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Abstract: We propose in this report a method for the qualitative analysis of the dynamics of piecewise affine models of gene regulatory networks. Especially adapted to the framework of piecewise affine dynamical systems, this method is based on the hierarchical organization of such systems, using the well-known algorithm of decomposition of the interaction graph into strongly connected components. In certain cases, this decomposition allows to reduce the study of the asymptotic dynamics of a high dimensional system into the one of several lower dimensional subsystems. Allied to a threshold elimination algorithm as a pre-processing treatment, this method is applied to a 9-dimensional system modeling the nutritional stress response of the bacterium *E. coli*. In this case, we manage to reduce the analysis of the whole system to the analysis of a 3-dimensional subsystem.

Key-words: Gene regulatory networks, piecewise affine systems, interaction graph, strongly connected components, hierarchical analysis, model reduction.

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Analyse hiérarchique de modèles affines par morceaux de réseaux de régulation génétique

Résumé : Nous nous intéressons dans le présent rapport à une classe de systèmes dynamiques continus linéaires par morceaux souvent utilisés pour modéliser la dynamique qualitative de réseaux de régulation génétique. Nous proposons ici une méthode d'analyse de ces systèmes basée sur la décomposition hiérarchique de leur graphe d'interactions. L'organisation hiérarchique d'un système dynamique repose sur l'algorithme de décomposition d'un graphe orienté en composantes fortement connexes. Dans le cadre des systèmes affines par morceaux, cette décomposition permet, dans certains cas, de réduire l'étude asymptotique de la dynamique d'un système de grande dimension à celle de plusieurs sous-systèmes de dimensions inférieures. Nous proposons également dans la dernière partie de ce rapport un algorithme simple d'élimination de seuils permettant dans certains cas d'affiner la décomposition en composantes fortement connexes. En utilisant cet algorithme en guise de pré-traitement, nous appliquons la méthode présentée ici à un système de dimension 9 modélisant la réponse de la bactérie *E.coli* à un stress nutritionnel. Nous parvenons dans ce cas à ramener l'étude à un sous-système de dimension 3.

Mots-clés : Réseaux de régulation génétique, systèmes affines par morceaux, graphe d'interactions, composantes fortement connexes, analyse hierarchique, réduction de modèles.

1 Introduction

This report deals with hierarchical organization and hierarchical analysis of a class of piecewise affine systems of differential equations. This particular class of systems was first introduced by L. Glass in the 70's [12] as a model of genetic regulatory networks. Various aspects of these systems have been extensively studied since then, see e.g. [2, 7, 14], as they provide algorithmic methods to analyse qualitative dynamics of interaction networks. A computer tool, the *Genetic Network Analyzer* (GNA), has besides been elaborated to compute qualitative simulations of piecewise affine systems of relatively high dimensions [6]. Theoretically, a qualitative study of the dynamical behavior of a piecewise affine system consists in computing a *transition graph*, the vertices of which correspond to different regions of the state space. A directed edge exists between two regions if and only if *there exists* a solution of the system passing in finite time from the first to the second region. A study of such a transition graph therefore allows one to deduce qualitative properties of the dynamics, such as the existence and the characterization of attractors.

Although finite, the size of the transition graph grows exponentially with the dimension of the system. For a piecewise affine system of dimension 10 for instance, the computation, and especially the analysis of the whole graph tends to be quite uneasy. This is mainly why many researchers have been particularly interested in the *structure* of regulatory networks, and especially in the links between structure and dynamics. The structure can be represented by an *interaction graph*, corresponding to the variables of the system and the mutual influences (both positive and negative) among themselves. Contrary to the transition graph, this interaction graph has a reasonable size (it actually has n vertices, n being the dimension of the system), which makes its analysis much easier. Perhaps the most famous result in this research field lies in the so-called Thomas' conjectures, that link the presence of positive (resp. negative) feedback loops in the interaction graph, with the notion of multistationarity (resp. homeostasis). Stated in the 80's, these conjectures are now proven for different classes of dynamical systems (see e.g. [13, 18] and references therein).

In the present report, we propose to decompose the interaction graph of a piecewise affine system in a hierarchical form, in order to offer an easier way to analyse the dynamical behaviors of the model. This decomposition, based on the strongly connected components of the graph, has already been performed for general classes of dynamical systems (see, for instance [19]). The existing theorems are nevertheless quite general, and not really well-adapted to the piecewise affine framework. Indeed, thanks to the specific form of the differential equations under study, the hierarchical decomposition of the interaction graph offers a quite easy way to analyse the asymptotic behavior of a high dimensional system, decomposing it into several smaller systems. This approach is to be linked with the general concept of model reduction, where the term "reduction" refers to the simplification of the interaction graph of the system. Rather than general theorems, we preferred to describe in the following a practical *methodology*, which can be quite easily tested on real examples of piecewise affine models of biological networks.

The paper is organized in three parts. We begin with some brief recalls about the piecewise affine framework. We notably recall the definition of the interaction graph of a piecewise affine system, followed with a brief description of regular and singular dynamics. The second section deals with the hierarchical organization of the interaction graph, and with the asymptotic qualitative analysis of the dynamical behaviors of a piecewise affine system, based on the hierarchical decomposition. We present in the last part an efficient algorithm that may help this analysis by simplifying the structure of the system. This algorithm has been successfully applied to a 9-dimensional system modeling the carbon starvation response network of *E. coli* bacterium, developped in [16, 17].

Our method is a rather general approach that can be applied to study the asymptotic behavior of general piecewise affine models of genetic regulatory networks. It should be considered as a first step in the analysis of attractors of these systems and it could also be applied to other models of increasing complexity of *E. coli*, and hopefully to other biological examples.

2 The framework of piecewise affine systems

2.1 Structure of a piecewise affine system

We start by giving some headlines about the piecewise affine framework used to model gene regulatory networks. It will consist of some basic definitions and properties that we use in the rest of the paper; for a more exhaustive formulation of those systems, the reader is referred to [6,7,14] and references therein.
In the following, a "piecewise affine (PWA) system" designates a dynamical system of the form:

$$\dot{x}(t) = K\left(x(t)\right) - \Gamma\left(x(t)\right) x(t) \tag{1}$$

The variable $x(t)$ is an n-dimensional vector of concentrations of different proteins produced by n interacting genes, and lies therefore in $\mathbb{R}^n_+$. For $x \in \mathbb{R}^n_+$, the production term $K(x)$ is a vector lying in $\mathbb{R}^n_+$ and the decay term $\Gamma(x)$ is an n-dimensional diagonal matrix $\Gamma(x) = \mathrm{diag}(\Gamma_1(x), \ldots, \Gamma_n(x))$, where the $\Gamma_i(x) > 0$, for all $i \in \{1, \ldots, n\}$. System (1) can be written as n ordinary differential equations:

$$\dot{x}_i(t) = K_i(x) - \Gamma_i(x) x_i \ , \quad x_i \geq 0 \ , \qquad i = 1, \ldots, n \tag{2}$$

The variable x_i represents a concentration, and lies in a nonnegative interval $[0, max_i]$. Therefore, the state vector $x(t)$ evolves within the set $\Omega = \prod_{i=1}^{n} [0, max_i]$. To each x_i, we associate p_i ordered positive constants:

$$0 < \theta_i^1 < \theta_i^2 < \cdots < \theta_i^{p_i} < max_i \qquad (p_i \in \mathbb{N}, p_i > 0)$$

called *thresholds*. We will denote with Θ_i the vector $(\theta_i^1, \ldots, \theta_i^{p_i})$. By convention, for each $i \in \{1, \ldots, n\}$, we set $\theta_i^0 = 0$ and $\theta_i^{p_i+1} = max_i$. These thresholds are essential and we will consider in the rest of the paper that the definition of a piecewise affine system includes the differential system (2) together with the n vectors Θ_i.

The production and degradation terms $K_i(x)$ and $\Gamma_i(x)$ share the same mathematical form:

$$\forall x \in \Omega \ , \ \forall i = 1, \ldots, n \ , \qquad K_i(x) = \sum_{l \in L_i} \kappa_i^l b_{il}(x) \ , \quad \Gamma_i(x) = \sum_{l \in L'_i} \gamma_i^l b'_{il}(x) \tag{3}$$

where L_i and L'_i are (possibly empty) finite sets of indices, κ_i^l and γ_i^l are positive constants and the functions b_{il} and b'_{il} are boolean valued:

$$b_{il} \ , \ b'_{il} \ : \Omega \longrightarrow \{0, 1\}$$

The functions b_{il} and b'_{il} are often called *regulation functions* (see [7]) and are mathematically expressed by boolean expressions over the boolean variables $\tilde{x}_i^j$ defined by: $\tilde{x}_i^j = s^+(x_i, \theta_i^j)$, where $i \in \{1, \ldots, n\}$, $j \in \{1, \ldots, p_i\}$ and s^+ is the so-called Heaviside (or step) function:

$$\begin{array}{rccc} s^+ : & [0, max] \times \mathbb{R}^*_+ & \longrightarrow & \mathbb{R} \\ & (x, \theta) & \longmapsto & \left\{ \begin{array}{l} 0 \text{ if } x < \theta \\ 1 \text{ if } x > \theta \end{array} \right. \end{array}$$

Remark 1 *Let us note that:*

- *With this definition, the function $s^+(., \theta)$ is undefined for $x = \theta$.*
- *For convenient notations, we will denote s^- the function $1 - s^+$, in that way we have: $\overline{\tilde{x}_i^j} = s^-(x_i, \theta_i^j)$.*

The important consequence of these definitions is that a dynamical system defined by differential equations (2) and (3) is well-posed over the hyperrectangle Ω of $\mathbb{R}^n_+$, except on a subset of Lebesgue

measure zero (first point of remark 1). To be more precise, let us denote $H_{i,j}$ the hyperplane of $\mathbb{R}^n$ of equation $x_i = \theta_i^j$, for $i \in \{1, \ldots, n\}$ and $j \in \{1, \ldots, p_i\}$ and let H be the subset:

$$H = \bigcup_{i=1}^{n} \left(\bigcup_{j=1}^{p_i} H_{i,j} \right)$$

The vector field $F(x) = K(x) - \Gamma(x)x$ has good properties on $\Omega \backslash H$ (on each open hyperrectangle delimited by H, it is an affine vector field, with uncoupled equations) but it is discontinuous on the hypersurface H. As we will see in the next section, this discontinuity of the vector field prevents us from defining global solutions in the classical sense, and forces us to consider, on the threshold hyperplanes, a special type of solutions known as *Filippov solutions* (see [10]).

