



Numerical simulation of piecewise-linear models of gene regulatory networks using complementarity systems



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HIGHLIGHTS

- An equivalence result between the Filippov and Aizerman–Pyatnitskii (AP) extensions.
- The reformulation of the AP-extension as a Complementarity System (CS).
- A theoretically sound and practically useful numerical simulation method.
- A time-integration method for the resulting CS with sliding motions.
- Illustration of the interest by an analysis of three synthetic networks.

ARTICLE INFO

Article history:

Received 23 January 2013
 Received in revised form
 15 November 2013
 Accepted 17 November 2013
 Available online 23 November 2013
 Communicated by S. Coombes

Keywords:

Nonsmooth dynamical systems
 Gene regulatory networks
 Piecewise-linear models
 Filippov solutions
 Differential inclusions
 Complementarity systems

ABSTRACT

Gene regulatory networks control the response of living cells to changes in their environment. A class of piecewise-linear (PWL) models, which capture the switch-like interactions between genes by means of step functions, has been found useful for describing the dynamics of gene regulatory networks. The step functions lead to discontinuities in the right-hand side of the differential equations. This has motivated extensions of the PWL models based on differential inclusions and Filippov solutions, whose analysis requires sophisticated numerical tools. We present a method for the numerical analysis of one proposed extension, called Aizerman–Pyatnitskii (AP)-extension, by reformulating the PWL models as a mixed complementarity system (MCS). This allows the application of powerful methods developed for this class of nonsmooth dynamical systems, in particular those implemented in the Siconos platform. We also show that under a set of reasonable biological assumptions, putting constraints on the right-hand side of the PWL models, AP-extensions and classical Filippov (F)-extensions are equivalent. This means that the proposed numerical method is valid for a range of different solution concepts. We illustrate the practical interest of our approach through the numerical analysis of three well-known networks developed in the field of synthetic biology.

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1. Introduction

When confronted with changing environmental conditions, living systems have a remarkable capacity to rapidly adapt their functioning. For instance, the response of a bacterial cell to the depletion of an essential nutrient leads to the upregulation and downregulation of the expression of up to several hundreds of genes [1]. The genes encode enzymes, transcription regulators, membrane transporters and other macromolecules playing a role in cellular processes. The control of the adjustment of gene expression levels is achieved by so-called *gene regulatory networks*, consisting of genes, RNAs, proteins, and their mutual regulatory interactions.

In order to understand how a particular network structure brings about observed changes in gene expression, mathematical models in combination with computer simulation are increasingly used, especially in the emerging field of systems biology [2]. The modeling of gene regulatory networks also plays a prominent role in synthetic biology, which aims at designing a network structure capable of producing a desired gene expression pattern, for instance a robust oscillation or an externally controlled switch [3]. The networks may be constructed *de novo* or obtained by rewiring a natural regulatory network.

A variety of formalisms are available for modeling gene regulatory networks [4,5]. For many purposes, approximate models based on simplifications of classical kinetic models have been proven useful [6–8]. First, the approximate models are easier to calibrate against experimental data, due to the fact that they reduce the number of parameters and the complexity of the rate equations. This may help relieve what is currently a bottleneck for modeling in systems biology, namely obtaining reliable estimates

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of parameter values. Second, the simplified mathematical form of the models makes them easier to analyze. Among other things, this makes it possible to single out the precise role of specific subnetworks [9,10] and to analyze the feasibility of control schemes [11].

In this paper we look at one particular class of approximate models of gene regulatory networks, so-called *piecewise-linear (PWL) models* [12]. The PWL models are systems of coupled differential equations in which the variables denote concentrations of gene products, typically proteins. The rate of change of a concentration at a particular time-point may be regulated by other proteins through direct or indirect interactions. The PWL models capture these regulatory effects by means of step functions that change their value in a switch-like manner at threshold concentrations of the regulatory proteins. The step functions are approximations of the sigmoidal response functions often found in gene regulation.

PWL models with step functions have favorable mathematical properties, which allows for the analysis of steady states, limit cycles, and their stability [13–16]. The use of step functions, however, leads to discontinuities in the right-hand side of the differential equations, due to the abrupt changes of the value of a step function at its threshold. These discontinuities are sometimes ignored, which is potentially dangerous as it may cause steady states and other important dynamical properties of the system to be missed. In order to deal with the discontinuities, several authors have proposed the use of differential inclusions and Filippov solutions [17–19]. These proposals to extend PWL models to differential inclusions differ in subtle but nontrivial ways, giving rise to systems with nonequivalent dynamics [19,20].

Currently, only few computational tools are available to support the analysis of the differential inclusions obtained from Filippov extensions of PWL models. Genetic Network Analyzer (GNA) provides a qualitative analysis of PWL models of gene regulatory networks (e.g., [21,22]). However, the analysis is based on hyperrectangular overapproximations of the differential inclusions proposed in [17], and it is currently not clear to which extent this introduces artifacts in the analysis. Moreover, the predictions obtained from this analysis are purely qualitative, describing possible transitions between state-space regions rather than giving numerical solutions. Alternatively, an algorithm based on the use of steep sigmoidal response functions in combination with singular perturbation theory has been presented [23,24].

