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## Marine biodiversity and chemodiversity - the treasure troves of the future

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## 2 **Marine Biodiversity and Chemodiversity – The Treasure** 3 **Troves of the Future**

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4 Stéphane La Barre

5 Additional information is available at the end of the chapter

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### 7 **1. Introduction**

8 Chemodiversity usually refers to small molecules that have a signaling (offensive or defensive)  
9 function, sometimes protective. This leaves aside larger molecules that are purely structural  
10 and those that participate in essential metabolic functions, and make up the bulk of the organic  
11 body mass of living organisms.

12 From cyanobacteria and bacteria to the largest metazoans, chemistry is the preferred mode of  
13 aquatic communication, thanks to the extraordinary solvation properties of water. Bacteria  
14 create biofilms inside which they communicate using their own chemical repertoire before  
15 colonizing new media, substrates or organisms. Microalgae form blooms which are maintained  
16 by releasing semiochemicals for cell-cell recognition. Fish rely on their extraordinary sense of  
17 smell to hunt or to migrate to some specific breeding spot. The extraordinary biodiversity of  
18 coral reefs is maintained by a highly complex chemical network of toxins and pheromones,  
19 some soluble, some dispersed with a mucus carrier or surface-coated. But not only: the amazing  
20 colors used for warning or for camouflage, the bioluminescence used in the dark correspond  
21 to very sophisticated assemblages of pigments, small metabolites or proteins, each organism  
22 having its own strategy to be visually recognized or to blend into the background.

23 Humans have only recently been aware of the extraordinary potential marine molecules for  
24 the design of new drugs, cosmetics and nutraceuticals. Well over 20000 natural molecules have  
25 been studied so far, and several have responded to the need for novel anticancer, antibiotic,  
26 anti-inflammatory or anti-pain agents etc. The necessity to preserve this exceptional resource,  
27 however, has only manifested itself in the delineation of protected areas and in the imple-  
28 mentation of codes of good practices regarding non-destructive boating and durable sampling  
29 protocols.

1 Over the last three decades, warning messages have been sent to the community about the  
2 destructive consequences worldwide economic development will have on biodiversity, both  
3 terrestrial and marine, during the 21st century. Direct impacts are caused by overexploitation  
4 and mismanagement of natural resources and improper recycling and disposal of waste  
5 products. Indirect impacts are caused by the accelerating volatilization of greenhouse mole-  
6 cules and their accumulation in the atmosphere where they may undergo undesirable  
7 speciation. Restitution of sulfur emissions to land may cause acidic rains and transfer of carbon-  
8 containing emissions to seawater increases its acidity, both leading to biodiversity destructive  
9 scenarios. Not to mention the release of man-made (synthetic) molecules, some of which like  
10 CFCs destroy the anti-UV ozone shield, others like PCBs accumulating along food chains and  
11 eventually killing top consumers. Synthetic molecules may respond to specific needs and  
12 criteria, but they will never replace natural molecules, in the same way as genetically trans-  
13 formed organisms will never replace wildlife diversity. Moreover, freak biological or chemical  
14 species should be eliminated safely once the purpose for which they were created has been  
15 fulfilled.

16 To-date, very little is said or written on the fate of natural chemodiversity within the context  
17 of local or general biodiversity collapse, both terrestrial and marine. After a brief historical  
18 account of the intricate connections between chemodiversity and biodiversity since life  
19 appeared on our planet, this chapter attempts to demonstrate that natural molecular diversity  
20 is a treasure to preserve for future generations, using a series of marine examples.

## 21 **2. Early chemodiversity was non-biotic**

### 22 **2.1. From single elements to simple organic molecules in a mineral world**

23 Chemistry is as ancient as the observable universe, ca. 13.7 billion years old according to  
24 present estimates. The simplest elements of the periodic table (namely, hydrogen, helium and  
25 traces of lithium) were formed as an immediate consequence of the Big Bang.

26 The *nuclear chemistry* of the galaxies and stars which developed during the following few billion  
27 years is the chemistry of very high energies, yielding a small and finite number of chemical  
28 species, some very short-lived. Carbon, oxygen and nitrogen came to existence. The data on  
29 star-forming elements is of spectroscopic nature. When decomposed and analyzed, the light  
30 emitted by these objects reveals the presence of spectral lines at set wavelengths, and their  
31 association forms fingerprints typical of individual elements when heated to incandescence.  
32 The solar system was formed about 4.6 billion years ago by the accretion of *simple molecular*  
33 *substances* from a giant cloud at the center of which most the concentrating matter formed the  
34 sun, the rest forming a disc from which primary planets, then satellites planets emerged under  
35 various scenarios.

36 Under very hot temperatures and no atmosphere, the molecular chemistry associated with  
37 proto-planets is dominated by inorganic entities, with very limited diversity in carbon  
38 chemistry. Carbon dioxide and water probably existed as soon as oxygen, a stellar product,

1 had been available to combine with hydrogen, yet early planet Earth was most likely very hot  
 2 and dry, precluding life and any of the complex chemistries it produces. This characterized  
 3 the Hadean, the first geologic eon (4.6 to 4.0 billion years until conflicting evidences such as  
 4 the presence of high  $d^{18}O$  (oxygen isotopic ratios) in zircons tentatively dated as early as 4.4  
 5 billion years led to a reassessment of the transition between the "molten" planet (and formation  
 6 of the moon) and the "solid" planet with a solid crust, a low temperature, and an atmosphere  
 7 of sorts, and the possible presence of liquid water. As well as this "cool early earth" hypothesis  
 8 [1], a partial explanation about the formation of oceans is that asteroids and perhaps comets  
 9 carrying huge amounts of ice collided with our planet, adding to the putative *de novo* conden-  
 10 sation into water during the degassing of rocks of the cooling planet. In the primitive atmos-  
 11 phere, heavier carbon dioxide became partly quenched by dissolving in oceanic waters, and  
 12 partly trapped under plate tectonic movements.

## 13 2.2. The chemical origin of life on earth — Chemodiversity goes organic

14 Any life form necessitates the capacity to harvest energy for its own benefit, to manage  
 15 chemical reactions within molecular boundaries that define it as an entity distinct from the  
 16 environment, i.e. *self* vs. *non-self*, and to have the potential to replicate itself.

17 Irrespective of when the right conditions were first met for life to emerge, a small set of small  
 18 organic molecules (reactants) is a prerequisite for the abiotic generation of life-essential  
 19 molecules, in the presence of water and of some catalytic trigger, and later of thermodynam-  
 20 ically favorable conditions for polymers to be built.

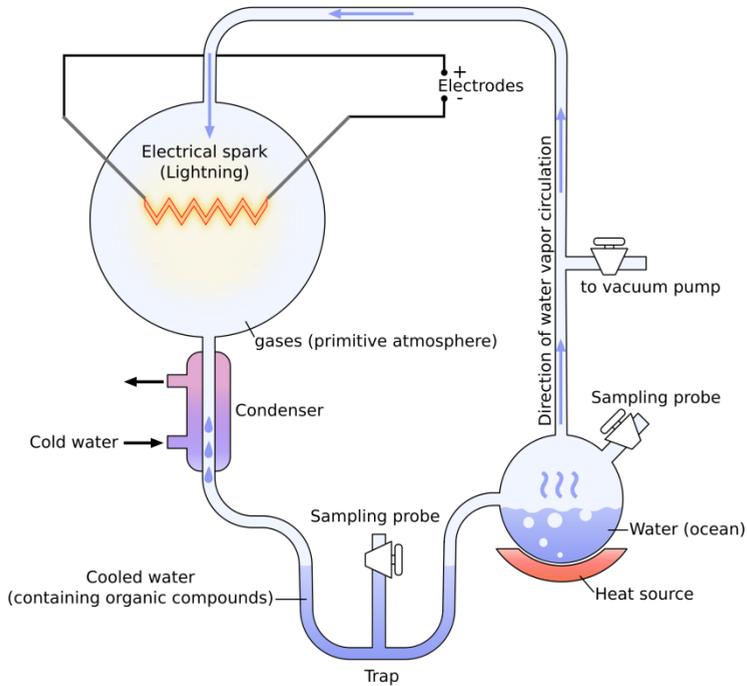
21 Different approaches have attempted to address the question of the chemical origin of life,  
 22 leading to apparently conflicting conclusions: the "prebiotic soup theory" and the "pioneer  
 23 organism theory", fueling heated debate among specialists, and also reflecting the uncertainties  
 24 that still remain on the greatest mystery in science. The following paragraph attempts to follow  
 25 the most generally accepted views and the most plausible scenario.

