A class of piecewise linear differential equations arising in biological models

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Abstract: We investigate the properties of the solutions of a class of piecewise-linear differential equations. The equations are appropriate to model biological systems (e.g., genetic networks) in which there are switch-like interactions between the elements. The analysis uses the concept of Filippov solutions of differential equations with a discontinuous righthand side. It gives an insight into the so-called singular solutions which lie on the surfaces of discontinuity. We show that this notion clarifies the study of several examples studied in the literature.

1 Introduction

Complex biological systems are often modelled by means of switch-like relations between the variables, involving step functions. Such behaviour involving thresholds has been shown experimentally in enzymatic or genetic networks: in the model, the rate of production of the enzyme (or gene) is often described by a sigmoid function, such as the Hill function $\Sigma(\xi, \theta, p) = \xi^p/(\xi^p + \theta^p)$, where the threshold is θ. If p is large, the function is similar to a step function. The general equations of the model can be written as (cf. [12]):

$$x_i' = f_i(x) - \gamma_i x_i \qquad i = 1, \cdots, n \tag{1}$$

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where the relative degradation rate γ_i of the component x_i is constant positive, and the production rate function f_i depends on the n components $x = (x_1, \cdots, x_n)$. We assume that f_i are piecewise constant positive functions whose values change as a variable x_i crosses a certain threshold θ_i^j (cf. the more precise description below). This system has been widely studied in the literature, mainly in the framework of genetic networks (cf. [6, 16]). In fact, it is a piecewise linear (PL) differential system of a special kind. The dynamical behaviour of the variables in each of the boxes between thresholds is simple; therefore, the description of the behaviour can be linked to Boolean automata, involving Boolean variables (corresponding to the continuous variable below or above a threshold). Many other problems arise and a lot of interesting work has been done in this domain (for more details see [12, 16]).

From a mathematical point of view, these systems are differential systems with discontinuous dynamics, and one of our goals in this paper is to show that the concept of Filippov solutions [1] can clarify and facilitate the study of such systems, in particular of the behaviour on the threshold planes.

Two different methods were developed for the study of the stationary points located on threshold hyperplanes. The first method [15] uses logical variables, while the second method [12, 13] uses a continuous homologous system of the PL system (see Section 4 for details). For example, the Hill function $\Sigma(\xi, \theta, p) = \xi^p/(\xi^p + \theta^p)$ approaches the step function when $p \to +\infty$. It was often used to define continuous homologues of the PL system [3, 4, 6]. Other functions may be used, like the logoid function [12], that are easier to handle. The system becomes then a system of ordinary differential equations with continuous right hand side, and the steady points are defined in the usual way. But when one comes to the limit of the step functions, it is not so simple to obtain rigorous results on the steady points and their nature.

Moreover, a remaining problem is that of the behaviour of the system on the threshold hyperplanes (and far from a steady state). First, we recall that the original system is, a priori, not defined on these hyperplanes. In fact, the literature on system (1) is mainly concerned with the non-singular solutions (we call non-singular solutions $x(t)$ of (1) solutions in which for each i, $x_i(t) = \theta_i^j$ only at isolated values of t). The problem of the definition of the solution and its behaviour on the threshold hyperplanes (called walls in [12]) is not clearly elucidated.

The aim of this paper is to study system (1) and to describe its singular solutions. Our approach will be to use the Filippov solutions of a discontinuous differential equations. The definition of these solutions enables one to define afterwards, in a clear and easy way, the singular steady points and solutions.

Let us motivate our approach: on the threshold hyperplanes, the PL system is not defined, nor are the steady points on these hyperplanes. The concept of Filippov solutions provides a way to define (by extension) the differential equation and its solution on these threshold hyperplanes. It is, in general, a differential inclusion, defined for every point. This new extended vector field enables the definition of the notion of solution everywhere, and also to compute all the steady points, either in the interior of the boxes (regular) or on the hyperplanes (singular). Moreover, their stability can be easily deduced. This concept clarifies the notion of "sliding motion" of a solution moving along a wall, that was almost completely ignored in previous work.

The paper is organized as follows. In Section 2 we specify the model and define the concept of boxes. In Section 3 we define the PL system on the threshold planes and we consider its solutions in the sense of Filippov. In Section 5, we describe the transition graph associated with the PL system (1). In Section 4 we discuss the regular and singular stationary points and we clarify some results in the literature. Section 6 illustrates our approach by means of some examples that were considered by several authors; we show the applicability of the method and its simplicity to deal completely with the problem.

2 The model and the boxes in the state space

Let us introduce some notations: we assume that, for each variable x_i, $i = 1, \cdots, n$, there are N_i thresholds $\theta_i^1, \cdots, \theta_i^{N_i}$ satisfying

$$\theta_i^0 < \theta_i^1 < \cdots < \theta_i^{N_i} < \theta_i^{N_i+1}$$

where $\theta_i^0 := 0$ and $\theta_i^{N_i+1} := +\infty$. These thresholds divide the positive cone $C = \{x : x_i \geq 0, i = 1, \cdots, n\}$ into boxes of dimension n, separated by the $(n-1)$-dimensional hyperplanes $x_i = \theta_i^j$. We assume that the f_i are constant positive in each box. The values of f_i differ from box to box, so that system (1) is a piecewise linear (PL) system.

In vector notations (1) can be rewritten as

$$x' = f(x) - \gamma x, \qquad x \in C, \quad f : C \to \mathbb{R}^n, \tag{2}$$

where $f = (f_1, \cdots, f_n)$ and $\gamma = \text{diag}(\gamma_1, \cdots, \gamma_n)$, and diag is the diagonal matrix corresponding to the vector.

In practice, (2) often involves step functions and is given by

$$x' = F(z(x)) - \gamma x, \tag{3}$$

where $F : \mathbb{R}^{N_1 + \cdots + N_n} \to \mathbb{R}^n$ is of class $\mathcal{C}^1$, and

$$z(x) = (z_1^1, \cdots, z_1^{N_1}, \cdots, z_n^1, \cdots, z_n^{N_n}), \qquad z_i^j = S(x_i, \theta_i^j).$$

Here $S(\xi, \theta)$ is the step function

$$S(\xi, \theta) = \begin{cases} 0 & \text{if} \quad \xi < \theta, \\ 1 & \text{if} \quad \xi > \theta. \end{cases}$$

In the interior of each box, the behaviour is linear and simple; the problems arise on the hyperplanes separating the boxes, where the vector field is not defined. In particular, a definition is needed for the singular steady points located on the thresholds (cf. section 3).

Definition 1 *Let $q : \{1, \cdots, n\} \to \mathbb{N}$, $i \mapsto q_i$ be a mapping satisfying $0 \leq q_i \leq N_i$. The n-box B defined by q is the subset of the positive cone C given by*

$$B = B_q := \{x \in C : \theta_i^{q_i} < x_i < \theta_i^{q_i+1}, i = 1, \cdots, n\}, \tag{4}$$

The value of f in this box is denoted by f^B.

