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Characterisation of Singular Domains in Threshold Dependent Biological Networks

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Abstract

Threshold-dependent networks which behave like piecewise smooth systems and belong to a class of systems with discontinuous right hand side are studied with piecewise linear differential equations. At threshold values and their intersections, known as switching boundaries and surfaces, the state of such networks is not defined because of singularity at such points. This study characterises, in terms of number, singular domains of any order in a network and the total number of such domains; and also proposes new definitions for walls, using Filippov's First Order Theory on characterisation of (sliding) wall. The finding of this study is presented as propositions I, II and III respectively. In particular, using proposition II the study identified two white walls previously considered transparent. Introducing monotonicity to definition of transparent wall is also seen to affect qualitative dynamics like source, sink and cycles.

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1. Introduction

Differential equations with discontinuous right-hand-side are applied in different areas of study [1, 2]. They include but are not limited to control problems [3], neural networks [4] and gene regulatory networks [5, 6]. Due to its importance, different types of solutions exist for this class of problems [5] of which Filippov's is the most widely invoked [6-12]. Threshold-dependent networks from biology, such as gene regulatory networks can be considered as piecewise linear differential model with discontinuous right hand side [13]. The discontinuity observed in this class of threshold-dependent networks results from threshold boundaries known as the switching boundaries. Switching boundaries can be of different orders depending on the number of variables at play in the network. Intersection of two or more different switching boundaries is known as switching surfaces. Due to the wide application and acceptance of Filippov's approach to this class of problems, the threshold boundaries (or surfaces) are called Filippov's boundary (or surface). In biological networks, they represent variables' concentration levels (and may be referred to as concentration thresholds) and

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their intersections respectively. At these boundaries, the state of the variable is assumed to change. For instance, above a certain concentration level (that is, threshold value) a variable may be activated or deactivated depending on the effect of control of the activity of all other variables regulating its function [14, 15]. These switching boundaries, which can also be called (switching) hyperplanes, partition the state space of the network or systems into rectangular boxes [16] and segments [17] when step functions are used to describe the regulatory control resulting from the threshold. Within these boxes, the state of the network is known and can be defined as a linear function because of the use of step functions. On the contrary, the state of the network is considered not known at the threshold boundaries yielding the discontinuity observed in networks of such nature.

One of the major challenges of this class of network is defining a solution along the switching boundary. Filippov's approach is used to study the behaviour of this class of network [7, 9, 10, 12], especially at the threshold boundary. One of the results of Filippov is defining what is called sliding vector field at a (sliding) threshold boundary, where discontinuity exists. This provides an insight into the behaviour of solutions of the system in the neighbourhood of the threshold boundary. Within the vicinity of the threshold, a trajectory approaching a discontinuity boundary can either glide through, move away from, or slide on, it. This is how a threshold boundary is classified. Using Filippov approach, differential models with discontinuous right hand side have been investigated for different qualitative properties such as orbits [18-20], limit cycles [1] and sliding motions and solutions on threshold boundaries [11, 13]. As noted earlier, discontinuous boundaries have been selectively investigated for existence of solutions due to a conventional definition that is based on the flow of trajectory towards such domains. For instance, Sari and Gouze in [13] conclude that transparent walls are not candidate for sliding vector motion. Their conclusion is premised on the direction of flow of solution trajectories towards the wall. However, they failed to investigate if such walls are actually transparent let all providing a criterion for testing the transparency of a wall beyond direction of trajectories of focal points.

In recent times this class of problem was considered as fast-slow systems with delay [22-25]. To analyse the behaviour of solution at the switching boundary regularisation approach was adopted. In [21]the qualitative behaviour of the system is analysed in the neighbourhood of the threshold boundary. In the use of regularisation approach, two types of hyperplane are considered, sewing and sliding manifolds. These definitions were made using singular solution of the switching manifold [23, 24]. From these studies, it is obvious that transparent walls are not studied for sling vector field or motions because vector field cannot be defined on them. Noted also is the fact that the definition of the nature of these walls have not been reviewed since its introductions. Encouraged by the definition of sewing and sliding manifolds in [23, 24] with respect to singular solution an attempt is made to redefine the nature of these walls using focal points (as a limit solution) in the network.

If transparent walls are not candidates for sliding motion and there is no concrete criterion for determining transparency as noted earlier, then the need arises to provide for such. Secondly, if switching manifolds (walls) a more robust classification of the nature of walls can be made using focal points which are limit solutions. Within the limit of our knowledge, only regular domains have been characterised in terms of number in this class of network; so, a need arises to characterise singular domains in terms number. The objective of the study is to use Filippov's first order theory to provide a criterion for transparency and in addition introduce monotonicity to check behaviour of variables at such transparent walls; derive new definitions that shall capture some intrinsic behaviour in threshold-dependent systems, especially biological systems where relapse is known to occur and characterise singular domains in terms of number. To achieve its objective, the paper is organized as follows: Introduction is contained in section 1 while the system under study and the method of study are presented in section 2. In section 3, the result of the network is presented as propositions. Analysis of the results is verified in this section too to demonstrate the usefulness and applicability of the study. Discussion of the result of the study is done in section 4 whereas conclusion of the work is in section 5.

