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Numerical Simulation of Piecewise-Linear Models of Gene Regulatory Networks Using Complementarity Systems (Extended Abstract)

Vincent Acary, Hidde de Jong, Bernard Brogliato

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 mathematical tools. We present a method for the numerical analysis of one proposed extension, called Aizermann-Pyatnitskii (AP)-extension, by reformulating the PWL models as a mixed complementarity system. 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.**

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. 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.

A variety of formalisms are available for modeling gene regulatory networks [8], [20]. For many purposes, approximate models based on simplifications of classical kinetic models have been proven useful. 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 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 [1], [24] and to analyze the feasibility of control schemes [13].

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In this paper we look at one particular class of approximate models of gene regulatory networks, so-called *piecewise-linear (PWL) models* [16]. 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.

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

A *PWL model* of a gene regulatory network is defined by a set of coupled differential equations

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

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 $b_i^l : \Omega \setminus \Theta \to \{0, 1\}$ 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.

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

functions

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

and

$$s^-(x_j,\theta_j^k)=\begin{cases} 0 \text{ if } x_j > \theta_j^k \\ 1 \text{ if } x_j < \theta_j^k \end{cases}, \tag{3}$$

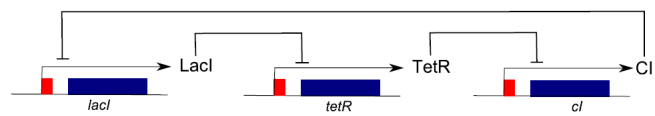
where x_j is a concentration variable, $j \in \{1,\dots n\}$, and θ_j^k a threshold for x_j, $k \in \{1,\dots p_i\}$. Notice that $s^-(x_j,\theta_j^k) = 1 - s^+(x_j,\theta_j^k)$. The step functions capture the switch-like character of gene regulation by transcription factors and other proteins. The regulation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

PWL models with step functions have favorable mathematical properties, which allows for the analysis of steady states, limit cycles, and their stability [10], [12], [14], [17]. 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 [15], [18], [22]. These proposals to extend PWL models to differential inclusions differ in subtle but nontrivial ways, giving rise to systems with nonequivalent dynamics [22].

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.*, [7]). However, the analysis is based on hyperrectangular overapproximations of the differential inclusions proposed in [15], 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 [19].

The aim of this contribution 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 (AP)-extension (see [15, Definition c), page 55] or [5]) of PWL models can be reformulated in the framework of complementarity systems or differential variational inequalities [3]. The AP-extension has been introduced in the context of PWL models of gene regulatory networks in [22], where it is shown that it leads to a more restrictive extension than the standard Filippov (F)-extension. The reformulation of the AP-extension as a mixed complementarity system allows us to employ the rich store of numerical methods available for these and other classes of discontinuous systems [2], [3]. Moreover, we show that under two reasonable biological assumptions, posing constraints on the admissible network structures, the AP- and F-extensions of PWL models, as well as the hyperrectangular overapproximation in [11], 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.

Concretely, we propose numerical methods for performing the time-integration of the AP extension of PWL models and for computing its equilibrium points. General results for convergence (and existence) are beyond the scope of this work, but we prove under the generic assumption that the regulation functions are multi-affine, that is, that they are affine with respect to each $s^+(x_j,\theta_j^k)$, $j \in \{1,\dots n\}$ and $k \in \{1,\dots p_i\}$, that the discrete one-step problem is solvable. In practice, we can therefore always numerically compute a solution of the time-discretized problem. This enables the computation of a selection in the set-valued AP-extension for the time-discrete systems. The simulation platform SICONOS implements the numerical methods for AP extensions of PWL models.



