



Brief paper

A mathematical framework for the control of piecewise-affine models of gene networks[☆]

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ABSTRACT

This article introduces results on the control of gene networks, in the context of piecewise-affine models. We propose an extension of this well-documented class of models, where some input variables can affect the main terms of the equations, with a special focus on the case of affine dependence on inputs. Some generic control problems are proposed, which are qualitative, respecting the coarse-grained nature of piecewise-affine models. Piecewise constant feedback laws that solve these control problems are characterized in terms of affine inequalities, and can even be computed explicitly for a subclass of inputs. The latter is characterized by the condition that each state variable of the system is affected by at most one input variable. These general feedback laws are then applied to a two-dimensional example, consisting in two genes inhibiting each other. This example has been observed in real biological systems, and is known to present a bistable switch for some parameter values. Here, the parameters can be controlled, allowing to express feedback laws leading to various behaviours of this system, including bi-stability as well as situations involving a unique global equilibrium.

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1. Introduction

This work deals with control theoretic aspect of a class of piecewise-affine differential equations, which has been introduced in the 1970s by Glass (1975) to model genetic and biochemical interaction networks. Various aspects of the autonomous dynamics of these equations have been studied by different authors, e.g. Edwards, Siegelmann, Aziza, and Glass (2001), Farcot (2006), Glass (1975) and Gouzé and Sari (2003). Besides theoretical aspects, they have been used also as models of concrete biological systems (de Jong, Geiselmann, Batt, Hernandez, & Page, 2004; Ropers, de Jong, Page, Schneider, & Geiselmann, 2006), and efficient procedures have been proposed to identify their parameters (Drulhe, Ferrari-Trecate, de Jong, & Viari, 2006; Perkins, Hallett, & Glass, 2004). This proves their possible use as models guiding experimental researches on gene regulatory networks. Such experiments have been carried out extensively during the recent years, often on large scale systems, thanks to the extraordinary developments of

large throughput methods used in the investigation of biochemical systems.

Furthermore, recent advances have shown that such networks may not only be studied and analyzed on existing biological species, but also synthesized in labs (Becksei & Serrano, 2000; Elowitz & Leibler, 2000; Gardner, Cantor, & Collins, 2000). This latter aspect strongly motivates the elaboration of a control theory for these systems (Andrianantoandro, Basu, Karig, & Weiss, 2006; Hasty, Isaacs, Dolnik, McMillen, & Collins, 2001; Kobayashi et al., 2004). This work is an attempt in this direction: piecewise-affine models are treated in the case where production and degradation terms can be modified during an experiment, a fact we model by introducing continuous input variables to control the system.

The biological interpretation of these inputs is that an additional biochemical compound is added to the system, or some physical parameter is changed. Such a modification may then activate, or inhibit the production or degradation rates of species involved in the system. Among concrete realizations, some specific inhibitors or activators could be introduced in the system, as is done in synthetic biology (Kobayashi et al., 2004). Other techniques, such as directed mutagenesis, the use of interfering RNA (siRNA and miRNA) (Isaacs, Dwyer, & Collins, 2006; Isaacs et al., 2004), could also modify production or degradation rates. More radically, gene knock-in or knock-out techniques could be handled within this framework, their on/off nature being described by restricting the input values to a discrete set.

Being piecewise linear, the models that are studied here can be seen as particular switched or hybrid systems. As such, they

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might be handled using more general tools, tailored for these broad classes (El-Farra, Gani, & Christofides, 2005; Johansson, 2004; Sun & Ge, 2005). However, whereas a specialization of these techniques would concern steady states and their stability, we propose more specific feedback laws, notably to control trajectories across a prescribed sequence of boxes, which might include oscillatory behaviours. Moreover, we take advantage of the specific form of systems we consider.

