Alternative frameworks for analysis of gene regulatory networks with delay

Alternative rammeverk for analyse av genregulatoriske nettverk med tidsforsinkelse

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Philosophiae Doctor (PhD) Thesis 2010:53

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Ås, November 2010

Summary

When trying to understand the role and functioning of a gene regulatory network (GRN), the first step is to assemble components of the network and interactions between them. It is important that models are kept simple but nevertheless capture the key processes of the real system. There is a large body of theoretical and experimental results showing that underlying processes of gene regulation, such as transcription and translation, do not occur instantaneously. Therefore the delay effects are everywhere in GRNs, but they are not always well-represented in mathematical models. The scope of the present work is to incorporate delays into a well-established differential equation model for GRNs and to apply alternative mathematical frameworks for analysis of the obtained delayed system.

Due to a huge amount of equations and parameters involved, it is widely accepted that no analysis is possible without a considerable simplification of the underlying model. The non-linear, switch-like character of many of interactions in gene expression has motivated the most common simplification, so-called Boolean-like formalism. To simplify the model one uses the step functions and the corresponding limit system. It leads to the subdivision of the phase space into regions at the boundary of which discontinuities may occur. Using this simplification for analysis of delayed GRNs we face two main mathematical challenges: to analyze the stability properties of steady states and to reconstruct the limit trajectories in switching domains. Papers I and II of my thesis are addressed to answer these two questions.

There is one more effect which is indisputably important for any reasonable model of GRNs, namely an effect of stochasticity, which may be caused by uncertainty in data, random fluctuations in the system, or simply due to a large number of interacting genes. In Paper III we propose an analytic stochastic modeling approach, which incorporates intrinsic noise effects directly into a well established deterministic models of GRNs with and without delay, and study the dynamics of the resulting systems.

In Paper IV we suggest a method which covers very general Boolean genetic networks with delay and thus opens for a more complete qualitative analysis of such networks. The method extends the Filippov theory of differential inclusions to the case of multivalued Volterra operators.

We believe that the proposed frameworks can provide good insights into deeper understanding of the complicated biological and chemical processes associated with genetic regulation.

Sammendrag

For å forstå rollen og funksjonene av et genregulatorisk nettverk (GRN) er det først og fremst nødvendig å sette sammen komponentene av nettverket og å analysere samhandlinger mellom dem. Det er viktig at modeller beholdes enkle, men samtidig gir et realistisk bilde av nøkkelprosessene i det reelle systemet. Det finnes flere teoretiske og eksperimentelle resultater som viser til at de genregulatoriske prosessene som transkripsjon og translasjon ikke skjer simultant. Tidsforsinkelser er normalt i GRN, men de er ikke representert i de fleste matematiske modeller. Hensikten med denne avhandlingen er å inkorporere tidsforsinkelser inn i veletablerte differensialligning-modeller av GRN og å benytte alternative rammeverk for analyse av de nyutviklede modellene med tidsforsinkelse.

Grunnet mange ligninger og parametre involvert i systemet er det vanlig å forenkle den underliggende modellen. Den ikke-lineære, sprangvise oppførselen av mange variabler i gen uttrykk har motivert den mest utbredte forenklingen, såkalt Boolsk formalisme. For å forenkle modellen bruker man i så fall trinnfunksjoner og det tilhørende grensesystemet. Det fører til en oppdeling av faserommet i regulære områder, og ved grensene mellom disse områdene kan diskontinuitet forekomme. Bruk av denne forenklingen for å analysere tidsforsinket GRN medfører to matematiske utfordringer: å undersøke stabilitet til likevektspunkter og å rekonstruere løsningskurver i singulære domener. Artikler I og II av min avhandling har til hensikt å svare på disse to spørsmålene.

Spesielt viktig for en god GRN modell er stokastiske effekter. Disse stokastiske effektene kan forekomme på grunn av usikkerhet i dataene, tilfeldige endringer i systemet eller av den grunn at antall av gen interaksjoner er stort. I artikkel III setter vi opp en analytisk stokastisk modell ved å inkorporere indre støy inn i veletablerte modeller av GRN med og uten tidsforsinkelse samt å undersøke dynamikk til de resulterende systemene.

I artikkel IV foreslår vi en metode som dekker generelle Boolske genetiske nettverk med tidsforsinkelse. Dette åpner for en mer komplett kvalitativ analyse av slike nettverk. Metoden utvider Filippovs teori av differensialinklusjoner til multivaluerte Volterra operatorer.

Vi mener at de foreslåtte rammeverkene vil kunne gi innsikt i en grundigere forståelse av de kompliserte biologiske og kjemiske prosessene som beskriver gen regulering.

List of papers

The thesis is based on the following papers:

Paper I

I. Shlykova, A. Ponosov, A. Shindiapin A., and Yu. Nepomnyashchikh, *A general framework for stability analysis of gene regulatory networks with delay*, Electron. J. Diff. Eqs., Vol. 2008 (2008), No. 104, pp. 1-36

Paper II

I. Shlykova, A. Ponosov, *Singular perturbation analysis and gene regulatory networks with delay*, Nonlinear Analysis: Theory, Methods and Applications, Vol. 72, No 9-10, (2010), pp. 3786-3812

Paper III

I.Shlykova, A. Ponosov, *Stochastically perturbed gene regulatory networks*, submitted to Journal Stochastic Processes and their Applications

Paper IV

I.Shlykova, A. Bulgakov, A. Ponosov, *Functional differential inclusions generated by functional differential equations with discontinuities*, submitted to Journal Nonlinear Analysis: Theory, Methods and Applications

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Chapter 1

Introduction

1.1 Gene regulatory network

Gene regulatory network (GRN) consists of a set of genes, proteins, small molecules, and their mutual regulatory interactions. The network is responsible for providing a cell in the organism with the right amount of the proteins necessary for development of the embryo or maintaining the life functions of the organism [10].

