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Introductory Article

A future for systems and computational neuroscience in France?

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Abstract

This special issue of the Journal of Physiology, Paris, is an outcome of NeuroComp'06, the first French conference in Computational Neuroscience. The preparation for this conference, held at Pont-à-Mousson in October 2006, was accompanied by a survey which has resulted in an up-to-date inventory of human resources and labs in France concerned with this emerging new field of research (see team directory in http://neurocomp.risc.cnrs.fr/). This thematic JPP issue gathers some of the key scientific presentations made on the occasion of this first interdisciplinary meeting, which should soon become recognized as a yearly national conference representative of a new scientific community. The present introductory paper presents the general scientific context of the conference and reviews some of the historical and conceptual foundations of Systems and Computational Neuroscience in France.

One aim of Computational Neuroscience is to develop analysis and calculus methods and exploratory models to aid in understanding the links between structures and functions in the brain, at different scales in space and time. Two approaches are generally distinguished, one synthetic and "bottom up", where the brain is viewed as a nested hierarchy of Russian doll sub-elements, and the other "top down", more prediction driven. In the former case, no assumption is made about the functionality of the system and the emergent properties of the "whole" are derived from the "parts" and their interactions. In the latter case, in a kind of Bayesian approach, the prior knowledge of the global operation realized by the system is used to dissect out the generating components and organizational principles (Churchland and Sejnowski, 1988, 1992). A direct application of this dual approach in the field of Neuroscience has been to provide a better understanding of brain functions and dysfunctions, by integrating different levels of description ranging from molecules to behavior. Another aim is to explore new methods for visualizing, merging and processing information fed by multiple biological sources/sensors/modalities. The next frontier, to be reached with the help of generalized brain databases and neuroinformatics, is the production of innovative technological devices, and biologically-driven cybernetic tools: brain activity will be used to control in real-time distributed man-made artifacts such as robotic machines and virtual computing devices (see Fig. 1).

1. Foundations of systems and computational neuroscience

Research in Integrative (or Systems) Neuroscience has its real beginnings in France at the beginning of the 1940s at the Institut Marey, when Alfred Fessard installed his first electrophysiology lab with the help of Louis Lapicque and Henri Piéron. After the Second World War, between 1946 and 1960, Alfred Fessard was joined by a series of talented scientists such as Pierre Buser, Ladislav Tauc, Jacques Paillard and Jean Scherrer. Together, they created under his leadership a unique research group, whose development was nurtured principally by the Centre National de la Recherche Scientifique (CNRS) (at a time

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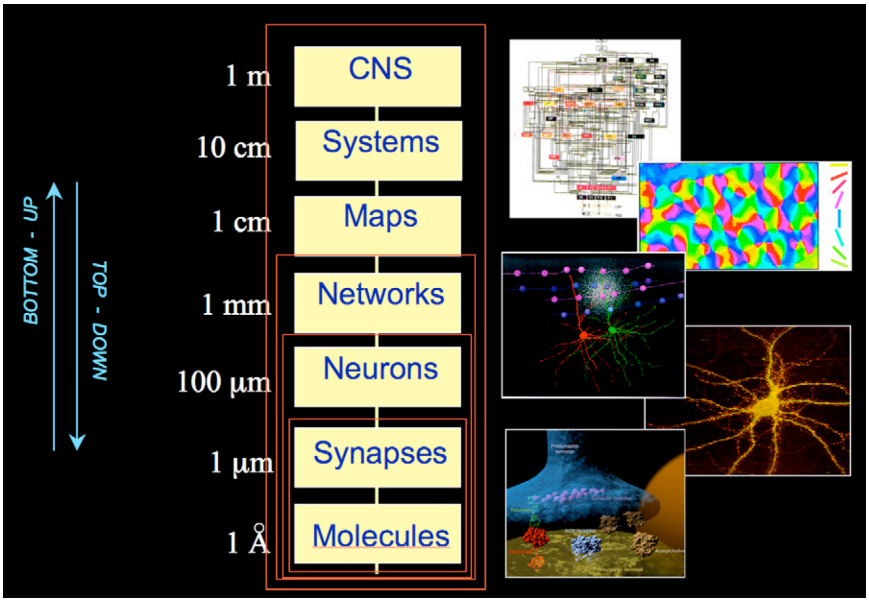

