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Piecewise affine models of regulatory genetic networks: review and probabilistic interpretation

Madalena Chaves and Jean-Luc Gouzé*

Abstract

A formalism based on piecewise-affine (PWA) differential equations has been shown to be well-suited to modelling genetic regulatory networks. In this paper, we first review some results concerning the qualitative study of these models: we partition the phase space into *domains* bounded by the threshold hyperplanes. Inside each domain, the system is affine. To define solutions on the surfaces of discontinuity, we use the approach of Filippov, which extends the vector field to a differential inclusion. We obtain a transition graph, describing qualitatively the possible transitions of solutions between domains. In a second part of the paper, we give a new probabilistic interpretation of these transitions, by computing the proportion of the volume of the domain that crosses to one of its adjacent domains. We apply this idea to the model of the bistable switch and to parameter estimation from experimental transition probabilities.

1 Introduction

The regulation of gene expression plays a fundamental role in the functioning of cells. New mathematical modelling and computational techniques will be essential to the understanding of these genetic regulatory networks (see [3] for a review). The principal modelling challenges come from incomplete knowledge of the networks, and the dearth of quantitative data for identifying kinetic parameters required for detailed mathematical models. Qualitative methods overcome both of these difficulties and are thus well-suited to the modelling and simulation of genetic networks.

The **first part** of the paper is a paraphrase of results obtained by the authors and collaborators, that are mostly taken from [1] and [9], and the references therein; it recalls the basis of the modelling of genetic regulatory networks with PWA differential equations. From a mathematical point of view, what is interesting in these dynamical systems (possibly of large dimensions, until several thousands) is that a global qualitative analysis (assisted by a computer) is possible and gives nontrivial results. This is to compare with classical nonlinear ordinary differential equations where, for dimensions greater than three, nothing is possible except a local analysis around the equilibria, if the equilibria are computable. Moreover, in the PWA case, the analysis is itself qualitative, and does not depend too much on the exact values of the parameters of the model; instead, it depends only on inequalities between these parameters.

In a **second part**, which is the original part of the paper, we build on the qualitative transition graph given by the above analysis. This graph describes the possible transitions between regions of the trajectories. We give a probabilistic interpretation of the transitions: often, the biologist can only measure the fact that a gene is highly or weakly expressed at some time. In this case, although the precise numerical values of the variables are not available to the biologist, he will be able to have an estimation (frequency) of the probability of transition from one domain to another. We compute these probabilities of transitions between domains, and show that it can give some informations about the parameters of the model: for the classical model of the bistable switch, we are able to estimate the expression rates.

*COMORE, INRIA, 2004 Route des Lucioles, BP 93, 06902 Sophia Antipolis, France. Emails: madalena.chaves@inria.fr, jean-luc.gouze@inria.fr

2 Piecewise-Affine Models of Genetic Regulatory Networks

Piecewise affine models of genetic networks are built with discontinuous (step) functions; such models are originally due to Glass and Kauffman [7]. The use of such step functions has been motivated by the experimental observation that the activity of certain genes change in a switch-like manner at a threshold concentration of a regulatory protein. It is best illustrated with an example: the schematic diagram in Figure 1 describes a simple genetic regulatory network. In this example, the genes a and b code for the proteins A and B, which in turn control the expression of the two genes a and b. Protein A inhibits gene a and activates gene b above certain threshold concentrations, which are assumed to be different. Similarly protein B inhibits gene b and activates gene a above different threshold concentrations. Such a two-gene network could be found as a module of a more complex genetic regulatory network from a real biological system.

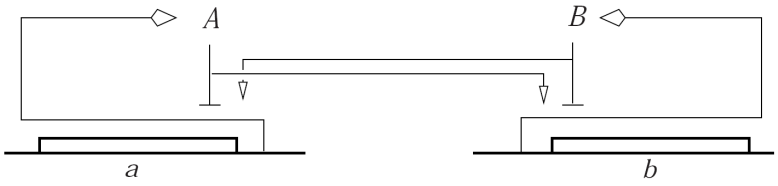

Figure 1: Example of a genetic regulatory network of two genes (a and b), each coding for a regulatory protein (A and B).