With a slight abuse of language, we will call in the following a *hyperrectangular* domain of Ω an n-dimensional hyperrectangle included in Ω, the faces of which are parallel to the axes and delimited in each direction i by two hyperplanes H_{i,j_1} and H_{i,j_2}, where $j_1 < j_2$ (we recall the convention that $\theta_i^0 = 0$ and $\theta_i^{p_i+1} = max_i$). Such a domain Δ is unequivocally characterized by a finite set of *discrete equations* of the form:

$$\begin{cases} s^+(x_i, \theta_i^0) = \cdots = s^+(x_i, \theta_i^{j_1}) = 1 \\ s^+(x_i, \theta_i^{j_2}) = \cdots = s^+(x_i, \theta_i^{p_i}) = 0 \end{cases}$$

in each direction $i \in \{1, \ldots, n\}$. Particularly, and according to the literature on PWA systems, elementary domains defined by:

$$D = \prod_{i=1}^{n} \left]\theta_i^{j_i}, \theta_i^{j_i+1}\right[\qquad j_i \in \{0, \ldots, p_i\}$$

will be called *regulatory domains* or *boxes*.

Remark 2 *To be complete and in accordance with the different articles about PWA systems, the regulatory domain D defined above is a product of* open *intervals:* $\left]\theta_i^{j_i}, \theta_i^{j_i+1}\right[$*, except if $j_i = 0$ (or, respectively if $j_i = p_i$). In those cases, we will replace the open interval with the semi-open interval:* $\left[0, \theta_i^1\right[$ *(respectively:* $]\theta_i^{p_i}, max_i]$*).*

Let us consider a simple example to illustrate these definitions.

Example 1
We consider a 2-dimensional piecewise affine system:

$$\begin{cases} \dot{x}_1 = K_1(x) - \Gamma_1(x)x_1 \quad , \quad p_1 = 2 \\ \dot{x}_2 = K_2(x) - \Gamma_2(x)x_2 \quad , \quad p_2 = 3 \end{cases} \tag{4}$$

The phase space Ω is represented on figure 1. The hyperrectangular domain Δ highlighted in this figure is mathematically defined by:

$$\Delta = \left]\theta_1^1, \theta_1^2\right[\times \left]\theta_2^2, max_2\right]$$

and its discrete equations are:

$$\begin{cases} s^+(x_1, \theta_1^1) = 1 \\ s^+(x_1, \theta_1^2) = 0 \\ s^+(x_2, \theta_2^1) = s^+(x_2, \theta_2^2) = 1 \end{cases}$$

The whole domain Ω is composed of 12 boxes, that can be labeled (see figure 1) by words $w = w_1 w_2$ where $w_1 \in \{0, 1, 2\}$ and $w_2 \in \{0, 1, 2, 3\}$.

□

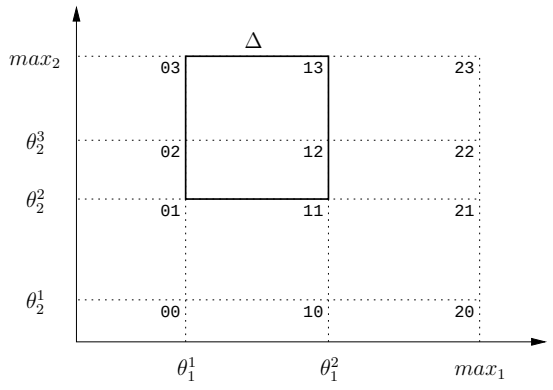


Figure 1: 2-d phase space of system (4)

The definition of a PWA system is therefore composed of two main elements which are the n threshold vectors Θ_i, $i = 1 \dots n$ and the piecewise affine vector field $F(x) = K(x) - \Gamma(x)x$. This definition is quite heavy and an usual way to schematically represent a PWA system is to draw its *interaction graph*.

Definition 1 (Interaction graph) *Consider an n-dimensional PWA system Σ ($n \in \mathbb{N}^*$) given by n vectors Θ_i, $i = 1 \dots n$, of p_i ordered strictly positive real numbers and n differential equations defined by (2) and (3). The* interaction graph *of Σ is the finite directed graph $\mathcal{G}_\Sigma = (\mathcal{V}, \mathcal{E})$ where:*

- *the set of vertices $\mathcal{V} = \{v_1, \dots, v_n\}$ (a vertex $v_i \in \mathcal{V}$ represents a gene),*
- *the set of edges $\mathcal{E} \subset \mathcal{V} \times \mathcal{V}$ is defined as follows: for all couples of vertices $(v_i, v_j) \in \mathcal{V}^2$, there exists an edge from v_j to v_i (noted $(v_j, v_i) \in \mathcal{E}$) if and only if there exists an index $l \in L_i \cup L_i'$ (see equations (3)) such that one (or both) of the regulation functions b_{il} and b'_{il} explicitly depends on $s^+(x_j, \theta_j^k)$ for some k.*

In other words, there exists an edge (v_j, v_i) in $\mathcal{G}_\Sigma$ if and only if the variable x_j appears in the production term $K_i(x)$ or in the decay term $\Gamma_i(x)$ of the variable x_i. We then say that x_j influences *x_i (or more rapidly that gene j influences gene i).*

Let us remark here that such an interaction graph is not equivalent to a full PWA system. Indeed in order to properly define the dynamics, we should also consider the values of the different parameters κ_i^l and γ_i^l together with the values of the different thresholds (see next section). However, the interaction graph essentially captures the interactions between genes and therefore captures the *structure* of the system.

Remark 3 *For a lot of examples in the literature, edges of the interaction graph are often labeled with a sign + or −, indicating whether the interaction is positive (activation or induction) or negative (repression or inhibition). Let us note here that such a labeling is only possible for particular PWA systems. Indeed, for a general system, a gene j may have both positive and negative action on a gene i (see the following example).*

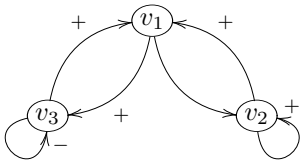
Example 2
Consider the three dimensional piecewise affine system given by:

$$(\Sigma) \begin{cases} \dot{x}_1 = \kappa_1^0 s^+(x_2, \theta_2^1) s^+(x_3, \theta_3^1) - \gamma_1^0 x_1 \ , & p_1 = 2 \\ \dot{x}_2 = \kappa_2^0 + \kappa_2^1 s^-(x_1, \theta_1^1) + \kappa_2^2 s^+(x_2, \theta_2^1) - \left(\gamma_2^0 + \gamma_2^1 s^-(x_1, \theta_1^2)\right) x_2 \ , & p_2 = 1 \\ \dot{x}_3 = \kappa_3^0 + \kappa_3^1 s^+(x_1, \theta_1^1) + \kappa_3^2 s^-(x_3, \theta_3^1) - \left(\gamma_3^0 + \gamma_3^1 s^-(x_1, \theta_1^2)\right) x_3 \ , & p_3 = 1 \end{cases}$$

The phase space of this system is the three dimensional hyperrectangle:

$$\Omega = [0, max_1] \times [0, max_2] \times [0, max_3]$$

It is composed of $3 \times 2 \times 2 = 12$ *boxes, that can be labeled by words* $w = w_1w_2w_3$ *where* $(w_1, w_2, w_3) \in \{0, 1, 2\} \times \{0, 1\}^2$.
The interaction graph of Σ *is represented by:*



According to remark 3, this graph has been signed with respect to the signs of the interactions. The edge (v_1, v_2) *however could not be signed because* x_1 *has both positive and negative action on* x_2 *(see the second equation of system* Σ*).*

□

2.2 Dynamics of a piecewise affine system

In order to define properly the dynamics of system (1), we will have to partition Ω in different domains of the form:

$$D = D_1 \times \cdots \times D_n \tag{5}$$

where, for each $i \in \{1, \ldots, n\}$, D_i is one of the following:

1. $D_i = \left[0, \theta_i^1\right[$,
2. $D_i = \left]\theta_i^j, \theta_i^{j+1}\right[$, for some $j \in \{1, \ldots, p_i - 1\}$,
3. $D_i = \left\{\theta_i^j\right\}$, for some $j \in \{1, \ldots, p_i\}$,
4. $D_i =]\theta_i^{p_i}, max_i]$

If, for all $i \in \{1, \ldots, n\}$, D_i is not a singleton (cases 1, 2 and 4), then the domain D defined by (5) is a regulatory domain, as we defined it in the previous section. In that case the domain is also called *regular*. Otherwise, (i.e. if for at least one i the set D_i is reduced to a singleton), the domain D is called a *singular* or *switching* domain (see [7]). The *order* k of a singular domain D is the number of i such that D_i is reduced to a singleton. The *support* of D, noted $\mathrm{supp}(D)$ is the $(n-k)$-dimensional affine subspace containing D. We will respectively denote $\mathcal{D}_r$ and $\mathcal{D}_s$ the sets of regular and singular domains.

