21st International Symposium on
Mathematical Theory of Networks and Systems
July 7-11, 2014. Groningen, The Netherlands

Switching network dynamics over parameter space

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May 1, 2014

Introduction

Experimental data on gene regulation is often qualitative, with the only information available is the presence of either up-or down- regulation in pairwise interactions. Since majority of the parameters in a model of such a network are not constrained by data, it is important to understand how different choices of parameters affect the dynamics and, therefore, the predictive power of such a model.

Continuous time Boolean networks (CTBN), or switching networks, represent an attractive platform for qualitative studies of gene regulation. A system of equations representing a Boolean network with $i = 1, \ldots, N$ variables can be written

$$\dot{x}_i = -x_i + \Lambda_i(S(x_1), S(x_2), \ldots, S(x_N)), \tag{1}$$

where Λ_i is a piecewise constant function with finitely many values. For each variable x_i is real-valued and the corresponding Boolean variable takes values

$$S(x_j) = 1 \text{ if } x_j > \theta_j \quad \text{and} \quad S(x_j) = 0 \text{ if } x_j \leq \theta_j$$

for some threshold θ_j. Multiple thresholds per variable are also possible in which case the variable $S(\cdot)$ has multiple integer values. To a real-valued trajectory $(x_1(t), x_2(t), \ldots, x_N(t)) \in \mathbb{R}^N$ we can associate a sequence of *states* of the system $(S(x_1(t)), S(x_2(t)), \ldots, S(x_N(t)))$. The subset of $\mathbb{R}^N$ corresponding to each state is called a *domain*.

The parameters of the system are real values attained by functions Λ_i, which are constant on each domain. The dynamics of (1) in each domain is linear and easily solvable.

ISBN: 978-90-367-6321-9

Upon crossing a boundary of a domain, at least one variable crosses its threshold, and therefore the state of the system, as well as the right hand side of (1), changes. Assuming that we can link solutions on the boundaries of the domains [4, 5], a global solution is a concatenation of solutions in individual domains. Thus the individual trajectories for a finite time are easily computable. While computing a full trajectory and long term dynamics for a given initial condition is challenging [6], but doable, understanding long term dynamics of all initial conditions, as well as changes to this global dynamics as function of multiple parameters remains a significant challenge.

Results

In our contribution we develop a numerical approach to study global dynamics over a parameter space for switching networks. This approach is based on an observation that, in the context of applications, the associated nonlinear systems are only meaningful down to a particular scale due to modeling assumptions and limits to accurate experimental measurements. Understanding of identifiable dynamic structures that exist over reasonable ranges of parameter space is of primary importance. Recently, [1, 2] introduced a computational method based on Conley's approach to dynamics [3] which provides a finite algebraic-combinatorial description of the global dynamics over large regions of parameter space. Because this description is finite and queryable, it is referred to as a Database for the Dynamics. The results obtained by this method provably capture the dynamics at a predetermined spatial scale.

Phase space

To apply this approach to CTBN at a fixed value of the parameters, we analytically solve equations in each domain. These solutions are represented as a collection of maps, that map initial conditions in boundary of a domain to the exit points in the same boundary. The dynamics of (1) can be fully characterized by a set of maps between closed sets $\mathcal{S}_{i,k} \subset \mathbb{R}^{N-1}$, where each set $\mathcal{S}_{i,k}$ is defined by $x_i = \theta_i$ for some i, intersected with a collection of half spaces $x_{j_1} \geq \theta_{j_1}$ or $x_{j_2} \leq \theta_{j_2}$ for all the other variables. We call each $\mathcal{S}_{i,k}$ a *wall*. To numerically study this collection of maps, we first find a compact set $C_{i,k}$ in each $\mathcal{S}_{i,k}$ that contains all long-term dynamics. We then progressively subdivide each $C_{i,k}$ to smaller and smaller rectangles up to a predefined level of subdivision. At each stage we map all initial conditions in a particular rectangle to the exit boundary and construct an outer approximation of the image by rectangles from the subdivision on the exit side. This can be viewed as a map taking an entry rectangle to a set of exit rectangles, which is an outer approximation of the true dynamics. Repeating this process for every rectangle at a given subdivision level, we construct a graph where each vertex represents a rectangle and each oriented edge represents the fact that there is a solution connecting the first rectangle to the second rectangle.

