Monday 9 July
15:30–17:30, Terrace 2A

Systems biology

S.42-4
Encoding differential gene activation in non-equilibrium transcription cycles

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Gene transcription is one of the most complex enzymatic processes in eukaryotic cells. Nevertheless, conceptually simple models based on binding affinity of transcription factors have been widely used to describe the regulation of transcription rate. Here I will show by means of mathematical theory that the kinetics of gene state transitions, including active, refractory and inactive states, determine how transcription factor occupancy is decoded by the transcriptional machinery. Using optogenetic-like light control of a GATA-type transcription factor, key theoretical predictions are confirmed experimentally. Our data show that a gene can become induced at maximal rate by only fleeting transcription factor occupancy of its regulatory elements and that, in turn, differential gene regulation by a common transcription factor does not require differences in binding site affinity.

S.42-2
Real-time metabolomics reveals the decision mechanism for cell division in *E. coli*

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Molecular determinants of microbial cell division timing and their relation to nutritional input are largely unknown. To assess potential limiting factors for the first cell division, we starve *Escherichia coli* cultures and then feed with glucose pulses over a range of frequencies. Using real-time metabolomics at a resolution of about 10 seconds, we then follow the dynamics of metabolism over several hours of pulses. For low pulse frequencies that are insufficient for cell division, real-time metabolomics and microfluidic single-cell microscopy revealed that cells rapidly synthesize proteins and nucleic acids from glucose pulses despite expected biosynthesis shutdown. Above a critical pulse frequency that allows division, the cells exhibited a lag time until the first division. This lag time shortened as nutrient pulse frequency increased. By a series of experiments we then identified a single protein as the limiting factor for the first cell division, whose abundance can quantitatively explain both the dependence of lag time on frequency and the existence of a critical frequency for division. We formulated a dynamic model that quantitatively relates lag time to the synthesis from nutrient pulses and protease-dependent degradation of this protein and corroborated it experimentally. This work provides the first basis for quantitative prediction of bacterial division using information about molecular determinants and the nutrient input.

S.42-1
Executable biology: from mechanistic insights to therapeutic applications in cancer

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Cancer is a highly complex cellular state where mutations impact a multitude of signalling pathways operating in different cell types. In recent years it has become apparent that in order to understand and fight cancer, it must be viewed as a system, rather than as a set of independent cellular activities. In this talk, I will discuss some of the progress made towards achieving such a system-level understanding using the design of executable computer programs that mimic biological phenomena, an approach known as *Executable Biology*. I will describe our studies to better understand aberrant signaling programs in leukemia, breast cancer and glioblastoma (brain cancer); and to identify novel combination treatments to overcome drug resistance. These computational cancer programs have been shown to improve our understanding of the mechanistic rules that drive cancers and pave the way for better detection, diagnosis and personalised treatment of patients.

S.42-3
Cell cycle regulation by systems-level feedback controls

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Strict alternation of chromosome replication (during interphase) and segregation (during M phase) is a fundamental aspect of cell cycle control. Switching back-and-forth between interphase and M phase must be irreversible in the sense that, once a cell commits itself to a new round of DNA replication, it must not back up and initiate another round of DNA replication before it goes through M phase. Worse yet would be to back up and make a second try to segregate chromosomes without replicating the DNA. These characteristics of interphase–M phase transitions are best explained by bistable switches, which have different activation and inactivation thresholds, resulting in a hysteresis effect. 25 years ago, we proposed that the activity of the mitosis-inducing protein kinase, Cdk1:CycB, is controlled by an underlying bistable switch generated by positive feedbacks involving inhibitory phosphorylations of the Cdk1 subunit. The phosphorylation of mitotic proteins by Cdk1:CycB is counteracted by the PP2A:B55 protein phosphatase, which is inhibited during M phase by a stoichiometric binding partner, ENSA-P, which is itself activated by Greatwall-kinase. Using mathematical modelling and biochemical reconstitution experiments, we showed that the BEG (B55-ENSA-Greatwall) pathway also represents a bistable switch controlled by the activity of Cdk1:CycB. Therefore interphase–M phase transitions are made robust by two interlinked bistable switches controlling the kinase (Cdk1:CycB) and the phosphatase (PP2A:B55), with the suppression of futile cycling in protein phosphorylation and dephosphorylation. Using human cells carrying an ATP-analogue-sensitive version of Cdk1, we show that both bistable switches contribute to the hysteresis of interphase–M phase transitions, consistent with our mathematical model. Perturbation experiments also confirm an intermediate state between interphase and M phase, as predicted by the model, which is not apparent during normal transitions.

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