THE CIRCUITS OF LIFE

Less than 200 years ago, it became clear that all living organisms are made of cells. Nowadays, we know that cells are little creatures that thrive in the realm of the senses. A simple bacterium in a pond and a cell of the human body have something in common: both recognise a large number of ambient signals that control the cell's behaviour and may even influence its properties.

The molecular basis is a network of interacting proteins that processes the incoming information and fulfils all kinds of regulatory tasks. The proteins of the network are synthesised by the expression of the genes that encode the construction plan of each protein and, in turn, some of these gene-born proteins regulate which other genes will be expressed in the future and hence which proteins will contribute to the regulatory circuitry. Sophisticated regulatory circuits of proteins and genes, other nucleic acids and even metabolites together determine the function and the destiny of a cell. This complex network is not easy to understand. Although all cells in the human body contain the same genes, the cells of the brain and the liver, for example, are composed of different proteins, which allows them to fulfil different, organ-specific functions, while also sensing, processing, and even sending out signals to other cells that may differ accordingly.

Understanding the network of molecules that control the formation, maintenance and differentiation of stem cells, for example, and also finding the critical regulatory events that make them safely repair an organ, is certainly a challenge with the highest practical relevance. On the other hand, it is obvious that many states of disease, including cancer, involve alterations in regulatory control circuits.

However, there is another way how regulatory networks impact the quality of our daily life. The feasibility and costs of biotechnological processes for the production of pharmaceuticals, food or biomass depend on regulatory networks as well.

Systems biology – a transdisciplinary science

Since so many molecular components are involved, the systems of cellular regulation are complex. Intuitive understanding of a complex system and predicting its behaviour through plausibility arguments in general is error-prone and sometimes impossible as the non-linear interactions of its components may cause counter-intuitive effects. However, computer simulations can help as causality still holds. This is the reason why the weather forecasts became much better when good computer models were at hand. In biology, the regulatory processes within cells can be emulated by making mathematical models that are brought to life by running computer simulations. Computer models are not only helpful in simulating the dynamic behaviour of regulatory circuits, they also help to identify the many new molecules that are currently not even known to play essential roles. This innovative and quite successful discipline, which relies heavily on computer models to achieve its task, is called 'systems biology'.

Gaining a true systems level understanding of molecular life processes requires transdisciplinary approaches where traditional field boundaries are overcome. However, finding a common language is sometimes as difficult as the scientific questions that are to be solved. In order to promote communication and to foster this essential transdisciplinary work, several systems biology research centres have been founded in Europe in the last couple of years.

The Magdeburg Centre for Systems Biology (MaCS)

To gain an international competitive edge and to establish an interdisciplinary research landscape in the fast growing and increasingly successful field of systems biology, the German Federal Ministry of Education and Research initiated the 'Research Units for Systems Biology (FORSYS)' programme in 2006. Within the FORSYS initiative, four collaborative centres located in Freiburg, Heidelberg, Potsdam and Magdeburg received €45m of funding from 2007-2011 for a strong and sustained promotion of Systems Biology research in Germany.

The FORSYS centre in Magdeburg (MaCS) is a joint venture of the University of Magdeburg and the Max Planck Institute for Dynamics of Complex Technical Systems. At MaCS, bioscientists, bioprocess engineers, computer scientists, mathematicians, medical doctors, process engineers and experts in systems and control theory work closely together. This interdisciplinary atmosphere and the closeness of basic and application oriented research are particularly stimulating. Meanwhile, MaCS became an indispensable element within the research centre 'Dynamic Systems: Biosystems Engineering', one of the three research centres of the Otto von Guericke University. At the same time it belongs to the centres of excellence of Saxony-Anhalt, which will be cofinanced until 2015. A new research building for Systems Biology will be completed until 2013.

The main research focus at MaCS is on the structure and dynamics of molecular networks involved in signal transduction, cellular regulation and metabolism. A broad choice of computational and systems theoretical methods has been established and, in part, newly developed in order to investigate the structure and dynamics of molecular networks in general. At MaCS, these methods are applied to biomedical problems, eg. cellular infection biology or the immune response, and also to the production of biologicals. Within a wide network of national and international cooperation, phenomena such as cancer or chronic pain are also addressed.

