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Piecewise Constant Feedback Control of Piecewise Affine Gene Network Models

Etienne Farcot and Jean-Luc Gouzé

COMORE INRIA, UR Sophia Antipolis
2004 route des Lucioles
BP 93, 06902 Sophia Antipolis, France
{`etienne.farcot`, `gouze`}@sophia.inria.fr

Abstract. The use of hybrid dynamical systems to model gene regulation is impelled by the switch-like behaviour of the latter. Piecewise affine differential equations is one of the most extensively studied among such kind of models. We propose an extension of this class, introducing some input variables. A special focus is given to degradation and production rates being affine functions of the inputs. Some generic control problems are proposed, formulated in terms of an underlying discrete structure. Piecewise constant feedback laws that solve these problems are characterized in terms of affine inequalities. These general feedback laws are then applied to a well-known two dimensional example: the *toggle switch*. It is shown how to control this system toward various behaviours, especially bistability and bisimilarity with a discrete quotient.

1 Introduction

This work deals with control theoretic aspect of a class of piecewise-affine differential equations, introduced in the 1970's [5] to model gene networks, and since widely studied, both theoretically [5], and to model concrete biological systems [2, 9]. Furthermore, recent advances have shown that gene networks may be synthesized in labs [4, 8]. This fact strongly motivates the elaboration of a control theory for such systems [6, 8]. This work is an attempt in this direction: input variables are added to the original models to represent some physico-chemical influence on production and degradation rates. Among concrete realizations, one may use specific inhibitors or activators, introduced in a chosen quantity. Other techniques, such as directed mutagenesis, the use of interfering RNA [7], would also fit within the present framework. Mathematically, similar approaches have been proposed for multiaffine dynamical systems on rectangles [1], which would apply here, but these more general techniques are much less efficient than the specific methods introduced here. More details and references can be found in [3].

2 Piecewise Affine Models

The general form of models considered here is:

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

The state vector x represents (mRNA or protein) concentrations: x_i is the expression level of the i th gene among n . Then, $u \in \mathcal{U} \subset \mathbb{R}_+^p$ is an input variable, meaning that additional biochemical species can be introduced in the system, or that some physical parameter (e.g. light intensity or temperature) is modified. In any case, input variables are bounded: $\mathcal{U} = \prod_{j=1}^p [0, U_j]$. $\kappa(x, u) \in \mathbb{R}_+^n$ is a production term, and $\Gamma(x, u)$ a diagonal matrix, with positive diagonal entries γ_i representing degradation rates. For a fixed u , both are piecewise constant functions of x with a rectangular underlying partition, due to the switch-like nature of gene regulation.

Succinctly, the continuous dynamics is as follows: in any rectangle \mathcal{D} in phase space, all trajectories are explicitly known, and tend toward a so-called *focal point* $\phi(\mathcal{D}, u)$. If $\phi(\mathcal{D}, u) \in \mathcal{D}$, one has a stable steady state and the system stays in \mathcal{D} forever. Otherwise, the system leaves \mathcal{D} in finite time, reaching another rectangular region. Repeating this provides well defined trajectories. This naturally leads to a discrete quotient of the dynamics, often called *state transition graph*, denoted $\text{TG}(u)$: rectangular regions are the states of this discrete system, and its transitions are defined as those pairs $(\mathcal{D}, \mathcal{D}')$ such that at least one continuous trajectory crosses \mathcal{D} and \mathcal{D}' successively.

3 Control Problems

We focus on piecewise constant feedback control laws: $u = u(x)$, and the restriction $u|_{\mathcal{D}}$ is constant for each \mathcal{D} . This relies on the assumption that threshold crossings, or switchings, can be detected accurately. Then, typical control problems are as below, where \mathcal{V} denotes the set of vertices of TG , i.e. of rectangular regions in state space:

Global Control Problem: Let TG^\heartsuit be a transition graph. Find a feedback law $u : \mathcal{V} \rightarrow \mathcal{U}$ such that $\text{TG}(u) = \text{TG}^\heartsuit$.

Locally, at a region \mathcal{D} , solving this problem is tantamount to finding an input $u(\mathcal{D})$ such that $\phi(\mathcal{D}, u(\mathcal{D})) \in \mathcal{D}'$, where \mathcal{D}' is easily deduced from the arrows in $\text{TG}(u)$ having \mathcal{D} as initial vertex. Since the vector $u(\mathcal{D})$ can be chosen arbitrarily in \mathcal{U} , this yields a *controllable focal set*, which is the whole set in which focal points can be chosen: $\phi(\mathcal{D}, \mathcal{U})$. A transition $(\mathcal{D}, \mathcal{D}')$ is then said *controllable* if $\phi(\mathcal{D}, \mathcal{U}) \cap \mathcal{D}' \neq \emptyset$. This non-emptiness condition is equivalent to a system of affine inequalities, in the case when production and degradation terms are affine functions of u : $\Gamma(\mathcal{D}, u) = \text{diag}(\Gamma(\mathcal{D})u + \gamma^0(\mathcal{D}))$, and $\kappa(\mathcal{D}, u) = \kappa(\mathcal{D})u + \kappa^0(\mathcal{D})$, where $\kappa(\mathcal{D}) \in \mathbb{R}^{n \times p}$, $\kappa^0(\mathcal{D}) \in \mathbb{R}_+^{n \times 1}$, $\Gamma(\mathcal{D}) \in \mathbb{R}^{n \times p}$ and $\gamma^0(\mathcal{D}) \in \mathbb{R}_+^{n \times 1}$.

