BP 5: Systems Biology & Gene Expression and Signalling

Time: Monday 15:00–16:45 Location: H 1028

BP 5.1 Mon 15:00 H 1028

Mathematical modeling of drug-induced receptor internalization in breast cancer cells — •Mirjam Fehling-Kaschek[1], Diana Peckys[2], Jens Timmer[1], and Niels de Jonge[3] — [1]University of Freiburg — [2]Department of Biophysics, Saarland University — [3]Leibniz Institute for New Materials, Saarbrücken

About 20% of breast cancer tumors over-express the HER2 receptor. Trastuzumab, an approved drug to treat this type of breast cancer, is an antibody directly binding at the HER2 receptor and inhibiting cell growth. The goal of our study was to understand the early impact of trastuzumab on HER2 internalization and recycling in the HER2-positive SKBR3 cell line. To this end, single cell fluorescence microscopy, monitoring the state of HER2 expression on the membrane, was combined with mathematical modeling to derive the flux of HER2 receptors from and to the membrane. We constructed a dynamic multi-compartment model based on ordinary differential equations to account for intracellular HER2 production and distribution of HER2 receptors between membrane ruffles and flat regions of the cell by internalization and recycling processes. To account for the heterogeneity in cell size and HER2 expression in SKBR3 cells, the dynamic model was expanded to a mixture model. The model describes the experimental observation that drug induced receptor internalization occurs preferentially in cells containing membrane ruffles, while internalization in non-ruffled cells happens at a much smaller rate. Our analysis shows that the common hypothesis of constitutive HER2 recycling back to the plasma membrane is not supported by the data.

BP 5.2 Mon 15:15 H 1028

Effect of ultra small carbon nanodots on the gene expression of primary human hematopoietic stem cells — •Stefan Fasbender[1], Lisa Zimmermann[1], Ron-Patrick Cadeddu[2], Rainer Haas[2], and Thomas Heinzel[1] — [1]Experimental Condensed Matter Physics, Heinrich-Heine-University Dusseldorf — [2]Department of Haematology, Oncology and Clinical Immunology, University Hospital Dusseldorf

Carbon nanodots (CDs) are often considered as nontoxic alternative to inorganic quantum dots. They show potential in a wide range of biomedical applications like long term imaging of normal and malignant cells in vivo and in vitro, cancer diagnostics and therapeutic tumor cell targeting. Here we prepare fluorescent CDs by thermal decomposition of citric acid and diethylentriamine [1] using microwave irradiation. Primary human hematopoietic stem cells (CD34+) obtained from the leukapheresis products of four healthy donors are exposed to a concentration of 500 ug/ml CDs for 36 hours. Via flow cytometry we demonstrate a significant uptake of the particles into the cells and the effect on the gene expression is studied using the Clariom S microarray.

[1] Qu et al., Light: Science & Applications, 2015, 4, e364

BP 5.3 Mon 15:30 H 1028

Computational analysis on the regulation of σ/anti-σ factor operons — •Hao Wu and Georg Fritz — LOEWE Center for Synthetic Microbiology, Phlipps University Marburg, Germany

Bacterial alternative σ factors are subunits of RNA polymerase that determine its promoter specificity, thereby regulating crucial processes like cell homeostasis and stress responses. In the absence of input signals, σ factors are sequestered by their cognate anti-σ factors. Meanwhile, many σ/anti-σ factor pairs are co-expressed in operons, most of them are auto-regulated by the σ factor, implying a regulation module with a positive and a negative feedback at the same time. Strikingly, there are two distinct mechanisms to activate this module: One involves the active degradation of anti-σ factors upon input signal detection, constituting a non-equilibrium sensing mechanism, while the other one relies on a reversible conformational change of the anti-σ factor to a non-functional form, resembling an equilibrium sensing mechanism. Here we conducted a comprehensive computational study on the quantitative properties of this important regulatory module. While many characteristics prove independent of the sensing mechanism, we identified some major differences between their dynamical properties. Interestingly, in the responsive regime the activation of σ factor level becomes very slow for the non-equilibrium sensing mechanism, while it remains fast for the equilibrium sensing mechanism. These results deepen our understanding of the σ/anti-σ factor regulation module and help us to explain the choice of the two distinct sensing mechanisms in different physiological contexts.