The equations modeling the example network in Figure 1 can be written down as

$$\left\{ \begin{array}{rcl} \dot{x}_a & = & \kappa_a s^+(x_b,\theta_b^1)s^-(x_a,\theta_a^2) - \gamma_a x_a \\ \dot{x}_b & = & \kappa_b s^+(x_a,\theta_a^1)s^-(x_b,\theta_b^2) - \gamma_b x_b \end{array} \right. \tag{1}$$

where $s^+(x_s,\theta_s)$ is equal to 0 when $x_s < \theta_s$ and equal to 1 when $x_s > \theta_s$ and $s^-(x_s,\theta_s) = 1 - s^+(x_s,\theta_s)$. In this model, gene a is expressed at a rate κ_a if the concentration x_b of protein B is above the threshold θ_b^1 and the concentration x_a of protein A is below the threshold θ_a^2. Similarly, gene b is expressed at a rate κ_b if the concentration x_a of protein A is above the threshold θ_a^1 and the concentration x_b of the protein B is below the threshold θ_b^2. Degradation of both proteins is assumed to be proportional to their own concentrations, so that the expression of the genes a and b is modulated by the degradation terms $\gamma_a x_a$ and $\gamma_b x_b$ respectively. We suppose that $\theta_j^1 < \theta_j^2$ for $j = a,b$.

Such a model is readily generalized to models containing both expression and degradation terms for each gene:

$$\dot{x}_i = f_i(x) - \gamma_i x_i$$

where $f_i(x)$ represents the expression rate of gene i, depending on the whole state $x = (x_1,\cdots,x_n)^T$ and γ_i is the (relative) degradation rate. However, the expression rates of (1) have the additional property of being constant for values of x_a and x_b belonging to intervals that do not contain thresholds values θ_i^j. This can be rewritten by detailing $f_i(x)$ as follows:

$$f_i(x) = \sum_{l=1}^{L_i} \kappa_{il} b_{il}(x)$$

where $b_{il}(x)$ is a combination of step-functions $s^{\pm}(x_r,\theta_r^j)$ and $\kappa_{il} > 0$ is a rate parameter. The generalized form of (1) is a piecewise linear model

$$\dot{x} = f(x) - \gamma x \tag{2}$$

where the model is affine within hyper-rectangles of the state-space (γ is the diagonal matrix $(\gamma_1,\ldots,\gamma_n)$).

The dynamics of the piecewise-linear system (2) can be studied in the n-dimensional state-space $\Omega = \Omega_1 \times \Omega_2 \times \cdots \times \Omega_n$, where each Ω_i is defined by $\Omega_i = \{x_i \in \mathbb{R}_+ \mid 0 \le x_i \le max_i\}$ for some positive parameter $max_i > \max_x\left(\frac{f_i(x)}{\gamma_i}\right)$. A protein encoded by a gene will be involved in different interactions at different concentration thresholds, so for each variable x_i, we assume there are p_i ordered thresholds $\theta_i^1,\cdots,\theta_i^{p_i}$ (we also define $\theta_i^0 = 0$

and $\theta_i^{p_i+1} = max_i$). The $(n-1)$-dimensional hyperplanes defined by these thresholds partition Ω into hyper-rectangular regions we call *domains*. Specifically, a domain $D \subset \Omega$ is defined to be a set $D = D_1 \times \cdots \times D_n$, where D_i is one of the following:

$$\begin{array}{lcll} D_i & = & \{x_i \in \Omega_i | 0 \leq x_i < \theta_i^1\} & \\ D_i & = & \{x_i \in \Omega_i | \theta_i^j < x_i < \theta_i^{j+1}\} & \text{for } j \in \{1, \cdots, p_i - 1\} \\ D_i & = & \{x_i \in \Omega_i | \theta_i^{p_i} < x_i \leq max_i\} & \\ D_i & = & \{x_i \in \Omega_i | x_i = \theta_i^j\} & \text{for } j \in \{1, \cdots, p_i\} \end{array}$$

Let $\mathscr{D}$ be the set of domains in Ω. A domain $D \in \mathscr{D}$ is called a regulatory domain if none of the variables x_i has a threshold value in D (it is the full hyperrectangle). In contrast, a domain $D \in \mathscr{D}$ is called a switching domain of order $k \leq n$ if exactly k variables have threshold values in D [10]. The corresponding variables x_i are called switching variables in D. The two sets of domains are respectively denoted by $\mathscr{D}_r$ and $\mathscr{D}_s$.

2.1 Classical Solutions and Focal Points

For any regulatory domain D, the function $f(x)$ is constant for all $x \in D$, and it follows that the piecewise-affine system (2) can be written as an affine vector field

$$\dot{x} = f^D - \gamma x, \;\; x \in D \tag{3}$$

where f^D is constant in D. Restricted to D, this is a classical linear ordinary differential equation. We assume that the parameters $\{\theta_i^j\}, \{\gamma_i\}, \{\kappa_{il}\}$ are all fixed. For any initial condition $x(t_0) \in D$, the unique solution is given by

$$x(t) = \phi(D) + e^{\gamma(t_0 - t)}(x(t_0) - \phi(D)), \tag{4}$$

where $\phi(D)$ satisfies the linear system $\gamma\phi(D) = f^D$. Clearly $x(t) \to \phi(D)$ monotonically until $x(t)$ reaches the boundary of the regulatory domain D.