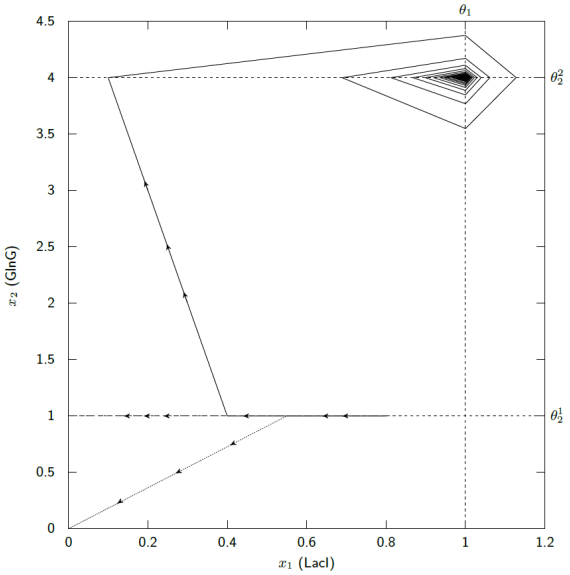
(a)

$$\begin{cases} \dot{x}_1 &= -\gamma_1\, x_1 + \kappa_1\, s^+(x_2,\theta_2^2) \\ \dot{x}_2 &= -\gamma_2\, x_2 + \kappa_2\, s^-(x_1,\theta_1)\, s^+(x_2,\theta_2^1) \end{cases}$$

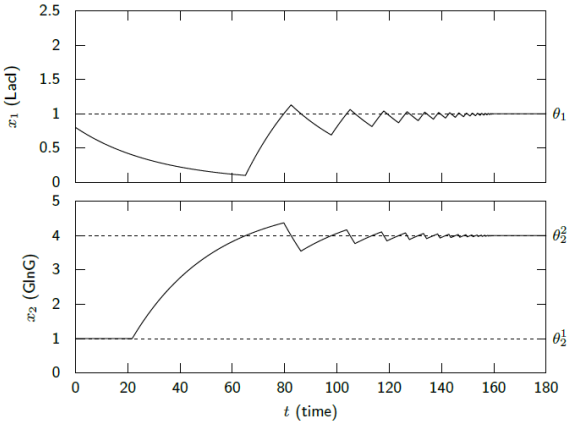
(b)

Fig. 1. (a) Oscillator with positive feedback consisting of two genes [6]. The external control by the inducer molecule IPTG is not shown in the figure. (b) PWL model corresponding to the network in (a). The variables x_1 and x_2 represent the concentrations of the proteins LacI and GlnG, respectively. The following parameter values have been used in the simulations: $\gamma_1 = \gamma_2 = 0.032$, $\kappa_1 = 0.08$, $\kappa_2 = 0.16$, and $\theta_1 = 1$, $\theta_2^1 = 1$, and $\theta_2^2 = 4$. The time and concentration variables as well as the parameters in the model have been rescaled so as to make them dimensionless, in the same way as in [21]. The dashed lines represent the threshold concentrations of the variables.

We illustrate the interest of our numerical simulation approach by means of the analysis of three synthetic networks published in the literature: the repressilator [21], an oscillator with positive feedback [6], and the IRMA network [9]. 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 (Figures 1 and 2). 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 growth medium for the third. We believe these examples demonstrate that the numerical simulation approach developed in this contribution provides a useful extension of the toolbox of modelers of gene regulatory



(a)



(b)

Fig. 2. Simulation of synthetic oscillator network with positive feedback in Figure 1. (a) Trajectories corresponding to several solutions starting from the initial state $x^0 = (0.78, 1)^T$ located on the repulsive discontinuity segment separating the basins of attractions of the two asymptotically stable equilibrium points. (b) Simulation trace of the damped oscillation that corresponds to the trajectory converging towards $x = (\theta_1, \theta_2^2)^T = (1, 4)^T$. Notice that time is a dimensionless variable in the model [21]. Physical time can be reconstructed by multiplying the rescaled time variable in the model by $2/\ln 2$ min.

networks.

The results summarized in this extended abstract are described at length in [4].

References

[1] W. Abou-Jaoude, M. Chaves and J.-L. Gouzé (2011). A theoretical exploration of birhythmicity in the p53-Mdm2 network. *PLoS ONE*, 6 (2), e17075.

[2] V. Acary, O. Bonnefon and B. Brogliato (2010). Time-stepping numerical simulation of switched circuits with the nonsmooth dynamical systems approach. *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*, 29 (7), 1042—1055.

[3] V. Acary, B. Brogliato (2008). *Numerical Methods for Nonsmooth Dynamical Systems. Applications in Mechanics and Electronics*. Lecture Notes in Applied and Computational Mechanics, vol. 35, Springer, Berlin, 2008.

