

Daniella Schittler

INSTITUTE FOR SYSTEMS THEORY AND AUTOMATIC CONTROL, UNIVERSITY OF STUTTGART

e-mail: schittler@ist.uni-stuttgart.de

Christian Breindl

INSTITUTE FOR SYSTEMS THEORY AND AUTOMATIC CONTROL, UNIVERSITY OF STUTTGART

Frank Allgower

INSTITUTE FOR SYSTEMS THEORY AND AUTOMATIC CONTROL, UNIVERSITY OF STUTTGART

Model selection of networks that are robust against kinetic uncertainties

Gene regulatory networks are driving major biological processes, such as cell differentiation. Dynamical models can often be built on a small number of key regulators, but are usually hampered by the lack of quantitative knowledge about the detailed interaction kinetics. Thus, it is desirable to deduce certain system properties already from the qualitative interaction structure.

This study aims at selecting prototypes of minimalistic three-node network motifs, that can serve as a genetic switch model driving cell differentiation. As a selection criterion, we demand that a candidate model must be able to produce the biologically observed three cell states: a progenitor, and two differentiated cell types. The goal is to find necessary conditions on the interaction structure such that a network exhibits the required stable steady states, and to classify the robustness of this capability. For this model selection, we employ a qualitative modeling framework based on ordinary differential equations, but requiring only few qualitative assumptions on the genetic interactions. The robustness of a model is defined as the maximum perturbation on the interaction functions under which the model criteria are still fulfilled, and thus measures the validity of the model if only qualitative knowledge is available.

In particular, we focus on the role of the operator combining the interactions acting on the same node: These can be connected in an OR-fashion (i.e. ingoing activators and inhibitors act independently of each other), or in an AND-fashion (resulting e.g. from complex formations at gene promoters). We show that neither the OR-networks selected as models for the system are a subset of the AND-networks selected as models, nor vice versa; but among them are networks that meet the selection criteria for OR- as well as for AND-kinetics. This nonempty set of models can be regarded as robust not only against quantitative uncertainties, but also against uncertain knowledge about the exact interaction conjunctions. Furthermore, the network connectivity is directly correlated to the robustness of the network capability to meet the model selection criteria. In conclusion, for some specific interaction networks it may be uncritical whether they are modeled with OR- or AND-interaction kinetics, but also in many cases only one of the two options can successfully result in a model that reproduces the system properties.