Students and young scientists easily overcome the historically rooted borders between molecular biology and the theory and systems oriented sciences. In this respect, MaCS puts a great emphasis on the education of students of systems biology from the undergraduate to the PhD level. The course programme, called Biosystems Engineering and taught at the Otto von Guericke University, combines subjects from molecular biosciences, chemistry and physics with mathematics, systems and engineering sciences. The Otto von Guericke University will prioritize the study program Biosystems Engineering and further extend the laboratory capacities. The Magdeburg students are already contributing to a new generation of multidisciplinary trained experts required by industry and academia.

Systems biology delivers results of practical relevance

Systems biology opens new ways in research and application. Let us consider two examples. Firstly, in an approach called bottom-up modelling, a high number of experimental findings are integrated into a single, coherent computational model. The computer simulates the functional interaction of molecules, which for experimental reasons, cannot be directly observed. Simulation results suggested several new and, in fact, unexpected mechanisms of T-cell activation in the immune system that could be experimentally confirmed. This success clearly demonstrates that computation can accelerate discovery and save costs in an area that is highly relevant to human health.

Another field of application is biotechnology. Dynamic and stoichiometric modelling of metabolic processes in the photosynthetic bacterium Rhodospirillum rubrum have led to a deep and quantitative understanding of the cellular bioenergetics and its coupling with the photosynthetic electron transport chain. The simulation of the growth of R. rubrum cells in real-time is now used for the optimal operation of a bioreactor. This improves yields at reduced costs and even makes a new set of products available to the market.

Systems biology: for systems biologists only?

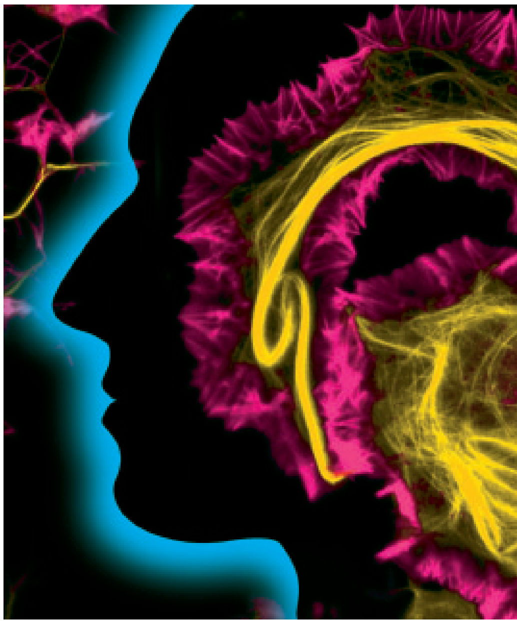
With their essentially transdisciplinary approaches, systems biologists face the challenge to disseminate their results to scientists in more traditional fields and to involve them in ongoing research. Most classical molecular biologists are not primarily inclined towards maths and, traditionally, have other ways to communicate than through lists of equations. However, running simulations to see how a system behaves or checking the compliance of a model with experimental findings does not necessarily require any mathematical skills at all. Models can be made in the form of intuitively understandable graphical representations of molecular mechanisms that even approach the cartoonlike schemes that molecular biologists are so used to. In the background, the computer automatically translates the picture into equations and runs the simulations that show how the biological system dynamically behaves. We are developing such systems at MaCS in cooperation with computer scientists.

Automatically the right conclusions

Modern analytical techniques deliver so many high-quality experimental data that drawing the right conclusions is now the bottleneck. With the help of so-called reverse engineering algorithms, one can reconstruct a regulatory network directly from experimental data sets. MaCS scientists apply and also develop such algorithms. It has been proven mathematically that one of these algorithms finds all the alterative network models that are able to explain the supplied experimental data sets without admitting more players than is absolutely necessary. Based on the proof of completeness, one can design a minimal set of experiments that directly identify the right model. Reverse engineering algorithms can automatically reconstruct complex networks from complex data sets where intuitive interpretations are error-prone or even impossible.

Taking the next steps to innovation

Although the immediate benefit for practical applications is already evident, systems biology is just about to develop into a key technology. At this early stage, systems biology's future impact on the life sciences in general will depend on funding the right mixture of basic and application oriented research. Research agencies and research organisations will play key roles in this respect.



FORSYS
Research Units for Systems Biology

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