A general form of local problem is then:

$$\exists u \in \mathcal{U}, \forall i \in \{1 \dots n\}, \theta_i^- < \phi_i(\mathcal{D}, u) < \theta_i^+ \quad (P)$$

and its solution is known. Denoting $T^\pm = \text{diag}(\theta_1^\pm \dots \theta_n^\pm) \in \mathbb{R}^{n \times n}$, one gets

Proposition 1 *An input u solves problem (P) if and only if it satisfies:*

$$\begin{cases} (\kappa(\mathcal{D}) - T^- \Gamma(\mathcal{D})) u > T^- \gamma^0(\mathcal{D}) - \kappa^0(\mathcal{D}) \\ (\kappa(\mathcal{D}) - T^+ \Gamma(\mathcal{D})) u < T^+ \gamma^0(\mathcal{D}) - \kappa^0(\mathcal{D}) \end{cases} \quad (\star)$$

Two particularly interesting forms of transitions are depicted in figure 1: if all transitions in $\text{TG}(u)$ are of one of these two forms, this graph yields a deterministic transition system, in which every path represents a continuous trajectory of the original system.

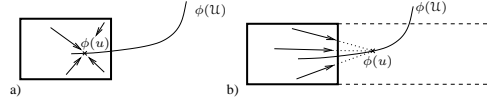


Fig. 1. Among all points in the focal set $\phi(U)$, one has to chose a particular u . Case a) is to make a region invariant, while in b), one has to find an input u such that $\phi(u)$ is situated 'behind' a single facet of the box under consideration.

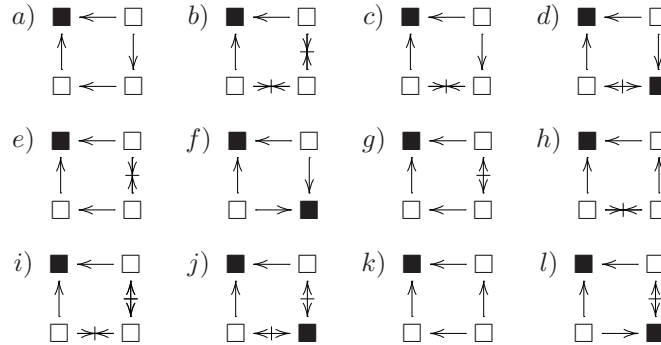
4 The Toggle Switch Example

One considers two genes inhibiting each other, often called *toggle switch*, and notably used as a building block of larger biological circuits [4, 6, 8]. Its biological function is that of a switch between two steady states, each being a long-term response to some transient induction. Here we suppose that the autonomous system is not bistable, and that a scalar input can affect the decay rates:

$$\begin{array}{c} \textcircled{1} \xrightarrow{-} \textcircled{2} \\ \textcircled{2} \xrightarrow{-} \textcircled{1} \end{array} \quad \begin{cases} \frac{dx_1}{dt} = \kappa_1^1 \mathfrak{s}^-(x_2, \theta_2^1) + \kappa_1^0 - (\gamma_1^1 u + \gamma_1^0) x_1 \\ \frac{dx_2}{dt} = \kappa_2^1 \mathfrak{s}^-(x_1, \theta_1^1) + \kappa_2^0 - (\gamma_2^1 u + \gamma_2^0) x_2 \end{cases}, \quad (2)$$

where $\mathfrak{s}^-(x, \theta)$ is the decreasing Heaviside (or step) function.

Solving a system of the form (\star) at each of the 4 rectangular regions in this system, yields all the possible graphs $\text{TG}(u)$. Below are those obtained for a particular set of parameters, see [3] for details. The disposition of vertices reflects the geometry of state space, and \blacksquare represent regions containing a steady state.



One can see that the upper-left vertex is always fixed, whatever the input value. The lower-right vertex, on the other hand, may be fixed or not. a) is the autonomous case. It appears that bi-stability may be ensured for transition graphs:

d), f), j) and l). Another objective may be to require that the graph be deterministic, with transitions as in figure 1 only. Here, this may be achieved by inputs associated to the graphs g) and j). The first presents a single global equilibrium, while j) is bistable.

5 Conclusion

Among modern advances in cell biology, *synthetic biology* is one of the most striking and promising topic, which might involve control theoretic problems in the years to come. For gene regulatory networks modeled by piecewise affine differential equations, we have characterized the piecewise constant feedback laws that solve some qualitative control problems. An important follow-up of this work would be the analysis of more global control problems. In particular, instead of an explicit transition graph, one may aim at satisfying a formal property, like bi-stability or bisimilarity as exemplified in section 4. Systematizing this with the aid of tools from model checking might lead to efficient algorithms. Also, the input u may model uncertainties of the system. In particular, a property that holds for all u (or whose negation is not controllable) could be called robust with respect to uncertainties, like for example the existence of at least one steady state in section 4.

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