The total number of n-boxes is equal to

$$m_n = \prod_{i=1}^{n} (N_i + 1)$$

In the box B, (2) reduces to the linear system $x' = f^B - \gamma x$. Thus, the solutions are given by

$$x(t) = \Phi^B + (x(t_0) - \Phi^B)\mathrm{e}^{\gamma(t_0 - t)}, \tag{5}$$

where $\Phi^B = \gamma^{-1} f^B$. When $t \to +\infty$, $x(t) \to \Phi^B$, until $x(t)$ encounters the boundary of the box B. The solutions given by (5) are curves originated at $x(t_0)$ and converging toward Φ^B, called the focal point of box B [3, 4]. If $\Phi^B \in B$, then $x = \Phi^B$ is a stable node of (2). This proves the following result.

Theorem 1 *If $\Phi^B \in B$ then $x = \Phi^B$ is an asymptotically stable stationary point of (2).*

We only consider throughout the paper the generic case where the focal point Φ^B does not lie on the threshold hyperplanes which constitute the boundary of B. The face separating two adjacent n-boxes will be called a $(n-1)$-box or a wall. More precisely, let B_1 and B_2 be two n-boxes defined by the mappings q^1 and q^2, such that there exists an index j satisfying $q_i^1 = q_i^2$ if $i \neq j$ and $q_j^1 = q_j^2 + 1$. The $(n-1)$-box W separating the n-boxes B_1 and B_2 is the subset of the positive cone C given by

$$W = \{x \in C : x_i = \theta_i^{q_i} \text{ if } i = j, \theta_i^{q_i} < x_i < \theta_i^{q_i+1} \text{ if } i \neq j\}$$

where the mapping $q = q^1$. Notice that the PL system is not defined on the set W.

Theorem 2 *If $f_i^B < \gamma_i \theta_i^{q_i}$, all trajectories in B that are encountering the wall $x_i = \theta_i^{q_i}$ are leaving the box B. Similarly, if $f_i^B > \gamma_i \theta_i^{q_i+1}$, all trajectories in B that are encountering the wall $x_i = \theta_i^{q_i+1}$ are leaving the box B. If $\theta_i^{q_i} < f_i^B/\gamma_i < \theta_i^{q_i+1}$, all trajectories in B that are encountering the walls $x_i = \theta_i^{q_i}$ or $x_i = \theta_i^{q_i+1}$ enter the box B from these walls.*

Proof Suppose that $f_i^B < \gamma_i \theta_i^{q_i}$ and the trajectory $x(t)$ encounters the wall $x_i = \theta_i^{q_i}$ at time t_0. Then $x_i(t_0) - \Phi_i^B > 0$ and, according to (5), the component $x_i(t)$ of $x(t)$ is decreasing. Thus $x_i(t) < \theta_i^{q_i}$ for $t > t_0$, that is, the solution $x(t)$ leaves the box. The proof is similar in the other cases. ∎

Following Plahte et al. [12], a wall separating two boxes will be called a black wall (resp. a white wall) if trajectories leave (resp. enter) both boxes from the wall. It will be called a transparent wall if trajectories enter one box from the wall and leave the other box.

We have to consider also the $(n-2)$-boxes which are the common faces of four adjacent n-boxes. Let B_1, B_2, B_3 and B_4 be four n-boxes defined by the mappings q^1, q^2, q^3 and q^4, such that there exist two indices j and k satisfying $q_i^1 = q_i^2 = q_i^3 = q_i^4$ if $i \neq j$ and $i \neq k$ and

$$q_j^1 = q_j^2 = q_j^3 + 1 = q_j^4 + 1, \quad q_k^1 = q_k^2 + 1 = q_k^3 + 1 = q_k^4$$

The $(n-2)$-box P separating the n-boxes B_1, B_2, B_3 and B_4 is the subset of the positive cone C given by

$$P = \{x \in C : x_i = \theta_i^{q_i} \text{ if } i \in \{j,k\}, \theta_i^{q_i} < x_i < \theta_i^{q_i+1} \text{ if } i \notin \{j,k\}\}$$

where the mapping $q = q^1$. Notice that the PL system is not defined on the set P.

More generally we must consider the $(n-k)$-boxes which lie in the intersection of k threshold hyperplanes.

Definition 2 *Let $k = 1, \cdots, n$ be an integer. Let I be a subset of $\{1, \cdots, n\}$ having k elements. Let $q : \{1, \cdots, n\} \to \mathbb{N}$, $i \mapsto q_i$ be a mapping satisfying*

$$1 \leq q_i \leq N_i \text{ if } i \in I \text{ and } 0 \leq q_i \leq N_i \text{ if } i \notin I$$

The $(n-k)$-box defined by (I,q) is the subset of the positive cone C given by

$$B = B^{(I,q)} = \{x \in C : x_i = \theta_i^{q_i} \text{ if } i \in I, \theta_i^{q_i} < x_i < \theta_i^{q_i+1} \text{ if } i \notin I\}$$

The total number of $(n-k)$-boxes is equal to

$$m_{n-k} = \prod_{i=1}^{n} (N_i + 1) \sum_{1 \leq i_1 < \cdots < i_k \leq n} \frac{N_{i_1}}{N_{i_1}+1} \cdots \frac{N_{i_k}}{N_{i_k}+1}$$

The boundary of any k-box is the union of k'-boxes where $0 \leq k' \leq k-1$.

It is easy to see that the total number of boxes is equal to

$$m_0 + m_1 + \cdots + m_n = \prod_{i=1}^{n} (2N_i + 1).$$

Having described the partition of the state space, we will define the concept of Filippov solution.

3 Filippov solutions of the PL system

To provide the existence and the possibility for solutions to be continued on all boxes, it is necessary to define the right-hand side of system (2) at the points of discontinuity of the function f. The simplest way to achieve this is the convex definition of Filippov [1]. For each point $x \in C$, a subset $F(x) \subset \mathbb{R}^n$ is specified. If at the point x the function f is continuous, the set $F(x)$ consists of one point which coincides with the value $f(x)$ of the function f at this point. If x is a point of discontinuity of the function f, $F(x) - \gamma x$ is in general a set, given by the convex hull of the regular vector fields surrounding x (see below). This set gives a differential inclusion and enables to define the notion of solution everywhere.

Definition 3 *A solution in the sense of Filippov of (2) is a solution of the differential inclusion*

$$x' \in F(x) - \gamma x$$

that is, an absolutely continuous function $x(t)$ for which $x'(t) \in F(x(t)) - \gamma x(t)$ almost everywhere.

In the remaining of this section we explain how to construct the set $F(x)$ at discontinuity points of f.

Let us first consider the case where x belongs to a wall W separating two n-boxes B_1 and B_2. Following [1], the set $F(x)$ is the convex set

$$F(x) = \text{conv}(f^{B_1}, f^{B_2})$$

where conv denotes the convex hull. Consider the linear segment $F(x) - \gamma x$ joining the endpoints of the vectors $f^{B_1} - \gamma x$ and $f^{B_2} - \gamma x$. If this segment does not intersect the hyperplane containing the wall W, that is, the wall W is transparent, the solutions pass from one side of the wall W to the other. If this segment intersects the hyperplane containing the wall W (Fig. 1), that is, the wall W is black or white, the intersection gives the vector $f^W - \gamma x$ which determines the velocity of motion

$$x' = f^W - \gamma x \tag{6}$$

on the wall W. Such a solution is called a *sliding motion*.

