Location

Motorway München-Salzburg – Exit Bernau
– direction Prien, Rimsting, Eggstätt, Seeon

Railway München-Salzburg (www.bahn.de)
Station Traunstein 20 km, station Bad Endorf 18 km, or station Prien 22 km – from there by Taxi or HMGU Shuttle Bus

Airport München, 80 km (www.munich-airport.de)
or Airport Salzburg, 60 km (www.salzburg-airport.com)
– from there by taxi

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German Research Center for Environmental Health

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

MDC Berlin-Buch

HELMHOLTZ ZENTRUM FÜR UMWELTFORSCHUNG UFZ

Forschungszentrum Jülich in der Helmholtz-Gemeinschaft

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Spring School 2008 on Systems Biology in Kloster Seeon

April 23 - 26, 2008

HELMHOLTZ ASSOCIATION
OF GERMAN RESEARCH CENTRES

Alliance on Systems Biology

HELMHOLTZ ASSOCIATION

Objective:

The spring school 2008 in Kloster Seeon is the first event in a series of Systems Biology symposia and workshops in the Helmholtz Association. The workshop adresses in particular the training of PhD students and junior scientists. Methods, strategies and scientific projects in Systems Biology will be presented in tutorials and progress reports. The spring school is suposed to stimulate the exchange of information and contacts between projects and young scientists in the Helmholtz Alliance.

Registration:

The conference fee (450 €) includes three night accommodation and meals.
Please register online at:

http://www.interplan.de/reg/springschool08/

For questions about registration and payment please contact:

Elvira Dieringer
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Timetable:

Wednesday, April 23

15.00 – 18.00 *Arrival at Kloster Seeon*

19.00 – 20.30 *Dinner*

Thursday, April 24

07.30 – 09.00 *Breakfast*

09.00 – 09.15 Opening Address

09.15 – 10.30 Steffen Klamt, MPI-Magdeburg

10.30 – 11.00 *Coffee break*

11.00 – 12.30 Thomas Höfer, Bioquant

12.30 – 13.30 *Lunch*

13.30 – 14.30 Jana Wolf, HU-Berlin

14.30 – 15.30 Andreas Beyer, TU-Dresden

15.30 – 16.00 *Coffee break*

16.00 – 16.20 Progress Report, UFZ

16.20 – 17.20 Fabian Theis, HMGU

ab 17.30 Postersession

19.00 – 20.30 *Dinner*

Friday, April 25

07.30 – 09.00 *Breakfast*

09.00 – 10.00 Ralf Zimmer, LMU-München

10.00 – 11.30 3 Progress Reports, HMGU

10.30 – 11.00 *Coffee break*

11.30 – 12.30 Volker Stümpflen, HMGU

12.30 – 13.30 *Lunch*

13.30 – 14.30 Rolf Kötter, FZJ

14.30 – 15.30 Simon Eickhof, FZJ

15.30 – 16.00 *Coffee break*

16.00 – 17.00 3 Progress Reports, HZI/DKFZ

17.00 – 18.00 Hauke Busch, DKFZ

18.00 – 18.10 Closing remarks

19.00 – 20.30 *Dinner*

Saturday, April 26

07.30 – 09.00 *Breakfast*

09.00 – 11.00 *Departure*

Abstracts:

Dr. Steffen Klamt, MPI-Magdeburg

Structural and functional analysis of cellular networks

Systems Biology aims at a holistic analysis and understanding of cellular networks. An ultimate goal of this emerging interdisciplinary field is the construction of dynamic models relying on (ordinary, stochastic, partial) differential equations. However, in networks with hundreds of players and interactions, the knowledge on mechanistic details and kinetic parameters is often too limited for building dynamic models with high predictive power. Modeling techniques for large-scale networks are therefore often solely based on the known network structure. Such qualitative and topological approaches still deliver useful insights in the architecture and functioning of these networks and provide tools for reasoning and hypotheses generation.

