

How to control a biological switch: a mathematical framework for the control of piecewise affine models of gene networks

Etienne Farcot, Jean-Luc Gouzé

▶ **To cite this version:**

Etienne Farcot, Jean-Luc Gouzé. How to control a biological switch: a mathematical framework for the control of piecewise affine models of gene networks. [Research Report] RR-5979, INRIA. 2006, pp.22. inria-00094853v2

HAL Id: inria-00094853
https://inria.hal.science/inria-00094853v2

Submitted on 21 Sep 2006

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

How to control a biological switch: a mathematical framework for the control of piecewise affine models of gene networks

Etienne Farcot — Jean-Luc Gouzé

N° 5979

Septembre 2006

Thème BIO



ISSN 0249-6399 ISRN INRIA/RR--5979--FR+ENG

INRIA
SOPHIA ANTIPOLIS

How to control a biological switch: a mathematical framework for the control of piecewise affine models of gene networks

Etienne Farcot*, Jean-Luc Gouzé†

Thème BIO — Systèmes biologiques
Projet Comore

Rapport de recherche n° 5979 — Septembre 2006 — 22 pages

Abstract: This article introduces preliminary 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. This class is illustrated with the example of two genes inhibiting each other. This example has been observed on real biological systems, and is known to present a bistable switch for some parameter values. Here, the parameters can be controlled. 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 the two dimensional example, showing how to control this system toward various behaviours, including the usual bi-stability, as well as situations involving a unique global equilibrium.

Key-words: gene regulatory networks, piecewise-linear, control

* etienne.farcot@sophia.inria.fr
† gouze@sophia.inria.fr

Unité de recherche INRIA Sophia Antipolis
2004, route des Lucioles, BP 93, 06902 Sophia Antipolis Cedex (France)
Téléphone : +33 4 92 38 77 77 — Télécopie : +33 4 92 38 77 65

Contrôler un interrupteur biologique. Un cadre mathématique pour le contrôle des modèles affines par morceaux de réseaux de régulation génétique

Résumé : Cet article présente certains résultats préliminaires sur le contrôle des réseaux génétiques, dans le contexte des modèles affines par morceaux. Une extension de cette classe de modèles est proposée, dans laquelle certaines variables d'entrée peuvent affecter, en particulier de manière affine, les principaux termes des équations. Cette nouvelle classe est illustrée au moyen d'un exemple impliquant deux gènes s'inhibant mutuellement. Un tel exemple a été observé biologiquement, et présente deux points d'équilibres stables pour certaines valeurs des paramètres, jouant un rôle d'interrupteur biologique. Quelques problèmes génériques de contrôle sont proposés, formulés de façon qualitative. Ceci en accord avec le caractère qualitatif sous-jacent aux modèles affines par morceaux. Des solutions à ces problèmes génériques sous forme de lois de contrôle retro-actives et constantes par morceaux sont caractérisées, au moyen de systèmes d'inéquations affines. Pour certaines sous-classes d'entrées, les solutions de ces inéquations sont décrites explicitement. Ces sous-classes d'entrées sont telles que chaque variable d'entrée agit sur une variable d'état au plus. Ces lois de contrôle sont illustrées sur l'exemple des deux gènes en mutuelle inhibition, montrant comment conduire ce système vers des comportements désirés, comme la bi-stabilité, ou l'équivalence de comportement avec un quotient discret.

Mots-clés : réseaux génétiques, linéaire par morceaux, contrôle

1 Introduction

This work deals with control theoretic aspect of a class of piecewise-affine systems of differential equations. This particular class has been introduced in the 1970's by Leon Glass [16] to model genetic and biochemical interaction networks. It has led to a long series of works by different authors, dealing with various aspects of these equations, *e.g.* [6, 11, 13, 16, 17]. Besides theoretical aspects, they have been used also as models of concrete biological systems [8, 22]. 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 in this domain have shown that such networks may not only be studied and analyzed on existing biological species, but also synthesized [2, 12, 15, 21], leading to artificial networks with a desired behaviour. This latter aspect especially motivates the elaboration of a theory for the control of these systems. This work is an attempt in this direction: piecewise affine models are treated in the case where production and degradation terms are possibly modified by an experimentalist, a fact we model by introducing continuous input variables $u \in \mathcal{U} \subset \mathbb{R}^p$.
The biological interpretation of inputs for systems of the form (1) is that an additional biochemical compound is added to the system, or some physical parameter is changed. Such a modification may then supposedly activate, or inhibit the production of species involved in the system without input. They might also have an effect on the degradation rates of some species. The latter may be of the same nature as the effect on production rates, or consist in a simultaneous scaling of all degradation rates, in case of a dilution of the growth medium. Among concrete realizations, one may mention the use of specific known inhibitors or activators, that could be introduced in a chosen quantity. Other techniques, such as directed mutagenesis, the use of interfering RNA (siRNA and miRNA) [20], could be used to 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. In section 3 we will present the formalization of models with inputs, which are suited to describe all above situations.
Other works have dealt with control problems involving models of biochemical networks. Especially, a series of papers consider control problems on multi-affine dynamical systems defined on rectangles [3, 4, 18]. The starting point of the different methods and algorithms presented in these works 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). Since the systems considered in the present paper are piecewise-affine, and more precisely affine in rectangular regions of state space, they are a special case of multi-affine system on each such rectangle. Hence, the mentioned procedures could be applied directly, and allow for the control of all trajectories toward a chosen facet. However, taking into account the specificity of our systems with respect to more general classes permits several improvements. First, we are not only able to control trajectories so that they escape a rectangle via a desired facet, but also to characterize inputs forcing all trajectories to stay in a rectangle for all times, and converge toward an asymptotically stable equilibrium point. Moreover, from an algorithmic point of view, it is worth mentioning that we propose a set of $2n$ inequalities to be checked for an input be valid, improving drastically the complexity of a blind application of general techniques designed for multi-affine systems.
In a more general perspective, the underlying motivation of this work is thus to provide some control-theoretic tools that are dedicated to the class of piecewise affine models. As already mentioned, the need for such theoretical tools is urged by recent advances in the design and analysis of elaborate biological systems, involving both synthetic and natural regulatory networks [19, 21]. Among these synthetic networks, some small sub-modules are often considered as important building blocks, to be plugged to larger systems. One of these blocks involves two genes inhibiting each other, and behaves as a *toggle switch* [15], for appropriate parameter values. A model of this simple system will serve us as an example.

The paper is organized in three main sections, all of which are illustrated using the toggle switch example. Hence, a first reading of the paper may rely on this sole example, and skip the more abstract material presented in the text, except maybe section 2. In the latter, the autonomous piecewise affine models of gene networks are introduced. Their main properties and some notations we use afterwards are presented. Then, in section 3, piecewise affine models with inputs are defined. The inputs are presented as piecewise constant feedback laws. The most obvious properties of systems with inputs are stated, and two subclasses are introduced. These are defined by special forms of dependence of the variables on the inputs: one class corresponds to production and decay terms being affine functions of the input u, the other class relies on the additional assumption that

each state variable may be controlled by at most one input variable. Then, in section 4, we formulate generic control problems. These problems are essentially qualitative, and concern the control of trajectories through a prescribed sequence of rectangular regions in phase space. As an elementary problem, we focus on the control of a single transition at a fixed rectangular domain, where the autonomous dynamics is affine. In a given domain $\mathcal{D}$, it is possible to provide necessary and sufficient conditions, so that a constant input u forces all trajectories to stay inside $\mathcal{D}$ for all subsequent times. Similar conditions are given, under which all trajectories escape $\mathcal{D}$, notably through a single prescribed facet. A final section discusses the results, and the possible outcomes of this work.
These methods permit, in the toggle switch example, to control a system toward bi-stability, when autonomous parameters only allow a single stable equilibrium. Also, it is possible to ensure that the behaviour of this system is entirely known from its most natural discrete abstraction. These two goals are achieved via a feedback control on degradation rates of the system.

2 Piecewise affine models: the autonomous case

2.1 Formal description of the model

The general form of the autonomous piecewise affine models we consider may be written as:

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

$\kappa : \mathbb{R}^n_+ \to \mathbb{R}^n_+$ is a piecewise constant production term and $\Gamma : \mathbb{R}^n_+ \to \mathbb{R}^{n\times n}_+$ is a diagonal matrix whose diagonal entries $\Gamma_{ii} = \gamma_i$, are piecewise constant functions of x, and represent degradation rates of variables in the system. The fact that κ and the γ_i's are piecewise constant 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 ith gene among n. As such, it ranges in some interval of nonnegative values noted $[0, \mathsf{max}_i]$. When this concentration x_i reaches a threshold value, some other gene in the network, say gene number j, is suddenly produced (resp. degraded) with a different production rate : the value of κ_j (resp. γ_j) changes. For each $i \in \{1 \cdots n\}$ there is thus a finite set of threshold values :

$$\Theta_i = \{\theta_i^1 < \cdots < \theta_i^{q_i - 1}\} \subset]0, \mathsf{max}_i[\tag{2}$$

The extreme values 0 and max_i are not thresholds, since they bound the values of x_i, and thus may not be crossed. However, a conventional notation will be : $\theta_i^0 = 0$, and $\theta_i^{q_i} = \mathsf{max}_i$.
Now, at a time t such that $x_i(t) \in \Theta_i$, there is some $j \in \{1 \cdots n\}$ such that $\kappa_j(x(t^+)) \neq \kappa_j(x(t^-))$, or $\gamma_j(x(t^+)) \neq \gamma_j(x(t^-))$.
It follows that each axis of the state space will be usefully partitioned into open segments between thresholds. Since the extreme values will not be crossed by the flow (see later), the first and last segments include one of their endpoints :

$$\mathcal{D}_i \in \left\{[\theta_i^0, \theta_i^1[, \ ]\theta_i^{q_i-1}, \theta_i^{q_i}]\right\} \cup \left\{]\theta_i^j, \theta_i^{j+1}[\,|\, j \in \{1 \cdots q_i - 2\}\right\} \cup \Theta_i \tag{3}$$

Each product $\mathcal{D} = \prod_{i=1}^n \mathcal{D}_i$ defines a rectangular *domain*, whose dimension is the number of $\mathcal{D}_i$ that are not singletons. When $\dim \mathcal{D} = n$, one usually says that it is a *regulatory domain*, or *regular domain*, and those domain with lower dimension are called *switching domains*, or *singular domains*, see [9]. We use the notation $\mathscr{D}$ to represent the set of all domains of the form above. Then, $\mathscr{D}_r$ will denote the set of all regulatory domains, and $\mathscr{D}_s$ the set of all switching domains. The underlying sets are respectively denoted $|\mathscr{D}|$, $|\mathscr{D}_r|$ and $|\mathscr{D}_s|$, *i.e.* for example $|\mathscr{D}| = \bigcup_{\mathcal{D}\in\mathscr{D}} \mathcal{D}$ is the whole state space, while $|\mathscr{D}_r| = \bigcup_{\mathcal{D}\in\mathscr{D}_r} \mathcal{D}$ is the same set with all threshold hyperplanes removed.

