CeNS/IDK-NBT Summer School
"NanoScience and Systems Biology"

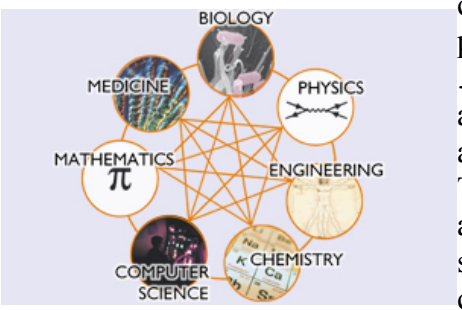
Abstracts (as of July 4, 2005)

Monday & Tuesday, July 25-26 (Morning & Afternoon Sessions)

Systems Biology: the Past, Present and Potential

Eduardo Mendoza
Munich Systems Biology Forum & LMU Center for NanoScience

Systems Biology, the study of network behaviour in biological systems, is aptly described as a network of scientific disciplines itself (s. figure below. Source: Institute of Systems Biology). Interactions in such a network enable novel approaches to biological complexity, particularly through a tight integration of predictive modelling and quantitative experimentation. Though such joint experimenter-modeler scenarios are not new, the breadth of disciplines involved brings a new quality to the task of their effective execution. The talk will begin by describing how, in this regard, an understanding of each discipline's "history" of studying biological systems is key to mastering the challenges of collaboration. In a second part, the talk will discuss and comment on the results of a recent Systems Biology Benchmark Study sponsored by several US research agencies (including NSF, NIH, National Cancer Institute). This study provides a fairly comprehensive and current view of the field's "status quo". Finally, the potential for breakthroughs in medical science and practice, particularly through a combination of nanotechnology and systems biology, will be briefly outlined.



Metabolic Networks I: The Challenge of Complexity

Eberhard O. Voit
Georgia Institute of Technology and Emory University Medical School

Biochemical systems consist of metabolites and reactions that form two types of networks, which are superimposed upon each other. One network is characterized by the distribution of fluxes of mass between pools of metabolites, while the second network consists of signals that control the distribution of material. Taken together, even small biochemical systems can exhibit behaviors that are impossible to predict without a mathematical approach. This first lecture on metabolic network analysis pinpoints some of the sources of complexity and unpredictability and proposes Biochemical Systems Theory (BST) as a powerful approach to describing, analyzing, and manipulating regulated metabolic networks. It explains how to set up systems models and discusses some mathematical and computational methods of analysis.

Metabolic Networks 2: Case Studies

Eberhard O. Voit
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The second lecture on metabolic network analysis discusses specific biochemical systems. The first is sphingolipid metabolism in yeast. This system consists of about fifty variables and is relatively closed. It is interesting, because it combines metabolic features with signaling functions *in vivo* that are involved in differentiation, cell cycle arrest, stress responses and many other phenomena. The demonstration will focus primarily on model design. The second case addresses glycolysis in yeast. The focus here is the combination of information from gene expression and from enzyme kinetic data. Together these data sets yield insights that are both new and sometimes counterintuitive. The third case deals with the trehalose cycle in yeast. The biochemistry of the system is fairly well understood, which allows model design without too many assumptions. The focus here is on the specific roles of each of the numerous control mechanisms that are known to exist at the genomic and the metabolic level.

(Biological) Pathways as (Mathematical) Morphisms

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A 'pathway' is an abstract concept, employed in molecular- and cell biology, to represent biochemical reaction networks in the context of metabolism and cell signalling.

For most research projects the focus is on one pathway, network, or system. The main reason is that experiments can be expensive and time consuming but also because mathematical tools are primarily developed for the analysis of a single system, rather than systems of systems.

For an understanding of functional activity in cells, it is however clear that we require a conceptual framework to discuss the interaction of subsystems (modules), the coordination of pathways, or to model the temporal evolution of one model into another (e.g. to account for changes during cell differentiation).

