BP 4: Systems Biology & Gene Expression and Signalling

Time: Monday 15:00–17:30 Location: ZEU 250

Invited Talk BP 4.1 Mon 15:00 ZEU 250

Antibiotic-induced gene expression noise and cross-protection at the single-cell level — •Tobias Bollenbach — University of Cologne, Germany

Antibiotics elicit drastic changes in microbial gene expression, including the induction of stress response genes. While certain stress responses are known to 'cross-protect' bacteria from other stressors, it is unclear if cellular responses to antibiotics can have a similar protective role. By measuring the dynamic genome-wide transcriptional response of *Escherichia coli* to four antibiotics, we found that trimethoprim induces a rapid and strong acid stress response pulse which protects bacteria from subsequent exposure to acid. We then combined microfluidics and time-lapse imaging to monitor survival and the dynamics of acid stress response induction in single cells. The fraction of surviving cells followed a simple exponential decay and thus appeared consistent with a memoryless Poisson process. Interestingly, however, the noisy expression of one of the major acid resistance genes explained the great spread in single-cell survival times. Simultaneous measurements of gene expression and pH using a ratiometric sensor revealed that cells with higher expression of acid resistance genes upon trimethoprim exposure maintain higher intracellular pH and survive the acid shock better. The seemingly stochastic single-cell survival times under acid stress therefore become predictable once their underlying molecular cause is identified. Overall, this work provides a roadmap for the systematic identification of molecular mechanisms behind single-cell cross-protection between antibiotics and other stressors.

BP 4.2 Mon 15:30 ZEU 250

Origin and consequences of the exponential decay of viability of Escherichia coli during starvation — •Severin Schink[1], Elena Biselli[1], Constantin Ammar[1,2], and Ulrich Gerland[1] — [1]Technische Universität München, Physik Department — [2]Ludwig-Maximilians-Universität München, Institut für Informatik

Surviving nutrient limitation is an important part of the microbial life cycle. When carefully starved of all energetic substrates, Escherichia coli shows an exponential decay of viability, with the rate depending on environment and genetics. In this work we identify the exponential decay to be a consequence of the energetic needs of the cell for maintenance. When no carbon resources are available in the medium, the only external possibility for energy production are resources freed by lysed cells in the population. Such a cannibalistic process, in which dying cells release resources that can sustain the remaining live cells, naturally leads to an exponential decay of viability. The death rate of a starved population is thus a measure for the maintenance rate, and allows quantitative studies of environmental and genetic perturbation, as exemplified by the study of knock-outs of the stress response sigma factor rpoS.

BP 4.3 Mon 15:45 ZEU 250

Magnetogenetic Manipulation of Intracellular Signalling — •Cornelia Monzel[1], Chiara Vicario[1], Domenik Lisse[2], Mathieu Coppey[1], Jacob Piehler[2], and Maxime Dahan[1] — [1]Laboratoire Physico-Chimie, Institut Curie, CNRS UMR168, 75005 Paris, France — [2]University of Osnabrück, Department of Biology, 49076 Osnabrück, Germany

Many cell functions rely on the coordinated activity of signalling pathways at a subcellular scale. However, there are few tools capable of probing and perturbing signalling networks with a spatial resolution matching the intracellular dimensions of their activity patterns. Here, we develop a generic magnetogenetic approach based on functionalized magnetic nanoparticles (MNPs) targeting an intracellular protein of interest. Upon protein recruitment the MNP-protein complexes act as nanoscopic hot spots that can be displaced by magnetic forces to provide molecularly graded information to the cell and to trigger a signal transduction pathway that brings about a cellular response. We demonstrate that magnetic nanoparticles based on the natural iron storage protein ferritin are ideally suited for intracellular applications. We use these ferritin MNP to manipulate Rho-GTPases - a set of molecular switches known to regulate cell morphology via complex spatiotemporal patterns of activity. The MNP-Rho-GTPase mediated stimulus is then shown to trigger morphological and signalling activity.

BP 4.4 Mon 16:00 ZEU 250

Cause and Cure of Sloppiness in Ordinary Differential Equation Models — •Christian Tönsing[1], Jens Timmer[1,2,3], and Clemens Kreutz[1,2] — [1]Institute of Physics, University of Freiburg, Germany — [2]Center for Biosystems Analysis (ZBSA), University of Freiburg, Germany — [3]BIOSS Centre for Biological Signalling Studies, University of Freiburg, Germany

For the purpose of mathematical modeling of biochemical reaction networks by the frequently utilized nonlinear ordinary differential equation (ODE) models, parameter estimation and uncertainty analysis is a major task.

In this context the term sloppiness has been introduced recently for an unexpected characteristic of nonlinear ODE models. In particular, a broadened eigenvalue spectrum of the Hessian matrix of the objective function covering orders of magnitudes is observed, although no such hierarchy of parameter uncertainties was expected a priori.

In this work, it is shown that sloppiness originates from structures in the sensitivity matrix arising from the properties of the model topology and the experimental design. It will be clarified that the intensity of the sloppiness effect is controlled by the design of experiments, i.e., by the data. Thus, we conclude that the assignment of sloppiness to a model as a general characteristic is incomplete without discussing experimental design aspects. Furthermore, we validate this proposition by presenting strategies using optimal experimental design methods in order to circumvent the sloppiness issue and show results of non-sloppy designs for a benchmark model.

