons correspond to fermions. This analogy is based firstly on the shape of their temporal distributions (for biolons and orgons) and the corresponding energy distributions (for bosons and fermions). Intuitively, this is associated to the proliferative nature of biolons, which corresponds to the possibility of superposing bosons. Reciprocally, orgons have a limited growth possibility, and do not proliferate, in a similar way that fermions obey exclusion principles.

Notice that the fractality associated to orgons is crucial, in particular with respect to the analysis in chapter 10. In this sense, then, orgons are associated to the singularities that determine/constitute the biolon as a level of organization.

Our analysis, in chapter 6 (Longo & Montévil 2011a) allows us to further characterize the theoretical distinction between orgons and biolons. Typically, as we said, an organism or a cell is in an extended critical transition; as a result, it is fundamentally a specific object, associated to and defined by a historical cascade of symmetry changes. This highly peculiar situation can then be assimilated to the theoretical object that is the biolon. On the contrary, we mentioned also in chapter 6 that regulation of cells, typically, can lead to a situation where the organ has a more or less generic status. This status is associated also to the conditions of viability of the organism. As a result, we propose to understand orgons as having generic behaviours, in a sense tangentially to the whole structure of determination of the organism. Notice also that symmetrizing measurements, as defined in chapter 7, usually are performed at or at least via the level of an organ, and need a symmetrization of the corresponding biolon, with respect to this organ, for example.

11.2.1 INTERMEZZO: THEORETICAL *TUTEURS*

There is another aspect of biological theoretical symmetries that is not grasped by the notion of organ alone, when we consider that the latter are specified in particular by their fractal-like properties.

Indeed, theoretical approximate symmetries can be used to locally determine biological organization. Let us describe the situation by an analogy. If one wants to grow a vine in such a way that it grows approximately vertically, then one usually use a vine pole. The vine will attach itself to the pole, wind itself around it, and *in fine* grows as intended. Other, examples are splints and pacemakers used in medicine. Some explanations are needed, as to why these examples are similar. Splints constraint the regeneration of bones in such a way that they take again a correct shape. Pacemakers are an interesting example since

the regularization is mostly temporal, in this case. However, it is also not associated to development or regeneration (it only preserve the function).



Figure 11.1: *A vine pole*. The vine winds itself around the pole, and grows following its curve (a straight line here). By analogy, we develop the theoretical notion of tuteur, which corresponds to the constitution of an approximate symmetry by an organism in order for it to develop its organization.

All these examples correspond either precisely or more or less loosely to the french term of *tuteur*. Now, we can analyze the situation more theoretically. What happens in cases where such tuteurs are used in relation with biological organization? In our theoretical framework, we have a (restricted) genericity of the object and a corresponding specificity of the trajectory. By introducing these external elements, such (sub-)trajectories are constrained, so that they stay near a geodetic trajectory: the trajectory that is associated to the constraint.

All the above cases are exogenous examples; however, the most compelling cases are encountered when one considers endogenous tuteurs. This expression of endogenous tuteur is, of course, an oxymoron *stricto sensu*, but we can nevertheless endow it of a theoretical meaning. This meaning is again that of a restricted genericity of the object (an aspect of the organism, usually) and a corresponding restricted specificity of the trajectory, but there is more to say about this situation.

It is interesting, here, to consider an analogy with renormalization in quantum field theory. Originally, the word renormalization has been used to describe the dynamic of objects in a liquid, where the interaction with the liquid can be approached by a renormalized mass of the considered object. The apparent or effective mass of the object is therefore altered by external conditions (which can be separated of the object). On the contrary, the situation in quantum field theory is that an object (say an electron) cannot be separated from the associated fields (as a matter of fact, even the vacuum is not independent of fields). In this case, renormalization is therefore intrinsic to the determination of objects, and the effective parameters are dependent on the level of energy considered.

Similarly, endogenous tuteurs are intrinsically constituted by the organism, both on ontogenetic and phylogenetic time scales. The specific trajectories that they allow is limited in time and have a contingent nature. When it is a process that occurs in the early development, it is often the case that the effectivity of a tuteur is a condition of possibility of the viability of the organism either on a short or on a longer time scale. In this case, the tuteur features a significant phylogenetic robustness, which precisely results from the instability of the

viability when this tuteur is not used (or is transformed). On the opposite, tuteurs can have a relatively superficial nature with respect to ontogenesis and phylogenesis, meaning that they are not necessary for the viability of the organism and that they can change rapidly in evolution. It is noteworthy that, as usual, time plays in biology a similar role than in physics.

11.3 WHERE ARE UP AND DOWN?

Renormalization usually follows and allows to exhibit a scale invariant structure in the determination of a system. The corresponding mathematical and theoretical leverage, which allows to understand the situation, is the corresponding scale (or conformal) symmetry. For statistical physics, this symmetry can be shown asymptotically, for large scales, as a fixed point by renormalization. However, in the case of an organism, we usually have a variety of such structures in an also more approximated sense than in physics. The question then arises, as to how we should proceed to approach them, and in particular how they can be articulated in order to provide an account of the structure of coherence of the organism.

11.3.1 INTUITIVE APPROACH OF THE SINGULAR DIRECTIONS

Let us consider a tissue in an organism and assume that, somewhat like in the physics of critical phenomena, we want to renormalize it. In order to do so, we have to define how we can look at it from an upper scale (and in a less refined way), in the context of an organism. The correct way to define such a renormalization is normally to follow the structure of interactions, which are, here, involved in the tissue. For physical critical phenomena, the structure of the interactions is given in particular by space. For example, in the Ising model, only spatial neighbours interact directly. Thus, the renormalization follows this structure by merging neighbours; and the final result (the classes of universality) depends crucially on the dimension of space. The properties of space, therefore, determines the way one should go from one scale to another². But in the biological situation, starting from cells, what is the “natural” structure we should follow? In other terms the question is: in what abstract “direction” is the upper scale, when we start from the level of the tissue?

For such a direction to be relevant (in the renormalization sense), this direction has to be anomalous, by which we mean that the structure of interactions should not trivially vanish by changing the scale. The simplest situation for this, is a scale symmetry and a fractal-like structure. Let us go back to the considered tissue and assume, for example, that it is a liver tissue. Then, we see that we have a choice among different fractal-like structures to follow:

- The vascular structure, coming from two sources (hepatic portal vein, from the main digestive organs and hepatic arteries, more directly from the heart). The vascular structure is of course also prolonged by exiting veins.
- The lymphatic system.
- Nervous structures.

²In momentum space, this remark is also equivalently valid, but the point of view is slightly different.

- Bile canaliculi and latter bile ducts.

See, for example, Mitra & Metcalf (2009) for more details on the anatomy of the liver. This enumeration is not particularly meant to be exhaustive; however, it clearly shows that there are different fractal structures which meet at the tissular level.

Now, somewhat reciprocally, let us look at one of these structures, for example the vascular system, and try to renormalize by starting from it. In this case, however, we are starting from a macroscopic³ branch. If we want to look at smaller scales, there are different directions in which we can go: either we follow the structure's topology or we follow the structure of the branch, aiming at the cells that compose it. From a physical perspective, usually, the second part is irrelevant or neglected, because the branches are understood as homogeneous⁴.

Now, it is not obvious whether the (down) direction corresponding to cells constituting arteries is relevant or not. In order for this direction to be relevant, it must be associated to some kind of anomalous behaviour. Starting again from the tissular level (the tissue constituting the arteries), we see that fractal structures are again encountered. For large blood vessels, they are mostly found in the tunica adventitia. Here, we will indicate the vasa vasorum (blood vessels of the blood vessels) and the nervi vascularis (nerves of the blood vessels). The latter are in particular related to the muscular contraction of the blood vessel, so that they are directly related to vasoconstriction. The vasa vasorum are also involved in vasodilation and vasoconstriction, by the transport of hormones (and other substances) directly at the tissular level of the blood vessels. We mention just a part of arteries (and veins) regulation, but the concept is crucial since it allows the vascular structure to have a dynamic nature, adapted to the organism's activity changes. We focused on arteries, but, of course, the underlying structure gets even more complex if we consider the largest and most active "blood vessel", which is the heart (Noble 2002) and which has a scale-free signature down to the level of mitochondria network, see chapter 2 or Aon, Cortassa & O'Rourke (2004).

11.3.2 SINGULAR DIRECTIONS AND THEIR INTERACTIONS

As we have seen above, even assuming that all fractal-like organs are genuinely prefractals (that is, theoretically justified fractal structures, which are limited in concrete realization by the available scaling range), the geometry of the organism is far from fractal. On the contrary, the geometry on which interactions occur is based on a variety of fractal structures, which are "mixed" at their small scale limit.

What is worse, the large components of these fractal-like structures are not themselves necessarily homogeneous to small parts, from a biological point of view. On the contrary, they are constituted by other structures, having decidedly different natures. It is, for example, the

³Here and in the following macroscopic will mean that we are far from the cellular level. When we consider the top or the tops of a structure, we will state it explicitly.

⁴This does not necessarily preclude a physical approach of the morphogenetic principles in action, such as using diffusion-limited aggregation Lorthois & Cassot (2010). However, such approaches will not provide an account of the relationships of the considered processes with the organism ... and will also be undermined by a level and a nature of randomness beyond the physical theoretical structure used.

case for the tree structures, when we consider their structural and, below, cellular constituents. Notice that in order to be described, or even just measured, fractal-like structure nevertheless need to be described in a homogeneous way, in particular with respect to the properties whose fractal-like features are exhibited. Typically, this can be obtained by considering purely spatial or temporal properties; but other quantities can also be used.

As a consequence of these considerations, we have two different situations which are associated to fractal-like structures when space is involved. On the one hand, they are indeed described as *vertical* structures, when the upper description corresponds to the same cells (or more generally constituents) than the lower description. This is typically the case for situations described by the physical notion of criticality, see, for example, sections 2.5.2 and 2.5.3, and Mora & Bialek (2011). On the other hand, they can be *diagonal* structures, where the constituents differ when we follow the structure's scaling behaviour. Typical structures having this feature are the tree shaped organs. In the latter case, an account of vertical scaling should usually complete the elementary description of this structure, in order to understand how it relates with its components.

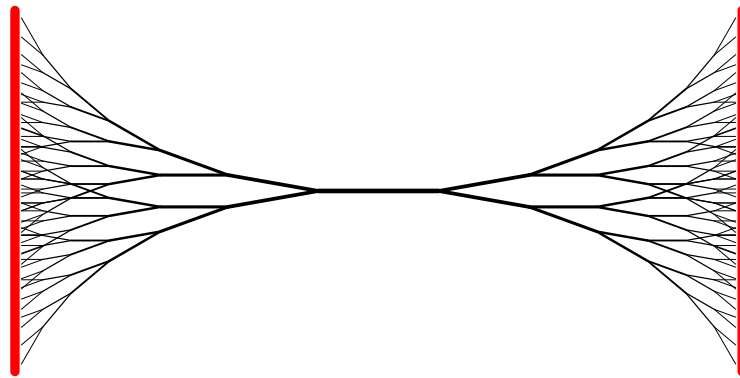
Now, and this is crucial, when we look at the tissular level, we observe different fractal-like structures. We can take two different points of view to describe the situation:

- From the point of view of the fractal-like structures, their possible interactions at the tissular level is mediated by the cells, and their structure of determination. For example, the interaction between what happens in lactiferous ducts and what happens in the vascular system is mediated by the cells, which, among other things, react to the prolactin (secreted in the pituitary gland) transported by the vascular system. The interactions between the two structures are of course not limited to this hormone; in particular, there are free energy transfers that occur and that are also mediated by the cells. Note also that we are, here, considering only examples of what happens at this level and between these two structures, we are not describing the complete structure of determination of lactation, which *in fine* involves the whole organism.
- If one consider two cells in distant parts of the body; then at least a significant part of their interactions is mediated by one or more fractal-like structures. Considering a cell, then, it has tight relationships with various part of the body, via the fractal-like structures that appear in the tissue where this cell is.

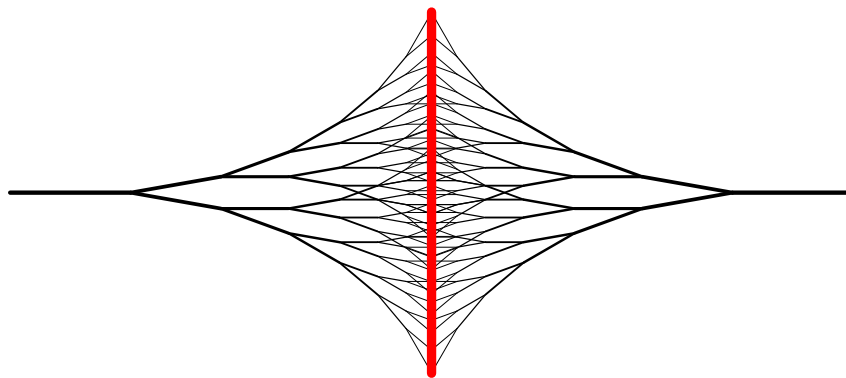
Notice that the first point of view is more consistent with the quantum analogies recalled earlier. Indeed, in quantum field theories bosons are the particles that mediate the interactions between particles representing “matter”, the fermions. Correspondingly, then, we have interactions between organs that are mediated by sub-biolons (cells). In this situation, we have interactions between two relatively regular (i.e. symmetric) singularities, which are mediated by the highly singular objects that are cells in an extended critical transitions.

11.3.3 WHERE ARE UP AND DOWN?

We have not yet answered the question of this section. To state it more accurately, this question is the following: considering the singular directions described above, how, *in fine*,



(a) Interaction of cells via an organon



(b) Interaction of organs via the cellular level

Figure 11.2: *Two objects interactions in our framework.* Here we have chosen to represent organs by trees for illustrative purposes; however one should keep in mind that different geometrical structures are possible as the basis of the organs. Moreover, it is crucial to keep in mind, that the relevant biological objects is not exactly the geometry of the structure but the interactions that it supports.

does a part of the organism relates to the whole that is the organism. In the usual terms of scale hierarchy, this question then reads: where, in the abstract sense, are up and down?

In physical renormalization (of phase transitions), the answer to this question is that, *in fine*, the whole and the parts are asymptotically symmetric, as the determination at a scale and at another larger scale appear as a fixed point by renormalization. In this sense, then, in comparison with our current analysis, the physical case can be seen as degenerate, so that our present question leads to a trivial answer.

However, in the case of the organism, the situation is not that simple. The approximate fixed points that we may find, in connection with fractal structures, have an entirely orgonic nature: they do not allow to approach the whole organism. They are also associated to heterogeneities, as we said.

Let us consider the vascular system⁵. This case is a diagonal organon in the above sense,

⁵Notice that we will not take the cells of the vascular system into account in order to simplify the discussion.

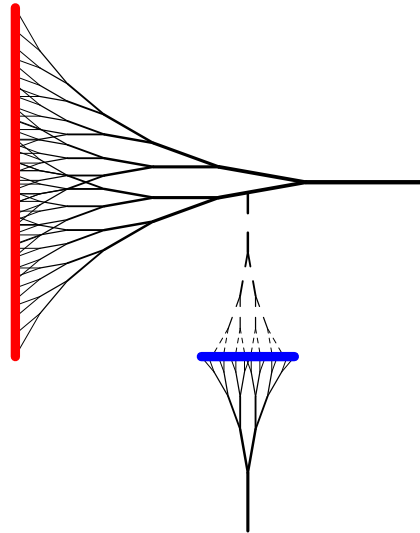


Figure 11.3: *A diagonal organ and the supplementary direction corresponding to the composition/behaviour of one of its macroscopic parts.* In red, we represent the cells involved at the small scale limit of the organ and, in blue, the cells composing a macroscopic part of the organ (say a systemic artery). Notice that, again, the link between these cells is relevant if and only if it contributes to the structure of interactions supported by the main organonic structure.

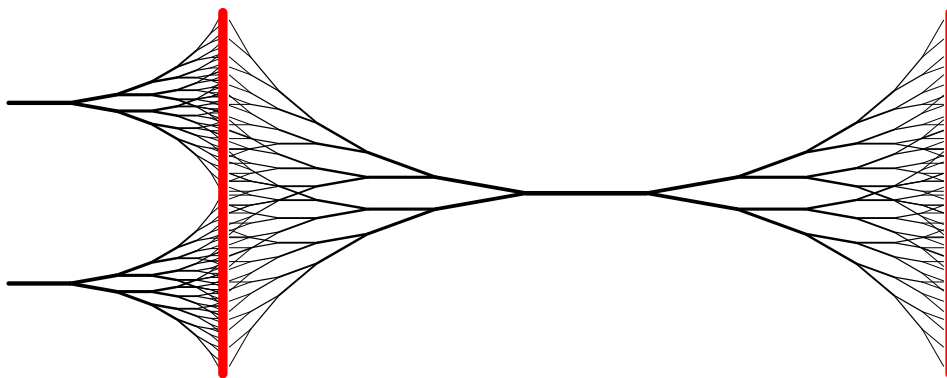


Figure 11.4: *Two organs are related to the rest of the organism via a third organ.* This structure correspond to the situation of most organs, which have a small scale limit with a limited spatial extent, and therefore need the mediation of other organs to be associated to all cells.

which means that it is particularly associated to a difficult situation. Notice, as a word of caution, that it is not a random choice and that this case will show to have distinctive features with respect to our question. Indeed, the first of these features is that its small scale structure is approximately space filling; all cells are close to a capillary, or from another perspective, the small-scale part of the vascular system is present in every tissue. As a result, we already have, here, an intuitive contact point with the whole, in the sense of “all cells”.

