BP 20: Regulation and Signaling

Time: Thursday 9:30–12:00 Location: C 243

Invited Talk BP 20.1 Thu 9:30 C 243

Modeling noisy concentration gradients inside single cells — Filipe Tostevin[1], Pieter ten Wolde[2], and •Martin Howard[1,3] — [1]Dept of Mathematics, Imperial College London, SW7 2AZ, UK — [2]AMOLF Institute, Amsterdam, The Netherlands — [3]Dept of Systems Biology, John Innes Centre, Norwich NR4 7UH, UK

Many biological systems require precise positional information to function correctly. Examples include positioning of the site of cell division and determination of cell fate during embryonic development. This positional information is often encoded in concentration gradients. A specific protein is produced only within a small region, and subsequently spreads into the surrounding space. This leads to a spatial concentration gradient, with the highest protein concentration near the source. By switching on a signal only where the local concentration is above a certain threshold, this gradient can provide positional information. However, intrinsic randomness in biochemical reactions will lead to unavoidable fluctuations in the concentration profile, which in turn will lead to fluctuations in the identified position. We therefore investigated how precisely a noisy concentration gradient can specify positional information. We found that time-averaging of concentration measurements potentially allows for great precision to be achieved even with remarkably low protein copy numbers. We have applied our results to a number of examples in cell biology, including positioning of the site of cell division in yeast.

Invited Talk BP 20.2 Thu 10:00 C 243

Non-equilibrium dynamics of gene expression — •Johannes Berg — Institute for Theoretical Physics, Cologne University, Zülpicher Str.77, 50937 Köln

The dynamics of gene expression is characterized by two key elements: (i) The transcription of genes is driven by transcription factor molecules. The number of transcription factors present in a cell changes constantly, keeping the system out of equilibrium. (ii) The transcription of a gene involves a small number of molecules, leading to a noisy dynamics marked by large fluctuations.

In this talk I discuss a simple mapping between models of gene expression and stochastic systems driven out of equilibrium. Using this mapping, results of nonequilibrium statistical mechanics such as the Jarzynski equality and the fluctuation theorem are demonstrated for gene expression dynamics. Applications of this non-equilibrium approach include the determination of mRNA degradation rates and regulatory interactions between genes from experimental gene expression data.

BP 20.3 Thu 10:30 C 243

Links between biochemistry and regulatory network design in a bacterial stress response system — •Georg Fritz[1], Christiane Koller[2], Korinna Burdack[2], Ulrich Gerland[1], and Kirsten Jung[2] — [1]Institute for Theoretical Physics, Universität zu Köln — [2]Department of Microbiology, LMU München

The evolutionary driving forces and constraints that have shaped the design of biomolecular networks are poorly understood in general. Here, we focus on a conditional stress response system, the Cad system of *E. coli*, which is triggered under acidic stress only if lysine is abundant externally. Through lysine import, decarboxylation, and cadaverine export, it effectively expels H^+ from the cytoplasm. A salient feature of the Cad system is that its expression is transient, even when the low-pH and high-lysine conditions for its induction persist. The transient behavior is believed to be caused by a negative feedback via external cadaverine.

We have experimentally recorded the dynamics of the Cad system with a high time resolution, and formulated a quantitative model for its function and regulation. Our analysis suggests that the system design is linked to the biochemical properties of a key system component, the antiporter CadB: Limited specificity of the antiporter causes a futile transport cycle at high external cadaverine levels. Interestingly, the external cadaverine threshold for the negative feedback appears quantitatively consistent with the specificity of the antiporter, suggesting that the regulatory feedback and the biochemistry of the antiporter are evolutionarily linked.

BP 20.4 Thu 10:45 C 243

Fluorescence cross-correlation spectroscopy measurements in vivo reveal the asymmetric incorporation of siRNAs into RISC and the localisation of the complex in human cells — Thomas Ohrt, •Wolfgang Staroske, Jörg Mütze, and Petra Schwille — Biophysics Group, BIOTEC/TU Dresden

Short double stranded RNA molecules have emerged as key regulators of gene expression, controlling developmental programs as well as functioning as a defence mechanism against viruses and transposons. Small RNAs use Argonaute-containing complexes called RNA-Induced Silencing Complex (RISC) to identify cognate RNA transcripts whose expression is to be silenced. By combining laser scanning microscopy, fluorescence correlation and cross-correlation spectroscopy (FCS/FCCS) and biochemical methods, we have exploited the interaction of short interfering RNAs with RISC in vivo. We established a functional and stable EGFP-Ago2 expressing 293 cell line, with expression levels suitable for FCS/FCCS. Using this in vivo system combined with highly sensitive FCS and FCCS it is possible to gain vast information on relative binding, concentration and mobility. Analysis of various microinjected fluorescently labelled siRNAs with FCCS showed the asymmetry dependent incorporation of the antisense strand into RISC over time in human cells. Measurements in various cell compartments showed the localisation of loaded RISC complex in human cells.