I am going to discuss the concept of a pathway, its use in systems biology and provide a formal definition. Towards this end I introduce a system-theoretic framework in which a pathway model is considered a single mathematical object (vector field or morphism). This should enable us to discuss interrelations and interactions of multiple subsystems to realise higher-levels of organisation.

I shall argue that there is nothing more practical than a good theory.

System identification of biochemical networks, esp. gene regulatory networks

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It is now widely recognized that extracting knowledge from large-scale data sets requires mathematical modeling of the underlying processes. Traditional modeling methods in biochemistry and cellular biology are bottom-up approaches where models are constructed by piecing together information about individual components (usually obtained in vitro). The systems biology approach, however, lends itself naturally to top-down approaches where models are built directly from data obtained from intact cells. The two lectures will survey some of the existing top-down modeling approaches.

We also discuss two new methods, under development at the Virginia Bioinformatics Institute, to build models directly from data, one continuous and based on calculus, and the other discrete and based on computational algebra. Each of these methods has strong and weak points but these are largely non-overlapping, making the idea of combining them very attractive. Another important issue for top-down modeling is the development of criteria for experimental data sets that suit individual modeling methods. We will address this issue briefly in the context of these two methods.

An integrated approach for analyzing functional structures and systems in a model organism

Dieter Oesterhelt
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tba

July 25 Evening Session

On metabolite correlations and metabolomics data analysis

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The advent of large data sets derived from 'omics' research brought about an increasing interest in biological understanding of these data sets. Reverse engineering biological networks from such data is now a much desired goal, whether the data originated from genomics, proteomics or metabolomics. The latter has been under intensified research with numerous novel technical developments and several data sets being published. Statistical tools such as principal components analysis and correlation analysis have been widely to analyze data though the link between their results and biological functions is at best tenuous. Here we study the phenomenon of metabolite correlations in metabolomics data by providing possible interpretations for them in terms of the regulation of the underlying biochemical network. These interpretations were derived with the help of the metabolic control analysis framework. Analyses based solely on metabolite scatter plots are encouraged to be carried out devoid of scale, for example using z-scores.

Orhan Camoglu
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Deciphering the complex networked organization of proteins is essential to understand the functions of life. A genome-wide functional network shows physical interactions as well as functional associations like inhibition, activation, and phosphorylation between the proteins of an organism. Existing high-throughput techniques that target discovery of interacting proteins provide relatively small coverage of the *C. elegans* genome (e.g., 5,600 interacting pairs in Wormbase as of March 2005). Our goal is to construct a probabilistic high-coverage *C. elegans* network by integrating multiple data sources. Many possible machine learning approaches can be applied to predicting functional linkages between proteins. Among these methods, Bayesian networks (BN) and support-vector machines (SVM) have certain advantages. First, both methods allow for combining highly dissimilar types of data. Second, both methods accommodate missing data. We have built *C. elegan*} probabilistic networks using both BN and SVM approaches. We have integrated various data sources and different gold standards. The preliminary *C.elegans* network contains all of the 19,000 *C. elegans* genes and about 14 million probabilistic functional interactions.

In order to utilize the constructed functional network, a number of analysis algorithms can be developed for discovering biologically relevant information. Examples are mining of frequently occurring motifs, checking motif occurrence, computing whole-graph and subgraph similarities, finding the best path between a pair of nodes under given constraints, finding the best neighbors of a given set of nodes, and finding common properties of a given set of nodes. We have developed random walk and network flow algorithms for predicting members of a partially known pathway. We have tested our algorithms on the *C. elegans* apoptosis pathway using a leave-one-out benchmark.

Our results show that a network constructed from multiple information sources is able to capture functional linkages between the members of a pathway significantly better than a network built using a single data source.