However, we can also take a dramatically different point of view. The vascular system is simple in the sense that it can be described as an oriented flow of matter when we consider its ability to be the medium of cells interaction. This flow approximately follows a fractal tree. Starting, say, from the capillaries, this tree corresponds then to a progressive mixing of blood (see figure 11.5 in section 11.4.5). This mixing is determined by the geometrical structure of the veins, whilst the content of the blood is determined by whatever happened at the tissular level. Then, the top of the fractal structure, roughly the heart⁶, corresponds to blood which has gone through all capillaries and which is, therefore, a mixing of the various cellular products. This mixed blood is then projected again, through the arterial tree, in all cells and tissues of the organism. Thus, the top of the vascular tree has also properties associated to the whole, in the sense here of a mixing of (a part of) the various cellular product. Another reason for this status is that the whole determination of the dynamic of the blood goes through the particular part that is the heart. By the latter, we mean that the mechanical forces allowing this flow are mainly produced by the heart, so that the determination of the dynamic of the blood has the heart as an intermediary between the various integrations (by hormonal and nervous means, typically) and the resulting rhythm. Therefore, the heart is a focal point of the structure of coherence when analyzed with respect to the vascular system. Notice, that in the case of insects, for example, the vascular system is open, but there is nevertheless such a structure, with a central aorta and an heart. The tracheal system, however, has no such central location but has a certain number of “macroscopic” pores.

Now we will give a precise answer to our question. This question is: when can we say that an organ (or a given cellular activity) has decidedly a functional role, or, equivalently, when is an organ articulated to the whole (and therefore unquestionably an organ)? The answer is clearly not at the orgonic level only, since most organs are spatially confined (in organs, in the classical sense, such as the lungs). Therefore, there is, in spite of the singular structure of organs, no direct link between a randomly chosen organ and a theoretical object associated to the whole of the organism. In order to overcome this difficulty, we propose to assume that, when one considers an organ, the whole of the organism is met when the interactions supported by this organ (“renormalized” interactions) propagates *in fine* to all cells of an organism. This can typically be mediated by another or even a succession of other organs, see figure 11.4 for an illustration. Typically, the function of lungs can be understood this way since their fractal structure is microscopically limited to a spatially limited sector, but this sector is coupled with the vascular system which propagates the lungs gaseous exchanges to all cells.

⁶Our theoretical framework is in fact more precise. *Stricto sensu*, different organs interact macroscopically here. One of them is the fractal structure of blood vessels. Another is the muscular dynamic of the heart and its proper dynamic.

Notice that the organs that directly have the ability to be related to the whole of the organism in this way seem to be in a limited number. To our knowledge, the main organs which are sufficiently widespread in the body are the vascular system, the lymphatic system (which is slower) and the nervous system. Another system that can be understood also this way is the mechanical integrity of the system, which can be described in terms of tensegrity (Donald 2003), but its possible singular structure should be clarified first. However, It is clear that the structure of mechanical forces leads to radical symmetry changes at the cellular level, including differentiation (Hinz 2006), gene expression (Brouzés & Farge 2004) and is at least partially determined by the collective activity of cells (Dhimolea et al. 2010).

11.3.4 RECAPITULATION AND PRECISION

Let us summarize what is the picture of the situation that we already have obtained.

- We have *vertical organs*, a typical example for this is the activity of the retina or the mitochondrial network of cardiomyocytes, as described in section 2.5.2. In such situations, a progressive taking into account of the interactions, associated to a singular behaviour, corresponds to a renormalization of the properties of the cells (spiking activity for neuronal networks typically), with elementary components corresponding to more and more cells. The local behaviours, i.e. the behaviour of a cell, is not dominated by an average behaviour but collectively fluctuates in clusters of arbitrary sizes. In such cases, we have a change of level of organization in the sense of chapter 10, see also Bailly, Gaill & Mosseri (1988); Bailly (1991b, 1991a). These situations are physically associated, in general, with infinite susceptibilities and the system can react drastically to stimuli of any size, since it has patterns of any sizes (intuitively this kind of behaviour is not limited to strictly monofractal structures, over a limited range of scales).
- We have also *diagonal organs*, and our paradigmatic example of the latter will be the vascular system. In this case, we have a fractality over elements which have a homogeneity which does not correspond to the same cells. On the contrary, there are a variety of structures for arteries (elastic or muscular), but the biological crucial point is that, following our example, muscular arteries tune the vascular system's structure and regulate it in association with the levels of activity of the various parts of the body. However, the last description is heuristic, and we can try to integrate it to our framework. This regulation is performed in various ways, but is mainly mediated, to our knowledge, by the nervous and the vascular system (via hormones, for example). The latter are then associated to fractal-like structure, which allows to integrate the activity of an organ and of different organs.

This kind of organ can be associated to one (or more) focal points, which corresponds to a temporary localization of the various interactions at their other scales but which can also be organic in its own right. Typical examples are the heart, the lymphatic nodes,

In a quite practical manner, this distinction corresponds to concrete movements of the observer. For a vertical organ, we only need to zoom out in order to see the fractality, whilst for a diagonal organ, we need to zoom out and translate the observing apparatus.

The above distinction can be relaxed, at least in part, if one considers that we see the whole organism at a small scale. More precisely, let us assume that we see all the elements of the organs which have a size between given boundaries, say al and l . In this case, zooming out is changing these boundaries to $2al$ and $2l$, for example, and it allows us to see the relevant objects without translation. This operation is of course difficult in practice, especially *in vivo*, but it is relevant with respect to the structure of determination of the organism. Notice also that the nervous system is particular with respect to this distinction, as it includes nerves, which seem to be mainly of the diagonal kind and nervous center, which are more vertical.

Last but not least, we have found that the functionality of an organ is found when, after the possible mediation of different organs, the corresponding interactions reach all cells of the organism. Notice that this approach is crucially different from the straightforward idea of an interaction of every cells with each other, since we have, here, an organ or more generally organs as intermediaries between cells (and therefore scale changes, associated to singularities). Therefore, the situation is different from bacteria in a test tube interacting in an unstructured (non singular) way, for example. What we want to approach here is indeed the constitution of a new level of organization, as described in chapter 10.

Here, we should again compare the situation with physical renormalization. As we said, in physical situations, the globality of the interactions is obtained via a scale symmetry which allows to obtain a fixed point of the partial (with respect to the scale range) structure of the interactions. In other words, since we cannot understand the whole directly (because of its strong coherence structure), we nevertheless achieve a theoretical — including quantitative — approach of the system by exhibiting a symmetry between these partial interactions and “all” interactions (at sufficiently large scale). The organism is elusive because such a procedure cannot be performed directly. However, we propose to follow the “visible” (observable) structures of interactions of the organism, which are the organs when the relevant structures are chosen to be singular (associated to a change of level of organization). However, one cannot find the global structure of coherence of the system by only looking at it in this manner. Somewhat like the scale symmetry used in renormalization, we also need to find some way to “globalize” a partial account of interactions. Such a globality can be found, at least tentatively, at the level of all cells, after an orgonic “transformation”. Note also that, at various scales, the organs can be related with the environment and with each other. For example, it seems that the lungs are macroscopically associated to the diaphragm and to the environment (air). Another elementary example of a large scale coherence given to the organ via the environment is the structure of the visual field. If one turns off the light, the retina does not receive light coherently, without the mediation of a neuronal coherence structure and associated protensive effects (both of them are however clearly *also* relevant). In Werner (2010), this kind of idea are also discussed in the case of the brain.

Of course, this is far from enough to have something even close to the theoretical power of the symmetry of a critical state, but one should also keep in mind that we are not planning to obtain a physical form of invariance.

11.4 A SCHEME OF THE ORGANIZATION OF A METAZOAN

We have analyzed the question of the scale directions and spoken informally of organs as a structure supporting interactions between cells and cells as an intermediary between organs. We have also relatively informally used renormalization terminology. We will now specify our scheme of the structure of coherence of the organism.

11.4.1 REINTRODUCTION OF THE COMPACIFIED TIME

We need to establish a certain level of commensurability, or homogeneity between the “renormalization” corresponding to the different organs. In order to do so, we will first remark that, unlike in the case of equilibrium phase transitions, the biological situation typically involves time. This is, for instance, the case when we consider the vascular system, since the interactions take the form of a flow in the vascular structure. The way, in which the latter mediates interactions between cells, takes typically the form of an oriented flow of matter, which, therefore, occurs over time.

Moreover, the time associated to the vascular systems dynamics, is not any temporal quantity. On the contrary, it precisely corresponds to the time that we associated to the compactified temporal dimension, in chapter 3. Moreover, this correspondence is confirmed by the temporal properties, with respect to interspecific allometries, of other organs (lungs, guts, muscles, ...). Therefore, we propose to associate θ with the renormalization parameter (usually space scale, for critical phenomena).

However, corresponding to the different organs, we have different times which vary approximately allometrically (with respect to the adult mass of organisms). Therefore, we can associate them to different compactified times $\theta_1, \dots, \theta_n$. However, these times are allometrically proportional, so we can write them $a_1\theta, \dots, a_n\theta$. The coefficient a_1, \dots, a_n should be considered stable with respect to intraspecific allometry. For a precise specie, organism, or organism at a given time, they are, in general, however, associated to symmetry changes, as described in chapter 7. These symmetry changes are related to individuation at the considered level (mammals, species, individual, individual at a given time) and also *in fine* to the biological measurement performed, as we discussed extensively in chapter 7. Notice also that discrepancies between the a_i should occur in a given observed temporal trajectory (as a consequence of individuation).

By the introduction of θ , we will have a scheme that can be allometrically covariant (modulo the symmetry changes). Notice also that θ is oriented so that it only grows except when approaching 1. When consider the latter we will write for the sake of clarity $\theta \rightarrow 1 (= 0)$.

One should already emphasize that the introduction of a form of renormalization where a temporal dimension plays the role of the parameter is conceptually different from the usual forms of renormalization. Indeed, even when renormalization is applied to a dynamical system, it corresponds to a dynamic seen at different time scales. Here, the idea is different, we are considering a flow of interactions associated simultaneously to time and orgonic scales (the scales of the fractal structures).

We can also make a topological remark. An organ, such as the one associated to fractal structure of the vascular system, has a relatively straightforward interpretation with respect to compacified time. It can indeed be interpreted as a flow of matter in a relatively circular way (from cells to the heart and from the heart to the cells⁷). A similar but also crucially different organ, associated to a flow of matter, is the case of lungs. The difference comes from the macroscopic association with the environment, which leads to a loss of the possible interactions between cells by this medium, and introduces a discontinuity in the part of the compacified time that we will associate to the upper scale of the organ. This discontinuity is quite meaningful; it corresponds to the coupling with the environment.

On the opposite, vertical organs seem more difficult. A pedagogical example of a vertical organ can be found in flocks of birds, where the collective behaviour is understood as regular collapses and reorganization of the collective structure (Vanni, Luković & Grigolini 2011), which are associated to the critical fluctuations (and the finite size of the system). This allows a high susceptibility of the group to external stimuli. In this case, therefore, we have a succession of more coherent (macroscopic) behaviour and more disorganized (local behaviour), which are temporally organized in a coherent way, with respect to our framework (except that it does not occur in an organism). In an organism, the compacified time corresponding to a vertical organ will be in general associated, on one side, to its constitution of a global behaviour and on the other side, to the time for the global behaviour to determine the local behaviours.

11.4.2 ORGONIC OPERATORS

We can now provide an analog of the renormalization operator in a formal manner. Let us consider that the flow of interactions associated to an organ i can be written as an operator $\hat{\Theta}_i(\theta_i, n_i)$, where n_i is the number of iterations of this procedure. We will assume that the values of θ_i are in $[0, 1[$ and will associate conventionally 0 (we are working on a compacified interval so $0 = 1$) to the cellular level. Similarly, $1/2$ will be associated to the large-scale limit. Typically, if we consider a physical critical situation, $\theta = 1/2$ corresponds to the infinite size limit. More precisely, if we note λ the scale, the physical renormalization operator $R(\lambda)$ can be understood as $R(\lambda) = R(\tan(\pi\theta)) = \hat{\Theta}(\theta)$, for $\theta \in [0, 1/2]$. We will return to this crucial point latter. See also figure 11.5, in section 11.4.5 for an illustration in the case of the vascular system.

Now, $\hat{\Theta}_i(0, 1)$ corresponds to an iteration of the compacified time seen from the cellular level. As we said in section 11.3, in most cases, this does not lead to an account of the participation of this organ to the whole organism directly. We can combine this organ with another organ via the cellular level, following the situation in figure 11.2b. We will formally write this cellular level as a theoretical unknown object $X_{i,j}$, but which is associated to relatively straightforwardly identifiable cells. The combination, therefore, reads $\hat{\Theta}_j(0, 1)X_{i,j}\hat{\Theta}_i(0, 1)$ ⁸. The functionality of the organ $i = k_0$ finally appears via combinations of the following form:

⁷Of course the situation is far more complex, and, for example, mammals typically have a particular organization with respect to the lungs, but, in any cases, we need to handle far more complex situations.

⁸Time goes from right to left in this symbolic expression in order to be consistent with the usual composition of function: we first apply $\hat{\Theta}_i(0, 1)$, then $X_{i,j}, \dots$

$$\hat{F}_{i_a} = \left(\prod_{m=1}^N \hat{\Theta}_{k_m}(0, 1) X_{k_{m-1}, k_m} \right) \hat{\Theta}_i(0, 1) \quad (11.1)$$

Where, X_{k_{N-1}, k_N} concerns all cells. Notice that different combinations can be performed, which is marked by the index a (and that they can also be iterated). One should notice that this procedure involves as many upward and downward transformations than there are organic operators. Similarly, the compactified time spent to perform these operations which occur successively is:

$$\sum_{m=0}^N a_m \quad (11.2)$$

Notice that this does not take into account the temporal contribution of the mediation at the cellular level $X_{i,j}$.

There are a certain number of points that need clarification. First we do not have, yet, an account of the macroscopic interactions between organs or between organs and the environment. If one keeps the form of the organic operator given above, then there are two main ways in which we can proceed.

1. First other organs can alter an organic operator $\hat{\Theta}_i$, for example by altering the weight of the different parts of the system (this is typically the role played by muscular arteries and their regulation) or by altering the coefficient a_i of the compactified time (the heart typically operates this way). Notice that this situation is, in a sense, a renormalization of the operator $\hat{\Theta}_i$, which is macroscopically associated to other organic structures. This situation is, therefore, particularly general in the case of diagonal organs. An intuitive picture of the situation can be found in figure 11.3.
2. A more radical situation is the alteration of the nature of the interactions which are renormalized by $\hat{\Theta}_i$. In such a case, this change should be taken into account directly. For example, let us assimilate the interactions of the vascular system (understood as the structure of blood vessels) to a flow which is conservative⁹ (but of an only partially determined nature, see below) except at the cellular level (or equivalently, at the level of capillaries). Then such a disruption would correspond to an injection of chemicals or a haemorrhage. If one considers the lungs in a similar way, we have by contrast a normal loss of conservation at the level of the nose, which is associated to the coupling with the environment. In both cases, we have a situation which can be formalized as:

$$\hat{\Theta}_i(\theta_i(1), n_i) \mathcal{E} \hat{\Theta}_i(\theta_i, n_i + \theta_i(1)) \quad (11.3)$$

⁹This is a crude assumption, and typically other interactions can occur, for example via the macroscopic level of the lymphatic system.

Where $n_i + \theta_i(1)$ denotes the partial integration that already occurred and \mathcal{E} represents, here, an interaction with the environment, but we could have also considered another organ. For example, the fluxes in the lymphatic system (re)join the vascular system, near the top of its structure (subclavian vein), after going through lymphatic nodes.

Notice that if two organs interact when approaching $\theta_i = 1/2$ and $\theta_j = 1/2$, then the macroscopic coupling is especially relevant. In this case, the interactions can alter deeply $\hat{\Theta}_i$ (and $\hat{\Theta}_j$). It is important to remark that it is, in a sense, what occurs in the coupling of two (or more) parts of an organ (and this leads to the singular nature of an organ, associated to the propagation in scales).

Now, one should notice that there are, in general, two intrinsic singular points in the behaviour of $\hat{\Theta}_i(\theta_i)$. The first corresponds to the limit $\theta_i \rightarrow 1/2$ and is associated to the *globalization* of the interactions *in the organ*. The simplest observable trace of it are the scaling of the fractal-like structure of organs (see chapter 2), but the complexification of the interactions is also crucial (it is associated to the degree of heterogeneity of the parts of the organ at a scale). Further research would of course be required to identify clearly what can be objectivized in the neighbourhood of this point. However, the conceptual point is that this point is in principle singular because it corresponds at least to the change of scale of a singular structure (in the form a virtual infinite scale limit, for example). From another point of view, it corresponds to the approximately infinite complexity of the contribution of all cells of the body to the “exact” determination of the content of blood.

The other singular point corresponds to the limit $\theta \rightarrow 1(= 0)$, where we are going from upper scales to the smaller scales, and, *in fine*, to the cellular level. We will discuss it in the following subsection.

11.4.3 CELLULAR LEVEL

In this scheme, we focused mainly on the organs. However, in order to discuss the limit $\theta \rightarrow 1(= 0)$, we need to have a better description of the cellular level which we described formally (and elusively) by X . This level has a proper structure, which corresponds to tissues. As a result, the relevant objects are cells, their local interactions, and the small-scale limit of organs (of the organism).

The small scale limit of the organ is what matters crucially in our scheme, so that we have to understand the relationship between the cellular level and

- the upward direction (integrative direction) $\hat{\Theta}_i(\theta_i)$ (increasing θ_i from $\theta_i = 0$), which is the basis of the singular relationship of the tissue with the rest of the organism.
- the downward direction $\theta \rightarrow 1(= 0)$, which is the basis for macro regulation by the organism (not the tissular regulation that occurs via cells' local interactions).

