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Neuroscience and computation

From January 7th to April 12th 2002, the Emile Borel Center at the Henri Poincaré Institute (I.H.P.) in Paris welcomed for the first time a postgraduate program fully dedicated to Computational Neuroscience. The planning and final organization of this teaching and research-dedicated program were initiated by an interdisciplinary team of researchers working in Systems Neuroscience and Theoretical Physics. The fact that this unusual enterprise received, in addition to the help of the I.H.P., the combined support of the Centre National de la Recherche Scientifique, the French Ministry of Education and Research, the French Ministry of Foreign Affairs, the Ecole Normale Supérieure, three Parisian Science Universities (Paris 6, 7 and 11) and the Collège de France, is a sign of the growing importance of theoretical and modeling approaches in Neuroscience. A teaching faculty composed of 14 foreign experts gathered and gave lectures for the Neuroscience PhD program of Paris 6, and the joint Cognitive Science PhD program of Paris 6, E.H.E.S.S., Ecole Polytechnique and Ecole Normale Supérieure. The whole series of lectures and seminars were attended by several hundred French students and junior researchers. During the same time period, a series of international symposia was organized, and the present issue of the Journal of Physiology (Paris) comprises scientific written contributions corresponding to a selection of the oral presentations.

The contributors, theorists and experimentalists, develop their own models as explanatory tools of a given field, or acquire data that become central to the validation of computational models. The underlying theoretical approaches range from simple and enlightening models that may be solved exactly, yielding equations that relate the key parameters of the problem in a quantitative manner, to detailed biophysical models of neurons and networks that aim at realism and comprehensiveness. In this latter case, a complexity level is added, and the model dynamics is most often studied numerically. Even though system neuroscience remains an experimental discipline highly dependent on available tools of observation, modeling has been constantly exerting a conceptual influence on this experimental field, and this is now largely recognized.

1. Impact of modeling in neuroscience

The impact of modeling on neuroscience can be felt at several levels. First, it has shaped our understanding of the integrative function of excitable cells, ever since the pioneering work of Louis Lapicque, who introduced in 1907 the 'integrate-and-fire' model well before intracellular recordings were mastered [14]; the integrate-and-fire model is still widely used by modelers of networks (see e.g. [4]). Some fifty years later, Hodgkin and Huxley published a seminal paper, which was to become a Nobel prize winner, that elucidated the mechanisms of action potential generation and propagation [11]. By combining recordings from the squid giant axon and numerical resolutions of non-linear differential equations, an explicit model of the trajectory of membrane potential was formulated as a function of activation and inactivation constants of identified ionic channels.

As a third example, much of our understanding of synaptic integration at the single cell level still comes from the "cable theory" of Wilfred Rall, who gained strong insights into dendritic function by solving the parabolic differential equation that describes membrane potential equalization [21]. This paved the way for numerical studies of dendritic function using compartmental models. Such studies allow researchers to investigate how nonlinearities of the dendritic membrane affect the operating principles of neurons. The consequence is that the integration step realized by single neurons along their dendrites and spines could no longer be seen as a simple thresholding operation applied to the linear combination of multiple inputs weighted by their respective synaptic strength, as in McCulloch and Pitts' formalism [18]. As anticipated by Rodolfo Llinas [15] and Tomaso Poggio [20], the neuron should be considered as a complex computing element, that may extract spatio-temporal correlations from its inputs and perform non-linear operations on them [1,3,6]. Theory has also shed new light on how neurons produce specific discharge patterns, thanks to bifurcation theory and (multi-parameter) singular perturbation theory, and how they encode information on synaptic inputs in these spike trains.

A decisive impact of the theoretical field can be found not only when considering the local input-output transformation performed by individual cells, but also when analyzing the emergence of collective properties at the network level. Theory and modeling of distributed systems entered a period of fast growth starting at the turn of the 1970s and even more significantly at the beginning of the 1980s. Over the years, a number of theoretical studies have taken in its literal sense the concept of cell assembly introduced by the famous Canadian psychophysiologist Donald Hebb, and portrayed in his recently re-edited essay "The Organization of Behavior", [9]. These studies have investigated how the collective behavior of large populations of units may lead to a distributed representation of information [7,10,13,17]. A landmark was set by John Hopfield, who showed that major features of associative memory could be accounted for by a simple model of attractor neural network [12]. This model, which could be solved using methods borrowed from the Statistical Mechanics of disordered systems [2], showed the power of the physical approach for studying the collective dynamics of large neuronal networks. The last decades have deepened our understanding of the collective properties of large networks, to the point that theoretical models are now shaping to a large degree our understanding of the dynamics of many brain areas, from the generation of selectivity in visual or other sensory cortices, persistent activity in association cortices in relationship with working memory, to synchronization, to mention just a few examples. Finally, theory is also guiding research on synaptic plasticity and learning [5,8].