Noice-enhanced categorization in a recurrently reconnected neural network

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We investigate the interplay of recurrence and noise in neural networks trained to categorize spatial patterns of neural activity. We develop the following procedure to demonstrate how, in the presence of noise, the introduction of recurrence permits to significantly extend and homogenize the operating range of a feedforward neural network. We first train a two-level perceptron in the absence of noise. Following training, we identify the input and output units of the feed-forward network, and thus convert it into a two-layer recurrent network. We show that the performance of the reconnected network has features reminiscent of nondynamic stochastic resonance: the addition of noise enables the network to correctly categorize stimuli of subthreshold strength, with optimal noise magnitude significantly exceeding the stimulus strength. We characterize the dynamics leading to this effect and contrast it to the behavior of a more simple associative memory network in which noise-mediated categorization fails.

Modeling Cell-Cell Communication

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Communication processes play a crucial role in the interplay of different organisms in the rhizosphere. We first consider the communication mechanism called "quorum sensing", which allows a coordinated reaction e.g. for pathogenic bacteria. The bacteria produce signal molecules on a low level. If their density exceeds a certain threshold, the genetic network switches its behavior and produces at a much higher rate these signal molecules; at the same time other processes are initiated. The first basic models were adjusted to the quorum sensing system of the well-studied water bacterium *Vibrio fischer*i. Now the insights from
the basic model can be used to create a model for bacteria in the rhizosphere, e.g. *Burkholderia cepacia*. This is part of a more general space-time modeling of functional interactions of organisms in the rhizosphere.

The Development of Multiscale Simulation of a Bacterial Phosphorelay Sensory Transduction System

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The BvgAS two-component system controls virulence in the human respiratory pathogen Bordetella pertussis, the etiological agent of whooping cough. BvgAS is unlike orthodox two-component signal transduction systems in that it employs a four step phosphorelay from the sensor protein BvgS to the response regulator BvgA, instead of the more common two step phosphotransfer. Further, B. pertussis displays at least three distinct phenotypic phases, each characterized by maximal expression of some genes and minimal expression of others. We are engaged in the development of a computational model of this signal transduction and gene expression pathway which we intend to employ in exploring the following questions. First, what are the levels of BvgA~P (phosphorylated response regulator) in each phenotypic phase? Does the concentration of BvgA~P vary in a stepwise or continuous fashion in response to changes in signal compound concentration? Second, what is the advantage of employing a 4-step phosphorelay instead of a 2-step phosphotransfer system? Can a 2-step phosphorelay mediate three phenotypic phases? Third, BvgAS regulates its own transcription; what is the effect of this autoregulation?

The computational model is being developed in a methodical fashion. In vitro experiments are modeled by ordinary differential equations of chemical kinetics in order to obtain kinetic parameter estimates. This suggests gaps in the experimental literature and experiments best suited to fill those gaps, which are then performed. Completed versions of the model are then simulated using deterministic (ODE), stochastic (Gillespie's algorithm) or multiscale (tau leaping, slow-scale SSA or hybrid) chemical kinetics algorithms, depending on what is appropriate.
Preliminary results indicate that the full complexity of the three phenotypic phases of B. pertussis cannot be achieved without incorporating the phosphorelay (i.e. by simple two-step phosphotransfer) or BvgAS autoregulation in the model.

High-frequency biolevers for single-molecule biophysics experiments

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The ability to perform real time measurements at the single-molecule level will shed light onto the understanding of the biophysics of folding pathways and energy landscapes [1]. We have designed and fabricated novel high-frequency cantilevers for use in Single-Molecule Force Spectroscopy (SMFS) experiments that provide direct biomechanical information of individual molecules; including the rare variations that are averaged over in complementary bulk ensemble measurements. By scaling all three dimensions of the cantilever, the nanoscale cantilevers maintain a high resonant frequency without sacrificing their low stiffness spring constants. We target to attain cantilevers with unloaded spring constants on the order of tens of millinewtons per meter that maintain bandwidths extending into the hundreds of kilohertz range in fluid with ~10pN√Hz force resolution and ~50ms fluidic response time. Increasing the fundamental resonant frequency opens up new bandwidth over which noise is distributed – improving the signal-to-noise ratio. When operating in the force-clamp [2], the improved temporal resolution will provide insights into the structure and function of single molecules from the level of RNA and DNA to protein.