Prof. Thomas Höfer, Bioquant Heidelberg

Modeling the spatio-temporal dynamics of cellular processes

In the first part of the lecture, mathematical tools are introduced for describing systems with biochemical reactions and molecular transport. Particular attention is given to reaction-diffusion systems for which typical behaviors – diffusive target search, spatial gradients, traveling waves, and Turing structures – are introduced. In the second part, a reaction-diffusion model for autocrine and paracrine dynamics of the T-lymphocyte growth factor, Interleukin-2, is analysed. The model and its experimental tests have led to new insight on the biological functions of feedback regulation and intercellular competition in Interleukin-2 signaling.

Dr. Jana Wolf, Humboldt Universität Berlin

Mathematical modelling of signal transduction

The understanding of the relationship between design, regulation and function of cellular networks is one of the most interesting problems in systems biology and approached by theoretical and experimental analyses. In contrast to metabolic systems where modelling has been applied early, signal transduction and gene regulatory processes were only more recently studied by theoretical approaches. In the last decade models for a number of important signal transduction pathways have been developed, e.g. EGFR pathway, JAK-STAT, or Wnt signalling. The necessity of such an approach results from the fact that signalling processes play a crucial role for various cellular functions, such as proliferation, differentiation, survival or the formation of cell-cell contacts. However, notwithstanding extensive experimentation our understanding of signalling networks is still limited. Difficulties arise from the fact that corresponding networks vary under different circumstances and in different cells types. Underlying reasons could be variations in protein concentrations or regulations. The hope is that a detailed understanding of the functioning of signalling pathways in normal and disease states can serve as a basis for the prediction of effective inhibitors and rational therapies. We will here introduce mathematical modelling and analysis of signal transduction processes. We will discuss signalling core models which allow general insights into the relation of design principles and dynamical behaviour. In addition, detailed models for the EGF and Wnt mediated signalling will be analysed. These pathways are frequently deregulated in human cancers and we will use mathematical modelling to investigate the effect of specific oncogenic perturbations.

Dr. Andreas Beyer, TU-Dresden

Elucidating transcriptional regulatory networks with expression QTL

Most cellular responses to external stimuli as well as differentiation of cells involve transcriptional changes. Understanding the regulation of these changes is crucial for modeling stress response and differentiation at the system level. Here I will introduce a stochastic simulation technique utilizing measurements of expression quantitative trait loci (eQTL). Such data provide a rich source of transcriptional regulatory relationships, yet, they cannot mechanistically explain such associations. By mapping eQTL data onto physical protein interaction networks it becomes possible to tease out regulatory pathways that are likely to transmit the information from a regulator to the regulated target gene. Such pathways can be simulated as electric circuits, where the strength of 'current' on each edge in the network reflects the importance of that protein interaction for the transcriptional regulation of the target gene. The application of this algorithm, which is termed “eQTL Electric Diagrams” (eQED), to yeast eQTL data will be presented.

Dr. Dr. Fabian Theis, Helmholtz Zentrum München

Some qualitative results of microRNA-regulation in signaling pathways

We discuss how top-down and bottom-up modeling approaches can both yield a deeper understanding of biological problems. Methodically, our goal is to twofold: (a) to build qualitative models and analyze them using statistical methods, and (b) to develop dynamical models to predict regulation in a quantitative fashion. Commonly (a) can be achieved on a larger scale than (b), where mostly small network are modeled due to the huge number of parameters involved in dynamical simulations.
Our core biological interest is the influence of microRNA regulation in genetic networks: using diverse target site predictions, we develop an integrated network of regulatory control and analyze topological structures on different scales. The global perspective identifies network motifs responsible for the coordinated regulation of subsets of genes by microRNAs. Locally, we find network motifs consisting of transcription factors and microRNAs, and reconcile their linkage design with expression patterns. Qualitatively, we model the action of regulators in a small sub network responsible for lineage differentiation of hematopoietic cells.
For the quantitative modeling, we analyze how a macroscopic biological structure - here the mid-hindbrain boundary (MHB) controlling development of mid- and hindbrain - is maintained using a regulatory system, in which we now only begin to understand microRNA influences. We propose a multi-cellular model of a regulatory network that explains the maintenance of the MHB. In a Þrst step we develop a boolean model by logically analyzing the gene expression pattern around the MHB. We then build up dynamic ODE models to further explore the differences between the regulatory networks obtained from the boolean analysis, and Þnd that they react differently to perturbations of the steady state. This implies that the regulatory network underlying the maintenance of the MHB is robust against deletion of links and prohibitive towards misplaced gene expression.