Theorem 3 *Assume that W is in the hyperplane $C_i^j = \{x \in C : x_i = \theta_i^j\}$ and W is black or white, that is, $(f_i^{B_2} - \gamma_i\theta_i^j)(f_i^{B_1} - \gamma_i\theta_i^j) < 0$. The constant vector f^W in (6) is given by*

$$f^W = \alpha f^{B_1} + (1-\alpha) f^{B_2}, \qquad \alpha = \frac{f_i^{B_2} - \gamma_i\theta_i^j}{f_i^{B_2} - f_i^{B_1}}. \tag{7}$$

The focal point Φ^W is the intersection of the linear segment $\Phi^{B_1}\Phi^{B_2}$ with the hyperplane C_i^j:

$$\Phi^W = C_i^j \cap \operatorname{conv}(\Phi^{B_1}, \Phi^{B_2}).$$

Proof The segment joining the endpoints of the vectors $f^{B_1} - \gamma x$ and $f^{B_2} - \gamma x$ is expressed by

$$\alpha f^{B_1} + (1-\alpha) f^{B_2} - \gamma x, \qquad 0 \le \alpha \le 1.$$

The value of α in (7) is found from the condition $\alpha f_i^{B_1} + (1-\alpha) f_i^{B_2} - \gamma_i\theta_i^j = 0$ which means that the vector $f^W - \gamma x$ is in the hyperplane $x_i = \theta_i^j$. Since $(f_i^{B_2} - \gamma_i\theta_i^j)(f_i^{B_1} - \gamma_i\theta_i^j) < 0$, one has that $0 < \alpha < 1$. From (7) one has that

$$\Phi^W = \alpha\Phi^{B_1} + (1-\alpha)\Phi^{B_2}, \qquad 0 < \alpha < 1.$$

Thus, Φ^W is the intersection of the linear segment $\Phi^{B_1}\Phi^{B_2}$ with the hyperplane C_i^j. ∎

If W is transparent, trajectories of (2) in B_1 and B_2 can be joined into a single continuous trajectory satisfying the PL system. In the other case, when W is black or white, there is no indication of how a solution can be continued. If we consider the solutions of the PL system in the sense of Filippov then it is possible to continue a solution into black and white walls. First, assume that the wall is black. A continuous function $x(t)$ defined on the time interval $I = [a, b]$, which on a part $[a, c]$ of I lies in the box B_1 (or B_2) and there satisfies equation (2), and on the rest $[c, b]$ of I lies in the wall W and satisfies equation (6), is also a solution of (2) in the sense of Definition 3. Now, assume that the wall is white. A continuous function $x(t)$ defined on the time interval $I = [a, b]$, which on a part $[a, c]$ of I lies in the wall W and satisfies equation (6), and on the rest $[c, b]$ of I lies in the box B_1 (or B_2) and there satisfies equation (2), is also a solution of (2) in the sense of Definition 3.

If W is black, then near the wall all the solutions are approaching it from both sides as t increases, and none of them can leave W. A solution which passes through a point of the wall W at $t = t_0$ will therefore remain on W for $t > t_0$ until it reaches the boundary of W. If W is white, then a solution which passes through a point of the wall W at $t = t_0$ may either go off the wall W into the box B_1 or B_2, or remain on W for $t > t_0$. In the later case the solution may go off W at any moment. On a white wall the motion is therefore unstable.

Let us now describe the velocity of motion along a $(n-2)$-box P which is in the intersection of two threshold hyperplanes. This box is the common face of four n-boxes B_1, B_2, B_3 and B_4 (Fig. 2). Let $x \in P$. Then $F(x)$ is the smallest convex set

$$F(x) = \mathrm{conv}(f^{B_1}, f^{B_2}, f^{B_3}, f^{B_4})$$

containing the vectors f^{B_i}, $i = 1, \cdots, 4$. In general the intersection of $F(x) - \gamma(x)$ and the $(n-2)$-hyperplane containing P does not consist of only one point. In generic cases, this intersection is a linear segment or is empty. If it is empty then there are no solutions lying on P. If it is nonempty then one obtains a differential inclusion

$$x' \in f^P - \gamma x, \tag{8}$$

which determines the velocity of motion along P.

Theorem 4 *Assume that P is in the $(n-2)$-dimensional hyperplane $C_{ik}^{jl} = \{x \in C : x_i = \theta_i^j, x_k = \theta_k^l\}$. The set f^P in (8) consists of all points $\alpha_1 f^{B_1} + \alpha_2 f^{B_2} + \alpha_3 f^{B_3} + \alpha_4 f^{B_4}$, where the α_i are the positive solutions of the linear system*

$$\begin{array}{l} \alpha_1 + \alpha_2 + \alpha_3 + \alpha_4 = 1, \\ \alpha_1 f_i^{B_1} + \alpha_2 f_i^{B_2} + \alpha_3 f_i^{B_3} + \alpha_4 f_i^{B_4} = \gamma_i \theta_i^j, \\ \alpha_1 f_k^{B_1} + \alpha_2 f_k^{B_2} + \alpha_3 f_k^{B_3} + \alpha_4 f_k^{B_4} = \gamma_k \theta_k^l. \end{array} \tag{9}$$

The focal set $\Phi^P = \gamma^{-1} f^P$ is the intersection of the smallest convex containing the focal points Φ^{B_1}, Φ^{B_2}, Φ^{B_3} and Φ^{B_4}, with the hyperplane C_{ik}^{jl}:

$$\Phi^P = C_{ik}^{jl} \cap \mathrm{conv}(\Phi^{B_1}, \Phi^{B_2}, \Phi^{B_3}, \Phi^{B_4}).$$

Proof For $x \in P$, the smallest convex set containing the vectors $f^{B_i} - \gamma x$, $i = 1, \cdots, 4$, is a set of all vectors of the form

$$\alpha_1 f^{B_1} + \alpha_2 f^{B_2} + \alpha_3 f^{B_3} + \alpha_4 f^{B_4} - \gamma x, \quad \alpha_i \geq 0, \quad \sum \alpha_i = 1. \tag{10}$$

This vector belongs to the hyperplane C_{ij}^{kl} if and only if the α_i are the positive solutions of the linear system (9). From (10) one has that

$$\Phi^P = \alpha_1 \Phi^{B_1} + \alpha_2 \Phi^{B_2} + \alpha_3 \Phi^{B_3} + \alpha_4 \Phi^{B_4}, \quad \alpha_i \geq 0, \quad \sum \alpha_i = 1.$$

Thus, Φ^P is the intersection of C_{ik}^{jl} with $\mathrm{conv}(\Phi^{B_1}, \Phi^{B_2}, \Phi^{B_3}, \Phi^{B_4})$. ∎

This construction may be continued on all intersections of threshold planes. Let k be an integer $1 \leq k \leq n$. Let $B = B^{(I,q)}$ be a $(n-k)$-box. This box is in the common boundary of 2^k n-boxes $B_j = B^{q'}$, $1 \leq j \leq 2^k$, where q' is a mapping satisfying $q'_i = q_i$ if $i \in I$ and $q'_i = q_i$ or $q'_i = q_i - 1$ if $i \in I$. The set $F(x)$ is the convex set

$$F(x) = \mathrm{conv}(F^{B_j}, 1 \leq j \leq 2^k)$$

containing the vectors f^{B_j}, $1 \leq j \leq 2^k$. The $(n-k)$-hyperplanes C^B containing the box B is given by

$$C^B = \{x \in C : x_i = \theta_i^{q_i}, i \in I\}$$

In general the intersection of $F(x) - \gamma(x)$ and the $(n-k)$-hyperplane C^B does not consist of only one point. If it is empty then there are no solutions lying on P. If it is nonempty then one obtains a differential inclusion

$$x' \in f^B - \gamma x \tag{11}$$

which determines the velocity of motion along B.