The dynamics on regular domains, called here *regular dynamics* can be defined quite simply, due to the simple expression of the flow in each $\mathcal{D} \in \mathscr{D}_r$. On sets of $\mathscr{D}_s$ on the other hand, the flow is in general not uniquely defined. It is anyway possible to define solutions in a rigorous way, yielding what will be mentioned as the *singular dynamics*. Let us describe these two parts of the dynamics successively.

2.1.1 Regular dynamics

Regulatory domains are of particular importance. They form the main part of state space, and the dynamics on them can be expressed quite simply. Actually, on such a domain $\mathcal{D}$, the production and degradation rates κ and γ are constant, and thus equation (1) is affine. Its solution is explicitly known, for each coordinate i :

$$\varphi_i(x,t) = x_i(t) = \frac{\kappa_i}{\gamma_i} - e^{-\gamma_i t}\left(x_i(0) - \frac{\kappa_i}{\gamma_i}\right), \tag{4}$$

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

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

is an attractive equilibrium point for the flow (4). If it does not belong to $\mathcal{D}$, it is not a real equilibrium for the 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 $\mathcal{D}$. Then, the continuous flow can be reduced to a discrete-time dynamical system, with a state space supported by the boundaries of boxes in $\mathscr{D}_r$. This system will be precised in section 2.2.

2.1.2 Singular dynamics

On singular domains, the piecewise constant functions κ and γ_i are not defined, and there is thus no chance to apply standard theorems about existence and unicity of solutions of (1). As a remedy, one has to consider a set-valued version of the regular dynamics, applying the general notion of solution of a differential equation with discontinuous right-hand side introduced by Filippov [14]. Solutions, in this sense, that stay in a singular domain for a while are often called *sliding modes*. This technique was first applied to systems of the form (1) by Gouzé and Sari, in [17], and has been used in several studies since this first work, for example [8, 9, 22, 6]. We refer the interested reader to the mentioned literature for more thorough treatments of singular solutions. What will be needed in this paper is the fact that solutions can be rigorously defined on $\mathscr{D}_s$.

2.2 Discrete representations

Since models of the form (1) are essentially qualitative, it is common to consider a discrete – both in time and space – analogue, which only yields a coarse grained description of the dynamics. In the context of gene regulation network models, this qualitative representative is usually seen using a *transition graph* $\mathsf{TG} = (\mathcal{V}, \mathcal{E})$, where $\mathcal{V}$ is in bijective correspondence with the finite set of regulatory domains, $\mathscr{D}_r$, described in the previous section. In other words, this graph only bears the regular the dynamics. Some information about the singular dynamics may however be retrieved from this graph.

A convenient notation for $\mathcal{V}$ will be the following: the domain $\mathcal{D} \in \mathscr{D}_r$, with closure of the form $cl(\mathcal{D}) = \prod_{i=1}^{n}[\theta_i^{a_i-1}, \theta_i^{a_i}]$, is represented in $\mathcal{V}$ by the integer vector $a = (a_1, \ldots, a_n)$. For sake of brevity, such vectors will often be denoted as strings : $a = a_1 \ldots a_n$. Hence, $\mathcal{V} = \prod_{i=1}^{n}\{1 \cdots q_i\}$. We note $\mathsf{c} : \mathscr{D}_r \to \mathcal{V}$ the bijective *coding application*, which maps a domain to its corresponding vertex in $\mathcal{V}$. We sometimes write the code of a regular domain as a subscript : $\mathcal{D}_a = \mathsf{c}^{-1}(a)$.

Then, $\mathcal{E} \subset \mathcal{V} \times \mathcal{V}$ is a set of transitions, defined informally by the existence of a continuous trajectory between their initial and terminal vertices. A precise definition will be given later on. Observe that each vertex in TG may usually have several outgoing edges, *i.e.* this is a non deterministic graph. Adopting a global point of view, full trajectories of the original system (1) are represented by infinite paths in TG. This qualitative version of the dynamics induces of course a loss of information : each regular continuous trajectory admits a well-defined qualitative representative – under mild assumptions, given later – but in general many paths in TG do not represent any continuous trajectory.

Since the finite sets $\mathscr{D}_r$ and $\mathcal{V}$ are in bijective correspondence via c, we indifferently consider ϕ as a map with one or the other of these two sets as domain of definition, *i.e.* one identifies ϕ and $\phi \circ \mathsf{c}^{-1}$. Let us introduce another useful mapping, namely the *discretizing mapping* $\mathsf{d} = (\mathsf{d}_1 \ldots \mathsf{d}_n) : |\mathscr{D}_r| \to \mathcal{V}$, which associates to a point lying inside a regular domain the discrete representative of this domain. This is similar to c, except that it acts on points in state space, whereas c acts on the set of regular domains.

The transitions of $\mathcal{E}$ can be described more precisely. Actually, it can be shown that a transition $a \to a'$ may

occur if and only if $\phi(a)$ has the same position as a' with respect to a. By this we mean that $a'_i - a_i$ and $\phi_i(a) - a_i$ have the same sign, for all i. Hence, $\mathcal{E}$ can be described in a purely combinatorial manner, *i.e.* in terms of $\mathsf{d}_i \circ \phi$, which is a finite map $\mathcal{V} \to \mathcal{V}$. Then, regular trajectories correspond to transitions $a \to a'$ such that $a - a' = \pm \mathbf{e}_i$, for some vector $\mathbf{e}_i$ of the canonical basis of $\mathbb{R}^n$. For more details we refer to [13], and references therein. Since trajectories hitting some codimension 2 or more singular domain are rare, and involve technicalities in their definition, see section 2.1.2, we ignore them in the following.
To summarize this discussion, we may now provide a more explicit definition of TG.

Definition 1 (transition graph)**.** $\mathsf{TG} = (\mathcal{V}, \mathcal{E})$, where:

- $\mathcal{V} = \prod_{i=1}^{n} \{1 \cdots q_i\}$.
- $(a, b) \in \mathcal{E}$ if and only if $b = a$ and $\phi(a) = a$, or

$$b \in \{a + \mathbf{e}_i \,|\, i \in \mathsf{d}_i(\phi(a)) > a_i\} \cup \{a - \mathbf{e}_i \,|\, i \in \mathsf{d}_i(\phi(a)) < a_i\}.$$

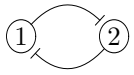
Since the transitions between adjacent regular domains are determined by the position of focal points, the following hypothesis will be useful in the rest of the paper :

H1. $\quad \forall \mathcal{D} \in \mathscr{D}_r, \quad \phi(\mathcal{D}) \in |\mathscr{D}_r|.$

Hypothesis **H1** means that the focal points all lie inside the domain $|\mathscr{D}|$, and that none of them is on the boundary of a box. The first aspect implies that $|\mathscr{D}|$ is positively invariant, and thus can be considered as the only region where relevant dynamics take place. The second one excludes a (rare) case which would otherwise cause technical complications without improving the model.

Before concluding this section with an example, it remains to say that TG, as a support of a discrete dynamical system, induces spurious trajectories in general. The proportion of those infinite paths in TG that have a counterpart in a continuous system of the form (1), called *admissible trajectories*, can even be negligible, asymptotically [13]. One possible consequence – though not a major purpose – of the control theoretic aspects we deal with in the next section, could be to reduce the discrepancy between the regular part of a piecewise affine system and its symbolic representation.

Example. *Let us introduce a well-known example with two variables, that will serve as a guide for intuition throughout this paper. It consists in two genes which inhibit each other, and behaves as a switch between two stable equilibria. This simple loop has been investigated both mathematically [7], using a model with smooth sigmoids as activation functions, and experimentally [15]. In the latter, this network has been synthesized, showing that its real-life behaviour is in accordance with mathematical analysis. The latter predicts a phase portrait (for a large set of parameter values) presenting two stable steady states, and a saddle point whose unstable manifold forms the boundary between the attracting basins of the two other equilibria. The biological function of such a system is that of a switch between two steady states: each of these is a long-term, permanent response to some transient induction, which may lead to one or the other of the steady states. This is the* toggle switch *mentioned in the introduction, and serving as a building block for larger biological circuits [19, 21].*
In the context of piecewise-affine models of the form (1), the interaction graph and system of differential equations describing such a system are thus the following:



$$\begin{cases} \dfrac{dx_1}{dt} &= \kappa_1^0 + \kappa_1^1 \mathsf{s}^-(x_2, \theta_2^1) - \gamma_1 x_1 \\ \dfrac{dx_2}{dt} &= \kappa_2^0 + \kappa_2^1 \mathsf{s}^-(x_1, \theta_1^1) - \gamma_2 x_2 \end{cases}, \tag{5}$$

where $\mathsf{s}^-(x, \theta)$ is the decreasing Heaviside (or step) function, which is one when $x < \theta$, and zero when $x \geqslant \theta$. A usual notation for the interaction graph uses $\dashv$ to denote inhibition, and $\to$ to denote activation.
The two constants κ_i^0 represent the lowest level of production rates of the two species in interaction. It will be zero in general, but may also be a very low positive constant, in some cases where a gene needs to be expressed permanently. Remark that in this example, gene interactions only affects production terms, and thus degradation rates γ_i are positive constants.

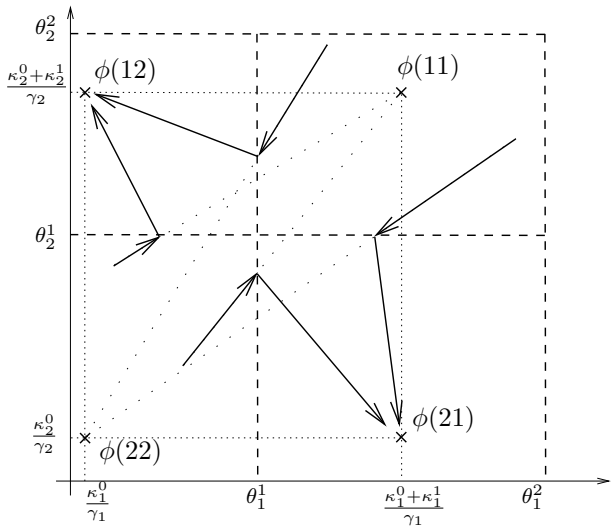


Figure 1: The dashed lines represent threshold hyperplanes, and the dotted lines indicate the coordinate of the focal points in the four regular domains. Arrows represent schematic flow lines, pointed toward focal points. This phase space is consistent with the transition graph : domains 11 *and* 22 *both escape towards* 12 *and* 21*, and each of these contains an asymptotically stable equilibrium point, namely its own focal point. Note that pieces of trajectories are depicted as straight lines above, which is the case when all degradation rates γ_i coincide. However, this only aims at simplifying the picture, and the γ_i are not supposed uniform in the present study.*

Then, the transition graph of (5) is easily found to be

$$\mathsf{TG} = \quad \boxed{12} \longleftarrow \boxed{22} \quad \uparrow \quad \downarrow \quad \boxed{11} \longrightarrow \boxed{21} \tag{6}$$

provided the parameters are consistent with the interaction graph of the system. The constraints that must be fulfilled to ensure this consistency are the following:

$$\left\{ \frac{\kappa_1^0}{\gamma_1} < \theta_1^1, \qquad \frac{\kappa_2^0}{\gamma_2} < \theta_2^1, \qquad \frac{\kappa_1^0+\kappa_1^1}{\gamma_1} > \theta_1^1, \qquad \frac{\kappa_2^0+\kappa_2^1}{\gamma_2} > \theta_2^1 \right\} \tag{7}$$

Actually, the Heaviside function s^- *is decreasing, always denoting an inhibition effect. But if the above conditions are not satisfied, the inhibition is not effective, in the sense that it does not lead to a change of state in* TG*. Geometrically, the conditions ensure that focal points belong to the half-spaces they ought to, and that the system presents bi-stability. They might be called* structural constraints *on parameters. The phase space of system (5) may be depicted, see figure 1.*

3 Control of piecewise affine systems

In this section the models with inputs are defined, and their main properties are introduced. Starting with a general form of systems with inputs, we provide a more and more particular formulation, in order to obtain properties that are not expressible for the most general systems, but hold in the specific cases we exhibit.

