Research Plan

My research focuses on the **modelling and analysis of intracellular regulation processes**. The ultimate goal is the development and application of mathematical methods to facilitate a better systemic understanding of these processes for particular subsystems and the organization of molecular regulation mechanisms in general. My group works in close collaboration with partners from molecular and cellular biology. I focus in particular on the following topics:

1. Dynamic modelling of intracellular regulation processes
2. Statistical sampling-based approaches for parameter estimation and predictions
3. Analysis methods for intracellular regulation networks based on their network topology

Figure 1 summarizes my research activities and interests, along with raised third party funding and lectures I teach and which are closely related to these topics and thus suitable to attract students. These will be described in more detail in the following.

**Figure 1**: Overview of my research topics, including third party funding and teaching activities.

Current **modelling studies** focus on the following projects:

1. **Mathematical modelling and systems-theoretical investigation of regulation mechanisms of secretion at the trans-Golgi network** (in collaboration with **Dr. Angelika Hausser** and **Prof. Monilola Olayioye**, Institute for Cell Biology and Immunology, University of Stuttgart, Germany; Project coworker: Dipl.-Ing. Patrick Weber)

2. **Quantitative investigation of signalling pathways related to cancer** such as MAPK or EGF signalling (in collaboration with **Prof. Monilola Olayioye**, Institute for Cell Biology and Immunology, University of Stuttgart, Germany; Project coworker: Chantal Göttler (student project))

3. **Model-based analysis of the spindle-assembly checkpoint in Schizosaccharomyces pombe** (in cooperation with **Dr. Silke Hauf**, Friedrich-Miescher Laboratory of the Max-Planck Institute)
Research plan Jun.-Prof. Dr. Nicole Radde, January 2014

Representative publications:


These application-oriented projects have strongly influenced the focus of my methodologically-based research activities, which focuses on the analysis of intracellular regulation processes. I work on advanced statistical approaches for model calibration, in particular, parameter estimation via experimental data, reliability of model predictions and model-based design of experiments, and on the development of novel analysis techniques for regulatory networks with complex network structures. These two topics very much complement the detailed knowledge of the biological experts, and thus highly facilitate a systemic understanding of regulatory processes within cells. Both will be described in more detail in the following.

Model calibration: Statistical sampling-based methods for inferring dynamical network models

When developing models for intracellular regulation networks, we often face the problem of estimating parameters from experimental data. This is usually formulated as an optimization problem with an objective function that describes the discrepancy between model prediction and real data. These inverse problems are often ill-posed, since the dataset is sparse and does not contain enough information to infer parameters uniquely. Standard estimators such as least squares or maximum likelihood estimators are not appropriate for these settings, and more global approaches are required.

In our working group we use statistical sampling-based approaches for the identification of parameters and for further issues such as model selection and model-based experimental design. These approaches provide besides point estimates also information about uncertainties and variances, in the parameter space as well as for model predictions. Thus, they are generally suitable to handle such ill-posed problems. However, because of their enormous computing time, in practice their application is currently limited to small- to medium size models only. This is particularly the case for the identification of parameters for differential equation models, which have to be solved by numerical integration in order to evaluate the likelihood function. In our group we investigate and develop advanced Markov Chain Monte Carlo sampling methods especially for these models.

Partners:
– Prof. Holger Fröhlich, Univ of Bonn, Germany
– Dr. Ben Calderhead, Univ College London, UK

Representative publications:


Network analysis: Analysis of biological networks with complex feedback structure

Modelling the dynamics of intracellular networks with differential equations based on chemical reaction kinetics has become a standard approach in the last decade. Examples are molecular interactions in signalling pathways, metabolic reactions or regulatory interactions. This leads to non-linear equations with underlying interaction graph, which describes the interactions between the molecules in the network. From experiments we often have a qualitative knowledge about these networks, we have for example an idea how the interaction graph looks like, while detailed information about the exact kinetics of the interactions is missing. In our working group we focus on the question how network
topology and dynamic behaviour are related. In this model class, feedback mechanisms are particularly interesting, since these are connected to bifurcations and complex behaviour. While the role of single feedback loops is well-characterized, to date there exist only few methods for more complex networks with interrelated feedback structure that go beyond pure simulation of the models, which rely on specification of the exact kinetics and the parameters. In our working group we develop new approaches that combine algorithms from graph theory with the vast theory of dynamical systems. Examples are the effect of time delays in specific graph topologies, or the circuit-breaking algorithm for an efficient characterization of fixed points of regulatory network models based on their interaction graph topology.

Future work will include further development of these methods and in particular up-scaling to larger network models. Furthermore, we will continue to apply our feedback methods to specific regulatory network models in order to understand the role of the network topology in a systematic way.

**Partners:**
- **Dr. Murad Banaji**, University of Portsmouth, U.K.
- **Prof. Andreas Weber**, University of Bonn, Germany

**Representative publications:**