Definition 1 Given a regulatory domain $D \in \mathscr{D}_r$, the point $\phi(D) = \gamma^{-1} f^D \in \Omega$ is called the *focal point* for the flow in D.

Generally we make the assumption that $\phi(D) \notin \text{supp}(D')$, for all $D' \subseteq \partial D$, for otherwise solutions can take infinite time to reach a focal point in the boundary of their domain ($\text{supp}(D')$ is the supporting hyperplane containing the domain D'). This is a special case of a more general assumption we make in Section 2.3. In the example network of Figure 1, it can easily be checked that for the regulatory domain D^{13} (see Figure 3(a)), the state equations reduce to

$$\begin{aligned} \dot{x}_a &= \kappa_a - \gamma_a x_a, \\ \dot{x}_b &= \kappa_b - \gamma_b x_b. \end{aligned}$$

Hence the focal point of D^{13} is $\phi(D^{13}) = (\kappa_a/\gamma_a, \kappa_b/\gamma_b)$, which lies outside D^{13}, in the domain D^{25} in fact, under some assumptions concerning the parameters. Thus solutions in D^{13} will flow towards $\phi(D^{13}) \in D^{25}$ until they leave the domain D^{13}. Different regulatory domains will usually have different focal points. In general, all solutions in a regulatory domain D flow towards the focal point $\phi(D)$ until they either reach it or leave the domain D. What happens when a solution leaves a regulatory domain D and enters a switching domain in the boundary of D? Since the step functions are not defined when a variable x_i takes some threshold value $\theta_i^{q_i}$, the vector field is undefined on the switching domains. We need to precise our definition of solutions.

2.2 Solutions in switching domains

In switching domains, the PWA system (2) is not defined, since in a switching domain of order $k \geq 1$, k variables assume a threshold value. If solutions do not simply go through a switching domain, it is necessary to give a definition of what a solution can be on that domain. Classically, this is done by using a construction originally proposed by Filippov [6] and recently applied to PWA systems of this form [8, 5].

The method consists of extending the system (2) to a differential inclusion,

$$\dot{x} \in H(x), \tag{5}$$

where H is a set-valued function (i.e. $H(x) \subseteq \mathbb{R}^n$). If D is a regulatory domain, then we define H simply as

$$H(x) = \{f^D - \gamma x\}, \tag{6}$$

for $x \in D$. If D is a switching domain, for $x \in D$, we define $H(x)$ as

$$H(x) = \overline{co}(\{f^{D'} - \gamma x \mid D' \in R(D)\}), \tag{7}$$

where $R(D) = \{D' \in \mathscr{D}_r | D \subseteq \partial D'\}$ is the set of all regulatory domains with D in their boundary, and $\overline{co}(X)$ is the closed convex hull of X. For switching domains, $H(x)$ is generally multi-valued so we define solutions of the differential inclusion as follows.

Definition 2 A solution of (5) on $[0,T]$ *in the sense of Filippov* is an absolutely continuous function (with respect to t) $\xi_t(x_0)$ such that $\xi_0(x_0) = x_0$ and $\dot{\xi}_t \in H(\xi_t)$, for almost all $t \in [0,T]$.

In order to more easily define these Filippov solutions, it is useful to define a concept analogous to the focal points defined for regulatory domains, extended to deal with switching domains.

Definition 3 Let $D \in \mathscr{D}_s$ be a switching domain of order k. Then its *focal set* $\Phi(D)$ is

$$\Phi(D) = supp(D) \cap \overline{co}(\{\phi(D') \mid D' \in R(D)\}). \tag{8}$$

Hence $\Phi(D)$ for $D \in \mathscr{D}_s$ is the convex hull of the focal points $\phi(D')$ of all the regulatory domains D' having D in their boundary, as defined above, intersected with the threshold hyperplane $supp(D)$ containing the switching domain D (Figure 2).

It is possible to show that

$$H(x) = \gamma(\Phi(D) - x) \tag{9}$$

which is a compact way of writing that $H(x) = \{y \in \mathbb{R}^n \mid \exists \phi \in \Phi(D) \text{ such that } y = \gamma(\phi - x)\}$. The Filippov vector field is defined by means of the focal set.