The difficult point is that cells are also in an extended critical transition; therefore, they have the corresponding structure of determination, described by ubiquitous symmetry changes. What happens in the tissue is, therefore, a stabilization of the cellular symmetry changes (and firstly of cellular division Sonnenschein & Soto (1999)), in particular when

this symmetry changes are anomalously transported via the orgonic structure and lead to dramatic responses of the organism. At the same time, a part of the symmetry changes which are relevant (with respect to an organ) are also crucial for the organism. Symmetry changes contribute to its variability and its constitution of an extended zone of viability (zone of extended critical transition).

One should notice that the account of cells is usually extremely limited in the perspective of the study of an organ. For example, the standard approach to neuronal networks focus only on their spiking activity (Petitot 2008), and in relatively homogeneous zones (where symmetries of the structure can be analyzed and used).

There are numerous aspects which are nevertheless relevant with respect to the integration in an organism. Firstly, the extended critical transition associated to cells leads to consider the historicity of their trajectories. The main aspect of this historicity is probably cellular differentiation (in development). It seems indeed that the latter determines most of the relevant basic symmetries corresponding from the orgonic point of view; however, a considerable variety of symmetry changes can also occur. In particular, the $\theta \rightarrow 1 (= 0)$ brings interactions to the cells which can lead to a variety of responses and transformation of cells. Note that all drugs are based on this principle (in the hope that only certain macroscopical effects will be produced).

The relevant aspects of cellular determination are, therefore, corresponding to a “renormalized” cell. By the latter, we mean a cell which is for a significant part determined (as a specific object, see chapter 6) by the interactions in the tissue and by the integration in the organism¹⁰.

The cellular level is also crucial because it mediates the interactions between organs. As a result, the transformation of the interactions between organs at small size occurs via the cellular level and can, therefore, be sensible to small variation of the determination of this level. From another point of view, the complexity of the interactions on which an organ operates, and which is involved in the regulation of a cellular level, is reinforced by these combinations.

11.4.4 SYMMETRIES AND SINGULARITIES

In this scheme, we have two types of singularities. The first is associated to the integration of interactions in an organ, whilst the second is associated to the regulation at the cellular level and therefore to the following integration of this organ or of another which meets this cellular level.

In this proposal we have therefore two paths for the changing of level of organization, in the sense of chapter 10. The first, which we will assimilate to the limit $\theta_i \rightarrow 1/2$ corresponds to the formation of the orgonic level whilst the second corresponds to the limit $\theta_i \rightarrow 0$ and corresponds in general to the regulation of the organism (see also Bailly & Longo 2011) on the cells, but in the particular case where all cells are concerned, we posit that this constitutes the level of the organism, via all orgonic transformations of the form 11.3.

¹⁰It is possible to understand the relevant aspects of cells as organs of this biolon (think, for example, to the myocytes, the spiking activity of neurons, or even secretions)

From the point of view of the symmetries, we already see that cells by themselves can generate symmetry changes which can be amplified by the orgonic structures. In our scheme, we have indeed orgonic structures which handle more or less generically the transformation of interactions. However, this does not seem satisfactory since the amplification is partial and above all because this amounts to consider the cells as the sole generator of symmetry changes (and is an hypothesis). We would like to find a path for the generation of symmetry changes in our scheme itself. This question is of course difficult, but let us try to point some possible directions.

First, it is not “bare” cells¹¹ that appear in our scheme, but cells which are “regulated” and, therefore, connected to the various activities occurring within the organism. This multiplies the variety of interactions between distant, differentiated cells or parts of the body, and therefore the organizational change possibilities.

Second, an orgonic flow of interactions is associated to the environment and to other organs in various ways (for example in the case of a diagonal organ, see figure 11.3). This can transform regulation and therefore directly the activity of cellular regions. Notice that this is precisely the point in the case of cognition.

Third, as we will see in the next section, the operator can introduce randomness.

Fourth, for all the reasons above, changes of the operators \hat{O}_i can occur. Such a transformation deforms the structure of the interactions in the organism. The point is therefore that the orgonic operators are not invariant, but are, *in fine*, constituted by the activity of the organism. More precisely, certain aspects of them are robust, especially when an important change leads to the collapse of the viability of the organism (massive death of cells, or from an orgonic point of view, loss of the singularities), whilst other can change dramatically without a loss of functionality (the functional structure of the brain, for example and especially when injuries occur). For example, the human body can accommodate tumors of 150 kg (O’Hanlan 1994).

From the point of view of viability, the loss of an organ (for example the collapse of its singular or dynamic nature) typically leads to a loss of function (a plethora of functions in the more common sense). This loss can generate cellular death or macroscopical collapse of other organs which combined leads to the loss of the orgonic extended critical transition (death of the organism). Note that this does not imply that all cells die in the process. However, moderate variations of the organs (including of their singular limit) does not constitute an issue. On the contrary, it seems to us that it is the “normal regime of determination of the organism.

11.4.5 SOME FURTHER REMARKS

In chapter 8 and in Bailly & Longo (2009), there is the mention of the relevance of the coupling of levels of organization to anti-entropy, but there is no straightforward way to assess this contribution. Since we tried to formulate a scheme of the organization of the organism, we have gained more insight on such contributions. What our scheme emphasizes

¹¹Let us recall that the bare coupling constants, in quantum field theory, are the “constants” when we do not take into account interactions (without renormalization, but at a given level of energy).

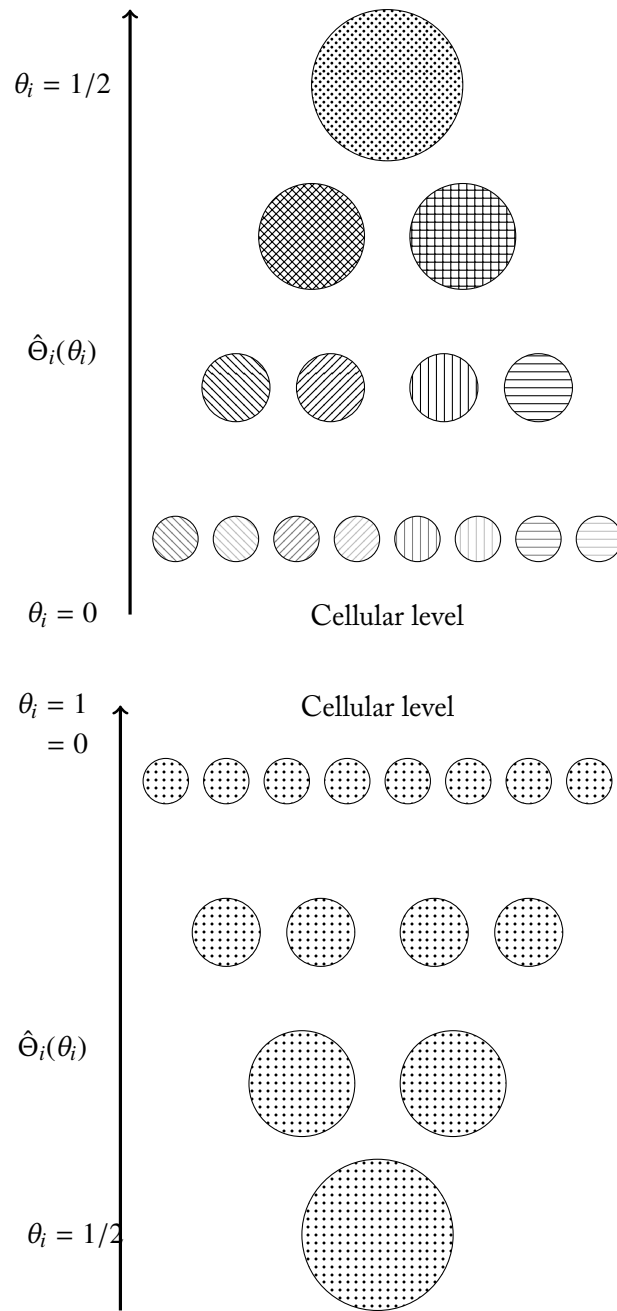


Figure 11.5: *Orgonic operator and anti-entropy, the case of the vascular system.* The transformations generated by the orgonic operator is assimilated to the flow in compacified time and in the scale structure of a sample of blood. Here, we represent the blood content by the pattern in each vessel. The heterogeneity of blood is generated only by the cellular (or tissular) level. However, figure 11.6 shows that the regulation path can intrinsically lead to randomness. Notice that we have represented a situation where the interactions are unstable with respect to an iteration of the compacified time.

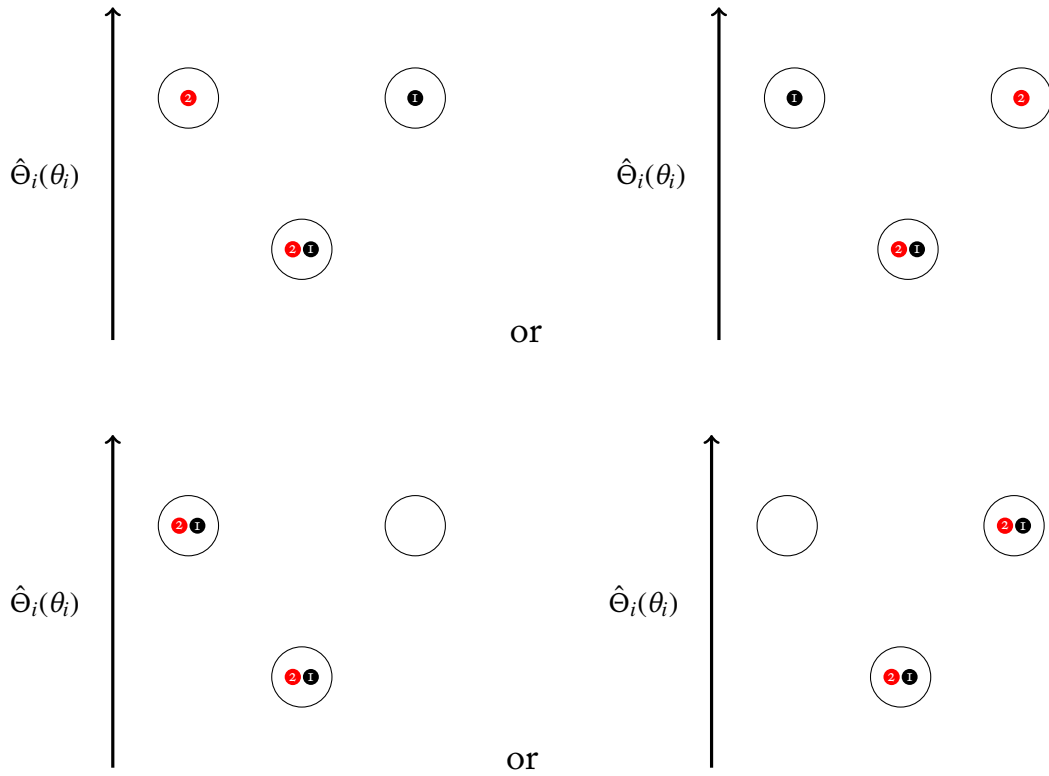


Figure 11.6: *Blood vessels and randomness*. In this schema, we illustrate randomness generated by finite (small) number of distinguishable objects in blood. here we consider one representative for each kind, and consider the possible results after the branching of the main artery. The principle is remarkably similar to the situation for dividing bacteria (Cai, Friedman & Xie 2006).

in general is the progressive taking into account of heterogeneous contributions via fractal structure (which leads to the orgonic operator). Another crucial point is the existence of organs which gain a functional role via one or a sequence of other organs. Therefore, we should have contributions combining these different aspects.

The simple case of a transport of matter in a tree structure can be approached, at a first approximation, relatively straightforwardly (the vascular system, typically). Note as a preliminary word of caution that we are not interested in the physical modelizations of the vascular system (or other organs), which are based on friction, elasticity, etc., and aim to find a specific trajectory associated to the blood flow of a generic blood. On the contrary, it is the traces of the specificity of the organisms which we want to find, here, in blood, and that are of interest to us.

In this case, a first approximation of the operator $\hat{\Theta}_i(\theta_i)$ corresponds to the fusion of blood from different origins (for $0 < \theta_i < 1/2$, or in biological terms for veins), for example a fusion at each integer value of $\tan(\theta_i)$. Similarly, the downward operator $\hat{\Theta}_i(\theta_i)$ for $1 < \theta_i < \theta$ corresponds to successive divisions of blood, say for integer value of $\tan(\theta_i)$ (for arteries). See figure 11.5 for an illustration where the singularities are truncated.

From the point of view of entropy, we have a mixing of heterogeneous systems which produces entropy at each step of the integration, see figure 11.5 (inferior part). On the contrary, the splitting is relatively homogeneous if the number of elements of each kind is high in all arteries (as we represented in figure 11.5 (inferior part)). This splitting, however, leads to randomness when the number of objects of certain kinds is low (see figure 11.6). Interestingly, the basic properties of this randomness is similar to the randomness introduced by elements in small number in dividing bacteria (Cai, Friedman & Xie 2006). When this number is high, the partitioned system will be equal to their mean.

It is interesting to approach the situation in terms of statistical mechanics and entropy. If all components are indiscernible, the splitting and mixing does not change entropy because the permutation of the components does not lead to the distinction of two different zones. If one can distinguish two kinds of components and we are mixing them we produce entropy called entropy of mixing. On the contrary if one splits a system where all particles are distinguishable in two, we have a loss of configuration (position) entropy $S \propto N$ (N , the number of elements). In a sense, at the limit, all particles are separated so that the entropy goes to 0. Notice that this situation is associated to the Gibbs paradox, see for example Sethna (2006). From a biological standpoint, the situation involves components of various natures and frequencies.

Interestingly the situation is formally very close to that of chapter 8 section 8.6. If one assumes that the two compartments that we are mixing have components in proportion $q_i^{(1)}$ and $q_i^{(2)}$ and in high number, we can use equation 8.19.

$$S^{(1)} \simeq N^{(1)} \sum_j q_j^{(1)} \log(1/q_j^{(1)}) \quad S^{(2)} \simeq N^{(2)} \sum_j q_j^{(2)} \log(1/q_j^{(2)}) \quad (11.4)$$

The same holds for the component obtained after the mixing.

$$S^{(3)} \simeq N^{(3)} \sum_j q_j^{(3)} \log(1/q_j^{(3)}) \quad (11.5)$$

Let us note $N^{(3)} = N$, $N^{(1)} = \alpha N$ and $N^{(2)} = (1 - \alpha)N$. Now let us consider the contribution of the elements that compartment 1 and 2 have in common (these elements correspond to the same index in the summation).

We have $N_j^{(1)} = \alpha N q_j^{(1)}$ and $N_j^{(2)} = (1 - \alpha)N q_j^{(2)}$, so that

$$N_j^{(3)} = \alpha N q_j^{(1)} + (1 - \alpha)N q_j^{(2)} \quad (11.6)$$

$$q_j^{(3)} = \alpha q_j^{(1)} + (1 - \alpha)q_j^{(2)} \quad (11.7)$$

This yields an entropic term j

$$S_j^{(3)} = -N q_j^{(3)} \log(q_j^{(3)}) = -N (\alpha q_j^{(1)} + (1 - \alpha)q_j^{(2)}) \log(\alpha q_j^{(1)} + (1 - \alpha)q_j^{(2)}) \quad (11.8)$$

The entropy produced is then:

$$S_j^{prod} = S_j^{(3)} - S_j^{(1)} - S_j^{(2)} \quad (II.9)$$

$$= -N\alpha q_j^{(1)} \log \left(\frac{\alpha q_j^{(1)} + (1-\alpha)q_j^{(2)}}{q_j^{(1)}} \right) - N(1-\alpha)q_j^{(2)} \log \left(\frac{\alpha q_j^{(1)} + (1-\alpha)q_j^{(2)}}{q_j^{(2)}} \right) \quad (II.10)$$

we write $\beta_j = \frac{q_j^{(2)}}{q_j^{(1)}}$

$$S_j^{prod} = -N\alpha q_j^{(1)} \log(\alpha + (1-\alpha)\beta_j) - N(1-\alpha)q_j^{(2)} \log\left(\frac{\alpha}{\beta_j} + 1 - \alpha\right) \quad (II.11)$$

Notice that this quantity vanishes for $q_j^{(1)} = q_j^{(2)}$ ($\beta_j = 1$) because the compartments are already homogeneous. The entropy production is the result of the heterogeneity of the concentrations, here.

For the elements that are only in one compartment initially (say compartment 1), we have

$$S_j^{(3)} - S_j^{(1)} = -N\alpha q_j^{(1)} \log(\alpha q_j^{(1)}) + N\alpha q_j^{(1)} \log(q_j^{(1)}) \quad (II.12)$$

$$S_j^{prod} = -N\alpha q_j^{(1)} \log(\alpha) \quad (II.13)$$

Notice that when a distinguishable class of objects comes from only one initial compartment, the iteration of the procedure (say $\alpha_n = \alpha_0 n^{-k}$, see section 2.3.3.1), while keeping the number of objects of this type high, yields

$$S_{j,n}^{prod} \propto N\alpha_n q_j^{(1)} k \log(n) \quad (II.14)$$

or a contribution per object of this kind of

$$k \log(n) \quad (II.15)$$

Therefore, the entropic contribution of this components diverges. Notice that what we are doing is paradoxical since we are considering that the *number* of particles remains high in spite of the increasing dilution.

This point is crucial and corresponds to an usage of the thermodynamic limit. More precisely, we have two infinities here. We have the infinite iteration of the dilution operation and an infinite number of objects. To take the limit, we are making the number of objects in all compartments and the number of iteration of the dilution ($\hat{\Theta}_i(\theta_i)$ when $\theta_i \rightarrow 1/2$) tend to infinity, which yields a divergence of the volumic entropy (when the fusion of two compartments adds at least one compound). This divergence is the singularity associated to the limit $\theta_i \rightarrow 1/2$ in this case and corresponds to the approximately infinite physicochemical complexity of the living system.