2. Materials and Methods

This section is to introduce discontinuous system of the nature to be considered in this work. Let

$$\Sigma = \{x \in \Re^n : h(x) = 0\} \tag{1}$$

and define a smooth function $B : \Re^n \to \Re$ with the property that $B_x(x) \neq 0$ on Σ, where $x \in \Re^n$. Then consider a discontinuous system given as

$$x'(t) \in F(x(t)) \tag{2}$$

with $x_0(0) = X_0 \in \Re^n$, where $F(X(t))$ satisfies

$$F(x) = \begin{cases} f_1(x) & \text{if } x \in H_1 \\ f_2(x) & \text{if } x \in H_2 \end{cases} \tag{3}$$

and

$$H_1 = \{x \in \Re^n : h(x) > 0\} \tag{4}$$

$$H_2 = \{x \in \Re^n : h(x) < 0\} \tag{5}$$

.

Equation (1) defines the discontinuity boundary which partitions the state space into H_1 , the upper half plane and H_2 the lower half plane. Equation (1) shall be referred to as hyperplane or wall in this work. Equation (2) is known as differential inclusion problem in control problems. Within H_1 and H_2, the state of the system is known but not on Σ as defined in equation (1). At the threshold boundary (that is, the wall), define

$$f_w = \bar{co}\{f_1(x), f_2(x)\} = (1 - \alpha)f_j + \alpha f_i \tag{6}$$

where $\alpha \in [0, 1]$ and $\bar{co}(V)$ is the smallest closed convex set containing V [9, 10]. This is the nature of the class of problems to be discussed here.

Definition 1. ([9, 13]). An absolutely continuous function $x_t : [0, \tau) \rightarrow \Re^n$ is said to be the solution of equation (2) in the sense of Filippov if for almost all $t \in [0, \tau)$ it holds that $x_0(0) = x_0$ and $x_t'(t) \in F(x(t))$, where $F(x(t))$ is the closed convex hull defined as given in equation(6). The reader is referred to [13] for more on this.

One of the many challenges of this class of problem is defining a solution on the threshold hyperplane with respect to x_0. As a way out, closed convex hull defined as the smallest set containing a set, which is equation (6), is proposed for defining vector motion on the threshold hyperplane [13]. It uses convex combination of $f_1(x)$ and $f_2(x)$ to make definition of a vector field on the threshold hyperplane possible [12, 13]. When such vector fields are defined, then the behaviour of its trajectory in the neighbourhood of the hyperplane is used to characterise the nature of the hyperplane. This characterisation determines whether a hyperplane shall be investigated for existence of solution or not. For instance, transparent walls are considered asymptotically stable but not white walls. Black walls can be stable or not [25, 26, 13].

The interest in this study is not on the stability of domains in this network but characterisation of the threshold hyperplane and singular domains respectively. However, the discussion of the results shall make use of stability of domains to highlight the importance of this study and to show that the findings of this study, with respect to nature of walls, performs better than existing ones in [13, 25]. Therefore, we refer to [13] (theorems 1 and 6) for stability of domains and [17] for stability of regular steady point (RSP) and singular steady point (SSP). The stability used in this paper is in line with stability in [13]

2.1. Gene Regulatory Networks

Let $Z_i : \Re^+ \rightarrow [0, 1]$ be a regulatory function, where $i = 1, 2, ..., n$ and suppose the system given below (see [32]) exists

$$\dot{x}_i(t) = g_i(x, Z) = F_i(Z) - G_i(Z)x_i \tag{7}$$

where $x_i = (x_1, x_2, ..., x_n)^T \in \Re^n$ represents the concentration of the ith variable, F_i and G_i are bounded multilinear polynomial functions defining the production and degradation rates respectively. Most often, the regulatory function Z is used to define the switching behaviour in gene regulatory networks. As such, either step function is used as Z in which case $Z_i : \Re^+ \rightarrow \{0, 1\}$, or a sigmoid function is used so that $Z_i : \Re^+ \rightarrow (0, 1)$. The focus of this study is on the use of step function as switching function. So, consider

$$Z(x, \theta) = \begin{cases} 1 & \text{if } x > \theta \\ 0 & \text{if } x < \theta \end{cases} \tag{8}$$

where θ is a threshold for the variable x. With equation (8), the discontinuity at the threshold boundary becomes clear. It then follows that the hyperplane of interest coincides with the threshold value of the variable of interest.