Fig. 1. Spatial integration scales in the nervous system and nested hierarchy of levels of organization. The spatial scale at which structural and functional organization can be identified varies over many orders of magnitude. Icons to the right represent structures at distinct levels in a bottom-up fashion: (bottom) a chemical synapse, (middle-bottom) a biological cell reconstruction, (middle) a full network model, (middle-top) map of orientation preference in a mammalian primary visual cortical area; (top) the subset of visual areas forming visual cortex and their interconnections (adapted from Frégnac et al., 2007).

when the new National Research Agency (ANR) was not yet ruling the game). It is remarkable to note that most of the current dominant group of leaders and elders in the field of Cellular and Systems Neuroscience in France are to a certain extent spiritual sons of scientists trained at this remarkable historical research center. The most illustrative example is the success story of the American–Austrian Nobel Prize laureate, Eric Kandel: some of his pioneer observations linking neural network architecture and intrinsic properties of cells to function and behavior in Aplysia were made during his stay in Ladislav Tauc's lab, when he moved from Marey to the new CNRS campus of Gif-sur-Yvette. Alfred Fessard, whose scientific interests were open to theoretical biology as well as to experimental neurophysiology, was also the first leading scientist to create a seminar in “Computational Neurosciences” in the 70s, when he was Professor at the College de France (a seminar in which some of us had the pleasure to participate). Sadly, the witnesses of this golden era are gone: the time where talented Americans emigrated for France to do their PostDocs is unfortunately over; the Institut Marey no longer exists and its ashes are now buried in the clay courts of the Roland Garros Tennis Stadium (host to the French Open).

Nevertheless, after an intensive phase of dissemination under the leadership of Fessard's disciples in the 1960s and 1970s, Systems Neuroscience reached a recognized status in French research. In particular, new techniques in Brain Imaging have revitalized the search for macroscale structure–function correlation (e.g. Del Cul et al., 2007) and strengthened intensive collaborative efforts between CNRS, INSERM, INRIA and CEA (http://www.meteore-service.com/neurospin/) with, in some cases, the prospective support of industrial partners (http://www.icm-institute.org/). Beyond its advances in the experimental domain, Systems Neuroscience requires today a constructive integration with other scientific fields including mathematics, physics, computer science and psychology. Interdisciplinarity is necessary to develop the modelling frameworks and computing resources needed to deal with the huge amount of data now being generated and with the complexity of biological phenomena. It is important to note that, after a period of silence maintained for more than 10 years (around the 1980s), some efforts were reactivated at the institutional national level to specifically foster interdisciplinarity (Ministère de la Recherche et de la Technologie (MRT) Sciences de la Cognition; Programmes interdisciplinaires du CNRS: PIR Cognisciences, Neuroinformatique; Actions Concertées Incitatives (ACI): ACI Cognition, ACI Neurosciences Computationnelles, ACI Neurosciences et Mathématiques; Agence Nationale de la Recherche (ANR): ANR Neuroscience, ANR Robotique). These pioneer actions were initiated not by politicians but by distinguished scientists such as Jean-Pierre Changeux and Alain Berthoz. It is also fair to note that, in spite of these short-lived initiatives, the amount of funding in France in Systems Neuroscience (e.g. reviews in Bullier et al., 2000; Chamak, 2004) has remained well below that achieved in leading technological countries such as the USA, Japan, and even within Europe. Two illustrative comparisons with other European countries can be found in Germany, with the creation of interdisciplinary centers of excellence in Computational Neuroscience (Bernstein Centres – http://www.bernstein-zentren.de/en/), and in the UK, where a similar initiative has been led by the EPSRC in the field of computing intelligence (www.epsrc.ac.uk & www.gatsby.ucl.ac.uk). Both initiatives were launched with budgets of more than 50 million euros, injected within a very short time-period. The prospects of similar structuring actions and budgets look much grimmer for French Neuroscientists, in the present era of unfulfilled promises. . ..

