

1st SysBioMed Workshop on Systems Biology for Medical Applications

26th February – 2nd March 2007

Puerto de la Cruz, Tenerife (Canary Islands)

Participants

Scientist

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Michael White, University of Liverpool, UK

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Nicolas Le Novère, EMBL-EBI, Cambridge, UK

Nils Blüthgen, University of Manchester, UK

Olaf Wolkenhauer, University of Rostock, Germany

Pierre de Meyts, NovoNordisk, Denmark

Robert Jaster, University of Rostock, Germany

Thomas Höfer, Humboldt University, Berlin, Germany

Rosita Cottone, Federal Ministry of Education and Research, Berlin, Germany

Maike Heidelberger, Project Management Agency Jülich, Germany

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Astrid Lunkes, European Science Foundation, Strasbourg, France

Karsten Schürrie, Society for Chemical Engineering and Biotechnology (DECHEMA e.V.), Frankfurt, Germany

Research topic

Single cell imaging; apoptotic signalling

Modelling gene regulatory networks

Modelling Enzyme Kinetics

Reverse engineering of gene regulatory networks

Single cell analysis of caspase activation during apoptosis

Robustness and cellular design principles

Parameter estimation and optimal experimental design

Modelling fragility of robust tumor, metabolism

Real time single cell Imaging; NFκ-B pathway

Power-law modelling in biomedicine

Modelling neuronal signalling

Modelling MAPK cascades

Statistical vs. Mathematical Models

Insulin signalling

Signal Transduction in Pancreatic Fibrosis

Molecular immunology and mathematical models

Guest

Guest

Guest

Partner

Co-ordinator

Findings

The first preparatory workshop round served to gather a group of young scientists from the SB and medical research fields, including clinicians, who discussed the future options of SB approaches in medical research.

There obviously is a need for employing SB in current biomedical research: For decades of efforts in elucidating the mechanisms behind severe diseases the traditional reductionist approach has delivered a huge amount of sound information on the molecular pathologies, the cells, and the signalling and metabolic pathways involved.

However, the more information has been obtained the more the unexpectedly high complexity of many disease conditions has become apparent. The most prominent example is diabetes of both types. Despite more than 50 years of intense research in the field there is still no 'whole picture' of the interplay of the many underlying mechanisms causing the symptoms. For instance, one still does not understand the role of the cell types involved in the disease: β -cells, adipocytes, muscle cells, not to mention the cells of the immune systems or the role of the brain regulating appetite. Genetic research on 'risk genes' often showed that completely unexpected genes turn out to be relevant. All the knowledge accumulated so far resembles a huge puzzle of partial information on pathways from physiological, genetic, molecular and clinical data. For these reasons the European market leader in diabetes care, NovoNordisk of Denmark, has already embarked on SB projects at its Hagedorn Research Institute. Bayer AG of Leverkusen, Germany, and GlaxoWellcome, Stevenage UK, are also reported having launched SB initiatives in drug discovery.

The participants of the workshop agreed that assembling the puzzle of the pieces of information available from all relevant sources and levels will be key to gain deeper insights into the complex pathologies of major diseases. SB is expected to allow for the definition of mechanisms and the evolution of realistic models of disease conditions. In the discussion the participants looked at different major diseases with regard to the potential of SB approaches to increase knowledge: tumor diseases, immunological disorders, neurological disorders, infectious diseases, diabetes and ageing (considered a disease).

The outcome of the thorough discussions is best reflected in the proposals for the next round of focused workshops which can be understood as a list of priority projects promising successful applications of SB:

Diabetes: great industrial interest; huge problem that requires a new (systems) approach;

Basal Ganglia Disorders: covers a range of relevant pathologies, including Parkinson's disease, Huntington's chorea, schizophrenia, attention-deficit hyperactivity disorder, Tourette syndrome, drug addiction.

Regulation of Inflammatory Gene Expression: Inflammation is associated with problems that relate to various diseases; allows the study of environmental effects (e.g. epigenetics of T- & B-cells)

Apoptosis & Cell Cycle: chrono-therapy: i.a. very important for understanding and optimising chemotherapies

From Networks to Cell Fate - Colon cancer: a problem for which existing knowledge, data and experimental systems provide an ideal basis to explore systems biology in a translational effort.

Single-Cell Technologies: indispensable tool for generation of high value data on cellular physiology, includes phospho-proteomics; from images to models.