Definition 2 [8]: Let $\Omega = \Omega_1 \times \Omega_2 \times ... \times \Omega_n$ be the partitioning of phase space of (7) by the threshold hyperplanes where $\Omega_i = \{x \in \Re_+ : 0 \leq x \leq max_i\}$. A domain D is defined to be a set $D = D_1 \times D_2 \times ... \times D_n$ where D_i is one of the following:

$$D_i = \{x_i \in \Omega_i : 0 \leq x_i < \theta_i^1\} \tag{9}$$

$$D_i = \{x_i \in \Omega_i : \theta_i^j < x_i < \theta_i^{j+1}\}, \quad j = \{1, 2, ..., p_i - 1\} \tag{10}$$

$$D_i = \{x_i \in \Omega_i : \theta_i^{p_i} < x_i \leq max_i\} \tag{11}$$

$$D_i = \{x_i \in \Omega_i : x_i = \theta_j^i\}, \quad j = \{1, 2, ..., p_i\} \tag{12}$$

The threshold hyperplane partitions the state space of the network into two different domains known as regulatory and switching [8],or regular and switching [27]. Regulatory (or regular) domain refers to boxes where the state of the network is known. This is given by any of equations (9) to (11). It then follows that a domain is regulatory or regular if none of its variables' concentration is at a threshold value which can be interpreted as

$$D_i = \{x_i \in \Omega_i : x_i \neq \theta_i, \}$$

or

$$D_i = \{x_i \in: \Omega_i : x_i < \theta_i, x_i > \theta_i\}$$

Switching (or singular) domain, similarly, is where the state of the network cannot be determined because at least one variable assumes a threshold value. So, D is called a switching (or singular) domain of order $k \leq n$, denoted D^k, if exactly k variables have threshold values in D^k. x_s in this case is called a switching variable. This is an intersection of a box and hyperplane and given by a combination of equation (12), with or without, any or some of equations (9) to (11). Mathematically speaking, a singular domain is defined as

$$D = (x_s = \theta_s, x_r \neq \theta_r)$$

where subscripts s and r denote switching (or singular) and regulatory (or regular) variables respectively.

Example 1

To illustrate these domains, consider a two dimensional network (that is, a network with two variables only) whose variables have one threshold each. The state space of the network is shown in Figure 1. There are four regular boxes in this network given as $B_i \quad i = 1, 2.3, 4$ These boxes are defined as follows

$$B_1 = \{x_1 < \theta_1, x_2 < \theta_2\}$$

$$B_2 = \{x_1 > \theta_1 x_2 < \theta_2\}$$

$$B_3 = \{x_1 > \theta_1, x_2 > \theta_2\}$$

$$B_4 = \{x_1 < \theta_1, x_2 > \theta_2\}$$

The switching domains for example 1 are the following

$$D_1{}^1 = \{x_1 < \theta_1, x_2 = \theta_2\}$$

$$D_2{}^1 = \{x_1 > \theta_1 x_2 = \theta_2\}$$

$$D_3{}^1 = \{x_1 = \theta_1, x_2 < \theta_2\}$$

$$D_4{}^1 = \{x_1 = \theta_1, x_2 > \theta_2\}$$

$$D_5{}^2 = \{x_1 = \theta_1, x_2 = \theta_2\}$$

As the superscript denotes, D_1^1 to D_4^1, known as walls, are of order 1 because only one variable switch at a time in them whereas D_5^2 , called centre, is a switching domain of order two because the two variables switch simultaneously. Total number of regulatory domains in a network where each x_i has m_i thresholds have been obtained for this class of network [28, 8]. It is given as

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

The number of switching domains in this network has not been given in literature and as such, it is one of the main result of this study shall present in section 3.

Consider the piecewise linear model presented below

$$\dot{x}_i(t) = \beta_i S^{\pm}(x, \theta) - \gamma_i x_i \tag{13}$$

where

$$S^{\pm}(x, \theta) = 1 - S^{\mp}(x, \theta)$$

is same as equation (8). Within a box B_i, equation of motion given by (7) becomes

$$\dot{x}_i = f_i{}^{B_i} - \gamma_i x_i \tag{14}$$

In vector form, equation (14) is given as

$$\dot{X} = F^B - \Gamma X \tag{15}$$

where F^B and Γ are diagonal matrices which give the production and degradation rate function in the system.
Within a box, B_i, the solution of (14) is given as

$$x_i(t) = \frac{f_i}{\gamma_i} + (x_0 - \frac{f_i}{\gamma_i})e^{-\gamma_i(t-t_0)} \tag{16}$$

and in finite time, $t \to \infty$, the solution trajectory approaches

$$\phi_i^{B_i} = \frac{f_i}{\gamma_i} \tag{17}$$

which is called the focal point of the box B_i. The set of all focal points in the network is given in vector form as

$$\Phi = \{\phi_i^{B_i}\}_{i=1}^{n}$$

It is obvious from equation (16) that solution curves of equation (14) are straight lines inside a box. These curves, which are directed towards the focal point of their respective boxes, originate from a different point on a threshold hyperplane and might show corners [29]. As observed earlier, if the solution trajectory hits a threshold wall one may be at a loss for what to do. Sequel to this, a threshold wall is said to be transparent if solutions trajectory can be extended through it. That is to say, if trajectory can cross through it. A threshold wall is said to be white if solution trajectory rebounds from it while a wall is said to be black if trajectories slide on it. These definitions are good but fail to capture qualities such as relapse in biological network, where a variable can regain or loss its position in the curse of discharging its duty. For black walls, Filippov proposes a way to define a vector field on it. This class of walls are considered stable [13]. But white walls are never stable. Though the interest of this study is not in the stability or otherwise of these classes of domains, it is important to note that a definition that captures the actual happening within a threshold wall can really affect the stability properties of walls. For results on stability (of box and wall), see Theorems 1 and 6 (respectively) in [13].