Theorem 5 *The set f^B in (11) consists of all points $\sum_{j=1}^{2^k} \alpha_j f^{B_j}$ where the α_j are the positive solutions of the linear system*

$$\begin{array}{l} \sum_{j=1}^{2^k} \alpha_j = 1 \\ \sum_{j=1}^{2^k} \alpha_j \Phi_i^{B_j} = \theta_i^{q_i}, \qquad i \in I \end{array} \tag{12}$$

The focal set $\Phi^B = \gamma^{-1}$ of the box B is the intersection of the smallest convex containing the focal points Φ^{B_j}, $j = 1, \cdots, 2^k$ with the hyperplane C^B:

$$\Phi^B = \mathrm{conv}(\Phi^{B_j}, 1 \leq j \leq 2^k) \cap C^B \tag{13}$$

The positive solutions of (12) depend on at most $2^k - k - 1$ arbitrary constants. Thus Φ^B is generically empty or a simplex of dimension

$$\mathrm{dim}\Phi^B = \min(n, 2^k - 1) - k$$

The differential inclusion (8) or (11) means that the motion is not determined in a unique way on the intersection of threshold hyperplanes by this concept of Filippov solutions. If we would need to choose between these different trajectories, a more specific concept of solutions would be necessary (see the conclusion).

4 Regular and singular stationary points

We now show the utility of this concept of Filippov's solutions in the study of the singular steady states.

Snoussi and Thomas [15] introduced the concepts of regular stationary points (RSP) and singular stationary points (SSP) in models comprising step functions. A RSP is a stationary point where none of the variables has a threshold value. A SSP is a stationary point where one or more variables has a threshold value. The RSPs are simply defined by putting $x' = 0$ in (2), that is, by the equation

$\gamma x = f(x)$. This equation has a solution, if an only if, for some box B, the focal point Φ^B belongs to B. According to Theorem 1, $x = \Phi^B$ is an asymptotically stable RSP. Since the PL system is not defined on the threshold planes, SSPs cannot be defined by $x' = 0$.

In the present paper, we use the concept of solutions of (2) in the sense of Filippov, so we have no problem with the definition of stationary points. Indeed the point $x = c$ is called a stationary point for the PL system (2), if it is a solution, that is, if $x(t) \equiv c$ is a solution (in the sense of Filippov) of (2), that is

$$0 \in F(c) - \gamma c$$

A SSP is a stationary point which belongs to some threshold plane. On a wall, the behaviour and SSP are easy to describe: the solutions of (6) are curves lying on the wall W and converging toward the focal point $\Phi^W = \gamma^{-1} f^W$. If $\Phi^W \in W$, then $x = \Phi^W$ is a stable node of (6). This proves the following result.

Theorem 6 *Let $\Phi^W \in W$. If W is a black wall, then $x = \Phi^W$ is an asymptotically stable stationary point (in the sense of Filippov) of (2). If W is a white wall, then $x = \Phi^W$ is an unstable stationary point (in the sense of Filippov) of (2).*

Hence it follows easily:

Theorem 7 *SSPs cannot be located in transparent walls. There is an SSP on a black (or white) wall W if and only if $\Phi^W \in W$. If a SSP belongs to a black (resp. white) wall, then it is an asymptotically stable (resp. unstable) solution of (2).*

Proof On a transparent wall there is no sliding motion. Hence SSPs cannot be located in transparent walls. Let $x = p$ be a SSP which belongs to a black or white wall W. Then, one has $p = \Phi^W$. Hence $\Phi^W \in W$ and, by Theorem 6, it is an asymptotically stable (resp. unstable) solution of (2), if W is black (resp. white). ∎

Our definition, compared to that of Snoussi and Thomas, is clearer (see [15], p. 984) and makes the mathematical computation easy. To avoid the difficulties of [15] in the definition of SSPs, Plahte et al. [12, 13] suggested to define a stationary point of the PL system as the limit of stationary points of homologous continuous systems, when the steepness of the sigmoid functions increases to infinity. The stationary point is said to be singular if this limit lies in some threshold plane. With this definition, that is not so obvious to handle the concept of SSP at the limit.

Since the sliding motion on $(n-k)$-boxes, $k > 1$, is given by a differential inclusion, the analysis of SSPs lying in the intersection of threshold hyperplanes is more delicate.

Theorem 8 *Let k be an integer, $k = 1, \cdots, n$. There is an SSP on the $(n-k)$-box P if and only if $\Phi^P \cap P \neq \emptyset$.*

Proof Let $p \in P$ be a stationary point. Then $x(t) \equiv p$ is a solution of the differential inclusion (8). Thus $p \in \Phi^P$ and $\Phi^P \cap P \neq \emptyset$. ∎

If Φ^P does not consist of only one point p, which is the case in generic systems if $k > 1$, then p is not an isolated steady point, and the solution is not unique (cf. conclusion). If $\Phi^P = \{p\}$, then $x = \Phi^P$ is a stable node of (8). Hence it can be an asymptotically stable SSP of (2), in the case where any solution of (2) in the sense of Filippov, starting in a neighborhood of p, tends to a point in the box P. Further analyses are needed to study the stability. Some indications can be inferred from the transition graph.

5 The state transition graph

In this section, we define an "extended" transition graph showing the transition between all the boxes of any dimension.

The state transition graph for system (2) is a directed graph representing the passage of the trajectories from box to box. To each k-box, $k = 0, \cdots, n$, is associated a vertex. Let us define the edges. Let B be an n-box and B' an n'-box, $0 \leq n' \leq n-1$, included in the boundary of B.

1. If there is a solution of (2) lying in B and terminating in B', then the state transition graph contains the directed edge $B \to B'$.

2. If there is a solution of (2) lying in B and beginning in B', then the state transition graph contains the directed edge $B' \to B$.

Let B be a k-box, $1 \leq k \leq n$, and B' a k'-box, $0 \leq k' \leq k-1$, included in the boundary of B.

1. If the focal set Φ^B defined by (13) is empty, then there is no edge $B \to B'$ or $B' \to B$ in the state transition graph.

2. If $\Phi^B \neq \emptyset$ and there is a solution of the differential inclusion (11) lying in B and terminating in B', then the state transition graph contains the directed edge $B \to B'$.

3. If $\Phi^B \neq \emptyset$ and there is a solution of the differential inclusion (11) lying in B and beginning in B', then the state transition graph contains the directed edge $B' \to B$.