GRN would consist of one or more input signals, regulatory proteins that integrate these signals, several target genes, and the mRNAs and proteins produced from those target genes. The net effects are changes in cell phenotype and function. The regulatory network can be viewed as on Fig. 1:

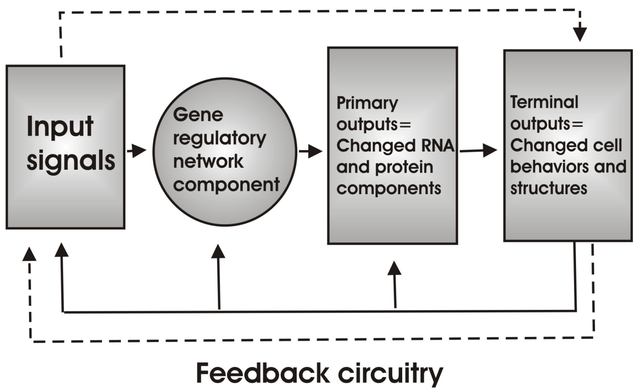

Fig. 1 (picture by courtesy of U.S. Department of Energy Genome Programs)

Regulation of gene expression by signals from outside and within the cell plays important roles in many biological processes and can potentially occur at many stages in the synthesis of proteins [13], that include

(1) Transcriptional control, (2) Posttranscriptional control, (3) Transport to the cytoplasm, (4) Stability of the mRNA, (5) Translation control, and (6) Posttranslational modification of the protein product (Fig. 2).

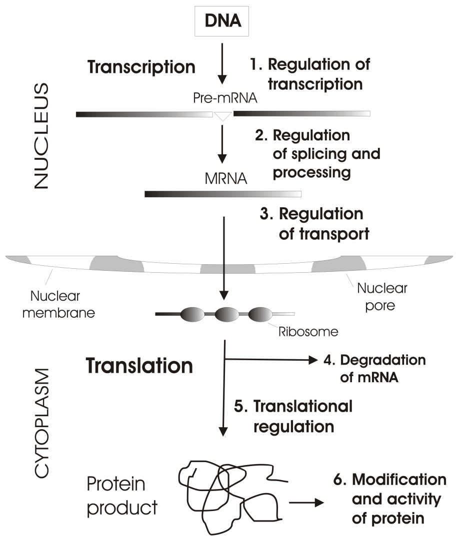

Fig. 2

Most genes are regulated in the part at the transcriptional level, therefore gene networks are concentrated on the control of transcription, i.e. how genes are up and down regulated in response to signals [24].

1.2 Modeling gene regulatory network

When trying to understand the role and functioning of a GRN, the first step is to assemble components of the network and interactions between them. Since development is a dynamic process in which the expression of genes can constantly change, gene network models need to have a dynamical aspect, i.e. they need to define a state variable for each component, and study how this state changes by the interactions in the network. This state variable can correspond to the concentration of mRNAs and proteins, or it can be a binary value corresponding to the qualitative statement that a gene is expressed or not.

GRNs are often described verbally in combination with figures to illustrate complicated interactions between network elements. There are different reasons for using mathematical models for describing and simulation of a given GRN. The most important is to explain the behavior of the network, i.e. to uncover based principles how the system functions under various conditions. Different behaviors of a network correspond to theoretical properties of the mathematical model, including number of steady states, different types of attractors and transient behaviors and structural stability. Steady states of the model correspond to potential cell type and oscillatory solutions to naturally cyclic cell types. Mathematical stability of these attractors can usually be characterized by the sign of higher derivatives at critical points, and correspond to biochemical stability of the concentration profile. There are of course numerous methods for studying models of GRNs, however, models are often characterized by many variables, complex non-linear function relations and numerous unknown parameters values. It may therefore be a very challenging task to determine the theoretical properties of the model. Thus, there is need for new or improved methods in order to handle these complex models.

1.2.1 Boolean networks

The simplest dynamic models - Boolean network models - were used as a model for GRNs already in the 1960's by Stuart Kauffman as [1], [8], [24]. In this approach each gene is treated as having two discrete states, ON or OFF, and Boolean network is defined as a network $G(V, F)$, where $V = (x_1, ..., x_n)$ contains the binary expression levels of genes $1, ..., n$ and $F = (f_1, ..., f_n)$ is a set of Boolean functions $f_i(x_{i_1}, ..., x_{i_k})$, one for each gene [25]. In every time step, the expression levels x_i are updated for every gene simultaneously via the functions f_i. As we have a discrete and bounded state space, the number of possible states is finite (for n genes we have 2^n possible states) and they always end in an attractor, which can either consist of one single state (point attractor) or several states, which were traversed in a certain order (cyclic attractor). Kauffman hypothesized that attractors correspond to different cell types of an organism.

Boolean models distinctly simplify the examination of large sets of genes and are relatively easy to implement. A disadvantage of the logical approach is that the models have descriptive character and the abstraction of genes to ON/OFF switches makes it difficult or impossible to include many of the details of cellular biology [10].

1.2.2 Networks derived from differential equations

Differential equations are one of the most important modeling formalisms in mathematical biology, because they can model complex dynamic behavior like oscillations, cyclical patterns, multistationarity and switch-like behavior [3]. So it was only a short step to use them for modeling GRNs.

It is customary to describe GRNs by modeling the concentration changes of proteins, mRNAs and other molecules over time. An example of such differential equations approaches is a model proposed by Mestl et al. [23]

$$\dot{x}_i = F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i, \quad i = 1, \ldots, n, \tag{1.1}$$

where the functions F_i and G_i stand for the production and the relative degradation rate of the product of gene i, respectively, and x_i denotes the gene product concentration. The threshold function Z_i expresses the effect of the different transcription factors regulating the expression of gene and can be given by steeply sloped sigmoid functions or step function (Fig. 3).

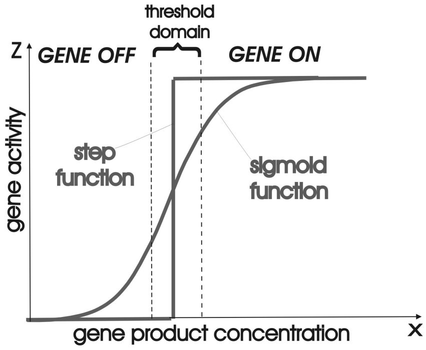

Fig. 3

1.2.3 Time delay models

The models described above do not take into account time delay effects, but to predict actual dynamics, it may be necessary to consider that the various underlying processes in gene networks, such as transcription, translation and transport, can take a time on the order of hours. The protein synthesis starts with activation of the corresponding gene, continues with mRNA-synthesis, transportation of the mRNA out of the cell nucleus, and synthesis of the proteins [4], [20]. As it was observed in [14] there is an average delay of around 10-20 min between the action of a transcription factor on the promoter of a gene and the appearance of the corresponding mature mRNA in the cytoplasm. The synthesis of a typical protein from mRNA takes around 1-3 min. An extreme example is furnished by the human dystrophin gene, which requires 16 hours to be transcribed [29]. Therefore time-delay is essential in gene regulation and presents one of the critical factors that should be considered in reconstruction of GRNs.