BP 4.5 Mon 16:15 ZEU 250

Engineering orthogonal synthetic timer circuits in bacteria — •Marco Mauri[1], Daniela Pinto[2], Stefano Vecchione[1], Hao Wu[1], Thorsten Mascher[2], and Georg Fritz[1] — [1]LOEWE-Center for Synthetic Microbiology (SYNMIKRO), Philipps-University Marburg, Germany — [2]Institut für Mikrobiologie, Technische Universität Dresden, Germany

The rational design of synthetic circuits in bacteria is often restricted by cross-reactions between circuit components and physiological processes within the heterologous host. Here, we present a strategy to overcome these restrictions by using extracytoplasmic function sigma factors (ECFs). These are reversible binding subunits of the bacterial RNA polymerase, which are activated upon environmental stress conditions. ECFs represent ideal orthogonal regulators because there exist over 90 phylogenetic ECF groups recognizing distinct target promoters. To explore their potential for synthetic circuit design, we evaluate several heterologous ECFs in *Escherichia coli* and *Bacillus subtilis*. After a quantitative study of simple switches, we use a computational model to predict the behaviour of a cascade with two and three ECFs, which we find in excellent agreement with experimental data. We show that in both organisms these "autonomous timers" sequentially activate a series of genes with a defined time delay. These results not only serve as a proof of concept for the application of ECFs as organism-independent building blocks for synthetic biology, but could also be used to introduce a timing hierarchy among the expression of biosynthetic pathway components in biotechnological applications.

BP 4.6 Mon 16:30 ZEU 250

Local Riemannian geometry of model manifolds and its implications for practical parameter identifiability — •Daniel Kaschek[1], Daniel Lill[2], and Jens Timmer[1] — [1]Physikalisches Institut, Universität Freiburg — [2]Systems Biology Ireland, University College Dublin

When dynamic models are fitted to time-resolved experimental data, parameter estimates can be poorly constrained albeit being identifiable in principle. This means that along certain paths in parameter space, the negative log-likelihood does not exceed a given threshold but remains bounded.

This situation, denoted as practical non-identifiability, can only be detected by Monte Carlo sampling or systematic scanning by the profile likelihood method. In contrast, the Fisher information matrix which is based on second-order model sensitivities in the optimum reveals no information about the boundedness at all.

Here, we show that for some dynamic models the information about the bounds is already contained in the Christoffel symbols, which are

also computed from model sensitivities up to order two at the optimum. Assuming constant Christoffel symbols in the geodesic equation, approximate Riemannian normal coordinates are constructed. The new coordinates give rise to an approximative log-likelihood, featuring flat directions and bounds similar to that of the original log-likelihood.

BP 4.7 Mon 16:45 ZEU 250

Cellular memory couples sporulation and spore revival — Alper Mutlu[1,2], Stephanie Trauth[1,2], Marika Ziesack[2], Jan-Philip Bergeest[2], Karl Rohr[2,3], Nils Becker[2,3], Thomas Höfer[2,3], and •Ilka Bischofs[1,2] — [1]MPI for Terrestrial Microbiology — [2]University of Heidelberg — [3]DKFZ Heidelberg

In bacteria, entry into and exit from dormancy are controlled by regulatory networks with little known overlap, indicating that the two processes operate independently from each other. Using *B. subtilis* as a model we developed an advanced time-lapse microscopy assay and a fluorescent marker that reports on a spore's differentiation history to study the effect of variable sporulation timing on nutrient-induced spore revival. We find that spores exhibit long-term phenotypic memory of their differentiation history. Modeling and experiments with re-programmed cells suggest that this memory creates a quantity versus quality trade-off to generate fewer but more efficient spores. We therefore suggest that phenotypic memory contributes to the emergence of complex adaptive traits.

BP 4.8 Mon 17:00 ZEU 250

Inflammatory diseases from the network perspective — •Piotr Nyczka[1], Amke Caliebe[2], Silke Szymczak[2], Carolin Knecht[2], Kristina Schlicht[2], Michael Krawczak[2], and Marc-Thorsten Hütt[1] — [1]Jacobs University Bremen, Germany — [2]Christian Albrechts University of Kiel, Germany

We have studied gene expression patterns (provided to us by the KORA study within the framework of the sysINFLAME systems medicine consortium) of human patients with inflammatory diseases with respect to the gene centric metabolic networks.

Despite the fact of dealing with very noisy data we were able to find clear evidence of prominent differences between two inflammatory diseases: Psoriasis and Inflammatory Joint Disease, from the perspective of these networks. This difference was clearly visible even on purely topological level and result was robust across two diffrent human metabolism models, and different parameter values.

This is definitely important result and could be a serious step forward in further understanding of these diseases, from the network perspective. We will also discuss results regarding protein network perspective and give some more details about human metabolism and methods we use.

BP 4.9 Mon 17:15 ZEU 250

Designing Synthetic Networks and Experimentation in silico: A Generalized Evolutionary Algorithm Approach — •Christian Fleck — Laboratory of Systems and Synthetic Biology, Wageningen University, The Netherlands

Evolution has led to the development of biological networks that reliably respond to environmental signals. Elucidating, understanding and then reconstructing important network motifs is one of the principal aims of Systems & Synthetic Biology. In this work we present a generalised in silico evolutionary algorithm that simultaneously finds network structures and reaction rates that satisfy defined objectives. By using a schema description of model properties and employing recombination between pairs of networks, the algorithm is able to explore large regions within the search space. We show the utility of our algorithm by finding robust synthetic oscillators, and, by using multi-objective optimisation to find a set of oscillators and feed-forward loops that are optimal at balancing competing objectives. Notably, we highlight that protein dimerisation is an important aspect of oscillating networks. We go on to discuss our results in the context of understanding network evolution in nature and in the laboratory. Furthermore, we suggest how in silico evolution can aid the efficiency of directed evolution experiments for designing synthetic circuits. The use of optimisation algorithms to design robust networks should enable synthetic biologists to construct new systems that produce increasingly complex responses.