In both cases, the crucial point is that it is the interactions with the cellular level $\theta_i = 0$ which provide the heterogeneity needed for the entropy production to be $\neq 0$. When we keep the system finite, both contributions remains finite, and the lowering of entropy by the cellular level remains finite, but at the limit both contribution diverge, and the necessary cancellation of this divergences is a further justification for the introduction of a new quantity (anti-entropy). Notice the strong analogy with critical phenomena: to fluctuations correspond the heterogeneity and we need also the thermodynamic limit¹². The combination of the two leads to a breaking (divergence) of intensive entropy.

11.5 CONCLUSION

We have described a scheme of biological organization which is of course only a tentative and under-specified approach. In our scheme, we have a tentative (partial) synthesis of an important part of the concepts that we used earlier. Notice that other aspects that were only mentioned here, such as protention, can probably be articulated to this scheme in a relatively straightforward manner.

The crucial question asked here is that of the constitution of the objectivity of the organism's unity, coherence and variability. In our approach, the singularities play a crucial role as a path for the constitution of new level of organization. In our frame, we tried to approach how the singularities which have observable traces (the organs associated to fractal-like structures) can relate to each other and *in fine* to the whole organism (and in a sense constitute the latter).

In this scheme the extended critical transition is mainly the coupling of two divergent directions for orgonic singularities (and their functional coupling). The first corresponds to the large scale singularity in the taking into account of an increasing part of the interactions in the organ and the other corresponds to its impact on cells, which are also typically associated to other organs. Notice that future work could in particular apply a similar scheme for the cells in the organisms since they are biolons in our frame.

The major extension that our scheme needs is the question of the formation of the biological organization. Notice that we can approach this problem as a form of temporal integral or from another point of view the iteration of our scheme with an increase which corresponds to the formation of new organs, differentiation of cells, etc.

In this case we already have a straightforward consequence of our approach: the singular coupling of organs at the cellular level remains approximately invariant throughout the developmental process (more precisely inasmuch it is functional). Therefore, the growth of these organs is coupled and should lead to geometrical consequences on their spatial structure. This point is precisely an aspect that we met in our discussion of experimental results, in section 2.3.3.3, (see also Maina & van Gils 2001).

We think that this conceptual and partially mathematical sketch of biological organization can lead to particularly interesting theoretical (and hopefully also empirical) research.

¹²Notice that it would be interesting also to couple this limit with allometry.

Conclusion 12

CONTENTS

| | |
|-------------------------------|-----|
| 12.1 Recapitulation | 271 |
| 12.2 Perspectives | 274 |

12.1 RECAPITULATION

THE aim of this thesis is to develop original theoretical approaches which, we hope, could be useful in the perspective of a theory of biological systems. This aim can also be understood as a participation to the constitution of a theory of organisms. In order to do so, the crucial difficulty is to provide an account of biological objects in a way that objectivizes them.

Since an important part of the relatively robust relationships in biology are found through the notion of scaling, we first reviewed experimental results which uses this approach, in chapter 2. The meaning of such results is given by the mathematical concepts mobilized. The main categories of biological scaling are the following: first allometry, where the scale is given by the size of the organism, and second intrinsic fractal-like structures of a biological system. In the latter category, we have fractal-like situations in space (organs), time (biological time series), space-time (anomalous diffusion, criticality) and in abstract spaces (networks). The conclusion of this survey is that the situation is relatively subtle. Scale symmetries are relevant and approximate scaling is found in a considerable variety of cases. This approach provides a unique grasp on biological phenomena and allows to exhibit instabilities of more classical measurement (dependence of surfaces on the resolution of measurement, typically). However, these symmetries are not exactly adequate for describing biological phenomena. Variability is clearly shown almost ubiquitously, where the data available are sufficient. This variability can be put in relation with various factors, corresponding in particular to the history of the object considered (for example, habits or phylogenetic history).

Starting from the temporal allometries described in the previous chapter, a strong distinction can be made between the physical rhythms and the biological rhythms: the latter

scale like $M^{1/4}$, where M is the mass of the organism. In chapter 3, this leads us to consider a second, compactified temporal dimension, associated to these proper biological rhythms. The frame so obtained is articulated to empirical time series, which allows us to provide a geometrical representation of biological variability. This frame provides an approach where questions can be raised and, at least in part studied, on phylogenetic, ontogenetic (including pathological) and intra-individual (non-stationarity) tendencies, moreover variability can also be considered.

In chapter 4, we considered a more “local” feature of cognitive and biological time. We focused on the so-called “extended present” as a result of protentional and retentional activities (memory and anticipation). The closest and simplest analog to retention in physical theories is relaxation phenomena, which have been a basis for our approach. However, protention (or anticipation) seems to be outside the scope of physics. We proposed then an elementary mathematized approach of protention, which allowed to introduce simple notions of biological inertia and of global protentional activity.

The following chapter, chapter 5, is a relatively technical interlude, where we have presented some specific examples and more fundamental results on the role of symmetries and symmetry breaking in physics. More precisely, we presented Noether’s theorem, which relates invariant quantities and symmetries in a remarkably general manner. Another crucial situation that we discussed is the case of spontaneous symmetry breaking (criticality); this situation leads to the introduction of renormalization methods. The latter allows to approach phenomena exhibiting a global coherence structure.

In a more general setting, but with the examples of this technical background, we have raised the question of the theoretical role of symmetries in biology, in chapter 6. In order to do so we have contrasted the physical situations which are characterized by the stability of the theoretical symmetries, and the biological situations where these theoretical symmetries are unstable. More precisely the theoretical determination in physics is given *in fine* by the theoretical symmetries, and it is these symmetries that allows to define generic objects and to determine their specific trajectories (in combination with the geodetic principle usually). On the contrary, we propose that the biological situations are characterized by an instability of the theoretical symmetries, or in other words ubiquitous changes of theoretical symmetries. It follows that the biological object (its theoretical symmetries) is specific and that its trajectories are generic (they cannot be determined specifically because of the lack of stable symmetries). This provides a strong definition of variability (specificity of the theoretical symmetries of biological objects) and of historicity of biological objects, as a cascade of symmetry changes. This abstract account justifies the duality already proposed in Bailly & Longo (2008), and is also a further development of the notion of extended critical transitions. In a mathematically practical sense, this means that biological objects are theoretically not well captured by usual equational forms (which always assume theoretical symmetries).

Following this hypothesis, chapter 7 discusses the theoretical nature of biological measurement. We should first recall that *all* physical theories have an intrinsic theoretical account of measurement. For this reason and because biology is a natural science this question is crucial for a theoretical biology. We analyzed two different strategies in biological measure-

ment. The first concerns an approach focused on symmetrization, or in other words, on the constitution of a restricted genericity of the object. This approach is based on the control of symmetry changes occurring at various time scales (phylogenetic, ontogenetic, cognitive, ...). We have provided a mathematical skeleton corresponding to this analysis and that applies to allometry, but could also in principle be generalized to a wide class of symmetries. The second approach focuses on the specificity of a biological object, the measurement therefore defines, through its symmetry changes, one (or a sequence of) dominating symmetries. Notice that, *in fine* the distinction between these two approaches is porous since the biological objects remain specific. However, the question can be raised whether the “global” consequences of biological symmetry changes can be measured (and in what sense).

In chapter 8, we come back to the notion of anti-entropy, introduced in Bailly & Longo (2009), as it seems to be a candidate for a global account of biological symmetry changes. We analyze anti-entropy in terms of theoretical symmetries, which allows to further specify its biological meaning. We also exemplify the role of the associated randomness in the constitution of biological organization in phylogenetic, ontogenetic and in the regenerative processes.

Starting from this point, we focus on the question of biological levels of organization, which is crucial in order to have a finer understanding of the biological fabric of symmetry changes (variability, on all time scales). In chapter 9, we start from the question of closure which is a notion traditionally used to understand autonomous systems. We provide an account based on the notion of the maintaining of time symmetries of certain aspects of a system. With other criteria, this defines a notion of constraint. Closure is, in this context, a certain relationship of interdependence between constraints. This can be relatively simply analyzed in a situation of scale separation. In this case, the conclusion is particularly interesting: we have a decoupling of the condition of closure (as a multi-scale condition) and of the global dynamic (which occurs mainly at the slowest time scale). On the contrary, it seems that a coupling of scales, associated to singularities in processes, can lead to specific signature for closure.

In chapter 10, we discuss first the question of interscale reductionism. Using physical situations, we showed that at least two cases can be distinguished. First the composition of the interactions of elementary parts can behave nicely, so that macroscopical degrees of freedom are determined by the combination of the contributions of the parts. In this case, the system behaves at the thermodynamic limit as the sum of its parts. On the contrary, critical situations behave like a global structure of coherence, so that the macroscopic description is broken and the sum of (the contributions) of its parts diverge. This lead the physicists to introduce new ideas for the intelligibility of the situation: renormalization methods. By this methods, the behaviour of the system is not understood as the sum of its parts, but it can achieved by the iterative consideration of a part of the interactions of the system. This partial interactions are symmetric to partial contribution at other scales, therefore the methods provides an explicit global account of the interactions, without the actual summation of all contributions (which diverge) and by partial summations only. Such situations give an original account of interscale reductionism, and are in a sense, at the edge of it. We consider a generalization of this situation as a strong theoretical characterization of the notion of

level of organization (following Bailly (1991b)), where the transition from a level is given by the breaking of its theoretical determination, in particular by intensive singularities. This has been applied to biology and can be interpreted as a particular link between fractals and biological vital functions. It also further specifies extended criticality on the basis of strong singularities (cf: Ginzburg criterion for example).

The final chapter of this thesis, chapter 11, provides a tentative scheme of the structure of coherence of the organism, based in particular on the notion of level transition, as given above. We have approached biological organization via a language inspired by the renormalization used in physics. In our scheme, however, the strategy we have sketched involves a “renormalization” where compactified time plays a crucial role, as identified to the scaling parameter, with two limit anomalies: 0 (small scale) and 1/2 (large scale). The crucial point of our approach is to try to have a global account of biological interactions in the organism, without the assumption of a perfect knowledge of them, but by focusing on the singular structure of their relation and transformations. This allowed us, in particular, to propose a further characterization of the link between functions and fractal-like structures. The coherence structure itself is also associated to a proper variability. We finally illustrate this scheme with the entropy of the vascular system, which leads to a further justification for our introduction of anti-entropy.

12.2 PERSPECTIVES

The theoretical proposals we made in this work are attempts towards a theoretical biology. It is possible that they remain epicycles, and miss crucial theoretical leverages that would highly simplify the theoretical situation. We hope that, in any cases, these proposals will prove useful for a better understanding of the living state of matter.

In the line of our words in introduction, we have approached biological from different angles. Each one of this angles lead to possible further development. By order of chapter we can provide a short, non-exhaustive list of questions.

CHAPTER 3 How can we precisely articulate the various biological proper rhythms? As we have seen, this is a crucial question for chapter 11. Notice that we have compared the variability of the heart rhythm of diseased and healthy cases, from empirical time series. With the correct rescaling, such a comparison can be performed, *mutadis mutandis*, for different rhythms recorded for the same individual.

CHAPTER 4 How is protention related to criticality? Recent work, Vanni, Luković & Grigolini (2011), approach the question of the fast collective behaviour responses in flocks of birds in particular, and aim at finding whether the situation can be understood as a propagation of information or is more subtle because of criticality.

CHAPTER 6 This chapter raises, of course, a lot of questions. The main question is: how can we objectivize living phenomena, whilst their symmetries are unstable? A more precise question is, however, that of the precise form of randomness that the biological symmetry changes leads to.

CHAPTER 7 The main question raised by this chapter is that of the exact relation between two different measurements, in general. *In fine*, this directly leads to the question of the structure of determination of biological systems, and is associated to biological randomness.

CHAPTER 8 Can we measure, directly (or indirectly) and macroscopically anti-entropy (or variations of anti-entropy)? A positive answer would have important consequences for the above, when anti-entropy is understood as a measure of symmetry changes.

CHAPTER 9 Can closure lead to a macroscopic signature? This would allow a strong link between closure and empirical results. We have shown that such a signature requires a situation where scales are not separable.

CHAPTER 10 How are fractal-like structures associated to the biologic symmetry changes? Elements of answer are given in chapter 11, but they are very preliminary. A more precise answer would in particular help for the question on anti-entropy, and would also further specify considerably the framework of extended critical transitions.

The chapter 11 is by itself a very preliminary account and a perspective; its development can be of considerable help for the rest of these questions. As we said in introduction, these research angles are complementary, and, in general, it is not straightforward as to which one of them can (relatively) easily deepen the understanding of the others, by a conceptual critical transition.

As a final perspective, we can remark that the scheme in chapter 11, if it can be clearly associated to symmetry changes, can lead to a close relation between the compactified time and symmetry changes. Biological time can possibly be understood by the unifying concept of an amount (flow) of symmetry changes. Such an approach of time, based precisely on the difficulty of the objectivization of biological systems, can probably allow to recover a theoretical and hopefully experimental homogeneity on the ground of the irregularity of biological objects.

Listings A

In this annex, we will provide some code that have been used in our work. The most crucial part is the code used for chapter 3, which allow to obtain the visualization of beat-to-beat time series in our theoretical framework.

A.1 CRAN R PROGRAMMS FOR CHAPTER 3.

The functions we give here allow to represent beat-to-beat time series. However, any other time series of the same nature (internal rhythm) could be approached with the same functions.

This function loads the data which are assumed to be in a text file per day, with the time of an heartbeat for each row, and columns : 1 is hours, 2 is minutes, 3 is seconds and 4 is milliseconds, the result is a vector containing the time of each heartbeat, in milliseconds.

```
`load_beat_annot` <-  
function(file){  
  x=read.table(file)  
  beat<-x$V1*60*60*1000 + x$V2*60*1000 + x$V3*1000 + x$V4  
  return(beat)  
}
```

This function builds the instantaneous beat to beat interval from a beat position vector, the result is a array of the beat position (in milliseconds) and beat to beat interval (in minutes).

```
`build_int` <-  
function(beat){  
  N=length(beat)  
  hr<-matrix(nrow=N,ncol=2)  
  # Fill first column with beat positions  
  hr[1:N,1]=beat[1:N]  
  # and second column with heart rate instant values  
  hr[1,2]=(beat[2]-beat[1])/(1000) # not a real data
```

```
hr[2:N,2]=(beat[2:N]-beat[1:N-1])/(1000)
hr[,2]<-hr[,2]
hr=hr[60/200<hr]
hr=hr[hr<60/20]
return(hr)
}
```

Graphical representation of our 2-dimensional structure in 3-dimensional embedding space. N is the renormalization factor, AA and MM are respectively the first and last beat taken into account, ϕ allows to set the phase of the external time, $X1$ and $X2$ are the estimated parameters, m_add is a Boolean stipulating if we are using a new graph or adding the graph to a preexisting one, $offset$ is a shift of the graph along the (z) allowing to compare different structures and RRR changes the radius of the compactified time.

```
library(misc3d)
`scheme` <-
function(N,m_intt0,beat0,AA,MM,phi,X1,X2,m_add,offsett,RRR){
  NN=length(m_intt0)
  nbeat=beat0[1:NN]/1000-beat0[1]/1000
  m_intt=1*(1:NN)/(1:NN)*RRR*N
  mm=X2
  RR=X1/(2*pi)*(24*60*60)
  lin=X2*nbeat
  art2=cbind(nbeat[AA:MM],offsett+(lin[AA:MM]+RR*sin(2*pi/(24*60*60)
    *(nbeat[AA:MM]+phi)))+m_intt[AA:MM]*cos(2*pi/N*(AA:MM))
    ,(RR*cos(2*pi/(24*60*60)*(nbeat[AA:MM]+phi)))+m_intt[AA:MM]
    *sin(2*pi/N*(AA:MM)))
  vtri <- local({
    nn=MM-N-2-AA
    z <- art2[c(1:nn,(1:nn)+1),]
    x <- art2[c((1:nn)+1,(1:nn)+N+1),]
    y <- art2[c((1:nn)+N,(1:nn)+N),]
    makeTriangles(x, y, z, color="green3")
  })
  drawScene.rgl(vtri , screen=list(x=0, y=0, z=25), add = m_add,
    perspective = TRUE,aspect=c(1,1))
  axes3d(perspective = TRUE)
  par3d(scale = c(1,1,1))
  lines3d(c(0,nbeat[length(nbeat)]),c(0,lin[length(lin)]),c(0,0), color="red1")
  lines3d(nbeat[AA:MM],(lin[AA:MM]+RR*sin(2*pi/(24*60*60)*(nbeat[AA:MM]+phi))
    +m_intt[AA:MM]*1.001*cos(2*pi/N*(AA:MM)),(RR*cos(2*pi/(24*60*60)
    *(nbeat[AA:MM]+phi)))+m_intt[AA:MM]*1.001*sin(2*pi/N*(AA:MM))
    , color="blue1")
}
```

This function provides the derivative of our scheme, allowing to see the structure of the variability. The parameters have the same meaning that in the previous function.

```
library(misc3d)
`schemed` <-
function(N,m_intt0,beat0,AA,MM,phi,X1,X2,m_add,offsett){
  NN=length(m_intt0)
  nbeat=beat0[1:NN]/1000-beat0[1]/1000
  m_intt=1/m_intt0*2*pi
  mm=X2*N
  RR=X1*N/(2*pi)*(24*60*60)
  art2=cbind(nbeat[AA:MM]-nbeat[AA],offsett+(mm+RR*2* pi/(24*60*60)
            *cos(2*pi/(24*60*60)*(nbeat[AA:MM]+phi)))+m_intt[AA:MM]*N
            *cos(2*pi/N*(AA:MM)),(-RR*2*pi/(24*60*60)*sin(2*pi/(24*60*60)
            *(nbeat[AA:MM]+phi)))+m_intt[AA:MM]*N*sin(2*pi/N*(AA:MM)))
  vtri <- local({
    nn=MM -N -2 -AA
    z <- art2[c(1:nn,(1:nn)+1),]
    x <- art2[c((1:nn)+1,(1:nn)+N+1),]
    y <- art2[c((1:nn)+N,(1:nn)+N),]
    makeTriangles(x, y, z, color="green3")
  })
  drawScene.rgl(vtri , screen=list(x=0, y=0, z=25), add = m_add,
                perspective = TRUE,aspect=c(1,1))
  axes3d(perspective = TRUE)
  par3d(scale = c(1,1,1))
}
```

Example of use:

```
#loading datas
#day 1
beat1=load_beat_annot("20611a")
#day 2
beat2=load_beat_annot("20611b")
beat2=beat2+60*60*1000*24
#day 3
beat3=load_beat_annot("20611c")
beat3=beat3+60*60*1000*24*2
#combination
beat=c(beat1,beat2,beat3)
intt=build_int(beat)

#estimation of the parameters
```

```
mm=mean((1/intt))/mean(intt)
varr=mean((1/intt*1/intt-mm)^2 *intt)/mean(intt)/2
X1=sqrt((mm-sqrt(mm*mm-2*varr))/2)
X2=sqrt((mm+sqrt(mm*mm-2*varr))/2)

#offset for the external rhythm
phi=6900

#Application
scheme(1000,intt,beat,1,length(intt),phi,X1,X2,FALSE,0,1)
schemed(200,intt,beat,1,27310,phi,X1,X2,FALSE,0)
```

A.2 C PROGRAM TO SIMULATE ISING MODEL IN CHAPTER 5.