2.2.1 Regular dynamics

Over a regular domain $D \in \mathcal{D}_r$, the production and decay terms $K_i(x)$ and $\Gamma_i(x)$ defined by (3) are constants:

$$\forall x \in D\ ,\quad K_i(x) = \kappa_i^D \geq 0\ ,\quad \Gamma_i(x) = \gamma_i^D > 0\ ,\qquad i = 1 \ldots n$$

System (1) is therefore a simple affine system in D, with n uncoupled equations:

$$\dot{x}_i = \kappa_i^D - \gamma_i^D x_i\ ,\quad x \in D$$

which can be explicitly solved, given an initial condition $x(0) \in D$:

$$x_i(t) = \frac{\kappa_i^D}{\gamma_i^D} - e^{-\gamma_i^D t}\left(x_i(0) - \frac{\kappa_i^D}{\gamma_i^D}\right)\ ,\quad \text{for all } t \in \mathbb{R}_+ \text{ such that } x(t) \in D \tag{6}$$

It follows that $x(t)$ monotonically[1] converges towards the point:

$$\phi(D) = \left(\phi_1^D, \ldots, \phi_n^D\right) = \left(\frac{\kappa_1^D}{\gamma_1^D}, \ldots, \frac{\kappa_n^D}{\gamma_n^D}\right) \tag{7}$$

[1]By this we mean that for each i, $x_i(t)$ is a monotone function of t.

which is an asymptotically stable equilibrium for the flow. This point is often called *focal point* of the domain D. In the literature about PWA systems, it is generally assumed that for any regular domain D, the focal point $\phi(D)$ belongs to $\Omega\backslash H$, i.e. $\phi(D)$ does not lie on a threshold hyperplane. Therefore $\phi(D)$ lies in a regular domain $D' \in \mathcal{D}_r$. We have then to consider two cases, whether $D' = D$ or not. If $D' = D$ then the solution $x(t)$ defined by (6) belongs to D for all $t \in \mathbb{R}_+$. So $\phi(D)$ is indeed an asymptotically stable equilibrium. In the other case, the trajectory escapes the domain D, i.e. there exists a finite time $t^* > 0$ such that $x(t^*)$ belongs to a singular domain that bounds D. Let us suppose that this singular domain is $(n-1)$-dimensional. It then bounds another regular domain noted D_1(we say that the singular domain is a *wall* between D and D_1). Sometimes it happens that the solution can be continued in D_1 without difficulties (see [2] and references therein). The switching domain is then called *transparent wall* (see figure 2). However, it might happen that the two solutions in D and D_1 are both directed towards the same switching domain. The latter is then called *black wall* (see figure 2) and the analysis leads to mathematical difficulties: we have to consider solutions in the sense of *Filippov* [10].

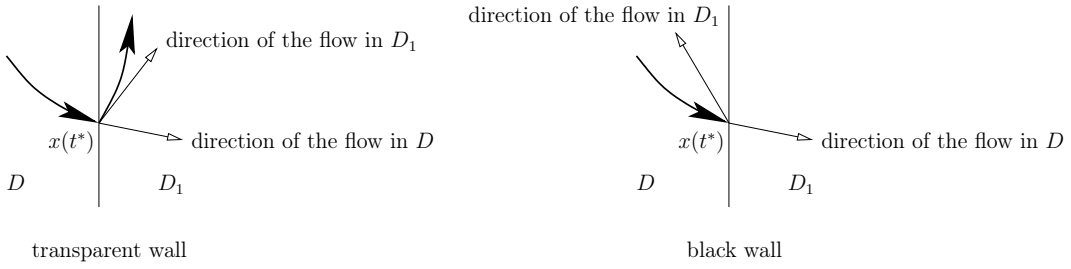


Figure 2: Transparent and black walls

2.2.2 Singular dynamics

Over a singular domain $D \in \mathcal{D}_s$, we already mentioned that the vector field is undefined. We thus cannot solve the differential equation in the classical sense. We can nevertheless use a weaker notion of solution which is known as *Filippov* solution (see [10]). We simply give here a brief summary of essential points, interested readers will find more details in PWA literature (see e.g. [2]).

Let $D \in \mathcal{D}_s$ be a singular domain and $x_0 \in D$ an initial condition lying in D. The Filippov method consists in extending the system (1) to a differential inclusion:

$$\dot{x} \in H(x) \ , \quad x(0) = x_0 \in D \tag{8}$$

where $H(x)$ is a set-valued function defined by:

$$H(x) = \overline{\text{co}} \left(\left\{ \kappa^{D'} - \gamma^{D'} x \mid \ D' \in R(D) \right\} \right) \tag{9}$$

where $R(D) = \{D' \in \mathcal{D}_r \mid \ D \subseteq \partial D'\}$ is the set of all regulatory domains which have D in their boundary and $\overline{\text{co}}(X)$ is the closed convex hull of X.

In the case where $H(x_0) \cap \text{supp}(D) = \emptyset$, then the solution does not stay in D and instantaneously escapes towards a regulatory domain: D is a transparent wall. In the other case, we define a solution in the sense of Filippov as an absolutely continuous function $\xi(t)$ defined on $[0, T]$ such that $\xi(0) = x_0$ and $\dot{\xi}(t) \in H(\xi(t))$ for almost all $t \in [0, T]$. Such a solution exists for all initial condition x_0 but is not guaranteed to be unique though, because of the generalization of the differential equation to a differential inclusion. To get a feeling of what happens let us consider the case of a black wall as defined previously (see figure 3). When arriving in $x^* \in D$, the solution, in the sense of Filippov, can be continued by *sliding* along the switching domain D.

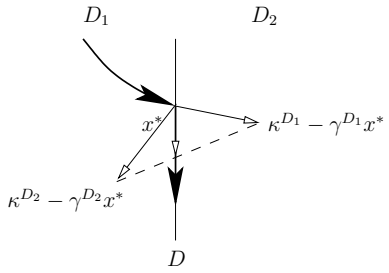


Figure 3: A sliding mode

Several authors have thus studied the dynamics of PWA systems using Filippov method (see notably [1,2,7,14]). Following [1,7], we will here use a slightly different definition of the differential inclusion (8-9):

$$\dot{x} \in H(x) = \overline{\text{rect}}\left(\left\{\kappa^{D'} - \gamma^{D'} x \mid \ D' \in R(D)\right\}\right) \tag{10}$$

where $\overline{\text{rect}}(X)$ designates the smallest closed hyperrectangle, the faces of which are parallel to the axes, containing the set X. This definition is clearly an over-approximation of (9) (see figure 4). Following the same authors, we define, for a switching domain D the notion of *target equilibrium*

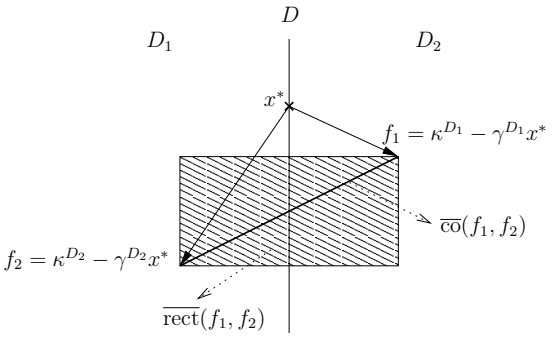


Figure 4: Representations of $H(x)$ according to (9) and (10)

set, which is a generalization of the focal points of regular domains:

Definition 2 *Let $D \in \mathcal{D}_s$ be a switching domain. The target equilibrium set of D, noted $\Psi(D)$ is defined by:*

$$\Psi(D) = supp(D) \cap \overline{rect}(\{\phi(D') \mid \ D' \in R(D)\})$$

We recall that $\overline{rect}(X)$ is the smallest hyperrectangle, the faces of which are parallel to the axes, that contains the set X.

Let us remark here that this definition of target equilibrium set can be extended to a regular domain D by simply posing: $\Psi(D) = \{\phi(D)\}$.