Notice that

- if W is a transparent wall separating two n-boxes B_1 and B_2, then the state transition graph contains the edges

$$B_1 \to W \to B_2 \quad \text{or} \quad B_1 \leftarrow W \leftarrow B_2$$

- if W is a black wall separating two n-boxes B_1 and B_2, then the state transition graph contains the edges

$$B_1 \to W \leftarrow B_2$$

- if W is a white wall separating two n-boxes B_1 and B_2, then the state transition graph contains the edges

$$B_1 \leftarrow W \to B_2$$

This state transition graph contains in some sense the state transition graph defined in [3, 4]. These authors restricted their attention to the case where all walls are transparent. They considered the graph whose vertices are the n-boxes. A directed edge $B_1 \to B_2$ between two boxes means that B_1 and B_2 are two adjacent boxes separated by a transparent wall W and that the solutions lying in B_1 leave the box B_1 from the wall W and the solutions lying in B_2 enter the box B_2 from the wall W.

6 Examples

This section is intended to illustrate the applicability of our approach by some typical examples which appeared in the literature. In the following examples, we consider the form (3) of the PL system. If there is only one threshold value θ_i^1 for the variable x_i, we denote it simply θ_i and we denote $z_i = S(x_i, \theta_i)$. Whenever necessary, we specify z_i^j as z_i^{j+} and we denote $z_i^{j-} = 1 - z_i^{j+}$.

6.1 Example of Plahte, Mestl and Omholt [12]

In this first example we have the case of an asymptotically stable SSP in a black wall; we obtain the unstability of the other SSPs.

Consider a two dimensional system with one threshold value θ_i for each variable x_i. The equations are

$$\begin{aligned} x_1' &= k_1(z_1^+ z_2^- + z_1^- z_2^+) - x_1, \\ x_2' &= k_2 z_1^- - x_2. \end{aligned} \tag{14}$$

The positive cone is separated in four boxes B^{00}, B^{01}, B^{10}, and B^{11} (Fig. 3). Assume that $k_1 > \theta_1$ and $k_2 > \theta_2$. The focal points are $f^{00} = (0, k_2) \in B^{01}$, $f^{01} = (k_1, k_2) \in B^{11}$, $f^{10} = (k_1, 0) \in B^{10}$ and $f^{11} = (0, 0) \in B^{00}$. By Theorem 1, f^{10} is an asymptotically stable RSP. The wall W_1 is white, W_2 is black, W_3 and W_4 are transparent. By Theorem 3, the sliding motion on W_1 is given by

$$x_2' = k_2 - \theta_1 k_2/k_1 - x_2$$

and the sliding motion on W_2 is given by

$$x_2' = \theta_1 k_2/k_1 - x_2$$

Let us assume that $k_1 < 2\theta_1$ and $k_2/k_1 > \theta_2/\theta_1$ (other cases can be handled similarly). The focal point $f^{W_1} = (\theta_1, k_2 - \theta_1 k_2/k_1)$ belongs to W_1 and the focal point $f^{W_2} = (\theta_1, \theta_1 k_2/k_1)$ belongs to W_2. By Theorem 7, f^{W_1} is is an unstable SSP and f^{W_2} is an asymptotically stable SSP. Moreover, the point $P = (\theta_1, \theta_2)$ belongs to the convex set $\text{conv}(f^{00}, f^{01}, f^{10}, f^{11})$. By Theorem 8, P is a SSP; it is unstable. The behaviour is easy to read almost exhaustively on the state transition graph (Fig. 3).

6.2 Example of Snoussi and Thomas [15]

Here we obtain the exact location (and not only the detection) of the SSP. This example was proposed in [15] as an illustration of the method of detection of SSPs. Consider a two-dimensional system with two threshold values $\theta_i^1 < \theta_i^2$ for each variable x_i. The equations are

$$\begin{aligned} x_1' &= k_1 z_1^1 + k_3 z_2^2 - x_1, \\ x_2' &= k_2 z_1^2 + k_4 z_2^1 - x_2. \end{aligned} \tag{15}$$

The positive cone is subdivided in nine boxes B^{ij}, $i, j = 0, 1, 2$ (Fig. 4). Let us assume that $\theta_1^1 < k_1 < \theta_1^2$, $\theta_1^1 < k_3 < \theta_1^2 < k_1 + k_3$, and $\theta_2^1 < k_2 < \theta_2^2$, $\theta_2^1 < k_4 < \theta_2^2 < k_2 + k_4$. The focal points are

$f^{00} = (0, 0) \in B^{00}$, $f^{10} = (k_1, 0) \in B^{10}$, $f^{20} = (k_1, k_2) \in B^{11}$, $f^{01} = (0, k_4) \in B^{01}$, $f^{11} = (k_1, k_4) \in B^{11}$, $f^{21} = (k_1, k_2 + k_4) \in B^{12}$, $f^{02} = (k_3, k_4) \in B^{11}$, $f^{12} = (k_1 + k_3, k_4) \in B^{21}$ and $f^{22} = (k_1 + k_3, k_2 + k_4) \in B^{22}$.

By Theorem 1, f^{00}, f^{10}, f^{01}, f^{11} and f^{22} are asymptotically stable RSPs. Let us determine the SSPs. A wall W separating the boxes B^{ij} and B^{kl} is denoted by $W = (B^{ij}, B^{kl})$. The walls $W_1 = (B^{00}, B^{01})$, $W_2 = (B^{00}, B^{10})$, $W_3 = (B^{10}, B^{11})$ and $W_4 = (W^{01}, W^{11})$ are white. All other walls are transparent. By Theorem 3, the sliding motion on W_1 is given by $x_1' = -x_1$; its focal point is $f^{W_1} = (0, \theta_2^1) \in W_1$. By Theorem 3, the sliding motion on W_2 is given by $x_2' = -x_2$; its focal point is $f^{W_2} = (\theta_1^1, 0) \in W_2$. By Theorem 3, the sliding motion on W_3 is given by $x_1' = k_1 - x_1$; its focal point is $f^{W_3} = (k_1, \theta_2^1) \in W_3$.

By Theorem 3, the sliding motion on W_4 is given by $x_2' = k_4 - x_2$; its focal point is $f^{W_4} = (\theta_1^1, k_4) \in W_4$. By Theorem 7, f^{W_1}, f^{W_2}, f^{W_3} and f^{W_4} are unstable SSPs.

Consider now the intersections of the threshold planes. One has

$$(\theta_1^1, \theta_2^1) \in \operatorname{conv}(f^{00}, f^{01}, f^{10}, f^{11}), \qquad (\theta_1^2, \theta_2^2) \in \operatorname{conv}(f^{11}, f^{21}, f^{12}, f^{22}).$$

By Theorem 8, $P_1 = (\theta_1^1, \theta_2^1)$ and $P_2 = (\theta_1^2, \theta_2^2)$ are SSPs; they are unstable. Moreover

$$(\theta_1^1, \theta_2^2) \notin \operatorname{conv}(f^{01}, f^{11}, f^{12}, f^{02}), \qquad (\theta_1^2, \theta_2^1) \notin \operatorname{conv}(f^{10}, f^{20}, f^{21}, f^{11}).$$

By Theorem 8, $P_3 = (\theta_1^1, \theta_2^2)$ and $P_4 = (\theta_1^2, \theta_2^1)$ are not stationary points. Hence (15) has eleven stationary points, five of them are regular, and six are singular. Notice that in our approach, the SSPs belonging to white walls are not only detected but also located in the corresponding wall (compare with [15], p. 981-982). It is also interesting to see that much of the dynamical behaviour can be read on the transition graph (Fig. 4).