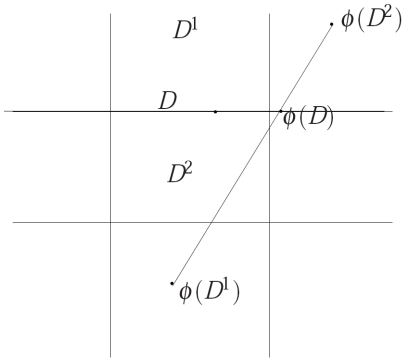

Figure 2: Illustration of the definition of the focal set on a switching surface D according to the Filippov definition of solutions. The convex hull of the points $\phi(D^1)$ and $\phi(D^2)$ is simply the segment that links them, so that (8) implies that $\phi(D)$ is the intersection of this segment with supp(D). Starting from D^1, a typical trajectory will converge towards $\phi(D^1)$ and reach the surface D, then slide on D until the focal set $\phi(D)$.

If $\Phi(D) = \{\ \}$, with D a switching domain, solutions will simply cross D; otherwise, sliding mode is possible and convergence takes place "in the direction" of $\Phi(D)$. If $\Phi(D) \cap D = \{\ \}$, solutions eventually leave D. In the case where $\Phi(D) \cap D$ is not empty, it can be assimilated to an equilibrium set within D towards which all solutions will converge in the following sense (see [1]):

Lemma 1 *For every regulatory domain $D \in \mathscr{D}_r$, all solutions ξ_t of (2) in D monotonically converge towards the focal point $\Phi(D)$. For every switching domain $D \in \mathscr{D}_s$, the non-switching component $(\xi_t)_i$ of the solution ξ_t in D monotonically converges towards the closed interval*

$$\pi_i(\Phi(D)) = \{\phi_i \in \Omega_i \mid \phi \in \Phi(D)\},$$

the projection of $\Phi(D)$ onto Ω_i, if $(\xi_0)_i \notin \pi_i(\Phi(D))$. Every switching component $(\xi_t)_i$ of the solution ξ_t in D is a constant $(\xi_t)_i = \pi_i(\Phi(D)) = \theta_i^{q_i}$.

Basically, this means that convergence does not take place towards $\Phi(D)$, but towards the smallest hyper-rectangle that contains $\Phi(D)$. Indeed, if $\Phi(D)$ is neither empty, nor a singleton, and ξ_{t_0} belongs to $\Phi(D)$, the Filippov vector field at this point is defined as $H(\xi_{t_0}) = \gamma(\Phi(D) - \xi_{t_0})$ and there is no guarantee that no element of $H(\xi_{t_0})$ points outside of $\Phi(D)$ (we know however that a solution stays at ξ_{t_0}). Due to the structure of the differential equations, it is on the other hand certain that the transient solution does not leave the smallest hyper-rectangle $\Pi(D)$ containing $\Phi(D)$.

We then have the following corollary

Corollary 1 *All solutions ξ_t in D converge towards $\Pi(D)$, if $\xi_0 \notin \Pi(D)$. For all solutions ξ_t in D, $\Pi(D)$ is invariant.*

Corollary 2 *If $\Phi(D)$ is a point, all solutions ξ_t in D converge monotonically towards $\Phi(D)$.*

3 Stability and state transition graph

The stability analysis of the various equilibria is a direct consequence of the analysis in the previous section. It is easily seen that equilibria $\bar{x}_r$ in some $D \in \mathscr{D}_r$ are asymptotically stable. In a switching domain $D \in \mathscr{D}_s$, recall that solutions are defined by considering the differential inclusion $H(x)$. We say that a point $y \in \Omega$ is an equilibrium point for the differential inclusion if

$$0 \in H(y), \tag{10}$$

where H is computed using the Filippov construction in (7). In other words, there is a solution in the sense of Filippov, ξ_t, such that $\xi_t(y) = y$, $\forall t > 0$. We call such a point a *singular equilibrium point*. It is easily seen that, for y to be an equilibrium point inside D, it must belong to $\Phi(D)$. Also, since Assumption 1 below prevents $\Phi(D)$ from intersecting the border of D, we then have that $\Phi(D) \subset D$. Every element ϕ of $\Phi(D)$ is then an equilibrium when $\Phi(D) \subset D$ so that, for every $\phi \in \Phi(D)$, there exists a solution $\xi_t(\phi) = \phi$ for all t.

