BP 20: Regulation

Time: Thursday 9:30–13:00 Location: H 1058

Invited Talk BP 20.1 Thu 9:30 H 1058

Precision of sensing, memory, and fluctuating environments — •Robert Endres[1,2] and Gerardo Aquino[1,2] — [1]Division of Molecular Biosciences, Imperial College, London, UK — [2]Centre for Integrative Systems Biology and Bioinformatics, Imperial College, London, UK

Biological cells are known to sense their chemical environment with astonishing accuracy, crucial for nutrient scavenging, mating, immune response, and development. It is unknown if this sensing near the single-molecule detection limit is due to highly precise single measurements or due to learning over time. In this work, we analyze if cell memory can allow cells to sense beyond current estimates of the fundamental physical limit. By merging Bayesian inference with information theory, we derive analytical formulas which show that memory helps for sensing of correlated fluctuating environments, but not for sensing of strongly uncorrelated fluctuating environments. Despite many analogies with problem-solving strategies in engineering, our theory shows fundamental differences in interpreting noisy stimuli in the microscopic and macroscopic world.

BP 20.2 Thu 10:00 H 1058

Precision and synchronization of coupled genetic oscillators — •David J. Jörg[1], Luis G. Morelli[1,2], and Frank Jülicher[1] — [1]Max Planck Institute for the Physics of Complex Systems, Nöthnitzer Str. 38, 01187 Dresden, Germany — [2]Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstr. 108, 01307 Dresden, Germany

Biological systems rely on oscillatory processes serving as pacemakers to control important functions during development and life. Within cells, periodic patterns of activity can be generated by oscillations of protein concentrations. Intracellular fluctuations in protein numbers impair the precision of oscillations and thus limit their viability as pacemakers. In multicellular systems, communication between cells can couple their dynamics, give rise to synchronization, and affect the precision of oscillations. To study the effects of coupling on cell-autonomous oscillators in small cell clusters, we have devised a generic stochastic model that comprises negative feedback oscillators coupled through mutual regulation of protein production. We found that average coupling delays determine whether coupling improves or impairs the precision of oscillations and the ability to synchronize.

BP 20.3 Thu 10:15 H 1058

Rare switching in non-stationary gene regulation networks — •Nils Becker and Pieter Rein ten Wolde — AMOLF Institut, Amsterdam

Rare barrier-crossing events act as dynamical bottlenecks in a broad variety of physical and biological systems. Examples include crystal nucleation, earthquakes, population genetics, protein folding and genetic switches. In biological systems, the switch-like response to a time-dependent signal can be central to their function. For in- stance, metastable biochemical networks switch in response to time- dependent stimuli in a switch-like manner, and sensory cells react stochastically to weak transient signals. Here the system response depends on the temporal characteristics of the input and cannot be characterized by a single rate constant. We present a novel enhanced sampling method, Non-Stationary Forward Flux Sampling, that al- lows efficient simulation of rare events in these systems. Using the method, we investigate the time-dependent response of a model system based on the phage-lambda genetic switch.

BP 20.4 Thu 10:30 H 1058

Sources of Stochasticity in Protein Synthesis — •David Gomez[1,2], Rahul Marathe[1], and Stefan Klumpp[1] — [1]Max Planck Institute of Colloids and Interfaces, Science Park Golm, 14424 Potsdam, Germany. — [2]Freie Universität Berlin, Arnimalle 14, 14195 Berlin, Germany

All living organisms are unique, even isogenic one in the same environmental conditions or have the same history. An explanation of such behavior is given by the fluctuations of the biochemical reactions within them. These fluctuations are become important when the number of the molecules involved in the biochemical reactions is low. Because the number of proteins, DNA, RNA are often small in the cell, one can expect large variation in the biochemical reactions.

The objective of this work is to model the variations of the protein synthesis in the by cell birth-death processes. To do that, we considered protein synthesis in cells, that after a cell division time, T , divide into two daughter cell. This process is done either in a deterministic or a stochastic way. In a first approximation the volume of the cells was not considered, but to describe protein concentrations, the growth and division of the cell volume was also incorporated into the model.

The consideration of the volume in our model, leaves us the opportunity to study regulatory cell processes, which are concentration-dependent, such as the negative feedback regulation model.