6.3 Example of Thomas [12]

We consider a gene regulatory model investigated by Thomas [16] and studied by Plahte et al. [12]. These authors use for their study a continuous approximation of the system by logoids. We recall briefly their approach and results afterwards. We obtain a complete analysis of the example. Consider the three dimensional system with one threshold value θ_i for each variable x_i.

$$\begin{aligned} x_1' &= k_1 z_2^- z_3^+ - \gamma_1 x_1, \\ x_2' &= k_2 z_1^+ z_3^+ - \gamma_2 x_2, \\ x_3' &= k_3(z_1^- + z_2^+ - z_1^- z_2^+) - \gamma_3 x_3. \end{aligned} \tag{16}$$

The positive cone is separated in eight boxes B^{ijk}, $i, j, k = 0, 1$. Assume that $0 < g_i < 1$, where $g_i = \gamma_i \theta_i / k_i$, $i = 1, 2, 3$. The focal points are

$\Phi^{000} = \Phi^{010} = \Phi^{011} = \Phi^{110} = (0, 0, k_3/\gamma_3) \in B^{001}$, $\Phi^{100} = (0, 0, 0) \in B^{000}$, $\Phi^{001} = (k_1/\gamma_1, 0, k_3/\gamma_3) \in B^{101}$, $\Phi^{101} = (k_1/\gamma_1, k_2/\gamma_2, 0) \in B^{110}$, and $\Phi^{111} = (0, k_2/\gamma_2, k_3/\gamma_3) \in B^{011}$.

Thus, (16) has no RSPs. Let us determine the SSPs. All walls are transparent. Hence there is no sliding motion on the walls. The SSPs must lie on the intersection of two or more threshold planes. Let $C_{ij} = \{x \in C : x_i = \theta_i, x_j = \theta_j\}$. Let $P_1 = \{x \in C_{23} : x_1 > \theta_1\}$ $P_2 = \{x \in C_{13} : 0 \le x_2 < \theta_2\}$ and $P_3 = \{x \in C_{12} : x_3 > \theta_3\}$. By Theorem 4, the sliding motion on P_i is given by the differential inclusion

$$x_i'(t) \in k_i A_i - \gamma_i x_i(t), \qquad x_i(t) \in P_i$$

where

$$A_1 = [\min(0, g_2 - g_3), \max(g_2, 1 - g_3)],$$

$$A_2 = [\min(0, g_1 - g_3), \max(g_1, 1 - g_3)],$$
$$A_3 = [\min(1 - g_1, 1 - g_2), \max(1, 2 - g_1 - g_2)].$$

By Theorem 8, one has an SSP on P_i if and only if the corresponding focal set intersects P_i, that is,

$$k_i A_i/\gamma_i \cap P_i \neq \emptyset \tag{17}$$

For $i = 1$, condition (17) is equivalent to $g_1 < \max(g_2, 1 - g_3)$. For $i = 2$, condition (17) is equivalent to $g_3 > g_1 - g_2$. For $i = 3$, condition (17) is equivalent to $g_3 < 2 - g_1 - g_2$. Hence the cube $0 < g_i < 1$, $i = 1, 2, 3$, in parameter space is separated into four different regions, in which one, two or three SSPs may exist on P_i, $i = 1, 2, 3$ (Fig. 6).

The line $P_2' = \{x \in C_{13} : x_2 > \theta_2\}$ is the common edge of the boxes B^{010}, B^{110}, B^{011} and B^{111}. One has $C_{13} \cap \mathrm{conv}(\Phi^{010}, \Phi^{110}, \Phi^{011}, \Phi^{111}) = \emptyset$. By Theorem 4, there is no sliding motion on P_2'. Also, one has

$$C_{12} \cap \mathrm{conv}(\Phi^{000}, \Phi^{100}, \Phi^{010}, \Phi^{110}) = \emptyset, \quad C_{23} \cap \mathrm{conv}(\Phi^{000}, \Phi^{010}, \Phi^{011}, \Phi^{001}) = \emptyset.$$

Hence, there is no sliding motions on the segments $P_3' = \{x \in C_{12} : 0 \leq x_3 < \theta_3\}$ and $P_1' = \{x \in C_{23} : 0 \leq x_1 < \theta_1\}$.

Let us now consider the intersection of the three threshold planes. By Theorem 8, the point $P = (\theta_1, \theta_2, \theta_3)$ is a SSP if and only if it belongs to the convex set containing all focal points Φ^{ijk}, $i, j, k = 0, 1$. This case arises if and only if $g_1 + g_3 > g_2$, $g_2 + g_3 > g_1$ and $g_1 + g_2 + g_3 < 2$ (see Fig. 6 which represent the domain in parameter space in which P is a SSP).

Let us now consider the continuous approach of [12]. When the step functions $z(x)$ in (3) are replaced by continuous approximations $Z(x, \delta)$, the resulting system

$$x' = F(Z(x, \delta)) - \gamma x, \tag{18}$$

is a continuous analogue of (3). Here

$$Z(x, \delta) = (Z_1^1, \cdots, Z_1^{N_1}, \cdots, Z_n^1, \cdots, Z_n^{N_n}), \qquad Z_i^j = \Sigma(x_i, \theta_i^j, \delta),$$

and $\Sigma(\xi, \theta, \delta)$ is a sigmoid function, such that the steepness increases when $\delta \to 0$, that is,

$$\lim_{\delta \to 0} \Sigma(\xi, \theta, \delta) = S(\xi, \theta).$$

Plahte et al. [12] considered the SSPs of (16) as the limits of the corresponding continuous analogue

$$\begin{aligned} x_1' &= k_1 Z_2^- Z_3^+ - \gamma_1 x_1, \\ x_2' &= k_2 Z_1^+ Z_3^+ - \gamma_2 x_2, \\ x_3' &= k_3 (Z_1^- + Z_2^+ - Z_1^- Z_2^+) - \gamma_3 x_3. \end{aligned} \tag{19}$$

of (16). They detected a steady state $(x_1^2(\delta), x_2^2(\delta), x_3^2(\delta))$ satisfying

$$\lim_{\delta\to 0} x_1^2(\delta) = \theta_1, \quad \lim_{\delta\to 0} x_2^2(\delta) = k_2(1-g_3)g_1/\gamma_2, \quad \lim_{\delta\to 0} x_3^2(\delta) = \theta_3,$$

This limit belongs to P_2 if and only if $g_3 > 1 - g_2/g_1$. They also detected a steady state $(x_1^3(\delta), x_2^3(\delta), x_3^3(\delta))$ satisfying

$$\lim_{\delta\to 0} x_1^3(\delta) = \theta_1, \quad \lim_{\delta\to 0} x_2^3(\delta) = \theta_2, \quad \lim_{\delta\to 0} x_3^3(\delta) = k_3(1-g_1g_2)/\gamma_3.$$

This limit belongs to P_3 if and only if $g_3 < 1 - g_1g_2$. Notice that the domains of existence in parameter space of these two SSPs are included in our domains (Fig. 6).