3.1 Some plausible types of controls

The biological interpretation of inputs for systems of the form (1) is that an additional biochemical compound is added to the system, or some physical parameter is changed. Such a modification may then supposedly activate, or inhibit the production of species involved in the system without input. They might also have an effect of dilution, thus increasing the degradation rates of some species. In order to take all these plausible effects into

account in a single model, we propose the following general form of systems with inputs:

$$\frac{dx}{dt} = \kappa(x,u) - \Gamma(x,u)x \tag{8}$$

where $u \in \mathcal{U}$ is an input variable that can be chosen in its domain $\mathcal{U} \subset \mathbb{R}_+^p$, meaning that p additional biochemical species can be introduced in the system by an experimentalist, or a robot. It may also represent stimuli that are not of chemical nature, such as for example modifications of the light intensity or temperature. In any case, we shall only deal with bounded input variables. We denote the upper bounds of each input coordinate by p positive real numbers U_j, providing us with an input domain of the form

$$\mathcal{U} = \prod_{j=1}^{p} [0,\, U_j].$$

It seems reasonable that $p \leqslant n$, a fact we assume in the sequel. This continuous set of inputs will always be used hereafter. If discrete variables are better suited to describe some input quantities (for example if a gene is completely turned on, or off), it will suffice to consider finite subsets of the intervals $[0,\, U_j]$, and restrict all the treatments that we propose to these subsets. For example, if the input u_j takes values in some finite set $\mathcal{U}_j = \{u_j^1, \dots u_j^k\}$, with ordered u_j^i's, one shall set $U_j = u_j^k$, so that $\mathcal{U}_j \subset [0,\, U_j]$. Then, one may solve the corresponding continuous problem, and check afterwards whether at least one of the discrete values in $\mathcal{U}_j$ is also a solution or not.

In the present work, we focus on piecewise constant feedback control laws. In other words $u = u(x)$, and moreover the restriction $u|_{\mathcal{D}}$ is constant for each $\mathcal{D} \in \mathscr{D}_r$. This relies on the assumption that threshold crossings, *i.e.* switchings, can be detected accurately, and with no significant time delay. A consequence of this choice is that the input may be unambiguously seen as a function $\mathcal{V} \to \mathcal{U}$, see sections 2.1, 2.2 for general notations and 4.1 for more detail on the definition of u.

The precise form of $\kappa(x,\cdot)$ and $\Gamma(x,\cdot)$, seen as functions of the input u, may not be arbitrary, and should be realizable in real systems. More precise forms of these functions will be assumed later on, but we first provide the basic facts that do not depend directly of this specific form.

The choice of a feedback loop depending on the regulatory domain of the current state, rather than on its precise quantitative value, has nice consequences on the dynamics. Actually, the behaviour of the system is exactly similar to what is described in section 2, except that focal points depend on the input u. The latter being constant in each regulatory domain $\mathcal{D}_a$, the flow of (8) clearly takes the same form as in the autonomous case, the focal point of such a domain being now of the form :

$$\phi(a,u) = \left(\frac{\kappa_1(a,u)}{\gamma_1(a,u)} \cdots \frac{\kappa_n(a,u)}{\gamma_n(a,u)} \right), \tag{9}$$

where the vector u has a fixed value, that can be chosen according to some specified purpose.

The *controllable focal set* is the whole set in which focal points can be chosen, *i.e.* the set of all focal points obtained by varying the input in its whole domain : $\phi(a,\mathcal{U})$. Although the term *focal set* is often employed when using Filippov solutions [17], with a quite different meaning, we shall sometimes use it as an abbreviation, omitting *controllable*. This will never be ambiguous in the present study.

Since $\mathcal{U}$ will most often be a compact subspace of $\mathbb{R}_+^p$, and $\phi(a,\cdot)$ a continuous map, the focal set will generally be a p-dimensional compact subspace of $\mathbb{R}_+^n$. The possible successors of the domain $\mathcal{D}_a$ will then be given by the regular domains with subscript in the following set:

$$\mathcal{S}(a) = \{a + \operatorname{sign}(b-a) \,|\, b \in \mathcal{V},\, \mathcal{D}_b \cap \phi(a,\mathcal{U}) \neq \varnothing\}. \tag{10}$$

where $\operatorname{sign} : \mathbb{R} \to \{-1,0,1\}$ gives the sign of its argument.

The use of $\operatorname{sign}(b-a)$ is intended to define successors only among regular domains that are adjacent to $\mathcal{D}_a$, even in the case when $\mathcal{D}_b$ is not.

This focal set is constrained by the specific choice of inputs. Let first assume that both production and degradation terms are affine functions of u, in each regular domain. Then, $\phi(a,\cdot)$ will be a fractional linear map and computing $\mathcal{S}(a)$, can be understood as computing the intersection of an algebraic manifold and a n-rectangle, as will be detailed in sections 3.2 and 4.2.

The following notation will be used in case of affine dependence on inputs:

$$\left\{\begin{array}{rcl}\kappa_i(x,u) & = & \displaystyle\sum_{j=1}^{p}\kappa_i^j(x)u_j+\kappa_i^0(x)\\ \gamma_i(x,u) & = & \displaystyle\sum_{j=1}^{p}\gamma_i^j(x)u_j+\gamma_i^0(x),\end{array}\right. \tag{11}$$

with piecewise constant functions κ_i^j and γ_i^j. This can be interpreted as follows, considering production rates, the case of degradation rates being identical. For each $i\in\{1\cdots n\}$, and for a fixed x, $\kappa_i(x,\cdot)$ is a function of u, and has the biological meaning of a production rate. Then, the κ_i^j functions can be understood as the coefficients of κ_i, once it is assumed that the latter is affine in u. Thus, these κ_i^j functions may not always have a definite biological meaning. They may be interpreted as the relative strengths of the different inputs, in their influence on κ_i. In some sense, this choice is mostly relevant in the case when there is no interaction amongst the inputs.
Now, for biochemical inputs, the autonomous case must correspond to an absence of input, *i.e.* to $u_i=0$. For physical inputs the autonomous case may in general correspond to a nonzero input value, which could then be decreased or increased by the user. Thus, in order to allow a decrease of production or degradation rates when the input is varied, the coefficients in (11) can possibly be negative. However, it is required that, for all i, $\gamma_i(x,u)>0$ because biochemical compounds always degrade. It is also important that $\kappa_i(x,u)\geqslant 0$, since otherwise the concentration x_i could reach negative values. These requirements can be satisfied by imposing simple restrictions on the parameters in (11).

H2. *For all $i\in\{1\cdots n\}$, and all $a\in\mathcal{V}$, $\gamma_i^0(a)>0$, $\kappa_i^0(a)\geqslant 0$. Moreover*

$$\left\{\begin{array}{rcl}\displaystyle\sum_{\substack{j\in\{1\cdots p\}\\ \gamma_i^j(a)<0}}\gamma_i^j(a)U_j & > & -\gamma_i^0(a)\\ \displaystyle\sum_{\substack{j\in\{1\cdots p\}\\ \kappa_i^j(a)<0}}\kappa_i^j(a)U_j & \geqslant & -\kappa_i^0(a)\end{array}\right.$$

Actually, the left-hand sides above are easily seen to be the infimum, among all inputs, of the linear parts of affine functions κ_i and γ_i. Remark that since we consider feedback control in this work, the inputs above should be written $u_j(x)$, but this has no influence on the expression of κ_i and γ_i as functions of the inputs, and would harden the reading of (11).
For any x in a fixed regulatory domain $\mathcal{D}_a$, all $\kappa_i^j(x)$ and $\gamma_i^j(x)$ are constant, and we shall write $\kappa_i^j(a)$ and $\kappa_i(a,u)$, as well as $\gamma_i^j(a)$ and $\gamma_i(a,u)$.
The coefficients in equation (11) may be put in matrix form: let $\kappa(x)=(\kappa_i^j(x))_{i,j}\in\mathbb{R}^{n\times p}$, $\kappa^0(x)=(\kappa_i^0(x))_i\in\mathbb{R}_+^{n\times 1}$, $\Gamma(x)=(\gamma_i^j(x))_{i,j}\in\mathbb{R}^{n\times p}$ and $\gamma^0(x)=(\gamma_i^0(x))_i\in\mathbb{R}_+^{n\times 1}$. Then, equation (11) can also be written as:

$$\Gamma(x,u)=\mathrm{diag}\left(\Gamma(x)u+\gamma^0(x)\right)\qquad\text{and}\qquad\kappa(x,u)=\kappa(x)u+\kappa^0(x). \tag{12}$$

Geometrically, **H2** imposes that matrices $\kappa(a)$ and $\Gamma(a)$ belong to polyhedral sets in $\mathbb{R}^{n\times p}$, which are defined in terms of the maximal input values U_j. Identifying $\mathbb{R}^{n\times p}$ and $\mathbb{R}^{np}$, these polyhedral sets contain the nonnegative orthant and for each other orthant, a simplex defined by the inequalities above (and those defining the orthant's boundary).

3.2 Classes of systems with inputs

In our chase for specific inputs, we may further assume that at most one input variable is acting on each state variable. Then, either the influence of u appears on the production term, or on the decay rate of each x_i. This can be formulated using two functions $\sigma,\varsigma:\{1\cdots n\}\to\{1\cdots p\}$, such that for each i in $\{1\cdots n\}$, all coefficients in the matrices $\kappa(x)$ and $\Gamma(x)$ are zero, except maybe $\kappa_i^{\sigma(i)}$ and $\gamma_i^{\varsigma(i)}$.

$$\left\{\begin{array}{rcl}\kappa_i(x,u) & = & \kappa_i^{\sigma(i)}(x)u_{\sigma(i)}+\kappa_i^0(x)\\ \gamma_i(x,u) & = & \gamma_i^{\varsigma(i)}(x)u_{\varsigma(i)}+\gamma_i^0(x).\end{array}\right. \tag{13}$$

and moreover

$$\forall i \in \{1 \cdots n\}, \forall a \in \mathcal{V}, \quad \text{either } \kappa_i^{\sigma(i)}(a) = 0 \quad \text{or } \gamma_i^{\varsigma(i)}(a) = 0. \tag{14}$$

Note that both may still be zero.
In order to clarify further discussions, we now give a name to the two classes of inputs we have presented. These are the only classes of systems that we shall consider in the following.