### 26 2.2.1. The Miller-Urey laboratory experiments

27 The prebiotic soup theory stems from the early experiments of Stanly Miller and Harold Urey  
 28 [2] which led to the condensation within days of a suite of five amino acids by exposing a sterile  
 29 mixture of methane ( $CH_4$ ), ammonia ( $NH_3$ ), carbon monoxide ( $CO$ ) and hydrogen ( $H_2$ ) - i.e.  
 30 the "primitive gases", to a constant flux of hot water ( $H_2O$ ), while discharging electric sparks  
 31 (to simulate thunder) into the gas mixture. New species such as hydrogen cyanide ( $HCN$ ),  
 32 formaldehyde ( $HCHO$ ) and reactive intermediates (acetylene, cyanoacetylene etc.) are formed  
 33 in one-step, while amino acids and other biomolecules are formed from these reactants under  
 34 reducing conditions (Fig. 1), i.e. the Strecker synthesis.

35 Some 50 years later, Bada and collaborators (in [3]) reanalyzed archived samples of Stanly  
 36 Miller's experiments in which the gaseous mixture included hydrogen sulphide ( $H_2S$ ),  
 37 methane ( $CH_4$ ), ammonia ( $NH_3$ ), and carbon dioxide ( $CO_2$ ). In the case of this experiment  
 38 (unreported by Miller at the time), no less than 27 compounds, including the 20 "regular" amino  
 39 acids and 3 new ones were found. Specifically, the presence of hydrogen sulphide and carbon

- 1 dioxide as reactants - originally proposed to simulate the influence of volcanic emissions - had  
 2 enriched the diversity of the reaction products with seven several sulphur-containing com-  
 3 pounds, including methionine and cysteine), and four amines as well.



4

5 **Figure 1.** The apparatus used by Miller and Urey in their 1953 simulated early-earth experiment on the chemical origins of life. In the original experiment, the gases of the primitive atmosphere were:  $\text{NH}_3$ ,  $\text{CH}_4$ ,  $\text{H}_2$  and water vapor. Other experiments were carried out under non-reducing conditions (using  $\text{CO}_2$ ,  $\text{N}_2$  and water) and UV exposure led to poor yields. In experiments simulating volcanic environments, Miller and Urey used  $\text{H}_2\text{S}$ ,  $\text{CH}_4$ ,  $\text{NH}_3$  and  $\text{CO}_2$  (see text).  
 6  
 7  
 8  
 9 (Graphics by Yassine Mrabet in [http://en.wikipedia.org/wiki/Miller-urey\\_experiment](http://en.wikipedia.org/wiki/Miller-urey_experiment))

#### 10 2.2.2. Other "prebiotic" laboratory experiments

11 Oró and collaborators [4] using similar experimental setups, established that adenine and other  
 12 nucleic bases, as well as several amino acids, could be formed from  $\text{HCN}$  and  $\text{NH}_3$  in water,  
 13 under reducing conditions.

14 In addition, simple sugars can be formed under putative prebiotic conditions [5], an essential  
 15 feature for the emergence of nucleosides [6] and RNA (qv. the RNA world). The Butlerow  
 16 reaction, i.e. the synthesis of a complex mixture of sugars (including ribose and arabinose)  
 17 from formaldehyde by the action of catalysts such as calcium hydroxide, has been known since  
 18 the 19th century under laboratory conditions.

### 1 2.2.3. *Transposing to "real" prebiotic conditions*

2 In order to transpose from lab experiments to real life situation, several criteria must be met  
3 in order to initiate amino acid synthesis: the reactants must be concentrated enough under an  
4 aqueous environment under favorable temperature and pH conditions.

5 The primitive soup theory relies on a stochastic occurrence of optimal conditions for the  
6 emergence of organic life. Polymerization necessitates suitable absorbing substrates and  
7 catalysts such as metal cations and imidazole derivatives and several others, to proceed in  
8 laboratory conditions. Charged submicronic montmorillonite clay particles would have  
9 helped activated monomers to selectively concentrate (electrostatic bonds) and induce  
10 covalent polymerization. Shallow lagoons in tidal zones may theoretically provide basic  
11 chemistry. Evaporation induces concentration and promotes the formation of eutectic  
12 complexes.

13 Contenders of the "primitive soup" scenario advocate that life may have arisen through  
14 chemoautotrophic processes occurring in oceanic depths in the vicinity of hydrothermal  
15 settings which would provide all necessary starting conditions [7]. In this "pioneer metabo-  
16 lism" scenario, the generation of homochiral metalloenzymes of extant organisms from  
17 inorganic transition metal precipitates (by chelation of alpha-hydroxyl and alpha-amino acids  
18 ligands) follows a stepwise evolution by autocatalytic feedback. This "hot volcanic" prebiotic  
19 chemistry is often opposed to the "cool oceanic" chemistry that typifies the primitive soup  
20 scenario.

21 It appears that the composition of the primitive atmosphere is not what it was thought to be  
22 at the time of Miller's experiments, certainly not as reducing, and the conditions afforded in  
23 the hydrothermal vent environments appear more amenable to prebiotic chemistry. Oligomers  
24 could have then been formed at liquid-solid interfaces [8].

25 However, prebiotic chemistry under early atmospheric conditions has opened the issue  
26 towards exobiology. Scientists of repute now speculate on an extraterrestrial origin of life, or  
27 at least in the alien seeding of life essential molecular building blocks on planet earth. But this  
28 is another story.

### 29 2.2.4. *Before and during the RNA world*

30 The recent finding that ribonucleic acids (RNAs) can perform a variety of hitherto unsuspected  
31 structural and metabolic functions in cells has given credit to Walter Gilbert's prediction [9]  
32 that an all-RNA world had preceded the nucleic acid-protein world as we know it today. The  
33 fact that RNA takes evolutionary precedence on DNA (itself regarded by some as a modified  
34 RNA better suited for the conservation of genetic information), or the fact that RNAs as a  
35 catalysts (ribozymes) take precedence on enzyme catalysts, stimulate intense experimental  
36 interest.

37 Nucleotide monomers can theoretically be surface-assembled as oligomers [10]. The longest  
38 strands serving as templates, direct synthesis of a complementary strand starting from  
39 monomers or short oligomers, and double-stranded RNA molecules can accumulate. Disso-

1 ciation of strands, one of which endowed with RNA polymerase activity, would lead to  
2 successive replication processes. Finally, the RNA world would have emerged from a mixture  
3 of activated nucleotides. However, the precise molecular mechanisms which initiated RNA  
4 oligomers in the first place, remain obscure. The monomers (nucleotides) must be activated  
5 and homochiral, before they can be assembled as strands on an absorbing mineral surface (e.g.  
6 montmorillonite clay) acting as a catalyst.

7 Interestingly, other nucleotide-like structures that may be formed under prebiotic conditions  
8 can reasonably qualify as RNA functional analogues and have been termed "alternative genetic  
9 systems" [11].

10 The existence in prebiotic conditions of AMP-derived cofactors that have acquired amino acid-  
11 like properties through post-translational modifications is possible, since these cofactors  
12 participate at all levels in the metabolism of extant life forms. As Maurel and Haenni [12] put  
13 it, "Coenzymes would be vestiges of catalytic nucleic enzymes that preceded ribosomal protein  
14 synthesis, and tRNAs can be viewed as large coenzymes participating in the transfer of amino  
15 acids."

