BP 28: Systems Biology & Gene Expression and Signalling

Time: Tuesday 9:30–12:30 Location: H44

Invited Talk BP 28.1 Tue 9:30 H44

Molecular Bioimaging of Genome Transcription — •Patrick Cramer — Max Planck Institute for Biophysical Chemistry, Göttingen

Our laboratory studies the molecular mechanisms of eukaryotic gene transcription by integrated structural biology and elucidates the systemic principles of genome regulation with the use of funcitonal genomics and computational biology. Based on crystal structures of RNA polymerase II in different functional states we obtained a molecular movie of transcription (Cheung and Cramer, Cell 2012). With the use of functional genomics we elucidated how the transcription cycle is coordinated with co-transcriptional events (Mayer et al., Science 2012), and how a mechanism of transcriptome surveillance removes aberrant non-coding RNAs (Schulz, Schwalb et al., Cell 2013). Unexpected insights into transcription regulation came from the crystal structure of RNA polymerase I (Engel et al., Nature 2013). We have also used cryo-electron microscopy (cryo-EM) to resolve the architecture of an early Pol II elongation complex bound by the capping enzyme, which explains how capping occurs when the RNA first emerges from the Pol II surface (Martinez-Rucobo, Mol. Cell 2015). In my talk I will concentrate on our latest work where we combined different structural biology techniques to provide insights into the mechanism of gene regulation during transcription initiation, which requires the coactivator complex Mediator (Plaschka et al., Nature 2015). We reconstituted a recombinant, functional 15-subunit core of the Mediator complex and used cryo-EM and crosslinking to determine the architecture of the RNA polymerase II-Mediator core initiation complex. This work indicates how Mediator controls transcription and opens the way to the assembly and structural analysis of larger initiation complexes containing additional factors. I will present the latest unpublished work and demonstrate that cryo-EM enables us to obtain near-atomic resolution for large macromolecular assemblies, including mammalian RNA polymerase II.

BP 28.2 Tue 10:00 H44

Modeling of Colicin E2 Expression — •Matthias Lechner[1], Mathias Schwarz[2], Madeleine Opitz[1], and Erwin Frey[1] — [1]Arnold Sommerfeld Center for Theoretical Physics (ASC) and Center for NanoScience (CeNS), Department of Physics, Ludwig-Maximilians-Universität München — [2]Institute for Biological and Medical Imaging, Technische Universität München and Helmholtz Zentrum München, Neuherberg, Germany

Regulation of mRNA translation plays a crucial role in many bacterial pathways. For this purpose, possible regulatory components are small, non-coding RNAs (sRNAs) or mRNA-binding proteins. An important system that includes a combination of these modes is the Colicin E2 system, in which SOS responses trigger the expression of the toxin colicin and its release protein. We present a simple, yet comprehensive, model of the colicin E2 regulatory network, and study both its deterministic and stochastic dynamics in detail. Its regulation can be reduced to three components: free mRNA, the mRNA-binding protein CsrA, and an effective sRNA that regulates CsrA. For the stationary state, we show that the production rate of sRNA tunes the magnitude of intrinsic fluctuations and the sharpness of mRNA thresholds. To study the dynamics, we incorporate a stochastic SOS response system into our model. The CsrA regulation filters out short-lived activation peaks, and delays the release of toxin after prolonged SOS signals. Our model thus describes Colicin E2 expression dynamics in detail and reveals the importance of the specific components for toxin release. Moreover, we give an outlook on the role of further components.

BP 28.3 Tue 10:15 H44

Control of single cell somitogenesis — •Jose Negrete JR[1], Laurel Rohde[2,3], Ravi Desai[2,3], Andrew C. Oates[2,3], and Frank Jülicher[1] — [1]Max Planck Institute for the Physics of Complex Systems, Dresden, Germany — [2]Francis Crick Institute, London, United Kingdom — [3]University College London, United Kingdom

Embryo somitogenesis is preceded by the spatiotemporal evolution of a kinematic wave of cyclic genes such as her1. It is conjectured that this wave is at the same time modulated by the presence signaling gradients. In this work we have developed a theoretical formalism for analyzing the dynamics of her1 at the single cell level. Remarkably these cells show an oscillatory transient when they are disassociated from the embryo and positioned far from each other, suggesting that autonomous dynamics play an important role in somitogenesis. We have been able to identify the key parameters that are modulated during the evolution of her1 and from these we developed predictions that can be tested in experiment. In particular the parameters of the reaction rates of her1 are non-stationary suggesting that these are controlled by the signaling system.

BP 28.4 Tue 10:30 H44

Physical limits to spatiotemporal cellular signaling — •Vaibhav Wasnik[1] and Karsten Kruse[2] — [1]Saarland University, Saarbrucken, Germany — [2]Saarland University, Saarbrucken, Germany

Cells need to respond to spatiotemporal signals. Physical limits on the detection of such signals are poorly understood. Here we study the detection of spatiotemporal Ca^{2+}-signals by the conventional Protein Kinase C-α (PKC$-\alpha$). Protein kinases C are ubiquitously expressed and, together with Calmodulin, form the basic read-out module for Ca^{2+}-signals. In order to activate PKC-α, it needs to simultaneously bind to Ca^{2+} and to Diacylglycerol (DAG) on the plasma membrane. On the membrane, PKC-α forms clusters. We explore the consequences of cluster formation for signal transduction. In particular we show that PKC-α acts as a low pass filter and determines the accuracy of the readout. Our study highlights the possible role of collective effects for cellular signal transduction.