Model-Integration: Looking at the larger picture, we require methodologies to identify (to define the boundaries of) subsystems (modules), explore these in experiments and then integrate models thereof. The techniques should shape the design of experiments. The programme is clearly different but complementary to data integration efforts in bioinformatics, addressing models across (spatial and temporal) scales as well as functional levels. Going from genes to disease pathologies.

The experts agreed on these priorities - i.e. well defined questions that can be investigated within a few years - based on a catalogue of essentials that ideally should be granted to the largest possible extent:

- Established animal models and knock-ins available
- In vitro and ex-vivo models; in vitro measurements
- In vivo imaging
- Single cell experiments feasible
- Data at different levels available
- Possibility to identify subsystems
- Knowledge on environmental aspects in regulation of gene expression (epigenetic vs. genetic factors)
- Quantitative spatio-temporal data (signalling) accessible
- Genes and dynamics should be known
- Ability to cross or integrate levels (model integration)
- Availability of bioinformatics approaches (data integration)
- Opportunities to combine basic research with clinical research
- Need to improve pathological understanding
- Outcome should be therapeutic agents (for which a choice should be available) and understanding why and how they work, options for individualised treatment
- Interest of industry to invest (more)

The organisers plan to invite more clinical researchers from the fields named above to the next round of *exploratory* workshops. The scientists advocating research in the distinct

disease areas will care for attracting the experts needed. In addition the SYSBIOMED partners will benefit from the ESF's large network of medical researchers in order to win "the right people" for the task. The second workshop series is tentatively scheduled for the month of July at either Brussels or Frankfurt.

Input from Winter School

The 1st COSBICS Winter School on Systems Biology for Medical Applications (February 27th- March 2nd, 2007) was combined with the SYSBIOMED-Workshop. Some of the scientific lectures confirmed the assumption that SB could deliver valuable insights into medically relevant phenomena. For instance, Katja Rateitschak and Olaf Wolkenhauer from Rostock were able to demonstrate that the modeling of a signalling pathway involved in apoptosis could help to sort out alternative hypotheses based on genetic control and protein-protein interactions. The refined model they presented was well in line with experimental data. Jörg Stelling's group from Zurich is exploring the principles of 'cellular robustness'. He applied the concepts of control theory to the modeling of the the circadian clock. The group arrived at a model that explained the relevance of certain physiological threshold values for the oscillating behaviour – a knowledge that could possibly serve to optimise chemotherapies. Michael White gave an impressive demonstration of the potential of 'real-time single cell imaging' as a source of otherwise inaccessible high value data. His group is able to track individual proteins involved in the NFκ-B signalling pathway. Thomas Höfer, Humboldt University Berlin, shed light on the interplay of the cells of the immune system. Focusing at the complex genetic and external factors of the differentiation of naive T cells he presented an *in silico* model which allowed for the study certain combinations. Robert Jaster, Rostock University, Germany, is studying the mechanisms of the signalling pathways responsible for the progression of pancreatic tumors. His talk showed that modelling the Ras-Raf kinase signalling and the (JAK)-signal transducer and activator of transcription (STAT)- pathway could serve to understand the highly prolific growth of the cancer cells and the role of cytokines involved.

Networking with other SB initiatives

The participation of representatives of national and transnational SB initiatives is a key objective of the SSA ensuring that information on ongoing and planned projects and

initiatives is widely disseminated and exchanged in the community. The combination of the first SYSBIOMED workshop with the first COSBICS Winter School was especially helpful. Moreover, Maike Heidelberger and Veronika Simons, both of the Project Management Agency Jülich, Germany, and in charge of co-ordinating/managing HepatoSys (a German initiative in SB research on hepatocytes), FORSYS (German Research Centres for Systems Biology) and SysMO (Systems Biology of Microorganisms) were present and informed the audience on these efforts. Astrid Lunke, European Science Foundation (ESF), Strasbourg, is a SYSBIOMED partner. She presented the ESF networking platforms *Frontiers in Functional Genomics* and *Functional Dynamics in Complex Chemical and Biological Systems*. ESF's forward look *Towards a European Strategy for Synthetic Biology* is currently being drafted and is expected to deliver input for SB research projects. A very interesting new instrument is ESF's *EuroBioFund* programme which was set up in 2006. It seeks to identify future grand challenges in the life sciences which require a coordinated European approach. Identification of these topics is based on ideas put forward by the scientific community. Financing comes from the EC, industry, charities and other public and private funding organisations across Europe. *EuroNanoPar* (European Nanomaterial Proactive Assessment of Risk) is the first example of such a project.