SYMBIONIC: A European Initiative on the Systems Biology of the Neuronal Cell

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To understand how genes, proteins and metabolites make up the whole organism, a systemic view is demanded, that is to conceive genes and proteins more as part of a network than as isolated entities. Molecular function becomes then a function of cellular context and not only an individual property. This change of attitude is accompanied by the recognition that bioinformatics plays an indispensable role in extracting information from the huge amounts of data stemming from recent "-omics" research. Such systemic view of cells demands the capacity to quantitatively predict, rather than simply qualitatively describe, cell behavior. In fact, in parallel with the data-driven research approach that focuses on speedy handling and analyzing of the currently available large-scale data, a new approach called "model-driven research" is gradually gaining power. Model-driven research aims at setting up a biological model by combining the knowledge of the system with related data and simulates the behavior of the system in order to understand its biological mechanisms.

The neuronal cell represents a very fascinating and highly complex system. In addition to the basic biochemical processes that are common to all types of eukaryotic cells, such as gene transcription, protein synthesis, and metabolism, neurons are electrically excitable and able to receive and propagate excitation via thousands of synaptic contacts. Traditionally, computational neurobiology has devoted its efforts to model the electrical properties of neural membranes, rather than the intracellular aspects, since the pioneering work by Hodgkin and Huxley in the early 1950's. On the contrary, elucidating intracellular signaling pathways is one of the most fundamental issues in current biology, with important implications for human health. In the last years scientists have realized that the neuronal function could only be truly understood when the morphology of cellular compartments, the location of proteins, and the kinetics of intracellular cascades are taken into account. The post-synaptic component is now viewed as a complex, dynamic assembly of proteins, located in the plasma membrane but also in the cytoplasm. The shape of the neuron is no longer considered to be fixed, but on the contrary processes like dendritic spine remodeling have been recognized as crucial for plasticity events. The overall features of a model neuron could be viewed as the result of the interaction of, at least, six main classes of cellular processes: protein-protein signaling networks, metabolic and enzymatic

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networks, regulative networks, membrane electrical excitation, synaptic communication, and development. All those neurobiological features have to be taken into account if we want to model a whole neuron or even a small part of a neuron realistically. In other words, we have to develop a Systems Biology (SB) of the neuron. Investigating neuronal biochemical processes requires a cross-disciplinary approach, involving on one hand quantitative experimental methods to study excitatory processes, large scale molecular networks and the kinetics of protein-protein interactions, and on the other hand computational modeling of intra-cellular processes and, as far as the synaptic transmission is concerned, inter-cellular communication. Thus, an integration of different experimental and modeling approaches is crucial for a comprehensive description of the cell and for a complete biological understanding of the neuronal behavior. Several scientific and technological expertise are required in order to cope with the great heterogeneity of intracellular processes that must be investigated and described by computational models in such a comprehensive view. We believe that the SB approach is the right one to take into account both the complexity of the neuron and the inter-disciplinary nature of the scientific research in this field.

A comprehensive and quantitative understanding of neurons, in the form of an in-silico model of a prototype cell, shall substantially contribute to the rational design of treatments for human neurological and neurodegenerative diseases. Lay Line Genomics (LLG) is an Italian biotech company, based in Roma and Trieste, whose activity is focused on neurodegenerative diseases. In 2002 LLG promoted an Expression of Interest (EoI) submitted to the European Commission, aimed at launching a large-scale European initiative for the simulation of a neuronal cell. The EoI enabled to coordinate a broad scientific network of research institutions and industries. By then, large-scale projects in the field of SB had already been launched in Japan and the USA, aimed at the computational simulation of whole cells, but not of neurons and not in Europe. Therefore such an initiative would capitalize on the enormous scientific potential of European expertise in cell and molecular neurobiology and neurophysiology, functional genomics, proteomics, bioinformatics, biophysics and computational biology, and would fill a significant gap in the international scientific arena.

Following the initial idea of the EoI, LLG is now project coordinator of a Specific Support Action (SSA) called SYMBIONIC funded by the European Commission within the FP6 (www.symbionicproject.org). Additional funding has come recently from the Area Science Park in Trieste (Italy). The project started in November 2003 and will last 24 months. The three main partners are LLG, the International School for Advanced Studies (SISSA-ISAS) in Trieste and the University of Barcelona. Over 20 other research institutions and industries (in the computing and pharmaceutical areas) from Europe and Israel collaborate to the project. SYMBIONIC is the first step towards the long-term objective of the initiative that was put forward with the 2002 EoI, being the driving force for the creation of a European in-silico exhaustive model of the neuronal cell. This first phase is carried on through a training and dissemination program and several collaboration activities:

- Collaborate and coordinate with other European SB initiatives.
- Train a new generation of young scientists in neuronal SB, both in the computational and experimental fields.
- Disseminate knowledge about the SB of neuronal cell, even to non-specialized audience.
- Contribute to standards.
- Give birth to more ambitious European research and technological projects.
- Raising the awareness of biotech/pharmaceutical and computer industries about the great potential of neuronal SB.