C1 (affine dependance on inputs)**.**
Refers to systems of the form (8), where production and degradation terms are all affine functions of u, of the form (11).

C2 (single input per variable)**.**
Refers to systems of the class **C1***, where at most one input affects each variable x_i, i.e. (13) and (14) are satisfied.*

Let us investigate more precisely the shape of the focal set $\phi(a, \mathcal{U})$, when the system belongs to the class **C1**. By definition, this set consists of those points $\varphi \in \mathbb{R}^n$ such that $\varphi = \phi(a, u)$ – also noted $\phi(u)$ in this discussion – for some $u \in \mathcal{U}$. Since a is fixed, one also abbreviates $\kappa_i^j(a)$ and $\gamma_i^j(a)$ into κ_i^j and γ_i^j, respectively. We shall do so in the rest of the paper, as soon as no confusion is possible. For **C1** systems, this writes

$$\forall i \in \{1 \cdots n\}, \quad \frac{\sum_{j=1}^p \kappa_i^j u_j + \kappa_i^0}{\sum_{j=1}^p \gamma_i^j u_j + \gamma_i^0} = \varphi_i,$$

where the denominator is nonzero, thanks to **H2**. Thus, the above may also be written as

$$\forall i \in \{1 \cdots n\}, \quad \sum_{j=1}^p \left(\kappa_i^j - \gamma_i^j \varphi_i\right) u_j = \gamma_i^0 \varphi_i - \kappa_i^0.$$

This is apparently an affine system of equations in $u_1, \ldots, u_p$. This system defines a manifold in $\mathbb{R}^n$, which is parameterized by the inputs u_i. Let us describe further properties of this manifold, without boundedness assumption on the u_i's. Hence, the controllable focal set $\phi(\mathcal{U})$ will be a bounded subset of the manifold we describe hereafter.
The solution of such a system, if it exists, may be expressed formally using Cramer formulas. Let us reason further in a formal way, ignoring problems related to degenerate systems or domains of definition, especially when dealing with rational functions. Since the coordinates $\varphi_1, \ldots, \varphi_n$ appear (linearly) in the coefficients of this system, Cramer formulas will lead to express each u_j as a (multivariate) rational function of φ's coordinates, say $u_j = \mathcal{R}_j(\varphi_1, \ldots, \varphi_n)$. Then, for each $i \in \{1 \cdots n\}$, one is led to $\varphi_i = \phi_i\left(\mathcal{R}_1(\varphi), \ldots, \mathcal{R}_p(\varphi)\right)$. Since each ϕ_i is a linear rational function of $u_1, \ldots, u_p$, the right hand side in the last equality is a multivariate rational function of $\varphi_1, \ldots, \varphi_n$. On a suitable domain, this may also be expressed as a vanishing condition on a multivariate polynomial in $\varphi_1, \ldots, \varphi_n$. Such a condition defines an algebraic manifold $\mathscr{M}$, of which $\phi(\mathcal{U})$ is thus a subset.
Although we do not detail further this discussion, the computations mentioned above may lead to practical implementations, be they symbolic or numeric. This might be a topic for later research. Let us only mention the fact that additional conditions, such as for instance symmetries on parameter values, may lead to $\mathscr{M}$ being more tractable, from an algorithmic point of view, *e.g.* $\mathscr{M}$ may be polyhedral.

Remark 1. It may happen that some inputs be ineffective in practice, due to hidden relations between κ_i and γ_i for some i, which make the ratio defining ϕ_i vanish into a constant. Avoiding this may be guaranteed for the class **C1**, in explicit terms:

H3. *For all* $i \in \{1 \cdots p\}, \exists j \in \{1 \cdots p\} \quad \gamma_i^0 \kappa_i^j \neq \gamma_i^j \kappa_i^0$.

Actually, some $\phi_i(a, \cdot)$ does not depend on u if whatever the latter is, $\kappa_i(a, u) = C\gamma_i(a, u)$, for some constant C. In other words, and for the class **C1**,

$$\sum_{j=1}^p \left(\kappa_i^j - C\gamma_i^j\right) u_j + \kappa_i^0 - C\gamma_i^0 = 0,$$

for all u, and omitting a. It appears that the left-hand side above, seen as a function of u, is an affine mapping, whose linear part either has rank 1, or it is identically zero. In the first case, the above equation cannot stand for all u. Hence all coefficients $\kappa_i^j - C\gamma_i^j$, for $j \in \{0 \cdots p\}$, must be zero for a degeneracy to occur, in which case all ratios κ_i^j/γ_i^j are equal (to C). Whence the formulation of **H3**. This hypothesis will always be done when dealing with **C1**, and thus **C2**, systems.

Note that **H3** only excludes very strong degeneracies. In particular, it is still possible when this hypothesis is satisfied, that ϕ is constant on a full subspace of $\mathcal{U}$. Anyway this subspace will be of dimension at most $p-1$ and thus of measure zero in $\mathcal{U}$.
Even if κ and Γ depend nonlinearly on u, it is relevant to describe the discrete representative of a system with input like (8). This is the theme of the next section. Before this, let us return to our example.

Example (continued 1). *Let us carry on with the already introduced example, involving two genes inhibiting each other. We suppose now that the structural constraints (7) are not satisfied, so that the autonomous system does not present bi-stability. We assume moreover that there is a way to control the degradation rates of the two genes, and only them. Hence we deal with a system in the class* **C2**. *Since, in the autonomous case, the degradation rates were constant, i.e. independent of the state vector x, one is here in a particular of equations (8) belonging to* **C2**. *The system of differential equations describing such a system are of the following form:*

$$\left\{ \begin{array}{rcl} \dfrac{dx_1}{dt} & = & \lambda_1^1 \mathsf{s}^-(x_2, \theta_2^1) + \lambda_1^0 - (\gamma_1^1 u_1 + \gamma_1^0) x_1 \\ \dfrac{dx_2}{dt} & = & \lambda_2^1 \mathsf{s}^-(x_1, \theta_1^1) + \lambda_2^0 - (\gamma_2^1 u_2 + \gamma_2^0) x_2 \end{array} \right. , \tag{15}$$

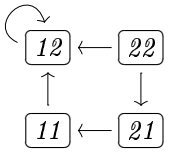
in the case of two inputs. If there is a scalar input u, one obtains a system of the form above, but where $u_1 = u_2 = u$. Since the inputs do not influence production rates in this particular example, the matrix-valued function $\kappa(x)$ is zero, see equation (12). In other words, and according to previous notations, one has here :

$$\kappa_1^0(x) = \lambda_1^1 \mathsf{s}^-(x_2, \theta_2^1) + \lambda_1^0, \quad \textit{and} \quad \kappa_2^0(x) = \lambda_2^1 \mathsf{s}^-(x_1, \theta_1^1) + \lambda_2^0.$$

Now, the transition graph of the autonomous case is given for the special input value u^0, according to **H2**. *The constraints that we suppose are fulfilled now take the following form :*

$$\Big\{ \frac{\lambda_1^0}{\gamma_1^0 + \gamma_1^1 u_1^0} < \theta_1^1, \qquad \frac{\lambda_2^0}{\gamma_2^0 + \gamma_2^1 u_2^0} < \theta_2^1, \qquad \frac{\lambda_1^0 + \lambda_1^1}{\gamma_1^0 + \gamma_1^1 u_1^0} < \theta_1^1, \qquad \frac{\lambda_2^0 + \lambda_2^1}{\gamma_2^0 + \gamma_2^1 u_2^0} > \theta_2^1 \Big\}. \tag{16}$$

The only difference with (7) appears in the third term above. It is not hard to show that this leads to the following transition graph:

$\mathsf{TG}(u^0) =$ 

The left-hand sides of the four inequalities (16) are the coordinate values of focal points, at the autonomous level u^0 of inputs. If, instead, u varies, these ratios change accordingly, yielding the focal set. Let us draw a picture of the phase space of system (15), in the cases when u is two dimensional, and scalar.
First, we treat the two-inputs case (15). With previous notations, one has $\varsigma = id$, since each u_i influences x_i, and whatever σ is it has no effect since $\kappa(x) = 0$. Here, the polynomial equations defining the manifold $\mathscr{M}$ supporting the controllable focal set are always satisfied. In other words, $\mathscr{M}$ is the whole plane, and focal sets are full-dimensional (i.e. two-dimensional) rectangles in phase space.
Observe that if $\lambda_i^0 = 0$, meaning that genes 1 and 2 are not expressed at all when turned off, $\mathscr{M}$ can be of dimension less than 2. Actually, $\kappa_1^0(x) = \lambda_1^1 \mathsf{s}^-(x_2, \theta_2^1)$ equals zero whenever $x_2 > \theta_2^1$, and similarly for $\kappa_2(x)$ with respect to x_1. Since $\kappa_i^0(x)$ is the numerator of $\phi_i(x)$, the latter is zero, whatever the input is. Hence, in the domains where at least one x_i is greater than its threshold, the corresponding focal set in constrained on a coordinate axis. This discussion is summarized in figure 2.

Now, suppose the input is a scalar, which we retrieve from (15) by setting $u_1 = u_2 = u$, as mentioned above. This gives:

$$\left\{ \begin{array}{rcl} \dfrac{dx_1}{dt} & = & \lambda_1^1 \mathsf{s}^-(x_2, \theta_2^1) + \lambda_1^0 - (\gamma_1^1 u + \gamma_1^0) x_1 \\ \dfrac{dx_2}{dt} & = & \lambda_2^1 \mathsf{s}^-(x_1, \theta_1^1) + \lambda_2^0 - (\gamma_2^1 u + \gamma_2^0) x_2 \end{array} \right.$$

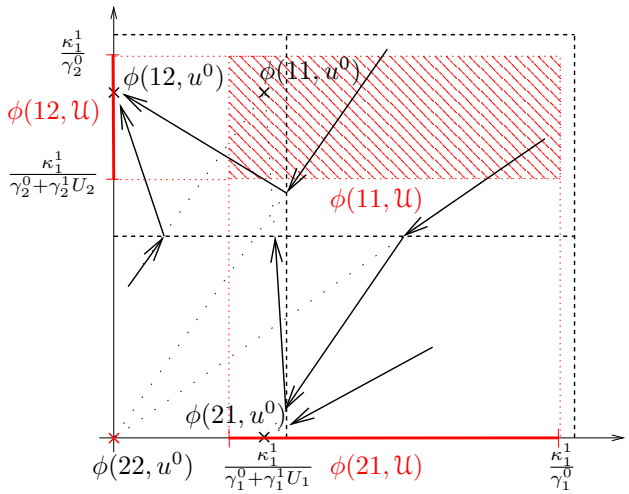


Figure 2: A system of the form (15), with the additional hypothesis that $\lambda_1^0 = \lambda_2^0 = 0$. As in figure 1, threshold lines are dashed. Focal sets are coloured in red. The autonomous case (i.e. $u = u^0$) leads to focal points that are situated in accordance with conditions (16). The arrows sketch pieces of trajectories of this autonomous case.