The aim of this paper is to propose a theoretically sound and practically useful method for the numerical simulation of gene regulatory networks described by PWL models. We notably show that the Aizerman & Pyatnitskii extension (see [17, Definition c, page 55] or [25]) of PWL models can be reformulated in the framework of complementarity systems or differential variational inequalities [26–28]. The Aizerman & Pyatnitskii extension has been introduced in the context of PWL models of gene regulatory networks in [19,20], where it is shown that it leads to a more restrictive extension than the standard Filippov extension. The reformulation as a complementarity system allows us to employ the rich store of numerical methods available for these and other classes of discontinuous systems [26,29]. Moreover, we show that under two reasonable biological assumptions, posing constraints on the admissible network structures, the different extensions of PWL models that have been proposed, as well as the hyperrectangular overapproximation in [22], are equivalent. This means that the numerical simulation approach developed in this paper is valid for a range of different solution concepts for PWL models of gene regulatory networks.

We illustrate the interest of our numerical simulation approach by means of the analysis of three synthetic networks published in the literature: the repressilator [30], an oscillator with positive feedback [31], and the IRMA network [32]. We develop PWL models of these networks, either from scratch or by adapting

existing ODE models, and numerically simulate the dynamic response of these networks to external stimuli. The simulations are shown to reproduce known qualitative features of these networks, notably the capability to generate (damped) oscillations for the first two networks, and a switch-on/switch-off response after a change in the growth medium for the third. We believe these examples demonstrate that the numerical simulation approach developed in this paper provides a useful extension of the toolbox of modelers of gene regulatory networks.

2. PWL models of gene regulatory networks

2.1. Definition of PWL models

The dynamics of genetic regulatory networks can be described by piecewise-linear (PWL) differential equation models using step functions to account for regulatory interactions [12,33,34]. In this section we briefly summarize the PWL modeling framework.

We denote by $x = (x_1, \dots, x_n)^T \in \Omega$ a vector of cellular protein or RNA concentrations, where $\Omega \subset \mathbb{R}_+^n$ is a bounded n -dimensional hyperrectangular subset of \mathbb{R}_+^n . For each concentration variable x_i , $i \in \{1, \dots, n\}$, we distinguish a set of constant, strictly positive threshold concentrations $\{\theta_i^1, \dots, \theta_i^{p_i}\}$, $p_i > 0$. At its thresholds a protein may affect the expression of genes encoding other proteins or the expression of its own gene. We call $\Theta = \bigcup_{i \in \{1, \dots, n\}, k \in \{1, \dots, p_i\}} \{x \in \Omega \mid x_i = \theta_i^k\}$ the subset of Ω defined by the threshold hyperplanes.

Definition 1 (PWL Model). A PWL model of a gene regulatory network is defined by a set of coupled differential equations

$$\begin{aligned} \dot{x}_i &= f_i(x) = -\gamma_i x_i + b_i(x) \\ &= -\gamma_i x_i + \sum_{l \in L_i} \kappa_i^l b_i^l(x), \quad i \in \{1, \dots, n\}, \end{aligned} \quad (1)$$

where κ_i^l and γ_i are positive synthesis and degradation constants, respectively, $L_i \subset \mathbb{N}$ are sets of indices of regulation terms, and $b_i^l : \Omega \setminus \Theta \rightarrow \{0, 1\}$ are so-called regulation functions.

Intuitively, (1) defines the rate of change of each concentration x_i as the difference of the rate of synthesis (the second term in the right-hand side) and the rate of degradation (the first term). The synthesis term depends on the concentrations of regulatory proteins through the regulation functions, which account for the interactions between the genes in the network. Degradation is described by a first-order term including contributions of growth dilution and protein degradation. While this is sufficient for the examples treated in this paper, the degradation term in (1) can be easily extended to include proteolytic regulators.

Each regulation function $b_i^l(\cdot)$ is defined in terms of *step functions*

$$\begin{aligned} s^+(x_j, \theta_j^k) &= \begin{cases} 1 & \text{if } x_j > \theta_j^k \\ 0 & \text{if } x_j < \theta_j^k \end{cases} \quad \text{and} \\ s^-(x_j, \theta_j^k) &= \begin{cases} 0 & \text{if } x_j > \theta_j^k \\ 1 & \text{if } x_j < \theta_j^k, \end{cases} \end{aligned} \quad (2)$$

where x_j is a concentration variable, $j \in \{1, \dots, n\}$, and θ_j^k a threshold for x_j , $k \in \{1, \dots, p_j\}$. Notice that $s^-(x_j, \theta_j^k) = 1 - s^+(x_j, \theta_j^k)$. The step functions capture the switch-like character of gene regulation by transcription factors and other proteins. The regulation functions are algebraic equivalents of discrete Boolean functions expressing the combinatorial logic of gene regulation [35].

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