One of the results of [1] concerns the link between the configuration of the state transition graph and the stability of an equilibrium (there is a technical assumption, called Assumption 1, that the focal points are not located on the switching thresholds). This discrete, qualitative description of the dynamics of the PWA system that underlies the qualitative simulation of genetic regulatory networks was originally due to Glass. It indicates the passages between the different domains making up the phase space. A state transition graph is a directed graph whose vertices are the domains of the system and whose edges are the possible transitions between these domains (easily determined by examining the PWA model). The transition graph of system (1) is illustrated in Figure 3. For a two-dimensional system, we show how this graph indicates the stability of singular equilibria:

Theorem 1 *Let the dimension of the PWA model be 2, and let D be a switching domain containing a singular equilibrium point $\phi(D)$. If for all regulatory domains $D' \in R(D)$ (that is, adjacent to D), there exists a transition from D' to D in the state transition graph, then $\phi(D)$ is asymptotically stable.*

This result is purely qualitative: it only depends on some inequalities between the parameters (threshold and focal points), but their actual values are not needed. It can be directly applied to show that the singular equilibrium $(x_a, x_b) = (\theta_a^2, \theta_b^2)$, corresponding to D^{19} on Figure 3, is asymptotically stable because there are transitions to D^{19} from D^{13}, D^{15}, D^{23} and D^{25}, the regulatory domains adjacent to D^{19}.

A generalization, but in a weaker form, of this theorem to dimension n is also available.

Theorem 2 *Assume $\Omega \subset \mathbb{R}^n$. Let $D \in \mathscr{D}_s$ be a switching domain of order $p \geq 1$ containing a singular equilibrium set $\Phi(D)$ that satisfies Assumption 1. If for all $D' \in R(D)$, there is a transition from D' to D in the state transition graph, then $\Pi(D)$ is asymptotically stable.*

Corollary 3 *Under the conditions above, if, moreover, $\Phi(D)$ is a point, it is asymptotically stable.*

These results are helpful for the qualitative analysis of the genetic regulatory networks. Moreover, a software GNA was built to analyze genetic networks [4].

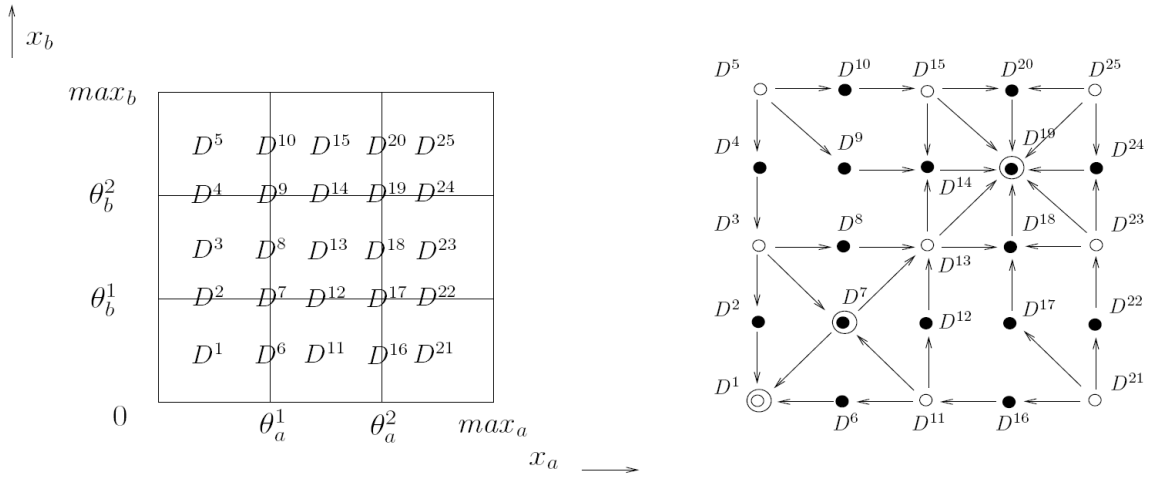

Figure 3: Subdivision of the state-space in 25 domains and transition graph of system (1)

4 A probabilistic interpretation of the transition graph

In this part, we explore the new idea of associating a *probability* of transition to each of the edges in the transition graph. Since PWA systems are deterministic, one way to assign such a probability $D_0 \to D_1$ is to compute the volume of the region $C \subset D_0$ that switches to D_1.

The goal is to relate dynamical aspects determined by the system's parameters (here, synthesis and degradation rates) to *probabilities* of transition between two state space regions. The idea is to apply these probabilities to the estimation of (some) parameters. Focusing for the present paper on 2-dimensional systems, we will write an analytical expression for the probability of transition between two given regions in terms of the system's parameters.

