Polynomial representations of piecewise-linear differential equations arising from gene regulatory networks

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Abstract

We describe generic sliding modes of piecewise-linear systems of differential equations arising in the theory of gene regulatory networks with Boolean interactions. We do not make any a priori assumptions on regulatory functions in the network and try to understand what mathematical consequences this may have in regard to the limit dynamics of the system. Further, we provide a complete classification of such systems in terms of polynomial representations for the cases where the discontinuity set of the right-hand side of the system has a codimension 1 in the phase space. In particular, we prove that the multilinear representation of the underlying Boolean structure of a continuous-time gene regulatory network is only generic in the absence of sliding trajectories. Our results also explain why the Boolean structure of interactions is too coarse and usually gives rise to several non-equivalent models with smooth interactions.

Keywords: gene regulatory networks, sigmoid functions, singular perturbation analysis, polynomial representation

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1. Introduction

Piecewise-linear systems of differential equations play an important role in many applications including hybrid dynamical systems [5], neural networks [16], genetic networks [4] and many others. Typically, such a system can be represented as a family of linear differential systems $\cdot x = A_\alpha x + f_\alpha$ where the system no. α is only effective if $x(t) \in D_\alpha$, where $\{D_\alpha\}$ is a partition of the phase space of the system (e.g. R^n or R^n_+). In biological applications such systems usually appear in complex models with Boolean interactions. For instance, gene regulatory networks can in many cases be described as a system of nonlinear ordinary differential equations of the form

$$\frac{dx_i}{dt} = F_i(z_1, ..., z_n) - G_i(z_1, ..., z_n)x_i, \quad i = 1, \dots, n, \tag{1}$$

where $x_i(t)$ are the gene concentrations at time t, and the regulatory functions F_i and G_i depend on the response functions $z_k = z_k(x_k)$, which control the activity of gene k and which are assumed to be step functions [4] representing two events: gene k is either activated, or deactivated. The system (1) splits then into 2^n linear diagonal systems and therefore becomes piecewise-linear. Such diagonal systems constitute an important subclass of general piecewise-linear systems. In some models (see e.g. [16]) the individual linear systems are not diagonal, but could be simultaneously transformed to a diagonal form.

One of the challenges in the study of piecewise-linear systems is existence of sliding modes, i.e. trajectories belonging to singular domains (= discontinuity sets) of the system. Mathematically, such solutions are a priori not defined. There are two well-established ways to describe sliding modes in piecewise-linear systems, both having certain advantages and disadvantages. One approach is based on differential inclusions (see e.g. [3], [6]), while the other utilizes singular perturbation analysis (see e.g. [8], [13], [15]), where smooth response functions of sigmoid-type replace the step functions.

The aim of the present paper is to continue and generalize analysis initiated in [8] and [15]. Exactly as in these papers, our starting point is the system (1) with Boolean response functions, which is regarded as an established model of gene regulatory networks. The mathematical and biological reasons for that can e.g. be found in [9] and are not discussed here. However, models with Boolean interactions represent a level of resolution which may be too coarse to describe sliding trajectories, while incorporating sigmoid-type responses helps to solve this problem. Minding this, we stress that unlike the paper [9] we derive sigmoid-based models from Boolean-based models, and not vice versa.

The main novelty of our paper compared to the works [8], [15] consists in replacing multilinear regulatory functions with general nonlinear functions. A mathematical motivation of our choice is closely related to specific properties of piecewise-linear systems. Indeed, a multilinear model is the simplest yet not the only model which can be associated with the same Boolean structure.

On the other hand, introducing general nonlinearities may be needed for full sensitivity analysis of the model with Boolean interactions, i.e. a description of what happens to the solutions of the system (1) in the presence of small perturbations of an arbitrary nature. This problem can be trivially solved in the case of smooth systems, where it is sufficient to apply the standard continuous dependence theorem. However, the system (1) is only piecewise smooth, so that small perturbations may cause drastic changes in the dynamics, both geometrically and topologically, and we show that it may indeed be the case if we include sliding trajectories into the analysis.

Possibilities to find a biological motivation for introducing nonlinear regulatory functions are discusses in Section 9.

The paper is organized in the following way.

In Sec. 2 we study general properties of the system (1) with smooth response functions. We prove that in this case the solutions are positive and defined on $[0, \infty)$. Sec. 3 deals with regular domains (i.e. those meeting no threshold lines) and singular domains (i.e. those where the right-hand side of the system (1) is discontinuous). This classification is crucial for the models with Boolean response functions. In Sec. 4 we show that if sliding modes are excluded from the model with Boolean response functions, then the property of multilinearity is generic, and there is no need for more general response functions. Sec. 5 explains how to apply the singular perturbation analysis to construct sliding trajectories in the Boolean-based model (1). In Sec. 6 and 7 we use the results of Sec. 5 to show that the multilinearity assumption is not generic if sliding modes are included into considerations. In Sec. 8 we address the problem of classification of generic systems (1) with Boolean response functions via polynomial representations ('recasting'). We prove, for instance, that the minimum degree of the representing polynomial is 2, 3, 4 or even 5 for certain types of domains. Finally, in Sec. 9 we discuss the main results of this paper.

2. Existence, uniqueness and other properties of solutions in the case of smooth response functions

In this paper we always assume that Boolean (i.e. step) functions are approximated with the help of *the Hill function* $z_k = H(x_k, \theta_k, q_k)$, where

$$H(x_k, \theta_k, q_k) = \frac{x_k^{1/q_k}}{x_k^{1/q_k} + \theta_k^{1/q_k}} \tag{2}$$

for $q_k > 0$. If $q_k \to 0$, then $H(x_k, \theta_k, q_k)$ tends to the step function that has the unit jump at the threshold θ_k. It is therefore convenient to denote this step function by $H(x_k, \theta_k, 0)$.

The usage of the Hill function has a long tradition in biology (see e.g. [10] for its relations to modeling of genes). However, in our approach it serves purely as a convenient representative of more general steep sigmoid functions, as the calculations involving the Hill function are well-established in singular perturbation analysis (see e.g. [8]). We remark, however, that the generality of our framework does allow to include more general sigmoid functions into the analysis.

Indeed, let $f_k : [0,1] \to [0,1]$ be smooth increasing functions with the properties $f_k(0) = 0$, $f_k(1) = 1$, and $f_k'(h) > 0$ as long as $f_k(h) \in (0,1)$. Then

$$S_k(x_k, \theta_k, q_k) = f_k(H(x_k, \theta_k, q_k)) \tag{3}$$

will be smooth sigmoid functions, as

$$\lim_{q_k \to 0} S_k(x_k, \theta_k, q_k) = f_k(H(x_k, \theta_k, 0)) = H(x_k, \theta_k, 0)$$

is the unit step function. Thus, the Hill function gives rise to very general sigmoid functions, including the so-called 'logoids' [7], which are useful in asymptotic analysis of gene regulatory networks. In this case, a multilinear regulatory function of a general sigmoid will be represented as a nonlinear regulatory function of the Hill function.

Example 1. Following [15] let us consider a gene regulatory network with two transcription factors. Assume that protein 1 and 2 are regulated by the logical functions XOR and NAND, respectively. If the regulatory effect is described by the Hill function (2), then this results (see [15] for details) in the system

$$\begin{aligned} \dot{x}_1 &= l_1(z_1 + z_2 - 2z_1 z_2) - \gamma_1 x_1 \\ \dot{x}_2 &= l_2(1 - z_1 z_2) - \gamma_2 x_2, \end{aligned} \tag{4}$$

where x_i denotes the concentration of gene product i (a transcription factor), γ_i are degradation parameters, l_i are the maximum synthesis rates.

Assume that the Hill function is replaced by the sigmoid S defined in (3). Then (4) can be regarded as a nonlinear system with the Hill response functions. For instance, if $f_k(h) = h^{\alpha_k}$, $\alpha_k > 1$, $k = 1, 2$, then we get a nonlinear system

$$\begin{aligned} \dot{x}_1 &= l_1(z_1^{\alpha_1} + z_2^{\alpha_2} - 2z_1^{\alpha_1} z_2^{\alpha_2}) - \gamma_1 x_1 \\ \dot{x}_2 &= l_2(1 - z_1^{\alpha_1} z_2^{\alpha_2}) - \gamma_2 x_2. \end{aligned}$$

In this section we study the well-posedness of the initial value problem

$$\begin{aligned} &\dot{x}_i = F_i(z_1, ..., z_n) - G_i(z_1, ..., z_n)x_i, \\ &x_i(t_0) = \alpha_i, \quad i = 1, ..., n, \end{aligned} \tag{5}$$

in the n-dimensional phase space $\mathbb{X}^n$, where

$$\mathbb{X}^n = \{(x_1, ..., x_n)|\ x_i > 0 \text{ for all } i = 1, ..., n\}$$

and the response functions z_k are all Hill functions.

More precisely, we suppose that the functions F_i, G_i and z_k satisfy the following three assumptions.

Assumption 1. $F_i(z_1, ..., z_n) \in C^1$ and $G_i(z_1, ..., z_n) \in C^1$, $i = 1, ..., n$, i.e. F_i and G_i, $i = 1, ..., n$, are continuously differentiable.

Assumption 2. $F_i(z_1, ..., z_n) \geq 0$ and $G_i(z_1, ..., z_n) > 0$ for all z_k satisfying $0 \leq z_k \leq 1$, $k = 1, ..., n$.

Assumption 3. $z_k = H(x_k, \theta_k, q_k)$ are given by (2), where $q_k \geq 0$, $\theta_k > 0$, $k = 1, ..., n$.

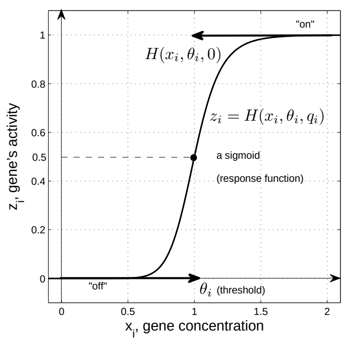

Figure 1: The Hill function $z_i = H(x_i, \theta_i, q_i)$, $q_i \geq 0$.

Since all $z_k \in [0,1]$, then these functions satisfy the following estimates:

$$0 \le F_i(z_1,...,z_n) \le \widetilde{F}_i, \quad 0 < \sigma_i \le G_i(z_1,...,z_n) \le \widetilde{G}_i \tag{6}$$

for all $z_k \in [0,1]$, $k,i = 1,...,n$, where $\widetilde{F}_i$, $\widetilde{G}_i$, σ_i are some constants.

The following theorem is the main result of this section.

Theorem 1. *Under Assumptions 1-3 with $q_k > 0$ for all $k = 1,...,n$ we have*

A. If $\alpha_i > 0$ for all $i = 1,...,n$, then there exists a unique solution $x(t) = (x_1(t),...,x_n(t))$ of the initial value problem (5) which is defined for all $t \ge t_0$ and which satisfies the condition $x_i(t) > 0$ $(t \ge t_0)$.

B. If $0 < \alpha_i \le \widetilde{F}_i/\sigma_i$, i=1,…,n, then $x_i(t) \le \widetilde{F}_i/\sigma_i$ for all $t \ge t_0$, i=1,…,n.

C. If $\alpha_i > 0$ for all i=1,…,n, then for any $\widehat{F}_i > \widetilde{F}_i$ $x_i(t) < \widehat{F}_i/\sigma_i$ for sufficiently large $t \ge T > t_0$.

Proof. As the functions F_i, G_i, $i = 1,...,n$, and $z_i = H(x_i,\theta_i,q_i)$ $(q_i > 0$, $i = 1,...,n)$ are C^1-functions, then the right-hand sides of (5) are Lipschitz, so that the local existence and uniqueness theorem is valid for (5).

To prove the global existence we assume that $x_i(t_0) = \alpha_i > 0$ for all $i = 1,...,n$ letting $x(t) = (x_1(t),...,x_n(t))$ be the solution of the initial value problem (5). Notice that if the function $x_i(t)$, $i = 1,...,n$, is nonnegative for some t, then for this t

$$-\widetilde{G}_i x_i(t) \le \dot{x}_i(t) \le \widetilde{F}_i - \sigma_i x_i(t). \tag{7}$$

Let us prove the statement A assuming the converse. Then there exists $i \in \{1,2,...,n\}$ and $t^* < \infty$ such that $x_i(t^*) = 0$. Let t^* be the first instant when $x_i(t)$ becomes zero, i.e. $x_i(t) > 0$ for all $t_0 \le t < t^*$ and $x_i(t^*) = 0$. Obviously, $t^* > t_0$. Since $x_i(t) > 0$ for $t \in [t_0,t^*]$, we have, due to (7), that

$$F_i - G_i x_i(t) \ge -\widetilde{G}_i x_i(t).$$

By the theorem on differential inequalities, $x_i(t) \ge \overline{x}_i(t)$, $t \in [t_0,t^*]$, where $\overline{x}_i(t) = \alpha_i e^{-\widetilde{G}_i(t-t_0)} > 0$ is the solution of the problem

$$\begin{aligned} &\dot{\overline{x}}_i(t) = -\widetilde{G}_i \overline{x}_i(t), \\ &\overline{x}_i(t_0) = \alpha_i. \end{aligned}$$

Hence $x_i(t^*) > 0$. This contradicts the choice of t^*. Therefore $x_i(t) > 0$, $i = 1,...,n$, for all $t \ge t_0$.

