Combinatorial Representations of Parameter Space

David Hien, Prof. Dr. Oliver Junge

Department of Mathematics, Technical University of Munich
Chair for Scientific Computing

TopMath
Mathematik mit Promotion

Technische Universität München
Universität Augsburg University
Elitenetzwerk Bayern

Abstract

Switching systems are ordinary differential equation which are used for modeling gene regulatory networks. A combinatorial representation of parameter space can be constructed for switching systems with step function (SF system) and piecewise linear nonlinearities (PL system). Others have implemented the construction of parameter graph and state transition graph for SF systems as a database. We adapted the construction of state transition graphs in order to allow the computation of a similar database for PL systems.

Regulatory Networks

A (gene) regulatory network is an annotated directed graph with

- nodes $V = \{1, \ldots, n\}$,
- edges $E \subset V \times V \times \{\rightarrow, \dashv\}$,

such that there is no $i, j \in V$ with $(i, j, \rightarrow) \in E$ und $(i, j, \dashv) \in E$.

Nodes of a regulatory network model e.g. proteins. Edges of the type $\rightarrow$ model an up-regulation or activation, meaning that if $1 \rightarrow 2$ a high concentration of the quantity modeled by 1 leads to an increase of the quantity modeled by 2. Similarly, edges of the type $\dashv$ model a down-regulation or repression, thus $1 \dashv 2$ implies that a high concentration of the quantity modeled by 1 leads to a decrease of the quantity modeled by 2.

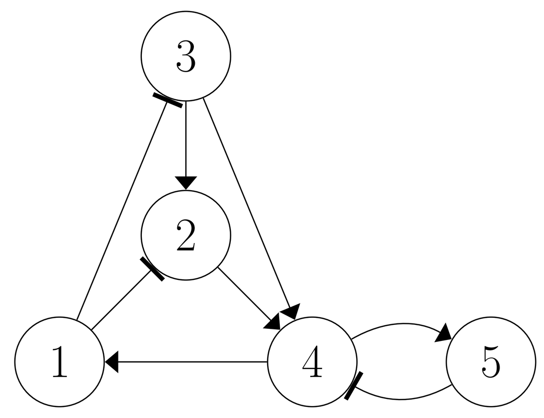

Fig. 1: A regulatory network

Switching Systems

Given a regulatory network with vertices $V = \{1, \ldots, n\}$, its associated switching system is the system of ordinary differential equations

$$\dot{x}_i = -\gamma_i x_i + \Lambda_i(x), \quad i = 1, \ldots, n$$

where each node i has an associated equation for $\dot{x}_i$.

For a fixed i, the equation consists of two parts

1. $-\gamma_i x_i$ with $\gamma_i > 0$ models a decay at rate γ_i,
2. $\Lambda_i(x)$ captures the influences of the inputs of node i and is of the form $\Lambda_i(x) = M_i \circ \sigma^i$ where
   (a) σ^i_j describes the influence of node j on node i
   (b) M_i is a logic function which combines all individual inputs to a scalar value

Example:

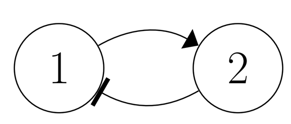

Fig. 2: A simple regulatory network

Consider the regulatory network in figure 2.

1. Defining σ^i_j: Since the nodes do not have self-loops, we set $\sigma^1_1 = 0$ and $\sigma^2_2 = 0$. For σ^2_1 and σ^1_2 piecewise linear functions are used which represent the respective interaction.
2. Defining M_i: Since the only input of node 1 is node 2 we set $M_1(x_1, x_2) = x_2$ to the projection on the second component. For the same reason, $M_2(x_1, x_2) = x_1$.

The resulting switching system is then

$$\begin{aligned} \dot{x}_1 &= -\gamma_1 x_1 + \begin{cases} u_{2,1}, & \text{if } x_2 < \theta^-_{2,1} \\ u_{2,1} - (u_{2,1} - l_{2,1}) \frac{x_2 - \theta^-_{2,1}}{\theta^+_{2,1} - \theta^-_{1,2}}, & \text{if } \theta^-_{2,1} \leq x_2 \leq \theta^+_{2,1} \\ l_{2,1}, & \text{if } x_2 > \theta^+_{2,1} \end{cases} \\ \dot{x}_2 &= -\gamma_2 x_2 + \begin{cases} l_{1,2}, & \text{if } x_1 < \theta^-_{1,2} \\ l_{1,2} + (u_{1,2} - l_{1,2}) \frac{x_2 - \theta^-_{1,2}}{\theta^+_{1,2} - \theta^-_{1,2}}, & \text{if } \theta^-_{1,2} \leq x_1 \leq \theta^+_{1,2} \\ u_{1,2}, & \text{if } x_1 > \theta^+_{1,2} \end{cases} \end{aligned} \tag{1}$$