We provide now the code for performing Monte-Carlo simulations of an Ising Model, with periodic bounding conditions. In order to perform these simulations efficiently, multi-threading is used, which allows to use multi-cpu hardware parallel computing capabilities.

The first part of the code defines preliminary variables and elementary functions. In particular, the function `modul` defines how the boundary conditions are handled (here there are periodic).

```
#include <apop.h>
#include <time.h>
#include <pthread.h>
#include <stdio.h>
#define NUM_THREADS 4
pthread_t callThd[NUM_THREADS];
pthread_mutex_t mutexsum;

struct thread_data{
    gsl_matrix * hr;
    int Size;
    int Nb;
    double beta;
    gsl_rng * r;
};

struct thread_data thread_data_array[NUM_THREADS];

double modul(int x,int nn){
    int res=x;
    if(x>nn-1)
        res-=nn;
    if(x<0)
```

```

    res+=nn;
    return res;
}

```

The following function performs Nb locale, pseudo-random updates of the system. The spins are chosen pseudo-randomly and updated according to the probabilities of each spin to flip. This probability depend on the the state of its neighbours.

```

static void* ising(void *threadarg){
    struct thread_data *my_data;
    my_data = (struct thread_data *) threadarg;
    gsl_matrix * hr=my_data->hr;
    int Size=my_data->Size;
    int Nb=my_data->Nb;
    double beta=my_data->beta;
    gsl_rng * r=my_data->r;
    int x=1;
    int y=1;
    double neighb=0;
    double ham1=0;
    double ham2=0;
    double ran=0;
    double proba=0;
    double temp=0;
    double tmod=1;
    for (int i =0; i< Nb; i++){
        ran=gsl_rng_uniform(r);
        temp=ran*Size;
        x=floor(temp);
        ran=temp-x;
        temp=ran*Size;
        y=floor(temp);
        ran=temp-y;
        tmod=1/(1+ (Nb-i)/Nb*(-0.5-0.05+floor(ran*2)));
        ran=10*ran- floor(ran*10);
        neighb=gsl_matrix_get(hr,modul(x+1,Size),y)+gsl_matrix_get(hr,
            modul(x-1,Size),y)+gsl_matrix_get(hr,x,modul(y+1,Size))
            +gsl_matrix_get(hr,x,modul(y-1,Size));
        ham1=exp(beta*1*neighb*tmod);
        ham2=exp(beta*-1*neighb*tmod);
        proba=ham1/(ham1+ham2);
        if((ham1==INFINITY)|| (proba>ran))
            gsl_matrix_set(hr, x, y, 1);
        else {

```

```
    gsl_matrix_set(hr, x, y, -1);
  }
}
pthread_exit((void*) 0);
}
```

The function bellow handles the different threads that are launched in parallel to simulate the system. The idea is then to have different threads which update the spin lattice in parallel. Since we are using concurrency, we have a an algorithm that is not deterministic, since the pace of each thread, with respect to the others, is not determined.

```
static void Ising(gsl_matrix * hr,int Size,int Nb,
                 double beta,gsl_rng * ar[]){
    pthread_t callThd[NUM_THREADS];
    void *status;
    pthread_attr_t attr;
    pthread_mutex_init(&mutexsum, NULL);
    pthread_attr_init(&attr);
    pthread_attr_setdetachstate(&attr, PTHREAD_CREATE_JOINABLE);

    for(int t=0; t<NUM_THREADS; t++){
        thread_data_array[t].hr=hr;
        thread_data_array[t].Size=Size;
        thread_data_array[t].Nb=Nb;
        thread_data_array[t].beta=beta;
        thread_data_array[t].r= ar[t];
        pthread_create(&callThd[t], &attr, ising, (void *)
                    &thread_data_array[t]);
    }
    pthread_attr_destroy(&attr);
    pthread_mutex_destroy(&mutexsum);
    for(int t=0; t<NUM_THREADS; t++) {
        pthread_join(callThd[t], &status);
    }
}
```

The main function is given bellow, which defines in particular the key parameters of the system: the size of the lattice, the number of iterations per thread and the temperature.

```
int main(){
    gsl_rng * ar[] ={ apop_rng_alloc(0),apop_rng_alloc(1),
                    apop_rng_alloc(2),apop_rng_alloc(3)};
    int Size=500;
    int Nb=2000000000;
    double beta=(1/2.2693)*0.943;
```

```
gsl_matrix *hr = gsl_matrix_alloc(Size,Size);
gsl_matrix_set_all(hr, 0);
Ising( hr, Size, Nb, beta, ar);
apop_matrix_show(hr);
gsl_matrix_free(hr);
pthread_exit(NULL);
}
```


Bibliography

- Agutter, P.S., & D.N. Wheatley. 2004. Metabolic scaling: consensus or controversy? *Theoretical Biology and Medical Modelling* 1:13. doi:10.1186/1742-4682-1-13.
- Almaas, E., A. Vázquez & A.-L. Barabási. 2007. Scale-free networks in biology. In *Biological networks*, ed. F. Képès. World Scientific Pub Co Inc.
- Als-Nielsen, J., & R. J. Birgeneau. 1977. Mean field theory, the ginzburg criterion, and marginal dimensionality of phase transitions. *American Journal of Physics* 45 (6): 554–560. ISSN: 00029505, doi:10.1119/1.11019.
- Altland, A., & B. Simons. 2006. *Condensed matter field theory*. Cambridge U. P.
- Amzallag, G. Nissim. 2002. *La raison malmenée. de l'origine des idées reçues en biologie moderne*. CNRS édition.
- Aoki, I. 1994. Entropy production in human life span: a thermodynamical measure for aging. *AGE* 17 (1): 29–31. ISSN: 0161-9152, doi:10.1007/BF02435047.
- Aon, M.A., S. Cortassa, E. Marbán & B. O'Rourke. 2003. Synchronized whole cell oscillations in mitochondrial metabolism triggered by a local release of reactive oxygen species in cardiac myocytes. *Journal of Biological Chemistry* 278 (45): 44735–44744. doi:10.1074/jbc.M302673200.
- Aon, M.A., S. Cortassa & B. O'Rourke. 2004. Percolation and criticality in a mitochondrial network. *Proceedings of the National Academy of Sciences* 101 (13): 4447. doi:10.1073/pnas.0307156101.
- Aon, M.A., B. O'Rourke & S. Cortassa. 2004. The fractal architecture of cytoplasmic organization: scaling, kinetics and emergence in metabolic networks. *Molecular and Cellular Biochemistry* 256 (1): 169–184. doi:10.1023/B:MCBI.0000009867.54552.09.
- Aon, M.A., M.R. Roussel, S. Cortassa, B. O'Rourke, D.B. Murray, M. Beckmann & D. Lloyd. 2008. The scale-free dynamics of eukaryotic cells. *PloS one* 3 (11): 3624. ISSN: 1932-6203, doi:10.1371/journal.pone.0003624.
- Aoyagi, N., K. Ohashi, S. Tomono & Y. Yamamoto. 2000. Temporal contribution of body movement to very long-term heart rate variability in humans. *Am J Physiol Heart Circ Physiol* 278 (4): H1035–H1041.

- Aspect, A., P. Grangier & G. Roger. 1982. Experimental realization of Einstein-Podolsky-Rosen-Bohm Gedankenexperiment: a new violation of Bell's inequalities. *Physical Review Letters* 49 (2): 91–94. doi:10.1103/PhysRevLett.49.91.
- Avnir, D., O. Biham, D. Lidar & O. Malcai. 1998. Is the geometry of nature fractal? *Science* 279 (5347): 39–40. doi:10.1126/science.279.5347.39.
- Baars, B.J. 1988. *A cognitive theory of consciousness*. Cambridge U.P.
- Bailly, F. 1991a. L'anneau des disciplines. *Revue Internationale de Systémique* 5 (3).
- . 1991b. Niveaux d'organisation, changements de niveaux, finalité. *Philosophica* 47:31–47. ISSN: 0379-8402.
- Bailly, F., F. Gaill & R. Mosseri. 1988. Fonctions biologiques, niveaux d'organisation et dimensions fractales. *Revue Internationale de Systémique* 2.
- . 1993. Orgons and biolons in theoretical biology: phenomenological analysis and quantum analogies. *Acta Biotheoretica* 41 (1–2): 3–11. doi:10.1007/BF00712769.
- Bailly, F., & G. Longo. 2003. Objective and epistemic complexity in biology. In *Invited lecture, international conference on theoretical neurobiology, new delhi*.
- . 2006. *Mathématiques & sciences de la nature: la singularité physique du vivant*. Hermann.
- . 2007. Randomness and determinism in the interplay between the continuum and the discrete. *Mathematical Structures in Computer Science* 17 (02): 289–305. doi:10.1017/S0960129507006007.
- . 2008. Extended critical situations: the physical singularity of life phenomena. *Journal of Biological Systems* 16 (2): 309. doi:10.1142/S0218339008002514.
- . 2009. Biological organization and anti-entropy. *Journal of Biological Systems* 17 (1): 63–96. doi:10.1142/S0218339009002715.
- . 2011. *Mathematics and the natural sciences; the physical singularity of life*. Preliminary version in French: Hermann, Vision des sciences. London: Imperial College Press.
- Bailly, F., G. Longo & M. Montévil. 2011. A 2-dimensional geometry for biological time. *Progress in Biophysics and Molecular Biology* 106 (3): 474–484. ISSN: 0079-6107, doi:10.1016/j.pbiomolbio.2011.02.001.
- Baish, J. W., & R. K. Jain. 2000. Fractals and cancer. *Cancer Res.* 60 (14): 3683–3688.
- Bak, P., C. Tang & K. Wiesenfeld. 1988. Self-organized criticality. *Physical review A* 38 (1): 364–374. doi:10.1103/PhysRevA.38.364.
- Balakrishnan, J., & B. Ashok. 2010. The role of hopf bifurcation dynamics in sensory processes. *Journal of Theoretical Biology*. ISSN: 0022-5193, doi:10.1016/j.jtbi.2010.04.006.

- Balleza, E., E. R. Alvarez-Buylla, A. Chaos, S.A. Kauffman, I. Shmulevich & M. Aldana. 2008. Critical dynamics in genetic regulatory networks: examples from four kingdoms. *PLoS ONE* 3, no. 6 (June): e2456. doi:10.1371/journal.pone.0002456.
- Bancaud, A., S. Huet, N. Daigle, J. Mozziconacci, J. Beaudouin & J. Ellenberg. 2009. Molecular crowding affects diffusion and binding of nuclear proteins in heterochromatin and reveals the fractal organization of chromatin. *The EMBO Journal*. doi:10.1038/emboj.2009.340.
- Bassingthwaighte, J.B., L.S. Liebovitch & B.J. West. 1994. *Fractal physiology*. New York: American Physiological Society.
- Batterman, R. W. 2005. Critical phenomena and breaking drops: infinite idealizations in physics. *Studies In History and Philosophy of Science Part B: Studies In History and Philosophy of Modern Physics* 36, no. 2 (June): 225–244. ISSN: 1355-2198, doi:16/j.shpsb.2004.05.004.
- . 2007. *Interttheory relations in physics*. <http://plato.stanford.edu/entries/physics-interrelate/>. First published in 2001.
- Baus, M. 1987. Statistical mechanical theories of freezing: an overview. *Journal of Statistical Physics* 48 (5): 1129–1146. ISSN: 0022-4715, doi:10.1007/BF01009537.
- Belitz, D., T. R. Kirkpatrick & T. Vojta. 2005. How generic scale invariance influences quantum and classical phase transitions. *Rev. Mod. Phys.* 77, no. 2 (July): 579–632. doi:10.1103/RevModPhys.77.579.
- Bell, J. 1998. *A primer in infinitesimal analysis*. Cambridge U.P.
- Berry, H., & H. Chaté. 2011. Anomalous subdiffusion due to obstacles : a critical survey. *arXiv:1103.2206v1:1–33*.
- Berthoz, A. 2002. *The brain's sense of movement*. Harvard U.P.
- Binney, J., N.J. Dowrick, A.J. Fisher & M.E.J. Newman. 1992. *The theory of critical phenomena: an introduction to the renormalization group*. Oxford U. P.
- Bishop, C.M. 1999. The maximum oxygen consumption and aerobic scope of birds and mammals: getting to the heart of the matter. *Proceedings of the Royal Society - Biological Sciences* 266 (1435): 2275–2281. doi:10.1098/rspb.1999.0919.
- Bokma, F. 2004. Evidence against universal metabolic allometry. *Functional Ecology* 18 (2): 184–187. ISSN: 1365-2435, doi:10.1111/j.0269-8463.2004.00817.x.
- Bonnarens, F., & T.A. Einhorn. 1984. Production of a standard closed fracture in laboratory animal bone. *Journal of Orthopaedic Research* 2:97–101. doi:10.1002/jor.1100020115.
- Boser, S.R., H. Park, S.F. Perry, M.G. Menache & F.H.Y. Green. 2005. Fractal geometry of airway remodeling in human asthma. *Am. J. Respir. Crit. Care Med.* 172 (7): 817–823. doi:10.1164/rccm.200411-14630C.

- Botzung, A., E. Denkova & L. Manning. 2008. Experiencing past and future personal events: functional neuroimaging evidence on the neural bases of mental time travel. *Brain and Cognition* 66 (2): 202–212. doi:10.1016/j.bandc.2007.07.011.
- Bourgine, P., & J. Stewart. 2004. Autopoiesis and cognition. *Artificial Life* 10:327. doi:10.1162/1064546041255557.
- Boxenbaum, H, & C DiLea. 1995. First-time-in-human dose selection: allometric thoughts and perspectives. *The Journal of Clinical Pharmacology* 35 (10): 957–966.
- Brigandt, I., & A. Love. 2008. *Reductionism in biology*. <http://plato.stanford.edu/entries/reduction-biology/>.
- Bros, J., & D. Iagolnitzer. 1973. Causality and local mathematical analyticity : study. *Ann. Inst. Henri Poincaré*. 18 (2).
- Brouzés, E., & E. Farge. 2004. Interplay of mechanical deformation and patterned gene expression in developing embryos. *Current Opinion in Genetics & Development* 14 (4): 367–374. ISSN: 0959-437X, doi:10.1016/j.gde.2004.06.005.
- Buiatti, M., & M. Buiatti. 2008. Chance vs. necessity in living systems: a false antinomy. In *Rivista di biologia biology forum*, 29. Vol. 101. 1. Anicia SRL.
- Buiatti, M., & G. Longo. 2011. Randomness and multi-level interactions in biology. *Arxiv preprint arXiv:1104.1110*.
- Bunde, A., S. Havlin, J.W. Kantelhardt, T. Penzel, J.H. Peter & K. Voigt. 2000. Correlated and uncorrelated regions in heart-rate fluctuations during sleep. *Physical review letters* 85 (17): 3736–3739. doi:10.1103/PhysRevLett.85.3736.
- Byers, N. 1999. E. Noether's discovery of the deep connection between symmetries and conservation laws. In *The heritage of Emmy Noether in algebra, geometry, and physics*, 67–81. Vol. 12. Tel Aviv: Israel mathematical conference.
- Cai, L., N. Friedman & X.S. Xie. 2006. Stochastic protein expression in individual cells at the single molecule level. *Nature* 440 (7082): 358–362. doi:10.1038/nature04599.
- Camalet, S., T. Duke, F. Julicher & J. Prost. 1999. Auditory sensitivity provided by self-tuned critical oscillations of hair cells. *Proteins: Structure, Function, and Bioinformatics* 28 (7): 1999. doi:10.1073/pnas.97.7.3183.
- Canals, M., R. Olivares, F. Labra & F.F. Novoa. 2000. Ontogenetic changes in the fractal geometry of the bronchial tree in *Rattus norvegicus* [in en]. *Biological Research* 33:31–35. ISSN: 0716-9760, doi:10.4067/S0716-9760200000100010.
- Canguilhem, G. 1972. *Le normal et le pathologique*. Presses universitaires de France.
- Carter, J.B., E.W. Banister & A.P. Blaber. 2003. Effect of endurance exercise on autonomic control of heart rate. *Sports medicine* 33 (1): 33–46.