BP 20.5 Thu 10:45 H 1058

Consequences of degradation and aging of messenger RNA — •Carlus Deneke, Angelo Valleriani, and Reinhard Lipowsky — MPI für Kolloid- und Grenzflächenforschung, Department of Theory and Bio-Systems, Potsdam, Germany

In gene expression, the transcription and degradation of mRNA plays a central role. Various degradation mechanisms exist that actively regulate the stability of mRNA. The stability not only determines the steady state amount of mRNA in each cell, it sets also important time scales when transcription is either turned on or off.

In this contribution, we present a theoretical framework that describes various transient phenomena in gene expression. It extends previous studies as it is capable of considering various biochemical mechanisms of degradation. Furthermore, it also fully accounts for the stochasticity of both, transcription and degradation of mRNA. This framework will allow to describe the response of the cell to external stimuli which modulate the transcription of certain genes.

BP 20.6 Thu 11:00 H 1058

Maximising positional information of morphogen gradients in the Drosophila embryo — •Tiago Ramalho and Ulrich Gerland — Arnold Sommerfeld Center, Dept. of Physics, Ludwig Maximilians Universität München, Theresienstr. 37 80333 München, Germany

Information about position along the antero-posterior axis in Drosophila can be encoded in morphogen spatial distribution profiles. To decode this position, a parameter estimation procedure must be implicitly used by the biological system. Fisher information, an abstract measure of the precision with which a parameter can be estimated is applied to this context and resulting optimal profiles are calculated. The information theoretical results are compared to a model which optimizes morphogen profiles for biological function.

15 min break

BP 20.7 Thu 11:30 H 1058

On the role of intrinsic noise on the response of the p53-Mdm2 module — Lidice Cruz[1], Nuris Figueroa[1], and •Roberto Mulet[1,2] — [1]Group of Complex Systems. Physics Faculty. University of Havana — [2]Quantum optics and statistics Institute of Physics Albert Ludwigs University of Freiburg

The protein p53 has a well established role in protecting genomic integrity in human cells. In particular, the p53-Mdm2 feedback loop seems to be the key circuit in the response of cells to damage. Recent measurements in individual human cells have shown that p53 and its regulator Mdm2 develop sustained oscillations over long periods of time, with essentially fixed frequency but variable amplitudes. Here, we propose that the noise that stabilizes the fluctuations is the intrinsic noise due to the finite nature of the populations of p53 and Mdm2 in a single cell.

We study three stochastic models of the p53-Mdm2 circuit. The models intend to capture the response of the p53-Mdm2 circuit in its basal state, in the presence of DNA damage, and under oncogenic signals.

We show that the in all the cases the noise induced by the finite size of the populations is responsible for the existence of sustained oscillations in the response of the p53-Mdm2 circuit. This noise alone can explain most of the experimental results obtained studying the dynamics of the p53-Mdm2 circuit in individual cells.

BP 20.8 Thu 11:45 H 1058

A kinetic model for RNA interference of focal adhesions — •Max Hoffmann[1,2] and Ulrich Schwarz[1,2] — [1]Bioquant, Heidelberg University, Heidelberg, Germany — [2]Institute for Theoretical Physics, Heidelberg University, Heidelberg, Germany

Focal adhesions are integrin-based cell-matrix contacts and transduce and integrate mechanical and biochemical cues from the environment. More than 150 different proteins localize to focal adhesions and have been systematically classified in the adhesome project (www.adhesome.org). First RNAi-screens have been performed for focal adhesions and corroborated the hierarchical structure suggested by the adhesome project. We have developed a kinetic model for RNA interference of the focal adhesion hierarchy with explicit representation of siRNA-concentration and implicit effects of mechanical force. For the first time a link is made between the dynamics of RNA interference and the assembly dynamics of focal adhesions. Our kinetic model shows a variety of features for focal adhesions under the influence of RNA interference. Two basic time scales of the dynamics of RNAi-influenced focal adhesions are verified: a short one for the adaptation of the focal adhesions to changes in the environment, and a much longer one that controls the siRNA-mediated knockdown. A sensitivity analysis provides insight into the response of the focal adhesions to rate or parameter changes. This knowledge can be used to optimize the effect of RNA interference on focal adhesions. We show that different force models can lead to largely differing results.