This lack of new initiatives as well as of recurrent support at the national level is slowing, if not impeding, progress made by the French scientific community in the field of Systems and Computational Neuroscience. Such a state of chronic insolvency is difficult to justify by governmental institutions, especially when the investment cost is evaluated in terms of the societal issues at stake. Functional and computational approaches in neuroscience have already produced significant impacts in human medicine, notably in neuroprosthetics. For instance, because we better understand the developmental features and coding/decoding specificities of basic cognitive functions, such as vision, hearing, multimodal perception, decisional processes, and motor coordination, more efficient techniques for educating dyslexic and autistic children are now available (see for instance the Scientific Learning Corporation created by brain scientists such as Mike Merzenich, http://www.scilearn.com/). Research in adult cerebral plasticity has led to better re-education protocols for patients with low-vision and age-related macular degeneration, which could be of major interest for the field of clinical neuro-ophthalmology (see for instance the lines of future research of the "Institut de la Vision", led by INSERM and the Hôpital Quinze-Vingt, to be open in 2008 in Paris). Neurophysiological and neuroimaging research in motor cortex have resulted in original behavioral protocols relieving instantly patients from phantom pain following amputation (Ramachandran and Hirstein, 1998; Ramachandran and Sandra, 1999). High-profile reports in the mainstream press have shown the importance of collaborations between surgeons, brain imagers and neuropsychologists in helping patients to recover from massive organ grafts (Farné et al., 2002). The development of deep brain electrical stimulation has also considerably improved the living conditions of some Parkinson's disease patients (Benabib et al., 1996). The field of sensory implants (Dobelle, 1976) and brain-prosthesis interfaces (Fetz, 1999; Musallam et al., 2004; Lebedev and Nicolelis, 2006; Scott, 2006) has immensely benefited from an increasing understanding of sensory and motor processing in cortical areas. Neuroprosthetics has now become an emerging field of application with the prospect of helping patients affected by locked-in syndrome or tetraplegia to communicate in real time with the outer world (Baudy, 1997; Hochberg et al., 2006).

2. Multiscaling and complexity issues

In the future, the study of biological structures as complex as the brain will depend on and profit from new and more powerful computational and mathematical tools. There are several reasons which make this stage of interdisciplinarity necessary and decisive. One is the need to solve the overwhelming difficulties met by traditional biologists in dealing with diversity and biological variability. Is this variability noise or information? To which degree of dissection and simplification should we proceed in our analysis of brain processes, to keep intact (and account for) the emergent functions of the intact living tissue/network?

For a long time, physicists excluded the biological disciplines from the application field of hard sciences, since two identical conditions may lead to different observations. Reasons for the lack of involvement of physicists in biology were the inherent difficulty in accessing brain structures in a non-invasive way, the relatively poor level of instrumentation (especially for visualizing activity across tissue depth), the lack of compatibility in the set of "observables" (physical measurements) that are monitored and the absence of a "grand theory" which could relate all experimentally derived variables. Indeed, most advanced brain imaging techniques (calcium two-photon imaging, PET, fMRI, BOLD, EEG-MEG) rely on various explicative variables (metabolic, haemodynamic) which differ greatly from those used to decipher the neural code and information transfer at a more microscopic level (current source density, evoked potentials, spike counts).