It is claimed in [12] that steady points may only exist on P_2 and P_3 which correspond to circuits in the transition graph (Fig. 5): in fact, it is easily seen that (19) also has a third steady state $(x_1^1(\delta), x_2^1(\delta), x_3^1(\delta))$ satisfying

$$\lim_{\delta\to 0} x_1^1(\delta) = k_1(1-g_3)g_2/\gamma_1, \quad \lim_{\delta\to 0} x_2^1(\delta) = \theta_2, \quad \lim_{\delta\to 0} x_3^1(\delta) = \theta_3.$$

This limit belongs to P_1 if and only if $g_3 < 1 - g_1/g_2$ and the corresponding domain of existence is included in our domain (Fig. 6).

7 Conclusions

The concept of Filippov solutions enables a rigorous and clear treatment of the problem of singular solutions. It can provide new tools for exploring the interesting problems arising from these threshold biological models.

In particular, we are able to compute the location of all the singular steady states. Theses steady states are important from a biological point of view because they give the possible distinct homeostatic behaviours of the genes network. Computationally, this problem can be time-consuming (in high dimensions) and it remains to study efficient algorithms.

In practice, the exact value of the parameters (such as the position of the threshold and the value of the function in each box) is often not exactly known, i.e. the parameter is only known to belong to some given interval. A very interesting problem would be to study the robustness of the results (for example, of the number and location of steady states) with respect to these intervals.

In this study, we only considered the generic case where the focal point does not lie on the threshold hyperplane. If this occurred under variation of a parameter, it could lead to non-smooth bifurcations (e.g. [2]).

Of course, the problem of the ambiguity of the dynamical behaviour in the case when the differential inclusion (8) is a set and not a single point remains open: it can be solved by choosing a behaviour among all the behaviors given by the differential inclusion, by some method of regularization ([17]), either by taking continuous homologous systems, or by the way of a stochastic process. But, considering the bases and goals of the study of this kind of mathematical genetic networks, one can also think that it is important to consider every possible behaviour, to be sure not to miss some trajectory. With such a point of view, it is interesting to keep the differential inclusion and study all the compatible behaviours: of course, corresponding algorithms and software have to be written, and are the subject of current work [7, 8, 9]. Such computer tools, based on the concepts developed in this paper, could facilitate the modelling, simulation and study of large genetic networks, and the comparison with the huge amount of experimental data available in genomics.

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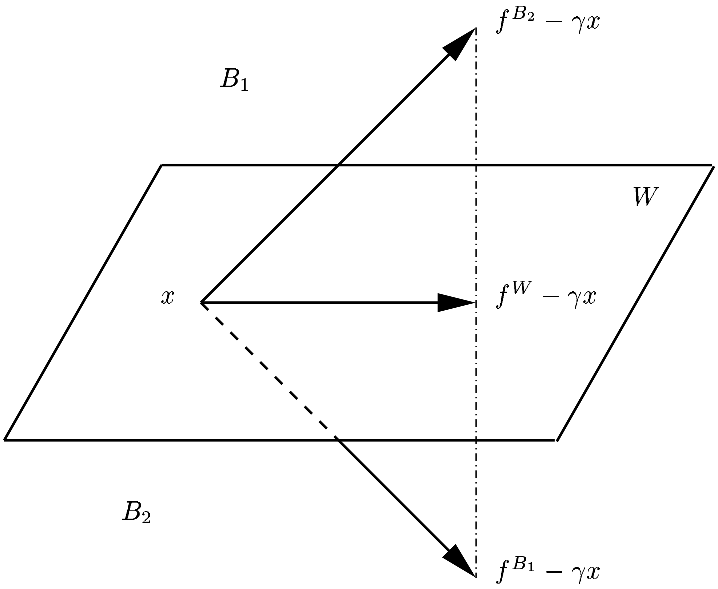

Figure 1: The velocity of motion along a threshold hyperplane.

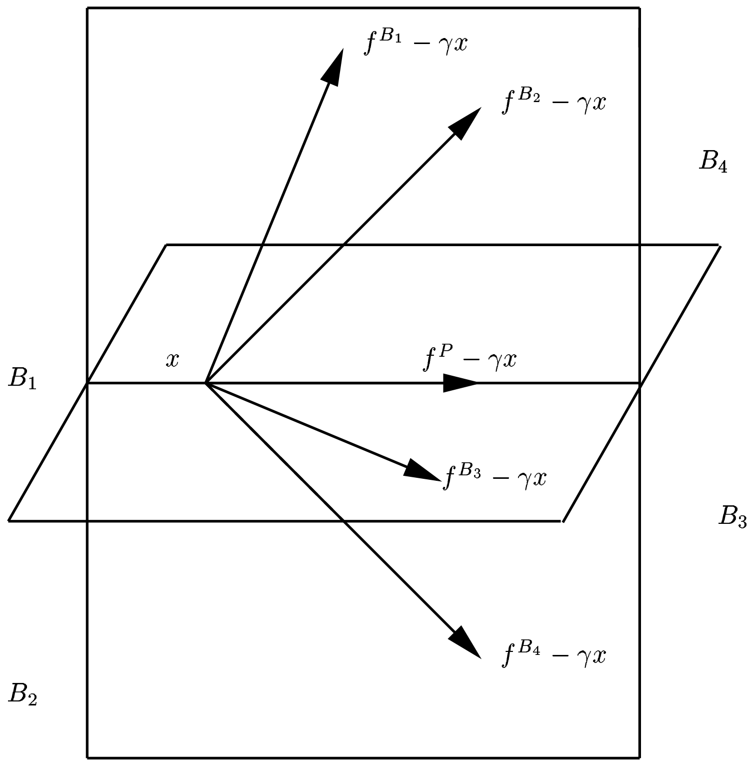

Figure 2: The velocity of motion along the intersection of two threshold hyperplanes.

