

Systems Biology:

From a Buzzword to a Life Sciences Approach

The last 18 months have brought important changes to the field of Systems Biology. While in the beginning it was largely associated with some outstanding individuals, working in isolation, it is now accepted as a new discipline open to researchers from a range of disciplines. Numerous Centres and professorial positions have been established at Universities worldwide. Together with the appearance of a new focussed IEE Journal Systems Biology (www.iee.org/sb) there is sufficient evidence for a longer lasting affair of and biology with systems theory.

For any emerging area of research there is a risk that at some point in future it is looked at as a buzzword with all its negative connotations. There are two main causes for this to happen: individuals (mis)use the new term as a means to attract research funding through relabeling old ideas and without actually embracing new approaches. Secondly an area can simply fail, for scientific reasons to realise the promises it made. What is therefore called for is a definition of systems biology that provides a realistic attitude towards the opportunities and hurdles of this field. In our view, systems biology is about methodologies, i.e., data-based mathematical modelling and simulation, that help an understanding of the dynamic interactions of cells and components within cells. For this vision to succeed, we require foremost experiments and technologies that generate quantitative, time-resolved data.

Definitions of Systems Biology

There are two prevailing interpretations of what Systems Biology is about: a) the integration of data, obtained from experiments at various levels and associated with the "omics family" of technologies, and b) the dynamic interactions of gene products, proteins and cells that bring about the structure and function of cells, respectively higher levels of organisation, such as for example tissue, organs etc. The first view is more an informatics perspective, developing tools for data integration and fusion, while the second approach is motivated by data-based mathematical modelling and simulation. The first camp would often motivate their

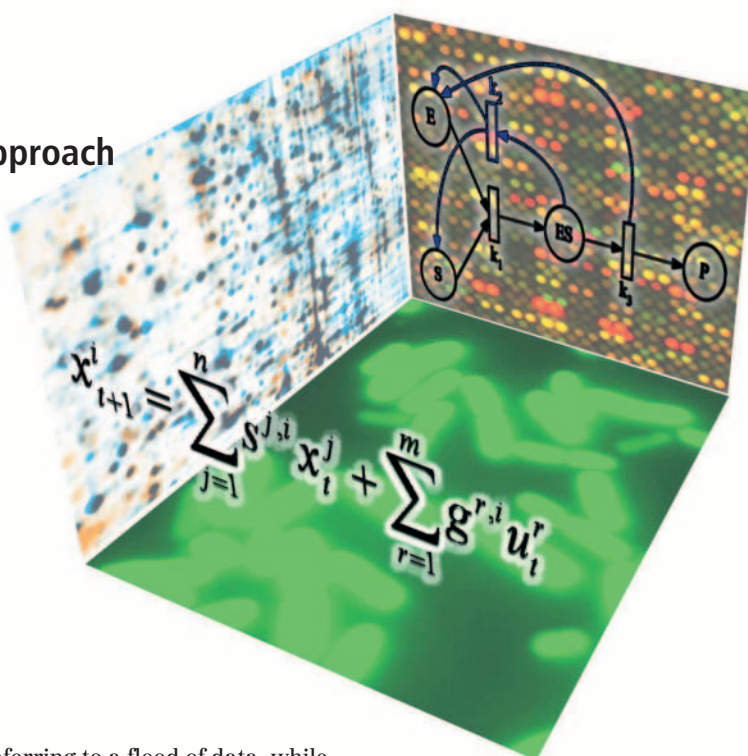
work by referring to a flood of data, while those interested in dynamic modelling of pathways are worried about the lack of quantitative, sufficiently rich data sets.

It is only natural that researchers, in their quest for research funds, develop an unexpected interest in new and emerging areas of research. While Systems Biology covers a broad spectrum of problems in the life sciences, to pass a test for a systems biology approach one must always be able to explain how the work relates to systems theory, specifically dynamic systems theory. The term "systems" in "Systems Biology" is, since the 1960s, associated with dynamic interactions, mathematical modelling, and simulation of biological pathways and networks. Fortunately this aspect of Systems Biology is not up for discussion.

Systems Biology signals a move away from just cataloguing and molecular characterisation of the components in cells, towards an understanding of the functionality and function of cellular networks. This requires more mathematical modelling than is comfortable for some scientists, and it has subsequently become common practice to replace the term "mathematical" with "computational" in an attempt to hide this fact.

The Systems Biology Approach

The complexity of molecular systems is fascinating and provides many interesting challenges for theoreticians with an interest in mathematical modelling and simulation. The overused term complexity is, in the context of systems biology, clearly defined



- the difficulties in dealing with many variables that are nonlinearly related in hierarchical, multilayered networks: observability,
- the difficulties in generating quantitative stimulus-response time series data: measurability,
- the difficulties in accounting for uncertainty, arising from a lack of observability and measureability.