A further obstacle to the application of hard sciences in neuroscience was linked to the dominance, during the second half of the last century, of concepts coming from systems theory and the engineering world. As underlined by Tomaso Poggio in a famous essay (Poggio, 1983), one of the main historical reasons explaining the conceptual distance between brain theoreticians and biologists was the relative ignorance of the nature and properties of the biophysical substrate that implements the elementary stages of neural information processing. The classical vision of the neuron and its integrative function as a summating unit, with multiple input lines, static synaptic gains, a postsynaptic threshold and a single 'all-or-none' spiking output reflected an incapacity to recognise the necessity of non-linear operations on graded, analogue input signals. Theoreticians dealing with McCulloch–Pitts assemblies were initially tempted to use only additions and subtractions, while the neuronal machinery of the brain is obviously capable of non-linear input–output relationships, such as temporal integration and division of excitation by inhibition, and thus of more elaborate computations. The existence of distributed local non-linearities in the process of assembly-making is an obvious indication of the complexity of living networks.

Times are changing, however. Increased efforts are being made in establishing correlations and, when possible, transfer functions between variables collected at different levels

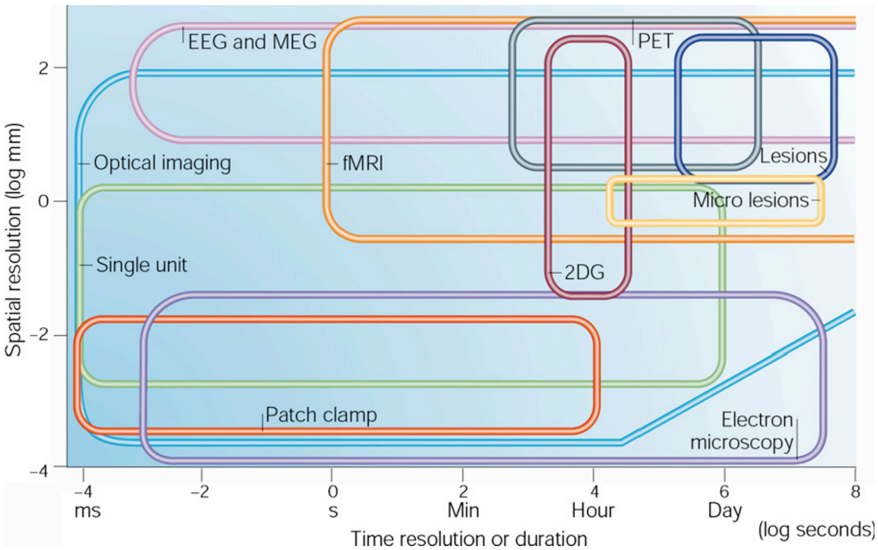

Fig. 2. Space and time-scale in brain activity measurements (from Amiram Grinvald, with permission).

of integration and scales of observation (Logothetis et al., 2001). New methods are now available in vivo, based on molecular tagging and microscopic visualization of activity in preselected circuits (e.g. in vivo two-photon and multiple fluorescent tagging techniques, transforming brain assemblies into rainbows of labelled cells ("Brainbow" technology, Livet et al., 2007)). With the help of physicists and even astronomers, neuroscientists have now elaborated tools allowing them to link various levels of integration and visualize in real time the collective dynamics of large, distributed ensembles of spiking elements. Examples of such achievements can be found in large-scale simulations of cortical modules with realistic non-linear spiking neurons, in the framework of the Blue Brain project led at EPFL by Henry Markram, with the help of IBM (http://bluebrain.epfl.ch/), and in the framework of Bio-I3 European funded projects such as Facets (facets-project.org) and Daisy (http://daisy.ini.unizh.ch/). Such tools find a natural application in the delineation of the parts of the brain, and more specifically of the cortical areas, involved in specific cognitive functions and in the genesis or processing of mental representations. They are also used in the field of information technology to develop computing architectures inspired from the living brain (e.g. European funding initiatives such as Future and Emerging TechnologiesBio-ICT; http://cordis.europa.eu/ist/fet/bioit.htm) (see Fig. 2).