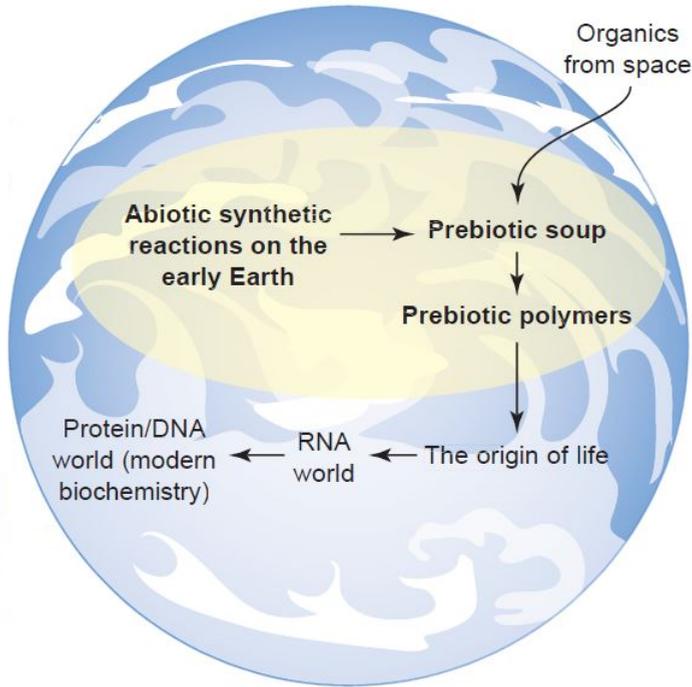
16 Ligand-substrate recognition must have followed from the selection of *aptamers* (molecules  
17 that bind specifically to one target molecule) from a pool of oligonucleic acids or peptides.  
18 Artificial selection of adenine-dependent ribozyme aptamers [13 ] indicates that the use of  
19 small exogenous cofactors (adenine) by ribozymes could have actively contributed to the  
20 expansion of the catalytic and metabolic repertoires of RNA species in the prebiotic RNA  
21 world. Modern catalytic equivalents of ribozymes are metalloenzymes, and adenine fills the  
22 same cofactor function as histidine.

23 Indeed, the RNA world was probably much more chemodiverse than sometimes described (a  
24 uniform soup), notwithstanding the fact that, as said before, tidal lagoons with the presence  
25 of catalytic elements such as clay submicronic particles, or the vicinity of hydrothermal vents  
26 would greatly favor polymerization and functional gains of prebiotic organic molecules.

#### 27 *Extra-terrestrial chemistry going organic*

28 Recent investigations [15] have led to the identification of many (> 100) prebiotic molecules  
29 (HCN, HCHO, glycoaldehyde etc.) in the composition of interstellar clouds and in the gas-  
30 phase chemical evolution in the atmospheres of various planets (i.e. corresponding to the first  
31 step of the Miller-Urey experiment). If the radicalar processes leading to the formation of these  
32 intermediate species are simple compared to the sophisticated biochemistry involved in  
33 terrestrial chemodiversity, they remain largely unknown and should help us better understand  
34 prebiotic chemistry. Different types of molecular processes are thought to be involved,  
35 including radiative association and recombination, surface-induced processes, photon or  
36 particle induced ionization, ion-molecule reactions, photon or particle induced dissociation  
37 and radical-molecule interactions.

38 Moreover, amino acids are known to occur extra-terrestrially since the 1970 discovery in the  
39 Murchison meteorite, of over 70 common and exogenous species under non-racemic propor-  
40 tions, some under relative abundances similar to those found with the original 1953 Miller-  
41 Urey experiment.



60

61 **Figure 2.** A depiction of the step-by step scenario involved in the origin of life on earth, attempting to integrate the  
 62 "metabolist" scenario into the "primitive soup" scheme (from: Bada and Lazcano, [14])

1 This was made possible through the activation of a multiple-component system [16].

2 This raises the problem of chirality, since on our planet, natural amino acids are all left-handed  
 3 (L-amino acids). It is speculated that the prevalence of the L- form may have been influenced  
 4 by polarized radiations from outer space [17]. In the laboratory, crystallization experiments in  
 5 a racemic mixture always follow the same enantiomeric form as that of the initiating nucleus,  
 6 further amplifying the "preference" for the L-form. Homochirality is an essential feature of  
 7 biopolymers, for which correct folding must be required for proper function [18].

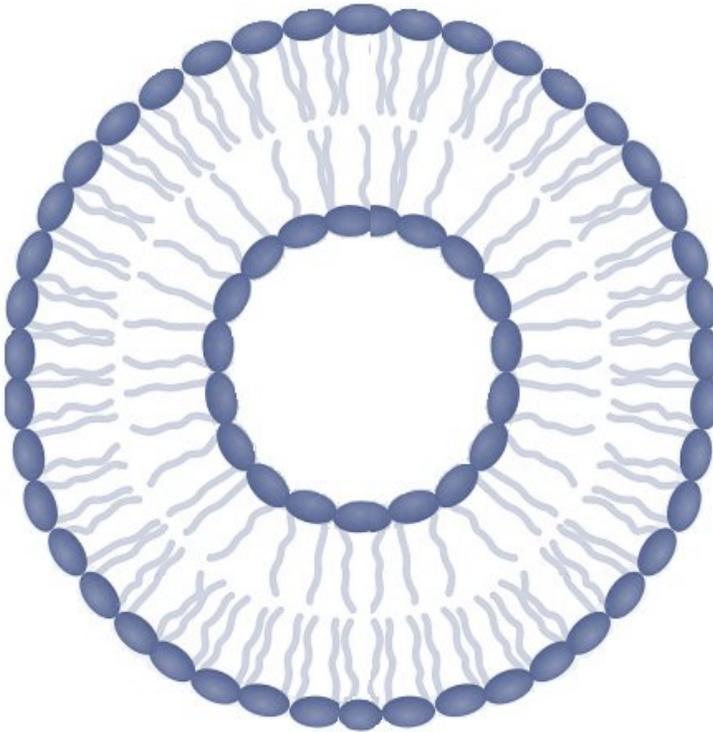
## 8 2.3. From proto-cells to living entities

### 9 2.3.1. *Self-assembling vesicles*

10 Self-organization of amphiphilic molecules (i.e. long chain fatty acids) into bilayers or into  
 11 vesicles can be readily observed in laboratory conditions. In live cells, membranes provide the  
 12 most elementary delineation of the self from the non self, i.e. it defines the basic identity of an  
 13 individual from its environment. In non-living systems, vesicles can selectively separate  
 14 solutes according to their affinities (polar or apolar) and even to their chiral properties [19].

### 1 2.3.2. *The amphiphilic double layer*

2 In particular, the double layer which separates the vesicular contents from the outside can  
3 selectively extract lipophilic substances from the environment and arrange them around the  
4 inner (hydrophobic) tails. Experimentally, this feature promotes concentration of e.g. apolar  
5 amino acids and their non-enzymatic condensation into dipeptides or small oligopeptides  
6 within the lipid bilayer. In addition, vectorial properties in phospholipidic vesicles are thought  
7 to influence the inner pH (making it lower than outer pH) in small vesicles, due to differences  
8 in the behavior of water molecules.



9

10 **Figure 3.** A phospholipid vesicle, with a double-layered membrane. Each layer includes a hydrophilic head (dark  
11 knobs) and a hydrophobic tail made up of long lipid chains. The aqueous environment inside the vesicle isolates en-  
12 trapped metabolites, biopolymers and catalysts, the whole structure acting as a reaction vessel.

### 13 2.3.3. *Vesicles as proto-cells*

14 The total synthesis of a simple cell is possibly the ultimate challenge in synthetic biology. It is  
15 experimentally possible to entrap nucleic acids inside self - forming phospholipid vesicles,  
16 acting as reaction vessels for e.g. polymerase chain reaction, enzymatic RNA replication and  
17 even protein synthesis, as demonstrated by Oberholzer and collaborators (reviewed in [19]).

1 The molecular pump scenario [20], in which peptides were initially synthesized through a  
 2 molecular engine could also have taken place inside such structures. In nature, the inclusion  
 3 of clay microparticles acting as catalysts is highly probable. Thus, phospholipid vesicles can  
 4 be regarded as useful experimental models of proto-cells [21], but many questions still need  
 5 addressing before considering them as early precursors of living cells.

