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Systems biology: understanding complex biological systems

The German government continues to strengthen Germany's position as a leading location of systems biology. Baden-Württemberg supports this mission with research institutions and projects with high potential for innovation. Many research activities are concentrated on mathematical modelling and simulation of the liver and on systematic research into pathways, networks and functions that are of relevance in the pathogenesis of severe diseases such as cancer.

Systems biology helps develop methods with which cellular processes can be investigated

"Everything flows" – this famous Greek aphorism also holds true for the biochemical reactions in the fascinatingly complex systems that characterise living organisms. However, molecular biology and genetics have long lacked the computer-based methods and capacities to study living systems, both in their entirety and their dynamics. Scientific findings tended to be based on snapshots, which could nevertheless be used to derive complex flowcharts of substance flows and their functional relationships.

The rapid development of computer technologies over the last 10 to 20 years or so has also opened up the door to dynamic approaches. Modern computing and storage capacities – mathematical algorithms and a new generation of effective hard- and software – now enable researchers to model and simulate biochemical relationships of unknown complexity. Particularly complex cases can be dealt with super computers like "Hermit" at the High Performance Computing Centre Stuttgart (HLRS) at the University of Stuttgart, which is one of three Gauss supercomputing centres in Germany. Hermit's computing capacity is in the petaFLOPS (floating point operations per second) range, which means that more than a quadrillion operations can be carried out per second. This huge capacity also allows highly complex life processes to be modelled in an acceptable time frame. Pieces of the puzzle that experimental biology has hitherto been unable to deliver can now be put in place with a high degree of accuracy, enabling scientists to predict how an entire system or parts thereof react to specific external interventions.

Data that create virtual life

Systems biology has become one of the most important fields of research, both in Germany and abroad. In 2010, the German Federal Minister of Research, Prof. Dr. Annette Schavan, called systems biology a "key technology in the life sciences". The objective is to make the data obtained with systems biology approaches available to all interested scientists as rapidly as possible. The platform iCHIP (www.ichip.de), which was established by the Heidelberg-based DKFZ, is an impressive web-based example of the management and analysis of systems biology data gathered in a clinical context. Another impressive example is the Large Scale Data Facility (LSDF) that is currently being set up at the Heidelberg BioQuant centre. With a storage capacity of around six petabytes, the LSDF is one of the largest European data storage systems used exclusively for the storage of life sciences data.

Systems biology used for bioproduction and bioeconomy

The systematic investigation and modelling of metabolic networks serves both basic research as well as the industrial application of biological principles. With regard to the bioproduction of pharmaceutically active ingredients and materials – from insulin to detergent enzymes and fine chemicals and bioplastics – the metabolism of production strains can be simulated using systems biology approaches. It is mainly microorganisms, single-celled organisms and small multicellular organisms such as algae and fungi that are used as production strains. Specific software can be used to change metabolic parameters and predict whether the modifications will lead to the sought-after product or fewer by-products. Systems biology can thus also be used for the economic exploitation of biological processes (bioeconomy). The quality of such virtual predictions depends decisively on the visualisation of data. Data visualisation is an important branch of informatics, as even the best data are useless if they cannot be presented clearly and do not allow interactions.

The University of Stuttgart has established the Visualisation Research Center (VISUS)[1], a central institution that focuses on different areas of scientific visualisation, including the development of solutions for the field of systems biology.

Towards a virtual liver

Systems biology has the eventual aim of being able to generate data relating to the entire human organism. However, for the time being systems biologists still need to focus on individual cells, tissues and organs. At the turn of the millennium, the German government planned the first systems biology funding round and decided to initially focus on the liver as a functional unit. As one of the most complex organs in the human body, the liver presented a huge challenge. However, the liver was not only chosen for reasons of scientific ambition, it was also chosen for its involvement in the pathogenesis of many different diseases. In addition, the liver is the principle organ of drug metablism. These are the many reasons why the German government decided to systematically fund systematic research into liver morphology, physiology and function.

Between 2004 and 2010, the German Federal Ministry of Education and Research (BMBF) provided around 36 million euros in funding for the initiatives HEPATOSYS I and II; the subsequent "Virtual Liver" competence network is being funded with a total of 43 million euros up until 2015. These beacon projects also involve research groups from Baden-Württemberg. In 2006, two out of four centres funded under the BMBF's FORSYS (Research Units of Systems Biology) initiative were awarded to Baden-Württemberg: FRISYS[2] in Freiburg and ViroQuant[3] in Heidelberg. A major objective of the FORSYS programme, which comes with a purse of €45 million, is the development of interdisciplinary and collaborative research units for systems biology at German universities, non-profit research institutions and industrial companies.

The Helmholtz Alliance on Systems Biology, a network consisting of six Helmholtz Centres and 12 other research institutions, was established in 2007 with the aim of elucidating diverse complex disease mechanisms, affected organs and tissues. The Alliance is funded with around 49 million euros and is coordinated by the DKFZ, which has been responsible for bringing on board many research projects in which a systems biology approach is used to elucidate the signalling pathways in cancer cells. These pathways are being investigated within the network on "Systems Biology of Signalling in Cancer (SBCancer)", which has already achieved initial successes. For example, the interdisciplinary team has built the first model of CD95-induced apoptosis using systems biology approaches: the death of cells is induced when a suitable molecule (ligand) binds to the CD95 surface receptor on the cell membrane.