There are two basic types of mathematical approaches to describe GRNs with delays: discrete and distributed [11], [15]. Mathematical models of the discrete delay approach assume the same length of the time for movement of macromolecules from their place of synthesis to the location where they exert an effect and can be described by the system [30]

$$\dot{x}_i = f(x_i(t), Z(x_i(t-\tau))), \;\; i = 1, \dots, n.$$

In the case of a distributed delay the derivative of a variable, which can be the concentration of a macromolecule, depends on an integral of a function of one or more variables over a specified range of previous time. The system

$$\dot{x}_i = f(x_i(t), Z(x_i^{del})), \;\; i = 1, \dots, n,$$

is an example of GRN with distributed delay. In this case $x_i^{del} = \int_{-\infty}^{0} x_i(t-\tau)G_i(x_i(t-\tau))d\tau$ and $\int_{-\infty}^{0} G_i(x_i(t-\tau))d\tau = 1$. The last equation expresses a normalization condition imposed for biological realism.

Guided by the fact that time delay may in many cases have a significant effect on the dynamical properties of a model [16], [17], [26], [27] the greater part of my thesis is devoted to the gene networks with delay. We consider the GRNs with distributed delays of the structure:

$$\begin{aligned} \dot{x}_i &= F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i \\ Z_i &= \Sigma(y_i, \theta_i, q_i) \\ y_i(t) &= (\Re_i x_i)(t), \quad t \geq 0, \;\; i = 1, \ldots, n, \end{aligned} \tag{1.2}$$

where the operators $\Re_i$ are bounded linear Volterra operators of the form

$$(\Re_i x_i)(t) = {}^0c_i x_i(t) + \int_{-\infty}^{t} K_i(t-s)x_i(s)ds, \quad t \geq 0, \;\; i = 1, \ldots, n.$$

(see Paper I for more details).

In a "real-world" GRN a number of genes is rather large, so that a theoretical or a computer-based analysis of such networks can be complicated. The most common simplification, so-called Boolean-like formalism, consists in replacing the smooth response functions Z_i in Systems (1.1) and (1.2) by much simpler step functions (as $q_i \to 0$)

$$Z_i = \begin{cases} 0 & \text{if} \;\; x_i < \theta_i \\ 1 & \text{if} \;\; x_i > \theta_i. \end{cases}$$

This leads to splitting the systems into a number of affine scalar systems. It is usually an easy exercise to describe dynamics of their solutions explicitly at least in the non-delay case. However, coupled together these simple systems can produce some complicated effects, especially when trajectories approach the singular domains, where a switching from one affine system to another occurs. There are two main challenges one faces when using boolean functions. Firstly, one has to describe effects occurring in the vicinity of thresholds, e.g. sliding modes or steady states belonging to the discontinuity sets of the system. Secondly, one needs to define continuous solutions in the switching domains and justify the translation from the simplified to the "real-world" model. The solution to the first problem in the non-delay case can be found in [19], [23]. In our Paper I we do stability analysis of stationary points which belong to the discontinuity sets of the system and describe an algorithm of localizing stationary points in the presence of delays.

The second problem in the non-delay case was studied in [21] by applying singular perturbation analysis and combining of two motions $\mathbb{X}^n$ and $\mathbb{Z}^n$. The problem how the dynamics of the smooth gene networks with delays is related to the simplified dynamics of the Boolean networks is studied in Paper II. We have shown that the solution for steep sigmoids approaches the limit solution uniformly in any finite time interval (when the sigmoids approach the step functions) by applying a modified algorithm of reducing delay equations to ordinary differential equations (Paper I) and Tikhonov's theory of singular perturbed differential equations.

Paper I: A general framework for stability analysis of gene regulatory networks with delay

This paper offers a method of formalizing the analysis of asymptotic properties of solutions to the system of the form (1.2) describing a GRN with distributed time-delays and autoregulation [19], [21], [22], [23]. We consider a rather general situation with an arbitrary number of delay variables. At first we describe a modified "linear chain trick" method, which helps us to remove the delay from the model and converts the system into a larger equivalent system of ordinary differential equations.

In the paper we assume that the dynamics of GRN are governed by the so-called "logoids" or "tempered nonlinearities" [22], which are closed to the step function. A very important advantage of the logoid nonlinearities is the localization principle. Roughly speaking we may remove all regular variables in the stability analysis, because they do not influence local properties of solutions around stationary points. On the other hand, this principle helps us to simplify both notation and proofs.

It is easy to define stationary points for the system if Z_i are all smooth ($q_i > 0$). However, in this case the stability analysis and computer simulations may be cumbersome and time-consuming. To simplify the model, one uses the step functions and the corresponding limit system. The latter becomes, however, discontinuous if at least one y_i assumes its threshold value. If a stationary point of the limit system does not belong to the discontinuity set, then the analysis of the dynamics of the perturbed smooth systems is almost trivial. However the situation is different, if a potential stationary point in the limit model belongs to the discontinuity set, then corresponding dynamics may be subject to irregularities. We define a stationary point of the limit system as a limit point for the sequence of stationary points to the smooth system as $q_i \to 0$ and provide the sufficient condition for existence of singular stationary points. Moreover, we show that the stability properties of the singular stationary points of the initial system and the reduced by the localization principle system are the same.

In the last section we provide the conditions that give asymptotic stability of singular stationary points in the black wall (switching domain which is hit by the solutions from either side). A part of the framework is based on asymptotic analysis of singularly perturbed matrices, where we apply Mathematica to be able to derive exact stability criteria.

Paper II: Singular perturbation analysis and gene regulatory networks with delay

This work is a generalization of [21]. The main innovation is the inclusion of delay effects into the system for gene regulatory networks. The paper is addressed to answer the second question posed by the Boolean-like formalism, i.e. to define continuous solutions in the switching domain and to provide a mathematical justification of the simplified analysis under the presence of delays.

We study System (1.2) assuming that all response functions Z_i are given by Hill function [21]. By applying the modified algorithm of reducing delay equations from Paper I we replace the initial system with an equivalent system of ordinary differential equations. We study the situations where exactly one of the variables y_i (Sections 5 and 6) or arbitrary many (Section 7) approach their threshold values. The emphasis is put on sliding modes along one or more thresholds, which requires singular perturbation analysis. To define the solution to the system in the switching domains we change the singular variables with the corresponding response functions. Taking into account that the response functions are the Hill functions, we get equations describing the solution's behavior in the switching domains. The main result of the paper Theorem 9 is presented in Section 7 and is based on Tikhonov's theorem. Theorem 9 provides sufficient conditions, which guarantee the existence of solutions and ensure the fact that solutions of the smooth problem go to the limit solution for delay problems. Moreover this theorem gives us theoretical grounds for application of singular perturbation analysis to singular domains of higher order. The case when few variables approach their thresholds is more complicated. At the same time analysis of this situation can give us more information that can be of great importance for obtaining the whole picture of the trajectories' behavior. In Section 8 we introduce a delay into a non-delay example from [21] and consider a singular domain of the second order. We focus on comparison of delay and non-delay cases and observe how introducing the delay influences the solutions' behavior. The presented graphs of motion in fast and slow times show a big difference between non-delay and delay cases.