BP 20.9 Thu 12:00 H 1058

Modeling MARCKS and Protein Kinase C binding at cellular membranes — •Sergio Alonso and Markus Bär — Physikalisch-Technische Bundesanstalt, Abbestrasse 2-12, 10587 Berlin, Germany

Phosphorylation and dephosphorylation of proteins are mechanisms of activation and deactivation which regulate many cell processes. MARCKS is a protein which binds to the membrane by electrostatic interaction. It is phosphorylated by Protein Kinase C and translocated from the membrane. In the cytoplasm phosphorylated MARCKS is dephosphorylated by phosphatases and can bind again at the membrane. The three processes give rise to a cyclic dynamics known as myristoyl-electrostatic switch. We propose a reaction-diffusion model obeying mass conservation for the binding, phosphorylation and dephosphorylation of MARCKS proteins. Furthermore, we add to the model the dynamics of binding and unbinding of PKC enzymes, which are activated by spikes of calcium.

BP 20.10 Thu 12:15 H 1058

Emergence of Information Transmission in a Prebiotic RNA Reactor — •Benedikt Obermayer[1], Hubert Krammer[2], Dieter Braun[2], and Ulrich Gerland[2] — [1]Department of Physics, Harvard University, Cambridge, USA — [2]Physics Department, Ludwig-Maximilians-Universität München

A poorly understood step in the transition from a chemical to a biological world is the emergence of self-replicating molecular systems. We study how a precursor for such a replicator might arise in a hydrothermal RNA reactor, which accumulates longer sequences from unbiased monomer influx and random ligation [1]. In the reactor, intra- and intermolecular base pairing locally protects from random cleavage. Analyzing stochastic simulations, we observe a strong bias towards long sequences with complex secondary structures, which would facilitate the emergence of ribozymes. Further, we find temporal sequence correlations that constitute a signature of information transmission, weaker but of the same form as in a true replicator.

[1] B. Obermayer, H. Krammer, D. Braun, U. Gerland, Phys. Rev. Lett. **107**:018101 (2011)

BP 20.11 Thu 12:30 H 1058

Physical limits of replication accuracy under nonequilibrium prebiotic conditions — Benedikt Obermayer[1] and •Ulrich Gerland[2] — [1]Department of Physics, Harvard University, USA — [2]Department of Physics, LMU München, Germany

Without the help of kinetic proofreading enzymes that can employ chemical energy to improve the accuracy of template-directed replication processes, the mutation rate of these processes is limited from below by fundamental principles of statistical physics. This limit is particularly relevant for prebiotic copying processes of a polynucleotide such as RNA, before the advent of kinetic proofreading enzymes. Under equilibrium conditions, the limit is directly related to a free energy of discrimination related to the difference in the thermodynamic stability of the correct and the incorrect products. However, when the system in which the copying process takes place is not in equilibrium, the lower physical limit on the mutation rate can be changed. We discuss a situation where physical nonequilibrium can improve the replication accuracy, optimize the conditions of the system, and relate our scenario to recent experiments on non-enzymatic template-directed copying processes.

BP 20.12 Thu 12:45 H 1058

One Dimensional Evolution of DNA-Fragment Replication — •Emanuel Worst[1], Eva Wollrab[1], Philipp Zimmer[2], Karsten Kruse[2], and Albrecht Ott[1] — [1]Universität des Saarlandes, Biologische Experimentalphysik, Postfach 151150, 66041 Saarbrücken — [2]Universität des Saarlandes, Theoretische Biologische Physik, Postfach 151150, 66041 Saarbrücken

We study the dynamics of an enzyme-based, self-replicating system consisting of DNA fragments and Taq DNA ligase. The aim is to achieve a dynamic equilibrium of self-reproducing DNA strands that evolve towards longer strands in a stepwise manner, through the occurrence of rare events. In the present realization, the ligation of DNA molecules A and B by Taq DNA ligase creates a DNA molecule T with a low probability. Hybridization of A and B on the template T brings the reactive 3‘-end (hydroxyl group) of A and 5‘-end (phosphate group) of B very close to each other. This increases the ligation probability by the Taq DNA-ligase and leads to strongly increased replication of T. Presently the autocatalytic reproduction of even longer strands is insufficient, it is prevented by strong side reactions. This is a problem, which needs to be addressed in the future.