6 *Protobiology* uses a bottom up approach when designing complex and functional protocells  
 7 from simple molecules and organic catalysts.

8 *Synthetic biology* uses a top-down approach to identify the minimal components of living cells  
 9 that will qualify, in other words to rediscover the basic cell before it underwent the complexities  
 10 of Darwinian evolution. Thus protocells are of exciting biotechnological interest in the quest  
 11 to optimize chemotherapies (cellular target recognition, kinetics of drug delivery).

12 Prebiotic chemistry is certainly more complex than previously thought, and chemodiversity  
 13 has undergone periods of expansion, especially through stochastic combinations during the  
 14 so-called RNA world, and during the development of proto-cells.

15 Chemodiversity as we know it today is mostly organic and is the result of complex biochemical  
 16 processes within living organisms that must constantly adapt to changing environments and  
 17 compete for their survival.

### 18 **3. Chemodiversity explodes with the emergence of life**

#### 19 **3.1. "Cool" carbon chemistry**

20 Our chemodiversity is usually classified as mineral or organic. Exploitable minerals are  
 21 solidified in the earth crust or deposited as sediments or conglomerates - geochemical cycles  
 22 connect the molten inner core of the planet with the biosphere through the displacement of  
 23 continental plates and volcanic activity. Organic chemodiversity is concentrated in the  
 24 biosphere, as the result of the present and past metabolic processes of marine and terrestrial  
 25 organisms. Chemically, organic molecules are carbon atoms and scaffolds of connected carbon  
 26 atoms, linked to hydrogen and covalently to heteroatoms e.g. oxygen, nitrogen, atoms but also  
 27 to sulfur, phosphorus and halogens or metal complexes (*coordination chemistry*) to form  
 28 functional groups. Larger organic molecules often adopt three-dimensional architectures that  
 29 confer them with the exquisite specificity required for recognition and binding to a defined  
 30 molecular target. Organic natural products are by far the largest contributors to marine and  
 31 terrestrial chemodiversity, and also the most labile in the face of anthropic and natural  
 32 influences that affect the stability of our ecosystems.

#### 33 **3.2. "Cool" oxygen biochemistry**

34 The chemistry of our oceans has evolved considerably [22], especially with the gradual  
 35 production of oxygen, which initially oxidized mantle rocks and dissolved reduced metals  
 36 such as iron then tended to precipitate, as evidenced by red strata in ancient sediment beds.

1 Free oxygen then started to rise in atmospheric concentrations, some of which was split by  
2 cosmic radiations to form the protective ozone layer. Respiration became possible and some  
3 life forms moved out of the oceans, and both aquatic and terrestrial species diversification  
4 started, and with it, organic chemodiversity. It should be emphasized that combustion occurs  
5 at oxygen levels only above 15% and organic matter would spontaneously burn at 25%  
6 concentrations - which explains that life is possible only if the present level (21%) is maintained  
7 around 20% and if genotoxic radiations can be efficiently filtered out. Oxygen is also toxic at  
8 the cellular level, if the production of (or exposure to) reactive oxygen species (ROS) or oxygen  
9 radicals cannot be counterbalanced by antioxidants or if the resulting damages cannot be  
10 repaired. When involved in regular intracellular signaling, ROS can be involved in the  
11 activation of defense metabolic pathways, and contribute to the enrichment of the metabolic  
12 repertoire of planktonic and benthic organisms.

### 13 **3.3. Biochemistry operates under very specific conditions**

14 With the exception of very few extremophiles that can live under elevated temperatures (above  
15 80°C) and hyper acidic environments pH < 2), most microorganisms are not tolerant to  
16 conditions found outside the biosphere. The biosphere represents a very narrow region less  
17 than one thousand times thinner than the globe's diameter, and comparable conditions have  
18 not been found on any other planet so far. This does not mean that dormant bacterial spores  
19 could not withstand intersidereal journeys - lichens have successfully resisted prolonged  
20 exposures in outer space during space craft experimentations. High biodiversity environments  
21 are usually found in warm, stable environments where nutrient cycling is efficient (without  
22 accumulation of wastes) - this is at least true for tropical rainforests and shallow water coral  
23 reefs.

#### 24 *Biodiversity explosions and mass extinctions (from [26])*

25 "Any lasting change in the biogeochemistry of any of the three components (atmosphere,  
26 seawater and land) will disrupt the interfacial equilibrium that supports the many thousands  
27 of life forms that interact constantly within an ecosystem. This has happened several times in  
28 the history of our planet since it became life-supporting. Changes in soil mineral strata indicate  
29 the occurrence of biodiversity-modifying events such as occupation by seas or the occurrence  
30 of an ice-age. Discrete organic layers may indicate the presence of a tropical rainforest or of a  
31 dry land savannah. Datable fossil evidence within these strata, together with paleontological  
32 reconstructions, point out the floristic and faunistic peculiarities of the times. Core drills in ice  
33 provide datable evidence of biogeoclimatic episodes within the last few millennia, while core  
34 drills in massive scleractinian corals give accurate calendar-like records of recurrent or of  
35 accidental climatic events affecting their biotope.

36 Speciation usually goes along with occupation of new territories and new habitats, the first  
37 colonizers having acquired the necessary adaptations to cope with evolving external demands  
38 – the Cambrian explosion (545 million years ago) being the most dramatic example of such  
39 adaptive diversification at all scales.

1 Along with this, evidences of accidental episodes of massive species extinctions are  
 2 witnessed by the sudden “disappearance” of terrestrial and of marine life, that are  
 3 attributable to tectonic, telluric or meteoritic impacts and to their profound and lasting  
 4 climatologic and geochemical consequences. The most significant mass extinction is  
 5 undoubtedly the Permian-Triassic Great Dying [23] where a 96% loss of all non-microbial  
 6 marine life occurred within ten million years. The precise causes of mass extinction events  
 7 may be in connection with continuous tectonic movements with their telluric and volcan-  
 8 ic outbreaks and their climatic consequences, to collisions with meteoritic bodies, and to a  
 9 lesser extent to the appearance of dominant predators, parasites or microbial diseases, or  
 10 to combinations thereof. Common with many extinction events, however, is the massive  
 11 release of greenhouse and of toxic gases (carbon dioxide, methane, hydrogen sulfide etc.).  
 12 The water solubility of CO<sub>2</sub> being nearly 30 times that of oxygen, water acidification occurs  
 13 that impacts preferentially all calcifying organisms with low metabolic rates and weak  
 14 respiratory systems: most coral genera died out during the Great Dying, along with  
 15 calcareous sponges, calcifying algae, echinoderms, bryozoans etc. [24].

16 Interestingly, profound taxonomic changes in all major phyla seem to follow extinction events,  
 17 resulting in a better adapted biodiversity. Nothing is known, however, on the consequence of  
 18 such changes in microbial life or on the putative role microbial associates had on the *reinven-*  
 19 *tion* (understand: adaptive evolution) of new species. As Falkowski [25] puts it, animals and  
 20 plants are merely new incarnations of ancient metabolic processes, but the ultimate key to  
 21 biodiversity may be held by bacteria ferrying the set of core genes that are necessary for life  
 22 to express itself”.

#### 23 **4. Marine biodiversity and chemodiversity today**

24 Water is an extraordinary medium and, in many respects, mysterious. Its outstanding  
 25 solvation properties are due to the capacity of the water dipoles (H-OH) to dissociate,  
 26 reorientate and accommodate salts and polar compounds in a monophasic system [27]. Salts  
 27 are essential to maintain osmotic balance and membrane polarization. Hydration is essential  
 28 for the catalytic properties of enzymes. Semiotic (communication) substances are usually  
 29 released as pheromones (intra-specific signaling) or allomones (against defense or predation).  
 30 In addition, apolar (long chains or cyclic) molecules can be associated with mucus and  
 31 dispersed. Some chemical cues are surface-adsorbed on dead substratum and serve as trans-  
 32 generation signaling, e.g. for the settlement of larvae near adult colonies. Fish have extraor-  
 33 dinary sensitive and selective receptors that allow them to detect specific chemical signatures  
 34 that influence their behavior.