1.2.4 Stochastic differential equations

Due to the uncertainty of biochemical reactions, extrinsic noise and fluctuations in the environment there is an accelerating interest in the development of stochastic models and simulation methods for describing the functions of intrinsic noise in GRNs. There is a large body of theoretical and experimental works showing that noise plays a very important role in gene regulation [5], [12], [18]. Therefore instead of taking a continuous and deterministic approach, some authors have proposed to use discrete and stochastic models of gene regulation. An example of discrete models is the master equation developed by Gillespie [7]

$$\frac{\partial}{\partial t}P(X_1, X_2, \ldots, X_N; t) = \sum_{\mu=1}^{M}[B_\mu - \alpha_\mu P(X_1, X_2, \ldots, X_N; t)].$$

The key element of this approach is the "distribution function" $P(X_1, X_2, \ldots, X_N; t) \equiv$ probability that there will be X_1 molecules of type 1, X_2 molecules of type 2, ... and X_N molecules of type N in V at time t. Thus, the master equation is simply the time-evolution equation for the probability function $P(X_1, X_2, \ldots, X_N; t)$, whereas the rate equations (1.1) and (1.2) determine how the state of the system changes with time.

The advantage of this kind of modeling is clear: one obtains a description of the dynamics which grasp the global properties of the network and disregard the dynamics of individual genes which may be irrelevant, uncertain, not available or measured inaccurately. However, using the master equation in modeling GRN has no links to the Boolean-like formalism. Another feature of GRN which is hardly recognizable within the master equation paradigm is mentioned in [12]. On a larger time scale (or in other words, if the gene activation times are small compared to the interaction times), stochastic effects are less visible and even may level out, it means that continuous and deterministic models like (1.1) or (1.2) actually provide a good and simpler approximation. The master equation approach does not explain when and why the stochastic effects can level out. In Paper III we try to incorporate stochastic effects directly to continuous and deterministic models of GRN without using the master equations.

Paper III: Stochastically perturbed gene regulatory networks

In this paper we incorporate stochastic effects directly to continuous and deterministic models by extending the right hand sides of Systems (1.1) and (1.2) with constant white noises whose diffusion coefficients depend on the steepness parameters q_i of the smooth response functions, only. Although the non-delay system is a particular case of the delay system, we have chosen to treat them separately. We have also chosen to study the situation when exactly one variable approaches its threshold value at a time, i.e. we only consider the case of singular domains of codimension 1 ("the walls"). In many cases it may simply be regarded as a generic situation. We provide a detailed analysis of two main cases that could occur in the limit: so-called "transparent wall", when the solutions just travel through such a wall, and "black wall" which is hit by the solutions from either side.

We prove that in the limit (i. e. as $q_i \to 0$) the stochastic dynamics approaches uniformly the deterministic dynamics of the corresponding piecewise linear systems. The main challenge here is, exactly as in the case of Systems (1.1) and (1.2), to be able to deal with the singularities that arise in the limit around discontinuities of the right hand sides. We make use of an approach that goes back to Yu. Kabanov and Yu. Pergamentshchikov who suggested a uniform version of the stochastic Tikhonov theorem in singular perturbation analysis. As the theory of stochastic singular perturbation analysis for delay equations does not exist, in the case of System (1.2) this technique is combined with a special method of representing delay equations as larger system of ordinary differential equations from Paper I.

The Kabanov-Pergamintshikov theorem gives us the uniform convergence of the entire solution to its deterministic approximation in the case of transparent wall. In the case of black walls the theorem only gives the convergence of the non-singular component of the solution. The uniform convergence of the singular component is an open problem.

One of the rewards of using the new stochastic model, is a mathematical explanation of why a deterministic model (with or without delay) provide a good approximation to a stochastic model in the case when the activation occurs much faster than the other processes.

1.2.5 Filippov's approach

Another approach for modeling GRNs is based on Filippov's theory of discontinuous differential equations [6]. The main motivation for this approach is to suggest a method which would cover very general discontinuous functional differential equations and in particular, very general Boolean genetic models with delay. As it was mentioned before delay effects are an important issue in genetic models. The approach suggested in Papers I and II only covers very special types of delay, namely distributed delays where the corresponding integral operators are finite dimensional. This analysis maybe suitable for certain biological applications, but a simple case of constant delays is not covered by this method. Another drawback of the analysis used in Papers I and II is that it treats the asymptotic study of steady states and the reconstruction of the limit solutions separately, because two different techniques are applied. For instance, it is not possible to conclude from the results obtained in these papers whether the limit solutions tend to the limit steady states.

A way to put together the asymptotic stability analysis and reconstruction of the limit trajectories was suggested in [9]. This approach exploits the concepts of differential inclusions and the Filippov solutions. Thus, a clear advantage of this approach is its more universal character and possibility to complete the asymptotic analysis around steady states of the network. Yet, the Filippov approach also has its disadvantages. For instance, using it one may obtain steady states that are not limits of the proper steady states coming from the smooth model.

Paper IV: Functional differential inclusions generated by functional differential equations with discontinuities

Unlike Papers I and II the present paper follows the approach based on multivalued mappings. Yet, the classical Filippov theory treats only the non-delay case. As we are interested in incorporating very general delays into a discontinuous system of differential equations, we use the language of Volterra operators and functional differential equations (see e.g. [2]). In order to implement the central idea of Filippov's theory, we suggest a formal procedure of obtaining a functional differential inclusion from a general discontinuous functional differential equation. This gives us a possibility to define an analogue of a Filippov solution for discontinuous functional differential equations and finally to apply the developed theory to gene regulatory networks with general delays.

We start with the particular case: families of functional differential equations that are discontinuous in one parameter and show how such a family gives rise to a well-defined functional differential inclusion. We study also basic properties of the resulting inclusions such as local existence, uniqueness of (Filippov) solutions and their continuous dependence on parameters (like the threshold value itself). We demonstrate as well how the existence of global solutions can be obtained. The key property which enables us to prove the announced results is the compactness of the constructed multivalued mappings in the weak topology of the Lebesgue space L_1^n.

In Section 3 we apply the obtained results to the scalar case of a gene regulatory network with delay.