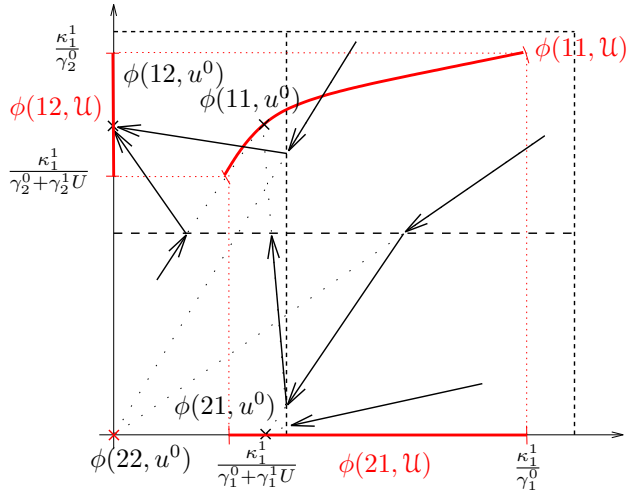


Figure 3: A system of the form (15), with one single input $u = u_1 = u_2$. We still suppose $\lambda_1^0 = \lambda_2^0 = 0$. Focal sets are coloured in red. Observe that in the case with two inputs, figure 2, focal sets are the rectangular envelope (i.e. smallest rectangle containing them) of those here depicted. Here again, the arrows represent pieces of trajectories of this autonomous case.

One has now the following:

$$\phi_i(a) = \frac{\kappa_i^0(a)}{\gamma_i^0 + \gamma_i^1 u}, \quad \textit{so that} \quad u = \frac{\kappa_i^0(a) - \gamma_i^0 \phi_i(a)}{\gamma_i^1 \phi_i(a)}$$

for $i \in \{1,2\}$, and any value of the qualitative state a. From this, the following constraint is derived, omitting a:

$$\left(\gamma_1^1\gamma_2^0 - \gamma_2^1\gamma_1^0\right)\phi_1\phi_2 + \kappa_1^0\gamma_2^1\phi_2 - \kappa_2^0\gamma_1^1\phi_1 = 0, \tag{17}$$

which is the polynomial equation in ϕ_1, ϕ_2 defining the manifold we call $\mathscr{M}$. Such an equation, using the additional fact that u belongs to the bounded set $[0, U]$, defines for instance $\phi(\mathcal{U})$ to be a piece of hyperbola, as depicted schematically in figure 3.

What can be foreseen is that even if the autonomous case presents a single global, stable equilibrium, some input values may lead to a bistable phase portrait. This guess will be confirmed later.

Next section deals with elementary cases of such local problems, which can be thought of as the required steps toward solving global problems of the form 1.

4 Specific control problems

Due to the intrinsically qualitative nature of piecewise affine models, it is possible here to formulate control problems in qualitative terms. This will be done with the aid of a discrete version of the control systems we investigate. We first present such discrete systems, and then more specific control problems will be considered.

4.1 Discrete mapping of systems with input

Once a feedback law is chosen, a system of the form (8) is equivalent to an autonomous system of the form (1). Then, a discrete system can be constructed, as described in section 2.2. Recall that the input laws we are looking for are assumed to be piecewise constant. In the form given at the beginning of the previous section, u is then a map $u : |\mathscr{D}_r| \to \mathcal{U}$. Since this map is supposed constant on each regular domain $\mathcal{D} \in \mathscr{D}_r$, there is a well-defined map from the set of regulatory domains to the set of input values, namely $\mathscr{D}_r \to \mathcal{U}$, $\mathcal{D} \mapsto u|_{\mathcal{D}}$. The latter will be identified with u in the following. Since $\mathsf{c} : \mathscr{D}_r \to \mathcal{V}$ is a bijection, we can also identify u and $u \circ \mathsf{c}^{-1}$, when dealing with the vertices of a transition graph instead of the domains in a continuous state space. Now, varying u may lead to changes of the discrete representative of the system under consideration. Refining the definition of discrete successors provided in (10), the following arises naturally: for $u \in \mathcal{U}$,

$$\mathcal{S}(a,u) = a + \operatorname{sign}\left(\mathsf{d}\big(\phi(a,u)\big) - a\right). \tag{18}$$

Actually, for a fixed u, and in a fixed domain $\mathcal{D}_a$, the corresponding focal point is $\phi(a,u)$. Under **H1**, there is a single domain $\mathcal{D}_b$ containing this focal point, whose subscript is given by $\mathsf{d}\big(\phi(a,u)\big)$. Then, varying a feedback law u amounts to varying $u(a)$ in the whole set $\mathcal{U}$, for all a. From this one gets an alternative definition for a's successors (10):

$$\mathcal{S}(a) = \bigcup_{u \in \mathcal{U}} \mathcal{S}(a,u)$$

Similarly, it is natural to define $\mathsf{TG}(u) = (\mathcal{V}, \mathcal{E}(u))$, where $\mathcal{V}$ is the same as in the autonomous case and, following definition 1 :

$$\mathcal{E}(u) = \bigcup_{a \in \mathcal{V}} \{a\} \times \Big\{ a + \varepsilon_i \mathbf{e}_i \,|\, i \in \{1 \cdots n\},\, \varepsilon_i = \operatorname{sign}\left(\mathcal{S}_i(a,u) - a_i\right) \Big\}, \tag{19}$$

Then, a generic control problem can be formulated in global terms, involving a desirable transition graph :

Problem 1 (global control problem). *Let* $\mathsf{TG}^\star$ *be a transition graph. Find a feedback law* $u : \mathcal{V} \to \mathcal{U}$ *such that* $\mathsf{TG}(u) = \mathsf{TG}^\star$.

This abstract formulation hides a number of arduous sub-problems, including of course the choice of a target transition graph $\mathsf{TG}^\star$. It is worth mentioning a fairly efficient way to define this graph: it consists in imposing some global property, expressed as a temporal logic formula [5]. Difficulties are due in large part to the global aspect of this formulation, which concerns a whole state space, or transition graph. Anyway, the target transition graph $\mathsf{TG}^\star$ may differ from the autonomous graph $\mathsf{TG}(u^0)$ only on a subset of edges. Hence, problem 1 includes local versions, where the feedback law is only sought on a subset of the vertices $\mathcal{V}$, see below.

Problem 2 (local control problem). *Let* $\mathsf{TG}^\star$ *be a transition graph, and* $\mathcal{V}^\star \subset \mathcal{V}$ *the subset of vertices, where outgoing edges of* $\mathsf{TG}^\star$ *differ from that of* $\mathsf{TG}(u^0)$. *Find a feedback law* $\widetilde{u} : \mathcal{V}^\star \to \mathcal{U}$ *such that* $\mathsf{TG}(u) = \mathsf{TG}^\star$, *where* $u|_{\mathcal{V}^\star} = \widetilde{u}$ *and* $u|_{\mathcal{V} \setminus \mathcal{V}^\star} = u^0$.

Now, we first elucidate the most elementary local problem, namely the problem 2 in the case where $\mathcal{V}^\star$ is a single vertex. Then, semi-global cases, involving sets $\mathcal{V}^\star$ with more than one element, are dealt with.

4.2 Control of a single box

The control of a one element vertex set $\mathcal{V}^\star = \{a\}$ corresponds, in a continuous state space, to the control of a single regular domain $\mathcal{D}_a$. We have seen in sections 2 and 3 that the dynamics in such domains is essentially determined by a focal point $\phi(a,u(a))$, which is an attracting equilibrium when it belongs to $\mathcal{D}_a$. When $\phi(a,u(a)) \notin \mathcal{D}_a$, on the other hand, all trajectories escape from $\mathcal{D}_a$ in finite time. According to this, we first treat the case when the only outgoing edge is a self-loop. In a second step, cases where at least one edge escapes from a are treated. The main observation will be that these two control problems are in fact of the same nature, and can be solved by a common method, which is described at the end of the present section.

4.2.1 Control making a regular region invariant

The first problem addressed here is that of controlling the flow in a single domain $\mathcal{D}_a$, so that no trajectory can escape from it. This corresponds to a situation where $\mathcal{D}_a$ represents a beneficial situation for the system, or a situation where $\mathcal{D}_a$ may lead to some dangerous states in the autonomous case. Preventing from such danger is then achieved by staying in $\mathcal{D}_a$.
In any case, if follows from previous discussions that the only possibility to preclude a qualitative change in behaviour at a state a, with a constant input $u(a)$ on $\mathcal{D}_a$, is to force $\phi(a, u(a))$ to be a stable equilibrium. In other words one has to find a constant $u = u(a)$ such that

$$\phi(a, u) \in \mathcal{D}_a. \tag{20}$$

Moreover, **H1** implies that $\phi(a, u)$ must in fact lie in the interior $\mathring{\mathcal{D}}_a$ of $\mathcal{D}_a$. Equation (20) is equivalent to a list of inequalities, which must be strict, due to the last remark. Namely, one has to satisfy :

$$\forall i \in \{1 \cdots n\}, \quad \theta_i^{a_i - 1} < \phi_i(a, u) < \theta_i^{a_i} \tag{21}$$

Figure 4 illustrates this problem.

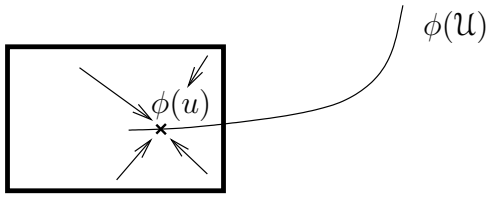


Figure 4: Among all points in the focal set $\phi(\mathcal{U})$, one has to find one on the form above, acting on u.