3. What can biology expect from computational methods and mathematics?

At the turn of the new millennium, theoreticians are not only trained in physics but take advantage of advanced mathematical tools specially devised to deal with non-linear processing as well as multiscaling (see for instance wavelet theory, Mallat, 1999). However biology, and neuroscience in particular, has not yet benefited as much as physics from the "unreasonable effectiveness of mathematics", to quote the physicist and Nobel prize winner Eugene Wigner (1960). This is probably because most of the relevant mathematical theories, such as the theory of bifurcations in dynamical systems or stochastic calculus, have only been developed in the second part of the 20th century and are not taught in our engineering schools and departments even at the Masters level. Note however a few success stories such as the topological approaches developed by René Thom in fields as diverse as morphogenesis and cardiac dynamics (Thom, 1971) and by the successors of Wilson and Cowan (1972) in the field of neurogeometry (Petitot and Tondut, 1999; Petitot et al., 2003; Bressloff et al., 2002; review of biological correlates in Frégnac, 2003).

Perhaps the most important difficulty lies in the large differences between the entities manipulated within various mathematical models. Rather simple, continuous state spaces with a rich approximation structure are commonly used in mathematical analysis, in differential calculus (Faugeras et al., 2004) and their applications to signal theory. In contrast, information theory and semantics use complex discrete data structures such as trees and graphs for which elaborate mathematical analysis tools are yet to be developed. One way to bridge this gap is to characterize continuous dynamics with discrete attributes, as done in the theory of attractor neural networks which relies on the theory of dynamical systems and their bifurcations (Samuelides and Cessac, 2007; Cessac and Samuelides, 2007). However, convergence to an attractor requires a stationary environment, which is definitely not the case for neural systems, since they operate dominantly in a perturbation mode far from steady-state equilibrium. It is also clear that adding informational redundancy and the spatio-temporal averaging of signals are crucial operating modes of biological systems. Probabilistic models are absolutely necessary here to provide such tools as stochastic calculus and mean field theory. The additional problem of the non-stationarity of the environment and the fact that learning and multiple-scale memory processes are central in neural systems raise very serious mathematical questions for existing theories. These issues must be tackled if we hope to be able to formulate general statements about the behavior of neural systems.

4. Conclusion

Assemblies of neurons, which form the basic relational architecture underlying mind processes, are perfect examples of the class of "complex systems" in which large numbers of interacting simple elements produce emergent complex behaviors. In spite of interesting advances (some of them are outlined in the present JPP issue), it is not excessively pessimistic to state that understanding and simulating this level of complexity is still today out of reach of all existing mathematical theories. This situation, and the need to study assembly dynamics at the right biological scale (which is enormous), leaves a prominent role for massive computer simulations to investigate these behaviors.

Computer science has today reached the computational power necessary for the large scale simulation of distributed systems as complex as neural networks and for the acquisition, processing, analysis, visualization and distribution of neuroscience data and knowledge bases. It should provide in the near future a wealth of theoretical and computational models for understanding the brain and its emerging functions. Neuroscience should benefit greatly from the development of distributed calculation platforms adapted to the simulation of virtual environments, and of innovative technological devices (robots, prostheses, intelligent sensors), all dedicated to the study and simulation of the brain.

These computer developments should of course be conducted in close coordination with biological observations that are becoming increasingly accurate, thanks to the availability of observation modalities at a large variety of spatio-temporal scales, such as simultaneous multi-electrode recordings, multiphotonic and optical imaging, functional magnetic resonance, magneto-encephalography (review in Grinvald, 2005). We are convinced that the feedback between modelling/simulation and observation will help the emergence of these most-needed new mathematics. An exciting possible outcome of this multi-disciplinary process could be the discovery of computational paradigms, e.g., for the processing of sensory information, that may be significantly different from what is known today: will neuroscience revolutionize computer science? A bet is made, whose outcome depends in great part on the importance in the immediate future the French state will give to funding issues in brain research.

5. Annex composed by Frédéric Alexandre and Thierry Vieville (NeuroComp)

5.1. The scientific community seen through the French "Neuro-Comp" initiative

The following information has been gathered at www.neurocomp.fr[1,2]. Sixty teams have been identified in France as working in the field of Computational Neuroscience (including 150 researchers with PhD). About 25% are composed by research teams with 6–8 permanent researchers (plus 8–10 PhD students in average), the remainder being smaller teams of 1–2 researchers embedded in larger interdisciplinary groups.

