



Preservation of dynamic properties in qualitative modeling frameworks for gene regulatory networks



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ABSTRACT

Mathematical modeling often helps to provide a systems perspective on gene regulatory networks. In particular, qualitative approaches are useful when detailed kinetic information is lacking. Multiple methods have been developed that implement qualitative information in different ways, e.g., in purely discrete or hybrid discrete/continuous models. In this paper, we compare the discrete asynchronous logical modeling formalism for gene regulatory networks due to R. Thomas with piecewise affine differential equation models. We provide a local characterization of the qualitative dynamics of a piecewise affine differential equation model using the discrete dynamics of a corresponding Thomas model. Based on this result, we investigate the consistency of higher-level dynamical properties such as attractor characteristics and reachability. We show that although the two approaches are based on equivalent information, the resulting qualitative dynamics are different. In particular, the dynamics of the piecewise affine differential equation model is not a simple refinement of the dynamics of the Thomas model

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1. Introduction

Gene regulation is the result of a complex interplay of molecular components forming large interaction networks. In such a network, there is a constant communication and interaction between gene products affecting gene regulation and the regulated genes altering the roles of the gene products. Mathematical modeling of gene regulatory networks gives insights into the underlying structure and dynamics of various biological systems. In particular, mathematical modeling can help to understand the cellular processes and properties that make a cell adaptable to different environments and conditions (see e.g. Ropers et al., 2011). If information on kinetic parameters is lacking, *qualitative formalisms* offer a well-established alternative to the more traditionally used differential equation models. Using only qualitative information on the network structure and the interactions between the components, these approaches allow obtaining an abstract description of the system's dynamics.

The discrete formalism of Thomas (1973) and Thomas and D'Ari (1990) is a qualitative method describing a gene regulatory network by a discrete function. Each network component is represented by a variable that takes integer values representing the different levels of gene activity. The information on how the behavior of one

component is governed by the values of the other components is captured in a discrete function. The component functions then constitute the coordinate functions of the update function of the network. To derive the dynamics of the system, Thomas introduced the asynchronous update method where only one variable changes per discrete time step, and only by a unit value. Since the state space is finite, the dynamics can be represented by a directed graph, the so-called asynchronous *state transition graph* (STG).

The particularities of the asynchronous update method result in a close correspondence of the discrete model to certain differential equation systems (Snoussi, 1989). Differential equation models consisting of step functions retain a continuous time evolution, yet can be seen as qualitative due to the close relation of step and discrete functions. Such piecewise affine differential equation (PADE) models approximate certain ordinary differential equation models (Glass and Kauffman, 1972, 1973). de Jong et al. (2004) have shown that they can essentially be captured by a discrete representation, which abstracts the continuous solution trajectories of the differential equations into transitions between different regions of the phase space. Again, the resulting dynamics can be represented by a directed graph, the *qualitative transition graph* (QTG).

In this paper, we aim at clarifying the relation between Thomas and PADE models by comparing the respective graphs capturing the dynamical behavior. Several results in this direction already exist. For example, attractors, including steady states and certain limit cycles, are related (Glass and Kauffman, 1972; Snoussi, 1989; Snoussi and Thomas, 1993; Chaves et al., 2010; Wittmann et al., 2009). Our goal here is to present a comprehensive comparison between the STG and the QTG.

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The paper is organized as follows. Section 2 presents a discrete modeling approach based on the Thomas formalism. PADE systems and the qualitative analysis developed by de Jong et al. (2004) are introduced in Section 3. In Section 4, we start comparing the two formalisms. Section 5 describes our main result characterizing transitions in the QTG using edges originating in corresponding vertices in the STG. We illustrate the application of this result with examples of relations between paths and attractors in the two graphs. The conclusion and perspectives for future work are given in Section 6.

This paper is the full version of an extended abstract included in the proceedings of IPCAT 2012 (Jamshidi et al., 2012).