Let us prove the statement B. Since for $x_i(t) > 0$, we have, due to (7), that

$$F_i - G_i x_i(t) \leq \widetilde{F}_i - \sigma_i x_i(t),$$

then again by the theorem on the differential inequalities, $x_i(t) \leq \underline{x}_i(t)$, where $\underline{x}_i(t)$ is the solution of the problem

$$\begin{aligned} &\dot{\underline{x}}_i(t) = \widetilde{F}_i - \sigma_i x_i(t), \\ &\underline{x}_i(t_0) = \alpha_i. \end{aligned}$$

This gives $\underline{x}_i(t) = \widetilde{F}_i/\sigma_i + (\alpha_i - \widetilde{F}_i/\sigma_i)e^{-\sigma_i(t-t_0)}$. Since $x_i(t_0) = \alpha_i \leq \widetilde{F}_i/\sigma_i$, we have the following estimate

$$\underline{x}_i(t) = \widetilde{F}_i/\sigma_i + (\alpha_i - \widetilde{F}_i/\sigma_i)e^{-\sigma_i(t-t_0)} \leq \widetilde{F}_i/\sigma_i.$$

Therefore $x_i(t) \leq \underline{x}_i(t) \leq \widetilde{F}_i/\sigma_i$ for all $t \geq t_0$.

Let us finally check the statement C. For $\alpha_i \leq \widetilde{F}_i/\sigma_i$ this follows from the statement B. If $\alpha_i > \widetilde{F}_i/\sigma_i$, then $x_i(t) \leq \widetilde{F}_i/\sigma_i + (\alpha_i - \widetilde{F}_i/\sigma_i)e^{-\sigma_i(t-t_0)} \to \widetilde{F}_i/\sigma_i < \widehat{F}_i/\sigma_i$ as $t \to \infty$.

□

3. Regular and singular domains

In this section we review a well-known terminology used in the theory of gene regulatory networks (see e.g. [7]) in connection with the system (1), which in this section is assumed to satisfy Assumptions 1-3 with $q_k = 0$ for all $k = 1, ..., n$. Thus, this system has discontinuous right-hand sides, as the functions $z_k = H(x_k, \theta_k, 0)$ become the step functions $z_k = H(x_k, \theta_k, 0)$, $k = 1, ..., n$ (see Fig. 1). If $z_k = B_k$ where $B_k = 0$ or 1 for any $k = 1, ..., n$, then the system (1) takes the shape

$$\dot{x}_i = F_i(B_1, ..., B_n) - G_i(B_1, ..., B_n)x_i, \quad i = 1, ..., n. \tag{8}$$

The vector $(B_1, ..., B_n)$ is called Boolean.

Below we use the notation which goes back to [8]. The set of all n-dimensional Boolean vectors is denoted by $\mathbb{B}^n$. Given a Boolean vector $\mathcal{B} \subset \mathbb{B}^n$, $\mathcal{B} = (B_1, ..., B_n)$, we write $\mathcal{R}(\mathcal{B})$ for *the regular domain (=the box)* consisting of all $(x_1, ..., x_n) \in \mathbb{X}^n$ satisfying $H(x_k, \theta_k, 0) = B_k$, $k = 1, ..., n$.

The phase space $\mathbb{X}^n$ contains 2^n open regular domains. Inside each regular domain the dynamics are governed by the simple affine system (8).

The complement of the union of all regular domains consists of *singular domains*. Given a nonempty subset S of the set $N = \{1, ..., n\}$ and a Boolean vector $\mathcal{B}_R = (B_r)_{r \in R}$, $R = N \setminus S$, we define the singular domain $SD(S, \mathcal{B}_R)$ as the set consisting of all $(x_1, ..., x_n) \in \mathbb{X}^n$, where $x_s = \theta_s$ for all $s \in S$ and $H(x_r, \theta_r, 0) = B_r$ for all $r \in R$.

A wall is a singular domain of codimension 1. Any wall is therefore defined by a number $j \in N$ and an $(n-1)$-dimensional Boolean vector $\mathcal{B}_R$, where $R = N \setminus \{j\}$. The total number of walls is evidently $n \cdot 2^{n-1}$.

It is easy to calculate the solutions of the system (8) in each regular domain. However, an additional analysis is required when a solution approaches a singular domain, where the right-hand side of the system (8) becomes discontinuous. One of the possible solutions (also adopted in this paper) relies on singular perturbation analysis, where one lets q_k be positive and defines the trajectories of (8) as the limit trajectories as $q_k \to 0$. This approach requires, however, additional information about the functions $F_i(z_1, ..., z_n)$ and $G_i(z_1, ..., z_n)$, $i = 1, ..., n$. In the forthcoming sections we will show that this additional information may be crucial for the solutions' behavior.

In the remaining part of the section we replace Assumption 1 with the following stronger assumption (the multilinearity assumption).

Assumption 4. The functions $F_i(z_1, ..., z_n)$ and $G_i(z_1, ..., z_n)$, $i = 1, ..., n$, are multilinear, i.e. linear in each variable z_k, $k = 1, ..., n$.

Then we get the following description of walls.

In a box $\mathcal{R}(\mathcal{B})$, $\mathcal{B} = (B_1, ..., B_n)$, $B_k \in \{0, 1\}$, $k = 1, ..., n$, the equations

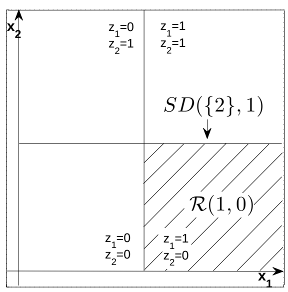

Figure 2: The illustration of the regular and singular domains.

are linear and all trajectories in $\mathcal{R}(\mathcal{B})$ head towards a point attractor called the focal point $P^f(\mathcal{B})$ of $\mathcal{R}(B)$. If $P^f(\mathcal{B}) \in \mathcal{R}(\mathcal{B})$, it is a stable point of the system and an attractor for all trajectories in $\mathcal{R}(\mathcal{B})$. If $P^f(\mathcal{B}) \notin \mathcal{R}(\mathcal{B})$, any trajectory passing through $\mathcal{R}(\mathcal{B})$ will eventually hit one of the walls delimiting $\mathcal{R}(\mathcal{B})$. If the trajectories cross the wall, the wall is called *transparent* (dashed line in Fig. 3). If trajectories head towards the wall from both sides, the wall is called *black* (black lines in Fig. 3), and if trajectories depart from the wall on both sides, the wall is called *white* (white line in Fig. 3).

Note that if one trajectory in $\mathcal{R}(\mathcal{B})$ approaches (leaves) a wall, then no trajectory in $\mathcal{R}(\mathcal{B})$ can leave (approach) this wall.

Notation to Fig. 3 *All types of walls presented in Fig. 3 are given for the system*

$$\begin{aligned} \dot{x}_1 &= 1 - z_1 - z_2 + 2z_1 z_2 - 1/3x_1, \\ \dot{x}_2 &= z_1 - z_1 z_2 - 1/3x_2, \end{aligned} \tag{9}$$

where $z_k = H(x_k, \theta_k, q_k)$, $q_k = 0.01$, $k = 1, 2$.

In what follows, we demonstrate that the behavior of the solutions in the non-multilinear case may be more complicated. For instance, instead of transparent wall we may obtain a wall with one white and one black side. That is why we in the forthcoming sections introduce a more rigorous description of walls as well as a new terminology for the three types of walls mentioned in this section.

4. Analysis in regular domains

In this section we consider the system (1) with $q_k = 0$ for all $k = 1, ..., n$ under Assumptions 1-3 in the maximal regular domain, which is the union of all 2^n boxes. Within each box (determined by a certain Boolean vector $\mathcal{B} = (B_1, ..., B_n)$) the system (1) becomes the system (8) with Boolean response functions. The right-hand sides of the system (8) only depend on the values of the functions F_i and G_i at $z_k = 0$ and 1. This suggests that F_i and G_i can be replaced by simpler functions, e.g. multilinear, giving an equivalent system in the sense that both produce the same systems (8) for all Boolean vectors (see e.g. [1], [4], [7]).

In this paper we explain, however, why this simple Boolean definition of equivalent systems does not hold, in general. The main reason for that was, in fact, discovered in the pioneer paper [8], where it was observed that the Boolean system (8) is too coarse to describe sliding modes of the model, i.e. trajectories belonging to the discontinuity set of the system (1). It was shown in [8] that using the Hill functions instead of the step functions and applying singular perturbation analysis solve the problem of sliding modes. Another approach, which we do not consider in this paper and which is based on the Filippov theory of discontinuous differential equations, was introduced in [3].

To this end, we suggest a more precise definition of equivalent systems, which takes into account a finer level of resolution given by the Hill response functions which replace Boolean response functions in (8).

First of all, we define the notion of limit dynamics. Let $\mathcal{D} \subset \mathbb{X}^n$, where $\mathbb{X}^n$ is the phase space of the system (1), and let $x^q(t)$, where $q = (q_1, ..., q_n)$, be the unique solution of this system satisfying the initial condition $x^q(t_0) = \alpha$, where α is independent of q (see the previous section for the corresponding existence theorem).

Definition 1. A function $x^0 : [t_0, t_1] \to \mathbb{X}^n$, for which

$$\lim_{q \to 0} \sup_{t_0 \le t \le t_1} |x^q(t) - x^0(t)| = 0,$$

will be called **a limit solution** of the system (1) satisfying the initial condition $x^0(t_0) = \alpha$.

A limit solution may or may not exist for a given α, but if it does, then we have the following definition.

Definition 2. The system (1) satisfying Assumptions 1-3 is said to be **equivalent** to a system

$$\dot{x}_i = \widetilde{F}_i(z_1, ..., z_n) - \widetilde{G}_i(z_1, ..., z_n)x_i, \tag{10}$$

again satisfying Assumptions 1-3, in a domain $\mathcal{D} \subset \mathbb{X}^n$ (or simply $\mathcal{D}$-equivalent) if for any limit solution $x^0(t)$ of the system (1), satisfying $x^0(t_0) = \alpha$ and the additional condition $x^0(t) \in \mathcal{D}$ for $t \in [t_1, t_2]$ and some $t_1, t_2,\ t_0 \le t_1 < t_2$, the limit solution $\widetilde{x}^0(t)$ of the system (10) satisfying the same initial condition $\widetilde{x}^0(t_0) = \alpha$ coincides with $x^0(t)$ on $[t_1, t_2]$, i.e. $x^0(t) = \widetilde{x}^0(t)$ for all $t \in [t_1, t_2]$.

Roughly speaking, this definition says that the limit solutions of two $\mathcal{D}$-equivalent systems, which satisfy the same initial condition, must coincide as long as they belong to the set $\mathcal{D}$. Or in other words, the difference between the proper solutions $x^q(t)$ and $\tilde{x}^q(t)$, $0 < q_k < q_0$, $k = 1, ..., n$, of two equivalent systems, which satisfy the same initial condition $x^0(t_0) = \tilde{x}^0(t_0) = \alpha$ becomes negligible in the limit, i.e. when all Hill response functions tend to the respective step functions, as long as their common limit belongs to the domain $\mathcal{D}$.

In what follows, a typical domain $\mathcal{D}$ will be the union of several (maybe none) regular domains $\mathcal{R}_1, ..., \mathcal{R}_s$ and several (maybe none) singular domains $SD_1, ..., SD_p$. We stress that $\mathcal{D}$ needs not to be open in the phase space $\mathbb{X}^n$.

The main result of this section says that an arbitrary nonlinear system is equivalent to a unique multilinear system in its maximal regular domain, i.e. if no sliding trajectories are taken into consideration.

Theorem 2. *Let* $\mathcal{D} = \bigcup_{\mathcal{B}\subset\mathbb{B}^n} \mathcal{R}(\mathcal{B})$. *Then for any system (1) satisfying Assumptions 1-3 there exists a unique* $\mathcal{D}$*-equivalent multilinear system*

$$\dot{x}_i = \overline{F}_i(z_1, ..., z_n) - \overline{G}_i(z_1, ..., z_n)x_i, \qquad i = 1, ..., n. \tag{11}$$

Proof.

Let $\mathbb{Z}^n = \{(z_1, ..., z_n)|\ z_k \in [0, 1] \text{ for all } k = 1, ..., n\}$. Let $I \subset \mathbb{R}$ be an arbitrary interval (for instance, $I = [0, \infty)$ or $I = (0, \infty)$) and let $h : \mathbb{B}^n \to I$ be an arbitrary given function. Below we construct a unique multilinear function $H : \mathbb{Z}^n \to I$ such that $H|_{\mathbb{B}^n} = h$.

Letting $\varphi(B, \zeta) = 1 - B + \zeta(2B - 1)$ we observe that this function is linear in ζ and satisfies

$$\varphi(B, B) = 1 \quad \text{and} \quad \varphi(B, 1 - B) = 0$$

for any Boolean variable B. Then for the multilinear (in z) function

$$\Phi(\mathcal{B}, z) = \prod_{i=1}^{n} \varphi(B_i, z_i) \quad (\mathcal{B} = (B_1, ..., B_n) \in \mathbb{B}^n, z = (z_1, ..., z_n) \in \mathbb{Z}^n)$$

we have

$$\Phi(\mathcal{B}, \mathcal{B}) = \prod_{i=1}^{n} \varphi(B_i, B_i) = 1$$

for any $\mathcal{B} \in \mathbb{B}^n$ and

$$\Phi(\mathcal{B}, \mathcal{B}') = \prod_{i=1}^{n} \varphi(B_i, B_i') = 0$$

for all $\mathcal{B}, \mathcal{B}' \in \mathbb{B}^n$, $\mathcal{B} \neq \mathcal{B}'$, because in the latter case at least one component of the Boolean vector $\mathcal{B}'$ (say B_j') satisfies $B_j' = 1 - B_j$.