- Cat, J. 2007. *The unity of science*. <http://plato.stanford.edu/entries/scientific-unity/#UniRedLogEmp>.
- Cavagna, A., A. Cimarelli, I. Giardina, G. Parisi, R. Santagati, F. Stefanini & M. Viale. 2010. Scale-free correlations in starling flocks. *Proceedings of the National Academy of Sciences* 107 (26): 11865–11870. doi:10.1073/pnas.1005766107.
- Chaline, J. 1999. *Les horloges du vivant: un nouveau stade de la théorie de l'évolution?* Hachette Littératures.
- Chandler, J.L.R., & G. van de Vijver. 2000. *Closure: emergent organizations and their dynamics*. New York Academy of Sciences.
- Cranford, J.A. 1983. Body temperature, heart rate and oxygen consumption of normothermic and heterothermic western jumping mice (*Zapus princeps*). *Comparative Biochemistry and Physiology - A* 74 (3): 595. doi:10.1016/0300-9629(83)90553-4.
- d'Alessio, P. 2004. Aging and the endothelium. *Experimental Gerontology* 39 (2): 165–171. ISSN: 0531-5565, doi:10.1016/j.exger.2003.10.025.
- Danchin, É., A. Charmantier, F.A. Champagne, A. Mesoudi, B. Pujol & S. Blanchet. 2011. Beyond dna: integrating inclusive inheritance into an extended theory of evolution. *Nature Reviews Genetics* 12 (7): 475–486. doi:10.1038/nrg3028.
- Dehaene, S., & J.-P. Changeux. 2005. Ongoing spontaneous activity controls access to consciousness: a neuronal model for inattentional blindness. *PLoS Biol* 3, no. 5 (Apr.): e141. doi:10.1371/journal.pbio.0030141.
- Dehaene, S., & N. Naccache. 2001. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. *Cognition* 79 (1-2): 1–37. ISSN: 0010-0277, doi:10.1016/S0010-0277(00)00123-2.
- Delamotte, B. 2004. A hint of renormalization. *American Journal of Physics* 72:170. doi:10.1119/1.1624112.
- Delides, A., I. Panayiotides, A. Alegakis, A. Kyroudi, C. Banis, A. Pavlaki, E. Helidonis & C. Kittas. 2005. Fractal dimension as a prognostic factor for laryngeal carcinoma. *Anticancer Res* 25 (3B): 2141.
- Demetrius, L. 2004. Caloric restriction, metabolic rate, and entropy. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 59 (9): B902–B915. doi:10.1093/gerona/59.9.B902.
- Descartes, R. 1724. *Les méditations métaphysiques*. chez Robert-Marc d'Espilly.
- De Vico, G., V. Peretti & G.A. Losa. 2009. Fractal organization of feline oocyte cytoplasm. *European Journal of Histochemistry* 49 (2): 151. ISSN: 2038-8306, doi:10.4081/939.
- Dhimolea, E., M.V. Maffini, A.M. Soto & C. Sonnenschein. 2010. The role of collagen reorganization on mammary epithelial morphogenesis in a 3d culture model. *Biomaterials* 31:3622–3630. doi:10.1016/j.biomaterials.2010.01.077.

- Dmi'el, R. 1970. Growth and metabolism in snake embryos. *Journal of Embryology and Experimental Morphology* 23 (3): 761–772.
- Donald, E. I. 2003. Tensegrity i. cell structure and hierarchical systems biology. *Journal of Cell Science* 1007:1157–1173. doi:10.1242/jcs.00359.
- Douady, S., A. Manning & B. Hennion. 2009. In the beginning there was shape. In *Origins of life: self-organization and/or biological evolution?* EDP Sciences. doi:10.1051/orvie/2009005.
- Duffin, R.J., & C. Zener. 1969. Geometric programming, chemical equilibrium, and the anti-entropy function. *Proceedings of the National Academy of Sciences* 63 (3): 629.
- Edelman, G.M., & G. Tononi. 2000. Reentry and the dynamic core: neural correlates of conscious experience. In *Neural correlates of consciousness: empirical and conceptual questions*, ed. T. Metzinger, 139–151. MIT Press.
- . 2001. *A universe of consciousness: how matter becomes imagination*. Basic Books.
- Edgar, G.A. 1993. *Classics on fractals*. Basic Books.
- Einstein, A., B. Podolsky & N. Rosen. 1935. Can quantum-mechanical description of physical reality be considered complete? *Physical Review* 47 (10): 777–780. doi:10.1103/PhysRev.47.777.
- Eke, A., P. Herman, L. Kocsis & L. R. Kozak. 2002. Fractal characterization of complexity in temporal physiological signals. *Physiological Measurement* 23 (1): R1. doi:10.1088/0967-3334/23/1/201.
- Esen, F., F.Y. Özbeıt & H. Esen. 2001. Fractal scaling of heart rate variability in young habitual smokers. *Turkish Journal of Medical Sciences* 4:317–322.
- Fabrizio, P., S. D. Pletcher, N. Minois, J.W. Vaupel & V.D. Longo. 2004. Chronological aging-independent replicative life span regulation by *msn2/msn4* and *sod2* in *saccharomyces cerevisiae*. *FEBS Letters* 557 (1–3): 136–142. doi:10.1016/S0014-5793(03)01462-5.
- Falconer, K.J., & J. Wiley. 2003. *Fractal geometry: mathematical foundations and applications*. New York: Wiley. ISBN: 0470848626.
- Feyerabend, P. K. 1985. *Problems of empiricism*. New York: Cambridge University Press, June. ISBN: 9780521316415.
- Feynman, R.P., & J. Gleick. 1967. *The character of physical law*. MIT press.
- Field, D.J. 1987. Relations between the statistics of natural images and the response properties of cortical cells. *Journal of the Optical Society of America A* 4 (12): 2379–2394. doi:10.1364/JOSAA.4.002379.

- Field, D.J., A. Hayes & R.F. Hess. 1993. Contour integration by the human visual system: evidence for a local association field. *Vision Research* 33 (2): 173–193. doi:10.1016/0042-6989(93)90156-Q.
- Fisher, M.E. 1998. Renormalization group theory: its basis and formulation in statistical physics. *Reviews of Modern Physics* 70 (2): 653–681. ISSN: 1539-0756.
- Fox Keller, E. 2002. *The century of the gene*. Harvard University Press.
- . 2005. Revisiting “scale-free” networks. *BioEssays* 27 (10): 1060–1068. doi:10.1002/bies.20294.
- Gabrys, E., M. Rybaczuk & A. Kedzia. 2005. Fractal models of circulatory system. symmetrical and asymmetrical approach comparison. *Chaos, Solitons & Fractals* 24 (3): 707–715. ISSN: 0960-0779, doi:10.1016/j.chaos.2004.09.087.
- Galileo, G. 1638. *Discorsi e dimostrazioni matematiche, intorno à due nuove scienze*. Elsevier.
- Ganti, T. 2003. *Chemoton theory*. Kluwer Academic/Plenum.
- Gerkema, M.P. 2002. Ultradian Rhythms. In *Biological rhythms*, ed. V. Kumar, 207. Springer. ISBN: 3540428534.
- Gheorghiu, S., S. Kjelstrup, P. Pfeifer & M.-O. Coppens. 2005. Is the lung an optimal gas exchanger? In *Fractals in biology and medicine*, ed. Gabriele A. Losa, Danilo Merlini, Theo F. Nonnenmacher & Ewald R. Weibel, 31–42. Mathematics and Biosciences in Interaction. Birkhäuser Basel. ISBN: 978-3-7643-7412-9, doi:10.1007/3-7643-7412-8_3.
- Giguere, L.A., B. Cote & J.F. St-Pierre. 1988. Metabolic rates scale isometrically in larval fishes. *Marine ecology progress series. Oldendorf* 50 (1): 13–19.
- Gillooly, J.F., A.P. Allen, V.M. Savage, E.L. Charnov, G.B. West & J.H. Brown. 2006. Response to Clarke and Fraser: effects of temperature on metabolic rate. *Ecology* 20 (2): 400–404. doi:10.1111/j.1365-2435.2006.01110.x.
- Gillooly, J.F., A.P. Allen, G.B. West & J.H. Brown. 2005. The rate of DNA evolution: effects of body size and temperature on the molecular clock. *Proceedings of the National Academy of Sciences* 102 (1): 140–145. doi:10.1073/pnas.0407735101.
- Gillooly, J.F., J.H. Brown, G.B. West, V.M. Savage & E.L. Charnov. 2001. Effects of size and temperature on metabolic rate. *Science* 293 (5538): 2248–2251. doi:10.1126/science.1061967.
- Glazier, D.S. 2005. Beyond the : variation in the intra- and interspecific scaling of metabolic rate in animals. *Biological Reviews* 80 (04): 611–662. doi:10.1017/S1464793105006834.
- . 2006. The 3/4-power law is not universal: evolution of isometric, ontogenetic metabolic scaling in pelagic animals. *Bioscience* 56 (4): 325–332. doi:10.1641/0006-3568(2006)56[325:TPLINU]2.0.CO;2.

- . 2009. Activity affects intraspecific body-size scaling of metabolic rate in ectothermic animals. *Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology* 179 (7): 821–828. doi:10.1007/s00360-009-0363-3.
- Glenny, R., S. Bernard, B. Neradilek & N. Polissar. 2007. Quantifying the genetic influence on mammalian vascular tree structure. *Proceedings of the National Academy of Sciences* 104 (16): 6858–6863. doi:10.1073/pnas.0610954104.
- Goldberger, A.L., L.A.N. Amaral, L. Glass, J.M. Hausdorff, P.C. Ivanov, R.G. Mark, J.E. Mietus, G.B. Moody, C.-K. Peng & H.E. Stanley. 2000. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* 101, no. 23 (June): e215–e220. doi:10.1161/01.CIR.101.23.e215.
- Goldberger, A.L., L.A.N. Amaral, J.M. Hausdorff, P.C. Ivanov, C.-K. Peng & H.E. Stanley. 2002. Fractal dynamics in physiology: alterations with disease and aging. *Proceedings of the National Academy of Sciences* 99 (Suppl 1): 2466. doi:10.1073/pnas.012579499.
- Goldberger, A.L., C.-K. Peng & L.A. Lipsitz. 2002. What is physiologic complexity and how does it change with aging and disease? *Neurobiology of aging* 23 (1): 23–26. doi:10.1016/S0197-4580(01)00266-4.
- Golding, I., & E.C. Cox. 2006. Physical nature of bacterial cytoplasm. *Physical Review Letters* 96 (9): 98102. doi:10.1103/PhysRevLett.96.098102.
- Goodman, R., & N.R. Wallach. 2009. *Symmetry, representations, and invariants*. Springer Verlag.
- Gould, S.J. 1989. *Wonderful life*. Norton.
- . 1997. *Full house: the spread of excellence from plato to darwin*. Three Rivers Pr.
- Günther, B., & E. Morgado. 2005. Allometric scaling of biological rhythms in mammals. *Biological Research* 38:207–212. doi:10.4067/S0716-97602005000200010.
- Hardy, J. D. 1934. The radiation of heat from the human body iii. *Journal of Clinical Investigation* 13 (4): 615–620. doi:10.1172/JCI100609..
- Hayflick, L. 2007. Entropy explains aging, genetic determinism explains longevity, and undefined terminology explains misunderstanding both. *PLoS Genet* 3, no. 12 (Dec.): e220. doi:10.1371/journal.pgen.0030220.
- Hellbrugge, T., J.E. Lange, J. Rutenfranz & K. Stehr. 1964. Circadian periodicity of physiological functions in different stages of infancy and childhood. *Annals of the New York Academy of Sciences* 117 (1 Photo-Neuro-Endocrine Effects in Ciradian Systems, with Particular Reference to the Eye): 361–373. doi:10.1111/j.1749-6632.1964.tb48193.x.
- Hempleman, S. C., D. L. Kilgore, C. Colby, R. W. Bavis & F. L. Powell. 2005. Spike firing allometry in avian intrapulmonary chemoreceptors: matching neural code to body size. *Journal of Experimental Biology* 208 (16): 3065–3073. doi:10.1242/jeb.01752.

- Herrlich, H. 2006. *Axiom of choice*. Vol. 1876. Springer Verlag. doi:10.1007/11601562.
- Hinz, B. 2006. Masters and servants of the force: the role of matrix adhesions in myofibroblast force perception and transmission. *European Journal of Cell Biology* 85 (3-4): 175–181. ISSN: 0171-9335, doi:10.1016/j.ejcb.2005.09.004.
- Hirsch, J., R. L. Leibel, R. Mackintosh & A. Aguirre. 1991. Heart rate variability as a measure of autonomic function during weight change in humans. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 261 (6): R1418–R1423.
- Holstein, B. 2000. A brief introduction to chiral perturbation theory. *Czechoslovak Journal of Physics* 50:9–23. ISSN: 0011-4626, doi:10.1007/s10582-000-0041-x.
- Horsfield, K. 1977. Morphology of branching trees related to entropy. *Respiration Physiology* 29 (2): 179. doi:10.1016/0034-5687(77)90090-1.
- Hubbell, S.P. 2001. *The unified neutral theory of biodiversity and biogeography*. Monographs in population biology. Princeton, New Jersey. Princeton University Press.
- Ivanov, P.C., L.A.N. Amaral, A.L. Goldberger, S. Havlin, M.G. Rosenblum, H.E. Stanley & Z.R. Struzik. 2001. From 1/f noise to multifractal cascades in heartbeat dynamics. *chaos* 11 (3): 641–652. ISSN: 10541500, doi:10.1063/1.1395631.
- Iyengar, N., C.-K. Peng, R. Morin, A.L. Goldberger & L.A. Lipsitz. 1996. Age-related alterations in the fractal scaling of cardiac interbeat interval dynamics. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 271 (4): 1078.
- Jensen, H.J. 1998. *Self-organized criticality, emergent complex behavior in physical and biological systems*. Cambridge lectures in Physics.
- Jeong, H., B. Tombor, R. Albert, Z.N. Oltvai & A.L. Barabási. 2000. The large-scale organization of metabolic networks. *Nature* 407 (6804): 651–654. doi:10.1038/35036627.
- Jones, C.G., J.H. Lawton & M. Shachak. 1994. Organisms as ecosystem engineers. *Oikos* 69, no. 3 (Apr.): 373–386. ISSN: 0030-1299.
- Kant, I. 1781. *Critique of pure reason*. transl. N. Kemp Smith, Palgrave Macmillan, this edition published 1929.
- . 1790. *Critique of judgment*. Hackett Publishing. ISBN: 0872200256.
- Karsenti, E. 2008. Self-organization in cell biology: a brief history. *Nature Reviews Molecular Cell Biology* 9 (3): 255–262. doi:10.1038/nrm2357.
- Kauffman, S.A. 1993. *The origins of order*. Oxford U. P.
- . 2001. Prolegomenon to a general biology. *Annals of the New York Academy of Sciences* 935:18–36. doi:10.1111/j.1749-6632.2001.tb03466.x.
- . 2002. *Investigations*. Oxford University Press, USA.
- Kay, I. 1998. *Introduction to animal physiology*. BIOS Scientific. ISBN: 1859960464.

- Khanin, R., & E. Wit. 2006. How scale-free are biological networks. *Journal of Computational Biology* 13 (3): 810–818. doi:10.1089/cmb.2006.13.810.
- Kim, S.-h., P. Kaminker & J. Campisi. 2002. Telomeres, aging and cancer: in search of a happy ending. *oncogene* 21:503–511. doi:10.1038/sj/onc/1205077.
- Kirkwood, T.B.L. 2008. Gerontology: healthy old age. *Nature* 455 (7214): 739–740. doi:10.1038/455739a.
- Kirman, C. R., L. M. Sweeney, M. E. Meek & M. L. Gargas. 2003. Assessing the dose-dependency of allometric scaling performance using physiologically based pharmacokinetic modeling. *Regulatory Toxicology and Pharmacology* 38 (3): 345–367. ISSN: 0273-2300, doi:10.1016/j.yrtph.2003.07.004.
- Kiyono, K., Z.R. Struzik, N. Aoyagi, S. Sakata, J. Hayano & Y. Yamamoto. 2004. Critical scale invariance in a healthy human heart rate. *Physical Review Letters* 93 (17): 178103. doi:10.1103/PhysRevLett.93.178103.
- Kleiber, M. 1932. Body size and animal metabolism. *Hilgardia* 6:315–353.
- . 1961. *The fire of life. An introduction to animal energetics*. New York: John Wiley & Sons, Inc.
- Kochen, S., & E.P. Specker. 1967. The problem of hidden variables in quantum mechanics. *Journal of Mathematics and Mechanics* 17:59–87. doi:10.1103/RevModPhys.38.447.
- Kopelman, P.G. 2000. Obesity as a medical problem. *Nature* 404 (6778): 635–643. doi:10.1038/35007508.
- Labra, F.A., P.A. Marquet & F. Bozinovic. 2007. Scaling metabolic rate fluctuations. *Proc. Natl. Acad. Sci. USA* 104 (26): 10900–10903. doi:10.1073/pnas.0704108104.
- Lambert, F.L. 2007. *Entropy and the second law of thermodynamics*. Downloadable from: <http://www.entropysite.com>.
- Lazebnik, Y. 2002. Can a biologist fix a radio? or, what i learned while studying apoptosis. *Cancer Cell* 2 (3): 179–182. doi:10.1007/s10541-005-0088-1.
- Lecointre, G., H. Le Guyader & D. Visset. 2001. *Classification phylogénétique du vivant*. Belin.
- Le Méhauté, A., R. Nigmatullin & L. Nivanen. 1998. *Flèches du temps et géométrie fractales*. Hermès.
- Lesne, A. 2003. Approches multi-échelles en physique et en biologie. Thèse d’habilitation à diriger des recherches. Université Pierre et Marie Curie.
- . 2006. Complex networks: from graph theory to biology. *Letters in Mathematical Physics* 78 (3): 235–262. ISSN: 1573-0530, doi:10.1007/s11005-006-0123-1.
- . 2008. Robustness: confronting lessons from physics and biology. *Biol Rev Camb Philos Soc* 83 (4): 509–532. doi:10.1111/j.1469-185X.2008.00052.x.