Consider a piecewise affine system of dimension 2, verifying Assumption 1. Assume that there are r_i thresholds for each variable $i = 1, 2$:

$$0 := \theta_i^0 < \theta_i^1 < \cdots < \theta_i^{r_i} < max_i := \theta_i^{r_i+1}, \tag{11}$$

where max_i is as defined in Section 2. Furthermore, assume that these thresholds are defined so that:

$$(\forall i = 1,2)\ \ (\forall k = 0,\ldots,r_i)\ \ \text{sign}(f_i(x) - \gamma_i x_i) = \text{const.},\ \ \forall\ \theta_i^k < x_i < \theta_i^{k+1}. \tag{12}$$

This is a general condition, since *virtual* thresholds can be added (i.e., even if it is not an activation threshold from variable i to another variable). From now on, a regular domain will be called a *box* (to distinguish them from the switching domains). To label the regular domains, we will use the notation:

$$B_{k_1 k_2}: \quad k_i \in \{0, 1, \ldots, r_i - 1\}, \quad \theta_i^{k_i} < x_i < \theta_i^{k_i+1}.$$

As an example, if $(r_1, r_2) = (1, 3)$, B_{12} denotes the rectangle $x_1 \in (\theta_1^1, max_1)$, $x_2 \in (\theta_2^2, \theta_2^3)$.

Consider a trajectory that starts in box B_{ij}. The possible transitions from this box are given by the state transition graph (see Section 3).

By assumption (12), the Jacobian of the system is sign-invariant in each box B_{ij}. This implies that, according to the transition graph, any trajectory starting in a box B_{ij} can *switch to one of two neighbor boxes*: $B_{i+s_1,j}$ and $B_{i,j+s_2}$, where $s_k = \text{sign}(f_k(x) - \gamma_k x_k)$ $(k = 1, 2)$ for $x \in B_{ij}$. Moreover, since solutions inside each box are uniquely defined, the initial condition in B_{ij} uniquely determines the next box to be visited. Let $\phi(t; x_0)$ denote the solution of system (2), for an initial condition x_0. Define

$$\begin{aligned} B_{ij}^1 &= \{x_0 \in B_{ij}:\ \phi(t;x_0) \in B_{ij}, \forall t < T;\ \phi(t;x_0) \in B_{i+s_1,j}, T < t < T + \Delta T\} \\ B_{ij}^2 &= \{x_0 \in B_{ij}:\ \phi(t;x_0) \in B_{ij}, \forall t < T;\ \phi(t;x_0) \in B_{i,j+s_2}, T < t < T + \Delta T\}, \end{aligned}$$

where T depends on x_0 and the various parameters $(\kappa_i, \gamma_i, \theta_i^k)$. B_{ij}^1 (resp., B_{ij}^2) is the set of initial conditions in B_{ij} generating trajectories for which the next visit is box $B_{i+s_1,j}$ (resp., $B_{i,j+s_2}$). We will say that the probability that a trajectory of the system switches from B_{ij} to $B_{i+s_1,j}$ is proportional to the volume of the region B_{ij}^1:

$$P_{ij\to i+s_1,j} = \frac{\text{Area}(B_{ij}^1)}{\text{Area}(B_{ij})}, \quad P_{ij\to i,j+s_2} = \frac{\text{Area}(B_{ij}^2)}{\text{Area}(B_{ij})}. \tag{13}$$

In Section 5 we will illustrate the computation of these probabilities as a function of the parameters κ_i and γ_i, for a simple example of the bistable switch.

To experimentally obtain measurements of the probabilities (13), one would need to perform N times the same experiment, with an initial state in B_{ij} (that is, initial concentrations of x in the region $[\theta_1^i, \theta_1^{i+1}] \times [\theta_2^j, \theta_2^{j+1}]$), and count the number of times N_1 (resp., N_2) that the system evolves to $B_{i+s_1,j}$ (resp., $B_{i,j+s_2}$). If $N_1 = N_2 = 0$, this means that the system remains in B_{ij} and $P_{ij\to i,j+s_2} = P_{ij\to i+s_1,j} = 0$. If $N_1 \neq 0$, then we expect $N = N_1 + N_2$ so that $P_{ij\to i+s_1,j} = N_1/N$ and $P_{ij\to i,j+s_2} = N_2/N = 1 - P_{ij\to i+s_1,j}$ (because we assume (12) which implies only two possible transitions).

These values can then be compared to the expressions in terms of the parameters, for estimation (see Section 5).