4.2.2 Escaping from a region through a single facet

Now, if our wish is to escape from a box $\mathcal{D}_a$, it is necessary and sufficient to find a constant u such that $\phi(a, u) \notin \mathcal{D}_a$, as follows from sections 2 and 3. In general however, it will not only be satisfactory to escape from $\mathcal{D}_a$, but more precisely to escape through a prescribed facet.
There are several strong arguments in favor of this more particular control problem. A simple one is that this control problem is often a local consequence of a more global situation, where a full sequence of boxes needs to be crossed successively. In such a case, when one has to leave a box $\mathcal{D}_a$, the next box to be encountered – and thus, the escaping walls – is prescribed as well. With a fixed successor or not, anyway, it is an important matter to obtain a controlled system which is properly related to its discrete representative, as discussed at the end of section 2.2. Actually, we have seen that if all continuous trajectories have a discrete representative in TG, many paths in this graph are not admissible with respect to any continuous system. A special case when the correspondence between a continuous and a discrete system is achieved, is the case when each regular vertex $a \in \mathcal{V}$ of the transition graph admits a unique successor, *i.e.* a unique outgoing edge. In this case the transition graph bears a deterministic finite-state automaton. Hence, given an initial rectangle, all trajectories will follow a uniquely defined sequence of rectangles. In this case it is said, for instance in [3], that the systems of the form (1) (resp. (8)), and their discrete analogue TG (resp. $\mathsf{TG}(u)$), are bisimilar, meaning here that they share the same reachability properties.

An illustration of this problem appears in figure 5.

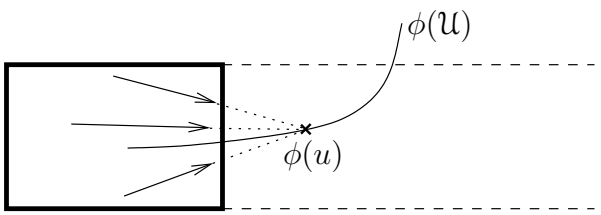


Figure 5: Here, one has to find an input u such that $\phi(u)$ is situated 'behind' a single facet of the box under consideration.

The problem can be now stated as follows: let $a \in \mathcal{V}$ be a vertex to be control-ed, $i \in \{1 \cdots n\}$ a prescribed escaping direction, and $\varepsilon \in \{+, -\}$ an orientation. Then, the sought input u must satisfy:

$$\begin{array}{lllll} \forall j \in \{1 \cdots n\} \setminus \{i\}, & \theta_j^{a_j - 1} & < & \phi_j(a,u) & < & \theta_j^{a_j} \\ \text{If} \quad \varepsilon = +, & \theta_i^{a_i} & < & \phi_i(a,u) & \leqslant & \theta_i^{q_i}, \\ \text{and if} \quad \varepsilon = -, & \theta_i^{0} & \leqslant & \phi_i(a,u) & < & \theta_i^{a_i - 1}. \end{array} \tag{22}$$

Now, the point is that both equations (21) and (22) have the same form. This will be written as follows

$$\exists u \in \mathcal{U},\ \forall i \in \{1 \cdots n\}, \quad \theta_i^- < \phi_i(a,u) < \theta_i^+, \tag{23}$$

where the thresholds $\theta_i^{\pm}$ are generic notations, and inequalities shall be weakened when concerning the boundaries of the whole domain. The remaining work is thus to define an input u such that the above system of inequalities is satisfied.

Remark 2. Although it is not our aim here, it is remarkable that (23) is also a generic formulation for target transition graphs $\mathsf{TG}^\star$ such that vertex a has multiple successors. It states actually the existence of an input u such that $\phi_i(a,u) \in R$, where R is any rectangular union of boxes, written $R = \prod_i]\theta_i^-, \theta_i^+[$.

4.2.3 Generic control law for a single box

We are now seeking a control u solving condition (23). Most often the domain a will be clear in a given context, and thus, omitted in any terms depending on it.
First, a special case has to be treated separately. This is the case $\phi_i = 0$, or equivalently $\kappa_i = 0$, for some i, which appears for example on figures 2 and 3.

Proposition 1. *Suppose that $\phi_i = 0$ for some $i \in \{1 \cdots n\}$.*
Then, either $\theta_i^- > 0$, and the problem (23) admits no solution, or $\theta_i^- = 0$, and whatever $u \in \mathcal{U}$, this problem is solved for the coordinate i. Hence in this case, problem (23) reduces to $n-1$ pairs of inequalities, involving coordinates different from i.

The proof of this proposition is quite immediate, and does not require further discussion. In the following propositions, it is implicitly assumed that coordinates for which $\phi_i = 0$ have been removed from problem (23), and that none of them concern an i such that $\theta_i^- > 0$.

Now we show how problem (23) can be solved.

Proposition 2. *Consider a system of the class* **C1**.
Let us introduce the following notation: $T^{\pm} = \mathrm{diag}(\theta_1^{\pm} \cdots \theta_n^{\pm}) \in \mathbb{R}^{n \times n}$.
Then, any $u \in \mathcal{U}$ satisfying the system below is a solution of problem (23).

$$\left\{ \begin{array}{lll} \left(\kappa - T^- \Gamma\right) u & > & T^- \gamma^0 - \kappa^0 \\ \left(\kappa - T^+ \Gamma\right) u & < & T^+ \gamma^0 - \kappa^0 \end{array} \right.$$

Note that the condition $u \in \mathcal{U}$ can also be written as pairs of inequalities on the coordinates u_j, of the form $0 \leqslant u_j \leqslant U_j$.

Proof. Start with equation (23). Then, let just replace ϕ by the fractional linear form it takes in the case of **C1** systems:

$$\exists u \in \mathcal{U},\ \forall i \in \{1 \cdots n\}, \quad \theta_i^- < \frac{\sum_{j=1}^p \kappa_i^j u_j + \kappa_i^0}{\sum_{j=1}^p \gamma_i^j u_j + \gamma_i^0} < \theta_i^+$$

Since, by hypothesis **H2**, the denominator above is positive, one obtains easily

$$\forall i \in \{1 \cdots n\}, \qquad \left\{ \begin{array}{lll} \displaystyle\sum_{j=1}^{p} (\kappa_i^j - \gamma_i^j \theta_i^-) u_j & > & \gamma_i^0 \theta_i^- - \kappa_i^0 \\ \displaystyle\sum_{j=1}^{p} (\kappa_i^j - \gamma_i^j \theta_i^+) u_j & < & \gamma_i^0 \theta_i^+ - \kappa_i^0 \end{array} \right. \tag{24}$$

Which, put in matrix form, is the claimed system. □

Remark 3. Observe that when $\theta_i^- = 0$, the corresponding inequality in (24) reduces to

$$\sum_{j=1}^{p} \kappa_i^j u_j > -\kappa_i^0,$$

which, by **H2**, is satisfied by any u such that $\kappa_i(a,u)$ is strictly greater than its infimum, and in particular by any u in the interior $\mathring{\mathcal{U}}$.

As far as no ambiguity is possible, we omit the argument a in functions κ_i^j and γ_i^j hereafter. For systems in the class **C2**, the inequalities can be solved by hand, and thus an explicit input may be expressed. Remind that, for these systems, there are two functions $\sigma, \varsigma : \{1 \cdots n\} \to \{1 \cdots p\}$, defining the input acting respectively on the production and degradation rates of a given variable, see (13) and (14). The last of these two equations imposes that for each i, at least one of the two coefficients $\kappa_i^{\sigma(i)}$ and $\gamma_i^{\varsigma(i)}$ is zero. Accordingly, we introduce $S : \{1 \cdots n\} \to \{0 \cdots p\}$, which is defined by $S(i) = \sigma(i)$ (resp. $\varsigma(i)$) if $\kappa_i^{\sigma(i)} \neq 0$ (resp. $\gamma_i^{\varsigma(i)} \neq 0$), and $S(i) = 0$ if $\kappa_i^{\sigma(i)} = \gamma_i^{\varsigma(i)} = 0$.
Let us also define some useful quantities: for $i \in \{1 \cdots n\}$, the bounds of $\phi_i(\mathcal{U})$ are for the class **C2**,

$$\phi_i^- = \min\left\{\phi_i(0),\, \phi_i(U_{S(i)})\right\} \qquad \text{and} \qquad \phi_i^+ = \max\left\{\phi_i(0),\, \phi_i(U_{S(i)})\right\}.$$

Actually, for the class **C2**, either ϕ_i is a function of $u_{\sigma(i)}$, or it is a function of $u_{\varsigma(i)}$. These two cases can be written as:

$$\phi_i = \frac{\kappa_i^{\sigma(i)} u_{\sigma(i)} + \kappa_i^0}{\gamma_i^0} \qquad \text{or} \qquad \phi_i = \frac{\kappa_i^0}{\gamma_i^{\varsigma(i)} u_{\varsigma(i)} + \gamma_i^0}. \tag{25}$$

Although depending on the sign of $\kappa_i^{\sigma(i)}$ and $\gamma_i^{\varsigma(i)}$ respectively, the sign of their derivative is constant. Hence all ϕ_i's are monotonic, and the bounds of their image are the images of their domain's bounds.
Clearly, the bounds of $\phi_i(\mathcal{U}) \cap]\theta_i^-, \theta_i^+[$ are $\max\left\{\phi_i^-, \theta_i^-\right\}$ and $\min\left\{\phi_i^+, \theta_i^+\right\}$. It follows that their preimages by ϕ_i

$$\phi_i^{-1}\left(\max\left\{\phi_i^-, \theta_i^-\right\}\right) \qquad \text{and} \qquad \phi_i^{-1}\left(\min\left\{\phi_i^+, \theta_i^+\right\}\right), \tag{26}$$

bound the possibly empty interval $]m_i^-, m_i^+[\subset [0, U_{S(i)}]$, of input coordinates that solve the control problem in direction i in the state space. In other words m_i^- and m_i^+ are respectively the min and max of the two values (26). Conveniently, these numbers may be easily expressed since here, ϕ_i is a monotonic real function of the form (25).
Then, for $q \in \{1 \cdots p\}$, define

$$\mu_q^- = \max_{i \in S^{-1}(q)} m_i^-, \qquad \text{and} \qquad \mu_q^+ = \min_{i \in S^{-1}(q)} m_i^+. \tag{27}$$

If $\mu_q^- < \mu_q^+$, any u_q between these values is such that $\phi_i(u_q)$ lies in the desired interval, *i.e.* $]\theta_i^-, \theta_i^+[$, for all i such that $S(i) = q$. Hence we get explicit input values in this case, as summarized in the following statement.

Proposition 3. *Consider a system belonging to the class* **C2**.
Then, inequalities (23) admit as solution if and only if, for all $q \in \{1 \cdots p\}$,

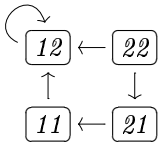
$$\mu_q^- < \mu_q^+,$$

where these quantities are defined as in (27) and above.

Moreover, any u *in the rectangle* $\prod_{q=1}^{p}]\mu_q^-, \mu_q^+[$ *solves these inequalities.*

Let us illustrate these propositions on our previous example.

Example (continued 2). *Let us recall the transition graph of the autonomous system, as we have assumed earlier:*

$\mathsf{TG}(u^0) =$ 

One may now consider local problems involving a single vertex in TG. *Let for example consider vertex* 21, *from which there is a single transition, to its horizontal neighbour, in the autonomous case:* $\boxed{11} \longleftarrow \boxed{21}$. *Suppose that our wish is to force a self-loop:* $\boxed{21}$.