[4] V. Acary, H. de Jong and B. Brogliato (2014). Numerical simulation of piecewise-linear models of gene regulatory networks using complementarity systems. *Physica D*, 269, 103–119. Also available as INRIA research report RR-8207 at `http://hal.inria.fr`.

[5] M.A. Aizerman and E.S. Pyatnitskii (1974). Foundation of a theory of discontinuous systems 1 & 2. *Automatic and Remote Control*, 35 (7), 1066—1079 & 1066—1079.

[6] M.R. Atkinson, M.A. Savageau, J.T. Myers, and A.J. Ninfa (2003). Development of genetic circuitry exhibiting toggle switch or oscillatory behavior in *Escherichia coli*. *Cell*, 113 (5), 597–608.

[7] G. Batt, H. de Jong, M. Page and J. Geiselmann (2008). Symbolic reachability analysis of genetic regulatory networks using discrete abstractions. *Automatica*, 44 (4), 982–989.

[8] H. Bolouri (2008). *Computational Modeling of Gene Regulatory Networks – A Primer*. Imperial College Press, London.

[9] I. Cantone, L. Marucci, F. Iorio, M.A. Ricci, V. Belcastro, M. Bansal, S. Santini, M. di Bernardo, and M.P. Cosma (2009). A yeast synthetic network for in vivo assessment of reverse-engineering and modelling approaches. *Cell*, 137(1):172–81.

[10] R. Casey, H. de Jong, and J.L. Gouzé (2006). Piecewise linear models of genetic regulatory networks: Equilibria and their stability. *Journal of Mathematical Biology*, 52(1), 27–56.

[11] H. de Jong, J.L. Gouzé, C. Hernandez, M. Page, T. Sari, J. Geiselmann (2004). Qualitative simulation of genetic regulatory networks using piecewise-linear models. *Bulletin of Mathematical Biology*, 66(2), 301–40.

[12] R. Edwards (2000). Analysis of continuous-time switching networks. *Physica D*, 146 (1-4), 165–199.

[13] R. Edwards, S. Kim, and P. van den Driessche (2011). Control design for sustained oscillation in a two gene regulatory network. *Journal of Mathematical Biology*, 62 (4), 453–479.

[14] E. Farcot and J.-L. Gouzé (2009). Periodic solutions of piecewise affine gene network models with non uniform decay rates: The case of a negative feedback loop. *Acta Biotheoretica*, 57 (4), 429–455.

[15] A.F. Filippov (1988). *Differential Equations with Discontinuous Right Hand Sides*. Kluwer, Dordrecht, The Netherlands.

[16] L. Glass and S.A. Kauffman (1973). The logical analysis of continuous non-linear biochemical control networks. *Journal of Theoretical Biology*, 39 (1), 103–129.

[17] L. Glass and J.S. Pasternack (1978). Stable oscillations in mathematical models of biological control systems. *Journal of Mathematical Biology*, 6, 207–223.

[18] J.L. Gouzé and T. Sari (2002). A class of piecewise linear differential equations arising in biological models. *Dynamical Systems*, 17(4), 299–316.

[19] L. Ironi, L. Panzeri and E. Plahte and V. Simoncini (2011). Dynamics of actively regulated gene networks. *Physica D*, 240(8), 779–794.

[20] G. Karlebach and R. Shamir (2008) Modelling and analysis of gene regulatory networks. *Nature Reviews Molecular Cell Biology*, 9 (10), 770–780.

[21] M.B. Elowitz and S. Leibler (2000). A synthetic oscillatory network of transcriptional regulators. *Nature*, 403 (6767), 335–338.

[22] A. Machina and A. Ponosov (2011). Filippov solutions in the analysis of piecewise linear models describing gene regulatory networks. *Nonlinear Analysis*, 74, 882–900.

[23] E. Plahte and S. Kjóglum (2005). Analysis and generic properties of gene regulatory networks with graded response functions. *Physica D*, 201 (1), 150–176.

[24] L. Tournier and M. Chaves (2009) Uncovering operational interactions in genetic networks using asynchronous Boolean dynamics. *Journal of Theoretical Biology*, 260 (2), 196–209.