The main interest of such sets lies in the following result, that can be found in [7]:

Lemma 1 *Given a singular domain $D \in \mathcal{D}_s$ and an initial condition $x_0 \in D$, any solution $\xi(t)$ of the differential inclusion:*

$$\dot{x} \in \overline{rect}\left(\left\{\kappa^{D'} - \gamma^{D'} x \mid \ D' \in R(D)\right\}\right) \quad , \quad x(0) = x_0$$

satisfies the property that for all $i \in \{1, \ldots, n\}$, $\xi_i(t)$ monotonically converges towards the orthogonal projection of $\Psi(D)$ on $[0, max_i]$:

$$\pi_i\left(\Psi(D)\right) = \{\psi_i \in [0, max_i] \mid \ \psi \in \Psi(D)\}$$

We conclude this part by an important remark concerning target equilibrium sets.

Remark 4 *To be in accordance with PWA literature, we should have defined first* focal sets *as done for instance in [2]. This definition though is quite heavy in our case because we did not make the following assumption:* $\exists \gamma > 0\,,\ \forall D \in \mathcal{D}_r\,,\ \gamma^D = \gamma$ *(i.e. the degradation terms are independent of the domains). We do not enter the details here, since definition 2 and lemma 1 will be sufficient for what follows.*

3 Hierarchical organization of piecewise affine systems

3.1 The strongly connected components decomposition

The notion of hierarchical organization of a PWA system relies on the well known strongly connected components (SCC) decomposition of the interaction graph. This work has already been done for more general dynamical systems (see e.g. [19]) according to a special definition of the interaction graph. For PWA systems, we will use the definition 1. According to this definition, the interaction graph of an n-dimensional PWA system Σ is a digraph[2] $\mathcal{G}_\Sigma = (\mathcal{V}, \mathcal{E})$ with $\mathrm{card}(\mathcal{V}) = n$. We recall that the set of edges $\mathcal{E}$ can be partially signed (see remark 3). We recall here some basics about digraphs (see e.g. [4] for more details):

Definition 3 *Let $G = (V, E)$ be a digraph. We define the relation "are mutually reachable" on the vertices set V: Two vertices $u, v \in V$ are mutually reachable (denoted $u \sim v$) if and only if there exist two (directed) paths ρ and ρ' such that ρ joins u to v (denoted $u \overset{\rho}{\rightsquigarrow} v$) and ρ' joins v to u (denoted $v \overset{\rho'}{\rightsquigarrow} u$).*

This relation is clearly an equivalence relation on the set V of vertices. The *strongly connected components* of the digraph G are then defined as the elements of $V/\sim$, that is to say the equivalence classes of the relation $\sim$. In other words, a strongly connected component of a digraph G is a maximal set of vertices $C \subseteq V$ such that for every pair $u, v \in C$, we have both $u \rightsquigarrow v$ and $v \rightsquigarrow u$, that is, u and v are reachable from each other.

The SCC decomposition of a digraph G consists in computing the strongly connected components of G: $C_1, \ldots, C_k$ and then to compute the digraph $G^{scc} = (V^{scc}, E^{scc})$ defined as follows:

- $V^{scc} = \{C_1, \ldots C_k\}$, and
- given $i, j \in \{1, \ldots, k\}$ the edge $(C_i, C_j) \in E^{scc}$ exists if and only if there are $u \in C_i$ and $v \in C_j$ such that $(u, v) \in E$.

It can be easily proven (see [4]) that the digraph G^{scc} contains no (oriented) cycles. It is called a *dag* (for directed acyclic graph). This is a key property of G^{scc}, because every dag can be *topologically sorted* (see [4], section 22.4). A topological sort of a dag can be viewed as a classification of its vertices in several hierarchical levels $H_0, H_1, \ldots$ such that the vertices of the first level H_0 are the vertices with no predecessors (they are called *roots*), and the predecessors of vertices of level H_i, $i > 0$ are contained in inferior levels H_j with $j < i$ (see figure 5). Because of this important property, dags are often used to represent events and precedence relations between them.

The SCC decomposition algorithm presented in [4] is interesting because it offers the possibility to compute the graph G^{scc} directly in topological sorted order. We just give here the principle of the algorithm, interested readers are referred to [4] for more details. This algorithm computes G^{scc} using two successive depth-first searches, the first one on the graph G and the second one on the graph G^T, which is the transpose of G. The graph G^T is simply defined as the graph (V, E^T), where $E^T = \{(u, v) \mid (v, u) \in E\}$ (i.e. G^T is obtained by reversing the edges of G). During the first depth-first search, *finishing times* for each vertex u (i.e. the times when u and its successors have been explored) are computed. In the algorithm, the second depth-first search of G^T is performed

[2] A digraph is a directed graph.

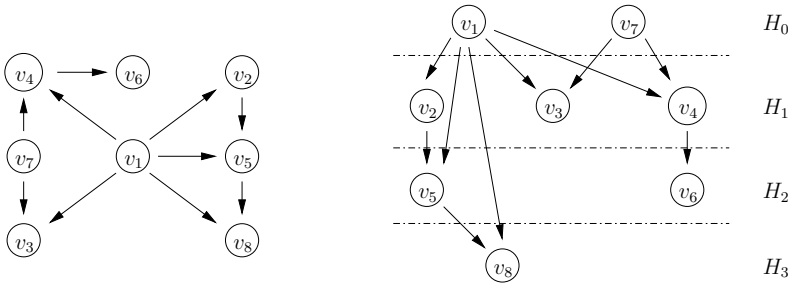


Figure 5: A dag (on the left) and its topological sort (on the right), with 4 levels.

in order of decreasing finishing times, to ensure the topological sort of G^{scc}. A proof of the correctness of this algorithm can be found in [4]. It runs in linear time of $\mathrm{card}(V) + \mathrm{card}(E)$.

The interest of SCC decomposition of the interaction graph of a PWA system is quite obvious. Indeed, when performing this decomposition, we isolate several subsystems involving groups of variables that "work" together. These subsystems are ordered in several hierarchical levels which can allow the decomposition of the analysis of the whole system. Let us illustrate this by a simple 4-dimensional example.

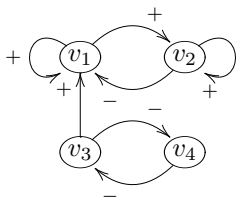
Example 3
Consider the PWA system:

$$(\Sigma)\begin{cases} \dot{x}_1 = \kappa_1^0 + \kappa_1^1 f_1(x) + \kappa_1^2 s^+(x_1,\theta_1^1)s^-(x_2,\theta_2^2)s^+(x_3,\theta_3^1)f_1(x) - \gamma_1 x_1 \ , & p_1 = 2 \\ \dot{x}_2 = \kappa_2^0 + \kappa_2^1 f_2(x) + \kappa_2^2 s^+(x_1,\theta_1^1)s^+(x_2,\theta_2^1)f_2(x) - \gamma_2 x_2 \ , & p_2 = 2 \\ \dot{x}_3 = \kappa_3^0 + \kappa_3^1 s^-(x_4,\theta_4^1) - \gamma_3 x_3 \ , & p_3 = 1 \\ \dot{x}_4 = \kappa_4^0 + \kappa_4^1 s^-(x_3,\theta_3^1) - \gamma_4 x_4 \ , & p_4 = 1 \end{cases} \tag{11}$$

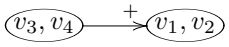
with:

$$\begin{cases} f_1(x) = \big(1 - s^-(x_1,\theta_1^2)s^+(x_2,\theta_2^1)\big) \\ f_2(x) = \big(1 - s^-(x_1,\theta_1^2)s^-(x_2,\theta_2^1)\big) \end{cases}$$

Its interaction graph is represented by:



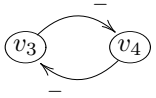
The SCC decomposition of this graph gives:



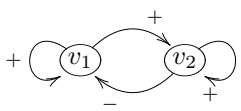
(12)

We have therefore decomposed system (11) into two isolated bidimensional subsystems with simple interaction graphs:

$$(\Sigma_1)\quad \begin{cases} \dot{x}_3 = \kappa_3^0 + \kappa_3^1 s^-(x_4,\theta_4^1) - \gamma_3 x_3 \\ \dot{x}_4 = \kappa_4^0 + \kappa_4^1 s^-(x_3,\theta_3^1) - \gamma_4 x_4 \end{cases}$$



$$(\Sigma_2)\quad \begin{cases} \dot{x}_1 = \kappa_1^0 + \kappa_1^1 f_1(x) + \kappa_1^2 s^+(x_1,\theta_1^1)s^-(x_2,\theta_2^2)f_1(x) - \gamma_1 x_1 \\ \dot{x}_2 = \kappa_2^0 + \kappa_2^1 f_2(x) + \kappa_2^2 s^+(x_1,\theta_1^1)s^+(x_2,\theta_2^1)f_2(x) - \gamma_2 x_2 \end{cases}$$