30 min break

Invited Talk BP 28.5 Tue 11:15 H44

The biosynthetic basis of budding yeast cell size control — •Kurt M. Schmoller, Jonathan J Turner, Mardo Koivomägi, Devon Chandler-Brown, and Jan M. Skotheim — Stanford University, Stanford, US

Cell size is an important physiological trait that sets the scale of all biosynthetic processes. Although physiological studies have revealed that cells actively regulate their size, the molecular mechanisms underlying this regulation have remained unclear. Using quantitative single cell microscopy, we identified the molecular mechanism coupling growth and division in budding yeast. As cells grow, they dilute a cell cycle inhibitor while keeping the upstream activator at a constant concentration, which results in a continuously increasing probability for cell cycle entry. Size control itself is ensured by a differential dependence of activator and inhibitor synthesis rates on cell size. We anticipate that such differential size dependence of protein synthesis may be a universal mechanism for cells to coordinate their proteome with cell size.

BP 28.6 Tue 11:45 H44

Integration of morphogen signals in neural tube patterning — •Marcin Zagórski[1], Anna Kicheva[1,2], Gašper Tkačik[1], James Briscoe[2], and Tobias Bollenbach[1] — [1]IST Austria, Klosterneuburg, Austria — [2]The Francis Crick Institute, London, UK

Early in vertebrate development, different neuronal subtypes are generated from neural progenitor cells arrayed along the dorsal-ventral axis of the neural tube. This pattern of neural progenitors is established by the morphogens Shh and BMP which form opposing concentration profiles and control the expression of target genes at defined positions. How the two morphogen signals are integrated to control target gene expression is poorly understood. To address this, we exposed naïve chick neural plate explants to a broad range of defined concentrations of the two morphogens. This allowed the construction of a decoding map that describes the dependence of the target gene expression pattern on the two morphogen concentrations. Strikingly, we obtained a similar map by using a maximum likelihood estimation method to extrapolate neural tube pattern from in vivo measurements of morphogen signaling profiles and gene expression. Both decoding maps correctly predicted target gene boundary shifts in embryos with altered Shh signaling. Moreover, a simple model of a gene regulatory network that integrates the morphogen signals was sufficient to recapitulate this behaviour, providing mechanistic insight into the observed shifts in target gene domains.

BP 28.7 Tue 12:00 H44

Stochasticity in DNA Replication of Archaea — •Jens Karschau[1], Ulrik Günther[2,3], and Alessandro de Moura[4] — [1]MPI PKS, Dresden, Germany — [2]MPI CBG, Dresden, Germany — [3]TU Dresden, Dresden, Germany — [4]University of Aberdeen, Aberdeen, UK

DNA is the building plan of every living organism, which is contained in either a linear or circular chromosome. Replicating this chromosome begins from origins—the starting points from which DNA–copying forks emerge. We previously showed for the linear case that finite ends set optimal configurations for origins to give fast overall replication time. This depends on their probability to activate as well as their relative distance to another [1].

Here, we discuss replication on a circular chromosome: where forks never stop at any ends, walk around the circle, and finally coalesce with another. The process bears similarity to a nucleation and growth process on a ring—as is in bacteria and archaea, with the latter carrying multiple origins. On the one hand, we again show that the optimal location of origins strongly depends on origin distance as well as their activation probability in conditions allowing for the chromosome to be copied only once. On the other hand, under favourable conditions, simultaneous re–replication with clustered origins in nearby groups actually minimises chromosomal duplication times. We relate our findings to published experimental data to distinguish between settings for optimal growth of an archaeal species.

[1] J Karschau, JJ Blow, APS de Moura, PRL, 2012.

BP 28.8 Tue 12:15 H44

A coarse-grained growth control theory for growth transitions — •Severin Schink[1], David Erickson[2], Ulrich Gerland[1], and Terence Hwa[2,3] — [1]Physics of Complex Biosystems, Physics Department, Technical University of Munich, Germany — [2]Department of Physics, University of California at San Diego, La Jolla, CA, USA — [3]Section of Molecular Biology, Division of Biological Sciences, University of California at San Diego, La Jolla, CA, USA

A grand challenge of systems biology is to predict the kinetic response of living systems following environmental perturbations. This task is typically approached in a bottom-up manner, by characterizing the temporal changes in gene expression patterns resulting from the applied perturbation, and deducing the underlying regulatory network. Progress towards quantitative predictive models has been limited however. A fundamental obstacle has to do with the large number of unknown interactions and parameters which vastly outnumber accessible data collected even by high-throughput methodology. In this study, we choose a top-down approach, based on phenomenological growth laws, previously developed for steady state growth. We extend these to the kinetic regime, and develop a coarse-grained flux-driven regulation theory to describe bacterial growth transitions and gene expression in response to transient nutrient changes. The theory is conceptually simple, analytically solvable, and captures the kinetics of bacterial growth transitions that occurs in response to nutrient up-shifts and down-shifts (also called diauxic shifts) quantitatively without free parameters.