Optimization of constrained multi-compartment models with application to somitogenesis

Abschlussarbeit (Master, Diplom)

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Prerequisites: basic knowledge in mathematical biology, multiobjective optimization, machine learning, and parameter estimation for dynamic systems including stability analyses

Background: Periodic behavior is a key motif in various gene regulatory networks, such as the one governing somitogenesis, which is the process of forming somites by budding off from the anterior end of the presomitic mesoderm (O. Cinquin 2007). The main aspect in this formation is the synchronization of oscillating Hes-genes by Delta-Notch signaling. For this a non-linear ordinary differential equations (ODE) multi-compartment model was already put forward in Tiedemann et al. 2007. It is liable to the following two constraints:
(i) Hes1 oscillation within each cell,
(ii) concomitant synchronization between adjacent cells.
Up to now parameter inference was mainly done empirically and should be optimized by means of computational approaches.

Objectives of the thesis: The kinetic constants of the multi-compartment model will be inferred by means of multiobjective optimization. A main aspect therein will be the definition of the conflicting cost functions and an analysis of the weighted composition thereof w.r.t. stability of the results. For the stability analysis a Bayesian approach should be applied in order to handle noisy measurements.

Schedule:
- literature review,
- inference of proper weighting for conflicting cost functions using toy models
- development of a theoretical model and computational method for the analysis of the interplay of the cost functions w.r.t stability of the results
- extend method for stability analysis by Bayesian approach in order to handle noisy data
- definition of cost functions for the somitogenesis model
- application of above method to the two compartment case
- generalization to n compartment case and inference of kinetic constants for the somitogenesis model

Preliminary exercises:
- *Computational part:* Using MATLAB or OCTAVE implement an algorithm for computing the Pareto frontier of the example in section 3 of the file Pareto.pdf. For testing apply it to the cost functions on page 6. Visualize and interpret your results.
- *Theoretical part:* Show that the *weighted-sum-algorithm* is not necessarily apt to compute the complete Pareto frontier. For which conditions does it compute the complete frontier (proof)? How could we expand the algorithm in order to prevent this issue?