2. Discrete formalism

Consider a gene network with n regulatory components. In the discrete modeling approach, the activity level of a component i is modeled by a discrete variable q_i , which takes its values in a finite set of natural numbers $Q_i = \{0, \dots, p_i\}$, $p_i \geq 1$. The state space of the discrete model is $Q = Q_1 \times \dots \times Q_n$, and the regulatory interactions are captured by a discrete update function $f = (f_1, \dots, f_n) : Q \rightarrow Q$. The function f uniquely determines the state transition graph $STG(f) = (Q, E)$, a directed graph with node set Q and edge set $E \subset Q \times Q$. For any $j \in \{1, \dots, n\}$, $q \in Q$ with $f_j(q) \neq q_j$, there is an edge $(q, q') \in E$, where $q'_j = q_j + \text{sgn}(f_j(q) - q_j)$ and $q'_i = q_i$, for all $i \in \{1, \dots, n\} \setminus \{j\}$. Here, $\text{sgn} : \mathbb{R} \rightarrow \{-1, 0, 1\}$ denotes the sign function. If $f(q) = q$, then $(q, q) \in E$ and q is called a *fixpoint*.

Unless f is Boolean, it is not possible to recover f from $G = STG(f)$. However, we may obtain from G a unitary update function $f^G : Q \rightarrow Q$ by setting

$$f_j^G(q) = q_j + \sum_{q' \in AS(q)} (q'_j - q_j), \quad \text{for } j \in \{1, \dots, n\}.$$

Here $AS(q) := \{q' \in Q \mid (q, q') \in E\}$ denotes the set of asynchronous successors of q in G .

Lemma 1. Let $f : Q \rightarrow Q$ be an update function and $G = STG(f)$. Then

$$STG(f) = STG(f^G).$$

Proof. Let $j \in \{1, \dots, n\}$ and $q \in Q$. By definition of $AS(q)$, there exists at most one $q' \in AS(q)$ such that $|q'_j - q_j| = 1$. This implies $\text{sgn}(f_j(q) - q_j) = q'_j - q_j$. Therefore, $\text{sgn}(f_j(q) - q_j) = \sum_{q' \in AS(q)} (q'_j - q_j)$, and the result follows. \square

The unitary update function f^G captures the information from the original update function f contained in $G = STG(f)$. If f is Boolean, f and f^G are the same.

Example 1. For $Q = \{0, 1\} \times \{0, 1, 2\}$ and the update function $f : Q \rightarrow Q$

q	00	01	02	10	11	12
$f(q)$	12	12	11	00	10	11

the state transition graph $STG(f)$ is displayed on the left of Fig. 2(a).

While the discrete formalism of R. Thomas provides a rather coarse representation of the dynamics of a gene regulatory network, the more traditionally used differential equation models offer a much more precise picture, which however requires detailed knowledge on reaction kinetics and parameters. A nice intermediate formalism bringing together discrete and continuous aspects is based on piecewise affine differential equations (Glass and Kauffman, 1972, 1973).

3. Piecewise affine differential equations

In this section, we present piecewise affine differential equations (PADE) and the qualitative modeling approach introduced by de Jong et al. (2004). While a number of refinements have been proposed (Batt et al., 2008), we use here the original approach for comparison with the Thomas formalism. Our focus will be on the qualitative dynamics associated with a system of PADEs, i.e., the discrete representation of all possible solution trajectories of the PADEs satisfying certain parameter constraints.