5 The bistable switch example

Mathematical models of the bistable switch are characterized by the existence of two stable steady states (or two stable modes), representing two distinct outcomes of the biological system [2]. We will study a general qualitative example of the bistable switch, $\dot{x} = \hat{\kappa}_1 s^-(y, \theta_2) - \gamma_1 x$ and $\dot{y} = \hat{\kappa}_2 s^-(x, \theta_1) - \gamma_2 y$, but considering that the two variables are normalized with respect to their respective thresholds (to reduce the number of free parameters) $x_1 = x/\theta_1$, $x_2 = y/\theta_2$, and $\kappa_i = \hat{\kappa}_i/\theta_i$ to obtain:

$$\begin{aligned} \dot{x}_1 &= \kappa_1 s^-(x_2, 1) - \gamma_1 x_1 \\ \dot{x}_2 &= \kappa_2 s^-(x_1, 1) - \gamma_2 x_2, \end{aligned} \tag{14}$$

with the assumption that (to guarantee existence of two steady states): $\frac{\kappa_i}{\gamma_i} > 1, \quad i = 1, 2$. For each variable i, the thresholds (11) are: $\theta_i^0 = 0$; $\theta_i^1 = 1$; $\theta_i^2 = \frac{\kappa_i}{\gamma_i}$, so the state space for system (14) is partitioned into four boxes: B_{00}, B_{01}, B_{10} and B_{11}. It is not difficult to check that the system has two stable steady states, located in the regions B_{10} and B_{01}. Solutions starting in B_{00} or B_{11} will eventually cross to either B_{10} and B_{01} (depending on the exact initial condition). Moreover, we can compute the separatrix line $x_2 = \sigma_{00}(x_1)$ which divides region B_{00} into the two regions B_{00}^1 and B_{00}^2: solutions with initial conditions above (resp., below) the line σ_{00} will eventually converge to the steady state in B_{01} (resp., B_{10}). A similar separatrix line σ_{11} can be computed for the region B_{11}. These curves are given by:

$$\sigma_{00}(x) = \frac{\kappa_2}{\gamma_2} - \left(\frac{\kappa_2}{\gamma_2} - 1\right)\left(\frac{\frac{\kappa_1}{\gamma_1} - x}{\frac{\kappa_1}{\gamma_1} - 1}\right)^{\frac{\gamma_2}{\gamma_1}}, \qquad \sigma_{11}(x) = x^{\frac{\gamma_2}{\gamma_1}} \tag{15}$$

These separatrix lines are represented in Fig. 5, and correspond to the locus of the points that go through $(x_1, x_2) = (1, 1)$. To simplify the presentation, we will assume that:

(A1) $\sigma_{00}(x = 0) > 0 \;\Leftrightarrow\; \left(\frac{\frac{\kappa_1}{\gamma_1}}{\frac{\kappa_1}{\gamma_1} - 1}\right)^{\frac{\gamma_2}{\gamma_1}} < \frac{\frac{\kappa_2}{\gamma_2}}{\frac{\kappa_2}{\gamma_2} - 1}$;

(A2) $\sigma_{11}(x = \frac{\kappa_1}{\gamma_1}) < \frac{\kappa_2}{\gamma_2} \;\Leftrightarrow\; \left(\frac{\kappa_1}{\gamma_1}\right)^{\frac{\gamma_2}{\gamma_1}} < \frac{\kappa_2}{\gamma_2}$;

where (A1) says that the line σ_{00} exits the box B_{00} through the axis $x_1 = 0$, and (A2) says that the line σ_{11} exits the box B_{11} through the axis $x_1 = \frac{\kappa_1}{\gamma_1}$. According to definition (13) we have:

$$P_{00\to 10} = \int_0^1 \sigma_{00}(x_1)\, dx_1, \quad P_{00\to 01} = 1 - P_{00\to 10}, \tag{16}$$

Similarly, we can compute the probability of a transition from B_{11} to B_{10}. To obtain the correct probability, we need to subtract the area corresponding to the region B_{10} (which is part of the area below σ_{11}), and only then divide by the total area of B_{11}:

$$P_{11\to 10} = \frac{1}{(\frac{\kappa_1}{\gamma_1}-1)(\frac{\kappa_2}{\gamma_2}-1)}\left\{\int_1^{\frac{\kappa_1}{\gamma_1}} \sigma_{11}(x_1)\,dx_1 - \left(\frac{\kappa_1}{\gamma_1}-1\right)\right\} \tag{17}$$

and $P_{11\to 01} = 1 - P_{11\to 10}$. For transitions from regions B_{10} or B_{01}, the theorical probability of transition to any other region is 0 so, in practice, we can expect very weak transition probabilities from these two regions, and one can say that $P_{01\to 01} = 1$ and $P_{10\to 10} = 1$. The expressions (16) and (17) can be written as:

$$P_{00\to 10} = b + \frac{1}{c+1}(a-1)(b-1)\left(1-\left(\frac{a}{a-1}\right)^{c+1}\right) \tag{18}$$

$$P_{11\to 10} = \frac{1}{(a-1)(b-1)}\left(\frac{1}{c+1}(a^{c+1}-1)-(a-1)\right), \tag{19}$$

in terms of the three parameters:

$$a = \frac{\kappa_1}{\gamma_1}, \quad b = \frac{\kappa_2}{\gamma_2}, \quad c = \frac{\gamma_2}{\gamma_1}.$$

