

## A system biology approach for modeling the brain: from genes to consciousness

**Jean-Pierre Changeux**

France cerebellum club, CNRS UMR 3571, Institut Pasteur, France

Given the tremendous complexity of brain organization, here I propose a strategy that dynamically links stages of brain organization from genes to consciousness, at four privileged structural levels: genes; transcription factors (TFs)–gene networks; synaptic epigenesis; and long-range connectivity. These structures are viewed as nested and reciprocally inter-regulated, with a hierarchical organization that proceeds on different timescales during the course of evolution and development. Interlevel bridging mechanisms include intrinsic variation-selection mechanisms, which offer a community of bottom-up and topdown models linking genes to consciousness in a stepwise manner. The proposed approach is to nest the various intertwined structural and functional levels that compose the brain into a coherent and open brain models community covering multiple timescales. A critical bridging role between the gene and neuronal levels is assigned to regulatory proteins termed TFs. TFs regulate disparate genes into coherent assemblies. The impact of the environment on brain synaptogenesis is modelled as activity-dependent selective stabilization pruning of synapses. Longrange connectivity, subject to developmental shaping through interactions with the physical, social, and cultural environment, is proposed to form the bridge between neuronal micro circuitry and higher cognitive functions by globally integrating the underlying neural organizations. A novel allosteric pharmacology of TFs is proposed for neuropsychiatric diseases.

The complete mapping of human and other genomes has indicated that the remarkable complexity of living organisms is expressed by less than 30,000 protein-coding genes. Thus, the observed complexity arises not so much from the relatively few components (in this case, genes), as from the large set of mutual interactions that they are capable of generating. In a similar fashion, the 302 neurons of the nematode *C. elegans* enables it to survive in the wild, much more successfully than complicated, state-of-the-art robots. It is not the number of neurons that is the crucial factor here, but rather their interactions and the resulting repertoire of dynamical responses that underlie the survival success of living organisms in a hostile (and often unpredictable) environment. The focus of research in biology is therefore gradually shifting towards understanding how interactions between components, be they genes, proteins, cells or organisms, add a qualitatively new layer of complexity to the biological world. This is the domain of systems biology which aims to understand organisms as an integrated whole of interacting genetic, protein and biochemical reaction networks, rather than focusing on the individual components in isolation.

While the term itself is of recent coinage, the field has had several antecedents, most notably, cybernetics, as pioneered by Norbert Wiener and W Ross Ashby (who indeed can be considered to be one of the founding figures of systems neuroscience along with Warren McCulloch) and the general systems theory of Ludwig von Bertalanffy, which have inspired other fields in addition to biology.

The recent surge of interest in systems thinking in biology has been fuelled by the fortunate coincidence in the advent of high throughput experimental techniques (such as DNA and protein microarrays) allowing multiplex assays, along with the almost simultaneous development of affordable high-performance computing which has made possible automated analysis of huge volumes of experimental data and the simulation of very large complex systems. Another possible stimulant has been the parallel growth of the theory of complex networks (comprising many nodes that are connected by links arranged according to some nontrivial topology) from 1998 onwards, which has provided a rigorous theoretical framework for analysis of large-scale networks, ranging from the gene interaction network to the Internet. Indeed, reconstructing and analyzing biological networks, be they of genes, proteins or cells, is at the heart of systems biology. The role of such “network biology” is to elucidate the processes by which complex behavior can arise in a system comprising mutually interacting components. While such emergent behavior at the systems level is not unique to biology to explain properties of living systems, such as their robustness to environmental perturbations and evolutionary adaptability, as the outcome of the topological structure of the networks and the resulting dynamics, is a challenge of a different order. As networks appear at all scales in biology, from the intracellular to the ecological, one of the central questions is whether the same general principles of network function can apply to very different spatial and temporal scales in biology. In this article, we look at a few examples of how using a network approach to study systems at different scales can reveal surprising insights. In young adults, the brain region for processing faces was active while the brain region for processing places was not. However, both the face and place regions were active in older people. This means that even at early stages of perception, older adults were less capable of filtering out the distracting information. Moreover, on a surprise memory test 10 minutes after the scan, older adults were more likely to recognize what face was originally paired with what house.