Prof. Ralf Zimmer, LMU-München

Graph- and network based methods in bioinformatics and systems biology

Several recent methods in bioinformatics rely and exploit network information for the analysis of large scale data sets e.g. genome-wide gene expression measurements. This talk introduces graph and network concepts (e.g. Petri Nets, Random graphs and Bayesian networks) and discusses the underlying techniques of methods for inferring and representing biological knowledge, e.g. for generating appropriate networks from databases and literature and for their application in addressing biological hypotheses about the experimental data.
New methods for inference and validation of hypotheses are demonstrated for a large data set of microarray experiments on arthritis (human patient, animal model and cell-line) samples.

Dr. Volker Stümpflen, Helmholtz Zentrum München

From Distributed Knowledge to Qualitative Models

The qualitative understanding of models in systems biology is fundamental for any further investigation of complex systems. Having relevant knowledge about potential associations and mutual interactions between different individual biological entities available is certainly one of the keys for accurate quantitative models and systematic experiments. The nature of the systems biological approach demands however for the association of many different knowledge resources starting from genomic databases over resources for biological networks up to knowledge hidden in literature. The lecture will discuss state-of-the-art methods and approaches capable to bring distributed knowledge into systems biological models. This will include technologies to access distributed resources, recent developments in textming as well as new approaches to combine the different knowledge with semantic approaches in a uniform way.

Prof. Rolf Kötter, Forschungszentrum Jülich

Contribution of a connectivity database (www.cocomac .org) to systems biology of brain networks

I will highlight the emerging benefits of using CoCoMac, our online database of primate brain connectivity (www.cocomac.org), in the context of research and training in systems biology. We had developed CoCoMac since 1997 collating and comparing published results from the growing body of detailed tracer studies in macaques (Stephan et al. 2001; Kötter 2004). Our ultimate aim is to build a large-scale circuit wiring diagram of the primate brain that might successfully predict a great deal of human brain activity and the effects of lesions (Sporns et al. 2005).
In line with developments in the American Human Brain Project and recent recommendations by the Neuroinformatics Committee of the Society for Neuroscience we have been integrating CoCoMac with a range of other neuroinformatics resources:
• Consequently, CoCoMac references NCBI's PubMed for registered journal publications providing the abstract and full bibliographic information at a single button click. Conversely, PubMed users can configure the NCBI interface to display available LinkOut to CoCoMac, which adds value by providing supplementary connectivity and mapping information as well as comments and discussion through online retrieval from CoCoMac.
• Bidirectional cross-links have also been implemented with BrainInfo (http://braininfo.rprc.washington.edu/), a comprehensive information system on nomenclature, location and fine structure of mammalian brain regions. A single mouse click in BrainInfo retrieves corresponding wiring information from CoCoMac.
• The wiring data from CoCoMac can be visualized on selected brain maps in Catacomb, a java-based neural modeling tool, which is freely available for download from http://askja.bu.edu/catacomb/. As a full-fledged neural simulation program Catacomb has the capability to convert the connectivity data to network models for exploration of the dynamics in real brain networks.
• Interfaces with Caret and the SuMS (Van Essen et al. 2001) link brain mapping and connectivity data with their spatial representations in monkey and human hemispheres. WebCaret users have direct access to CoCoMac data relevant to the selected brain regions displayed in separate windows. The newly introduced Regional Map (RM) in CoCoMac (Kötter and Wanke 2005) provides a coarse parcellation scheme of cerebral cortex taking into account a combination of microstructural, functional and topographic features. It serves the need to provide an intuitive and rather uncontroversial naming scheme applicable to human and macaque cerebral cortex. The coordinate-independent mapping of RM areas to familiar partitioning schemes (e.g., Brodmann, Bonin & Bailey, Van Essen) in CoCoMac allowed us to generate a spatial representation of RM on a cortical surface template using the Caret software. Thereby we link for the first time the large body of coordinate-independent tracing results to a spatially registered macaque brain and – using existing spatial deformation tools – to the results of neuroimaging studies in humans. • Most recently we have created a three-dimensional visualization software based on drawings from the stereotaxic macaque atlas published by Paxinos et al. (2000). The software links the atlas to mapping and connectivity information in CoCoMac and provides guidance for experimentalists including the option to dissect and manipulate individual brain structures in the cerebral cortex, thalamus and amygdala.
These interfaces provide exciting new opportunities to analyze structural and functional neuroimaging data in the context of underlying anatomical connectivity. We are currently curating and exploiting the data contained for the purposes mentioned above.