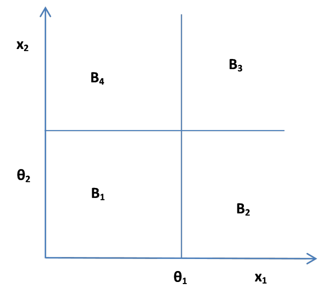

Figure 1: Network Partitioned by two thresholds θ_1 and θ_2 for x_1 and x_2 respectively

The definition of the threshold hypeprlane, depending on the behaviour of trajectory in the vicinity of the hyperplane, is of any of the following

- if a threshold hyperplane is such that trajectories depart from it and enter the adjacent boxes, then it is said to be **white**
- if a threshold hyperplane is such that trajectories approach it from either adjacent box, then it is said to **black**
- a threshold wall that is neither black nor white is said to **transparent**

As shall be shown later, this classification in a 'conventional sense' does not capture intrinsic behaviours in some systems, and as a result, this study shall propose new definitions that can capture such qualities.

2.2. *Filippov's First Order Theorem ([12])*

Let $x \in \Sigma$ and let $n(x)$ be the normal to Σ at x. Let $n^T(x)f_1(x)$ and $n^T(x)f_2(x)$ be the projections of $f_1(x)$ and $f_2(x)$ onto the normal to the hypersurface Σ, where $n^T(x)$ is the transpose of $n(x)$.
(a) Transversal intersection exists if, at $x \in \Sigma$,

$$[n^T(x)f_1(x)][n^T(x)f_2(x)] > 0 \tag{18}$$

(b) Sliding mode exists if, at $x \in \Sigma$,

$$[n^T(x)f_1(x)][n^T(x)f_2(x)] < 0 \tag{19}$$

From equation (18), it is evident that either $[n^T(x)f_1(x)] > 0$ and $[n^T(x)f_2(x)] > 0$ or $[n^T(x)f_1(x)] < 0$ and $[n^T(x)f_2(x)] < 0$. As explained in [14] the flow will enter H_1 or H_2 respectively in each of those cases. For equation (19) to be satisfied, then

$$[n^T(x)f_1(x)] < 0 \tag{20}$$

and

$$[n^T(x)f_2(x)] > 0 \tag{21}$$

or

$$[n^T(x)f_1(x)] > 0 \tag{22}$$

and

$$[n^T(x)f_2(x)] < 0 \tag{23}$$

Equations (18), (20) and (21), and (22) and (23) are used to characterise the hyperplane Σ as transparent, black and white respectively. Transparent hyperplane is same as transverse intersection given by equation (18), equations (20) and (21) gives the condition that guarantee a hyperplane to be black known as sliding hyperplane and equations (22) and (23) produces white wall called repulsive sliding hyperplane, see [14]. On the threshold hyperplane, Filippov's convex function has been defined as follows [12, 13]

$$f_w = (1-\alpha)f_j + \alpha f_i \tag{24}$$

where

$$\alpha(x) = \frac{n^T(x)f_j(x)}{n^T(x)(f_j(x) - f_i(x))} \tag{25}$$

and $0 \leq \alpha(x) \leq 1$. w stands for wall, $i : x_i < \theta_i$ and $j : x_j > \theta_j$
Filippov's First Order Theory shall be used to propose new characterisation or definition for the nature of threshold hyperplanes in networks that exhibit the properties under study. These definitions shall focus on the existence of convex constant $\alpha(x)$ given by equation (25) which is verifiable rather than the definitions presented earlier in subsection 2.1.

3. Result and Analysis

This section presents the result of this study. The results come in the form of proposition that will give new characterisation of walls and their nature. Examples of these walls are the threshold hyperplane, $x_1 = \theta_1$ and $x_2 = \theta_2$ shown in Figure 1 and defined as before. Sequel to the presentation shall be analyses of some networks (using the new results from this study) to expose the weakness in the existing definitions thereby highlighting the significance of our study.