Now, we put

$$H(z) = \sum_{\mathcal{B}\in\mathbb{B}^n} \Phi(\mathcal{B}, z)h(\mathcal{B}).$$

Due to orthogonality, $H(\mathcal{B}) = h(\mathcal{B})$ for any $\mathcal{B} \in \mathbb{B}^n$.

To see that the function H is uniquely defined, it is sufficient to prove that if a multilinear function $G(z)$, $z \in \mathbb{Z}^n$ equals 0 for all n-dimensional Boolean vectors, then it is identically equal to 0. Let $G(z) = a_1 + z_1 G_1(z_2, ..., z_n)$. Letting $z_1 = 0$ yields $a_1 = 0$, so that $z_1 = 1$ implies that $G_1(z_2, ..., z_n) = 0$ for any $(n-1)$-dimensional Boolean vector. Repeating this argument n times, we end up with the zero function.

By this, we have proved that there exist unique functions $\overline{F}_i(z_1, ..., z_n)$ and $\overline{G}_i(z_1, ..., z_n)$, which satisfy Assumption 2 and 4 and, in addition, the equalities $\overline{F}_i(\mathcal{B}) = F_i(\mathcal{B})$, $\overline{G}_i(\mathcal{B}) = G_i(\mathcal{B})$ for any Boolean vector $\mathcal{B} = (B_1, ..., B_n)$. This gives a unique multilinear system (11) which coincides with the system (1) in the domain $\mathcal{D}$.

In the final part of the proof we verify the conditions listed in Definition 2. To do it, we use the standard continuous dependence theorem for differential equations with smooth right-hand sides. Let $x^q(t)$, $\overline{x}^q(t)$ ($x^q(t_0) = \overline{x}^q(t_0) = \alpha \in \mathcal{R}(\mathcal{B})$ for some Boolean vector $\mathcal{B}$) be the solutions of the systems (1) and (11) respectively, with the latter system just constructed. As $x^0(t) = \overline{x}^0(t)$ within any interval $[t_0, t_0 + \delta]$ where $x^0(t) \in \mathcal{R}(\mathcal{B})$ (which is open in $\mathbb{X}^n$), we immediately obtain that $\lim_{q\to 0} \sup_{t_0 \le t \le t_0+\delta} \mid x^q(t) - \overline{x}^q(t) \mid = 0$.

□

The construction of an equivalent linear system is easy in the case of polynomials: we simply replace all powers z_k^n by z_k. For other functions we may need to use direct approximations.

Example 2. The nonlinear systems

$$\dot{x}_1 = (1 - 2z_1^5 z_2^3 + z_1^3 - 2z_1) - x_1, \quad \dot{x}_1 = (1 + \sin(\pi z_1/2) - x_1,$$
$$\dot{x}_2 = (z_2^2 - z_2 + z_1) - x_2 \quad \dot{x}_2 = e^{z_2^2} - x_2$$

are $\mathcal{D}$-equivalent to the multilinear systems

$$\dot{x}_1 = (1 - 2z_1 z_2 - z_1) - x_1, \quad \dot{x}_1 = (1 + z_1) - x_1,$$
$$\dot{x}_2 = z_1 - x_2 \quad \dot{x}_2 = (1 + (e-1)z_2) - x_2$$

respectively, where $\mathcal{D}$ is the union of all four regular domains.

Remark 1. The above theorem does not guarantee that the limit trajectories traveling between boxes will coincide, as it does not imply that the limit $\lim_{q\to 0} \sup_{t_0 \le t \le t_1} \mid x^q(t) - \overline{x}^q(t) \mid = 0$ if the limit solution hits a wall at some instant t' inside the interval (t_0, t_1). The theorem only guarantees that we get a uniform convergence on any *closed* subset of the set $[t_0, t') \cup (t', t_1]$, which is not enough. In the next sections we will show that including walls into the analysis, indeed, may cause problems due to existence of sliding modes. Before we address this important problem, we need to develop an algorithm of constructing the limit solutions for the case of the general nonlinear model (1). This will be done in the next section.

5. Singular perturbation analysis in codimension 1

In this section we discuss the properties of the solutions in a vicinity of attracting walls. We consider the system of equations (1) under Assumptions 1-3 ($q_i \ge 0$ for all $i = 1, ..., n$). Without losing generality we only study the case when the first variable x_1 is singular, i.e. stays close to its threshold value θ_1, while the others $x_2, ..., x_n$ are regular (they stay away from their respective thresholds, thus belonging to a certain regular box of dimension $n-1$). Let the wall in question be $SD(\{1\}, \mathcal{B}_R)$, where $\mathcal{B}_R = (B_r)_{r\in R}$, $B_r = 0$ or 1. It means, in particular, that we want to analyze the situation where $x_1 \to \theta_1$ and $z_r \to B_r$, $r \in R$, $R = N \setminus \{1\}$ at any instant t if $q_k \to 0$, $k = 1, ..., n$.

To simplify the notation we omit below the parameter q in $x^q(t)$ and $z^q(t)$, except for the final result.

It is convenient to rewrite the initial value problem (5) as follows:

$$\begin{aligned} \dot{x}_1 &= F_1(z_1, z_R) - G_1(z_1, z_R)x_1, \\ \dot{x}_R &= F_R(z_1, z_R) - G_R(z_1, z_R)x_R, \\ x(t_0) &= \alpha \notin SD(\{1\}, \mathcal{B}_R), \end{aligned} \tag{12}$$

where $x_R = (x_r)_{r\in R}$, $z_R = (z_r)_{r\in R}$, $F_R = (F_r)_{r\in R}$, G_R is the $(n-1)\times(n-1)$ matrix given by $G_R = diag[G_2, ..., G_n] = \begin{bmatrix} G_2 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & G_n \end{bmatrix}$.

First of all, we notice that since $x_1(t_0)$ is different from θ_1 and does not depend on q_1, then $\lim_{q_1\to 0} H(x_1(t_0), \theta_1, q_1)$ always exists and equals 0 or

1. The initial value of the function $z_1 = H(x_1, \theta_1, q_1)$ depends, however, on q_1. Therefore we denote this initial value by $z_1(0, q_1)$ observing that $z_1(0, q_1) \to B_1$ if $q_1 \to 0$, where $B_1 = 0$ or 1.

From (2) we derive also that $x_1 = H^{-1}(z_1, \theta_1, q_1) = \theta_1 \left(\frac{z_1}{1-z_1}\right)^{q_1}$, $z_1 \in (0, 1)$.

Following [8] we replace now x_1 with z_1 which yields the following equivalent initial value problem:

$$\begin{aligned} &q_1 \dot{z}_1 = \tfrac{z_1(1-z_1)}{H^{-1}(z_1,\theta_1,q_1)} \Big[F_1(z_1, z_R(x_R)) - G_1(z_1, z_R(x_R)) H^{-1}(z_1, \theta_1, q_1)\Big], \\ &\dot{x}_R = F_R(z_1, z_R(x_R)) - G_R(z_1, z_R(x_R)) x_R, \\ &z_1(t_0, q_1) = H(\alpha_1, \theta_1, q_1), \\ &x_R(t_0) = \alpha_R, \end{aligned} \tag{13}$$

where $q_k > 0$, $k = 1, ..., n$. According to the singular perturbation theory, this is *the full initial value problem.* The extra factors in the first equation stem from the derivative of z_1 with respect to x_1.

We want to construct the limit solutions as $q_k \to 0$, $k = 1, ..., n$, inside the wall $SD(\{1\}, \mathcal{B}_R)$, where the right-hand sides of the system are discontinuous.

The stretching transformation $\tau = \frac{t-t_0}{q_1}$ takes the system (13) into *the boundary layer system*

$$\begin{aligned} &z_1' = \tfrac{z_1(1-z_1)}{H^{-1}(z_1,\theta_1,q_1)} \Big[F_1(z_1, z_R(x_R)) - G_1(z_1, z_R(x_R)) H^{-1}(z_1, \theta_1, q_1)\Big], \\ &x_R' = q_1[F_R(z_1, z_R(x_R)) - G_R(z_1, z_R(x_R)) x_R], \end{aligned} \tag{14}$$

with the initial values $z_1(0, q_1) = H(\alpha_1, \theta_1, q_1)$, $x_R(0) = \alpha_R$, where the prime denotes differentiation with respect to the new time τ.

Letting $q_k \to 0$, $k = 1, .., n$, and assuming a priori that the limit solution belongs to the wall $SD(\{1\}, \mathcal{B}_R)$, i.e. that $x_1 \to \theta_1$ and $z_R \to \mathcal{B}_R$ we arrive at *the boundary layer equation*

$$z_1' = \frac{z_1(1 - z_1)}{\theta_1} \Big[F_1(z_1, \mathcal{B}_R) - G_1(z_1, \mathcal{B}_R)\theta_1\Big], \tag{15}$$

where $q_1 = 0$ and $z_1(0, 0) = B_1$.

It is sufficient for our purposes to apply the classical result on singular perturbations, known in the literature as Tikhonov's theorem (see e.g. [14]). To do it, we need the following assumptions:

Assumption 5. There is an isolated stationary solution $z_1 = z_1^*$ of the boundary layer equation (15) which satisfies $z_1^* \in (0, 1)$.

Assumption 6. The stationary solution $z_1 = z_1^*$ is locally asymptotically stable.
Assumption 7. The initial value $z_1(0,0) = B_1$ belongs to the domain of attraction Ω of the stationary solution $z_1 = z_1^*$.
Remark 2. Assumptions 6, 7 reflect the fact that the wall $SD(\{1\}, \mathcal{B}_R)$ attracts the trajectories of the system belonging to the box which corresponds to the Boolean value B_1. This results in sliding motion along the corresponding side of the wall, and Tikhonov's theorem explains how the sliding trajectories can be calculated. Sliding motion occurs e.g. in a vicinity of stationary points belonging to singular domains. The analysis around such points, also known as 'singular steady states', was initiated in [12] and developed in later works (see e.g. [3], [7], [13], [15]). Assumption 5 is of technical yet generic character; see [8] for more details.

Theorem 3. *If Assumptions 5-7 are fulfilled, then the solutions* (z_1^q, x_R^q) *of the full initial problem (13) and the solution* (z_1^*, x_R^*) *of* the reduced equations

$$\begin{aligned} &\dot{x}_R = F_R(z_1^*, \mathcal{B}_R) - G_R(z_1^*, \mathcal{B}_R)x_R, \\ &x_R(0) = \alpha_R \end{aligned} \tag{16}$$

are related by

$$\begin{aligned} &z_1^q(t) \to z_1^* \quad \textit{uniformly on } [s,T], \ \forall\ s, T, \ t_0 < s < T, \\ &x_R^q(t) \to x_R^*(t) \quad \textit{uniformly on } [t_0,T], \ \forall\ t_0 < T, \end{aligned} \tag{17}$$

as $q \to 0$.

Proof. For any initial value, the boundary layer system (14) and the boundary layer equation (15) have unique global solutions, which is ensured by the global existence theorem from Sec. 2. The other assumptions of Tikhonov's theorem are identical with Assumptions 5-7.

□

As an illustration, let us consider the system (1) under Assumptions 2, 3, 4 (i. e. the multilinear case). Clearly, the boundary layer equation (15) may have at most one solution z_1^* in the interval $(0,1)$.

Putting for simplicity

$$f(z_1) = F_1(z_1, \mathcal{B}_R) - G_1(z_1, \mathcal{B}_R)\theta_1, \tag{18}$$

we assume that the following inequalities are fulfilled

$$\begin{aligned} f(0) &> 0, \\ f(1) &< 0. \end{aligned} \tag{19}$$

Evidently, the conditions (19) provide an asymptotically stable stationary solution $z_1^* \in (0,1)$ of the boundary layer equation (15), so that Theorem 3 is applicable (Assumption 7 holds automatically because the domain of attraction of z_1^* is $[0,1]$). Equivalently, the conditions (19) make the wall $SD(\{1\}, \mathcal{B}_R)$ black (see e.g. [8]). Thus, this wall attracts the solutions from both sides, and Eqs. (16) describe the limit dynamics of these solutions in the wall.

Example 3. We consider the planar model

$$\begin{aligned} \dot{x}_1 &= 1 - z_1 - z_2 + 2z_1 z_2 - 1/3x_1, \\ \dot{x}_2 &= z_1 - z_1 z_2 - 1/3x_2, \end{aligned} \tag{20}$$

where we will describe the dynamics of the solutions in the wall $SD(\{1\}, 0)$ using Theorem 3. Let $\theta_1 = 1$.

The full initial problem will be

$$\begin{aligned} q_1 \dot{z}_1 &= \tfrac{z_1(1-z_1)}{H^{-1}(z_1,\theta_1,q_1)} \Big(1 - z_1 - 1/3H^{-1}(z_1, \theta_1, q_1) \Big), \\ \dot{x}_2 &= z_1 - 1/3x_2. \end{aligned} \tag{21}$$

In the limit we get the following system

$$\begin{aligned} z_1(1-z_1)\Big(2/3 - z_1\Big) &= 0, \\ \dot{x}_2 &= z_1 - 1/3x_2. \end{aligned} \tag{22}$$

Since the function $f(z_1) = 2/3 - z_1$ satisfies the conditions (19), we obtain from the first equation of (22) that there exists a unique stable stationary solution $z_1^* = 2/3$ giving the dynamics in the wall: $\dot{x}_2 = 2/3 - 1/3x_2$ or $x_2^*(t) = 2 + ce^{-1/3t}$.