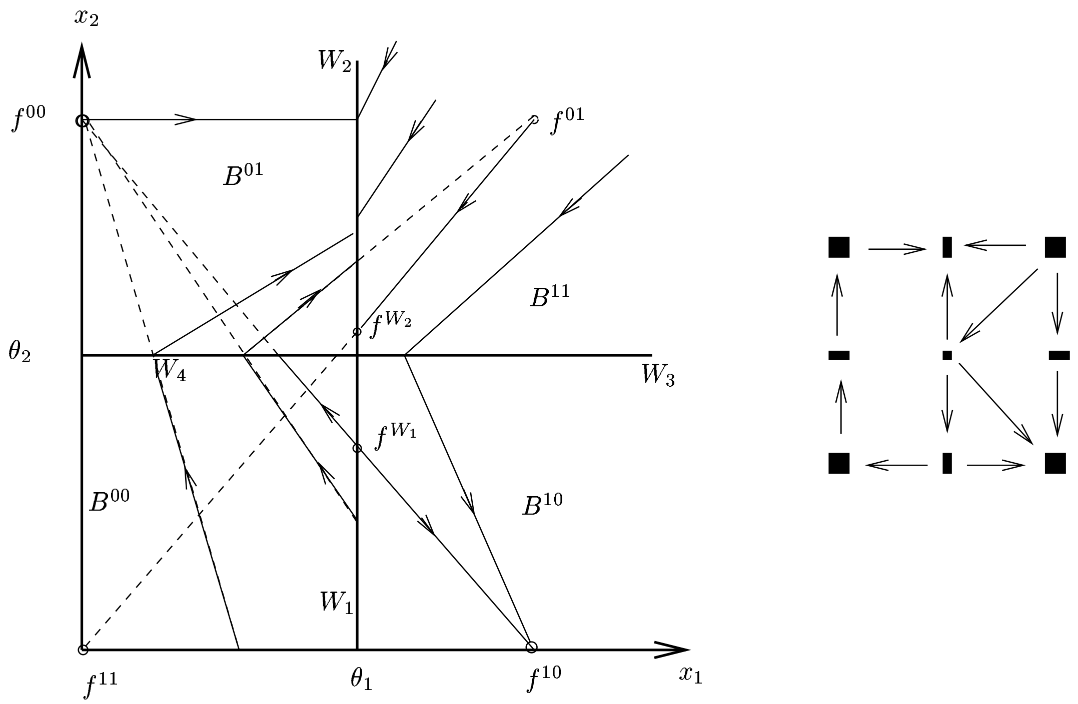

Figure 3: The flow and transition graph of (14). In the transition graph, the big squares are the boxes, the rectangles the planes between, and the small square is the point P.

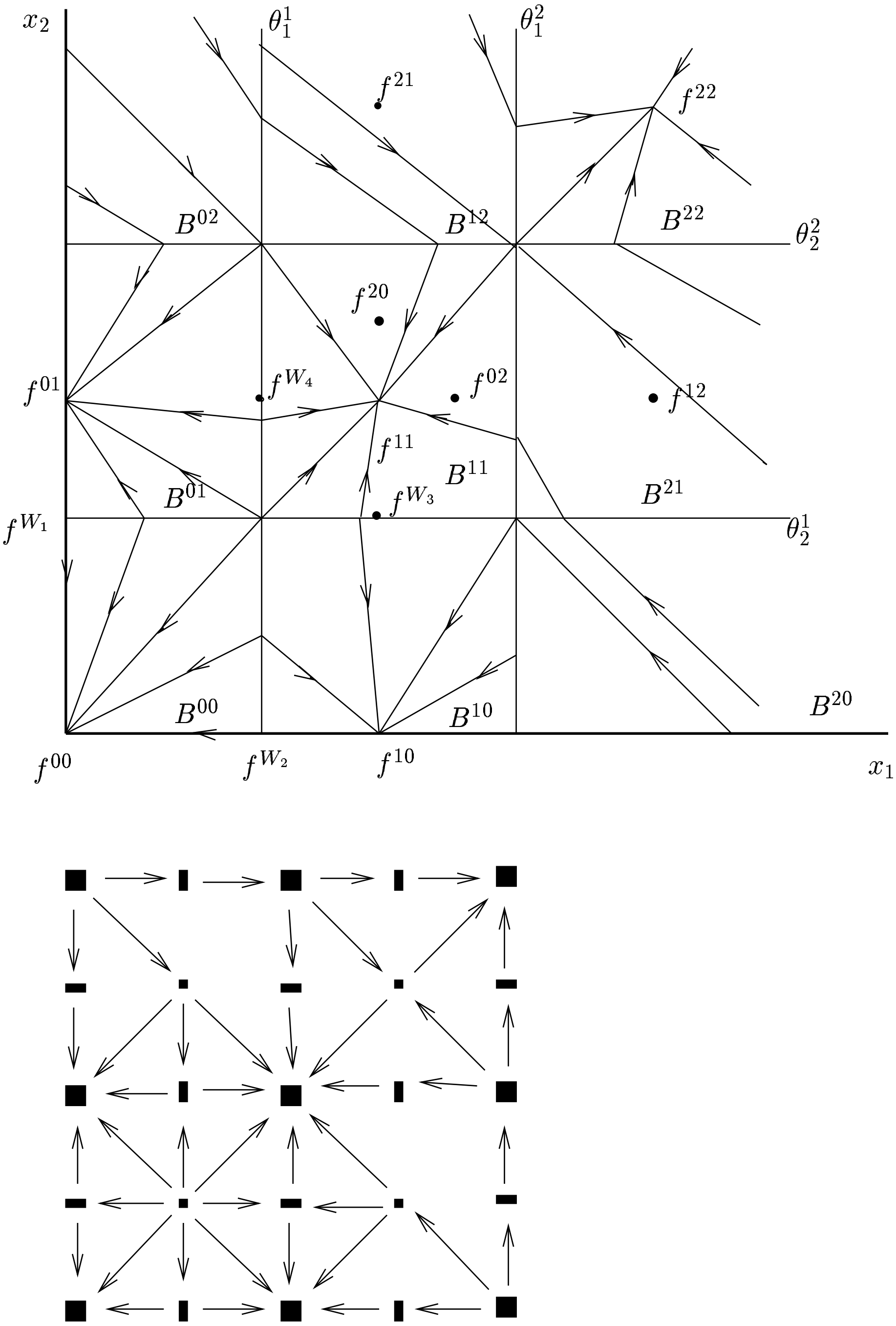

Figure 4: The flow and transition graph of (15). For the significance of the elements of the graph, see the figure above.

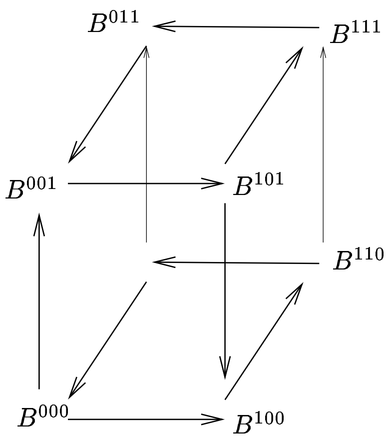

Figure 5: The transition graph of (16); all the walls are transparent and are not represented on the graph.

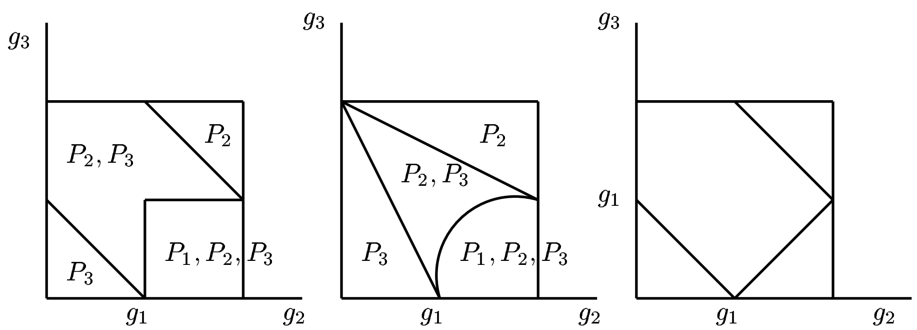

Figure 6: The domains of existence of SSP of (16 and 19), shown in the g_2-g_3 plane for an arbitrary value of g_1; compare with [12].