The next step is to generalize the developed theory to the case of simultaneous discontinuity in several parameters. The central results of the paper are an analogue of Filippov's theory for general functional differential equations discontinuous in several parameters (Section 4) and justification of the Boolean analysis of a gene regulatory network with a general delay (Section 5).

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Paper I

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A GENERAL FRAMEWORK FOR STABILITY ANALYSIS OF GENE REGULATORY NETWORKS WITH DELAY

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Abstract. A method to study asymptotic properties of solutions to systems of differential equations with distributed time-delays and Boolean-type nonlinearities (step functions) is offered. Such systems arise in many applications, but this paper deals with specific examples of such systems coming from genetic regulatory networks. A challenge is to analyze stable stationary points which belong to the discontinuity set of the system (thresholds). The paper describes an algorithm of localizing stationary points in the presence of delays as well as stability analysis around such points. The basic technical tool consists in replacing step functions by special smooth functions ("the tempered nonlinearities") and investigating the systems thus obtained.

1. Introduction

We study asymptotically stable steady states (stationary points) of the delay system

$$\begin{gathered}\dot{x}_i = F_i(Z_1,\dots,Z_m) - G_i(Z_1,\dots,Z_m)x_i \\ Z_k = \Sigma(y_{i(k)},\theta_k,q_k) \\ y_i(t) = (\Re_i x_i)(t) \quad (t\ge 0),\ i=1,\dots,n;\ k=1,\dots,m).\end{gathered} \tag{1.1}$$

This system describes a gene regulatory network with autoregulation [6, 8, 9, 10, 11], where changes in one or more genes happen slower than in the others, which causes delay effects in some of the variables.

Let us now specify the main assumptions put on the entries in (1.1).

The functions F_i, G_i, which are affine in each Z_k and satisfy

$$F_i(Z_1,\dots,Z_m)\ge 0,\quad G_i(Z_1,\dots,Z_m)>0$$

for $0\le Z_k\le 1$, $k=1,\dots,m$, stand for the production rate and the relative degradation rate of the product of gene i, respectively, and x_i denoting the gene product concentration. The input variables y_i endow System (1.1) with feedbacks which, in general, are described by nonlinear Volterra ("delay") operators $\Re_i$ depending on the gene concentrations $x_i(t)$. The delay effects in the model arise from the time required to complete transcription, translation and diffusion to the place of action of a protein [3].

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If $\Re_i$ is the identity operator, then $x_i = y_i$, and we obtain a non-delay variable. Non-delay regulatory networks, where $x_i = y_i$ for all $i = 1, \dots, n$ in their general form, i.e. where both production and degradation are regulated, were introduced in [6].

Remark. Below we will use the notation ${}^{\nu}c_i$, ${}^{\nu}K_i$, α_i, ${}^{\nu}v_i$, where the indexes ν and i indicate the number of an item and an equation, respectively.

In this paper we assume $\Re_i$ to be integral operators of the form

$$(\Re_i x_i)(t) = {}^{0}c x_i(t) + \int_{-\infty}^{t} K_i(t-s) x_i(s) ds, \quad t \geq 0, \ i = 1, \dots, n, \tag{1.2}$$

where

$$K_i(u) = \sum_{\nu=1}^{p} {}^{\nu}c_i \cdot {}^{\nu}K_i(u) \,, \tag{1.3}$$

$${}^{\nu}K_i(u) = \frac{\alpha_i^{\nu} \cdot u^{\nu-1}}{(\nu-1)!} e^{-\alpha_i u} \quad (i = 1, \dots, n). \tag{1.4}$$

The coefficients ${}^{\nu}c_i$ ($\nu = 0, \dots, p$, $i = 1, \dots, n$) are real nonnegative numbers satisfying

$$\sum_{\nu=0}^{p} {}^{\nu}c_i = 1$$

for any $i = 1, \dots, n$. It is also assumed that $\alpha_i > 0$ for all $i = 1, \dots, n$.

Example 1.1. Let

$${}^{1}K(u) = \alpha e^{-\alpha u}, \quad \alpha > 0 \quad \text{(the weak generic delay kernel)}, \tag{1.5}$$

$${}^{2}K(u) = \alpha^2 \cdot u e^{-\alpha u}, \quad \alpha > 0 \quad \text{(the strong generic delay kernel)}. \tag{1.6}$$

Kernels ${}^{1}K(u)$ and ${}^{2}K(u)$ ($\alpha = 0.7$) are illustrated in Figure 1 and Figure 2, respectively.

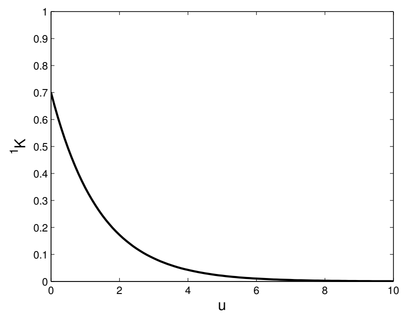

FIGURE 1. Kernel ${}^{1}K(u)$

The function ${}^{1}K(u)$ is strictly decreasing, while ${}^{2}K(u)$ tends to zero for large positive u and has maximum at time $T = \frac{1}{\alpha}$. If ${}^{2}K(u)$ is sharper in the sense

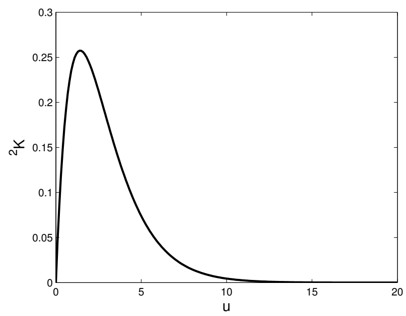

FIGURE 2. Kernel ${}^2K(u)$

that the region around T is narrower, then in the limit we can think of ${}^2K(u)$ as approximation the Dirac function $\delta(T-t)$, where

$$\int_{-\infty}^{\infty} \delta(T-t)f(t)dt = f(T).$$

The "response functions" Z_k express the effect of the different transcription factors regulating the expression of the gene. Each $Z_k = Z_k(y_{i(k)})$ ($0 \le Z_k \le 1$ for $y_{i(k)} \ge 0$) is *a smooth function* depending on exactly one input variable $y_{i(k)}$ and on two other parameters: the threshold value θ_k and the steepness value $q_k \ge 0$. A gene may have more than one, or no thresholds. This is expressed in the dependence $i = i(k)$. If different k correspond to the same i, then gene $i(k)$ has more than one threshold. If some i does not correspond to any k, then gene $i(k)$ has no threshold.