In the forthcoming sections we will be mainly focusing on the non-multilinear system (1), but we will also use multilinear systems for the comparison purposes.

6. Comparing dynamics in a vicinity of type I walls

In this section we start a comparison of the dynamics in multilinear and non-multilinear models. It is assumed that the general, i.e. non necessarily multilinear, system (1) satisfies the general Assumptions 1-3. We study the wall $SD(\{1\}, \mathcal{B}_R)$, where $x_1 = \theta_1$, $x_r \neq \theta_r$, $r \in R$, $R = N\backslash\{1\}$, $\mathcal{B}_R = (B_r)_{r\in R}$, $B_r = 0$ or 1.

In the multilinear case (i.e. if Assumption 1 is replaced by Assumption 4) the wall $SD(\{1\}, \mathcal{B}_R)$ may be white, black or transparent (see Sec. 3). Below we discuss the dynamics along a wall which becomes transparent in the multilinear case, but which, as we will see, may not be transparent in its proper sense in the non-multilinear case. That is why we introduce the following formal definition.

Definition 3. The wall $SD(\{1\}, \mathcal{B}_R)$ is of **type I** if the function $f(z_1)$ defined in (18) satisfies one of the following set of inequalities

$$\begin{array}{ccc} f(0) > 0, & \text{or} & f(0) < 0, \\ f(1) > 0 & & f(1) < 0. \end{array} \tag{23}$$

Of course, a similar definition can be written for an arbitrary wall $SD(\{k\}, \mathcal{B}_R)$ with the help of the corresponding function $f(z_k)$.

If the multilinearity assumption (4) is fulfilled, then the solutions that enter the wall from one side, will then depart from this wall from another side (see e.g. [7]). That is why the wall is *transparent*.

Example 4. Let us consider the following multilinear system

$$\begin{aligned} \dot{x}_1 &= (0.1 + 0.1z_1) - 0.34x_1, \\ \dot{x}_2 &= (1 - z_2) - 1.5x_2, \end{aligned} \tag{24}$$

where z_i are given by (2), $\theta_i = 1$, $i = 1, 2$, and its behavior in a vicinity of the transparent wall $SD(\{1\}, 0)$.

The boundary layer equation reads here as $z_1' = z_1(1 - z_1)(0.1z_1 - 0.24)$. Its stationary solutions are depicted in Fig. 5. As we can see, there are no stationary solutions within the open interval $(0, 1)$. The solution $z = 0$ is locally asymptotically stable, while the solution $z = 1$ is unstable. Geometrically, it corresponds to a transparent wall, where the solution hits the wall on its right side and departs from the wall on its left side.

In the remaining part of the section we assume that the system (1) satisfies Assumptions 1-3, i.e. the system is not necessarily multilinear. We study

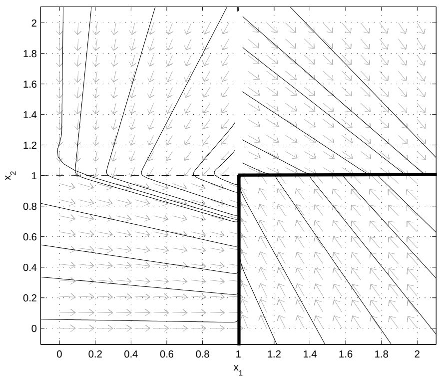

Figure 3: Trajectories of the system (9). This planar model has two black walls $x_1 = \theta_1$, $x_2 < \theta_2$ and $x_2 = \theta_2$, $x_1 > \theta_1$, one white wall $x_1 = \theta_1$, $x_2 > \theta_2$, and one transparent wall $x_2 = \theta_2$, $x_1 < \theta_1$.

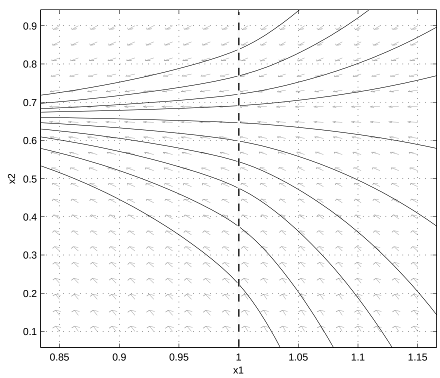

Figure 4: The solutions of the system (24), where $z_i = H(x_i, \theta_i, q)$, $\theta_i = 1$, $i = 1, 2$, $q = 0.01$.

the dynamics of the solutions around the type I wall $SD(\{1\}, \mathcal{B}_R)$. In this case, the function $f(z_1)$ (see (18)) may have roots inside the interval $(0,1)$. If some of the roots produce asymptotically stable stationary solutions of the boundary layer equation, then the dynamics may be very different from that in the multilinear case. As an illustration, we consider the following example.
Example 5. Let

$$\begin{aligned} \dot{x}_1 &= (0.1 - z_1^2 + 1.1 z_1) - 0.34 x_1, \\ \dot{x}_2 &= (1 - z_2) - 1.5 x_2, \end{aligned} \tag{25}$$

where z_i are given by (2), $\theta_i = 1$, $i = 1, 2$, the type I wall is $SD(\{1\}, 0)$.

Comparing Figs. 4 and 6 we observe that the dynamics of the respective systems (24) and (25) are very similar in the regular domains $\mathcal{R}(0,0)$ and $\mathcal{R}(1,0)$, but in a sufficiently small vicinity of the wall $x_1 = 1$ they become very different. The solutions of the quadratic system (25) do not cross the wall at all, but slide along it. The wall is attracting ('black') on its right side and repelling ('white') on its left side. The limit solutions can be obtained from the singular perturbation analysis and the following boundary layer equation: $z_1' = z_1(1 - z_1)(-z_1^2 + 1.1 z_1 - 0.24)$, the stationary solutions of which are shown in Fig. 7. The rightmost stationary solution in the interval $(0,1)$ is asymptotically stable, and this gives an attracting side of the wall. The leftmost stationary solution in the interval $(0,1)$ is unstable, and this determines a repelling side of the wall.

The observation that the trajectories are similar in the regular domains follows directly from Theorem 2. Indeed, if we formally replace z_1^2 with z_1, then the system (25) becomes the system (24), so that two systems are equivalent in the domain being the union of both regular domains and this replacement is 'invisible'. Yet, the replacement becomes more and more visible when the trajectories approach the wall. We conclude therefore from the example that multilinear systems may be too coarse to provide 'true' information about the real network with steep yet smooth sigmoids $H(x_k, \theta_k, q_k)$.
Remark 3. As we observed in the above example, the behavior of the solutions in a vicinity of the wall $x_1 = \theta_1$ depends heavily on the property of asymptotic stability of stationary solutions of the boundary layer equations for the systems (24) and (25), respectively. Sliding modes can only occur if the boundary layer equation has an asymptotically stable stationary solution $z_1^* \in (0,1)$, which is the case for the system (25). If the system is nonlinear, but the boundary layer equation still has no stable stationary solution inside $(0,1)$, then either $z_1 = 0$ or $z_1 = 1$ must be asymptotically stable, which again

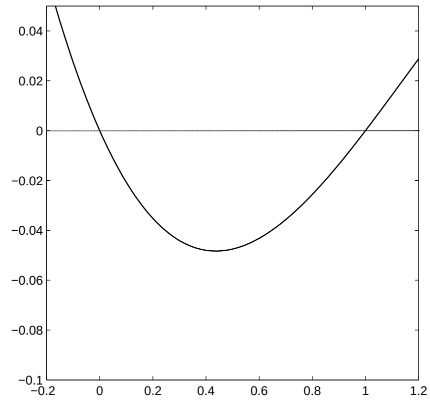

Figure 5: The stationary solutions of the boundary layer equation $z_1' = z_1(1 - z_1)(0.1z_1 - 0.24)$.

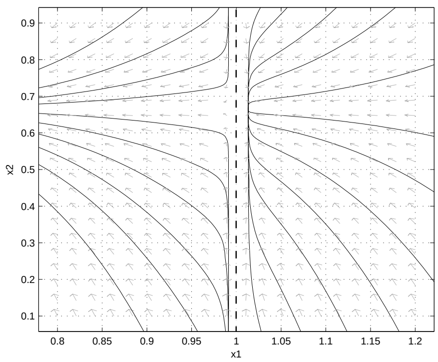

Figure 6: The solutions of the system (25), where $z_i = H(x_i, \theta_i, q)$, $\theta_i = 1$, $i = 1, 2$, $q = 0.01$.

gives solutions traveling through the wall $x_1 = \theta_1$, i.e. no sliding modes can occur, and the wall remains transparent, exactly as in the case of the system (24).

Below we summarize our observations in the form of a general theorem. To do it, we let $f(z_1)$ have m simple roots $z_1^{(1)}, z_1^{(2)}, ..., z_1^{(m)}$, $m \in \mathbb{N}$, inside the open interval $(0,1)$. Let us observe that if m is **an even number**, then the leftmost root and the rightmost root in $(0,1)$ provide different stability properties for the corresponding boundary layer equation. Let us observe further that only these two roots may influence the dynamics of the limit system. Indeed, as we know from Sec. 5, the initial values of the variable z_1 in the boundary layer equation (15) can in the limit be either 0 or 1, and these two values are either asymptotically stable stationary solutions themselves, or they belong to the domain of attraction of the *outmost* stationary solutions in the interval $(0,1)$.

For instance, if the leftmost solution $z_1^{(1)} \in (0,1)$ is asymptotically stable and the rightmost root $z_1^{(m)} \in (0,1)$ is unstable, then the value $z_1 = 0$ belongs to the domain of attraction of the asymptotically stable stationary solution $z_1 = z_1^{(1)}$, while $z_1 = 1$ is asymptotically stable itself. Thus, the wall will be black on its left side and white on its right side. To describe the limit dynamics to the left of the wall one should apply Theorem 3 for the leftmost root $z_1^{(1)}$, which also gives the limit dynamics in the wall, when the trajectories enter it from the left. The other side of the wall is obviously repelling.

We still can use Theorem 3 if we reverse the time, as in this case, $z_1^{(m)} \in (0,1)$ becomes asymptotically stable and the right side of the wall becomes attracting.

The main result of this section reads as follows.

Theorem 4. *Suppose that the system (1) satisfies Assumptions 1-3 and the function $f(z_1)$, which is given by (18), has only roots of multiplicity 1 in the open interval $(0,1)$ and satisfies one of the conditions described in (23). Then*

A. If $f(z_1)$ does not have any roots in the open interval $(0,1)$, then the wall $SD(\{1\}, \mathcal{B}_R)$ is transparent;

B. If $f(z_1)$ has at least one root in the open interval $(0,1)$, then the total number of roots within this interval $(0,1)$ is even and the wall $SD(\{1\}, \mathcal{B}_R)$ has one black and one white side.

Proof. Let us first prove statement A. Without loss of generality it can be assumed that $f(z_1) > 0$ for $0 \le z_1 \le 1$. Let us show that the solutions cross the wall $SD(\{1\}, \mathcal{B}_R)$ from the left to the right for $0 \le q_k \ll 1$, $k = 1, ..., n$.

For $q_k = 0$, $k = 1, ..., n$, the system (12) splits as follows:

$$\begin{array}{c} \dot{x}_1 = F_1(0, \mathcal{B}_R) - G_1(0, \mathcal{B}_R)x_1, \\ \dot{x}_R = F_R(0, \mathcal{B}_R) - G_R(0, \mathcal{B}_R)x_R, \\ x_1 < \theta_1 \\ \text{and} \\ \dot{x}_1 = F_1(1, \mathcal{B}_R) - G_1(1, \mathcal{B}_R)x_1, \\ \dot{x}_R = F_R(1, \mathcal{B}_R) - G_R(1, \mathcal{B}_R)x_R, \\ x_1 > \theta_1. \end{array} \tag{26}$$

It is sufficient to check that the focal points P^f for both systems belong to the right half-space $x_1 > \theta_1$. Indeed, $F_1(B_1, \mathcal{B}_R) - G_1(B_1, \mathcal{B}_R)x_1^f = 0$ implies that

$$x_1^f = \frac{F_1(B_1, \mathcal{B}_R)}{G_1(B_1, \mathcal{B}_R)} > \theta_1,$$

as $F_1(B_1, \mathcal{B}_R) - G_1(B_1, \mathcal{B}_R)\theta_1 > 0$, where $B_1 = 0$ or 1.

Assume now that $q_k > 0$, $k = 1, ..., n$. Let us choose an initial value α to the left of the wall in such a way that the solution $x(t, 0)$ of the limit system (26) crosses the wall $SD(\{1\}, \mathcal{B}_R)$ at some time τ inside a certain time interval $[t_1, t_2]$. We will check that the solution $x(t, q)$ of the system (12), where $q = (q_1, ..., q_n)$ ($q_k > 0$, $k = 1, ..., n$), which satisfies the same initial condition, uniformly converges to $x(t, 0)$. In particular, it also crosses the wall $SD(\{1\}, \mathcal{B}_R)$, which means that the wall is transparent for small $q_k > 0$ as well.