5.2. Domains of activity

Distribution of teams in terms of academic fields:

Integrative neuroscience and psychophysics	40%
Computer science and information processing	25%
Statistical physics and applied mathematics	25%
Neuroimagery and neuropsychology	10%

According to these statistics, the main neural systems presently studied are

Vision	Meso/macro	40%
Sensori-motor	Micro/meso/macro	35%
Olfaction	Micro/meso	5%

Only one team studies the auditory system.The remaining 20% is concerned with modelisaton of generic systems.

Here, the microscopic scale stands for studies at the cellular level, mesoscopic scale is concerned with cortical area and networks, and macroscopic scale is related to behavioral studies. The research topics are on average targeted to specific aspects of cognition (e.g. navigation, low-level perception, face recognition, etc.).

5.3. Tools and methods: from experiments to models

Theoretical tools and methods:

Analog neural networks (connectionism)	40%
Event-based neural networks	30%
Stochastic calculus and tools	20%
Learning and optimization framework	15%
Dynamical systems	15%

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[1] http://neurocomp.fr

[2] This web site claims to be a tool for the French community of the Computational Neurosciences. It lists the main teams of our field, presents a regularly updated calendar of organized events and gathers numerous resources particularly useful for our community (including) French colleagues working in other countries.

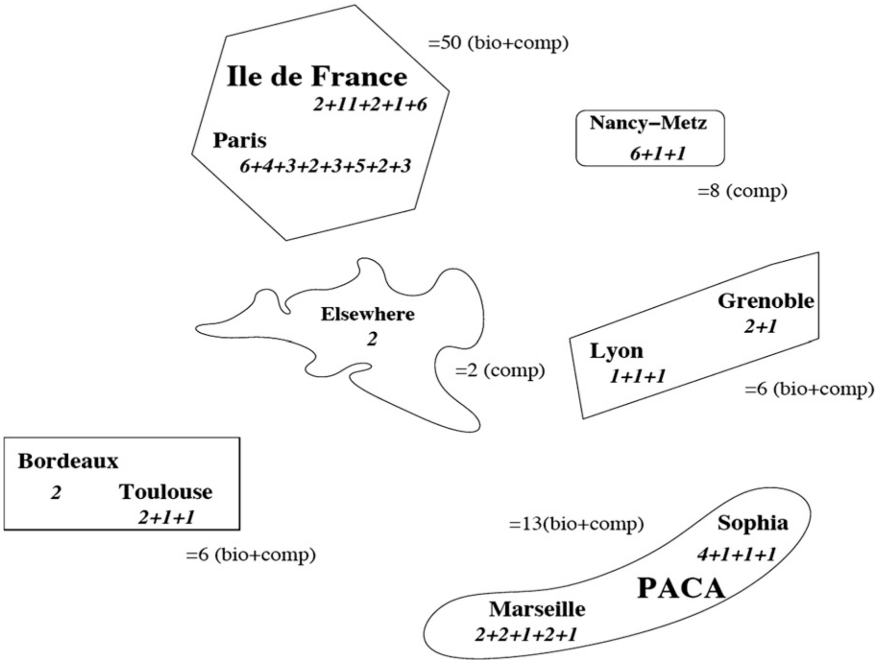

Fig. A.1. The geographical distribution of Systems and Computational centers in France (survey done at the end of 2006).

Most groups seem to use well-tractable analysis methods and develop more seldomly innovative (but risky) approaches. Software simulations (50%) and pure theoretical work (25%) seem of major use. Experimentation, psychophysics and behavioral studies (20%, including non-invasive EEG and oculomotricity (10%)), intra-cellular and biological measures (5%), brain imaging (5%, including robotic experimentation (5%)) are less represented in our survey.

A majority of the theoretical work is done in a few sites where experimentation is possible, whereas a quarter of team does not have a direct access to experimentation or experimental data. Some teams have solved this problem by strong association through grants with experimental labs. The stronger experimental labs also develop hosting facilities for teams of modelers.