In the vicinity of the threshold value θ_k the response function Z_k is increasing almost instantaneously from 0 to 1, i.e. gene $i(k)$ becomes activated very quickly. Thus, the response function is rather close to the step function that has the unit jump at the threshold $y_i = \theta_i$. There are many ways to model response functions. The simplest way is to use the unit step functions which are either "on": $Z_i = 1$, or "of": $Z_i = 0$. It corresponds to $q_k = 0$ ($k = 1, \dots, m$) in the above notation. In this case System (1.1) splits into a number of affine scalar delay systems, and it is usually an easy exercise (see Section 2) to find all their solutions explicitly. However, coupled together these simple systems can produce some complicated effects, especially when a trajectory approaches the switching domains, where a switching from one affine system to another occurs. Particularly sensitive is the stability analysis of the stationary points which belong to these switching domains. This may require the use of smooth approximations $Z_k(y_{i(k)}) = \Sigma(y_{i(k)}, \theta_k, q_k)$ (corresponding to the case $q_i > 0$) of the step response functions.

In this paper we will use approximations which were introduced in [9] and which are based on the so-called "tempered nonlinearities" or "logoids" (see the next section). This concept simplifies significantly the stability analysis of the steady states belonging to the discontinuity set of the system in the non-delay model [6], [10]. As we will see, the logoid approach is also efficient in the delay case.

Let us stress that a "real-world" gene network is always smooth. A number of genes may, however, be rather large, so that a theoretical or a computer-based analysis of such networks can be complicated. That is why a simplified approach based on step response functions ("boolean nonlinearities") is to be preferred. There are two main challenges one faces when using boolean functions. Firstly, one has to describe effects occurring in the vicinity of thresholds (e.g. sliding modes or steady states belonging to the discontinuity set of the system). Secondly, one needs to justify the transition from the simplified to the "real-world" model.

2. Response functions

In this section we describe the properties of general logoid functions and look at some examples.

Let $Z = \Sigma(y, \theta, q)$ be any function defined for $y \in \mathbb{R}$, $\theta > 0$, $0 < q < q^0$ and $0 \le Z \le 1$. The following assumptions describe the response functions:

Assumption 2.1. $\Sigma(y, \theta, q)$ is continuous in $(y, q) \in \mathbb{R} \times (0, q^0)$ for all $\theta > 0$, continuously differentiable w.r.t.(with respect to) $y \in \mathbb{R}$ for all $\theta > 0, 0 < q < q^0$, and $\frac{\partial}{\partial y}\Sigma(y, \theta, q) > 0$ on the set $\{y \in \mathbb{R} : 0 < \Sigma(y, \theta, q) < 1\}$.

Assumption 2.2. $\Sigma(y, \theta, q)$ satisfies

$$\Sigma(\theta, \theta, q) = 0.5, \quad \Sigma(0, \theta, q) = 0, \quad \Sigma(+\infty, \theta, q) = 1$$

for all $\theta > 0$, $0 < q < q^0$.

Clearly, Assumptions 2.1-2.2 imply that $Z = \Sigma(y, \theta, q)$ is non-decreasing in $y \in \mathbb{R}$ and strictly increasing in y on the set $\{y \in \mathbb{R} : 0 < \Sigma(y, \theta, q) < 1\}$. The inverse function $y = \Sigma^{-1}(Z, \theta, q)$ w.r.t. Z, θ and q being parameters, is defined for $Z \in (0, 1)$, $\theta > 0$, $0 < q < q^0$, where it is strictly increasing in Z and continuously differentiable w.r.t. Z.

Assumption 2.3. For all $\theta > 0$, $\frac{\partial}{\partial Z}\Sigma^{-1}(Z, \theta, q) \to 0$ $(q \to 0)$ uniformly on compact subsets of the interval $Z \in (0, 1)$, and $\Sigma^{-1}(Z, \theta, q) \to \theta$ $(q \to 0)$ pointwise for all $Z \in (0, 1)$ and $\theta > 0$.

Assumption 2.4. For all $\theta > 0$, the length of the interval $[y_1(q), y_2(q)]$, where $y_1(q) := \sup\{y \in \mathbb{R} : \Sigma(y, \theta, q) = 0\}$ and $y_2(q) := \inf\{y \in \mathbb{R} : \Sigma(y, \theta, q) = 1\}$, tends to 0 as $q \to 0$.

Proposition 2.5. *If Assumptions 2.1-2.3 are satisfied, then the function* $Z = \Sigma(y, \theta, q)$ *has the following properties (see* [12]*):*

1. *If* $q \to 0$*, then* $\Sigma^{-1}(Z, \theta, q) \to \theta$ *uniformly on all compact subsets of the interval* $Z \in (0, 1)$ *and every* $\theta > 0$*;*
2. *if* $q \to 0$*, then* $\Sigma(y, \theta, q)$ *tends to 1* $(\forall y > \theta)$*, to 0* $(\forall y < \theta)$*, and to 0.5 (if* $y = \theta$*) for all* $\theta > 0$*;*
3. *for any sequence* (y_n, θ, q_n) *such as* $q_n \to 0$ *and* $\Sigma(y_n, \theta, q_n) \to Z^*$ *for some* $0 < Z^* < 1$ *we have* $\frac{\partial \Sigma}{\partial y}(y_n, \theta, q_n) \to +\infty$.

Proof. Let $q \to 0$. Take a compact subset $A \subset (0, 1)$ and $\theta > 0$. There exist Z_1, Z_2 such as $0 < Z_1 < Z_2 < 1$ and $A \subset [Z_1, Z_2]$. Therefore $\int_{Z_1}^{Z} \frac{\partial}{\partial \zeta}\Sigma^{-1}(\zeta, \theta, q)d\zeta \to \int_{Z_1}^{Z} 0 d\zeta$ uniformly on $Z \in [Z_1, Z_2]$. Then $(\Sigma^{-1}(Z, \theta, q) - \Sigma^{-1}(Z_1, \theta, q)) \to 0$ uniformly on $Z \in [Z_1, Z_2]$.

According to Assumption 2.3 $\Sigma^{-1}(Z_1, \theta, q) \to \theta$. From two last statements we obtain $\Sigma^{-1}(Z_1, \theta, q) \to \theta$ uniformly on $Z \in A$. The Property 1 is proved.

To prove the Property 2 let us first consider the case $0 < y < \theta$. Assume that there exists $q_n \to 0$ such that $Z_n = \Sigma(y, \theta, q_n) \geq \delta > 0$, $Z_n \in [\delta, 0.5]$. As $y = \Sigma^{-1}(Z_n, \theta, q_n)$ for all n, this contradicts the uniform convergence of $\Sigma^{-1}(Z, \theta, q) \to \theta$ on the interval $[\delta, 0.5]$, as all Z_n belong to it (see the Property 1). A similar argument applies if y satisfies $\theta < y < 1$. We obtained the Property 2.