First of all, we observe that the set $\mathcal{A} = \{x(\cdot, q), q_k > 0\}$ is compact in the space of all continuous n-dimensional vector functions defined on $[t_1, t_2]$. This follows from the Arzela-Ascoli compactness theorem and the fact that this set of functions and the set of their derivatives are both uniformly (w.r.t. t and q) bounded on $[t_1, t_2]$. Thus, there exists a sequence which uniformly converges to some continuous function on $[t_1, t_2]$. We pick any such sequence $\{x(\cdot, q^{(m)})\}$ and denote its limit by u. Without loss of generality we may assume that for all $t \in [t_1, t_2]$ the function $u(t)$, and therefore $x(t, q^{(m)})$ for sufficiently large m, belong to the union of the wall with its two adjacent boxes. Due to the theorem on the continuous dependence on parameters in the left-hand box, $u_1(\tau) = \theta_1$, where $u_1(t)$ is the first component of the limit function $u(t)$. In fact, we only have two options for the trajectory $u(t)$: Either it stays in the wall for some period of time $[\tau, \tau+\sigma]$, or it crosses the wall at time τ reaching another box, and in this case $u(t)$ must be equal to $x(t,0)$ on some interval containing τ by the same theorem on continuous dependence applied for the right-hand box. In the latter case, the statement A would be proved, as the convergent sequence $\{x(\cdot, q^{(m)})\}$ was chosen to be arbitrary.

By assumption, we have $F_1(z_1, \mathcal{B}_R) - G_1(z_1, \mathcal{B}_R)\theta_1 = f(z_1) > 0$ for $0 \leq z_1 \leq 1$. Hence there exist $\delta > 0$, $\lambda > 0$ such that $F_1(z_1, z_R) - G_1(z_1, z_R)\theta_1 \geq \delta > 0$ for all z satisfying $0 \leq z_1 \leq 1,\ |z_r - B_r| < \lambda\ (r \in R)$.

On the other hand, $G_1(z_1, z_R) \leq \widetilde{G}_1\ (0 \leq z_k \leq 1,\ k = 1, ..., n)$ due to (6). Let $\varepsilon = \delta/2\widetilde{G}_1$. Then from the expression for $\dot{x}_1(t,q)$ we deduce that $\dot{x}_1(t,q) \geq \delta/2$ as long as

$$|x_1(t,q) - \theta_1| < \varepsilon \quad \text{and} \quad |z_r(x_r(t,q)) - B_r| < \lambda\ (r \in R). \tag{27}$$

Since the limit solution $x(t,0)$ crosses the wall from its left, we have that $\theta_1 - \varepsilon/2 \leq x_1(t,0) \leq \theta_1$ for all $t \in [\tau', \tau]$ and some $\tau' < \tau$. Due to the theorem on continuous dependence on parameters in regular domains, there exists $q_0 > 0$ such that the estimates (27) are fulfilled if $0 < q_k < q_0$ $(k = 1, ..., n)$ and $t \in [\tau', \tau]$. Moreover, as the values $x(t, q^{(m)})$ belong to union of the wall with its two adjacent boxes we may assume (by taking a smaller q_0) that the second estimate in (27) is fulfilled for all $t \in [\tau', \tau]$, $0 < q_k < q_0$. Let us pick any m satisfying $0 < q_k^{(m)} < q_0$ $(k = 1, ..., n)$ and consider the largest open interval I_m where the first estimate in (27) holds true. The interval is not empty, as $[\tau', \tau] \subset I$. On the other hand, for $t \in I_m$ we have that $\dot{x}_1(t, q^{(m)}) \geq \delta/2$ as long as $|x_1(t, q^{(m)}) - \theta_1| < \varepsilon$. This necessarily implies that the trajectory $x_1(t, q^{(m)})$ reaches the value $x_1 = \theta_1$ and crosses it inside the interval I_m. Due to the uniform convergence of this sequence, the function $u_1(t)$ will satisfy the property $\dot{u}_1(t) \geq \delta/2$ on the interval $[t_1, t_2] \cap (\bigcap_m I_m)$. In particular, $\dot{u}_1(\tau) \geq \delta/2$, which gives transversal intersection and hence proves the statement A.

Let us prove statement B. Assume that the leftmost stationary solution $z_1^{(1)} \in (0,1)$ of the boundary layer equation (15) is asymptotically stable, so that the stationary solution $z_1 = 0$ is unstable. Then $f(0) > 0$ and therefore $f(1) > 0$, which implies asymptotic stability of the stationary solution $z_1 = 1$ of the boundary layer equation (15). Hence, the rightmost solution $z_1^{(m)} \in (0,1)$ must be unstable, so that m must be even. To prove that the wall attracts the trajectories to the left of it, we observe that $z_1 = 0$, being the initial value for z_1 in the boundary layer equation, belongs the domain of attraction of $z_1^{(1)}$, so that from Theorem 3, we immediately obtain the desired result as well as the equation for the limit trajectories in the wall ('sliding modes').

Finally, we use the conditions $f(0) > 0, f(1) > 0$ to observe that the focal point of the box to the right of the wall $SD(\{1\}, \mathcal{B}_R)$ does not belong to the box to the left of the wall. This means that the limit trajectories to the right of the wall cannot cross this wall, which implies that the wall is repelling (white). To check that the solutions of the smooth system $q_k > 0$, $k = 1, ..., n$, approach the solutions of the limit system starting to the right of the wall, it is sufficient to apply a standard continuous dependence theorem (as we did in the proof of Theorem 2).

□

The last part of the proof deserves a small comment. The 'whiteness' of the right (resp. left) side of the wall is clearly equivalent to asymptotic stability of the stationary solution $z_1 = 1$ (resp. $z_1 = 0$) of the boundary layer equation.

In the next section we compare dynamics in a vicinity of black walls in the multilinear and non-multilinear cases.

7. Comparing dynamics in a vicinity of type II and type III walls

In this section we analyze the dynamics in a vicinity of attracting and repelling walls, which we in this paper call 'a type II wall' and 'a type III wall', respectively. We again consider the general system (1) under Assumptions 1-3, and then compare it with the corresponding multilinear system, where Assumption 1 is replaced by Assumption 4. Without loss of generality we will study the wall $SD(\{1\}, \mathcal{B}_R)$, i.e. $x_1 = \theta_1$, $x_r \neq \theta_r$, $r \in R$, $R = N \setminus \{1\}$, $\mathcal{B}_R = (B_r)_{r \in R}$, $B_r = 0$ or 1.

We start with attracting walls.

Definition 4. The wall $SD(\{1\}, \mathcal{B}_R)$ is of **type II** if the function $f(z_1)$ defined in (18) satisfies the following inequalities

$$\begin{aligned} f(0) &> 0, \\ f(1) &< 0. \end{aligned} \tag{28}$$

Below we will prove that a type II wall is always attracting, so that we can alternatively call it 'black' in both multilinear and non-multilinear case. Yet, as we will see, the properties of type II walls in the general case differ from those in the multilinear case.

Example 6. Let us consider the multilinear system

$$\begin{aligned}\dot{x}_1 &= (0.5 - 0.21z_1) - 0.47x_1, \\ \dot{x}_2 &= (1 - z_2) - x_2,\end{aligned} \tag{29}$$

where z_i are given by (2), $\theta_i = 1$, $i = 1, 2$, and its behavior in a vicinity of the wall $SD(\{1\}, 0)$.

The boundary layer equation is as follows: $z_1' = z_1(1-z_1)(-0.21z_1+0.03)$. Its roots are shown in Fig. 9. The boundary layer equation has one stationary solution ($z_1 = 1/7$) belonging to the interval $(0, 1)$, and this solution is asymptotically stable. The endpoints of this interval belong therefore to the domain of attraction of the only stable stationary solution. Singular perturbation analysis guarantees therefore that the wall $SD(\{1\}, 0)$ is attracting (black). The limit solution in the wall satisfies the equation $\dot{x}_2 = 6/7 - x_2$.

Some trajectories for $q = 0.01$ are depicted in Fig. 8.

From now on we assume that the system (1) satisfies Assumptions 1-3, i.e. it is not necessarily multilinear. In this case, the function $f(z_1)$ may have more than 1 root within the interval $(0, 1)$. To get a black wall we must assume that at least two roots give rise to stable stationary solutions of the boundary layer equation. As an illustration, let us consider the following example.

Example 7. We consider the nonlinear system of equations

$$\begin{aligned}\dot{x}_1 &= (0.5 - z_1^3 + 1.2z_1^2 - 0.41z_1) - 0.47x_1, \\ \dot{x}_2 &= (1 - z_2) - x_2,\end{aligned} \tag{30}$$

where z_i are given by (2), $\theta_i = 1$, $i = 1, 2$, the type II wall is $SD(\{1\}, 0)$.

Analogously to the previous section, the dynamics of the systems (29) and (30) are similar in the regular domains $\mathcal{R}(0, 0)$ and $\mathcal{R}(1, 0)$. Indeed, the replacement of z_1^3 and z_1^2 with z_1 converts the system (30) into the system (29), so that Theorem 2 does apply. In the regular domains this replacement is thus 'invisible'. On the other hand, a direct comparison of the respective trajectories of two systems in a sufficiently small neighborhood of the wall $x_1 = 1$ suggests that they behave differently. This follows from singular perturbation analysis presented in Sec. 5, as the boundary layer equation

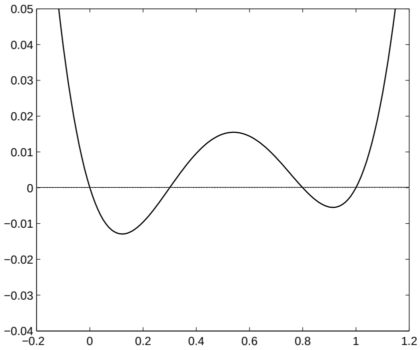

Figure 7: The stationary solutions of the boundary layer equation $z_1' = z_1(1-z_1)(-z_1^2 + 1.1z_1 - 0.24)$.

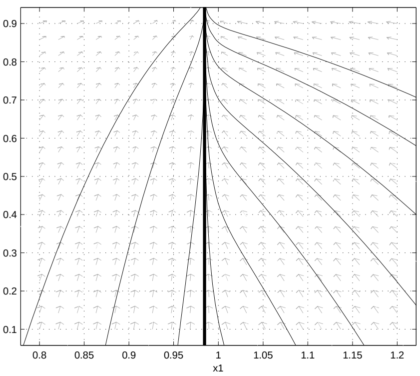

Figure 8: The solutions of the system (29), where $z_i = H(x_i, \theta_i, q)$, $\theta_i = 1$, $i = 1, 2$, $q = 0.01$.

reads now as $z_1' = z_1(1-z_1)(-z_1^3 + 1.2z_1^2 - 0.41z_1 + 0.03)$. Its roots are shown in Fig. 11.

Remark 4. Sliding modes do occur in both examples because the boundary layer equations have asymptotically stable stationary solutions inside $(0, 1)$. Yet, the drastic difference between the two dynamics reflects the fact that the boundary layer equation for the multilinear system (29) has only one asymptotically stable stationary solution in the interval $(0, 1)$, while the boundary layer equation for the second system (30) has two asymptotically stable stationary solutions in this interval.

Below we summarize our considerations in the form of a general theorem. We let the function $f(z_1)$ have m roots within the interval $(0, 1)$, say, $z_1^{(1)}, z_1^{(2)}, ..., z_1^{(m)}$, $m \in \mathbb{N}$. If m is **an odd number**, then the leftmost root and the rightmost root in $(0, 1)$ yield the stationary solutions with the same stability properties. To get a black wall we must assume that these two roots give rise to asymptotically stable stationary solutions. Applying Theorem 3 we get the dynamics of the solutions on both sides of the wall. Thus, the wall will be attracting or black, exactly as in the multilinear case. Yet, as we saw in the examples above, this 'blackness' may be of different character.

The main result of this section is

Theorem 5. *Suppose the system (1) satisfies Assumptions 1-3 and the function $f(z_1)$, which is given by (18), has only roots of multiplicity 1 in the open interval $(0, 1)$ and satisfies the conditions (28). Then*

A. The wall $SD(\{1\}, \mathcal{B}_R)$ is attracting (black).

B. If $f(z_1)$ has exactly 1 root in the interval $(0, 1)$, then the limit dynamics in this wall does not depend on the choice of the side of the wall;

C. If $f(z_1)$ has more than 1 root, then the number of roots within the interval $(0, 1)$ is always odd, the leftmost and the rightmost roots give stable stationary solutions of the associated boundary layer equation, but the limit dynamics in the wall depends on the choice of the side of the wall, i.e. it is different for the trajectories hitting the wall on its left and on its right.

Proof. First of all we observe that the conditions (28) guarantee the existence of at least one root of the function $f(z_1)$. This root defines an asymptotically stable stationary solution of the associated boundary layer equation, so that all the assumptions of Tikhonov's theorem are fulfilled. Therefore, we can apply Theorem 3 and get the equation describing the limit dynamics along the wall. This dynamics is independent of the choice of the regular

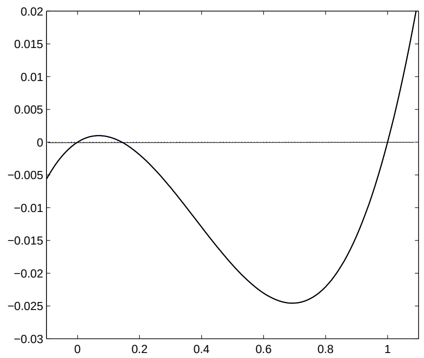

Figure 9: The stationary solutions of the boundary layer equation $z_1' = z_1(1-z_1)(-0.21z_1 + 0.03)$.