Other comparable techniques are those developed in a series of papers treating multi-affine dynamical systems defined on rectangles (Belta, Habets, & Kumar, 2002; Belta & Habets, 2004; Habets & van Schuppen, 2004). The starting point of these different methods and algorithms is the control of all trajectories of a multi-affine dynamical system toward a specified facet of a full-dimensional rectangle in state space. The input values have to satisfy a system of 2^{n-1} inequalities (one for each vertex of the exit facet). Being affine in rectangular regions of state space, the systems introduced here could be handled with these techniques. However, our method requires to check a number of inequalities that is proportional to n , and which can even be solved explicitly in some cases, improving drastically the complexity of a blind application of more general techniques.

The paper is organized into three main sections. In Section 2, the investigated model is introduced. Then in Section 3, we formulate generic control problems, whose solutions are characterized in Section 3.3. In Section 4 we illustrate the method on a classical two-dimensional example: the *toggle switch*, showing notably how to induce bi-stability in this system. A final section discusses the results, and the possible outcomes of this work.

2. Piecewise-affine models

2.1. The Autonomous case

The usual form of piecewise-affine gene network models may be:

$$\frac{dx}{dt} = \kappa(x) - \Gamma(x)x. \quad (1)$$

$\kappa(x) \in \mathbb{R}_+^n$ is a production term, and $\Gamma(x)$ a diagonal matrix with positive diagonal entries, representing degradation rates of the system. Both are piecewise constant with a rectangular underlying partition, see below.

The fact that κ_i and the γ_i are piecewise constant of x is due to the switch-like nature of the feedback regulation in gene networks. The variable x_i is a concentration (of mRNA or of protein), representing the expression level of the i th gene among n , and ranges in some interval of the form $[0, \max x_i]$. When x_i reaches a threshold value, some other gene in the network, say gene number j , is suddenly activated (resp. inhibited), and thus expressed with a different production rate: the value of κ_j (resp. γ_j) changes. For each $i \in \{1 \dots n\}$ there is thus a finite set of threshold values:

$$\theta_i = \{\theta_i^1 \dots \theta_i^{q_i-1}\}, \quad (2)$$

supposed ordered: $0 < \theta_i^1 < \dots < \theta_i^{q_i-1} < \max x_i$. Although the extreme values may not be crossed, we denote $\theta_i^0 = 0$, and $\theta_i^{q_i} = \max x_i$ by convention.

By definition of κ and Γ , the axes of the state space will be partitioned into open segments between thresholds. Since the extreme values will not be crossed by the flow, the first and the last segments include one of their endpoints:

$$\mathcal{D}_i \in \theta_i \cup \{[\theta_i^0, \theta_i^1), (\theta_i^{q_i-1}, \theta_i^{q_i}]\} \cup \{(\theta_i^j, \theta_i^{j+1}) \mid j \in \{1 \dots q_i - 2\}\}.$$

Each product $\mathcal{D} = \prod_{i=1}^n \mathcal{D}_i$ defines a rectangular *domain*, whose dimension is the number of non-singleton \mathcal{D}_i . When $\dim \mathcal{D} = n$, one usually says that it is a *regulatory domain*, or *regular domain*,

and those domains with lower dimension are called *switching domains*, or *singular domains*, see de Jong et al. (2004). In particular, singular domains of dimension $n - 1$ are often called *walls*.

Let \mathcal{D}_r and \mathcal{D}_s denote the collections of regulatory and switching domains, respectively. The underlying regions in state space are denoted by $|\cdot|$, i.e. for example $|\mathcal{D}_r| = \bigcup_{\mathcal{D} \in \mathcal{D}_r} \mathcal{D}$ is the whole state space with all threshold hyperplanes removed. On this set, the dynamics will be called hereafter *regular dynamics*.