BP 5.4 Mon 15:45 H 1028

Self-organised homeostasis of stem cells through competition for mitogens — Yu Kitadate[1,2], •David J. Jörg[3,4], Benjamin D. Simons[3,4,5], and Shosei Yoshida[1,2] — [1]Division of Germ Cell Biology, National Institute for Basic Biology, National Institutes of Natural Sciences, Okazaki, Japan — [2]Department of Basic Biology, School of Life Science, Graduate University for Advanced Studies (Sokendai), Okazaki, Japan — [3]Cavendish Laboratory, Department of Physics, University of Cambridge, United Kingdom — [4]The Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, UK — [5]The Wellcome Trust/Medical Research Council Stem Cell Institute, University of Cambridge, UK

How stem cell populations self-organise to control their density and maintain robust homeostasis is in many cases still elusive. Especially challenging to understand are facultative niche environments, in which stem cells lie dispersed among their progeny and only sporadically make contact with signal-releasing regions. How do such stem cells sense and control their density over large distances? We conjecture that stem cells compete for a limited supply of mitogens: by adjusting their fate behaviour according to the local mitogen abundance, a constant cell density is maintained throughout the tissue. Using the murine germ line as an example, we developed a theoretical model that quantitatively captures both the key features of stem cell density regulation and the regeneration kinetics after injury. This "mitogen competition model" provides a generic and robust mechanism of self-organised stem cell homeostasis in a facultative niche.

BP 5.5 Mon 16:00 H 1028

Proliferation rate inference with continuous labelling assays — Rode Julian[1], Brusch Lutz[1], and •Rost Fabian[1,2] — [1]Technische Universität Dresden, Dresden, Germany — [2]Max Planck Institute for the Physics of Complex Systems, Dresden, Germany

Precise estimates of proliferation rates are crucial for quantitative models of the development and maintenance of tissues. Continuous labelling assays are a popular approach to infer proliferation rates *in vivo*. In these assays, proliferating cells take up a label, e.g. BrdU, when synthesizing DNA for cell division. Intuitively, more cells take up the label per time if they proliferate faster. So far, the experimental and theoretical study of continuous labelling assays focused on the dynamics of the mean labelling-fraction but not on the labelling-fraction distribution dynamics. To study this distribution dynamics, we developed a stochastic model of continuous labelling assays. With the model, we study the effects of cell and sample level noise in the distribution of cell cycle lengths. Using simulated data as ground truth, we show that current inference methods give biased proliferation rate estimates. Therefore, we derive analytical results for the Likelihood for our model that can be used to achieve unbiased estimates of the proliferation rates *in vivo*.

Invited Talk BP 5.6 Mon 16:15 H 1028

Synchronization of synthetic gene oscillators — •Lev Tsimring — BioCircuits Institute, University of California, San Diego

One of the defining characteristics of life is the ability to keep time, which organisms often achieve by using internal genetic "clocks" to govern fundamental cellular behavior. While the gene networks that produce oscillatory expression signals are typically quite elaborate, certain recurring network motifs are often found at the core of these biological clocks. One common motif which leads to oscillations in many natural biological clocks is delayed auto-repression. We designed and constructed several synthetic gene circuits that use this motif, and observed robust "degrade-and-fire" oscillations of gene expression in bacteria E. coli. When gene oscillators in different cells are coupled by fast-diffusing chemical signals, they exhibit population-wide synchronization. We also predicted and observed intra-cellular synchronization of different gene oscillators indirectly coupled by a common degradation enzyme.