The full title of the project is "Coordinating a neuronal cell simulation initiative with ongoing EU-wide Systems Biology programs", since a key point is to coordinate all the existing efforts towards a broad European SB community, which is also the hope of the funding institution. SYMBIONIC closely collaborates with the SSA EUSYSBIO (EUropean SYStems BIOlogy network, www.eusysbio.org) since the beginning, for the main activities. In particular, joint workshops have been and will be co-organized on the occasion of the International Conferences on Systems Biology (ICSB) in 2004 and 2005, and scientific collaborations were and will be at the basis of the courses on computational and experimental SB organized by SYMBIONIC also in 2004 and 2005.

The SYMBIONIC training program is aimed at forming a new generation of young scientists in the highly inter-disciplinary field of neuronal SB. It is based on two main courses on computational and experimental methodologies for the neuronal SB and on other minor collaborations, in particular SYMBIONIC contributed to a practical course on SB funded by the European Science Foundation (ESF), held in Oxford in September 2004 and organized by the Oxford Brookes University, and it will take part in a lecture course in Austria in 2005, funded by the Federation of European Biochemical Societies (FEBS) and organized by EUSYSBIO. The first training activity organized by SYMBIONIC, a practical course on "Computational SB of the neuronal cell", was held in Trieste in December 2004. The course topics included methodologies to model neuronal shape and development, temporal-spatial properties of molecular networks, synapses, electrical excitation, signaling pathways and metabolism, molecular transport, genetic networks, and sensory transduction. We provided hands-on computer sessions to introduce some of the main softwares and standards used to model biochemical systems. The next course, in fall 2005, will be devoted to advanced experimental techniques for the neuronal SB.

An important event in the dissemination strategy was the ICSB2004 Satellite Workshop on "Industrial Perspectives of Systems Biology" in Heidelberg, Germany, where SYMBIONIC and EUSYSBIO invited key representatives from the pharmaceutical, biotech and academic world to discuss about the role of SB in current research strategies.

The network supporting the SYMBIONIC Action is constituted by a cross-disciplinary set of public and private institutions, each of them bringing specific competences. This is a first important result testifying the fact that the only possible way for a true scientific and technological progress is the leverage on public and private scientific expertise, jointly with a strong application-driven force. This is a major strategic issue: a true mixing between public and private research to strengthen the European capabilities in the high-technology areas. This will produce a significant fall-out on European industry and increase its competitiveness in the world-wide arena. The presence of a large pharmaceutical company in the SYMBIONIC network testifies, on one hand, the interest of the pharmaceutical industry to reduce as much as possible the time for "technology transfer" from the high-end research into novel application-oriented methods and tools.

A further relevant point that the initial promoters of SYMBIONIC attentively considered is the inclusion of small and medium enterprises (SMEs). High-Tech and Bio-Tech SMEs are very important in the present industrial tissue in Europe, constituting an essential resource of the European economy. Their involvement in the proposed Action can significantly contribute to strengthen their competitive advantage and their paradigmatic role in the economic European context. There are several technological areas where it is easy to predict a sizeable fall-out from Systems Biology initiatives originated directly or indirectly from this SSA. These researches will boost the laboratory activities and generate a consistent quantity of data available to the whole research community.

On a separate matter, the design and modeling of such a complex object as a cell will push at the extreme the actual capability of numerical modeling of complex systems. It will thus produce a strong driving force from other scientific and technological compartments that will be able to transfer specific tools and methods into the emerging area of Systems Biology. This will produce a relevant cross-fertilization, which will represent a major outcome of the SYMBIONIC initiative. Systems Biology will require substantial investments in terms of computing resources and computational strategies. In this respect SYMBIONIC will also address the discussion of future computational strategies (GRID, deployment of large-scale computational facilities, special purpose hardware). The relevance that Systems Biology is assuming in the field of high performance computing, methods and tools is also testified by the interest that this SSA initiative has catalyzed from major hardware companies, that support this initiative. In fact, they predict the explosion of this new area of high-end research where the complexity of models will be certainly accompanied by the need of deploying powerful computing infrastructures, new programming languages and standards for model representation.

All these technologies would result in a series of applications in the biomedical field with a significant impact on human health. A key point is to accelerate the drug discovery and development process, in order to reduce the final costs of drugs and animal testing in favor of computational screenings. The design of reliable in-silico screenings will also increase the rate of success of a candidate compound in the clinical phase. The availability of a comprehensive model of a neuronal cell, where its constituents can be accounted for in a quantitative form, would represent a formidable tool for the analysis of cell behavior under physiological and pathological conditions. Achieving this goal would be of paramount importance, not only for perfecting our understanding of the basic mechanisms of cell behavior, but also to provide a tool for detecting specific components crucially involved in disease. This will contribute to increase the comprehension of the cellular physiology of socially relevant neurodegenerative and neurological disorders such as Alzheimer's, Parkinson's and psychoses.

One of the major expectations of SYMBIONIC participants and at the same time one of the main project aims is to promote and give birth to new and more ambitious research projects. We firmly believe in the idea that the network contributing to the SYMBIONIC initiative is a critical mass of research groups and industries able to launch competitive projects, also in collaboration with other European key players in the field. This is already happening, as some of the SYMBIONIC partners are involved preparing new European projects in the “life science” and “information society technology” thematic areas of the FP6: at the border between these areas lies Systems Biology. Our hope is that the convergence of these actions will lead to a comprehensive and reliable computational representation of the neuronal cell.