Consider an n -dimensional phase space $\Omega = \Omega_1 \times \dots \times \Omega_n \subset \mathbb{R}_{\geq 0}^n$, where $\Omega_i = \{x_i \in \mathbb{R} \mid 0 \leq x_i \leq \max_i\}$, and $\max_i \in \mathbb{R}_{>0}$. For every continuous variable $x_i \in \Omega_i$ we assume $p_i \in \mathbb{N}$ thresholds $\theta_1^i, \dots, \theta_{p_i}^i$ satisfying the ordering

$$0 < \theta_1^i < \dots < \theta_{p_i}^i < \max_i, \quad \text{for all } i \in \{1, \dots, n\}. \quad (1)$$

In the comparison with the discrete formalism in Section 2, the value p_i chosen here corresponds to the maximal value p_i of the component range Q_i of a discrete model. The union of the threshold hyperplanes is denoted by $\Theta := \bigcup_{i \in \{1, \dots, n\}, j_i \in \{1, \dots, p_i\}} \{x \in \Omega \mid x_i = \theta_{j_i}^i\}$. We consider a set of PADEs in $\Omega \setminus \Theta$ of the form

$$\dot{x}_i = F_i(x) - G_i(x)x_i, \quad i \in \{1, \dots, n\}, \quad (2)$$

where the functions $G_i : \Omega \setminus \Theta \rightarrow \mathbb{R}_{>0}$ and $F_i : \Omega \setminus \Theta \rightarrow \mathbb{R}_{\geq 0}$ are linear combinations of products of step functions

$$S^+(x_i, \theta_l^k) = \begin{cases} 0 & \text{if } x_i < \theta_l^k, \\ 1 & \text{if } x_i > \theta_l^k, \end{cases}$$

and $S^-(x_i, \theta_l^k) = 1 - S^+(x_i, \theta_l^k)$ for $l \in \{1, \dots, n\}$.

To obtain a discrete representation of the PADE system, the state space is partitioned into a set of domains.

Definition 1. Consider a set of PADEs of the form (2) with phase space Ω and thresholds θ_l^j . The $(n-1)$ -dimensional hyperplanes corresponding to the equations $x_i = \theta_l^j$, $j \in \{1, \dots, p_i\}$, divide Ω into hyper-rectangular regions called domains. A domain $D \subset \Omega$ is defined by $D = D_1 \times \dots \times D_n$, where every D_i is given by one of the following equations

$$\begin{aligned} D_i &= \{x_i \mid 0 \leq x_i < \theta_1^i\}, \\ D_i &= \{x_i \mid \theta_l^k < x_i < \theta_{l+1}^k\} \quad \text{for } k \in \{1, \dots, p_i - 1\}, \\ D_i &= \{x_i \mid \theta_{p_i}^i < x_i \leq \max_i\}, \\ D_i &= \{x_i \mid x_i = \theta_l^k\} \quad \text{for } k \in \{1, \dots, p_i\}. \end{aligned}$$

By \mathcal{D} we denote the set of all domains in Ω . A domain $D \in \mathcal{D}$ is called a *singular domain*, if there exists $i \in \{1, \dots, n\}$ such that $D_i = \{x_i \mid x_i = \theta_l^k\}$ for some $k \in \{1, \dots, p_i\}$. The variable x_i is then called *singular variable*. The order of a singular domain is the number of its singular variables. A domain $D \in \mathcal{D}$ is called a *regular domain*, if it is not a singular domain. The set of regular and singular domains are denoted by \mathcal{D}_r and \mathcal{D}_s respectively.

It follows immediately that for any regular domain $D \in \mathcal{D}_r$, the functions $F_i(x)$ and $G_i(x)$ are constant on D . Thus (2) can be written as a linear system $\dot{x} = F^D - G^D x$, for all $x \in D$, where $G^D = \text{diag}(G_1^D, \dots, G_n^D)$ is a diagonal matrix with strictly positive entries and $F^D = (F_1^D, \dots, F_n^D)$ a positive vector. It is easy to see that solutions of (2) starting in a regular domain D converge monotonically towards the so-called focal point $\phi(D) := (G^D)^{-1} F^D$.

In agreement with de Jong et al. (2004), we will assume that all focal points lie in a regular domain. By definition of the regular domains, we can then encode the position of each focal point by strict inequalities involving the threshold values and the

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