The aim is that Systems Biology takes Genomics and Bioinformatics towards their natural conclusion – an understanding of the function and functioning of inter- and intra-cellular networks. For this programme to succeed, it is essential, that the area attracts new people for their different perspective. The emphasis is on methodologies rather than tools and technologies. Software tools are in this context only a means to an end. More important than computing power and software tools are measurement technologies and complex designs of experiments for generating data that are suitable for a systems approach. It is a well known fact from systems theory that the behaviour of a dynamic system can only be understood if it is systematically perturbed. This implies that we have to be in a position to define input signals, keep other variables constant, while observing output variables evolve over time. The need for repeated stimulus-response experiments highlights the need for a rethinking on behalf of the experimentalists.

The modelling process itself is more important than the model. The discussion between the experimentalist and the theoretician, to decide which variables to

measure and why, how to formally represent interactions in a mathematical form is the basis for successful interdisciplinary research in Systems Biology. In light of the complexity of molecular systems and the available experimental data, Systems Biology is the art of making the right assumptions in modelling. The modelling process and the model are to complement the biologist's reasoning – no more but no less either. Systems Biology is however not “holistic”. We cannot escape the reductionist approach that defines science. The complexity of systems in molecular and cell biology makes it necessary to focus on subsystems, study the whole through its parts, looked at in isolation. For a multi-level and multiple technologies approach the term “integrative” may be more appropriate. The current interest in “modules” and “motifs” of biochemical networks illustrates this. Systems Biology will hopefully bring about a new era in the life sciences but this is certainly not going to happen by means of “new age” approaches.

We should be under no illusion that it would be possible to build precise and accurate models of a cell or even organs. The concept of a “virtual cell” carries the risk of repeating the promises and failures in other areas, including for example Artificial Intelligence. The good news is that despite the complexity of these systems, successful examples of Systems Biology projects have already shown that it is possible to build predictive and useful models.

The cell is made up of molecules, like a car is made up from plastic and metal. But a soup of molecules is no more a cell than a heap of plastic and metal is a car. To understand the functioning and function of a cell we need to know the (static) relations and understand the (dynamic) interactions among the components that constitute it.

Example of a European Initiative

Within the European Union Framework Programme 6, Systems Biology has only recently emerged. A series of workshops on bioinformatics and computational systems biology suggest however that Systems Biology is likely to play a greater role in future EU funding initiatives [1]. There are however already smaller but well defined systems biology projects funded within the EU FP6 programme. One project (COSBKS) that is currently initiated is a joint effort of Rostock University (O. Wolkenhauer), the German Cancer Research Institute (DKFZ) in Heidelberg (U. Klingmüller), the Freiburg Centre for Data Analysis and Modelling (FDM, J. Timmer) in Germany, the

Beatson Institute for Cancer Research in Glasgow (W. Kolch), the Instituto de Investigaciones Marinas (C.S.I.C.) in Vigo, Spain (J. Banga) and the Institute of Mechanics and Biomechanics Bulgarian Academy of Sciences in Sofia, Bulgaria (V. Petrov). The COSBICS project investigates cancer related signal transduction pathways, using a systems biology approach. Based on quantitative immunoblots and supported by microscopy data, mathematical models that are based on nonlinear differential equations are derived in close collaboration with experimentalists. Instead of simply mapping the proteins in a pathway, COSBICS is concerned with “dynamic pathway modelling”, where parameter values are extracted directly from experimental time series. The project considers two signalling systems, independently and with respect to their interactions: The JAK-STAT pathway and the Ras/Raf/MEK/ERK pathway. Both systems are at the heart of a network that governs cell growth, differentiation and survival. The theoreticians in COSBICS investigate the role of feedback loops in control and regulation, spatio-temporal modelling, and parameter estimation. Different modelling paradigms are compared with regard to their value in supporting the design of experiments. Another important aspect of the COSBICS project is the interdisciplinary training programme for young researchers.

References

- [1] The workshop reports were produced within the thematic area ‘Life sciences, genomics and biotechnology for health’ and are available at www.cordis.lu/lifescihealth/genomics

Prof. Olaf Wolkenhauer
Systems Biology &
Bioinformatics Group
Fakultät für Informatik und
Elektrotechnik
University of Rostock,
Germany
www.sbi.uni-rostock.de
ow@informatik.uni-rostock.de



PD Dr. Ursula Klingmüller
Boveri Group Systems Biology of Signal Transduction
German Cancer Research Center (DKFZ)
Heidelberg, Germany
www.dkfz-heidelberg.de/systems_biology
U.Klingmueller@dkfz-heidelberg.de