Let $Z^* \in (0,1)$, $q_n \to 0$. Consider the sequences (y_n, θ, q_n) $(q_n \to 0)$ and $Z_n = \Sigma(y_n, \theta, q_n) \to Z^*$ for some $0 < Z^* < 1$. Then there exists a number N such that for all $n \geq N$ $Z_n \in [Z^* - \epsilon, Z^* + \epsilon] \subset (0,1)$. From Assumption 2.3 we have $\frac{\partial}{\partial Z}\Sigma^{-1}(Z_n, \theta, q_n) \to 0$ $(n \to \infty)$ uniformly on compact subsets of the interval $Z \in (0,1)$. The function $Z = \Sigma(y, \theta, q)$ is strictly increasing, thus invertible, so that $\frac{\partial \Sigma}{\partial y}(y_n, \theta, q_n) \to +\infty$. □

Here is an example of a function satisfying Assumptions 2.1-2.3.

Example 2.6. Let $\theta > 0, q > 0$. *The Hill function* is

$$\Sigma(y, \theta, q) := \begin{cases} 0 & \text{if } y < 0 \\ \frac{y^{1/q}}{y^{1/q} + \theta^{1/q}} & \text{if } y \geq 0. \end{cases}$$

However, the Hill function does not satisfy Assumption 2.4, as it never reaches the value $Z = 1$. This assumption is fulfilled for the following logoid function.

Example 2.7 ([6, 8])**.** Let

$$\Sigma(y, \theta, q) := L\left(0.5 + \frac{y - \max\{\theta, \sigma(q)\}}{2\sigma(q)},\ \frac{1}{q}\right), \quad (\theta > 0,\ 0 < q < 1),$$

where

$$L(u, p) = \begin{cases} 0 & \text{if } u < 0 \\ 1 & \text{if } u > 1 \\ \frac{u^p}{u^p + (1-u)^p} & \text{if } 0 \leq u \leq 1 \end{cases}$$

and $\sigma(q) \to +0$ if $q \to +0$.

The function Σ assumes the value $\Sigma = 1$ for all $y \geq \theta + \sigma(q)$ and the value $\Sigma = 0$ for all $y \leq \theta - \sigma(q)$, so that $\sigma(q)$ is the distance from the threshold θ to the closest values of y, where the response function Σ becomes 0 (to the left of θ) and 1 (to its right). However, it should be noticed that by definition θ may assume arbitrary positive values, so that $\sigma(q)$ may formally be larger than θ for some q, eventually becoming less that θ, because $\sigma(q) \to 0$ as $q \to 0$.

It is straightforward to check Assumptions 2.1-2.3 as well. Let us for instance verify the second part of Assumption 2.3. To do that, we keep fixed an arbitrary $Z \in (0,1)$, put $y_q = \Sigma^{-1}(Z, \theta, q)$ and choose any $\varepsilon > 0$. Then there exists $q_\varepsilon > 0$ such that $\sigma(q) < \varepsilon$ for $0 < q < q_\varepsilon$. As $0 < Z = \Sigma(y_q, \theta, q) < 1$ and $\Sigma = 0$ or 1 outside $(\theta - \sigma(q), \theta + \sigma(q))$, the value y_q must belong to the interval $(\theta - \sigma(q), \theta + \sigma(q))$. Thus, $|y_q - \theta| < \varepsilon$ for $0 < q < q_\varepsilon$, which proves the pointwise convergence $y_q \to \theta$ as $q \to 0$.

The following proposition will be used in this paper.

Proposition 2.8. *If Assumptions 2.1-2.4 are satisfied, then the function* $\Sigma(y, \theta, q)$ *has the following properties:*

1. *If* $y \neq \theta$, *then* $\Sigma(y, \theta, q) = 0$ *or* 1 *for sufficiently small* $q > 0$;
2. *If* $y \neq \theta$, *then* $\frac{\partial \Sigma}{\partial y}(y, \theta, q) = 0$ *for sufficiently small* $q > 0$.

Proof. According to Assumptions 2.2, 2.4, we have $\Sigma(\theta, \theta, q) = 0.5$ and $|y_1(q) - y_2(q)| \to 0$ as $q \to 0$, where $y_1(q) := \sup\{y \in \mathbb{R} : \Sigma(y, \theta, q) = 0\}$ and $y_2(q) := \inf\{y \in \mathbb{R} : \Sigma(y, \theta, q) = 1\}$. Then $\theta \in [y_1(q), y_2(q)]$. Let $y < \theta$ and put $\delta = \theta - y$. For sufficient small q we have $y_2(q) - y_1(q) < \delta$. Therefore $y < y_1(q)$ and $\Sigma(y, \theta, q) = 0$ for all $y < \theta$. The proof of the Property 2 follows directly from the first part. □

Property 2 from Proposition 2.5 justifies the following notation for the step function with threshold θ:

$$Z = \Sigma(y, \theta, 0) := \begin{cases} 0 & \text{if } y < \theta \\ 0.5 & \text{if } y = \theta \\ 1 & \text{if } y > \theta. \end{cases}$$

In what follows we only use the tempered response functions (called logoids in [9]); i.e., functions satisfying Assumptions 2.1-2.4. Thus, analysis based on the more traditional Hill function is not the subject of the present paper. However, some of the results below are still valid for the response functions, which satisfy Assumptions 2.1-2.3, but not necessarily Assumption 2.4.

3. Obtaining a system of ordinary differential equations

A method to study System (1.1) is well-known in the literature, and it is usually called "the linear chain trick" (see e.g. [5]). However, a direct application of this "trick" in its standard form is not suitable for our purposes, because we want any Z_i depend on y_i, only. Modifying the linear chain trick we can remove this drawback of the method.

In fact, the idea of how it can be done comes from the general method of representing delay differential equations as systems of ordinary differential equations using certain integral transforms (the so-called "W-transforms"). Those are much more general than the linear chain trick (see [7] for further details). Let us also mention here the paper [2] which demonstrates how such W-transforms can be applied to stability analysis of integro-differential equations. Finally, in [1] it is shown how the W-transforms can be used in stability analysis without reducing delay equations to ordinary differential equations.

The version of the linear chain trick used below was suggested in [11]. Here we only provide the final formula for the case of one delay operator (1.2), which is sufficient for our purposes. The formula follows from the general results proved in [11], but they can also be checked by a straightforward calculation.