The first one (Σ_1) *is the well known "biological switch" often used in the literature to illustrate the concept of* bistability *(see [3, 8] for theoretical aspects and [11] for experimental investigations). The second system is a negative loop (see [9] for an interesting analysis of simple negative feedback loop systems) with positive self-regulation of the two variables.*
Under the following assumptions, giving the relative positions of focal points with respect to the thresholds:

$$\begin{cases} 0 < \dfrac{\kappa_1^0}{\gamma_1} < \theta_1^1 < \dfrac{\kappa_1^0+\kappa_1^1}{\gamma_1} < \theta_1^2 < \dfrac{\kappa_1^0+\kappa_1^1+\kappa_1^2}{\gamma_1} < max_1 \\ 0 < \dfrac{\kappa_2^0}{\gamma_2} < \theta_2^1 < \dfrac{\kappa_2^0+\kappa_2^1}{\gamma_2} < \theta_2^2 < \dfrac{\kappa_2^0+\kappa_2^1+\kappa_2^2}{\gamma_2} < max_2 \\ 0 < \dfrac{\kappa_3^0}{\gamma_3} < \theta_3^1 < \dfrac{\kappa_3^0+\kappa_3^1}{\gamma_3} < max_3 \\ 0 < \dfrac{\kappa_4^0}{\gamma_4} < \theta_4^1 < \dfrac{\kappa_4^0+\kappa_4^1}{\gamma_4} < max_4 \end{cases} \tag{13}$$

a qualitative analysis can be made of these simple bidimensional PWA systems. The figure 6 presents the two phase portraits. System (Σ_1) *shows two asymptotically stable steady states whereas* (Σ_2) *shows an attractive cycle.*

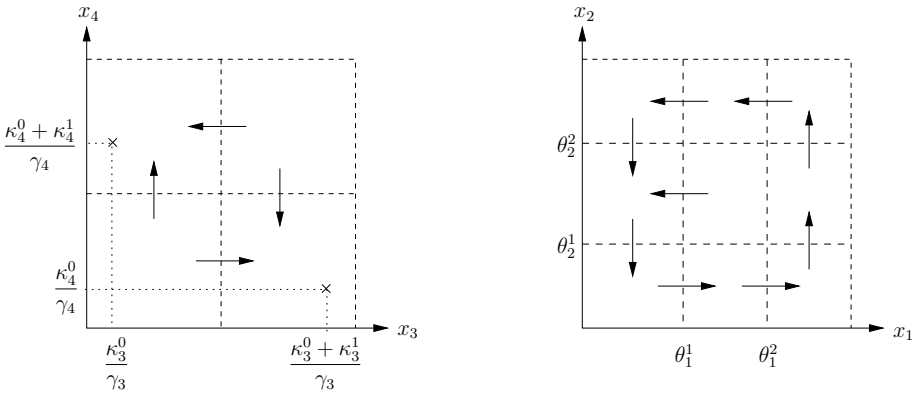


Figure 6: Phase portraits of subsystems (Σ_1) and (Σ_2).

□

The method of qualitative simulation of PWA systems used in this example to compute the phase portraits of (Σ_1) and (Σ_2) is the one exposed in [2,7]. For such simple systems, this analysis can be carried out directly. We nevertheless recall the existence of the GNA software [6] that implements this technique and allows to qualitatively analyse higher dimensional PWA systems. The SCC decomposition has besides been implemented as a GNA module [5].

It must be noted that subsystems (Σ_1) and (Σ_2) are isolated, that is, unrelated among themselves. To rebuild the whole system (Σ), one has to take into consideration the unique edge of the SCC graph (12), which corresponds to the term $s^+(x_3, \theta_3^1)$ of the first equation of system (11):

$$\dot{x}_1 = \kappa_1^0 + \kappa_1^1 f_1(x) + \kappa_1^2 s^+(x_1, \theta_1^1) s^-(x_2, \theta_2^2) \underbrace{\mathbf{s^+(x_3, \theta_3^1)}}\ f_1(x) - \gamma_1 x_1$$

The question that is addressed in the next section is whether it is possible to deduce the qualitative behavior of the system (11) (or at least a part of its behavior) from the qualitative analysis of the isolated subsystems (Σ_1) and (Σ_2). This issue can be of particular importance if the initial system dimension is high because in that case a direct qualitative analysis of the whole system can lead to a huge transition graph. From a practical point of view, it is often difficult to deduce interesting properties of the dynamics from such a graph.

3.2 Asymptotic analysis of hierarchical PWA systems

As we already said, the use of the SCC decomposition to analyse the behavior of a dynamical system is not new. In [19] for instance, Vidyasagar proposes to use such a decomposition for a general dynamical system with nonadditive interactions, in order to express the latter in a triangular form:

$$\dot{x}_i(t) = f_i\left(t, x_1(t), \ldots, x_i(t)\right) \ , \qquad i = 1, \ldots, m$$

Then, assuming that 0 is an equilibrium point for all isolated subsystems:

$$\dot{x}_i(t) = f_i\left(t, 0, \ldots, 0, x_i(t)\right)$$

he proves some powerful theorems (based on the general theory of dynamical systems) linking the stability of these equilibria and the stability of 0 as an equilibrium of the initial system. The underlying idea is actually quite simple: it consists in "injecting" the value of the equilibrium of the first subsystem into the second, then the value of the first and the second subsystem into the third, and so on until we obtain the whole system equilibrium.
Because of the discontinuities of the PWA vector fields, such general theorems are not directly applicable. We however propose in the following a technique specifically adapted to PWA framework that allows one to use the hierarchical organization of a PWA system for the analysis of its asymptotic dynamics. To present this method, we will use the system (Σ) presented in example 3 as an illustrating example.

Let us therefore consider the PWA system (11) and let us assume the inequalities (13) on the parameters, placing the different focal points with respect to the thresholds. The letter x designates the vector (x_1, x_2, x_3, x_4) lying in Ω (recall that Ω is the 4-dimensional hyperrectangle $\prod_{i=1}^{4}[0, max_i]$). In the following, we will use the abuse of language stated in the first part of this report: a *hyperrectangular domain* denotes an n-dimensional hyperrectangle, the faces of which are contained in threshold hyperplanes. We recall that such a domain is unequivocally denoted by a finite set of *discrete equations* (see example 1).
These domains will take an essential part because according to the definition of a PWA system (see equation (3)), the interactions between variables take place only by means of qualitative values, i.e. by means of terms of the form $s^+(x_i, \theta_i^j)$. Therefore, instead of "injecting" the exact value of an equilibrium into a subsequent system, we will only have to inject its *qualitative* value, that is, a set of discrete equations involving the discrete variables $s^+(x_i, \theta_i^j)$.

Let us first focus on the subsystem (Σ_1). As we said before, this system shows two attractors (see figure 6), which are the two regular steady states:

$$A = \left(\frac{\kappa_3^0 + \kappa_3^1}{\gamma_3}, \frac{\kappa_4^0}{\gamma_4}\right) \text{ and } A' = \left(\frac{\kappa_3^0}{\gamma_3}, \frac{\kappa_4^0 + \kappa_4^1}{\gamma_4}\right)$$

Remark 5 *There is actually a third equilibrium point which is the singular steady state* $(x_3, x_4) = \left(\theta_3^1, \theta_4^1\right)$. *We note here that this steady state is an equilibrium* in the sense of Filippov. *This steady state is of no importance here as it can be easily shown to be unstable (see [2] for a precise definition of stability and unstability of singular steady states).*

Let Δ and Δ' be the smallest hyperrectangular domains containing respectively the two steady states:

$$\Delta = \left]\theta_3^1, max_3\right] \times \left[0, \theta_4^1\right[\quad \text{and} \quad \Delta' = \left[0, \theta_3^1\right[\times \left]\theta_4^1, max_4\right]$$

These sets are given by their discrete equations:

$$\Delta : \begin{cases} s^+(x_3, \theta_3^1) = 1 \\ s^+(x_4, \theta_4^1) = 0 \end{cases} \quad \text{and} \quad \Delta' : \begin{cases} s^+(x_3, \theta_3^1) = 0 \\ s^+(x_4, \theta_4^1) = 1 \end{cases}$$

System (Σ_1) has therefore two types of trajectories: the first ones converging towards the attractor A and the second ones towards A' (we neglect here the trajectories leading to (θ_3^1, θ_4^1)). According to what type of attractors we are heading to, we respectively inject the discrete equations of Δ or Δ' into the system (Σ_2). We consequently have to consider two cases:

- If (x_3, x_4) converges towards A, then $s^+(x_3, \theta_3^1) = 1$ and the bidimensional system involving the variables x_1 and x_2 can be replaced by:

$$(\Sigma_2) \left\{ \begin{array}{l} \dot{x}_1 = \kappa_1^0 + \kappa_1^1 f_1(x) + \kappa_1^2 s^+(x_1, \theta_1^1) s^-(x_2, \theta_2^2) f_1(x) - \gamma_1 x_1 \\ \dot{x}_2 = \kappa_2^0 + \kappa_2^1 f_2(x) + \kappa_2^2 s^+(x_1, \theta_1^1) s^+(x_2, \theta_2^1) f_2(x) - \gamma_2 x_2 \end{array} \right.$$

- If, on the contrary, (x_3, x_4) converges towards A', then $s^+(x_3, \theta_3^1) = 0$ and thus we replace (Σ_2) by:

$$(\Sigma_2') \left\{ \begin{array}{l} \dot{x}_1 = \kappa_1^0 + \kappa_1^1 f_1(x) - \gamma_1 x_1 \\ \dot{x}_2 = \kappa_2^0 + \kappa_2^1 f_2(x) + \kappa_2^2 s^+(x_1, \theta_1^1) s^+(x_2, \theta_2^1) f_2(x) - \gamma_2 x_2 \end{array} \right.$$

We thus have removed the dependency in x_3 and therefore have reduced the analysis of the 4-dimensional system (11) to the analysis of two uncoupled bidimensional systems.