On $|\mathcal{D}_s|$ on the other hand, the flow is in general only defined in a weak sense, yielding what will be mentioned as the *singular dynamics*. In short, the latter is usually (de Jong et al., 2004; Ropers et al., 2006) presented as a set-valued version of the regular dynamics, applying the technique developed by Filippov, and first applied to systems of the form (1) in Gouzé and Sari (2003). We refer the interested reader to the mentioned literature for more thorough treatments of singular solutions. We just recall that walls such that flow lines are directed in opposite directions on their two sides are usually called *white (resp. black) walls* if repelling (resp. attracting). Moreover, it can be shown that the regular dynamics can be extended properly on any other wall – then called *transparent* – and thus on a dense subset of $|\mathcal{D}_s|$ in tame situations.

2.1.1. Regular dynamics

Regulatory domains form the main part of the state space. Moreover, on any $\mathcal{D} \in \mathcal{D}_r$, κ and Γ are constant, and thus Eq. (1) is affine. Its solution is explicitly known:

$$\forall i \quad \varphi_i(x, t) = x_i(t) = \frac{\kappa_i}{\gamma_i} + e^{-\gamma_i t} \left(x_i(0) - \frac{\kappa_i}{\gamma_i} \right), \quad (3)$$

and is valid for all $t \in \mathbb{R}_+$ such that $x(t) \in \mathcal{D}$. It follows immediately that

$$\phi(\mathcal{D}) = (\phi_1, \dots, \phi_n) = \left(\frac{\kappa_1}{\gamma_1}, \dots, \frac{\kappa_n}{\gamma_n} \right)$$

is an attractive equilibrium point for the flow (3). If it does not belong to \mathcal{D} , it is not a real equilibrium for system (1), since the flow will reach the boundary $\partial \mathcal{D}$ in finite time. At that time, the value of κ or Γ will change, and that of ϕ accordingly. The point $\phi(\mathcal{D})$ is often called *focal point* of the domain \mathcal{D} .

A convenient notation will be the following: each domain $\mathcal{D} \in \mathcal{D}_r$, with closure of the form $\text{cl}(\mathcal{D}) = \prod_{i=1}^n [\theta_i^{a_i-1}, \theta_i^{a_i}]$, can be represented by the integer vector $a = (a_1, \dots, a_n)$. Then one defines $\mathcal{V} = \prod_{i=1}^n \{1 \dots q_i\} \simeq \mathcal{D}_r$. Regular domains and their representatives in \mathcal{V} will be constantly identified, leading to talk about some “domain a ”, or noting focal points $\phi(a)$. Then, a *discretizing mapping* $d = (d_1 \dots d_n) : |\mathcal{D}_r| \rightarrow \mathcal{V}$ associates to a point lying inside a regular domain the discrete representative of this domain. One can also naturally define a set of transitions $\mathcal{E} \subset \mathcal{V} \times \mathcal{V}$, where $(a, b) \in \mathcal{E}$ iff some continuous trajectory successively crosses domains a and b . Hence one gets a *transition graph*, defined as the pair $\text{TG} = (\mathcal{V}, \mathcal{E})$. It can be shown that the following is appropriate, see e.g. Farcot and Gouzé (2006).

Definition 1 (Transition Graph). $\text{TG} = (\mathcal{V}, \mathcal{E})$, where $\mathcal{V} = \prod_{i=1}^n \{1 \dots q_i\}$, and $(a, b) \in \mathcal{E}$ if and only if $b = a$ and $d(\phi(a)) = a$, or $b \in \{a + \varepsilon_i \mathbf{e}_i \mid \varepsilon_i = \text{sign}(d_i(\phi(a)) - a_i) \neq 0\}$, where \mathbf{e}_i is the i th vector of the canonical basis of \mathbb{R}^n .

Observe that each vertex in TG may usually have several outgoing edges, i.e. this is a non-deterministic graph. Although in general many paths in TG do not represent any continuous trajectory, it can be shown that every regular solution of (1) admits a well-defined representative as an infinite path in TG, see Farcot (2006). An important point is that the transitions between adjacent regular domains are determined by the position of focal points.

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