- Lesne, A., & J.-M. Victor. 2006. Chromatin fiber functional organization: some plausible models. *Eur Phys J E Soft Matter* 19 (3): 279–290. doi:10.1140/epje/i2005-10050-6.
- Le Van Quyen, M. 2003. Disentangling the dynamic core: a research program for a neurodynamics at the large-scale. *Biological Research* 36:67–88. doi:10.4067/S0716-97602003000100006.
- Lewis, M., & D.C. Rees. 1985. Fractal surfaces of proteins. *Science* 230 (4730): 1163–1165. doi:10.1126/science.4071040.
- Lindner, A.B., R. Madden, A. Demarez, E.J. Stewart & F. Taddei. 2008. Asymmetric segregation of protein aggregates is associated with cellular aging and rejuvenation. *Proceedings of the National Academy of Sciences* 105 (8): 3076–3081. doi:10.1073/pnas.0708931105.
- Lindstedt, S.L., & W.A. Calder III. 1981. Body size, physiological time, and longevity of homeothermic animals. *Quarterly Review of Biology*:1–16. doi:10.1086/412080.
- Longo, G. 2009. Critique of computational reason in the natural sciences. In *Fundamental concepts in computer science*, ed. E. Gelenbe & J.-P. Kahane. Imperial College Press/World Scientific.
- . 2011. Interfaces de l'incomplétude. In *Les mathématiques*. Editions du CNRS.
- Longo, G., P.-A. Miquel, C. Sonnenschein & A.M. Soto. 2012. From information to organization in biology. *to appear*.
- Longo, G., & M. Montévil. 2011a. From physics to biology by extending criticality and symmetry breakings. *Systems Biology and Cancer, Progress in Biophysics and Molecular Biology* 106 (2): 340–347. ISSN: 0079-6107, doi:10.1016/j.pbiomolbio.2011.03.005.
- . 2011b. Protention and retention in biological systems. *Theory in Biosciences* 130 (2): 107–117. ISSN: 1431-7613, doi:10.1007/s12064-010-0116-6.
- . 2012. Randomness increases order in biological evolution. In *LNCS, proceedings of the colloquium in honor of Christian Calude, Auckland*. Submitted. Springer-Verlag.
- Longo, G., & P.-E. Tendero. 2007. The differential method and the causal incompleteness of programming theory in molecular biology. 10.1007/S10699-007-9111-x, *Foundations of Science* 12:337–366. ISSN: 1233-1821.
- Looijen, R. C. 2000. *Holism and reductionism in biology and ecology: the mutual dependence of higher and lower level research programmes*. Kluwer Academic Publishers.
- Lopes, R., & N. Betrouni. 2009. Fractal and multifractal analysis: a review. *Medical Image Analysis* 13 (4): 634–649. ISSN: 1361-8415, doi:10.1016/j.media.2009.05.003.
- Lorthois, S., & F. Cassot. 2010. Fractal analysis of vascular networks: insights from morphogenesis. *Journal of Theoretical Biology* 262 (4): 614–633. ISSN: 0022-5193, doi:10.1016/j.jtbi.2009.10.037.

- Losa, G.A. 2006. Do complex cell structures share a fractal-like organization? *Microscopic* 5:53–56.
- Losa, G.A., G. Baumann & T.F. Nonnenmacher. 1992. Fractal dimension of pericellular membranes in human lymphocytes and lymphoblastic leukemia cells. *Pathology, research and practice* 188 (4-5): 680.
- Luo, L., & D.M. O’Leary. 2005. Axon retraction and degeneration in development and disease. *Annual Review of Neuroscience* 28:127–156. doi:10.1146/annurev.neuro.28.061604.135632.
- Machta, B. B., S. Papanikolaou, J. P. Sethna & S. L. Veatch. 2011. A minimal model of plasma membrane heterogeneity requires coupling cortical actin to criticality. *Biophysical journal* 100 (7): 1668–1677. doi:10.1016/j.bpj.2011.02.029.
- Maina, J.N., & P. van Gils. 2001. Morphometric characterization of the airway and vascular systems of the lung of the domestic pig, *Sus scrofa*: comparison of the airway, arterial and venous systems. *Comparative Biochemistry and Physiology - A* 130 (4): 781–798. doi:10.1016/S1095-6433(01)00411-1.
- Makowiec, D., R. Galańska, A. Dudkowska, A. Rynkiewicz & M. Zwierz. 2006. Long-range dependencies in heart rate signals—revisited. *Physica A: Statistical Mechanics and its Applications* 369 (2): 632–644. ISSN: 0378-4371, doi:10.1016/j.physa.2006.02.038.
- Mandelbrot, B.B. 1983. *The fractal geometry of nature*. W.H. Freeman.
- Marbà, N., C.M. Duarte & S. Agustí. 2007. Allometric scaling of plant life history. *Proceedings of the National Academy of Sciences* 104 (40): 15777–15780. doi:10.1073/pnas.0703476104.
- Marineo, G., & F. Marotta. 2005. Biophysics of aging and therapeutic interventions by entropy-variation systems. *Biogerontology* 6 (1): 77–79. ISSN: 1389-5729, doi:10.1007/s10522-004-7387-6.
- Massin, M.M., K. Maeyns, N. Withofs, F. Ravet & P. Gerard. 2000. Circadian rhythm of heart rate and heart rate variability. *Archives of Disease in Childhood* 83 (2): 179–182. doi:10.1136/adc.83.2.179.
- Masters, B.R. 2004. Fractal analysis of the vascular tree in the human retina. *Biomedical Engineering* 6 (1): 427. doi:10.1146/annurev.bioeng.6.040803.140100.
- Mauroy, B., M. Filoche, E.R. Weibel & B. Sapoval. 2004. An optimal bronchial tree may be dangerous. *Nature* 427:633–636. doi:10.1038/nature02287.
- Maynard-Smith, J., & E. Szathmary. 1997. *The major transitions in evolution*. Oxford U.P.
- McCarthy, M.C., & B.J. Enquist. 2005. Organismal size, metabolism and the evolution of complexity in metazoans. *Evolutionary Ecology Research* 7 (5): 681.
- McShea, D.W., & R.N. Brandon. 2010. *Biology’s first law: the tendency for diversity and complexity to increase in evolutionary systems*. University of Chicago Press.

- Misslin, R. 2003. Une vie de cellule. *Revue de Synthèse* 124 (1): 205–221. doi:10.1007/BF02963405.
- Mitra, V., & J. Metcalf. 2009. Functional anatomy and blood supply of the liver. *Anaesthesia & Intensive Care Medicine* 10 (7): 332–333. ISSN: 1472-0299, doi:10.1016/j.mpaic.2009.03.012.
- Moran, D., & R.M.G. Wells. 2007. Ontogenetic scaling of fish metabolism in the mouse-to-elephant mass magnitude range. *Comparative Biochemistry and Physiology - A* 148 (3): 611–620. doi:10.1016/j.cbpa.2007.08.006.
- Mora, T., & W. Bialek. 2011. Are biological systems poised at criticality? 10.1007/s10955-011-0229-4, *Journal of Statistical Physics* 144 (2): 268–302. ISSN: 0022-4715.
- Mortola, J.P., & C. Lanthier. 2004. Scaling the amplitudes of the circadian pattern of resting oxygen consumption, body temperature and heart rate in mammals. *Comparative Biochemistry and Physiology - A* 139 (1): 83–95. doi:10.1016/j.cbpb.2004.07.007.
- Mugur-Schächter, M. 2002. Objectivity and descriptonal relativities. *Foundations of Science* 7:73–180. ISSN: 1233-1821, doi:10.1023/A:1016095424229.
- Nagel, E. 1961. *The structure of science: problems in the logic of scientific explanation*. Harcourt, Brace & World.
- Nagy, K.A. 2005. Field metabolic rate and body size. *Journal of Experimental Biology* 208 (9): 1621–1625. doi:10.1242/jeb.01553.
- Nelson, T.R., B.J. West & A.L. Goldberger. 1990. The fractal lung: universal and species-related scaling patterns. *Cellular and Molecular Life Sciences* 46:251–254. doi:10.1007/BF01951755.
- Nickles, T. 1973. Two concepts of intertheoretic reduction. *The Journal of Philosophy* 70, no. 7 (Apr.): 181–201. ISSN: 0022-362X, doi:10.2307/2024906.
- Nicolas, F. 2006. Quelle unité pour l'œuvre musicale? In *Les mathématiques, les idées et le réel physique*. Paris: Vrin.
- Nicolis, G., & I Prigogine. 1977. *Self-organization in non-equilibrium systems*. New York: Wiley.
- Nietzsche, F. 1886. *Jenseits von gut und böse*.
- Niklas, K.J., & B.J. Enquist. 2001. Invariant scaling relationships for interspecific plant biomass production rates and body size. *Proceedings of the National Academy of Sciences* 98 (5): 2922–2927. doi:10.1073/pnas.041590298.
- Noble, D. 2002. Modeling the heart—from genes to cells to the whole organ. *Science* 295 (5560): 1678–1682. doi:10.1126/science.1069881.
- . 2006. *The music of life*. Oxford: Oxford U. P.

- . 2008. Claude bernard, the first systems biologist, and the future of physiology. *Experimental Physiology* 93 (1): 16–26. doi:10.1113/expphysiol.2007.038695.
- . 2010. Biophysics and systems biology. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 368 (1914): 1125. doi:10.1098/rsta.2009.0245.
- . 2011. *The music of life: sourcebook*. Oxford.
- Noether, E. 1918. Invariante Variationsprobleme. *Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen* 235–257.
- Nottale, L. 1993. *Fractal space-time and microphysics: towards a theory of scale relativity*. World Scientific.
- Nykter, M., N.D. Price, M. Aldana, S.A. Ramsey, S.A. Kauffman, L.E. Hood, O. Yli-Harja & I. Shmulevich. 2008. Gene expression dynamics in the macrophage exhibit criticality. *Proceedings of the National Academy of Sciences* 105 (6): 1897. doi:10.1073/pnas.0711525105.
- Nykter, M., N.D. Price, A. Larjo, T. Aho, S.A. Kauffman, O. Yli-Harja & I. Shmulevich. 2008. Critical networks exhibit maximal information diversity in structure-dynamics relationships. *Physical Review Letters* 100 (5): 58702. doi:10.1103/PhysRevLett.100.058702.
- Nyström, T. 2007. A bacterial kind of aging. *PLoS Genet* 3 (12): e224. doi:10.1371/journal.pgen.0030224.
- Ochs, M., J.R. Nyengaard, A. Jung, L. Knudsen, M. Voigt, T. Wahlers, J. Richter & H.J.G. Gundersen. 2004. The number of alveoli in the human lung. *Am. J. Respir. Crit. Care Med.* 169 (1): 120–124. doi:10.1164/rccm.200308-11070C.
- Odling-Smee, F. J., K. N. Laland & M. W. Feldman. 2003. *Niche construction: the neglected process in evolution*. Princeton University Press. ISBN: 9780691044378.
- O'Hanlan, K.A. 1994. Resection of a 303.2-pound ovarian tumor. *Gynecologic oncology* 54:365–365.
- Olshansky, S., & S. Rattan. 2005. At the heart of aging: is it metabolic rate or stability? *Biogerontology* 6:291–295. ISSN: 1389-5729, doi:10.1007/s10522-005-2627-y.
- Oppenheim, P., & H. Putnam. 1958. The unity of science as a working hypothesis. In *Concepts, theories, and the mind-body problem*, ed. H. Feigl, M. Scriven & G. Maxwell. Vol. 2. University of Minnesota Press.
- Overduin, J.M., & P.S. Wesson. 1997. Kaluza-Klein gravity. *Physics Reports* 283:303–380. doi:10.1016/S0370-1573(96)00046-4.
- Pattee, H.H. 1972. *The nature of hierarchical controls in living matter*. Vol. 1. Academic Press: New York.

- . 1973. *Hierarchy theory*. Braziller.
- . 1982. Cell psychology: an evolutionary approach to the symbol-matter problem. *Cognition and Brain Theory* 5 (4): 325–341.
- Patterson, F., & E. Linden. 1981. *The education of koko*. Holt, Rinehart, / Winston.
- Paumgartner, D., G.A. Losa & E.R. Weibel. 1981. Resolution effect on the stereological estimation of surface and volume and its interpretation in terms of fractal dimensions. *Journal of microscopy* 121 (Pt 1): 51.
- Peng, C.K., S. Havlin, H.E. Stanley & A.L. Goldberger. 1995. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos: An Interdisciplinary Journal of Nonlinear Science* 5 (1): 82–87. doi:10.1063/1.166141.
- Peng, C.K., J.E. Mietus, Y. Liu, C. Lee, J.M. Hausdorff, H. E. Stanley, A.L. Goldberger & L.A. Lipsitz. 2002. Quantifying fractal dynamics of human respiration: age and gender effects. *Ann Biomed Eng* 30 (5): 683–692. doi:10.1114/1.1481053.
- Peng, C.-K., J. Mietus, J.M. Hausdorff, S. Havlin, H.E. Stanley & A.L. Goldberger. 1993. Long-range anticorrelations and non-gaussian behavior of the heartbeat. *Phys. Rev. Lett.* 70, no. 9 (Mar.): 1343–1346. doi:10.1103/PhysRevLett.70.1343.
- Perazzo, C.A., E.A. Fernandez, D.R. Chialvo & P. Willshaw. 2000. Large scale-invariant fluctuations in normal blood cell counts: a sign of criticality? *Fractals* 8 (3): 279–283. doi:10.1142/S0218348X00000329.
- Perfetti, C.A., & S.R. Goldman. 1976. Discourse memory and reading comprehension skill. *Journal of Verbal Learning and Verbal Behavior* 15 (1): 33–42. ISSN: 0022-5371, doi:10.1016/S0022-5371(76)90004-9.
- Perutz, M.F.E. 1987. Schrödinger's what is life? and molecular biology. In *Schrödinger*, ed. Kilmister. Cambridge University Press.
- Peters, R.H. 1986. *The ecological implications of body size*. Cambridge U. P.
- Petitot, J. 2003. The neurogeometry of pinwheels as a sub-riemannian contact structure. *Journal of Physiology, Paris* 97 (2-3): 265–309. doi:10.1016/j.jphysparis.2003.10.010.
- . 2008. *Neurogéométrie de la vision*. Ed de l'École Polytechnique.
- Pezard, J., L. and Martinerie, F.J. Varela, F. Bouchet, D. Guez, C. Derouesné & B. Renault. 1998. Entropy maps characterize drug effects on brain dynamics in alzheimer's disease. *Neuroscience Letters* 253 (1): 5–8. ISSN: 0304-3940, doi:10.1016/S0304-3940(98)00603-X.
- Phillips, J.C. 2009a. Scaling and self-organized criticality in proteins I. *Proceedings of the National Academy of Sciences* 106 (9): 3107–3112. doi:10.1073/pnas.0811262106.

- . 2009b. Scaling and self-organized criticality in proteins II. *Proceedings of the National Academy of Sciences* 106 (9): 3113–3118. doi:10.1073/pnas.0811308105.
- Piedrafita, G., F. Montero, F. Morán, M.L. Cárdenas & A. Cornish-Bowden. 2010. A simple self-maintaining metabolic system: robustness, autocatalysis, bistability. *PLoS Comput Biol* 6, no. 8 (Aug.): e1000872. doi:10.1371/journal.pcbi.1000872.
- Pikkujamsa, S.M., T.H. Makikallio, L.B. Sourander, I.J. Raiha, P. Puukka, J. Skytta, C.-K. Peng, A.L. Goldberger & H.V. Huikuri. 1999. Cardiac interbeat interval dynamics from childhood to senescence: comparison of conventional and new measures based on fractals and chaos theory. *Circulation* 100 (4): 393. doi:10.1161/01.CIR.100.4.393.
- Pilgram, B., & D. T. Kaplan. 1999. Nonstationarity and 1/f noise characteristics in heart rate. *Am J Physiol* 276 (1 - Pt - 2): R1–9.
- Rabinowitz, J. D., & E. White. 2010. Autophagy and metabolism. *Science* 330 (6009): 1344–1348. doi:10.1126/science.1193497.
- Renner, U., G.M. Schütz & G. Vojta. 2005. Diffusion on fractals. In *Diffusion in condensed matter*, ed. Paul Heitjans & Jörg Kärger, 793–811. Springer Berlin Heidelberg. ISBN: 978-3-540-30970-3, doi:10.1007/3-540-30970-5_19.
- Ribeiro, T.L., M. Copelli, F. Caixeta, H. Belchior, D.R. Chialvo, M.A.L. Nicolelis, S. Ribeiro & O. Sporns. 2010. Spike avalanches exhibit universal dynamics across the sleep-wake cycle. *PloS one* 5 (11): 11167–11177. ISSN: 1932-6203, doi:10.1371/journal.pone.0014129.
- Risser, L., F. Plouraboué, A. Steyer, P. Cloetens, G. Le Duc & C. Fonta. 2006. From homogeneous to fractal normal and tumorous microvascular networks in the brain. *Journal of Cerebral Blood Flow & Metabolism* 27 (2): 293–303. doi:10.1038/sj.jcbfm.9600332.
- Rosen, R. 2005. *Life itself: a comprehensive inquiry into the nature, origin, and fabrication of life*. Columbia U. P.
- Rosberg, A. G., K. D. Farnsworth, K. Satoh & J. K. Pinnegar. 2011. Universal power-law diet partitioning by marine fish and squid with surprising stability–diversity implications. *Proceedings of the Royal Society B: Biological Sciences* 278 (1712): 1617–1625. doi:10.1098/rspb.2010.1483.
- Rubner, M. 1883. über den Einfluss der Körpergröße auf Stoff- und Kraftwechsel. *Zeitschrift für Biologie* 19:535–562.
- Ruud, J.T. 1954. Vertebrates without erythrocytes and blood pigment. *Nature* 173 (4410): 848.
- Saetzler, K., C. Sonnenschein & A.M. Soto. 2011. Systems biology beyond networks: generating order from disorder through self-organization. *Seminars in Cancer Biology* In - Press - Corrected - Proof. ISSN: 1044-579X, doi:10.1016/j.semcancer.2011.04.004.