35 Water participates in all life-essential molecular processes, from the most basic (e.g. Miller's  
 36 experiment) to the most complex enzymatic processes, and it has allowed virtually all types  
 37 of interatomic and molecular interactions that have resulted in the highly complex and diverse  
 38 chemical diversity observed in our oceans today.

## 1 4.1. Minerals and geochemical cycles

2 The mineral world is massively involved in global geochemical processes, and in the compo-  
3 sition of solutes in the oceans, as salts and inorganic carbon sources. The cycling of elements  
4 is both tectonic and biogenic. Metals are essential catalysts of many organic reactions, and salts  
5 are actively involved in osmotic balance and membrane polarization. The availability of  
6 heteroatoms (P, S, halogens in particular) is (and has been originally) fundamental in the  
7 evolution of natural organic chemistry, because of their involvement in life-essential processes.

## 8 4.2. Prokaryotes and prokaryote chemistry

9 "Creative" chemistry is the work of living creatures, and Eubacteria and Archaea are probably  
10 the best organic chemists ever. Microbes are the drivers of global biogeochemical processes,  
11 and their genes have survived the great extinction events [28]. They have set the stage for other  
12 organisms to adapt and evolve. The capacity for pioneer organisms to modify their environ-  
13 ment for the benefit of other life forms is termed metabiosis, and it has been largely docu-  
14 mented in soil biology [29], but somewhat overlooked in aquatic ecosystems. They can occupy  
15 every niche of the biosphere, utilize different carbon and/or energy sources available in order  
16 to generate ATP, the energy currency of all biochemical processes.

17 A distinction is made between chemotrophs and phototrophs as primary producers of organic  
18 molecules.

### 19 4.2.1. Chemotrophs

20 Chemotrophic Archaea and Bacteria that live in oxygen-depleted environments (e.g. in the  
21 vicinity of hydrothermal vents) derive their energy from the oxidation of reduced inorganic  
22 compounds and use (i) carbon dioxide as sole carbon source or (ii) lipids, sugars or proteins  
23 to form their own organic compounds. Many scientists believe that life originated in the oceans,  
24 in the absence of light and in the vicinity of underwater tectonic/volcanic activity, under similar  
25 conditions to post-Hadean times.

26 Archaea are recognized among the most abundant living entities in the oceans, participating  
27 in major biochemochemical cycles, such as the Methanogens that produce most the atmospheric  
28 methane greenhouse gas. Halophilic Archaea thrive in hyper saline environments like in the  
29 Dead Sea, sometimes in hyper alkaline conditions (pH around 12). On the other hand,  
30 extremophilic Archaea can be found in hot sulfur springs under pHs as low as 2. They are  
31 either anaerobic and reduce hydrogen sulfide to sulfur, or aerobic and oxidize sulfur to sulfuric  
32 acid. Thermophilic (50-70°C) and hyperthermophilic (70 to 118°C) Archaea produce thermo-  
33 stable enzymes of major biotechnological importance, e.g. in DNA amplification using  
34 polymerase chain reaction (PCR), in food industry, etc.

35 Chemotrophic Eubacteria include chemoautotrophs which utilize inorganic sources and  
36 environmental CO<sub>2</sub>, (like nitrogen-fixing soil bacteria, iron and manganese-oxidizing hydro-  
37 thermal bacteria) and chemoheterotrophs which degrade existing organic substrates. Many  
38 bacteria (Gram-positive Actinomycetes, Bacillus, Gram-negative gamma-Proteobacteria) are

1 chemotrophs, and produce a wide array of bioactive compounds, many of which have strong  
 2 antibiotic potential (examples are given in [30] vol.1, chapter 7). Interestingly, hydrothermal  
 3 vents are crowded with invertebrates (mollusks, crustaceans and worms) that cultivate  
 4 chemotrophic bacteria that provide them with organic nutrients.

#### 5 4.2.2. *Phototrophs*

6 Phototrophs harvest solar photons as the energy source to carry out their cellular energy  
 7 processes.

8 Most phototrophs carry out photosynthesis, a process by which carbon dioxide is converted  
 9 into organic material, used structurally (generally as polymers or supramolecular complexes)  
 10 or functionally for the regulation of cellular processes, or stored as reserves.

11 A trans-membrane electrochemical gradient is created, which is utilized by ATP synthase, to  
 12 create ATP (adenosine triphosphate), the key molecule that fuels biochemical processes in the  
 13 cell, from the oxidation of glucose. Oxygen is generated in the process. Archaea may fix carbon  
 14 and some use light as energy source to create metabolic energy but none is capable of  
 15 photosynthesis with the use of complex electron-transfer chains. Halophilic archaea use  
 16 bacteriorhodopsin instead - a pigment that activates a transmembrane proton pump.

17 Photosynthesis began as an anoxygenic process that later evolved to produce oxygen, thus  
 18 allowing the evolution of aerobic metabolism. Photoautotrophs include most producers of  
 19 primary biomass, from cyanobacteria to algae, plants and are involved as photosymbionts in  
 20 vegetal (e.g. lichen) and animal (e.g. coral) biological photosystems. They are the base of simple  
 21 or highly complex marine and terrestrial food chains.

#### 22 4.2.3. *Heterotrophs - the good, the bad and the ugly*

23 Many bacteria derive their energy from the breakdown of organic substances produced by  
 24 living or dead multicellular organisms. They are instrumental in the recycling of dead organic  
 25 matter, and many strains live as commensals or symbionts of most eukaryotes, to help the  
 26 host's digestion with nutrient assimilation or with the energy-yielding catabolism of proteins,  
 27 carbohydrates and lipids into small, usually water-soluble monomers. A highly diverse  
 28 microflora is generally associated with good health at the single host's level as well as whole  
 29 ecosystems. Pathogens are maintained but their numbers are regulated by complex peer-  
 30 induced antibiotic and bacteriostatic pressure. In corals, metabolic efforts to adapt or com-  
 31 pensate lasting stress (temperature, salinity, hypoxia sometimes in combination) will affect the  
 32 host's resistance, favor the dominance of opportunistic and aggressive strains and dramatically  
 33 reduce microbial diversity, leading to a range of necrotic diseases. In humans, obesity and  
 34 consequential diabetes and cardiovascular diseases strongly correlate with poor feeding habits  
 35 and deficient gut microflora [31].

36 Some strains are downright lethal after acquiring multi-resistance to existing antibiotics, and  
 37 if provided with conditions that trigger their inherent but normally unexpressed pathogenic-  
 38 ity. Some exciting scientific advances have been made since the discovery of quorum sensing

1 in bacteria, the detailed study of microbial biofilms, and in the understanding of lethal  
2 epidemics (e.g. caused by *Vibrio* species). However, by and large, metagenomic studies have  
3 clearly shown that eukaryotic and prokaryotic biodiversity (and hence chemodiversity) are  
4 strongly correlated.

### 5 4.3. Eukaryotes and Eukaryote-associated chemistry

6 Cyanobacteria are thought to have enriched the primitive atmosphere in oxygen, promoting  
7 biodiversity through repeated endosymbioses, i.e. successive fusion-acquisition processes that  
8 led to the complex metabolic machineries of higher plants (origin of plastid organelles) while  
9 ancestral bacteria became incorporated as mitochondria in most eukaryotes. Other organelles  
10 are suspected to have generated from similar mechanisms. Many eukaryotes have successfully  
11 colonized non-aquatic environments.

12 This increase in biodiversity has itself led to competition for existing resources: food, space,  
13 access to light etc.

14 In non-motile organisms (algae, halophytes and some benthic invertebrates) in which escape  
15 responses are not possible, species-specific assortments of physical protections and/or  
16 chemical defenses have evolved to discourage predators. Their remains are collectively termed  
17 biominerals. Some growth forms (encrusting, massive, cryptic) may also

18 resist whole-organism or whole-colony predation, or restrict their access.

