Systems Biology goes Europe: Omics United!

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A principal challenge for the life sciences is to understand the "organisation and dynamics" of those components that make up a living system, i.e., to investigate the spatial *and* temporal relationships between (macro-)molecules, cells, tissue, organs, and organisms that give rise to cause and effect in living systems. A major problem is that networks of cellular processes are regulated through complex interactions among a large number of genes, proteins, and other molecules. The fundamental goal of Systems Biology is to understand the nature of this regulation in order to gain greater insight into living systems and, ultimatively, manipulate them. This is achieved not only through cataloguing and characterising physical components, but also by the integration of this information through mathematical modelling and subsequent simulation of "networks" or "pathways" composed of interacting (macro-)molecules. As well as technological innovation that allow accurate, high-throughput, and spatio-temporal measurements, what is needed are theories or methodologies that explain observations.

PRINCIPLE CHALLENGES IN SYSTEMS BIOLOGY

The cell is a self-controlled and self-regulating dynamic system consisting of components that are interacting in space and time. The relationships that prevail between structure, function, and regulation in cellular networks are still largely unknown. Systems Biology aims to identify and explain these relationships through an integrated effort of both, experimental and theoretical methodologies. For instance, mining "bioinformatic data" can, at most, identify associations between elements or variables, rendering inferences about cause-and-effect relationships a "scientific art-form". There is general agreement that a systems approach is necessary to understand the causal and functional relationships that generate the dynamics of biological networks and pathways.

While bioinformatics is usually associated with vast amounts of data available in databases, the systems-biological description of cellular processes often suffers from a lack of data. There is therefore a need "to fuse data" obtained by using different technologies and to "combine information" from experiments conducted by various research groups.

So far, the introduction of new technologies has given rise to new research areas classed as "the omics", including genomics, proteomics, transcriptomics, metabolomics, and physiomics. The reason why these technologies define separate areas is that each provides us with a different but complementary perspective. However, for a more complete picture of cellular dynamics it appears to be necessary to combine our efforts, i.e., technologies, methodologies, and experiments.

Predictive mathematical modelling of the behaviour of biological systems often meets difficulties because the necessary mechanistic details and kinetic parameters are difficult to obtain. For Systems Biology to fulfil its promise, it is thus crucial to investigate particular systems or problems integrating those technologies *and* methodologies available.

The bewildering complexity of genetic pathways, as well as the costs and effort of experiments, forces us to concentrate on models that are parts of a larger whole. It is therefore of vital importance to have methodologies that identify the key elements in a system and to estimate the error that is an inevitable consequence of necessary simplifications and assumptions in mathematical modelling. Mathematical modelling allows us to formalise and integrate existing knowledge in a precise way, providing formal methods of analysis, and therefore forms a central component in Systems Biology.

While we are trying to answer how groups of genes, cells, and organisms control dynamic responses to environmental stimuli, it is for biomedical applications of particular importance to understand the consequences of changes at the gene level, i.e., to "scale understanding" from genes, to cells, to organs, and organisms.

Summary of challenges in Systems Biology:

1. Mathematical and computational modelling of selected biological systems, with a particular focus on modular representations of functional units.
2. Experimental and formal methods for validation, analysis, and reduction of large-scale dynamic mathematical models.
3. Descriptions of how a network topology constrains intracellular signal processing.
4. Modelling in time *and* space; integrating biophysical and evolutionary constraints on the function of biological systems.
5. Identification of causal relationships, feedback, and circularity from experimental data; investigations into the regulation, control, stability and robustness of cellular systems.
6. Estimation of model parameters from experimental data; experimental design.
7. Fusion of data, visualization of information, integration of models and simulators.
8. Scaling models across time scales and description levels (genes, transcript, proteins, cells, organisms, …).

These challenges can only be answered by large-scale national and international efforts and should be considered as a major focus in the EU over the coming years.

OUTLOOK

In the life sciences the shift of focus away from the molecular characterisation of the "nuts and bolts" of a cell to an understanding of functional activity must be paralleled with a change in the way we think about molecular systems, from "mining genomic data" to the development of "systems and signal-oriented methodologies". Systems biology is therefore as much about a new way of thinking as it is about collecting more facts.

Systems biology attracts new people, new disciplines and new ideas to the life sciences. And new ideas are necessary if we are to make sense of the data and information that is being accumulated in this post-genomic era of the life sciences. Systems biology means connecting people and ideas.

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