In focus: Center Systems Biology in Stuttgart

In early 2006, the Center Systems Biology[4] (CSB) was established at the University of Stuttgart. It is a prime example of an interconnected and interdisciplinary research network in which scientists from the biological, systems and engineering sciences from Stuttgart University and other universities and research institutions work closely together. The first projects involved researchers from the Proteome Center at the University of Tübingen and the Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology (IKP), which is part of the Stuttgart-based Robert Bosch Hospital. The CSB now brings together seven faculties and works closely with researchers from the SimTech cluster of excellence. The CSB develops modelling and simulation methods to investigate entire systems, which are mainly used for applications in red and white biotechnology. Red biotechnology focuses on applications for medical and pharmaceutical areas; white biotechnology focuses on applications in industrial biotechnology, a major priority being "metabolic engineering", a practice that involves optimising genetic and regulatory cell processes whose goal is to increase the cell's production of a certain substance.

The Center Systems Biology is also involved in a broad range of national and international initiatives, including FORSYS, HEPATOSYS and the Virtual Liver competence network. Prof. Dr. Matthias Reuss, senior director of the CSB, has been involved in systems biology approaches for investigating the liver right from the launch of HEPATOSYS in his role as the spokesperson of the Detoxification competence network. Together with his partners, Reuss was able to achieve important milestones in elucidating the metabolisation of drugs in human liver cells, including developing a model of the cytochrome P450 complex that plays a key role in catalysing the oxidation of organic substances. The CSB is now focusing on the whole organ and seeks to deliver a multi-scale representation of liver physiology on the molecular, cellular, tissue and organ level. It is also carrying out research into new drugs and methods for the treatment of cancer with a particular focus on the transport of drugs to their targets.

In focus: BioQuant in Heidelberg

The liver is the central metabolic organ in human physiology: every day, it metabolises more than 10,000 different metabolic products. Due to its complex metabolic pathways and structures, the liver poses a particular challenge for scientists. The Virtual Liver network takes on the challenge.

The BioQuant centre (Quantitative Analysis of Molecular and Cellular Biosystems) was established in 2007 at the University of Heidelberg with the objective of obtaining an in-depth understanding of inflammatory liver diseases, in particular those caused by viruses. Embedded in BioQuant, a ViroQuant junior research group is specifically focused on modelling the complete viral infection cycle with the aim of identifying host-virus interactions and their role in the pathogenesis of viral diseases. In so doing, the researchers are developing virus propagation models as well as cellular immune response models with the aim of identifying new target molecules for antiviral drugs.

Another junior research group affiliated with the BioQuant is focusing on epidermal systems and is developing a mathematical model to elucidate how individual stem cells lead to constantly renewing tissue with a specific structure and different cell types. The CellNetworks RNAi Screening Facility, which was established at the BioQuant under the ViroQuant initiative in 2007, plays a key role in the investigations being undertaken by the aforementioned junior research groups as well as many other systems biology approaches. The CellNetworks RNAi Screening Facility provides a screening platform for assay automation and automated microscopy enabling the high-throughput screening of siRNA (short single strand RNA with a length of 21 nucleotides) with which the expression of certain genes can be suppressed.

The BioQuant centre also has a strong commitment to interdisciplinary research and is involved in several large national systems biology consortia and networks, including the aforementioned consortia that are focused on liver research, MedSys (Medical Systems Biology) and GerontoSys (Systems Biology for Health in Old Age). In addition to its research goals, BioQuant is also committed to implementing systems biology education infrastructures, including the course “Mathematics for Systems Biology”. It established a major new curriculum for systems biology in the international master’s programme “Molecular Biosciences” in the winter semester 2008/2009. Moreover, BioQuant has also initiated an international student exchange programme with the Universities of Amsterdam, Manchester and Tokyo, which is also dedicated to systems biology.

In focus: ZBSA and FRISYS in Freiburg

The second Baden-Württemberg FORSYS centre was established at the ZBSA (Center for Biological Systems Analysis) at the University of Freiburg. Researchers involved in FRISYS (Freiburg Initiative for Systems Biology) are focused on the regulation of stem cell development. The systems analysis of signalling processes in embryonic stem cells of zebra fish provides the researchers with new insights into the growth and differentiation of human cells, which can be used for the development of new regenerative therapies. A major research aspect focuses on the regulatory systems that help cells prevent the development of tumours. Time-resolved analyses have provided insights into the expression of genes and the differentiation of cells. The researchers have thus been able to gain a comprehensive picture of the temporal dynamics as well as the structure, function and evolution of the stem cell network. The FRISYS team also uses its skills in teaching, notably in the newly established master’s programme “Bioinformatics and Systems Biology” and in a PhD programme.

The Life Imaging Center (LIC), which was established at the ZBSA in 2008, provides important impulses for the systems biology issues dealt with in Freiburg. It gives researchers access to state-of-the-art microscopes, image analysis and visualisation technologies, which also enable the long-term monitoring and hence research into dynamic processes.

Systems biology activities at the ZBSA also focus on plant research. A “4D Analyzer” platform for live-cell imaging helps the researchers to obtain insights into the temporal course of reactions in three-dimensional molecular networks, for example in the roots of Arabidopsis thaliana, which is a popular model organism used by researchers around the world. The researchers are for example focused on the interplay of external signals and endogenous development programmes in the formation of new plant organs. The moss Physcomitrella patens, which is another popular model plant and very suitable as production system for complex human biopharmaceuticals, is being used by FRISYS researchers dealing with the production of drugs for the treatment of age-related macular degeneration (AMD). Using systems biology approaches, the researchers from Freiburg are using a method known as “molecular pharming” to produce complement factor H in genetically modified moss cultures.

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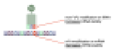

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