3.1. Proposition I: Nature of switching hyperplane

A characterisation of switching hyperplane (that is wall) is presented using the vector field equation (14) in the boxes adjacent to the dswitching hyperplane with the assumption that n^T as defined in subsection 2.2 is non-negative.
Let $B_j = \{x \in X^n : x_i < \theta_i\}$ and $B_k = \{x \in X^n : x_i > \theta_i\}$ be two boxes adjacent to a threshold wall $x_i = \theta_i$. Given that the conditions contained in equations (24) and (25) are satisfied by (20) at the threshold hyperplane Σ where $x_i = \theta_i$, then the nature of the hyperplane Σ can be defined as any of the following

- Σ is said to be transparent if

$$f_i^{B_j} = f_i^{B_k} \tag{26}$$

- Σ is said to be white if

$$f_i^{B_j} > f_i^{B_k} \tag{27}$$

- Σ is said to be black if

$$f_i^{B_j} < f_i^{B_k} \tag{28}$$

where $f_i^{B_\tau}$ refers to vector field equation (14) for x_i in the box $\tau = i, j$

3.2. Proposition II: Nature of walls

Another way of characterising a switching hyperplane using the focal points of boxes adjacent to the hyperplane is presented here.
Let Σ be a hyperplane where only one variable, x_i, is singular (that is where $x_i = \theta_i$) and $B_j = \{x \in X^n : x_i < \theta_i\}$ and $B_k = \{x \in X^n : x_i > \theta_i\}$ be two boxes adjacent to Σ with ϕ_j and ϕ_k the respective focal points of the boxes adjacent to Σ. Then

- Σ is said to be transparent if

$$x_i < \theta_i \Rightarrow \phi_j > \theta_i \quad \text{and} \quad x_i > \theta_i \Rightarrow \phi_k > \theta_i \tag{29}$$

or

$$x_i < \theta_i \Rightarrow \phi_j < \theta_i \quad \text{and} \quad x_i > \theta_i \Rightarrow \phi_k < \theta_i \tag{30}$$

In the event of (29), the new definitions which this study proposes is that the wall is **transparently increasing** while for (30) it is said to be **transparently decreasing**.

- Σ is said to be white if

$$x_i < \theta_i \Rightarrow \phi_j < \theta_i \quad \text{and} \quad x_i > \theta_i \Rightarrow \phi_k > \theta_i \tag{31}$$

- Σ is said to be black if

$$x_i < \theta_i \Rightarrow \phi_j > \theta_i \quad \text{and} \quad x_i > \theta_i \Rightarrow \phi_k < \theta_i \tag{32}$$

3.3. Proposition III: Number of switching hyperplanes

The stability of network of the nature considered here has been discussed [30, 31, 13]. The equilibrium of this network revolves around the focal points in the two domains - regulatory and switching respectively [13, 30]. The total number of regulatory domains has been obtained [28]. If the stability of this system can be discussed with respect to its switching domain, it will not be out of place to characterise singular domains of all orders. So, this subsection is for such result. First, number of walls is presented followed by pencils, centres and number of regulatory domains where k variables switch.

3.3.1. Walls

Let (13) be such that only one variable out of n variable switch at a time, where each variable has m_i thresholds. Then the number of walls belonging to $x_i = \theta_i$ is

$$m_i \prod_{j=1}^{n-1} (m_j + 1) \tag{33}$$

where $j = 1, 2, \cdots, i-1, i+1, \cdots, n$
The total number of walls in such network is given

$$\sum_{i=1}^{n} \left[m_i \prod_{j=1}^{n-1} (m_j + 1) \right] \tag{34}$$

3.3.2. Pencils

Let equation (13) be such that each variable x_i has m_i thresholds at which it interacts with other variables in the network. The number of pencils in such a network where k variables switch at a time is

$$\prod_{s=1}^{k} m_s \prod_{r=k+1}^{n} (m_r + 1) \tag{35}$$

The total number of such pencils is

$$\sum_{i=1}^{n} \left[\prod_{j=1}^{k} m_j \prod_{j=k+1}^{n-k} (m_j + 1) \right] \tag{36}$$

3.3.3. Centres

The number of centres in a network with n variables is

$$\prod_{s=1}^{n} m_s \tag{37}$$

3.3.4. Regular Domains where k variables switch

The total number of regular domains in a network where k variables switch at a time is

$$\prod_{i=1}^{n-k} (m_i + 1) \tag{38}$$

3.4. Verification of Results

Three networks to illustrate the effectiveness and advantage of our results over existing results are presented here. To achieve this, the following network examples from [25, 30, 32] are considered. The walls of the network from [32] agrees completely with our result on the definition of walls. The second example from [25] showed a wall as decreasing instead of increasing which changes and affects the qualitative properties of the network. In the third example [32], two new non-transparent walls were discovered. These were obtained from the result of this study.