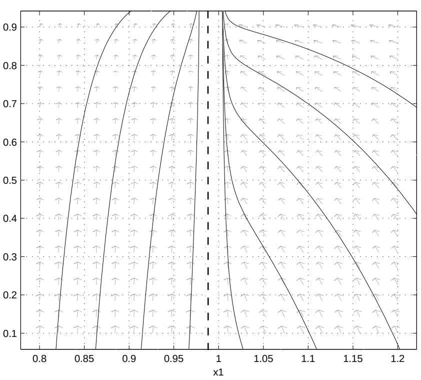

Figure 10: The solutions of the system (30), where $z_i = H(x_i, \theta_i, q)$, $\theta_i = 1$, $i = 1, 2$, $q = 0.01$.

domain the trajectories comes from, because both endpoints of the interval $(0,1)$ belong to the attraction basin of the same (unique) stationary solution.

If the function $f(z_1)$ has more than 1 root, then due to the conditions (28) the leftmost point $z_1^{(1)} \in (0,1)$ and the rightmost point $z_1^{(m)} \in (0,1)$ must be asymptotically stable stationary solutions of the boundary layer equation. Thus, the total number of roots inside (0,1) must be odd, and since all roots are simple, the wall is attracting. Finally, we again apply Theorem 3 from the previous section using the two stable stationary solutions in the equation giving the limit dynamics in the wall. Since these stationary points are different, the dynamics will be different as well depending on the regular box the particular trajectory comes from.

□

At the end of this section we prove a general result for the remaining type of walls.

Definition 5. The wall $SD(\{1\}, \mathcal{B}_R)$ is of **type III** if the function $f(z_1)$ defined in (18) satisfies the following inequalities

$$\begin{aligned} f(0) &< 0, \\ f(1) &> 0. \end{aligned} \tag{31}$$

Theorem 6. *Suppose the system (1) satisfies Assumptions 1-3 and the function $f(z_1)$ satisfies the inequalities (31). Then*

A. The wall $SD(\{1\}, \mathcal{B}_R)$ is repelling (white).

B. The function $f(z_1)$ has an odd number of roots within the interval $(0,1)$, the leftmost and the rightmost root being unstable stationary solutions of the boundary layer equation.

Proof. It is straightforward to observe that the inequalities (31) guarantee the existence of at least one stationary solution in the interval $(0,1)$. Unlike the previous theorem, the leftmost point $z_1^{(1)} \in (0,1)$ and the rightmost point $z_1^{(m)} \in (0,1)$ will in this case give unstable stationary solutions. An argument which is similar to one used in the proof of Theorem 4 and which relies upon the position of the focal points with respect to the wall, shows that both sides of the wall are white.

□

The last section treats the problem of how to find the minimum degree of the polynomial which provides a system equivalent to a given one. We solve this problem for walls and unions of walls and adjacent regular boxes.

8. Recasting and the minimum degree problem

We start with a definition.

Definition 6. Given a polynomial

$$P(z_1, ..., z_n) = \sum_{a_{i_1,i_2,...,i_n} \neq 0} a_{i_1,i_2,...,i_n} z_1^{i_1} z_2^{i_2} ... z_n^{i_n},$$

we denote by $e(P)$ the maximum of all exponents i_k, $k = 1, ..., n$.

In this section we study the following representation problem: Let the system (1) satisfy Assumptions 1-3 and let $\mathcal{D}$ be a subdomain of the phase space $\mathbb{X}^n$ of the system. Find a polynomial system (10) which is $\mathcal{D}$-equivalent to the system (1) (in the sense of Definition 2).

We can reformulate the problem using the convenient terminology from systems biology [11] for which the number

$$e(\widetilde{F}, \widetilde{G}) \equiv \max\{e(\widetilde{F}_k), e(\widetilde{G}_l) : \ k, l = 1, ..., n\}$$

is least possible. The last number simply describes the maximum exponent of all power factors $z_k^{i_k}$ included into all polynomial functions $\widetilde{F}_k$ and $\widetilde{G}_l$ that constitute the right-hand side of the system (10).

On the other hand, the number $e(\widetilde{F}, \widetilde{G})$ can be interpreted as the maximum value of the degrees of $\widetilde{F}$ and $\widetilde{G}$ considered as polynomials with respect to each of the variables $z_1, ..., z_n$. That is why we address the above minimization problem as to **the minimum degree problem**.

The central results of the previous sections can be now reformulated as follows.

Theorem 7. *Let the system (1) satisfy Assumptions 1-3.*

A. If $\mathcal{D}$ is the union of all regular subdomains of the phase space $\mathbb{X}^n$, i.e. $\mathcal{D} = \bigcup_{\mathcal{B} \subset \mathbb{B}^n} \mathcal{R}(\mathcal{B})$, *then* $e(\widetilde{F}, \widetilde{G}) = 1$.

B. If $\mathcal{D} = SD(\{1\}, \mathcal{B}_R)$ is a type I wall, then $e(\widetilde{F}, \widetilde{G}) = 2$.

C. If $\mathcal{D} = SD(\{1\}, \mathcal{B}_R)$ is a type II wall, then $e(\widetilde{F}, \widetilde{G}) = 3$.

Proof. Statement A follows directly from Theorem 2, which says that under the assumptions of Theorem 7 it is always possible to find multilinear functions $\widetilde{F}, \widetilde{G}$ providing a $\mathcal{D}$-equivalent system (10).

To prove statement B we need Theorem 4. As in the proof of this theorem, let us assume again that the first set of the equalities in (23) is satisfied, so that the leftmost root $z_1^l \in (0,1)$ of the function $f(z_1)$ given by (18) provides a stable stationary solution of the associated boundary layer equation, while the solution $z = z_1^r$, where $z_1^r \in (0,1)$ is the rightmost root of the function $f(z_1)$, is unstable. First of all, we observe that according to this theorem the limit dynamics in the wall is in this case completely characterized by the leftmost root z_1^l and the fact that the total number of roots in $(0,1)$ is even (so that the rightmost root z_1^r must be unstable). This observation and the representation (16) of the reduced equations, giving the limit dynamics in the wall, implies that any parabolic function of the shape $\widetilde{F}_1(z_1^l, B_R) - \widetilde{G}_1(z_1^l, B_R)\theta_1 \equiv \widetilde{f}(z_1) = a(z - z_1^l)(z - z_1^r)$, $a > 0$ would give the same reduced equations provided that

$$F_R(z_1^l, B_R) = \widetilde{F}_R(z_1^l, B_R) \quad \text{and} \quad G_R(z_1^l, B_R) = \widetilde{G}_R(z_1^l, B_R). \tag{32}$$

Evidently, these constraints allow for choosing $\widetilde{F}_R(z_1, ..., z_n)$, $\widetilde{G}_R(z_1, ..., z_n)$ to be linear in each variable and $\widetilde{F}_1(z_1, ..., z_n)$, $\widetilde{G}_1(z_1, ..., z_n)$ to be quadratic in z_1 and linear in each other variable. This completes the proof of statement B.

Similarly, statement C is implied by Theorem 5. In this case, both outmost stationary solutions $z = z_1^l$ and $z = z_1^r$ must be asymptotically stable, so that the corresponding function $\widetilde{f}(z_1)$ must have at least one root between z_1^l and z_1^r, which gives an unstable stationary solution. Thus, the resulting function $\widetilde{f}$ must be at least cubic

$$\widetilde{F}_1(z_1^l, B_R) - \widetilde{G}_1(z_1^l, B_R)\theta_1 \equiv \widetilde{f} = a(z - z_1^l)(z - z_1^r)(z - z_1^0),$$

where $z_1^0 \in (z_1^l, z_1^r)$ and $a < 0$ (as the conditions (28) must be satisfied for the function $\widetilde{f}$). In addition, the requirement to have the same reduced equations yields

$$\begin{aligned} F_R(z_1^l, B_R) = \widetilde{F}_R(z_1^l, B_R) \quad &\text{and} \quad G_R(z_1^l, B_R) = \widetilde{G}_R(z_1^l, B_R), \\ F_R(z_1^r, B_R) = \widetilde{F}_R(z_1^r, B_R) \quad &\text{and} \quad G_R(z_1^r, B_R) = \widetilde{G}_R(z_1^r, B_R). \end{aligned} \tag{33}$$

These constraints allow for choosing $\widetilde{F}_R(z_1, ..., z_n)$, $\widetilde{G}_R(z_1, ..., z_n)$ to be quadratic in z_1 and linear in each other variable, while $\widetilde{F}_1(z_1, ..., z_n)$, $\widetilde{G}_1(z_1, ..., z_n)$ can be always chosen to be cubic in z_1 and linear in each other variable. Thus, statement C is proved.

□

Remark 5. The proof of Theorem 7 suggests explicitly verifiable conditions for equivalence of the systems (1) and (10) in regular domains and type I and type II walls.

For regular domains the conditions are given by the equalities $F_1(\mathcal{B}) = \widetilde{F}_1(\mathcal{B})$, $G_1(\mathcal{B}) = \widetilde{G}_1(\mathcal{B})$ which should be valid for any n-dimensional Boolean vector $\mathcal{B}$.

To be able to study walls we, first of all, put a set of standard generic requirements on the functions

$$f(z_1) = F_1(z_1, B_R) - G_1(z_1, B_R)\theta_1 \quad \text{and} \quad \widetilde{f}(z_1) = \widetilde{F}_1(z_1, B_R) - \widetilde{G}_1(z_1, B_R)\theta_1, \tag{34}$$

saying that $z_1 = 0$ and $z_1 = 1$ should not be the roots of these functions, all their roots in the interval $(0, 1)$ should be simple and the total number of these roots should be finite.

For the type I wall $SD(\{1\}, \mathcal{B}_R)$ the conditions of equivalence are then given by (32) and, in addition, by the requirements that the total number of roots of both functions in (34) in the interval $(0, 1)$ is even, the functions have the same sign at $z_1 = 0$ and, finally, that the functions have the same leftmost (resp. rightmost) root in the interval $(0, 1)$ if $f(0) > 0$ (resp. $f(0) < 0$).

For the type II wall $SD(\{1\}, \mathcal{B}_R)$ the conditions of equivalence are given by (33) and, in addition, by the requirements that the total number of roots of both functions in (34) in the interval $(0, 1)$ is odd, the functions have the same sign at $z_1 = 0$ and, finally, that the functions have the same outmost roots in the interval $(0, 1)$.

We also remark that for the type III wall the notion of equivalence makes no sense, as the wall is repelling, so that the limit trajectories evolves from this wall towards the respective focal points, which means that the limit dynamics in this case only exists inside the regular boxes adjacent to the wall. Thus, to include type III walls into our equivalence paradigm, we need to consider domains that are strictly larger than such walls, for instance, domains including boxes.

A natural question arises as to whether it is possible to generalize the equivalence results listed in Theorem 7 to the case of unions of walls and boxes, which in this theorem are treated separately. This complicated problem is not studied in this paper in full. Below we only look at the sets which are unions of one wall and two adjacent boxes and show that the minimum degree problem is nontrivial even in this case.

We still consider the general system (1) satisfying Assumptions 1-3 and the wall $SD(\{1\}, \mathcal{B}_R)$. In this case it is again convenient to represent this system in the form (12). We wish to study $\mathcal{D}$-equivalence with respect to the domain

$$\mathcal{D} = \mathcal{R}(0, \mathcal{B}_R) \bigcup SD(\{1\}, \mathcal{B}_R) \bigcup \mathcal{R}(1, \mathcal{B}_R). \tag{35}$$

Below we introduce a more suitable notation for the equivalent polynomial system (10), which we have used up to now, and for its biggest exponent $e(\widetilde{F}, \widetilde{G})$.

Let

$$\begin{aligned} \dot{x}_1 &= F_1^m(z_1, z_R) - G_1^m(z_1, z_R)x_1, \\ \dot{x}_R &= F_R^m(z_1, z_R) - G_R^m(z_1, z_R)x_R, \end{aligned} \tag{36}$$

where $F_k^m(z_1, ..., z_n)$ and $G_k^m(z_1, ..., z_n)$, $k = 1, ..., n$, are all polynomials of degree at most m with respect to each of their variables z_k, $k = 1, ..., n$. In other words, $e(F_k^m) \le m$ and $e(G_k^m) \le m$ for all $k = 1, ..., n$.

We seek for the least possible value m such that the system (36) is $\mathcal{D}$-equivalent to the system (1), where the domain $\mathcal{D}$ is given by (35).

The results, which are summarized in Theorem 7 and which are obtained separately for walls and boxes, suggest $m = 3$ as a realistic answer. Indeed, inside boxes we can always choose multilinear functions, while in the walls we will at most need cubic polynomials. Unfortunately, the situation is not that simple, as shown in the two examples below.

Example 8. We consider the system

$$\begin{aligned} \dot{x}_1 &= -(z_1 - 0.05)(z_1 - 0.5)(z_1 - 0.1)(z_1 - 0.2)(z_1 - 0.3) + 1 - x_1, \\ \dot{x}_2 &= (1 - z_1)(1 - z_2) + 0.02 - x_2, \end{aligned} \tag{37}$$

where z_i are given by (2), $\theta_i = 1$, $i = 1, 2$. The domain $\mathcal{D}$ is the union of the type II wall $SD(\{1\}, 0)$ and two adjacent boxes $\mathcal{R}(0, 0)$ and $\mathcal{R}(1, 0)$.