19 Algae are generally non-toxic, but may contain antifeedants such as organohalogenes or  
20 polyphenols that are distasteful to fish [32].

21 Not all sessile, slow-moving and sedentary organisms enjoy an efficient physical protection.  
22 Fleshy invertebrate species and those that must be exposed to sunlight to perform photosyn-  
23 thesis may produce toxic or distasteful substances to discourage feeding by fish, crustaceans  
24 or other carnivores. Alcyonarian octocorals shelter photosymbiotic dinoflagellates, and are  
25 able to produce complex bouquets of cyclic terpenoids that are dissuasive against predators  
26 and efficient against space competitors. Sponges shelter biodiverse archaean, eubacterial and  
27 cyanobacterial communities and produce an amazing variety of metabolites (many are  
28 nitrogen containing and halogenated) as a functional consortium. Bryozoans shelter bacteria  
29 that produce highly complex and toxic molecules (e.g. bryostatins). Ascidiaceans can produce  
30 highly bioactive molecules, such as the depsipeptidic didemnins, in association with pro-  
31 chloron, i.e. cyanobacteria which they cultivate in their tissues. The purpose here is not to list  
32 the thousands of amazing molecules that are produced by benthic marine invertebrates, to  
33 which we must add the recently discovered highly diverse repertoire of planktonic organisms:  
34 [31] and its updated version [33] in press) and [34] are probably the most recent and compre-  
35 hensive texts on the subject.

36 Evolutionary reflections of chemical defenses in marine symbiotic systems have been recently  
37 proposed by [35]. Symbiotic and photosymbiotic systems that associate an invertebrate or algal  
38 host and its specific microbial consortium are common in tropical shallow water reefs, which  
39 concentrate at least one third of the total marine biodiversity and certainly the largest propor-

1 tion of all known "secondary" metabolites [26]. To these must be added marine fungi and  
2 actinobacteria that live in marine sediments.

3 A generally overlooked component of marine chemodiversity is mucus, sometimes constantly  
4 and abundantly produced by epithelial goblet cells of cnidarians, and also found in other  
5 sessile invertebrates, and also in fish. No two mucii are alike. In fish, it helps protecting scales  
6 from unwanted fouling by encrusters or parasites, as well as having intrinsic antibacterial and  
7 antiviral properties. Coral mucus has species-specific composition and plays a role equivalent  
8 to the organ-forming mesoderm of triploblastic organisms, in managing a highly biodiverse  
9 microbial fauna that recycles carbon, nitrogen and sulfur and provides an energy complement  
10 to symbiotic photosynthesis. To the coral associated bacteria mucus plays the role of a biofilm  
11 in which complex antibiotic interactions are at play to maintain microbial diversity.

12 Behavioral adaptations like "advertising" (aposematic) colors and body shapes make use of  
13 colored metabolites borrowed from the prey organisms and concentrated into superficial  
14 diverticula. Specialist predators like shell-less mollusks like dorid nudibranchs are beautifully  
15 colored and highly toxic. Several aeolid nudibranchs on the other hand use camouflage for  
16 similar reasons.

## 17 **5. Uses of marine natural products**

18 Marine biogenic molecules are used in a large variety of applications, industrial, medical,  
19 pharmaceutical, cosmetological, as food or associated to food, decoration...

### 20 **5.1. Housing and transportation matters**

21 These include the use of fossilized or detritic materials for construction and as chemical energy  
22 sources.

#### 23 *5.1.1. Construction materials*

24 Biogenic sand and rocks (e.g. sandstone) are used to create building, roads and associated  
25 structures. Urban architecture is mostly made of concrete structures, i.e. cemented biogenic or  
26 mineral sand and crushed rocks or debris.

#### 27 *5.1.2. Fossil fuels and biofuels*

28 Fossil fuels are consumed at the rate of 88 million barrels a day, in heat engines, to produce  
29 electricity, domestic heating, and in petrochemical chemistry (plastics, clothing, lubricants,  
30 polymers). Fossil fuels are non-renewable energy, since the production rate is about one-  
31 million times slower the consumption rate.

### 32 **5.2. Health and well-being**

33 This includes the use of biomineral or bioorganic materials in surgery, of cosmetics and skin  
34 care substances, and most of all of anticancer, antiviral, anti-pain, antibiotic, anti-inflamma-

1 tory, as well as insecticidal, anti-malarial or anthelmintic molecules, not to mention other  
2 domains of growing interest, such as Alzheimer's disease and schizophrenia.

3 The exploitation of marine natural products in folk medicine is very limited and concerns a  
4 few organisms that did not necessitate special underwater investigations, nor entail storage  
5 and conservation problems - of paramount importance since desiccation, oxidation and  
6 fermentation occur so rapidly. Exceptions are the occasional use of specific algae as insecticides  
7 and for ringworm treatment, or the ceremonial use of toxic or venomous organisms. Fixed and  
8 fleshy organisms were generally distasteful or toxic, sparing them for being considered as  
9 remedies. Corals, sponges and a few others have no nutritional value and represent the largest  
10 biomass of high-diversity systems in tropical zones.

11 It is only since just after WW2 that marine organisms emerged as a complementary source to  
12 traditional plant remedies, thanks to the co-occurrence of several factors, among which (i) the  
13 recent discovery of fungal antibiotics and the use of bacterial enzymes in bioprocesses, (ii) the  
14 development of adequate screening procedures, (iii) SCUBA exploration and later robot-  
15 sampling in oceanic depths. The development of synthetic chemistry soon became necessary  
16 to provide alternative sources for rare organisms, but also to find better analogues (more active,  
17 less toxic, more soluble, better tolerated, easier and cheaper to synthesize...).

18 A new biotechnological turn has recently been taken with the high capacity screening of vast  
19 libraries of synthetic analogues, with the development of biomimetic chemistry and with the  
20 use of genetic tools that allow bacterial carriers like *Escherichia coli* to produce a compound of  
21 interest after insertion of the set of genes sampled from the original biological source.

22 Marine molecular sciences have now come of age, but the exploration of novel natural products  
23 and of new biological activities must go on, especially in relation to marine microbes and to  
24 planktonic organisms.

25 Many (98 to 99%) of the known marine bacteria and archaea still cannot be cultivated using  
26 the existing apparatus and growth media. Knowing that invertebrates such as sponges,  
27 ascidians, bryozoans act as biological incubators of specific bacterial strains, isolated in  
28 specialized cells called bacteriocytes or allowed to interact synergistically, there is a world of  
29 possibilities opened for us to investigate. After all, we only discovered recently that bacteria  
30 have a form of social life within biofilms, have developed a chemical language that allows their  
31 populations to be regulated, have an instrumental role in carbon and nitrogen cycling in  
32 holobiont photosystems such as corals, lichens etc. and in biogeochemical cycles at large [28].

33 Indeed we still have no idea of the importance bacteria have in the production or in the  
34 modulation of the genetic expression of key metabolites hitherto attributed to their host  
35 organisms, except through limited attempts to cultivate the latter axenically. Using a systems  
36 biology approach, stress transcriptomics studies will undoubtedly help us achieve better  
37 control of the production of key enzymes or key defense metabolites from host organisms, as  
38 well as evaluate the optimal conditions for the maintenance of a rich and diverse microflora  
39 using metagenomics.

40 The purpose here is not to list the bioactive molecules that have been discovered, elucidated,  
41 synthesized, nor to detail their bioactivities. Excellent reviews are regularly updated on the

1 subject, presented by natural products chemists and pharmacologists. Interactive databases  
2 include standard spectral information, and sophisticated algorithms are available as aids for  
3 structure elucidation and as dereplication tools. Two recent and outstanding information  
4 sources are [31] and its updated version [33], and [34].