Before carrying on and completing the analysis of this special system, we have to justify that such a simplification is correct. The proof that follows concerns the current example, however it is pretty straightforward and can easily be generalized to any similar situation. It relies on the fact that Δ and Δ' are *invariants* for the flow of subsystem (Σ_1). Let us recall the classical definition in dynamical systems theory:

Definition 4 *Let $\dot{x} = F(x)$ be an autonomous dynamical system over the open $U \subset \mathbb{R}^n$, and let $\varphi : (t, x) \mapsto \varphi(t, x)$ denotes its flow over U. A subset $\Lambda \subseteq U$ is a (positive) invariant for the flow if:*

$$\forall t \in \mathbb{R}_+ \, , \; \varphi(t, \Lambda) \subseteq \Lambda$$

As A and A' are regular steady states of (Σ_1), Δ and Δ' are clearly positive invariants of the flow. In other words, once $(x_3(t), x_4(t))$ has reached Δ (resp. Δ'), then it stays in Δ (resp. Δ') for all subsequent times. We then show the following result: given (almost) any initial condition $(x_3^0, x_4^0) \in [0, max_3] \times [0, max_4]$, there exists a finite time $t^* \in \mathbb{R}_+$ such that $(x_3(t^*), x_4(t^*))$ belongs to Δ or Δ' and thus:

$$\forall t \geq t^* \, , \; (x_3(t), x_4(t)) \in \Delta \text{ (resp. } \Delta')$$

This result is quite obvious and directly comes from the qualitative analysis of the dynamics of system (Σ_1) (see fig. 6). For a better understanding of what happens, we make here an additional assumption:

$$\gamma_3 = \gamma_4 = \gamma$$

With uniform decay rates, the trajectories in each box are straight segments, and it becomes easy to draw the basins of attraction $\mathcal{B}(A)$ and $\mathcal{B}(A')$ of the two attractors (see figure 7). It must be

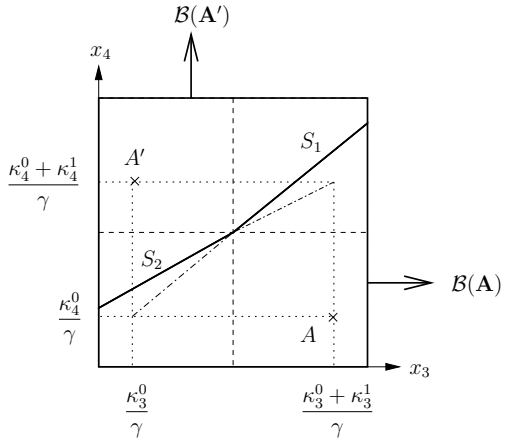


Figure 7: Basins of attraction of the two attractors A and A'.

noted that the points lying in the common boundary between $\mathcal{B}(A)$ and $\mathcal{B}(A')$ (which is composed

of the union of the two segments $S_1 \cup S_2$, see figure 7) will be supposed not to belong to these basins, as they all lead to the unstable steady state (θ_3^1, θ_4^1). According to remark 5, once they have reached this singular steady state, there actually exist solutions that leave this point in finite time, and may converge to A or A'. To simplify the analysis, we nevertheless decided here not to consider the region $S_1 \cup S_2$. It is of Lebesgue measure zero and this explains why the previous result holds for *almost* all initial condition. We are now able to formalize the previous statement:

Proposition 1 *Let $x^0 = \left(x_1^0, x_2^0, x_3^0, x_4^0\right)$ be a point in Ω such that $(x_3^0, x_4^0) \notin S_1 \cup S_2$ (i.e. (x_3^0, x_4^0) belongs to the disjoint union $\mathcal{B}(A) \cup \mathcal{B}(A')$), and let $x(t) = (x_1(t), x_2(t), x_3(t), x_4(t))$ be the solution of (11) with initial condition $x(0) = x^0$.*
Then, whatever x_1^0 and x_2^0, there exists a finite time $t^* \in \mathbb{R}_+$ such that $(x_3(t^*), x_4(t^*)) \in \Delta$ (respectively Δ') and the semi trajectory $\Xi = \{(x_1(t), x_2(t)) \mid t \geq t^*\}$ is the solution of system (Σ_2) (resp. (Σ_2')), starting from the point $(x_1(t^*), x_2(t^*))$ at time t^*.

According to this proposition, and after analyzing the phase portraits of systems (Σ_2) and (Σ_2'), we can complete the asymptotic qualitative analysis of system (11). We actually find two main attractors, which are a regular steady state contained in the box:

$$\left]\theta_1^1, \theta_1^2\right[\times \left[0, \theta_2^1\right[\times \left[0, \theta_3^1\right[\times \left]\theta_4^1, max_4\right]$$

and an attractive cycle contained in the region:

$$[0, max_1] \times [0, max_2] \times \left]\theta_3^1, max_3\right] \times \left[0, \theta_4^1\right[$$

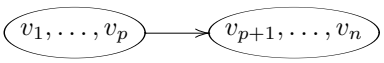
(see the right picture in figure 6 for a projection of this cycle).

Remark 6 *We speak here of asymptotic analysis because this method does not give us any indication about the transient behavior: $\{(x_1(t), x_2(t)) \mid t \leq t^*\}$. Actually, all we can say with this kind of techniques is that there exists a finite time after which the variables x_1 and x_2 will evolve regardless of the exact value of the variables x_3 and x_4.*

3.3 Generalization for other types of attractors

The previous case study raises two important points. The first one is that the SCC decomposition of system (11) is quite simple as it is composed of only two strongly connected components, joined by only one edge. We note here that if the SCC graph is more complicated, then the technique exposed can be theoretically generalized without main difficulties, provided that we can perform a qualitative analysis of the different subsystems and isolate their steady states. Of course, as the number of attractors of each systems, and the number of subsystems themselves grow, we will inevitably have to consider an exponentially growing number of cases, which can lead to a heavy algorithmic study.

The second point is that we have so far restricted ourselves to a very particular kind of attractors which are regular steady states. It must be noted that this is not a limitation for the method and other types of attractors can be considered as well (see for instance figure 8).
Consider, for $n \in \mathbb{N}^*$, an n-dimensional PWA system given by equations (2) and (3). Suppose that its SCC decomposition leads to the hierarchical graph:



Let y and z denote the subvectors:

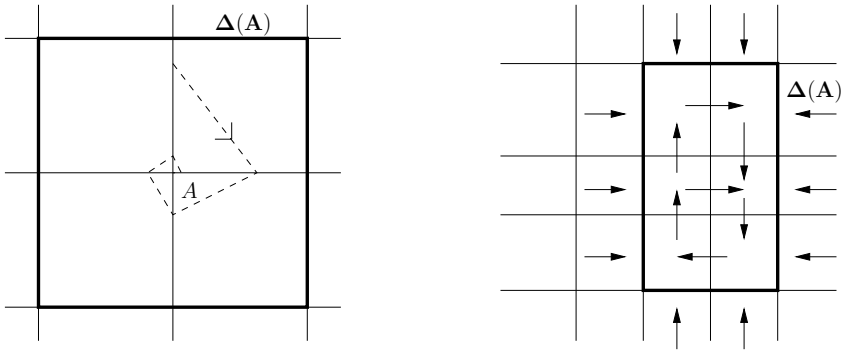
$$\begin{cases} y = (y_1, \ldots, y_p) & = (x_1, \ldots, x_p) \\ z = (z_1, \ldots, z_{n-p}) & = (x_{p+1}, \ldots, x_n) \end{cases}$$

and suppose that the y-subsystem has a unique global attractor $\mathcal{A} \subset \Omega_y = \prod_{i=1}^{p} [0, max_i]$. In order to apply the previous technique, we will have to define a *hyperrectangle hull* of $\mathcal{A}$:

Definition 5 *Let $p \in \mathbb{N}^*$ and $\Omega = \prod_{i=1}^{p} [0, max_i]$. Given a subset Λ of Ω, we call hyperrectangular hull of Λ (noted $\Delta(\Lambda)$), the smallest p-dimensional hyperrectangle, the faces of which are contained in threshold hyperplanes, that contains Λ. The set $\Delta(\Lambda)$ is unequivocally determined by a finite set of discrete equations of the form:*

$$\begin{cases} s^+(x_i, \theta_i^0) = \cdots = s^+(x_i, \theta_i^{j_1}) = 1 \\ s^+(x_i, \theta_i^{j_2}) = \cdots = s^+(x_i, \theta_i^{p_i}) = 0 \end{cases}$$

for each $i \in \{1, \ldots, p\}$.



A singular steady state

A more complex attractor

Figure 8: Two types of attractors (2d) with their hyperrectangular hulls.

Following the technique presented in the previous section, we state the following proposition:

Proposition 2 *If we suppose that the y-subsystem has a unique global attractor $\mathcal{A} \subset \Omega_y$, then the asymptotic behavior of the z-subsystem is the same as the asymptotic behavior of the z-system in which we have injected the discrete equations of the hyperrectangle $\Delta(\mathcal{A})$.*

Although we do not give the proof here, it mainly relies on the two key points precedently evoked:

- The set $\Delta(\mathcal{A})$ is a positive invariant for the subsystem in y,
- Given any initial condition $x^0 \in \Omega$, there exists a finite time $t^* \in \mathbb{R}_+$ such that $y(t^*) \in \Delta(\mathcal{A})$.