Assume that in the black wall $SD(\{1\}, 0)$ this system could be represented by an equivalent polynomial system of degree 3 ($m = 3$)

$$\begin{aligned} \dot{x}_1 &= F_1^3(z_1, 0) - G_1^3(z_1, 0)x_1, \\ \dot{x}_2 &= (1 - z_1) + 0.02 - x_2. \end{aligned} \tag{38}$$

For the system (37), the function $f(z_1)$ given by (18) reads as

$$f(z_1) = -(z_1 - 0.05)(z_1 - 0.5)(z_1 - 0.1)(z_1 - 0.2)(z_1 - 0.3),$$

so that the leftmost root is $z_1^l = 0.05$, and the rightmost root is $z_1^r = 0.5$. For the system (38) we must then have $f^3(z_1) = -a(z_1 - 0.05)(z_1 - 0.5)(z_1 - z_1^0)$, where $z_1^0 \in (z_1^l, z_1^r)$.

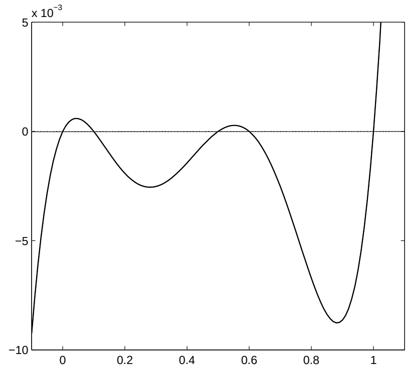

Figure 11: The stationary solutions of the boundary layer equation $z_1' = z_1(1-z_1)(-z_1^3 + 1.2z_1^2 - 0.41z_1 + 0.03)$.

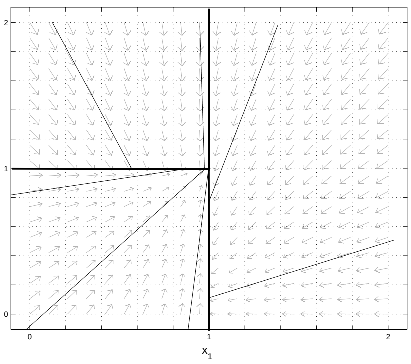

Figure 12: The solutions of the system (37), where $z_i = H(x_i, \theta_i, q_i)$, $\theta_i = 1$, $q_i = 0.001$, $i = 1, 2$.

Let $z_1^l = 0.05$, $z_1^r = 0.5$, $z_1^1 = 0.1$, $z_1^2 = 0.2$, $z_1^3 = 0.3$. Since $f(0) = f^3(0)$ and $f(1) = f^3(1)$, we get that $a = z_1^1 z_1^2 z_1^3 + (1 - z_1^1)(1 - z_1^2)(1 - z_1^3)$ and

$$z_1^0 = z_1^1 z_1^2 z_1^3 / (z_1^1 z_1^2 z_1^3 + (1 - z_1^1)(1 - z_1^2)(1 - z_1^3)) \approx 0,01. \quad (39)$$

Although $z_1^0 \in (0, 1)$, we have that $z_1^0 \notin (z_1^l, z_1^r)$. Hence, there does not exist a cubic (w.r.t. z_1) system which is $\mathcal{D}$-equivalent to the system (37).

The system (38) will always have z_1^0 (and not z_1^l) as the leftmost root of the function $f^3(z_1)$. This may lead to different dynamics of the regular variable x_2. For example, this is the case for the system

$$\begin{aligned} \dot{x}_1 &= -(z_1 - 0.05)(z_1 - 0.5)(z_1 - z_1^0) + 1 - x_1, \\ \dot{x}_2 &= (1 - z_1)(1 - z_2) + 0.02 - x_2, \end{aligned} \quad (40)$$

where z_1^0 is given by (39). See Fig. 13, Fig. 14 for the dynamics in the black wall $SD(\{1\}, 0)$. In the regular domains the systems (37) and (40) have the same dynamics in the limit $(q_i \to 0)$.

Similarly, let us assume that the degree of an $\mathcal{D}$-equivalent polynomial is 4 (i.e. $m = 4$). Therefore $f^4(z_1) = -a(z_1 - 0.05)(z_1 - 0.5)(z_1 - z_1^0)(z_1 - \bar{z}_1)$, where a is a parameter. Since the wall is black, we must have $z_1^0 \in (z_1^l, z_1^r)$ and $\bar{z}_1 \in (-\infty, 0)$. But then the conditions $f^4(0) = f(0)$ and $f^4(1) = f(1)$ cannot be satisfied. Thus, the assumption is not correct.

The next example treats the case of a type I wall, where the 'natural' assumption on the minimal degree m to be 2 and even 3 appears to be wrong in general.

Example 9. We consider the system

$$\begin{aligned} \dot{x}_1 &= (z_1 - 0.1)(z_1 - 0.2)(z_1 - 0.3)(z_1 - 0.4) + 1 - x_1, \\ \dot{x}_2 &= 1 - z_2 - x_2, \end{aligned} \quad (41)$$

where z_i are given by (2), $\theta_i = 1$, $i = 1, 2$, $SD(\{1\}, 0)$ is a type I wall, or more precisely, a wall which is white from the right side and black from the left side.

Assume that in the wall $SD(\{1\}, 0)$ this system could be represented by an equivalent polynomial system of degree 2 (i.e. $m = 2$)

$$\begin{aligned} \dot{x}_1 &= F_1^2(z_1, 0) - G_1^2(z_1, 0)x_1, \\ \dot{x}_2 &= 1 - z_2 - 1.5x_2. \end{aligned} \quad (42)$$

For the system (41) we have $f(z_1) = (z_1 - 0.1)(z_1 - 0.2)(z_1 - 0.3)(z_1 - 0.4)$, so that its leftmost root is $z_1^l = 0.1$. For the system (42) we must have

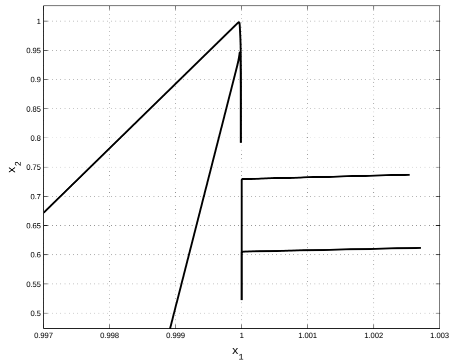

Figure 13: Some trajectories of the system (37) in a vicinity of the black wall $SD(\{1\}, 0)$, where $z_i = H(x_i, \theta_i, q_i)$, $\theta_i = 1$, $q_i = 0.00001$, $i = 1, 2$. The trajectories approaching the wall from the right side are attracted to the stationary point $(1, 0.52)$. The trajectories that approach the wall from the left side are attracted to the singular stationary point $(1, 0.97)$ and therefore remain in this black wall. (All coordinates are given for the limit case $q_i \to 0$).

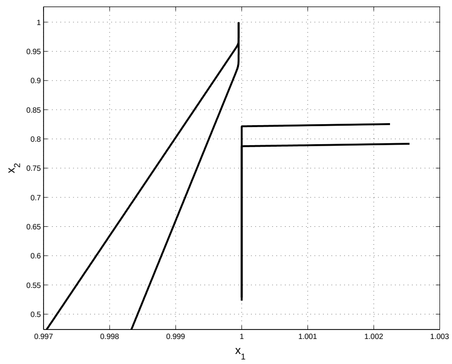

Figure 14: Some trajectories of the system (40) in a vicinity of the black wall $SD(\{1\}, 0$, where $z_i = H(x_i, \theta_i, q_i)$, $\theta_i = 1$, $q_i = 0.00002$, $i = 1, 2$. The trajectories approaching the wall from the right side are attracted to the singular stationary point $(1, 0.52)$. The trajectories that approach the wall from the left side are attracted to the singular stationary point $(1, 1.02 - z_1^0) \approx (1, 1.01)$ and therefore leave this black wall entering the intersection of walls $(1, 1)$. (All coordinates are given for the limit case $q_i \to 0$).

$f^2(z_1) = a(z_1 - 0.1)(z_1 - z^0)$, where a and z^0 are parameters. Indeed, the leftmost root is essential here for the dynamics in the wall, as it gives a stable stationary solution of the associated boundary layer equation. The conditions $f(0) = f^2(0)$ and $f(1) = f^2(1)$ give $z^0 = 1/15 < 0.1$. This, however, contradicts the fact that the root 0.1 is leftmost.

Similarly, assume that the degree of an equivalent polynomial is 3 (i.e. $m = 3$). Then $f^3(z_1) = a(z_1 - 0.1)(z_1 - z^0)(z_1 - z^1)$, where a, z^0 and z^1 are parameters. For a transparent wall we must have $z^1 \in (-\infty, 0) \cup (1, \infty)$. It is now easy to verify that the condition $f^3(0)/f^3(1) > 0$, which follows from (23), does not hold in this case.

Below we describe a solution to the minimum degree problem for the domain given by (35). We will need the following assumptions for this result.

Assumption 8. $F_k(0, \mathcal{B}_R) = F_k^m(0, \mathcal{B}_R)$, $F_k(1, \mathcal{B}_R) = F_k^m(1, \mathcal{B}_R)$, $G_k(0, \mathcal{B}_R) = G_k^m(0, \mathcal{B}_R)$, $G_k(1, \mathcal{B}_R) = G_k^m(1, \mathcal{B}_R)$ for any $k = 1, ..., n$.

Assumption 9. The functions $f(z_1) = F_1(z_1, \mathcal{B}_R) - G_1(z_1, \mathcal{B}_R)\theta_1$ and $f^m(z_1) = F_1^m(z_1, \mathcal{B}_R) - G_1^m(z_1, \mathcal{B}_R)\theta_1$ have the same leftmost root and the same rightmost root in the interval $(0, 1)$.

Remark 6. Assumption 8 reflects the fact that the original system and the equivalent polynomial system of degree m have the same limit dynamics (as $q_i \to 0$) in the regular domains $\mathcal{R}(0, \mathcal{B}_R)$ and $\mathcal{R}(1, \mathcal{B}_R)$. Assumption 9 in the case of type II walls is equivalent to the fact that two systems have the same limit dynamics in the wall $SD(\{1\}, \mathcal{B}_R)$ (i.e. on both sides), because the leftmost root governs the limit dynamics to the left of the wall, while the rightmost root regulates the limit dynamics to its right. In the case of type I walls Assumption 9 is actually stronger than simply coincidence of the two dynamics. Indeed, only one of the outmost roots is needed for the dynamics to coincide (see Theorem 7), the other must only satisfy an inequality constraint. However, below we will show that requiring the stronger assumption 9 gives the same solution to the minimal degree problem ($m = 4$), but on the other hand gives us an opportunity to treat both wall types in a same way.

We first treat type I walls. The minimal degree in this case is $m = 4$. Remember that we have already shown that $m = 2$ or $m = 3$ may not hold in general.

Theorem 8. *Suppose that the system (1) satisfies Assumptions 1-3. Let the function $f(z_1)$ given by (18) have only roots of multiplicity 1 in the open interval $(0, 1)$ and satisfy one of the conditions described in (23). Finally suppose that the function $f(z_1)$ has more than one real root in the interval*

$(0,1)$. *Then the system (1) is $\mathcal{D}$-equivalent to a polynomial system (36), where $\mathcal{D}$ is given by (35) and $m = 4$.*

Proof. Without loss of generality we may assume that it is the first set of inequalities in (23) which is satisfied, i.e. the wall $SD(\{1\}, \mathcal{B}_R)$ is black on its left.

Due to Remark 6 and Theorem 7 it suffices to construct a polynomial system (36) with $m = 4$, which satisfies Assumptions 8-9 and, in addition, the conditions (32).

We check first that the function $f(z_1)$ can be replaced by an equivalent polynomial function $f^4(z_1)$ of degree 4.

According to the above assumptions $f(z_1) = (z_1 - z_1^l)(z_1 - z_1^r)\widehat{f}(z_1)$, where the function $\widehat{f}(z_1)$ does not have any roots belonging to $(0, z_1^l) \cup (z_1^r, 1)$.

We define

$$f^4(z_1) = a(z_1 - z_1^l)(z_1 - z_1^r)((z_1 - z_1^0)^2 + \varepsilon), \tag{43}$$

where ε, z_1^0 and a are real parameters. Assumption 9 is then fulfilled for any $\varepsilon > 0$.

From Assumption 8, we conclude that $f^4(0) = f(0)$ and $f^4(1) = f(1)$ leading to

$$\begin{aligned} a((z_1^0)^2 + \varepsilon) &= \widehat{f}(0), \\ a((1 - z_1^0)^2 + \varepsilon) &= \widehat{f}(1). \end{aligned} \tag{44}$$

Thus,

$$\frac{(z_1^0)^2 + \varepsilon}{(1 - z_1^0)^2 + \varepsilon} = \frac{\widehat{f}(0)}{\widehat{f}(1)}. \tag{45}$$

Denoting $\widehat{f}(0)/\widehat{f}(1) = \alpha$ we easily check that the wall is of type I when $\alpha > 0$. Due to (45) we have

$$\varepsilon = \frac{\alpha(1 - z_1^0)^2 - (z_1^0)^2}{1 - \alpha}, \ \alpha \neq 1. \tag{46}$$

If $\alpha = 1$, then Eqs. (44) are e.g. satisfied for $z_1^0 = 0.5$ and any $\varepsilon > 0$.