5 Well over 20,000 secondary metabolites have been screened so far, but only a handful is now  
6 legally approved for use as prescription drugs or treatments by the Food and Drugs Admin-  
7 istration (FDA) and by the European Union since 1974 (see [36] and updates thereof in: [http://](http://marinepharmacology.midwestern.edu/clinPipeline.htm)  
8 [marinepharmacology.midwestern.edu/clinPipeline.htm](http://marinepharmacology.midwestern.edu/clinPipeline.htm)). Successful molecules and ana-  
9 logues have to undergo in-vitro, in-vivo (preclinical) tests and finally several rounds of clinical  
10 trials on patients, a process known as the clinical pipeline. On average, each development costs  
11 about one billion dollars over a period of ten years, and there is great pressure to discover and  
12 develop novel molecules, especially against various types of cancer, antibiotics against  
13 resistant strains, and molecules for the treatment of neurodegenerative diseases. With energy,  
14 food and housing, pharmaceuticals represent a primary resource in modern economy.

### 15 5.3. High-tech

16 Siliceous skeletons are transformed from dissolved silicic acid into very elaborate structures  
17 by diatoms and radiolarians. They not only serve a structural function: they allow sunlight to  
18 penetrate for photosynthesis, and there is evidence that harmful radiations are filtered out  
19 somewhat like our sunglasses, using embedded mycosporine-like amino acids as DNA-  
20 protective sunscreens [37]. Enzymes that are capable of creating optical-grade glass at room  
21 temperature are under investigation. Siliceous sponges produce glass spicules which are  
22 endowed with mechanical and optical properties unknown to manufacturers, and novel  
23 enzymatic approaches using sponge silicateins are investigated for nanotechnological and  
24 biomedical applications [38].

25 Shells of bivalve and gastropod mollusks, other than their interest as decorative items, often  
26 present amazing properties. Oyster nacre has osteo-inductive properties that could be used in  
27 bone tissue regeneration [39]. Abalone shells offer strong mechanical resistance to impact,  
28 thanks to its dual organic-limestone microscopically layered structure, inspiring novel  
29 bulletproof materials. Skeletons that are produced by sessile marine invertebrates are a great  
30 source of inspiration: some have tremendous flexibility and resilience to currents, like the  
31 horny skeleton of some gorgonians [40]; coral skeletons are used as temporary bone implants  
32 [41], coralline algae cements have amazing particle-aggregating properties, etc. Novel  
33 adhesives with high tensile strength are inspired from byssus filaments of mussels. Crab shells  
34 can provide a sustainable source of chitin and chitosan, which are used in a variety of medical  
35 and laboratory applications [42].

36 Bacteria can be modified genetically to produce pure toxins, antibiotics, polymers and enzymes  
37 with high added value. Cultivable bacterial strains offer exciting possibilities for the  
38 transformation or the recycling of a wide range of industrial materials and agricultural waste  
39 products. Experimental biofilms can produce weak currents with potential applications in  
40 sewage treatment plants.

## 1 **6. Management of biodiversity and chemodiversity**

2 Global anthropic influence is articulated on the exploitation of natural resources and the  
3 generation of wastes. Here are a few examples of man's use of biogenic resources, mineral and  
4 organic, fossil or live.

### 5 **6.1. Urban development**

6 The use of biogenic sand and limestone concretions usually involves no direct utilization of  
7 live organisms. Indirectly, the overexploitation of sand beds from littoral zones represents a  
8 double problem: the eradication of the epibenthic wildlife and with time, erosive changes in  
9 coastal profiling. Sand particles offer extended surfaces that are essential for microorganisms  
10 to recycle decaying organic debris and avoid the accumulation of toxic nitrites and nitrates.  
11 The exploitation of sands from coral reef atolls, together with the silting of coastal bays and  
12 leeward zones due to mining activities spillage are major sources of biodiversity loss.

### 13 **6.2. Energy**

14 The use of fossil hydrocarbons extracted from the Mexican Gulf, the Northern Sea etc., as  
15 energy sources results in the volatilization of carbon in the atmosphere at rates up to one  
16 million times faster than it took for phytoplankton to fix and sequester it into sediments as oil  
17 beds [25]. Atmospheric accumulation of carbon dioxide, methane, sulphur dioxide and other  
18 combustion products, create an artificial greenhouse effect after only 150 years of exploitation  
19 (now largely marine), adding to natural volcanic activity. Global warming and ocean acidifi-  
20 cation are both regarded as major potential sources of marine biodiversity destruction [43].

21 Biodiversity loss seems to be the inevitable toll to pay for a global economic expansion relying  
22 heavily on the use of biogenic productions. When such exploitations occur at the vicinity of  
23 marine biodiversity hotspots (coral reefs for example), which concentrate much of the useful  
24 and yet unexplored chemical diversity [26], we run into the risk of losing a lot of useful model  
25 molecules and end up with a hostile, impoverished microbial world instead [44].

### 26 **6.3. Drugs and ethics**

27 Drugs are basically dangerous when ingested, injected or applied externally without caution,  
28 and man has always made the difference between edibles and toxic or venomous substances,  
29 or foodstuff corrupted with microbes. Medicine men and witch doctors knew empirically how  
30 to use fresh plants and how to blend them to cure fevers, wounds and other ailments, and this  
31 knowledge was passed on exclusively to younger initiates who henceforth gained access to  
32 special social status and were highly respected. Today, bioactive substances are patented and  
33 the administration of prescription drugs is tightly controlled. As mentioned earlier, the drug  
34 industry is one of the very few primary sources of revenue in any country's economy. Explo-  
35 ration of novel sources of natural products in biodiversity hotspots, terrestrial or marine, is a  
36 touchy subject. Intellectual property should be shared in the benefit of local populations,  
37 eventually leading to their active participation in the cultivation and the preparation and

1 purification of extracts, on a non-destructive and sustainable basis. This is especially true for  
 2 developments that were guided by ethnopharmacological surveys, i.e. the participation of  
 3 local medicine men. Marine bioexploration, however, is almost exclusively based on system-  
 4 atic screening of marine plants, invertebrates and microbes, but it should be subjected to  
 5 territorial laws like the exploitation of forests, fishing zones or mines in a participative manner.  
 6 More specifically, endangered or rare species should be identified, and sampling procedures  
 7 be conducted in accordance with internationally established practices [45].

## 8 **6.4. Food**

9 We have purposely ignored aspects directly related to food, i.e. the exploitation of marine  
 10 resources through fisheries and the farming of selected fish and seafood species. The sustain-  
 11 able management of natural stocks and the influence of global warming on natural biodiversity  
 12 profiles is a major concern in the 21st century. Human population has almost trebled since  
 13 WWII, and *Homo sapiens* dominates terrestrial vertebrate biomass (half a billion tons) to the  
 14 point that meat protein supplies will be scarcer. After being a hunter-gatherer, man has become  
 15 a farmer and he is now turning towards artificially produced biomass that has food value,  
 16 grown from cultured transgenic cells. What next?

17 The management of natural sanctuaries that are subjected to minimal interference, with sizes  
 18 large enough to have a self-regenerating biodiversity (and chemodiversity), and tightly  
 19 controlled environmental connectivity, should be encouraged.

## 20 **7. Pollution**

21 Man does not always recycle the wastes he generates, far from it.

### 22 **7.1. Urban developments**

23 There are two major issues to consider: one is structural and the other is biological.

24 Structural issues are linked to urban planning and the exploitation of natural zones, and to the  
 25 fate of obsolete constructions and roads that cannot be recycled back into their original  
 26 components - the net result being a shift from marine destructive exploitation (sand) to  
 27 terrestrial pollution (discharges). Wherever possible, alternatives to marine sand must be  
 28 sought for housing, to save the resource and perhaps use recycled wood-based products and  
 29 recyclable organic polymers.

30 Biological issues emerge from the disposal of untreated sewage, of fertilizers, pesticides, drugs,  
 31 household maintenance products and industrial by-products. Regarding sewage, local  
 32 enrichment of waterways and coastal areas, especially in nitrogen and phosphorus, causes  
 33 toxic phytoplankton blooms, and unwanted algal proliferations that tend to displace indige-  
 34 nous species. This is especially true for complex oligotrophic ecosystems in which nutrients  
 35 are efficiently used and recycled. In coral reefs, bacterial charges are introduced directly or via

1 invasive algal proliferations [46], favoring the dominance of pathogenic strains and reducing  
2 the natural microbial diversity [47], [43].