This is exactly solving problem 2 at the single vertex $a^\star = 21$, *for the class* **C2**. *Since the latter is a subclass of* **C1**, *one may first apply proposition 2, as an illustration. The thresholds bounding the desired successor state are*

$$\theta_1^- = \theta_1^1,\ \theta_1^+ = \theta_1^2, \quad \textit{and}\ \ \theta_2^- = \theta_2^0 = 0,\ \theta_2^+ = \theta_2^1$$

As mentioned previously, the matrix $\kappa(x)$ *of equation (12), is zero here. Only the vector* $\kappa^0(x)$ *is possibly nonzero : in the considered state, the coordinates* $\kappa_i^0(a^\star)$ *are* $\kappa_1^0(a^\star) = \kappa_1^0 + \kappa_1^1$ *and* $\kappa_2^0(a^\star) = \kappa_2^0$. *Thus, the system of inequalities to be solved, as stated in proposition 2, is here the following:*

$$\begin{cases} -\gamma_1^1\theta_1^1 u_1 & > & \gamma_1^0\theta_1^1 - \kappa_1^0 - \kappa_1^1 \\ 0 & < & \kappa_2^0 \\ -\gamma_1^1\theta_1^2 u_1 & < & \gamma_1^0\theta_1^2 - \kappa_1^0 - \kappa_1^1 \\ -\gamma_2^1\theta_2^1 u_2 & < & \gamma_2^0\theta_2^1 - \kappa_2^0 \end{cases}$$

The second inequality is satisfied if and only if κ_2^0 *is nonzero, independently of the input* u. *This is a special case of remark 3.*
Now, since our system belongs to the class **C2**, *one may proceed further, illustrating proposition 3.*
We assume from now on that the parameters are in accordance with figure 6.
Let us suppose that $\gamma_1^1 > 0$ *and* $\gamma_2^1 < 0$, *which is consistent with the shape of focal sets in the one input case, on figure 6. This implies that* ϕ_1 *is decreasing with* u_1, *and* ϕ_2 *is increasing with* u_2, *and of course their reciprocal function have identical monotony. Then, the quantities defined above proposition 3 can be evaluated, step by step*

$$\max\left\{\phi_1^-, \theta_1^-\right\} = \theta_1^- = \theta_1^1 \quad \textit{and} \quad \min\left\{\phi_1^+, \theta_1^+\right\} = \phi_1^+ = \phi_1(0)$$

Then,

$$m_1^- = 0 \quad \textit{and} \quad m_1^+ = \phi_1^{-1}(\theta_1^1) = \frac{\kappa_1^0 + \kappa_1^1 - \gamma_1^0\theta_1^1}{\gamma_1^1\theta_1^1}.$$

since the latter is positive. Similarly,

$$m_2^- = \phi_2^{-1}\left(\max\{\phi_2(0), 0\}\right) = 0$$

since $\phi_2(0) = \frac{\kappa_2^0}{\gamma_2^0} \geqslant 0$, *and*

$$m_2^+ = \phi_2^{-1}(\min\{\phi_2(U_2), \theta_2^1\}) = \phi_2^{-1}(\theta_2^1) = \frac{\kappa_2^0 - \gamma_2^0\theta_2^1}{\gamma_2^1\theta_2^1},$$

based on $\phi_2(U_2) = \sup_u \phi_2(u) > \theta_2^1$, *which holds on figure 6, on which we rest here.*
Now, one has here $S = id$, *so that* $\mu_i^\pm = m_i^\pm$. *Hence the set of inputs solving our control problem at vertex* 21 *in* TG *is*

$$\left]0, \frac{\kappa_1^0 + \kappa_1^1 - \gamma_1^0\theta_1^1}{\gamma_1^1\theta_1^1}\right[\times \left]0, \frac{\kappa_2^0 - \gamma_2^0\theta_2^1}{\gamma_2^1\theta_2^1}\right[,$$

which is nonempty in the example of figure 6: its image by $\phi(21, \cdot)$ *is the intersection of the red shaded rectangle over* $\mathcal{D}_{21}$ *and* $\mathcal{D}_{21}$ *itself.*
The resulting transition graph is the following:

$$\mathsf{TG}(u) = \quad \begin{array}{ccc} \circlearrowright & & \\ \boxed{12} & \longleftarrow & \boxed{22} \\ \uparrow & & \downarrow \\ \boxed{11} & & \boxed{21} \circlearrowright \end{array} \tag{28}$$

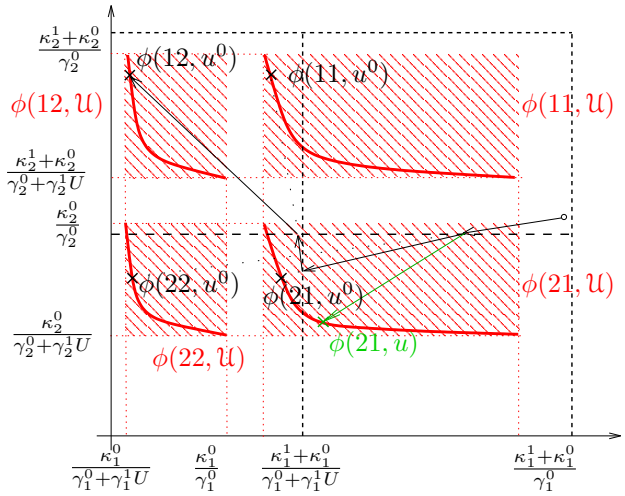


Figure 6: In the case when $\kappa_i^0 > 0$, focal sets are not constrained on the boundaries of the positive orthant. In each of the 4 regular domains, the focal set is supported by a manifold defined as in (17). The one input focal sets are red lines, and the two input ones are red shaded rectangles. In green, the focal point of $\mathcal{D}_{21}$, controlled to be an equilibrium, whereas this domain is not invariant in the autonomous case. Two pieces of trajectories are represented from a common initial point: the black one corresponds to the autonomous case, and the green one to the previous input. These orbits converge toward two distinct equilibria.

If one assumes now that there is a single input, this adds the constraint $u_1 = u_2 = u$, with $u \in \mathcal{U} = [0, U]$. Also, S is the constant function, since there is only one input coordinate. It follows that, noting $\mu^\pm$ in place of $\mu_i^\pm$,

$$\mu^- = \max\{m_1^-, m_2^-\} = 0.$$

and

$$\mu^+ = \min\{m_1^+, m_2^+\},$$

where $m_1^\pm, m_2^\pm$ are the same as in the two inputs case. Now, according to proposition 3, any input in $]\mu^-, \mu^+[$ provides a solution to our problem. The latter is nonempty on our graphical example. Actually, in figure 6, it parameterizes the intersection of $\mathcal{D}_{21}$ and the piece of red curve that represents $\phi(12, \mathcal{U})$. The obtained transition graph is, as in the two input case, that of (28). One may remark that this graph presents no transition between states 11 and 21. This corresponds to a white wall between the corresponding domains in phase space. Solving a second local problem at the state 11 may preclude this behaviour, by chosing $\uparrow$ *as the transitions to be* $\boxed{11}\rightarrow$ *controlled.*

The proposed local problem suffices here to ensure a global property of the system: from an autonomous system with a single equilibrium, one obtains a bistable system here, only acting on degradation rates when the system's state vector lies inside $\mathcal{D}_{21}$.

In any case, it is important to remark that proposition 2 and its specialization 3 both lead us to check $2n$ inequalities. In other words, the controllability of a single box can be checked using an algorithm that is linear with respect to n. This fact must be compared with the already known procedure for the control of multi-affine systems on rectangles [4, 18], which require inequalities at all vertices of a facet to be checked. The latter being a $n-1$-rectangle, this leads to 2^{n-1} inequalities, and the procedure has an exponential cost. Hence, our choice to investigate piecewise-linear dynamics leads to a specific procedure, yielding an important gain, when compared to the blind application of techniques devoted to more general systems. Moreover, equilibria for multi-affine systems are given by polynomial equations, while they are here given by affine equations. This explains why it is possible here to control a box so that it has no successor, which is not easily done in the more general context of multi-affine models.
Once the conditions in propositions 2 or 3 are checked, the choice of a satisfactory input can be made arbitrarily in the set they yield. The exact choice of these inputs may only have consequences that cannot be detected at the level of precision of the transition graph. Hence, this proposition allows a fully qualitative treatment of problem (23). This could thus lead to include control aspects in the existing framework of qualitative analysis of piecewise linear gene network models [8, 9, 22].

4.3 Control on a whole region

We consider the global control problem on our guiding example, since its low dimension allows for an exhaustive exploration of the transition graph.

Example (continued 3). *Given any vertex in* TG*, it is possible to compute all the neighbours towards which a transition might be controlled, thanks to the methods introduced in the previous section. Let us illustrate this with our example, which is governed by the equations (15), that we recall:*

$$\begin{cases} \dfrac{dx_1}{dt} &= \kappa_1^1 \mathsf{s}^-(x_2,\theta_2^1) + \kappa_1^0 - (\gamma_1^1 u_1 + \gamma_1^0)x_1 \\ \dfrac{dx_2}{dt} &= \kappa_2^1 \mathsf{s}^-(x_1,\theta_1^1) + \kappa_2^0 - (\gamma_2^1 u_2 + \gamma_2^0)x_2 \end{cases}$$

We suppose that parameter values are consistent with figure 6. Then, the controllable transitions at each vertex are the following:

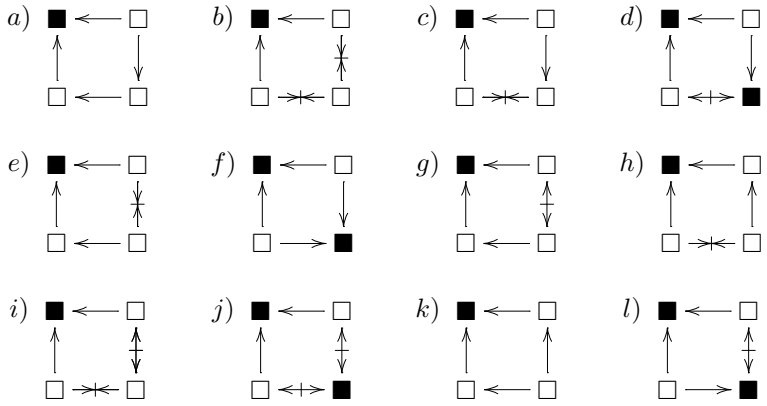
12 : *12* ↺	**22** : ← *22* ↓ *or* ← *22*
11 : ↑ *11* *or* ↑ *11* →	**21** : ← *21* *or* ↑ ← *21* *or* ↺ *21*

(29)

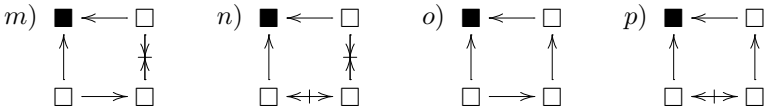
for a scalar input, while the case of planar inputs allows furthermore to control the following transition:

↑ *21*

For each vertex in table (29), the first proposed transition corresponds to the autonomous case. If the input is a scalar, focal sets in figure 6 are curves and not rectangles, and the last transition above at vertex 21*, towards* 22*, is not controllable. Here, the controllable transitions in (29) are directly read from the figures. Without such geometric hints – for example in higher dimension – they would of course be computed from proposition 3.*
Hence, the set of all controllable transitions graphs contains $16 = 1 \cdot 2 \cdot 2 \cdot 4$ *elements in the two inputs case, and* $12 = 1 \cdot 2 \cdot 2 \cdot 3$ *with a single input. In this case, it is possible, and even easy, to list all the controllable graphs. Then, according to a specific purpose, those graphs that are satisfying may be chosen, and problem 1 be solved with such an objective graph. Let just list all the possible transition graphs. To obtain a concise view of this graph, we represent self loops by filled squares, and omit the labels of vertices. Their disposition, yet, is in accord with the rest of the paper:* 12 – 22 / 11 – 21 *. With a single input the set of controllable graphs is:*



To which the following can be added if a second input variable is available:



The doubly oriented arrows correspond to black or white walls in phase-space. Black walls are those toward which the flow is directed from both sides, and appear as $\rightarrow\!\!\!\leftarrow$ *. White walls, on the other hand, are the unreachable (or unstable) ones, and appear as* $\leftarrow\!\!\!\rightarrow$ *. Both situations may be handled using Filippov solutions, see section 2.1.2.*
Let us consider some special control problems, now.
As could be seen from (29), vertex 12 *is always fixed, whatever the input value. Vertex* 21*, on the other hand, may be fixed or not, as we also have seen earlier. Here, it appears that bi-stability may be ensured in our system. This happens with four distinct global transition graphs:* $d)$*,* $f)$*,* $j)$ *and* $l)$*. Among those,* $d)$ *is the one we have already seen in some detail in the example, and* $f)$ *provides the only bistable configuration without white wall. Note that all solutions of this control problem can be achieved with a single input.*
Another objective may be to require that the graph be deterministic, i.e. knowing the initial vertex determines the whole series of transitions, see [3] for similar requirements. Here, this may be achieved by inputs associated to the graph $g)$*,* $j)$ *or* $p)$*. The first and last present a single global equilibrium, while* $j)$ *is bistable. All these graph present white walls. For that control problem, the use of a second input provides an additional solution, namely* $p)$*.*

Hence, as announced in the introduction, we propose control methods that ensure bi-stability in a system whose autonomous parameters lead to a single equilibrium.
As another solvable problem, the system can be made bisimilar to its associated transition graph, see section 4.2.2 and [3].

One may be surprised by the obvious asymmetry of the controllable graphs above: although equations (15) are symmetric in the two state variables, vertex 12 *above cannot be controlled, while* 21 *admits three to four controllable successors. This asymmetry is in fact a consequence of the special set of parameter values we have considered, which we have chosen to match with figure 6.*

It is clear that the exhaustive list presented in the above example can only be achieved because of the low number of states in TG. In a more general setting, even a single transition graph has a number of vertices that grows exponentially with the dimension of the state space, and thus can not be explored completely in a reasonable time length. Hence global control problems are not practical, and developing general algorithms seems of poor practical utility. However, on particular examples it is certain that most interesting control problems will involve several vertices, and that some typical structures might be found among those present in concrete regulatory systems. For example, semi-global problems could be considered, involving "safe" and "pathological" regions. Then, the input should be such that the latter are unreachable, and the former invariant, or even attracting. The study of semi-global problems should be a major concern in researches to come on this topic.

5 Conclusion

Among modern advances in cell biology, the synthesis of living systems, or so-called *synthetic biology*, is one of the most striking and promising topic. We have already mentioned examples published in [2, 12, 15], see also the review [1], among a voluminous literature. This emerging discipline is an engineering one, and as such requires some theoretical tools [19], some of whose are proposed in this article.
Actually, our goal here is to provide a mathematical formulation that captures some abstract characteristics of these techniques. By this, we mean that model (8) is not intended to describe a particular technique, but rather some common traits, whose most general description might be: "some parameters of the system can be modified by the experimentalist". Considering the particular case of gene networks, we focus on a class of models that have proved their efficiency in the last few years, formulated in (1). Then we put in equations the phrase above, and allow some parameters of the autonomous equations to be functions of an input u. Namely, both production and degradation coefficients in (1) are supposed to depend on u, leading to equation (8). Given this class of systems, it appears relevant to look for piecewise constant feedback control laws. Indeed, for any chosen law of this form, equations (8) reduce to a particular system of the form (1). Moreover, such input laws could be concretely implemented, provided threshold crossings can be detected, a fact that is not out of reach today [10].
We then study the most natural control problems arising within this framework. Special attention is given to local control problems, which are the necessary first steps towards solving more global problems. We also restrict this study to the case where the system parameters are affine functions of the input, distinguishing also

the special case when at most one input influences each state variable. This results in propositions 2 and 3, which provide explicit affine inequalities on the input, that ensure the solution of generic control problems. All along the paper, a system with two variables is used as an illustrative example, leading in the last section to an exhaustive description of its controllability properties, for any set of parameters that fits with figure 6. This example has been concretely implemented in vivo [15], thus providing a link with more concrete, experimentally oriented works.

Acknowledgments. This work was partially supported by the European Commission, under project Hygeia Nest-004995. The authors would also like to thank Delphine Ropers and Hidde de Jong for their helpful advice during the elaboration of this paper.

References

[1] E. Andrianantoandro, S. Basu, D.K. Karig, R. Weiss, *Synthetic biology: new engineering rules for an emerging discipline*, Mol Syst Biol, Vol. 2, msb4100073-E1-msb4100073-E14 (2006).

[2] A. Becksei, L. Serrano, *Engineering stability in gene networks by autoregulation*, Nature, 405:590-93 (2000).

[3] C. Belta, L.C.G.J.M. Habets, *Constructing decidable hybrid systems with velocity bounds*, 43rd IEEE Conference on Decision and Control, pp. 467-472 (2004).

[4] C. Belta, L. Habets, V. Kumar, *Control of multi-affine systems on rectangles with applications to hybrid biomolecular networks*, 41st IEEE Conference on Decision and Control, pp. 534-539 (2002).

[5] G. Batt, D. Ropers, H. de Jong, J. Geiselmann, R. Mateescu, M. Page, D. Schneider, *Validation of qualitative models of genetic regulatory networks by model checking: Analysis of the nutritional stress response in Escherichia coli*, Bioinformatics, 21(Suppl 1):i19-i28, (2005).

[6] R. Casey, H. de Jong, J.L. Gouzé, *Piecewise-linear Models of Genetic Regulatory Networks: Equilibria and their Stability*, J. Math. Biol., 52(1):27-56 (2006).

[7] J.L. Cherry, F.R. Adler, *How to make a biological switch*, J. Theor. Biol. 203:117-133 (2000).

[8] H. de Jong, J. Geiselmann, G. Batt, C. Hernandez, M. Page, *Qualitative simulation of the initiation of sporulation in Bacillus subtilis*, Bull. Math. Biol., 66(2):261-300 (2004).

[9] H. de Jong, J.L. Gouzé, C. Hernandez, M. Page, T. Sari, J. Geiselmann, *Qualitative simulation of genetic regulatory networks using piecewise-linear models*, Bull. Math. Biol., 66(2):301-340 (2004).

[10] S. Drulhe, G. Ferrari-Trecate, H. de Jong, A. Viari, *Reconstruction of switching thresholds in piecewise-affine models of genetic regulatory networks*, Hybrid Systems: Computation and Control, HSCC 2006, LNCS 3927, pp. 184-199 (2006).

[11] R. Edwards, H.T. Siegelmann, K. Aziza, L. Glass, *Symbolic dynamics and computation in model gene networks*, Chaos, 11(1):160-169 (2001).

[12] M.B. Elowitz, S. Leibler, *A synthetic oscillatory network of transcriptional regulators*, Nature, 403:335-338 (2000).

[13] E. Farcot, *Some geometric properties of piecewise affine biological network models*, J. Math. Biol, 52(3):373-418 (2006).

[14] A. F. Filippov, *Differential Equations with Discontinuous Righthand Sides*, Mathematics and Its Applications (Soviet Series), vol. 18, Kluwer Academic, Dordrecht, (1988).

[15] T.S. Gardner, C.R. Cantor, J.J. Collins, *Construction of a genetic toggle switch in Escherichia Coli*, Nature, 403:33 9-342 (2000).

[16] L. Glass, *Combinatorial and topological methods in nonlinear chemical kinetics*, J. Chem. Phys. 63:1325-1335 (1975).

[17] J.L. Gouzé, T. Sari, *A class of piecewise linear differential equations arising in biological models*, Dynamical systems, 17:299–316 (2003).

[18] L.C.G.J.M. Habets, J.H. van Schuppen, *A control problem for affine dynamical systems on a full-dimensional polytope*, Automatica 40, 21 - 35 (2004).

[19] Hasty, J., Isaacs, F., Dolnik, M., McMillen, D., Collins, JJ, *Designer gene networks: towards fundamental cellular control*, Chaos 11, 207-220 (2001).

[20] F.J. Isaacs, D.J. Dwyer,J.J. Collins, *RNA synthetic biology*, Nature Biotechnology 24, 545-554 (2006)

[21] Kobayashi H, Kaern M, Araki M, Chung K, Gardner TS, Cantor CR, Collins JJ, *Programmable cells: interfacing natural and engineered gene networks*, Proc. Natl. Acad. Sci. U.S.A., 101(22):8414-9 (2004).

[22] D. Ropers, H. de Jong, M. Page, D. Schneider, J. Geiselmann, *Qualitative simulation of the carbon starvation response in Escherichia coli*, BioSystems, 84(2):124-152 (2006).



Unité de recherche INRIA Sophia Antipolis
2004, route des Lucioles - BP 93 - 06902 Sophia Antipolis Cedex (France)

Unité de recherche INRIA Futurs : Parc Club Orsay Université - ZAC des Vignes
4, rue Jacques Monod - 91893 ORSAY Cedex (France)
Unité de recherche INRIA Lorraine : LORIA, Technopôle de Nancy-Brabois - Campus scientifique
615, rue du Jardin Botanique - BP 101 - 54602 Villers-lès-Nancy Cedex (France)
Unité de recherche INRIA Rennes : IRISA, Campus universitaire de Beaulieu - 35042 Rennes Cedex (France)
Unité de recherche INRIA Rhône-Alpes : 655, avenue de l'Europe - 38334 Montbonnot Saint-Ismier (France)
Unité de recherche INRIA Rocquencourt : Domaine de Voluceau - Rocquencourt - BP 105 - 78153 Le Chesnay Cedex (France)

Éditeur
INRIA - Domaine de Voluceau - Rocquencourt, BP 105 - 78153 Le Chesnay Cedex (France)
http://www.inria.fr
ISSN 0249-6399