On the one hand, 50% of the teams claim to be purely model-oriented, whereas only 20% of teams of "modelers" consider to study issues closely linked with experimental studies. On the other hand, only 20% of experimental teams consider their work being almost only (i.e. at 70–90%) centered on systems neuroscience. This situation shows that interdisciplinarity in Neuroscience is strongly represented , and that theoreticians and computer scientists do not limit their ambition to the study of abstract cognitive systems, but would like to compare their work with the biological reality. Not quantified, but still visible in the survey, is the fact that the identified teams consider a very specific set of biological models (mainly cat and monkey, mouse/rat for navigation, only marginally other species).

5.4. Geography and collaborations

The geographical distribution of the scientific community is schematized in Fig. A.1. It shows an expected concentration of half of the human resources in Paris and outside in Ile de France (mainly around Orsay) and in three important regional poles where both biologists and computer scientists can and do work together. The Nancy-Metz pole is also closely related to both Sophia and Ile de France teams. The good news is that there does not seem to be a dispersion of the computational neuroscience teams and resources all over the country, but rather a weighted repartition centered around natural/historical systems neuroscience poles.

Collaborations between teams are mainly involved in a pairwise relationship (65%). More than 40% are representing international collaborations. European and national projects drive 35% of these collaborations (surprisingly a small amount of them, but the budget support is higher than that provided through national ANR or ACI grants). A certain number of excellence networks, related to this domain but with a wider focus, have emerged through the constitution of national, European and international consortiums. The Paris-Ile-de-France Neuroscience School[3] and the Visual perception consortium (GDR-Vision)[4] are two major examples of such national networks. At the European level, the European Neuro-IT Network of Excellence[5], the consortiums supported by FET initiatives (e.g. Facets and Daisy) and the Neuroinformatics Coordinating Facility[6] have brought together most of the French high-profile groups in the field. However, 70% of the teams under survey declared not to be part of such macroscale networks.

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[3] http://www.paris-neuroscience.fr/enp/index.php
[4] http://www.gdr-vision.org
[5] http://www.neuro-it.net
[6] http://www.incf.org

6. Conclusion: the scientific challenges

In order to improve collaborations, the various teams under survey expressed two main wishes: (1) a wider access to experimental databases as well as to computational resources and software tools and (2) funding facilities making it possible to attract young researchers.

Three subfields have been identified as strong points of research:

1. Theoretical models, at the edge of the state of the art (including stochastic, learning, dynamical systems, information coding, etc.).
2. Development of emerging brain activity recording technics (optical-imaging with voltage sensitivities, new electrophysiological recordings, combination of several modalities (IRM, MEEG)).
3. Introduction of realistic experimentation (natural stimuli, robotic paradigm in complex environment, large-scale simulations).

while the collaboration between different fields (math/bio, neuro/comp, etc.) is indeed a precious asset.

Many projects under way are oriented towards the following scientific challenges:

1. Generic mesoscopic models (cortical maps), including links between micro/meso and meso/macro scales and adaptability in the wide sense.
2. Simulation of specific sub-system (e.g.: navigation, a given visual function, etc.) in order to simulate the underlying functionality at a realistic level.
3. Neuronal implementation of sensory, sensorimotor or cognitive functions (e.g.: olfaction, memory).

The use of large formalisms (e.g. Bayesian) and formal tools for biologically plausible neural network simulations is at the center of these challenges. These projects will have a definitive impact in fundamental, technological and clinical domains, as advocated by the National Plan Initiative for the Brain[7].

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[7] http://www.vie-publique.fr/actualite/alaune/recherche-plan-action-pour-neurosciences.html

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http://www.meteoreservice.com/neurospin/
http://www.icm-institute.org/
http://www.bernstein-zentren.de/en/
http://www.scilearn.com/
http://www.epsrc.ac.uk/
http://www.gatsby.ucl.ac.uk/
http://bluebrain.epfl.ch/