Dr. Simon Eickhoff, Forschungszentrum Jülich

Effective connectivity between cortical motor areas underlying normal and disturbed hand function

The work presented in this talk will give an overview on our recent work investigating the dynamic interactions within core motor areas of the cerebral cortex in healthy subjects as well as the disturbances of these networks in patients.
Using functional magnetic resonance imaging, we examined the cortical motor system in healthy subjects using a straightforward visually paced fist opening-closing task, either moving only one hand or both hands in-phase. Applying effective connectivity analysis we that demonstrated that the suppression of the ipsilateral primary motor cortex during unilateral movements is caused by top-down modulation but also inter-hemispheric inhibition. The latter, however, reversed into inter-hemispheric promotion of activity when both hands are moved in-phase. The hereby established methodology was subsequently transferred into clinical research by two fMRI studies investigating the pathophysiology of impaired hand function. In the first investigation examining subcortical stroke patients, it could be demonstrated that movements of the stroke–affected hand were associated with inhibitory influences from the contralesional to the ipsilesional M1. This inhibition was not present in healthy controls and which furthermore correlated with the degree of motor impairment. While this study showed the sensitivity of our approach for detecting pathological changes in cortical networks, the second one demonstrated its specificity in single subject analysis. Here we investigated two patients following heterotopic hand replantation and revealing that, in addition to joint adaptations (such as the inhibition of the remodelled hemisphere upon healthy hand movement), subject specific rearrangements in cortical connectivity could be identified. Importantly, these differences conformed very well to differences in behavioural capacities and clinical history, as the patient who received earlier and more intense rehabilitative exercise showed a significantly higher tonic and phasic recruitment of contralateral M1 and better manual abilities.

Dr. Hauke Busch, DKFZ Heidelberg

Using Gene Network Dynamics to Obtain a Bird's Eye View on Cellular Decisions

Translation of large-scale omic data into a coherent model of cellular regulation allowing to simulate, predict and control cellular behaviour is far from being resolved. The functional components that lead to a sustained cellular decision have been discussed controversially with respect to requiring a controlled interplay of protein signaling and gene regulation.
Combining these processes into one model is inherently difficult: protein signaling pathways and gene regulation are feedback-entangled processes, yet occurring on different time scales in the range of minutes and hours, respectively. This makes it practically impossible to experimentally observe all required functional cellular components at a sufficiently high sampling rate.
Here we show a possibility to circumvent the above problem via the investigation of the systemic behavior of gene regulatory networks. The long-term biological activity of a gene should be highly correlated with its expression dynamics on a time scale of hours or days. Hence, information on cellular processes lasting hours or days should be reflected by gene expression dynamics.
Using Hepatocyte Growth Factor-induced migration of primary human keratinocytes as an example, we infer a dynamic gene regulatory network model from time series measurements of DNA micro-array data. Key genes are identified based on their kinetic profile as well as their biological function. Using a genetic algorithm combined with a search for robust system solutions, we show how to build a phenomenological model that can predict in silico the necessary and sufficient time-ordered events that initiate, maintain and stop migration, all of which are verified in vitro.
The data analysis and modeling may provide a new way of obtaining a bird's eye view on the dynamic orchestration of various signaling pathways and a broad degree of interdependency that control cell migration and cellular decisions in general.