3.4.1. Example Networks

The three example networks are as follows
Example 2 [28]

$$\dot{x}_1 = Z_1 + Z_2 - 2Z_1Z_2 - \gamma_1 x_1$$

$$\dot{x}_2 = 1 - Z_1Z_2 - \gamma_2 x_2$$

Example 3 [26]

$$\dot{x}_1 = k_1\bar{Z}_2Z_3 - \gamma_1 x_1$$

$$\dot{x}_2 = k_2Z_2Z_3 - \gamma_2 x_2$$

$$\dot{x}_3 = k_3(\bar{Z}_1 + Z_2 - \bar{Z}_1Z_2) - \gamma_3 x_3$$

Example 4 [13, 27]

$$\dot{x}_1 = k_1Z_1^1 + k_3Z_2^2 - x_1$$

$$\dot{x}_2 = k_2Z_1^2 + k_4Z_2^2 - x_2$$

Example 2 is a network that has two variables with a threshold associated with each of the variables. Using the result of equation (33), the number of thresholds walls associated with these thresholds is $1(1+1) \times 1(1+1) = 4$. This is as shown in Figure 1. The network of this example has no pencil and just a centre. With the use of equation (8) in this example, the vector equation and their focal points inside the boxes B_i, $i = 1, 2, 3$ and 4 as defined by equations (14) and (17) respectively are as given below.

$$B_1 : \dot{x}_1 = -\gamma_1 x_1; \dot{x}_2 = 1 - \gamma_2 x_2 \quad \text{and} \quad (0, \gamma_2^{-1}) \tag{39}$$

$$B_2 : \dot{x}_1 = 1 - \gamma_1 x_1; \dot{x}_2 = 1 - \gamma_2 x_2 \quad \text{and} \quad (\gamma_1^{-1}, \gamma_2^{-1}) \tag{40}$$

$$B_3 : \dot{x}_1 = -\gamma_1 x_1; \dot{x}_2 = -\gamma_2 x_2 \quad \text{and} \quad (0, 0) \tag{41}$$

$$B_4 : \dot{x}_1 = 1 - \gamma_1 x_1; \dot{x}_2 = 1 - \gamma_2 x_2 \quad \text{and} \quad (\gamma_1^{-1}, \gamma_2^{-1}) \tag{42}$$

Threshold hyperplanes (walls) of this network as described in example 1 has the following characterisations:

$$D_1{}^1 = \{x_1 < \theta_1, x_2 = \theta_2\} \quad \text{is transparent.}$$

$$D_2{}^1 = \{x_1 > \theta_1 x_2 = \theta_2\} \quad \text{is black.}$$

$$D_3{}^1 = \{x_1 = \theta_1, x_2 < \theta_2\} \quad \text{is white.}$$

$$D_4{}^1 = \{x_1 = \theta_1, x_2 > \theta_2\} \quad \text{is black.}$$

D_1^1 is described as transparent in [32]. The focal points of the switching variable x_2 in boxes adjacent to $D_1{}^1$,which are B_1 and B_4, given by equations (40) and (41) satisfies propositions I and II. For instance, x_2 has the same focal points (which is greater than zero) in each of the said boxes. Inside B_1 , $x_2 < \theta_2$ but $\phi_2 > \theta_2$ (see [32] for the value of the constant) satisfying proposition II. Again, the production function for x_2, the switching variable, in the two boxes are the same (1 in each case). This satisfies Proposition I as well. The same analysis can be carried out for all the other threshold hyperplanes,

$D_2{}^1, D_3{}^1$ and $D_1{}^1$ to see that the proposition is effective in characterizing threshold hyperplanes.
Example 3 has three (3) variables with a threshold each. The use of proposition III shows that there are a total of twelve (12) threshold hyperplanes in the network. Each of the thresholds for the variable has four (4) walls associated with it. When the result of monotonicity of transparent walls is applied to these walls, it contradicts the result presented in [25].To see this, we refer to Figure 2 shown below.

The use of (29) or (30) on these walls given as the edges of the cube in Figure 2 reveals that the wall between the box $B_2 := x_1 < \theta_1, x_2 > \theta_2, x_3 < \theta_2$ and $B_3 := x_1 > \theta_1, x_2 > \theta_2, x_3 < \theta_2$ is not increasing in nature as shown in the flow diagram in [26]. Our result shows that the wall is actually transparently decreasing which produces Figure 2. From this it can be seen that the box (node), indicated as a source in [26] is not so. This node is the box B_2 represented as (010) on the flow diagram shown in Figure 2. The node that is a source from the result of this study is the box B_3 represented as (110) on Figure 2. To see clearer the usefulness of the results of this study, consider the focal point of these two boxes obtainable as $(0, 0, k_3\gamma_3^{-1})$. This means that the two boxes have the same focal point. From this focal point one sees that $x_1 < \theta_1 \Rightarrow \phi_1 = 0 < \theta_1$ and $x_1 > \theta_1 \Rightarrow \phi_1 = 0 < \theta_1$ which satisfies equation (30) and shows that the said wall is transparently decreasing. Again, the focal point of the box B_2 defined as a source by the flow diagram of [25] is 0 and contradicts that box as a source because the switching variable x_1 is trapped within that box at all times. The box B_3 , on the other hand, has the focal points of all the variables exiting the domain in finite time as each variable switch, showing that the said box is a source indeed. The focal points of these boxes as obtained agree quite well with those reported in [13] as well.