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July 26 Evening Session

Baris Sumengen
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Atomic Force Spectroscopy on Integrins

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Integrins are cell-surface receptors with multiple physiological and patho-physiological functions. They are involved in many fundamental cellular processes, like cell-matrix adhesion, cell proliferation and apoptosis. Furthermore, they act in concert with other receptors like human growth factors, and are the starting point of intra-cellular signalling networks. We use AFM to probe the function of integrins in different environments. Since integrins are force transducing proteins, atomic force spectroscopy is an ideal tool to investigate these receptors in their native environment. The here examined $\alpha_4\beta_1$ integrin of white blood cells plays an important role in immune responses. To get insight into crosstalk of $\alpha_4\beta_1$ with CXCR-4, a member of the G-protein coupled receptors, we fixed living human lymphoblasts on cantilevers and measured the interaction of the cells with the integrin-ligand VCAM-1 immobilized on a petri dish. Co-immobilized chemokine SDF-1, the ligand of CXCR-4, activates the integrin to an high affinity state and induces conformational changes. This results in higher adhesion forces and adhesion rates. Thus, we could directly demonstrate the crosstalk between $\alpha_4\beta_1$ and CXCR4.
To gain further insight into the affinity and structure changes during activation, we plan to functionally reconstitute integrins in tethered lipid bilayers and to image them with functionalized tips.

Single cell gene expression statistics of synthetic gene delivery systems measured by GFP fluorescence analysis

Gerlinde Schwake[1], **Maria Pamela David[1, 2]** and Joachim Rädler
LMU Physics Department and Center for NanoScience
Marine Science Institute, University of the Philippines, Diliman, Quezon City

Using quantitative fluorescence microscopy, we monitored the enhanced green fluorescence protein (EGFP) expression in a large number of individual cells in culture over time. Semi-automated microscopy allows real-time monitoring of fluorescence intensities of many individual cells and to generate vast amount of time courses by image processing. Gene transfer kinetics in two non-viral gene delivery systems were deduced using real-time fluorescence measurements. Significant differences seen between lipofectamine-mediated and linear polyethyleneimine (linPEI)-mediated transfection include the expression onset, which was three hours for lipofectamine and six hours for linPEI, and the maximum expression rate, which was approximately 10 GFP/s per cell for lipofectamine and 2 GFP/s cell for linPEI.

Controlled assembly and manipulation of biomolecules on the nanometer-scale

Stefan Kufer, Angelika Kardinal and Hermann Gaub
LMU Physics Department and Center for NanoScience

The controlled assembly of single biomolecules (especially of proteins) is one of the big goals in modern Nanotechnology. In our group a new immobilisation technique was used to anchor various fusion proteins in a controlled way to solid surfaces. To do this, a genetically modified form of the human DNA repair protein O^6-alkylguanine-DNA-alkyltransferase (hAGT) was used as a fusion-tag. With this immobilisation method it is possible to bind recombinant proteins covalently, selectively and site-directed to solid surfaces. We will use this technique to assembly single biomolecules with the tip of an AFM-cantilever.

Network Analysis of Pathogen and Pathogen-Host Systems

Arthur Yu-An Dong
Max-von-Pettenkofer Institute, LMU

Complex networks arise in diverse areas of natural and social sciences and network analysis has become an indispensible tool to understand their organization, evolution, and dynamics. The protein-protein interaction
(PPI) network of Kaposi's sarcoma related herpesvirus (KSHV), the first viral interactome available, was shown to possess unusual network properties distinct from those of cellular interactomes, with important consequences including increased attack tolerance. Interactions between KSHV and human proteins were successfully predicted and used to connect the viral interactome to the host interactome. Simulations demonstrated that network topology uniquely characterizes the combined pathogen-host system.