Importantly, all strongly connected components of this graph enclose recurrent dynamics. The strongly connected components form a partially ordered set, and each of them can be assigned a topological invariant, called *Conley index*. The partially ordered set of strongly connected components with the Conley index information, is called *Conley-Morse graph*. This object embodies all information about dynamics that is available on a given spatial resolution. We view this computable object as a fundamental descriptor of the dynamics at a fixed parameter value.

We describe next of how we compute changes in this object as parameters change.

Parameter space

We explain our approach to exploring the parameter space in a simplified setting: we will not discuss the process of wall subdivision. We consider a collection of walls $\{\mathcal{S}_{i,k}\}_{i,k}$ and construct a Conley-Morse graph G with vertices representing $\{\mathcal{S}_{i,k}\}_{i,k}$, and edges representing existence of at least on solution connecting walls of a given domain.

The key observation is that the graph $G = G(p)$, that depends on a multi-parameter p, can only change at discrete values of p. More importantly, for switching networks one can determine the structure of this parameter space subdivision without doing any simulations of the equations. More precisely, for a fixed compact set C in the parameter space we developed an algorithm that selects exactly one parameter value p per parameter domain. For collection of these parameters $\{p_i\}_i = 1^n$ we compute the associated graph $G(p_i)$, and know that we captured all possible graphs $G(p), p \in C$. Therefore this finite collection of $G(p_i), i = 1, \ldots, n$, captures all bifurcations detectable by Conley-Morse graphs.

To describe our construction, we observe that the graph $G(p)$ can change only when a target point of a domain either crosses a threshold, or crosses so called diagonal threshold. We illustrate the first of these conditions on a simple example, where we assume that the first equation of the system (1) has the form

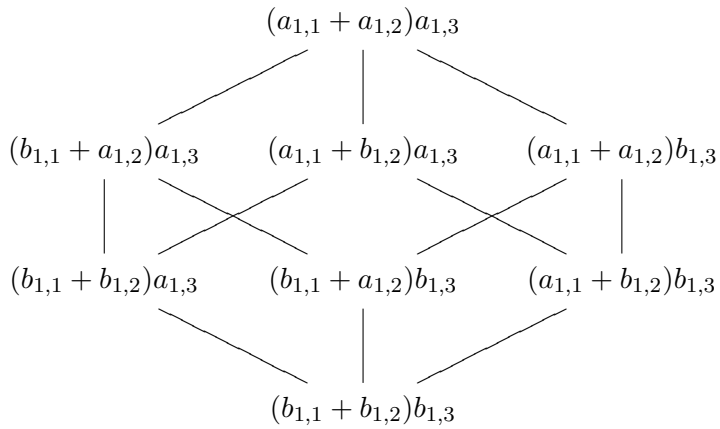
Example 0.1 Consider

$$\dot{x_1} = -x_1 + \left(\begin{cases} a_{1,1} & \text{if } x_1 > \tau_{1,1} \\ b_{1,1} & \text{if } x_1 < \tau_{1,1} \end{cases} + \begin{cases} a_{1,2} & \text{if } x_2 > \tau_{1,2} \\ b_{1,2} & \text{if } x_2 < \tau_{1,2} \end{cases} \right) \begin{cases} b_{1,3} & \text{if } x_3 > \tau_{1,3} \\ a_{1,3} & \text{if } x_3 < \tau_{1,3} \end{cases}$$

Consider a compact space C of parameters $a_{i,j}, b_{i,j}$ and thresholds $\tau_{i,j}$. Let $\{\tau_{j,1}\}_j$ be a collection of all thresholds which determine effect of x_1 on other variables.

The equation above represents regulation of a gene expression of x_1 by three regulators. If we assume that $a_{1,1} > b_{1,1}$ and $a_{1,2} > b_{1,2}$ then x_1 and x_2 up regulate x_1; we assume that $a_{1,3} > b_{1,3}$ which means that x_3 is a down-regulator. This information is represented Hasse diagram (2). For all parameters $a_{i,j}, b_{i,j}$ there are finitely many positions, relative to thresholds $\{\tau_{j,1}\}$, that the x_1 component of the target point can occupy. These positions are determined by all the ways that the partial order (2) can be extended to a linear order, and the ways how the resulting values can be placed in bins determined by the thresholds

$\{\tau_{j,1}\}$. For this particular form of the right hand side, there are 20 linear extension of the partial order (2). For each extension there are $(8+1)^k$ ways to place k thresholds between, above, and below the 8 values in (2).



(2)

This approach applied across all N variables leads to a finite set of parameters that represent all Conley-Morse graphs in C. We are implementing these methods and applying them to cell cycle dynamics where we compare dynamics of different models to each other and the experimental data.

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