BP 7: Coupled Problems in Biological Systems (Focus Session)

Focus session organized by Syn Schmitt and Nicole Radde, University of Stuttgart.

Time: Monday 11:15–13:00 Location: H45

Invited Talk BP 7.1 Mon 11:15 H45

Relating biological networks to gene expression patterns — •Marc-Thorsten Hütt — Jacobs University, Bremen, Germany

Understanding, how a gene expression pattern – the simultaneous measurement of gene activity for a large number of genes in a cell – emerges from the dynamics of a gene regulatory network is one of the key challenges at the interface of statistical physics and systems biology.

The last two decades have shown that the statistical physics of complex networks can serve as a powerful toolbox for addressing this challenge. The guiding questions are: (1) How is a gene expression pattern 'generated' by the underlying regulatory network? (2) What functional state (e.g., from the perspective of the cell's metabolic network) does the gene expression pattern define?

At the same time, the conceptual limitations of mapping an intricate biological system onto the formal language of nodes and links have become apparent.

Here I will describe recent developments in this field, starting from investigations of network topology and then moving to dynamics on graphs and, finally, to a network-guided interpretation of gene expression patterns in biology and medicine.

BP 7.2 Mon 11:45 H45

A basic mechanical model of muscular contraction — •Michael Günther, Daniel F.B. Haeufle, and Syn Schmitt — Universität Stuttgart, Institut für Sport- und Bewegungswissenschaft

There is a rich history of quantitative experiments on muscle contraction. Mainly two mathematical approaches are applied to disentangle this hairball. First, A.V. Hill (1938) observed a fibre's steady-state force-velocity relation to be a hyperbola. Later, A.F. Huxley (1957) suggested a mathematical model based on cross-bridges making filaments slide. Using eleven model parameters, Huxley could reproduce in 1973 Hill's relation including its modification from 1964. However, both approaches are not explanatory in a sense that they derive, e.g., the force-velocity relation from basic, physical principles and laws. This led us to ask: what mechanical structure can explain skeletal muscle contractions? As a possible answer, we have worked out a basic mechanical model that can explain, by a force equilibrium between four elements, altogether six characteristic relations of both steady-state and non-steady-state muscular contractions at once. Compared to modern Huxley-type models, the number of parameters is dramatically reduced: we need just six parameters in common plus another two for the steady-state and another three for known microscopic force-length relations specific to non-steady-state responses. We suggest therefore our reduced model to be a promising alternative for advancing causal understanding of the relation between structure and function incorporated into the skeletal muscle machinery.

BP 7.3 Mon 12:00 H45

Uncertainty analysis for dynamic models in systems biology — •Daniel Kaschek — Physikalisches Institut, Universität Freiburg, Deutschland

Dynamic models have gained increasing importance for the way we understand complex behavior in cell biology. Although the structure of such a model may be highly conserved between different cell types, experiments show that the parameter values are not. Therefore, reliable and efficient methods to determine parameter values from cell-type specific, time-resolved data are crucial for precise predictions.

Here, we present a collection of methods to determine parameter values, parameter uncertainty and uncertainty of prediction in non-linear dynamic models. Lie-group theory is employed to detect symmetries in the model and to eliminate structurally non-identifiable parameters. The profile-likelihood is introduced as an indispensable tool to determine parameter confidence bounds and explore the non-linear relationships between parameters. Also model predictions can be associated to special likelihood profiles and their uncertainty can thereby be accurately quantified. Finally, the method of Lagrangian multipliers is presented as a way to exploit the local structure of the likelihood, guide us quickly along the profile paths and make the likelihood-based methods even more efficient.

BP 7.4 Mon 12:15 H45

Predicted error pushes pointing movements into the goal — •Karl Theodor Kalveram[1,2], Tim Lauer[2], Sebastian Babl[2], Christina Binder[2], Anna Klubertanz[2], Kristin Roehr[2], Elena Wicharz[2], Darya Yatsevich[2], and Joachim Vogt[2] — [1]Universitaet Duesseldorf — [2]Technische Universitaet Darmstadt

Movements of a pointer connected to the forearm were perturbed by arbitrary changes of the geometry of the arm-pointer arrangement. Under discontinuous visual feedback (pointer visible only at beginning and ending of the movement), the error at the movement*s first stop was high and varied with the perturbations. Under continuous visual feedback (pointer always visible), the error remained low and was un-correlated with the perturbations. Inspection of the recorded kinematics revealed that neither negative feedback control nor feedforward control through an inverse kinematics model could explain these outcomes. The paper proposes an alternative non-linear mechanism that uses the phase relationship between observed velocity and position to predict the stop position from any interim state of the movement. This provides a prediction of the error, based on which one or several scaled force impulses can be released annihilating the error at movement end.

BP 7.5 Mon 12:30 H45

Migration patterns of dendritic cells in response to chemokines — •Veronika Bierbaum, Jan Schwarz, Michael Sixt, and Tobias Bollenbach — IST Austria, am Campus 1, 3400 Klosterneuburg

Dendritic cells are decisive components of the adaptive immune system. When they navigate through tissues, the two chemokines CCL19 and CCL21 guide them directionally. In an experimental-theoretical study, we develop a physical description of dendritic cell migration in response to a given chemokine field. We characterize cell migration as a function of this field through in vitro assays of precisely controlled immobilized chemokine patterns. We monitor cells in varying exponential or linear profiles using time-lapse microscopy. The trajectories of these cells can be characterized in terms of stochastic differential equations, which allow for separation of the stochastic and deterministic contributions to cell directionality and velocity. For CCL21, we find that the cells' directionality is higher in exponential as compared to linear profiles. This observation supports a scenario where the directionality is governed by the signal-to-noise ratio resulting from chemokine binding to the receptor. Cells with a defect in the chemokine signal transduction pathway show reduced ability of CCL21 recognition, consistent with biochemical studies. Our findings indicate that cell directionality, for a range of concentrations, is controlled by the quality of signal transduction.

BP 7.6 Mon 12:45 H45

The effect of model rescaling and normalization on sensitivity analysis on an example of a MAPK pathway model — Jakob Kirch, Caterina Thomaseth, Antje Jensch, and •Nicole Radde — Institute for Systems Theory and Automatic Control, University of Stuttgart, Stuttgart, Germany

The description of intracellular processes based on chemical reaction kinetics has become a standard approach, and parameter estimation poses several challenges. Sensitivity analysis can aid model calibration in various ways. Results can for example be used to simplify the model. However, models are usually subject to rescaling and normalization, which changes the variance of the output and hence also influences results of sensitivity analyses.

We investigate the effect of model rescaling and normalization to a reference experiment on the outcome of local and global sensitivity analyses. Results are exemplified on a model for the MAPK pathway. Results for differently scaled and normalized model versions are compared. We show that sensitivity analyses are invariant under simple rescaling of variables and parameters. By contrast, normalization to a reference experiment that also depends on parameters has a large impact on any sensitivity analysis, and in particular makes an interpretation difficult. This dependency should be taken into account when working with normalized model versions.