The values $\theta^-_{1,2}$, $\theta^+_{1,2}$, $\theta^-_{2,1}$ and $\theta^+_{2,1}$ are the threshold values for the step functions. It is assumed that $0 < l_{i,j} < u_{i,j}$, $0 < \theta^-_{1,2} < \theta^+_{1,2}$ and $0 < \theta^-_{2,1} \leq \theta^+_{2,1}$. Therefore, the piecewise linear function in the equation for $\dot{x}_2$ up-regulates x_2 while the piece-wise linear function in the equation for $\dot{x}_1$ down-regulates x_1.

State Transition Graph

The piecewise structure of the functions σ imposes a natural grid-like structure on phase space. State transition graphs are then constructed by combining this grid-structure with information about the dynamics between the cells of this grid.

Example:
Consider the regulatory network in equation 1. The threshold values $\theta^\pm_{1,2}$ and $\theta^\pm_{2,1}$ naturally subdivide phase space. The equation 1 along with information about the parameters can then be used to determine the dynamics along faces of the cells. The state transition graph is then constructed: its vertices are the cells of the phase space decomposition and its edges indicate reachability via the dynamics.

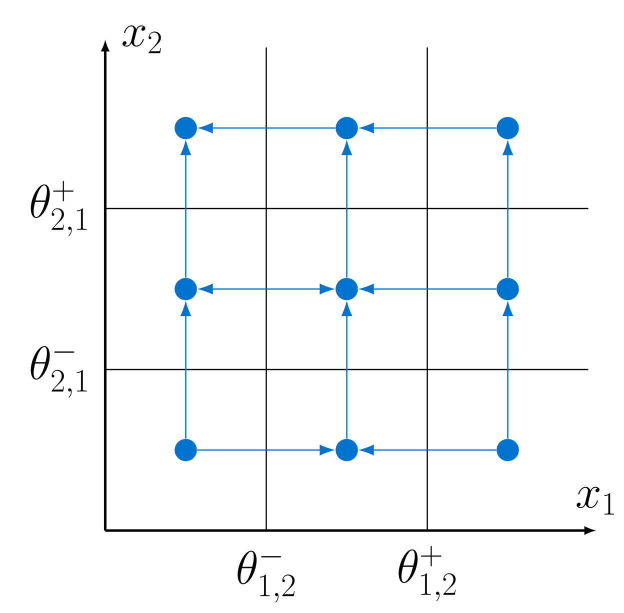

Fig. 3: Phase space decomposition with state transition graph (blue)

Parameter Graph

Given a regulatory network, its associated switching system depends on the parameters $\gamma_i, l_{i,j}, u_{i,j}, \theta^\pm_{i,j}$. The set of all parameters which define valid switching systems is the parameter space for the switching system. One can identify regions in parameter space which give rises to the same state transition graph. A parameter graph is then constructed which has these regions as vertices and regions are adjacent if they are reachable by the variation of a single parameter.

Combining parameter graph and state transition graph, a map

$$\text{DB} : \text{PG} \rightarrow \{G : G \text{ state transition graph}\}$$

is constructed which assigns every node in parameter space its corresponding state transition graph. This map can be used to investigate the global dynamics of the switching system over all of parameter space.

Computation of the Parameter Graph

For a given regulatory network the parameter graph can be computed in two steps

1. The parameter graph has a natural product structure with each factor describing the parameters which are associated to a single node in the network.
2. For each factor graph of the parameter graph, a system of polynomial inequalities is analyzed using its cylindrical algebraic decomposition.

Since the polynomial equations associated to a factor graph only depend on the structure of a single node, the cylindrical algebraic decompositions only have to be computed once and can then be reused. This is crucial since it avoids the doubly-exponential runtime of computation of cylindrical algebraic decompositions in applications.

References

1. Cummins, Bree, Tomás Gedeon, Shaun Harker, Konstantin Mischaikow and Kafung Mok. "Combinatorial Representation of Parameter Space for Switching Networks." SIAM J. Applied Dynamical Systems 15 (2016): 2176-2212.