Therefore, given measurements for the degradation rates and the probabilities of transition, it is possible to estimate the synthesis rates from (18) and (19). Let c be known, $P_{00\to 10} = p_{00}$ and $P_{11\to 10} = p_{11}$, then a is given by the solution of:

$$\left(\frac{a^{c+1}-1}{c+1}-(a-1)\right)^{-1}(p_{00}-1)p_{11} = \frac{1}{a-1}+\frac{1}{c+1}\left(1-\left(\frac{a}{a-1}\right)^{c+1}\right) \tag{20}$$

and b is given by

$$b = 1 + \frac{1}{(a-1)p_{11}}\left(\frac{1}{c+1}(a^{c+1}-1)-(a-1)\right) \tag{21}$$

in the domain of validity of the equalities (18)-(19) (assumptions A1 and A2 hold):

$$a^c < b < \frac{\left(\frac{a}{a-1}\right)^c}{\left(\frac{a}{a-1}\right)^c - 1}.$$

Note that the assumptions A1 and A2 can be dropped, but then the explicit expression for $P_{00\to 10}$ and $P_{11\to 10}$ must be modified according to the geometry of the separatrices, in particular the starting or ending points for the

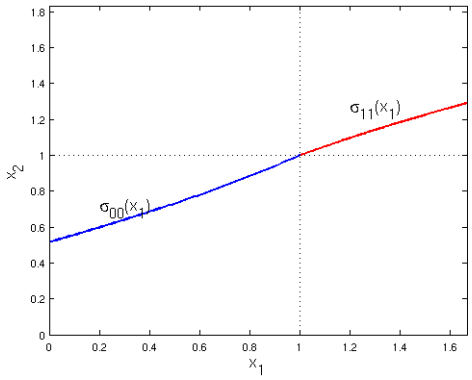

Figure 4: Separatrix functions satisfying assumptions A1 and A2.

integrals will change. The general case can be easily written down, but for reasons of space and presentation we will not give it here. To give a numerical example, assume that $\gamma_1 = 0.9$, $\gamma_2 = 0.6$, $p_{00} = 0.9$, and $p_{11} = 0.25$, to obtain $c = 2/3$ and, from equations (20) and (21), respectively: $a \approx 1.48$ and $b \approx 1.61$, which are inside the region of validity ($b \in (1.29, 1.89)$). The estimated synthesis rates are thus: $\kappa_1 \approx 1.33$ and $\kappa_2 \approx 0.96$. Finally, in Fig. 5 the probabilities are shown as functions of both a and b, for a fixed value of $c = 0.5$, in a domain where the functions (18)-(19) are valid. Observe that the probability $P_{00\to 10}$ remains at a fairly constant high level, while $P_{11\to 10}$ decreases significantly with b. This fact is interesting, because it shows that the dependence of the separatrix curve σ_{00} on b is in fact weak, and that increasing b leads essentially to increasing the area above the separatrix curve σ_{11} (see also Fig.5).

6 Conclusions

In this paper, after a first part dedicated to a review of results about PWA systems, we have given a probabilistic interpretation of the transitions in the second part. A method is suggested for parameter estimation, applicable to systems where the measurements are mostly qualitative. Assuming that the data consist of probabilities of transition between two different regions of the state space, and that (for instance) the degradation rates are known, one can estimate the synthesis rates. The method was described for 2-dimensional piecewise affine differential systems. Further work is needed for more complex systems.

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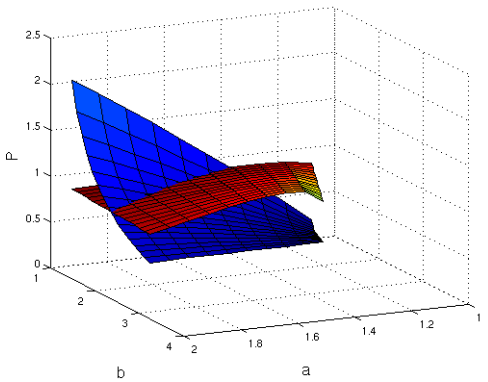

Figure 5: Probabilities $P_{00\to 10}$ (red surface) and $P_{11\to 10}$ (blue surface), as a function of a and b, for $c = 0.5$.

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