Obviously, as illustrated by the previous example, if the system in y shows several attractors, then a complete analysis leads to consider different cases:

Proposition 3 *Let $\mathcal{A}_1, \ldots, \mathcal{A}_p$ be the attractors of the y-subsystem, then the asymptotic behavior of the z-subsystem is the union of the asymptotic behavior of the z-systems (Σ_z^i) in which we have injected the discrete equations of the hyperrectangles $\Delta(\mathcal{A}_i)$, $i = 1 \ldots p$.*

Remark 7 *Contrary to the case of regular steady states, where the hyperrectangular hull is reduced to the box containing the steady state, for other attractors, the hull can contain many boxes, and can even be equal to the whole phase space. In those cases, the technique may fail to uncouple the two subsystems. This is actually to relate to a general issue for all model reduction techniques, which is the issue of* irreducibility *of systems.*

Another limitation of the presented approach is that its effectiveness is directly related to the SCC decomposition. Obviously it is not applicable if, for instance, the interaction graph of the initial system is already strongly connected. Following the same idea, it may happen for real biological high dimensional systems, that the SCC decomposition has a main strongly connected

component of relatively high dimension, which is not very satisfactory from a model reduction point of view. For this reason, we propose in the next part a simple algorithm that may be able to solve this problem, for certain systems, by "cutting" this main component into smaller ones. This technique has been successfully applied to the example of the carbon starvation in *E. coli* bacterium [16, 17].

4 Threshold elimination, application to a biological model

4.1 The principle of threshold elimination

We consider in this section an n-dimensional PWA system (Σ), given by equations (2) and (3). We compute, for each regulatory domain $D \in \mathcal{D}_r$, the focal point $\phi(D)$ with formula (7). We denote Φ the set of all focal points:

$$\Phi = \{\phi(D) \mid \quad D \in \mathcal{D}_r\}$$

We recall that for a qualitative analysis to be possible, we also have to give the relative positions of the focal points with respect to the different thresholds (see [7]).
The algorithm that we present here is based on the following lemma:

Lemma 2 *If, for some $i \in \{1, \ldots, n\}$, there exist $j_1, j_2 \in \{1, \ldots, p_i\}$ such that:*

$$\forall \phi \in \Phi\ , \quad \theta_i^{j_1} < \phi_i < \theta_i^{j_2}$$

let us denote by $\Delta^{(i)}$ the set $[0, max_1] \times \cdots \times \left]\theta_i^{j_1}, \theta_i^{j_2}\right[\times \cdots \times [0, max_n]$. We then have the two assertions:

(i) $\Delta^{(i)}$ is a positive invariant of (Σ).

(ii) Given any initial condition $x^0 \in \Omega$, there exists $t^* \in \mathbb{R}_+$ such that $x(t^*) \in \Delta^{(i)}$.

Proof
The first assertion is quite obvious (see figure 9 for an illustration).
Assertion (ii) can be easily deduced from lemma 1, as, for all domains D (both regular and singular) the attractive equilibrium set $\Psi(D)$ is contained in the set $\Delta^{(i)}$. $\diamondsuit$

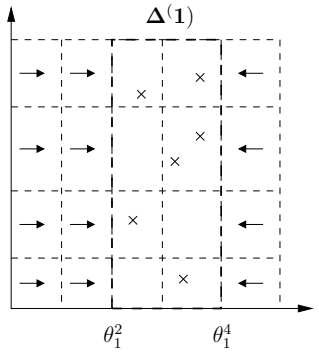


Figure 9: Illustration of lemma 2 (crosses are focal points and arrows represent the projection of the vector field of each regular domain on the x_1 axis).

Remark 8 *We recall that we consider solutions in the sense of differential inclusion (10). Nevertheless, let us remark that this lemma remains true for real Filippov solutions given by (9), because in both cases, the attractive sets[3] of all domains (both regular and singular) are contained within $\Delta^{(i)}$.*

[3]The notion of attractive set in the case of inclusion (9) is not defined in this report. Considering uniform decay rates, one can find a definition in [2].

This lemma provides us with a simple procedure that allows one to "eliminate" some thresholds in direction i: $\theta_i^1, \ldots, \theta_i^{j_1}$ and $\theta_i^{j_2}, \ldots, \theta_i^{p_i}$. Indeed, neglecting some unknown transient behavior, we are ensured that, after a finite time, the system will reach the set $\Delta^{(i)}$ and stay in it for all subsequent times. So, for an asymptotic analysis of system (Σ), one can pose:

$$\begin{cases} s^+(x_i, \theta_i^0) = \cdots = s^+(x_i, \theta_i^{j_1}) = 1 \\ s^+(x_i, \theta_i^{j_2}) = \cdots = s^+(x_i, \theta_i^{p_i}) = 0 \end{cases} \tag{14}$$

This elimination procedure presents two major advantages. First, it can be performed directly on the structure of the PWA system (provided the inequalities positioning the focal points with respect to the thresholds), regardless of its dynamics. Then, it can be performed independently in each direction $i \in \{1, \ldots, n\}$.

4.2 An algorithm based on hierarchical organization

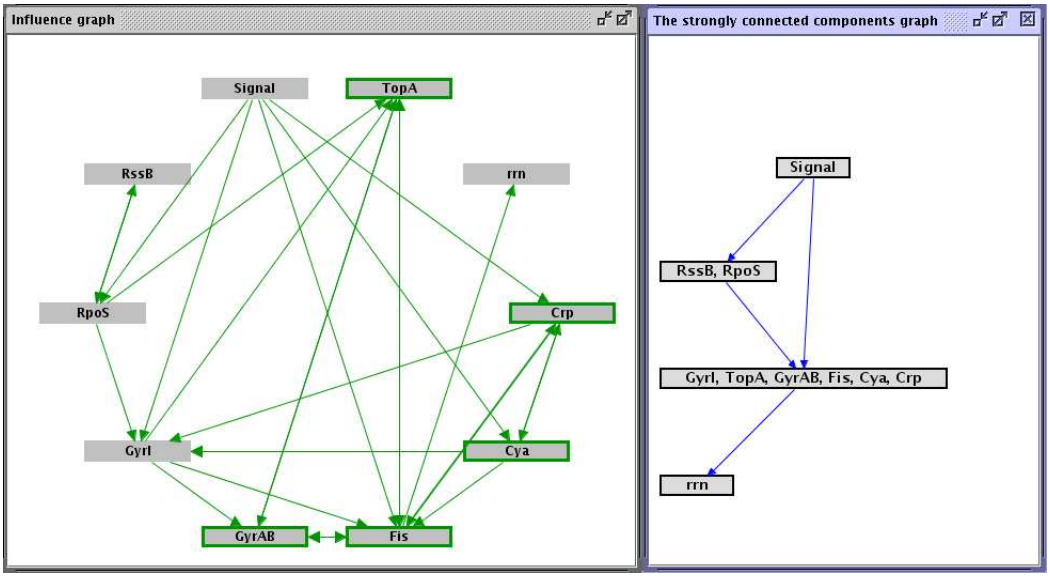
When performing the elimination procedure in a direction i, we obtain a set (14) of discrete equations (this set is possibly empty). Injecting these equations in the PWA system (Σ) implies to suppress in (Σ) some terms of the form $s^{\pm}(x_i, \theta_i^j)$ (for some j). According to definition 1, by doing so, we possibly cut some edges of the interaction graph $\mathcal{G}_\Sigma$ and therefore change the structure of (Σ). As a consequence, a first idea is to perform n successive eliminations in the directions $i = 1, \ldots, n$. Once this step is done, we obtain a (possibly) reduced PWA (Σ') (The term reduced must be understood here as the reduction of the edge set $\mathcal{E}$ of $\mathcal{G}_\Sigma$). If the system has effectively been reduced, we have to consider the set Φ' of the focal points of (Σ'). If $\Phi' \neq \Phi$, then we have to repeat the previous step, in order to obtain a new (possibly reduced) system (Σ'') etc.

This iterative procedure can be performed in finite time, as the graph $\mathcal{G}_\Sigma$ is finite, and each step consists in reducing its edge set $\mathcal{E}$. However, this is clearly not an optimal procedure. In order to be more effective, one has to apply the elimination procedure to the hierarchical graph $\mathcal{G}^{scc}$. Indeed, when applying the elimination procedure in direction i, we eliminate terms $s^{\pm}(x_i, \theta_i^j)$, that is, edges originating in v_i. Thus, once the elimination of a strongly connected component C is over, elimination performed on vertices v_k belonging to subsequent components will not affect it any more (as there is no edge originating in v_k and terminating in a vertex of C). According to this remark, we can give a general sketch for an elimination algorithm (see alg. 1). The critical step in this algorithm is obviously the loop on the line 4. Indeed, the effectiveness of the model reduction by threshold elimination is directly linked with the fact that "big" components can be decomposed in smaller ones.