Biomolecular Nanoscience and Systems Biology

Tim Liedl, Stefan Beyer, Michael Olapinski, Andreas Reuter, Eike Friedrichs, and Friedrich Simmel

There are many points of interaction between systems biology and nanotechnology. On the one hand, advanced, nanotechnology-based bioanalysis techniques may help satisfy the extreme demand for information about biological systems, which is needed as input for their computational treatment. Furthermore, nanodevices may be used as 'probes' which can stimulate and analyse biological systems in order to elucidate their dynamical behavior. Finally, ideas from systems biology can be fed back to nanotechnology to construct artificial, bioinspired reaction networks and to realize molecular regulation mechanisms for self-organization.

We here present several projects relevant to this endeavor: a device for DNA signal conversion, nanobioelectronics with nanopores and DNA, a DNA-'hand' able to grab and

release a protein, and a DNA conformational switch driven by a chemical oscillator. In addition, we present techniques, which enable the manipulation of biological molecules on the nanometer scale, such as e-beam lithography, micro-contact printing, and chip-based patch clamping.

Wednesday, July 27, 2005

TOPOLOGY AND INTERPLAY OF CELLULAR AND HERPESVIRUS PROTEIN INTERACTION NETWORKS

Yu-An Dong[1]*, Peter Uetz[2]*, Christine Zeretzke[3], Armin Baiker[3] Even Fossum[3], Bonnie Berger[1], Seesandra Rajagopala[2], Maria Roupelieva[3], Christine Atzler[3], Dietlind Rose[3]and **Jürgen Haas**[3#]
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The comprehensive yeast-two-hybrid analysis of intraviral protein interactions in two members of the herpesvirus family, Kaposi Sarcoma associated Herpesvirus (KSHV) and Varicella Zoster Virus (VZV), revealed 123 and 173 interactions, respectively. The topology of the resulting protein interaction networks differed significantly from previously reported biological networks in that the herpesvirus interactomes exhibited scale-free but not small-world properties and unusually low power coefficients <1 (cellular networks >2). Viral networks resemble single, highly coupled modules, whereas cellular networks are organized in separate functional submodules. Predicted and experimentally verified interactions between KSHV and human proteins were used to connect the viral interactome into a prototypical human interactome, thus simulating infection. Network analysis of the combined viral-host system showed that the viral network rapidly adopts cellular network features and that topology is a distinguishing feature probably reflecting global strategies to manipulate the host. Our study resulted in numerous biological hypotheses which remain to be investigated in detail. The availability of protein interaction networks in other herpesviruses and large-scale virus-host interaction data in the near future will boost our knowledge on the function of many still poorly characterised viral proteins and the phylogeny of herpesviruses. It will eventually lead to a considerably improved understanding of viral pathogenesis and evoke novel therapeutic strategies.

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NanoSystems Biology

Michael Roukes

tba

Molecular machines in the repair of DNA double-strand breaks

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DNA is constantly damaged and repair of DNA is fundamental to genome maintenance, cell survival and prevention of cancer development. DNA double-strand breaks are the most severe form of DNA damage and can lead to loss of chromosome arms, chromosome fusions and other large scale rearrangements in our genome. The

Mre11/Rad50/Nbs1 complex is the primary sensor of DNA double-strand breaks and can form large molecular bridges that capture and link DNA breaks in a process that involves ATP-hydrolysis. Related SMC protein complexes form ring structures around chromosomes or condense chromosomes using ATP-hydrolysis. We use X-ray crystallography to investigate the structure and mechanism of these molecular machines in genome maintenance processes. Our results suggest how ATP-driven conformational changes provide the force to alter DNA topology in order to facilitate DNA double-strand break repair and other genome maintenance processes