It follows from (46) that ε becomes positive provided

$$\begin{cases} z_1^0 \in (\frac{\sqrt{\alpha}}{\sqrt{\alpha}-1}, \frac{\sqrt{\alpha}}{1+\sqrt{\alpha}}), \text{ if } 0 < \alpha < 1; \\ z_1^0 \in (\frac{\sqrt{\alpha}}{1+\sqrt{\alpha}}, \frac{\sqrt{\alpha}}{\sqrt{\alpha}-1}), \text{ if } \alpha > 1. \end{cases} \tag{47}$$

Thus, for any function $f(z_1) = (z_1 - z_1^l)(z_1 - z_1^r)\widehat{f}(z_1)$ satisfying the imposed conditions there always exists a polynomial $f^4(z_1)$ of degree 4 given by (43), where z_1^0 satisfies the conditions (47), or $z_1^0 = 0.5$. For this z_1^0 we also have $a(z_1^0) = \frac{\widehat{f}(0)}{(z_1^0)^2+\varepsilon}$.

As the next step, we construct the functions $F_1^4(z_1, ..., z_n)$, $G_1^4(z_1, ..., z_n)$ of degree 4 (at most) with respect to z_1 and linear with respect to the other variables, which satisfy Assumption 8.

We can obviously put $G_1^4(z_1, ..., z_n)$ to be a multilinear function $G_1^1(z_1, ...z_n)$, as constructed in Theorem 2. In particular, $G_1^4(0, \mathcal{B}_R) = G_1(0, \mathcal{B}_R)$ and $G_1^4(1, \mathcal{B}_R) = G_1(1, \mathcal{B}_R)$ by this construction.

Next, we put $F_1^4(z_1, ..., z_n) = f_1^4(z_1) + G_1^4(z_1, ..., z_n)\theta_1$. Then $F_1^4(0, \mathcal{B}_R) = f_1^4(0)+G_1^4(0, \mathcal{B}_R)\theta_1 = f_1(0)+G_1(0, \mathcal{B}_R)\theta_1 = F_1(0, \mathcal{B}_R)$. Similarly, $F_1^4(1, \mathcal{B}_R) = F_1(1, \mathcal{B}_R)$.

Finally, we shall construct the functions $F_k^4(z_1, ..., z_n)$, $G_k^4(z_1, ..., z_n)$, $k = 2, ..., n$, which satisfy Assumption 8 and the conditions (32). For each k we can construct quadratic in z_1 functions $f_k(z_1)$ and $g_k(z_1)$ satisfying the conditions

$$f_k(0) = F_k(0, \mathcal{B}_R), \quad f_k(1) = F_k(1, \mathcal{B}_R), \quad f_k(z_1^l) = F_k(z_1^l, \mathcal{B}_R)$$

and

$$g_k(0) = G_k(0, \mathcal{B}_R), \quad g_k(1) = G_k(1, \mathcal{B}_R), \quad g_k(z_1^l) = G_k(z_1^l, \mathcal{B}_R)$$

respectively, and then simply put $F_k^4(z_1, ..., z_n) = f_k(z_1)$ and $G_k^4(z_1, ..., z_n) = g_k(z_1)$, which completes the proof of the theorem.

□

Our last result says that for type II (black) wall the minimal degree is $m = 5$. In the examples we have shown that $m = 3$ or $m = 4$ might not be enough.

Theorem 9. *Suppose that the system (1) satisfies Assumptions 1-3. Let the function* $f(z_1)$ *given by (18) have only roots of multiplicity* 1 *in the open interval* $(0, 1)$ *and satisfy the conditions (28). Finally, suppose that the non-linear function* $f(z_1)$ *has more than one real root in the interval* $(0, 1)$. *Then the system (1) is* $\mathcal{D}$*-equivalent to a polynomial system (36), where* $\mathcal{D}$ *is given by (35) and* $m = 5$.

Proof. Due to Remark 6 and Theorem 7 it suffices to construct a polynomial system (36) with $m = 5$, which satisfies Assumptions 8-9 and, in addition, the conditions (33).

We check first that the function $f(z_1)$ can be replaced by an equivalent polynomial function $f^4(z_1)$ of degree 5. According to the above assumptions $f(z_1) = (z_1 - z_1^l)(z_1 - z_1^m)(z_1 - z_1^r)\widehat{f}(z_1)$, where $z_1^m \in (z_1^l, z_1^r)$, where the function $\widehat{f}(z_1)$ does not have any roots belonging to $(0, z_1^l) \cup (z_1^r, 1)$.

We define

$$f^5(z_1) = a(z_1 - z_1^l)(z_1 - z_1^m)(z_1 - z_1^r)((z_1 - z_1^0)^2 + \varepsilon), \tag{48}$$

where ε, z_1^0 and a are real parameters. Assumption 9 is then fulfilled for any $\varepsilon > 0$.

From Assumption 8, we get $f^5(0) = f(0)$, $f^5(1) = f(1)$ giving

$$\begin{aligned} a((z_1^0)^2 + \varepsilon) &= \widehat{f}(0), \\ a((1 - z_1^0)^2 + \varepsilon) &= \widehat{f}(1). \end{aligned} \tag{49}$$

Thus,

$$\frac{(z_1^0)^2 + \varepsilon}{(1 - z_1^0)^2 + \varepsilon} = \frac{\widehat{f}(0)}{\widehat{f}(1)}. \tag{50}$$

Putting $\widehat{f}_1(0)/\widehat{f}_1(1) = \alpha$ we readily check that the wall is of type II when $\alpha > 0$. Due to (50) we have

$$\varepsilon = \frac{\alpha(1 - z_1^0)^2 - (z_1^0)^2}{1 - \alpha}, \ \alpha \neq 1. \tag{51}$$

If $\alpha = 1$, then Eqs. (49) are e.g. satisfied for $z_1^0 = 0.5$ and any $\varepsilon > 0$.

It follows from (51) that ε becomes positive provided

$$\begin{cases} z_1^0 \in (\frac{\sqrt{\alpha}}{\sqrt{\alpha}-1}, \frac{\sqrt{\alpha}}{1+\sqrt{\alpha}}), \ \text{if } 0 < \alpha < 1; \\ z_1^0 \in (\frac{\sqrt{\alpha}}{1+\sqrt{\alpha}}, \frac{\sqrt{\alpha}}{\sqrt{\alpha}-1}), \ \text{if } \alpha > 1. \end{cases} \tag{52}$$

Thus, for any function $f(z_1) = (z_1 - z_1^l)(z_1 - z_1^m)(z_1 - z_1^r)\widehat{f}(z_1)$ satisfying the imposed conditions there always exists a polynomial $f^5(z_1)$ of degree 5 given by (48), where z_1^0 satisfies conditions (52) or $z_1^0 = 0.5$. For this z_1^0 we also have $a(z_1^0) = \frac{\widehat{f}_1(0)}{(z_1^0)^2+\varepsilon}$.

Next, we construct the functions $F_1^5(z_1,...,z_n)$, $G_1^5(z_1,...,z_n)$ of degree 5 (at most) with respect to z_1 and linear with respect to the other variables, which satisfy Assumption 8.

The idea of the construction is borrowed from Theorem 8. We choose $G_1^5(z_1,...,z_n)$ to be multilinear and satisfying $G_1^5(0,\mathcal{B}_R) = G_1(0,\mathcal{B}_R)$, $G_1^5(1,\mathcal{B}_R) = G_1(1,\mathcal{B}_R)$ and then put $F_1^5(z_1,...,z_n) = f_1^5(z_1)+G_1^5(z_1,...,z_n)\theta_1$. It is easy to check that $F_1^5(0,\mathcal{B}_R) = F_1(0,\mathcal{B}_R)$ and $F_1^5(1,\mathcal{B}_R) = F_1(1,\mathcal{B}_R)$.

Finally, we construct the functions $F_k^5(z_1,...,z_n)$, $G_k^5(z_1,...,z_n)$, $k = 2,...,n$, which satisfy Assumption 8 and the conditions (33). For each k we can construct cubic in z_1 functions $f_k(z_1)$ and $g_k(z_1)$ satisfying the conditions

$$f_k(0)=F_k(0,\mathcal{B}_R),\ f_k(1)=F_k(1,\mathcal{B}_R),\ f_k(z_1^l)=F_k(z_1^l,\mathcal{B}_R),\ f_k(z_1^r)=F_k(z_1^r,\mathcal{B}_R)$$

and

$$g_k(0)=G_k(0,\mathcal{B}_R),\ g_k(1)=G_k(1,\mathcal{B}_R),\ g_k(z_1^l)=G_k(z_1^l,\mathcal{B}_R),\ g_k(z_1^r)=G_k(z_1^r,\mathcal{B}_R)$$

respectively, and then set $F_k^5(z_1,...,z_n) = f_k(z_1)$ and $G_k^5(z_1,...,z_n) = g_k(z_1)$.

The proof is complete.

□

Remark 7. If the function $f(z_1)$ has only one real root in the interval $(0,1)$, then we can always find a $\mathcal{D}$-equivalent multilinear system (36) in the case of the type I wall $SD(\{1\},\mathcal{B}_R)$ it is straightforward, as the wall is transparent and we can use Theorem 2.

If the wall $SD(\{1\},\mathcal{B}_R)$ is of type II, then it will be black, but its dynamics is governed by the only root z^* of the function $f(z_1)$ in the interval $(0,1)$. In this case we can reduce the minimum degree to the value $m = 3$ using the proof of the last theorem.

9. Discussion

In the paper we studied some mathematical challenges related to coarseness of time-continuous systems with Boolean interactions, in particular, those coming from mathematical models of gene regulatory networks with Boolean response functions. We showed that understanding the behavior of sliding trajectories is crucial for such an analysis. We also offered a description of all generic cases in regular domains, singular domains of codimension 1 and their combinations using the concept of polynomial recasting.

The framework for our analysis originates from the Boolean network approach and the piecewise linear modeling tradition closely related to this approach (see e.g. [4, Sect. 4,5,7]). The Boolean and piecewise structures come from the assumption that a gene is either 'on' or 'off' and that the response function is a step function. In the case of multiple genes, their interactions are described by means of logical operations 'AND', 'OR', and 'NOT'. The model has been further modified from Boolean-like to continuous by replacing Boolean response functions by steep sigmoid functions, where the representation of the logical operations 'AND', 'OR', and 'NOT' as the algebraic operations '*', '+', and '-' for the sigmoid functions has resulted in multilinear regulatory functions ([4], [2, Ch. 1.4.3], [7], [8]).

The approach we considered in this paper is of a different nature. The functional form for the regulatory functions was not a priori derived from any mathematical or biological reasoning. Rather, it was chosen from a set of functions optimal for the task. This can explain the level of generality of the problems studied in the paper. In particular, we assumed the regulatory functions to be as general as C^1-functions. In the introduction we discussed a mathematical motivation for such a choice. A possible biological motivation is more controversial, as the multilinearity assumption on regulatory functions is widely accepted in the literature (see e.g. [1], [2], [4], [9] and references therein), although our overall impression is that, in fact, not much is really known about the precise biological and mathematical mechanisms of gene regulations ([1], [4]).

Below we discuss possible reasons for introducing nonlinearity into the regulatory functions.

As we mentioned above, a typical way of justifying multilinearity of the regulatory functions in a system with Boolean response functions is based on the algebraic equivalence of nonlinear and linear Boolean functions (see e.g. [1, p. 80], [4], [7], [15]). As we showed in Sect. 4, this equivalence works perfectly well in the absence of sliding modes. Yet, taking them into account may destroy the above argument due to high sensitivity of sliding modes to small perturbations. We demonstrated that robustness can only be achieved if we include polynomials of higher degree. Definitely, this is a purely mathematical result which has no direct biological interpretation, although we do believe that any reliable model should possess basic mathematical properties (like robustness, well-posedness etc.).

Another source of nonlinearities may be due to the presence of steep response functions which are different from the standard Hill functions. There are several powerful mathematical methods for modeling response functions. For example, kinetic models of genetic regulation processes can be constructed by specifying the response functions. These models are derived from concrete biochemical mechanisms. In this framework the parameters of the model usually have a biochemical or physical meaning; for details see [1, Ch. 2, App. A], [2, Ch. 1.3.1, 1.3.2], [10], where the Hill functional form is derived from the analysis of the equilibrium binding of the transcription factor to its site on the promoter. Calculations with the Hill functions are well-elaborated, in particular, in the analysis of sliding modes [8], [13].

However, non-Hill response functions may naturally appear in a mathematical as well as in a biological context; see e.g. [4], [7], [10]. One way to combine the analysis of more general response functions S with the convenience of using the Hill function H is to represent the former via the latter: $S(x, \theta, q) = f(H(x, \theta, q))$. Under very general assumptions on f the function S becomes sigmoid-shaped, and, in fact, the converse is also true under some additional regularity hypotheses on the sigmoid S. The price one pays will be nonlinearity of the regulatory functions F and G, because the model 'multilinear F and G of non-Hill sigmoid functions' will be regarded as 'nonlinear F and G of the Hill function'.

Another reason for appearance of nonlinearities may be due to dependence of binding events on each other. Under the assumption of independence, models with multilinear response functions are justifiable, as multiplications of the probabilities of independent events yield functions that can be described in terms of products of probabilities of single events. Moving further from simple to complex situations, where dependence of binding events is allowed, may give more complicated expressions for regulatory functions [1, appendix B], [2, 1.4.2].

Finally, deducing the models from different biological formalisms may result in different functional forms. A prominent example is General Mass Action Paradigm which can be used in mathematical modeling of gene networks [2, Ch. 1], [4, p.82-83] and which produces highly nonlinear systems of differential equations.

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