2. Interplay between theory and experiment

The work of Hodgkin and Huxley provides a perfect example of a tight interaction between theory and experiment. Their model was grounded on voltage-clamp data, and its predictions were tested against the results of current-clamp experiments on the squid axon. Such a direct interplay between theory and experiment is the exception rather than the rule in Neuroscience, as in many other scientific fields. This is well illustrated by cable theory, which allowed scientists to tackle the difficult problem of synaptic integration at a time where recordings in dendrites of neurons could not be performed. This simple theoretical approach, relying on a linear equation, provided new concepts (e.g., space constant, voltage equalization) that enabled experimentalists to infer from intracellular recordings at the soma what was actually happening on dendrites. It also corrected a lot of misconceptions on the impact of synapses located on the soma or on the dendrites, and introduced many important new ideas on synaptic integration (role of dendritic spines, on the path inhibition...). Very similar remarks could be made concerning collective properties in neural networks: theoretical work makes it possible to explore all the consequences of a given explanatory model, without being limited by current observational constraints.

These experimental limitations are steadily dwindling. Over the last 20 years, we have witnessed the spectacular development of many new experimental techniques at multiple spatial and temporal scales of observations, from membrane molecules to interacting cortical areas, and from channel gating at the sub-millisecond scale to long term memory. Examples of such new techniques are intra-dendritic recordings using infra-red video-microscopy, intracellular recordings in the neocortex in vivo, dynamic clamp, simultaneous multiple recordings, two-photon calcium imaging, in vivo intrinsic and extrinsic optical imaging, fMRI or MEG. Patch-clamp recordings in dendrites and immunofluorescence studies shed a new light on the structural properties of neurons, reemphasizing the utmost importance of membrane nonlinearities. At the other end of the spectrum, imaging techniques find more specific applications in the unraveling of the localization of cognitive functions of cortical areas in the higher vertebrate brain and the genesis of mental representations. Analysis of the brain activity should be enriched in the near future by the combination of intracellular recordings together with optical imaging of microdomains (2-photons, voltage sensitive dyes), and simultaneous multiple extracellular recordings with stereotrodes sampling along the columnar or layer plane axis.

This explosion of techniques appeals to the parallel development of theoretical approaches for making sense of new experimental data that constantly challenge our vision of the nervous system. In particular, major problems still arise in the interpretation of macroscale activation patterns, because brain imaging techniques (such as fMRI, PET, EEG-MEG) are based on descriptive variables that differ from those used to monitor activity at a more microscopic level of organization. For instance, changes in metabolic or hemodynamic patterns reflect only partially the discrete, and more spatially distributed, changes in neural activity [16]. One should also strive not to fall again into the trap of phrenology reopened by modern brain imaging techniques and rather focus on elucidating in depth the computational implications of the complexity and diversity observed at the neuronal level.

An important challenge is to link the various levels of organization through space and time. Theoretical methods include powerful tools to understand the emergence of unique properties at a given integration level which are absent at a lower level of organization. They are particularly appropriate to apprehend the collective dynamics of large neuronal ensembles. However, the functions of the nervous system are not easily

deducible from the behavior of its neural structures in isolation. This was well illustrated by invertebrate electrophysiology, where neuromodulatory inputs from other structures reconfigure intrinsic excitability properties of cells, thereby changing the activity pattern of the network [19]. New methodological and conceptual tools will probably be necessary to understand dynamics at a higher level and unravel cognitive functions of cortical areas in the higher vertebrate brain, and the genesis of mental representations.

3. Topics covered in this special issue

In that context it has seemed fit to organize, within the framework of the IHP program, three topical workshops combining the viewpoints of theoreticians, with a dominant background in Mathematics, Theoretical Physics, Computer Science or Engineering, and experimentalists, trained in physiology, psychophysics and cognitive psychology:

From synaptic to brain imaging (14–16 January 2002)
Homeostasis, plasticity and learning: from experiments to algorithms (4–6 March 2002)
Functional representations and dynamics of cell assemblies (8–10 April 2002)

Given the success of these workshops, we decided to publish the proceedings of the *Trimester in Computational Neuroscience* as a special issue of Journal of Physiology (Paris). We asked all the participants (both faculty and invited workshop speakers) to write a contribution presenting a recent and exciting research development that might also be useful as a short tutorial on the issue discussed. A total of 24 participants contributed to this endeavor, and we wish to thank them for their efforts. Although this collection of manuscripts represents a random sampling of the topics discussed during the trimester, we decided on a simple plan, from cellular aspects to the integrated operation of the nervous system. The first part of the volume is dedicated to plasticity, which has been the subject of many lectures and the topic of the second workshop. The next two parts are devoted to the network level, with theoretical and experimental investigations into how computations are performed in specific systems. The second part deals with sensory systems and largely focuses on visual perception. The third part puts the emphasis on limbic and motor systems. Finally, the last part of the special issue presents approaches attempts to characterize dynamics at the brain and systems level. It groups data analyses of imaging experiments and theoretical contributions grounded in the concept of computation by attractors.

Finally we are grateful to the Scientific Committee of the Emile Borel Centre at I.H.P. for giving us this unique opportunity of organizing a trimester on Computational Neuroscience, and it is a pleasure to thank all the staff at I.H.P. for his kindness and remarkable efficiency.

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