BP 20.5 Thu 11:00 C 243

Boolean Model of Fission Yeast Cell Cycle predicts mutations — •Maria Davidich and Stefan Bornholdt — Intitute for Theoretical Physics

A Boolean model [1] of the key regulators of the fission yeast cell cycle was built. The advantage of the model is that it is purely constructed on a wiring diagram of known biochemical reactions; no extra parameters enter the model. However, even though one needs much less information about the system, the model reproduces the right sequence of protein activity states during the cell cycle. This sequence appears to be robustly implemented in the regulatory network, its last state G1 corresponds to the biggest attractor of the system. Surprisingly, this simple model can also describe mutations of the regulatory proteins. We test the model starting from the different initial conditions corresponding to overexpression and underexpression of the proteins. The tests show that other attractors agree with mutations found in experiments.

[1] Davidich M.I., Bornholdt S. Boolean network predicts cell sequence of fission yeast. www.arhiv.org/abs/0704.2200 (Submitted to PLOS ONE)

BP 20.6 Thu 11:15 C 243

On the effect of transcription factor fluctuations at promoter logic gates — •Christian Fleck, Moritz Gerstung, and Jens Timmer — Institute of Physics, Hermann-Herder-Str. 3a, University of Freiburg, Germany

Biological organism constantly respond to changing cellular and environmental signals. These signals are integrated at cis-regulatory modules or promoter logic gates. Hence, the output causally depends on the degree of occupancy of the individual target sides within the cis-regulatory module. Because many TFs are present in low copy numbers per cell, the regulatory processes are inevitably subject to noise. A substantial preliminary for an understanding of how noise alters the output of promoter logic gates is knowledge about how fluctuations in TF abundance affect single operator occupancy. The inherent non-linearity arising from the bimolecular interaction impedes the analytical investigation of this phenomenon substantially. We present a detailed analysis of a TF-operator interaction finding noise correction terms to the macroscopic description. While the correction is always negative for single binding sites, we discover more diverse effects on the logic gates comprising multiple binding sites.

BP 20.7 Thu 11:30 C 243

Compartment Model for IRE1 Signalling of the Unfolded Protein Response — •Ronny Straube — Department of Systems Biology, Max-Planck-Institute for Dynamics of Complex Technical Systems, Sandtorstr. 1, 39106 Magdeburg, Germany

In recent years it became apparent that sustained stress in the endoplasmic reticulum (ER) is related to the emergence of several neu-

rodegenerative diseases such as Alzheimer, Parkinson and ALS as well as diabetes and drug resistance of tumor cells. ER stress is caused by the accumulation of unfolded proteins in the secretory pathway. This leads to the activation of an extensive transcriptional response called Unfolded Protein Response (UPR) to restore ER homeostasis. UPR signalling occurs via 3 distinct and temporarily ordered pathways mediated by PERK, ATF6 and IRE1. As a result, proapoptotic and prosurvival signal molecules are activated simultaneously. So far it is unclear how the cell integrates this information to decide in favour of one or the other. However, recent experiments show that sustained signalling via the IRE1 pathway of the UPR promotes cell survival. Here, I propose the first model of the IRE1 signalling pathway which is based on the known molecular details of the interaction network and which shows good agreement with published experimental data.

[1] Lin et. al. (2007), Science **318**, 944-949.

BP 20.8 Thu 11:45 C 243

Mechanisms of sperm chemotaxis — •Benjamin M. Friedrich and Frank Julicher — Max-Planck Institute for the Physics of Complex Systems, Nöthnitzer Straße 38, Dresden

Sperm cells swim towards the egg propelled by a flagellum which beats regularly. In many species sperm show chemotaxis, i.e. they move upwards a gradient of chemoattractant molecules released by the egg. Sperm cells sample the local chemoattractant concentrations with receptors on the surface of their flagellum. A signaling cascade within the flagellum transduces the concentration stimulus and elicits a swimming response by changing the flagellar beat [1,2]. We propose an effective description of this signaling cascade and derive consequences for experiments. In the limit of low chemoattractant concentrations, the concentration stimulus is Poissonian shot noise since the binding of chemoattractant molecules to the receptors is a discrete process. We therefore study also the influence of fluctuations in the concentration stimulus on the chemotaxis mechanism and derive measures for the fidelity of chemotaxis.

[1] B. Kaupp *et. al.*: NCB **5**, 109 (2003)
[2] B.M.F., F.J.: PNAS **109** (2007)