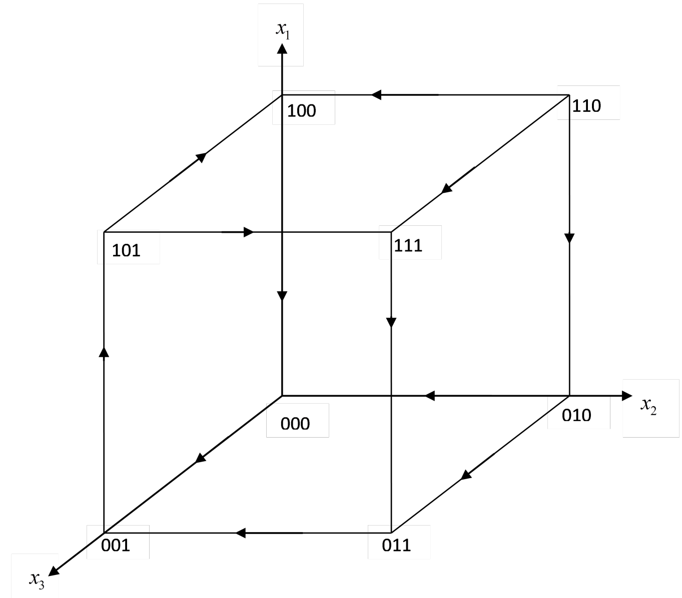

Figure 2: Flow Diagram of Example 3 Network

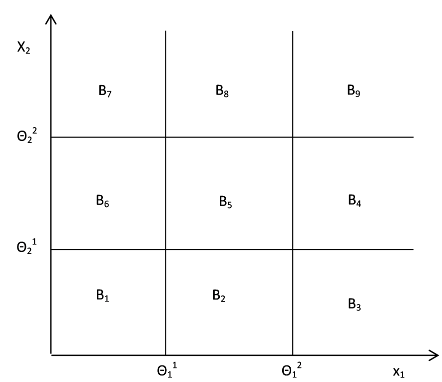

Figure 3: Phase Space Diagram of Example 4 Network

Finally, example 4 is a two-dimensional network whose variables have two thresholds each. The phase space diagram of the network is presented in Figure 3. As is evident from Figure 3, this network has eight boxes denoted B_1 to B_9. There are twelve one-dimensional domains (that is, walls) which are the edges of the corresponding boxes bounded by the threshold values, θ_1 and θ_2 respectively. The intersection points of the thresholds, (θ_1^i, θ_2^i) where $i = 1, 2$, is the centre and there are four of these centres in the network presented in example 4. See Figure 3. This can be verified using equations (36) and (37) of proposition III. Each threshold has three walls associated with it while each variable has six walls associated with it. Testing these walls to characterize them as black, white or transparent, using proposition I, revealed that there are two walls previously considered transparent in [13] which are actually white in nature. These are the walls between B_3 and B_4 on one side, and B_7 and B_8 on the other. To see this, observe that the vector motion for x_2 which switches between the boxes B_3 and B_4 in these boxes are respectively

$$\dot{x}_2 = k_2 + k_4 - x_2; \dot{x}_2 = k_2 - x_2 \tag{43}$$

while for the wall belonging to x_1 between the boxes B_7 and B_8 the vector equations are respectively

$$\dot{x}_1 = k_1 + k_3 - x_1; \dot{x}_1 = k_1 - x_1 \tag{44}$$

Using proposition I shows $f_2^{B_4} - f_2^{B_2} = k_4$ and $k_4 \neq 0$, meaning that the walls is not transparent. As such α defined by equation (25) can be found such that equation (24) can be defined on the wall. Similar thing can be conducted on equation (44) to show that the wall is not transparent. This notwithstanding, Proposition II can be used to characterize the said wall.
For this, the focal point of x_1 in the boxes of interest are

$$\phi_1^{B_8} = k_1 + k_3; \phi_1^{B_7} = k_1 \tag{45}$$

Apply proposition II to equation (45) to see that $x_1 < \theta_1^1 \Rightarrow \phi_1^{B_7} = k3 < \theta_1^1$ and $x_1 > \theta_1^1 \Rightarrow \phi_1^{B_7} = k_1 + k3 > \theta_1^1$, (see [28, 27] for details on the relationship between rate constants and threshold values). Thus, a conclusion can be reached that the wall is white and not transparent.
These walls though white can have Filippov vector motion de-

fined on them using equations (24) and (25). This non-unique vector motion can be obtained as follows

$$W_1 : (\dot{x}_1, \dot{x}_2) = (0, k_4 - x_2) \tag{46}$$

$$W_2 : (\dot{x}_1, \dot{x}_2) = (k_4 - x_2, 0) \tag{47}$$

Using the characterisation in propositions II, the flow diagram shown in Figure 4 is obtained.