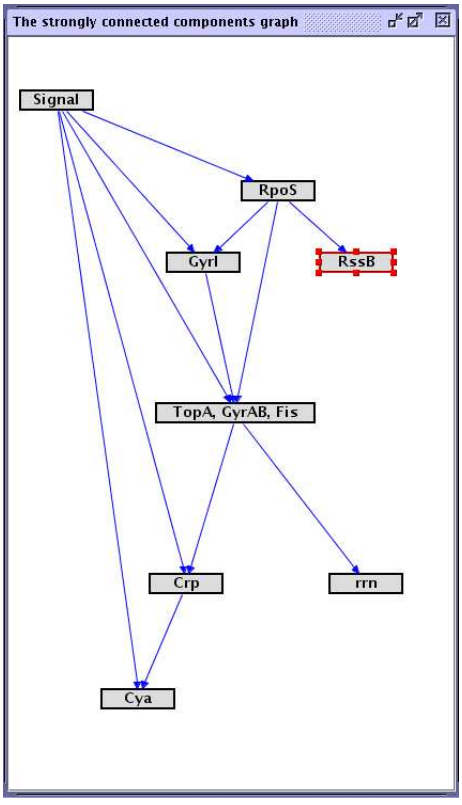
4.3 Application to an extended model of carbon starvation in *E-coli*

Such a method has shown to be quite effective to the analysis of a real biological example: the carbon starvation response network in the bacterium *E. coli*. The piecewise affine model of this network can be found in two different versions. The article [17] presents the biological phenomenon and gives a PWA model with 6 variables and one input signal. In [16], an extended version with 9 variables and one input signal can be found. A direct qualitative analysis of the 9-dimensional system using the GNA tool is quite difficult to perform, as the whole transition graph is too big. Specific qualitative simulations with several initial conditions can be performed though, but the analysis of the qualitative trajectories obtained is not easy as the phase space dimension is quite high. In consequence, the reduction algorithm proposed previously may be of relevance for such a system.

The figure 10a presents the interaction graph of the system, with its SCC decomposition. The SCC graph contains 4 components. The main one consists of 6 variables. A direct asymptotic analysis using this hierarchical structure is still difficult (it involves a study of a PWA system of dimension 6). Using the elimination algorithm, we manage to decompose this component into 4 components. The figure 10b presents the final decomposition. As we can see on this figure, the biggest component in the reduced model is of dimension 3. Provided an asymptotic analysis of the



(a)



(b)

Figure 10: (a): Interaction graph of extended model (on the left) and its SCC decomposition (on the right). (b): SCC decomposition of the reduced system (after threshold elimination). These pictures were generated thanks to the `GNA` software [6].

Algorithm 1 Threshold elimination of an n-dimensional PWA system.

Require: an n-dimensional PWA system (Σ) and a set of inequalities positioning the focal points with respect to the thresholds.

Ensure: the reduced n-dimensional PWA system (Σ') has the same asymptotic behavior as (Σ).

Compute the interaction graph $\mathcal{G}_\Sigma$
Compute the hierarchical graph $\mathcal{G}^{scc}$
/* *The SCC are denoted* $C_1, \ldots, C_m$*, they are hierarchically ordered: if* $1 \leq k_1 < k_2 \leq m$*, then there is no edge from* C_{k_2} *to* C_{k_1}*.* */
for $k = 1$ to m **do**
  repeat /* *Iterative elimination process in component* C_k*.* l *denotes the number of vertices of* C_k*.* */
    for $j = 1$ to l **do**
      Compute the set Φ of focal points
      Perform elimination in direction j /* *Some edges are possibly cut.* */
      Compute the new interaction graph
      Compute the new hierarchical graph
      Compute the new set Φ' of focal points
    end for
  until $\Phi' = \Phi$
end for
Build the reduced system (Σ')

dynamics of the subsystem {`TopA`, `GyrAB`, `Fis`}, the techniques presented in the previous part may be applied to study the asymptotic qualitative behavior of the whole system.

Remark 9 *An analysis of the behavior of the 3-dimensional subsystem can be found in [15]. This analysis is based on the E.coli system presented in [17] (i.e. not in extended version). However the elimination algorithm applied to both systems exhibits the same subsystem, involving the same variables. This subsystem seems therefore to play a central role in the carbon starvation response phenomenon.*

5 Conclusion

The method presented in this report has two main purposes. The first one, obviously, is that it provides an algorithmic way to analyse a PWA dynamical system of relatively high dimension, analyzing several smaller dynamical systems. From a mathematical point of view, this is to be related with the general concept of *model reduction*. The second purpose must be seen with a biological point of view. Indeed, since the PWA framework has been originally designed to model genetic and biochemical interaction networks, one must keep in mind that one of the main goals of the study of these systems is to get a better understanding of the modeled phenomena. Considering the example of the carbon starvation, the hierarchical analysis presented here allows one to isolate a group of three variables that seem to work together and play a central role in the dynamics of the whole system. Following this example, one may hope that this technique could be applied to higher dimensional systems and may help to identify some "modules" together with their possible interactions.

The concept of model reduction of a dynamical system is not a well-posed mathematical problem. Indeed, according to the expression of the differential equations of the system, there are many ways to *reduce* a system. The goal, however, is always the same: it consists in simplifying the system in order to make its dynamical study easier. In the present report, the term "reduction" must be understood in a very specific way. It corresponds to the reduction of the number of vertices and edges of the interaction graph. As we saw in the 4-dimensional example in the second part, cutting a particular edge may lead to uncouple two subsystems of the whole system, and therefore drastically simplify the analysis. We must be aware though that this situation is specific and for

higher dimensional systems such simplifications will certainly rarely happen. It is mainly for this reason that we proposed the threshold elimination algorithm in the third part. Indeed, this algorithm can be easily implemented and allows, as a preprocessing treatment, a rapid simplification of a system. But again, its efficiency clearly depends on the system. The application on the real example of carbon starvation response seems quite encouraging though. So as to show its practical relevance, the method presented here has to be tested on other examples of real biological models.

References

[1] G. Batt, H. de Jong, J. Geiselmann, M. Page, D. Ropers, and D. Schneider. Symbolic reachability analysis of genetic regulatory networks using qualitative abstraction. Technical Report RR-5362, INRIA, 2004.

[2] R. Casey, H. de Jong, and J.-L. Gouzé. Piecewise-linear models of genetic regulatory networks: equilibria and their stability. *J. Math. Biol.*, 52:27–56, 2006.

[3] J.L. Cherry and F.R. Adler. How to make a biological switch. *J. Theor. Biol.*, 203:117–133, 2000.

[4] T.H. Cormen, C.E. Leiserson, R. L. Rivest, and C. Stein. *Introduction to algorithms*. MIT Press, second edition, 2001.

[5] D.A. Cristescu. Algorithmic study on genetic regulatory networks. Technical report, Automatic control and computer science faculty, Politechnica University of Bucharest, 2006. internship report, INRIA.

[6] H. de Jong, J. Geiselmann, C. Hernandez, and M. Page. Genetic network analyser: qualitative simulation of genetic regulatory networks. *Bioinformatics*, 19(3):336–344, 2003.

[7] H. de Jong, J.-L. Gouzé, C. Hernandez, M. Page, T. Sari, and J. Geiselmann. Qualitative simulation of genetic regulatory networks using piecewise-linear models. *Bull. Math. Biol.*, 66:301–340, 2005.

[8] E. Farcot and J.-L. Gouzé. How to control a biological switch: a mathematical framework for the control of piecewise affine models of gene networks. Technical Report RR-5979, INRIA, 2006. url: https://hal.inria.fr/inria-00094853.

[9] E. Farcot and J.-L. Gouzé. Periodic solutions of piecewise affine gene network models: the case of a negative feedback loop. Technical Report RR-6018, INRIA, 2006. url: https://hal.inria.fr/inria-00112195.

[10] A.F. Filippov. *Differential equations with discontinuous righthand sides*. Kluwer Academic Publishers, Boston, 1988.

[11] T.S. Gardner, C.R. Cantor, and J.J. Collins. Construction of a genetic toggle switch in escherichia coli. *Nature*, 403:339–342, 2000.

[12] L. Glass. Combinatorial and topological methods in nonlinear chemical kinetics. *J. Chem. Phys.*, 63:1325–1335, 1975.

[13] J.-L. Gouzé. Positive and negative circuits in dynamical systems. *J. Biol. Sys.*, 6:11–15, 1998.

[14] J.-L. Gouzé and T. Sari. A class of piecewise linear differential equations arising in biological networks. *Dyn. Syst.*, 17(4):299–316, 2002.

[15] F. Grognard, J.-L. Gouzé, and H. de Jong. Piecewise-linear models of genetic regulatory networks: theory and example. In *Biology and control theory: current challenges*, Lecture Notes in Control and Information Sciences (LNCIS). Springer-Verlag. (to appear).

[16] D. Ropers. An extended model of the carbon starvation response in *Escherishia coli*. In preparation.

[17] D. Ropers, H. de Jong, M. Page, D. Schneider, and J. Geiselmann. Qualitative simulation of the carbon starvation response in *escherichia coli*. *Biosystems*, 84(2):124–152, 2006.

[18] C. Soulé. Graphic requirements for multistationarity. *ComPlexUs*, 1:123–133, 2003.

[19] M. Vidyasagar. Decomposition techniques for large-scale systems with nonadditive interactions: stability and stabilizability. *IEEE Transactions on Automatic Control*, (4):773–779, 1980.

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