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Single-molecule AFM measurements of cell adhesion on living cells: SDF-1 (CXCL12) mediated rapid activation of integrin VLA-4 – VCAM-1 bonds

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Atomic force microscopy (AFM) based force spectroscopy can be used for direct measurement and quantification of cell adhesion forces on living cells down to single-molecule interactions. This technique is used here to study the physiologic activation of alpha(4) integrins by the chemokine CXCL12 on living cells expressing the chemokine receptor CXCR4. At low physiologic concentration of CXCL12 the rupture force of a single pair of adhesion receptors increases from 40pN to 60-80pN, whereas at higher concentrations of CXCL12 it lowers the rupture forces back to 40pN. This study confirms that arrest chemokines such as CXCL12 can rapidly modulate the affinity of an integrin receptor. To date, this is the first direct measurement of chemokine induced affinity modulation of a single (adhesion) receptor as well as of the desensitization of a chemokine receptor, both measured on a molecular level on a living cell. AFM based force spectroscopy has evolved into a completely new pharmacological test for single-molecule interactions on living cells. This technique will be used to elucidate the mechanisms involved in both physiologic leukocyte homing as well as organ-specific tumor cell metastasis.

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Identification of ligands for orphan human NK cell receptors

Michael Ackmann
LMU Biozentrum

The role of natural killer (NK) cells in the immune system has evolved from being just naturally cytotoxic to being highly regulated. Today a modified missing self hypothesis is thought to explain the function of fully developed NK cells sufficiently. However the recent discovery of non-major-histocompatibility-complex- (non-MHC)-related inhibitory ligands for NK receptors in the mouse suggests that there is another layer of inhibitory regulation. This inhibition can be performed by ligands found on specialized immune cells like dendritic cells or macrophages.
The aim of the project is to show that this is also true in human. Therefore we identify ligands for orphan NK receptors using a systematic approach. It comprises the generation of a stably reporter gene transfected hematopoietic progenitor cell (HPC) line ("reporter HPCs"), differentiation of „reporter HPCs" into NK cells („reporter NK cells"), transient transfection of "reporter NK cells" for chimeric NK receptor expression and the identification of orphan NK receptor ligands via a reporter assay.

New Developments in Experimental Bioimaging

Joachim O. Rädler
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tba

Challenges in Bioimage Informatics

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The Center for Bioimage Informatics was established in 2003 with support from the US National Science Foundation to develop new information processing technologies for bioimages. The goal is to develop a digital library of biomolecular images that would facilitate a better understanding of complex biological processes. In this presentation, I will discuss some of the image processing and pattern recognition challenges that arise in the analysis two specific datasets: retinal image cross sections to study retinal detachment, and microtubule video data. Initial results on segmentation, classification, tracking and registration will be presented.

Evening Lecture?

Thursday, July 28, 2005

Experimental Proteomics: State of the Art

Freidrich Lottspeich
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tba

Cell-free genetic networks

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Dept. of Materials and Interfaces, The Weizmann Institute of Science

Biochemical computational elements in the cell, also known as networks, are made of interacting genes and proteins. Understanding design principles of naturally occurring networks opens an opportunity for mimicry within an artificial environment. An experimental approach is presented towards materializing the concept of artificial networks as a gateway to nanotechnology.

Control for DNA-based molecular machines

Friedrich C. Simmel
LMU Physics Department and Center for NanoScience

The unique chemical and mechanical properties of DNA can be used to construct simple nanoscale actuators. They can induce motion on the nanometer scale, bind and release other molecules or perform simple computations. For many applications it would be desirable to make the action of these devices dependent on environmental stimuli. Three different methods are explored to achieve such environmental control: 1) DNA devices can be controlled using gene regulatory mechanisms. 2) DNA devices can be driven by oscillating chemical reactions. 3) The action of a DNA device can be controlled by an enzyme-based DNA signal transducer.