- Saigusa, T., A. Tero, T. Nakagaki & Y. Kuramoto. 2008. Amoebae anticipate periodic events. *Physical Review Letters* 100 (1): 018101. doi:10.1103/PhysRevLett.100.018101.
- Salam, A. 1990. *Unification of fundamental forces*. 153. Cambridge University Press. ISBN: 0521371406.
- Sarkar, S. 1998. *Genetics and reductionism*. Cambridge University Press. ISBN: 9780521637138.
- Savage, V.M., A.P. Allen, J.H. Brown, J.F. Gilloly, A.B. Herman, W.H. Woodruff & G.B. West. 2007. Scaling of number, size, and metabolic rate of cells with body size in mammals. *Proceedings of the National Academy of Sciences* 104 (11): 4718. doi:10.1073/pnas.0611235104.
- Savage, V.M., J.F. Gilloly, W.H. Woodruff, G.B. West, A.P. Allen, B.J. Enquist & J.H. Brown. 2004. The predominance of quarter-power scaling in biology. *Ecology* 18:257–282. doi:10.1111/j.0269-8463.2004.00856.x.
- Schaffner, K.F. 1967. Approaches to reduction. *Philosophy of Science* 34, no. 2 (June): 137–147. ISSN: 0031-8248.
- Scheffer, M., J. Bascompte, W.A. Brock, V. Brovkin, S.R. Carpenter, V. Dakos, H. Held, E.H. Van Nes, M. Rietkerk & G. Sugihara. 2009. Early-warning signals for critical transitions. *Nature* 461 (7260): 53–59. doi:10.1038/nature08227.
- Schmidt-Nielsen, K. 1984. *Scaling*. Cambridge U. P.
- Schrödinger, E. 1944. *What is life?* Cambridge U.P.
- Schulte-Frohlinde, V., & H. Kleinert. 2001. *Critical properties of phi-4-theories*. World Scientific.
- Sen, S. 2010. Symmetry, symmetry breaking and topology. *symmetry* 2 (3): 1401–1422. doi:10.3390/sym2031401.
- Sethna, J. P. 2006. *Statistical mechanics: entropy, order parameters, and complexity*. New York: Oxford University Press. ISBN: 0198566778.
- Shinde, D. P., A. Mehta & R. K. Mishra. 2011. Searching and fixating: scale-invariance vs. characteristic timescales in attentional processes. *Europhysics Letters* 94 (6): 68001. doi:10.1209/0295-5075/94/68001.
- Shmulevich, I., S.A. Kauffman & M. Aldana. 2005. Eukaryotic cells are dynamically ordered or critical but not chaotic. *Proceedings of the National Academy of Sciences* 102 (38): 13439–13444. doi:10.1073/pnas.0506771102.
- Silva, C., & K. Annamalai. 2008. Entropy generation and human aging: lifespan entropy and effect of physical activity level. *entropy* 10 (2): 100–123. doi:10.3390/entropy-e10020100.
- Silverman, M. 2008. *Quantum superposition*. Springer Verlag.

- Sinclair, S.E., S. McKinney, R.W. Glenny, S.L. Bernard & M.P. Hlastala. 2000. Exercise alters fractal dimension and spatial correlation of pulmonary blood flow in the horse. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology* 88 (6): 2269–2278.
- Singer, D., O. Schunck, F. Bach & H.J. Kuhn. 1995. Size effects on metabolic rate in cell, tissue, and body calorimetry. *Thermochimica Acta* 251:227–240. ISSN: 0040-6031, doi:10.1016/0040-6031(94)02072-V.
- Smith, P.R., I.E.G. Morrison, K.M. Wilson, N. Fernández & R.J. Cherry. 1999. Anomalous diffusion of major histocompatibility complex class I molecules on hela cells determined by single particle tracking. *Biophys. J.* 76 (6): 3331–3344. ISSN: 0006-3495, doi:10.1016/S0006-3495(99)77486-2.
- Smith, T.G., G.D. Lange & W.B. Marks. 1996. Fractal methods and results in cellular morphology—dimensions, lacunarity and multifractals. *Journal of Neuroscience Methods* 69 (2): 123–136. doi:10.1016/S0165-0270(96)00080-5.
- Sohal, R.S., & R. Weindruch. 1996. Oxidative stress, caloric restriction, and aging. *Science* 273 (5271): 59–63. doi:10.1126/science.273.5271.59.
- Sole, R.V., S.C. Manrubia, M. Benton, S.A. Kauffman & P. Bak. 1999. Criticality and scaling in evolutionary ecology. *Trends in Ecology & Evolution* 14 (4): 156–160. doi:10.1016/S0169-5347(98)01518-3.
- Song, H.S., & P.M. Lehrer. 2003. The effects of specific respiratory rates on heart rate and heart rate variability. *Applied psychophysiology and biofeedback* 28 (1): 13–23. doi:10.1023/A:1022312815649.
- Sonnenschein, C., & A.M. Soto. 1999. *The society of cells: cancer and control of cell proliferation*. New York: Springer Verlag.
- . 2000. Somatic mutation theory of carcinogenesis: why it should be dropped and replaced. *Molecular Carcinogenesis* 29 (4): 205–211. doi:10.1002/1098-2744(200012)29:4<205::AID-MC1002>3.0.CO;2-W.
- Sornette, D., A. Johansen & I. Dornic. 1995. Mapping self-organized criticality onto criticality. *J. Phys. I France* 5 (3): 325–335. doi:10.1051/jp1:1995129.
- Soto, A.M., C. Sonnenschein & P.-A. Miquel. 2008. On physicalism and downward causation in developmental and cancer biology. *Acta Biotheoretica* 56 (4): 257–274. doi:10.1007/s10441-008-9052-y.
- Stern, G., J. Beel, B. Suki, M. Silverman, J. Westaway, M. Cernelc, D. Baldwin & U. Frey. 2009. Long-range correlations in rectal temperature fluctuations of healthy infants during maturation. *PLoS ONE* 4, no. 7 (July): e6431. doi:10.1371/journal.pone.0006431.

- Stewart, E.J., R. Madden, G. Paul & F. Taddei. 2005. Aging and death in an organism that reproduces by morphologically symmetric division. *PLoS Biology* 3 (2): e45. doi:10.1371/journal.pbio.0030045.
- Stewart, J. 2004. *La vie existe-t-elle ?* Editions Vuibert.
- Stiegler, B. 2001. *Nietzsche et la biologie*. Puf, Paris.
- Strocchi, F. 2005. *Symmetry breaking*. Vol. 732. Lecture Notes in Physics. Springer Verlag. doi:10.1007/b95211.
- Suki, B., A.L. Barabási, Z. Hantos, F. Peták & H.E. Stanley. 1994. Avalanches and power-law behaviour in lung inflation. *Nature* 368 (6472): 615–618. doi:10.1038/368615a0.
- Suzuki, M., K. Kaneko & S. Takesue. 1982. Critical slowing down in stochastic processes. I. *Progress of Theoretical Physics* 67 (6): 1756–1775. doi:10.1143/PTP.67.1756.
- Szpunar, K.K., J.M. Watson & K.B. McDermott. 2007. Neural substrates of envisioning the future. *Proceedings of the National Academy of Sciences* 104 (2): 642. doi:10.1073/pnas.0610082104.
- Taniguchi, Y., P. J. Choi, G.-W. Li, H. Chen, M. Babu, J. Hearn, A. Emili & X. S. Xie. 2010. Quantifying e. coli proteome and transcriptome with single-molecule sensitivity in single cells. *Science* 329 (5991): 533–538. doi:10.1126/science.1188308.
- Thamrin, C., G. Stern & U. Frey. 2010. Fractals for physicians. *Paediatric Respiratory Reviews* 11 (2): 123–131. ISSN: 1526-0542, doi:10.1016/j.prrv.2010.02.001.
- Tofani, S. 1999. Physics may help chemistry to improve medicine: a possible mechanism for anticancer activity of static and elf magnetic fields. *Physica Medica*, no. 4:291–294.
- Tolić-Nørrellykke, I.M., E.-L. Munteanu, G. Thon, L. Oddershede & K. Berg-Sørensen. 2004. Anomalous diffusion in living yeast cells. *Phys. Rev. Lett.* 93, no. 7 (Aug.): 078102. doi:10.1103/PhysRevLett.93.078102.
- Toll, J.S. 1956. Causality and the dispersion relation: logical foundations. *Phys. Rev.* 104, no. 6 (Dec.): 1760–1770. doi:10.1103/PhysRev.104.1760.
- Toulouse, G., P. Pfeuty & G. Barton. 1977. *Introduction to the renormalization group and to critical phenomena*. London: Wiley.
- Tredecce, J.R., G.L. Lippi, P. Mandel, B. Charasse, A. Chevalier & B. Picque. 2004. Critical slowing down at a bifurcation. *American Journal of Physics* 72:799. doi:10.1119/1.1688783.
- Trieb, G., G. Pappritz & L. Lützen. 1976. Allometric analysis of organ weights. I. Rats. *Toxicology and Applied Pharmacology* 35 (3): 531–542. doi:10.1016/0041-008X(76)90076-4.

- Tsallis, C., & U. Tirnakli. 2010. Nonadditive entropy and nonextensive statistical mechanics—some central concepts and recent applications. In *Journal of physics: conference series*, 012001. Vol. 201. IOP Publishing.
- Van Fraassen, B.C. 1989. *Laws and symmetry*. Oxford University Press, USA.
- Van Gelder, T. 1999. Wooden iron? Husserlian phenomenology meets cognitive science. In *Naturalizing phenomenology: issues in contemporary phenomenology and cognitive science*, ed. J. Petitot, F.J. Varela, B. Pachoud & J.M. Roy, 245–265. Stanford U. P.
- Vanni, F., M. Luković & P. Grigolini. 2011. Criticality and transmission of information in a swarm of cooperative units. *Phys. Rev. Lett.* 107, no. 7 (Aug.): 078103. doi:10.1103/PhysRevLett.107.078103.
- Van Saarloos, W., & D. A. Kurtze. 1984. Location of zeros in the complex temperature plane: absence of lee-yang theorem. *Journal of Physics A: Mathematical and General* 17 (6): 1301. doi:10.1088/0305-4470/17/6/026.
- Varela, F.J. 1979. *Principles of biological autonomy*. North Holland New York.
- . 1997. Patterns of life: intertwining identity and cognition. *Brain and Cognition* 34 (1): 72–87. doi:10.1006/brcg.1997.0907.
- . 1999. The specious present: a neurophenomenology of time consciousness. In *Naturalizing phenomenology: issues in contemporary phenomenology and cognitive science*, ed. J. Petitot, F.J. Varela, B. Pachoud & J.M. Roy, 266–314. Stanford U. P.
- Varela, M., L. Jimenez & R. Fariña. 2003. Complexity analysis of the temperature curve: new information from body temperature. *European Journal of Applied Physiology* 89:230–237. ISSN: 1439-6319, doi:10.1007/s00421-002-0790-2.
- Vaz, N.M., & F.J. Varela. 1978. Self and non-sense: an organism-centered approach to immunology. *Medical Hypotheses* 4 (3): 231–267. doi:10.1016/0306-9877(78)90005-1.
- Vilar, J. M. G., & J. M. Rubí. 2001. Thermodynamics “beyond” local equilibrium. *Proceedings of the National Academy of Sciences* 98 (20): 11081–11084. doi:10.1073/pnas.191360398.
- Von Förster, H. 1960. On self-organizing systems and their environments. In *Self-organizing systems*, ed. C. Yovits & S. Cameron. Pergamon Press.
- Waddington, G.H. 1977. Stabilisation in systems: chreods and epigenetic landscapes. *Futures* 9 (2): 139–146. ISSN: 0016-3287, doi:10.1016/0016-3287(77)90006-4.
- Wagner, C.D., B. Nafz & P.B. Persson. 1996. Chaos in blood pressure control. *Cardiovascular Research* 31 (3): 380. doi:10.1016/S0008-6363(96)00007.
- Wang, J., T. Michelitsch, A. Wunderlin & R. Mahadeva. 2009. Aging as a consequence of misrepair—a novel theory of aging. *Arxiv preprint arXiv:0904.0575*.

- Wang, Z., T.P. O'Connor, S. Heshka & S.B. Heymsfield. 2001. The reconstruction of Kleiber's law at the organ-tissue level. *Journal of Nutrition* 131 (11): 2967–2970.
- Weibel, E.R. 1994. Design of biological organisms and fractal geometry. In *Fractals in biology and medicine*. Vol. 1. Springer Verlag.
- Weibel, E.R., L.D. Bacigalupe, B. Schmitt & H. Hoppeler. 2004. Allometric scaling of maximal metabolic rate in mammals: muscle aerobic capacity as determinant factor. *Respiratory Physiology and Neurobiology* 140 (2): 115–132. doi:10.1016/j.resp.2004.01.006.
- Weiss, M., M. Elsner, F. Kartberg & T. Nilsson. 2004. Anomalous subdiffusion is a measure for cytoplasmic crowding in living cells. *Biophys. J.* 87 (5): 3518–3524. ISSN: 0006-3495, doi:10.1529/biophysj.104.044263.
- Werner, G. 2007. Metastability, criticality and phase transitions in brain and its models. *Biosystems* 90 (2): 496–508. doi:10.1016/j.biosystems.2006.12.001.
- . 2010. Fractals in the nervous system: conceptual implications for theoretical neuroscience. *Frontiers in Physiology* 1. ISSN: 1664-042X, doi:10.3389/fphys.2010.00015.
- West, B.J. 2006. *Where medicine went wrong: rediscovering the path to complexity*. Vol. Volume 11 of Studies of nonlinear phenomena in life sciences. World Scientific.
- . 2010. Fractal physiology and the fractional calculus: a perspective. *Frontiers in Physiology* 1. ISSN: 1664-042X, doi:10.3389/fphys.2010.00012.
- West, B.J., V. Bhargava & A.L. Goldberger. 1986. Beyond the principle of similitude: renormalization in the bronchial tree. *Journal of Applied Physiology* 60 (3): 1089–1097.
- West, B.J., M. Bologna & P. Grigolini. 2003. *Physics of fractal operators*. Springer Verlag.
- West, G.B., & J.H. Brown. 2005. The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization. *Journal of Experimental Biology* 208 (9): 1575–1592. doi:10.1242/jeb.01589.
- West, G.B., J.H. Brown & B.J. Enquist. 1997. A general model for the origin of allometric scaling laws in biology. *Science* 276 (5309): 122–126. doi:10.1126/science.276.5309.122.
- . 1999. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science* 284 (5420): 1677–1679. doi:10.1126/science.284.5420.1677.
- Weyl, H. 1983. *Symmetry*. Princeton Univ Pr.
- White, C.R., & R.S. Seymour. 2003. Mammalian basal metabolic rate is proportional to body mass $2/3$. *Proceedings of the National Academy of Sciences of the United States of America* 100 (7): 4046–4049. doi:10.1073/pnas.0436428100.

- Wildman, D.M., & M. Kling. 1978. Semantic, syntactic, and spatial anticipation in reading. *Reading Research Quarterly* 14 (2): 128–164.
- Wilson, B.J., G.L.W. Hart & A.C. Parcell. 2009. Cardiac inter-beat interval complexity is influenced by physical activity. *Medical Physiology Online* 2:e.
- Winfree, A.T. 2001. *The geometry of biological time*. Second. Springer Verlag.
- Witten, M.L., J.P. Tinajero, R.E. Sobonya, R.C. Lantz, S.F. Quan & R.J. Lemen. 1997. Human alveolar fractal dimension in normal and chronic obstructive pulmonary disease subjects. *Research communications in molecular pathology and pharmacology* 98 (2): 221.
- Yadav, C.K., M.K. Verma & S. Ghosh. 2010. Statistical evidence for power law temporal correlations in exploratory behaviour of rats. *Biosystems* 102 (2 - 3): 77–81. ISSN: 0303-2647, doi:10.1016/j.biosystems.2010.07.016.
- Yan, R., G. Yan, W. Zhang & L. Wang. 2008. Long-range scaling behaviours of human colonic pressure activities. *Communications in Nonlinear Science and Numerical Simulation* 13 (9): 1888–1895. ISSN: 1007-5704, doi:10.1016/j.cnsns.2007.01.006.
- Youngson, N.A., & E. Whitelaw. 2008. Production of a standard closed fracture in laboratory animal bone. *Annual Review of Genomics and Human Genetics* 9 (Sept.): 233–257. doi:10.1146/annurev.genom.9.081307.164445.
- Zamir, M. 2001. Fractal dimensions and multifractality in vascular branching. *Journal of Theoretical Biology* 212 (2): 183–190. doi:10.1006/jtbi.2001.2367.
- Zinn-Justin, J. 2007. *Phase transitions and renormalization group*. New York: Oxford University Press. ISBN: 0199227195.

Ce document a été préparé à l'aide de l'éditeur de texte Kile et du logiciel de composition typographique Lua^LA^TE^X.