4. Discussion

A regulatory domain (that is, box) in piecewise linear models of the nature discussed here can be stable or not. It is said to be asymptotically stable if its focal point is contained in the box as $t \to \infty$, otherwise it is said to be unstable. The same concept was adopted in [13] to study the stability of non-transparent walls. **That is, a threshold wall is said to be stable if the focal point of the vector defining motion on it belongs to the set defined by the closed convex hull of equation (6) in finite time**. If it is such that it resides on the wall as $t \to \infty$, then it is asymptotically stable. Based on this, it is expected that the qualitative properties of the network in example 3 should change due to the wrong classification of the walls described above. The stability analysis of the walls of the network which depends on the nature of walls is seen to be greatly affected. This will in turn affect cycles and some other properties of the network. It then follows that the definition proposed in this network is better and should be preferable as it can actually bring out some hidden qualities in the networks. From these qualitative properties, one can study the behaviour of the variables.

As seen from the result some walls were defined in a way that does not capture the intrinsic behaviour associated with biological regulatory networks. Such behaviours include relapses in elements involved in the regulatory activities. This is one of the reasons the two walls in example 4 previously thought to be transparent were not but white. Our conjecture in this case is that the focal point of the switching variable could not attain the threshold boundary let alone crossing it. As it approaches the threshold vicinity, relapse occurs in the production activity which decreases rise in variable's concentration that result in failure to stimulate switching which caused its focal point to drift away from the wall. Knowledge of such properties can help in identifying where there should be search for failures in such systems

The implication of equation (26) which is one of the results of this work is that if no α exists with respect to the wall of interest such that equation (24) holds, then the wall is transparent, a criterion for searching for transparent walls. Also by providing equation (35), one can know switching domain of any order $k < n$, in terms of number.

The study as presented used step function as threshold function which is limiting because it is a crude approximation of happenings within the vicinity of thresholds. Smooth functions such as Hill function is known to be better in studying systems with steep behaviour. We limited this study to step function because of the interest of the work which is to classify the threshold hypeplanes. It is the reason we proposed new definition

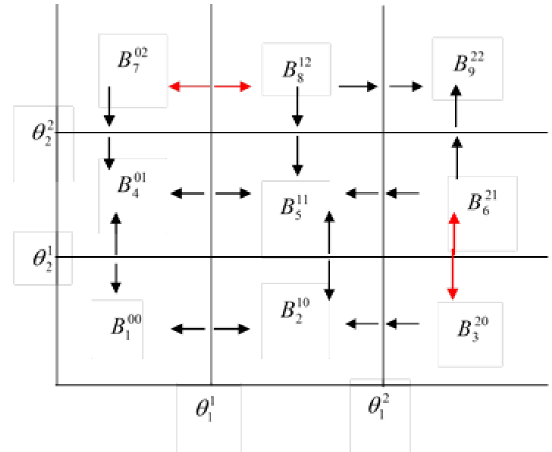

Figure 4: Flow Diagram across the Walls of Example 4 Network

based on the position of focal points in adjacent boxes to threshold walls to take care of relapses and rebounds in the vicinity of the threshold. One of the questions that arise from this study is how the new definition affects stability of singular solutions at threshold boundaries. For instance, solutions are not expected to stay on transparent wall. The two walls identified as white here were not studied for stability in [13]. Also the qualitative properties too have to change. Currently a work on the development of the propositions into theorems that can take care of stability and related qualitative properties is under way. Furthermore, with knowledge of how many singular domains are obtained in a network, one can study the stability of the entire system by investigating the relationship between the stability of regular and singular domains.

5. Conclusion

The work presented in this paper is piecewise linear models of threshold dependent networks. Such network is associated with rectangular regions bounded by the threshold hyperplane of the network. Dynamics of the system inside these rectangular regions can be given by piecewise linear differential equations (PLDE). These threshold hyperplanes as defined before failed to capture the real behaviour of the network in their vicinity. By using Filippov's method we proposed a definition which identified correctly some hyperplanes not properly defined before. The consequence of our condition for transparent walls is that the first task in walls analysis should be to test for transparency or not. By so doing, one can then know which walls to investigate for qualitative properties. Classifying transparent wall as decreasing or increasing reveals the behaviour of variable in the vicinity of threshold walls. This classification means that one can easily identify which variable is gaining or losing in function at the walls and as such take appropriate decision on what to do to obtain a better result at such places.

The characterisation of nature of walls presented in proposition I and II is considered from the point of view of focal

point and vector field of regulatory domains adjacent to the wall respectively. It is derived from Filippov's first order theory presented in section two. Furthermore, the result on switching domain obtained has not been given before to the best of our knowledge. It then follows that the results presented in this work, which is novel and applicable to real life problem, can be used with ease by non-mathematics researcher.
Again, Proposition III can be used to easily check the number of switching domains of order $k = 1, 2, ..., n$ involved in the network to have a guide on how to about the required analysis.

It is our hope that the results obtained in this work shall guide researchers in this area to obtain less spurious results.

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