### 3 **7.2. Energy**

4 Regarding energy-related matters, losses due extraction and transport (ship degassing, black  
5 tides due to wreckages etc.) are the cause of episodic but massive biodiversity destructions in  
6 littoral zones, by asphyxiating wildlife and by destroying skin protection barrier. The exploi-  
7 tation of light hydrocarbons from shales is currently the subject of intense debates, especially  
8 regarding its consequences on water quality [48]. The exploitation of gas hydrates represents  
9 an attractive energy source, but its exploitation may prove difficult to control, and its release  
10 from the thawing of the permafrost due to global warming difficult to evaluate [49].

### 11 **7.3. Synthetic drugs, artificial molecules, genetically modified organisms**

12 The modern world is global and highly competitive. Being positioned on an economic niche  
13 requires achieving results and outcompeting contenders, no matter what the human and  
14 environmental consequences are in the long term. Thousands of synthetic molecules - insecti-  
15 cides, herbicides, pharmaceuticals, conditioning agents, food additives, fuel additives,  
16 lubricants, household products, plasticizers, flame retardants, to name a few- have been  
17 synthesized without sufficiently questioning their degradability and speciation once released  
18 in the environment or abandoned, or offering detoxication, storage/disposal or reusability  
19 solutions. Highly reactive pesticides can cause immediate non-specific destruction to useful  
20 pollinizing insects and kill birds, others may insidiously find their way up the food chains and  
21 eventually poison top predators - this is the case of highly stable and carcinogenic biphenyl  
22 organohalogens. Chronic allergies and cancers are documented through the regular exposure  
23 to more and more food additives and household products. Specific information can be obtained  
24 from associative websites.

25 If there are no simple replacement solutions in most cases, perhaps revisiting global commer-  
26 cial practices, promoting local products and values and favoring educational resources  
27 (preferably non-virtual) centered on the practical resolution of local issues, will help establish  
28 respectable ethics and restore some dignity.

## 29 **8. Rearranging clouds in times of global changes?**

30 We are in the midst of the worldwide race for economic development and global trading, with  
31 their extraordinary demands on natural resources and their inevitable environmental issues.  
32 While striving to maintain social equilibrium at the same time, why not take a pause and ask  
33 ourselves not only where we are going, but simply how we are going? How can we know how  
34 we are going?

35 The prestigious graduate schools, the most popular jobs in western and industrialized  
36 countries are linked with the world of finance. Get closer to the sources, react faster and make

1 the optimal decision before anyone else does. Sophisticated algorithms are being developed  
 2 by highly paid experts to better analyze tendencies and make predictions, from a phenomenal  
 3 amount of cross-analyzed sources of diverse natures. Lists of potential customer's addresses  
 4 are sold, exchanged, stolen. Cloud metadata and then trituated and sent back to the average  
 5 human as a continuous shower of commercial ads, enticing e-mails, spurious spams, in the  
 6 hope of creating habits and develop ruinous compulsions? Along the same line, potential crime  
 7 scenes can now be anticipated with amazing probability rates by the Californian police, thanks  
 8 to the work of metadata experts.

9 Global changes are on the way, noticeable since the70's with the accelerating atmospheric  
 10 enrichment of greenhouse gases. Science and technology have made extraordinary progress  
 11 at the same time, but mostly dedicated to the continuing exploration of the unknown "before  
 12 it is too late", and too little to addressing pressing environmental issues with the huge losses  
 13 in biodiversity that are envisioned by many in the next decades. Cutting edge medical research  
 14 has been fuelled by the need to face new challenges, in cancerology, in microbial pathologies,  
 15 in immune or rare diseases. Highly efficient molecular investigations from gene mining to the  
 16 knowledge and control of their expression repertoire, whole organism approaches, continu-  
 17 ously updated cutting-edge equipment - are being applied to exploratory science and projec-  
 18 tions into future scenarios. Huge supercomputers are piling up petabytes of data waiting for  
 19 bioinformatics advances to organize and make sense of them, and in the quest of the reassuring  
 20 "big picture" that will once for all settle intellectual disputes, quench the thirst for the unknown,  
 21 and with the hope that, ultimately, some biogeoclimatic equilibrium will be automatically  
 22 restored no matter what.

23 How most of us are doing depends not on fluctuations of the stock market, nor on the price of  
 24 the latest hi-tech widget, nor on whether the next crime scene is going to take place in our  
 25 neighborhood, but on how fast our natural environment is going to degrade. Why not redirect  
 26 our priorities and efforts to better understand how our biosphere functions, how species  
 27 interact, how biomes are connected, how biodiversity is maintained in marine and terrestrial  
 28 environments?

29 We generate enormous amounts of data of genomic, chemical, taxonomic, pharmacological,  
 30 biotechnological value that can be better analyzed.

31 Dealing with environmental issues, the first question is the preparation of environmental  
 32 databases, our "clouds"- the crucial initial step. What "standard" environment will be suitable  
 33 to monitor long-term changes? Climatic changes being *global* (temperature rises, ocean  
 34 acidification etc.) and heavily influenced by human activities, one can only define a study zone  
 35 as representative of a "standard environment" if it is not *locally* impacted by *direct* human  
 36 interference (habitat destruction, introduction of alien species, chemical and microbiological  
 37 pollution...). Fluctuations in parameters of interest must not be subjected to amplitudes higher  
 38 than those of experimental (read: impacted) study zones, and sampling must be large and  
 39 statistically significant for the "standard" database to be robust and reliable enough to evidence  
 40 mild to severe changes in same parameters from experimental study zones. This applies not

1 only to physico-chemical parameters, but also to genomics, transcriptomics or metabolomics  
2 metadata (e.g. microbial metagenomics). We need markers within variables, sentinel species  
3 within populations, signatures within metabolomes, early responses within complete tran-  
4 scriptomic repertoires, and so on. Some advocate the use of artificial biological systems, a  
5 synthetic biology approach, to standardize sampling procedures. Whole-area imaging can  
6 make use of drones that interfere very little with wildlife and biological processes. Coupled  
7 with appropriate mathematical tools, automation can be achieved and time-dependent  
8 evolution of e.g. natural processes can be predicted.

9 Thus, whether comparing experimental vs. control areas, or monitoring the evolution of the  
10 same locality in time, or analyzing *connectivity*, enormous amounts of data are being generated  
11 that need trimming, arranging, cross-checking to be usefully interpreted. And beyond  
12 assessing the evolution of a situation, we need to predict, for example, the degradation in the  
13 biodiversity of impacted areas if no corrective action is taken. Neural networks that are  
14 "educated" by so-called genetic algorithms are currently very successfully exploited, in  
15 economics, in business, and in forensic science, to open what is known as "windows of  
16 opportunities" (to seize, but also to take corrective measures). These were created by scientists  
17 to treat scientific questions in the first place! Beyond our biosphere's apparent complexity,  
18 what it contains are quantitatively and qualitatively finite entities, subjected to predictable  
19 dynamics. There is no reason not to apply these analytical methods to create ready-to-use tools  
20 legislation can rely upon to regulate the appropriation of natural resources: water, wood, sand,  
21 fossil fuel, minerals... and wildlife. In the same way as DNA tests are used to help solve  
22 criminal investigation by 'showing irrefutable evidence', molecular tools applied to systems  
23 biology in association with multi-scale imaging tools can be tailored by analysts to guide our  
24 choices towards a more responsible management of natural resources.

25 We need a generation of motivated young analysts to use their skills to extract the useful  
26 information and blow away the dust. The big pictures might then emerge at last, as the clouds  
27 dissipate, ready to inspire us with a better scenario. The following phrase by Salvatore Manga  
28 no [50] "*Genetic Algorithms are good at taking large, potentially huge search spaces and navigating*  
29 *them, looking for optimal combinations of things, solutions you might not otherwise find in a life-*  
30 *time*" makes needle-in-the haystack problems tractable. After all, we live on a planet with finite  
31 resources, our only problem now is to make them last for the benefit of the generations to come.  
32 If machines can learn, hopefully humans can too....

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37 will always be remembered by those who knew him.

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