This section is divided into three parts. For a better understanding of the method we first (Subsection 3.1) consider a scalar equation

$$\begin{gathered} \dot{x}(t) = F(Z) - G(Z)x(t) \\ Z = \Sigma(y, \theta, q) \\ y(t) = (\Re x)(t), \quad (t \geq 0) \end{gathered} \tag{3.1}$$

and a three-term delay operator

$$(\Re x)(t) = {}^0c x(t) + \int_{-\infty}^{t} K(t-s)x(s)ds, \quad t \geq 0, \tag{3.2}$$

where $K(u) = {}^1c \cdot {}^1K(u) + {}^2c \cdot {}^2K(u)$, ${}^\nu c \geq 0$ $(\nu = 0, 1, 2)$, ${}^0c + {}^1c + {}^2c = 1$, where $t \geq 0$, and ${}^1K(u)$, ${}^2K(u)$ are defined by (1.5) and (1.6), respectively.

The second part (Subsection 3.2) provides a reduction scheme for a rather general delay equation.

Finally (Subsection 3.3), we use the second part to write down a system of ordinary differential equations which is equivalent to the main system (1.1).

Subsection 3.1. In trying to replace the delay equation (3.1) with a system of ordinary differential equations, let us introduce new variables:

$$ {}^1w(t) = \int_{-\infty}^{t} {}^1K(t-s)x(s)ds, \qquad {}^2w(t) = \int_{-\infty}^{t} {}^2K(t-s)x(s)ds, \tag{3.3}$$

It is easy to see that ${}^1\dot{w} = -\alpha \cdot {}^1w + \alpha x$ and ${}^2\dot{w} = \alpha \cdot {}^1w - \alpha \cdot {}^2w$. This is used in the standard linear chain trick. Applying it we obtain $Z = \Sigma({}^0cx + {}^1c \cdot {}^1w + {}^2c \cdot {}^2w, \theta, q)$. By this, the response function Z becomes a function of three variables, but we wanted only one.

Therefore we will use the modified variables

$$ {}^1v = {}^0c\,x + {}^1c \cdot {}^1w + {}^2c \cdot {}^2w, \quad {}^2v = {}^2c \cdot {}^1w \tag{3.4}$$

(We remark that $y = {}^1v$). Differentiating ${}^2v$ we obtain

$$ {}^2\dot{v} = {}^2c \cdot {}^1\dot{w} = \alpha(-{}^2c \cdot {}^1w + {}^2c \cdot x) = -\alpha \cdot {}^2v + \alpha \cdot {}^2cx. $$

Similarly,

$$\begin{aligned} {}^1\dot{v} &= {}^0c\,\dot{x} + {}^1c \cdot {}^1\dot{w} + {}^2c \cdot {}^2\dot{w} \\ &= {}^0c\,(F(Z) - G(Z)x) + \alpha(-{}^1c \cdot {}^1w + {}^1c\,x) + \alpha({}^2c \cdot {}^1w - {}^2c \cdot {}^2w) \\ &= {}^0c\,(F(Z) - G(Z)x) + \alpha(-{}^1c \cdot {}^1w + {}^1c\,x) + \alpha \cdot {}^2c \cdot {}^1w - \alpha({}^1v - {}^0c\,x - {}^1c \cdot {}^1w) \\ &= {}^0c\,(F(Z) - G(Z)x) + \alpha x({}^0c + {}^1c) - \alpha \cdot {}^1v + \alpha \cdot {}^2v. \end{aligned}$$

Thus, we arrive at the following system of ordinary differential equations:

$$\begin{gathered} \dot{x} = F(Z) - G(Z)x, \\ {}^1\dot{v} = {}^0c\,(F(Z) - G(Z)x) + \alpha x({}^0c + {}^1c) - \alpha \cdot {}^1v + \alpha \cdot {}^2v, \\ {}^2\dot{v} = \alpha \cdot {}^2c\,x - \alpha \cdot {}^2v, \end{gathered} \tag{3.5}$$

where $Z = \Sigma(y, \theta, q)$. This system is equivalent to (3.1) in the following sense. Assume that, (3.1) is also supplied with the initial condition

$$ x(s) = \varphi(s), \quad s < 0, \tag{3.6}$$

where $\varphi : (-\infty, 0]$ is a bounded, continuous function.

Then, as shown above, the triple $(x(t), {}^1v(t), {}^2v(t))$, where ${}^1v, {}^2v$ are given by (3.4) with ${}^1w, {}^2w$ defined by (3.3), satisfies System (3.5) and the initial conditions:

$$\begin{aligned} x(0) &= \varphi(0), \\ {}^1v(0) &= {}^0c\,\varphi(0) + \int_{-\infty}^{0} K(-s)\varphi(s)ds \\ &= {}^0c\,\varphi(0) + \int_{-\infty}^{0} ({}^1c\,\alpha\, e^{\alpha s} - {}^2c\,\alpha^2 \cdot s\, e^{\alpha s})\varphi(s)ds, \\ {}^2v(0) &= {}^2c \int_{-\infty}^{0} {}^1K(-s)\varphi(s)ds = \alpha \cdot {}^2c \int_{-\infty}^{0} e^{\alpha s}\varphi(s)ds. \end{aligned} \tag{3.7}$$

Conversely, assume that $x(s) = \varphi(s)$ $(s < 0)$ for some bounded, continuous function $\varphi(s)$ and that the triple $(x(t),{}^1v(t),{}^2v(t))$ satisfies (3.5) and (3.7). We want to check that $x(t)$ is a solution to (3.1). It is sufficient to show that ${}^1v(t) = (\Re x)(t)$.

We consider first the more difficult case ${}^2c \neq 0$. Going back to

$$ {}^1w = {}^2v\,({}^2c)^{-1}, \quad {}^2w = ({}^1v - {}^0c\,x - {}^1c \cdot {}^1w)({}^2c)^{-1} \tag{3.8} $$

and using (3.5) we easily obtain that ${}^1\dot{w} = -\alpha \cdot {}^1w + \alpha x$, ${}^2\dot{w} = -\alpha \cdot {}^2w + \alpha \cdot {}^1w$. The fundamental matrix $W(t)$ of the corresponding homogeneous system, i.e. the matrix-valued solution of the system with $\alpha x \equiv 0$, satisfying $W(0) = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$, is

$$ W(t) = e^{-\alpha t} \begin{pmatrix} 1 & 0 \\ \alpha t & 1 \end{pmatrix}. $$

Hence

$$ {}^1w(t) = e^{-\alpha t} \cdot {}^1w(0) + \alpha \int_0^t e^{-\alpha(t-s)} x(s)ds, $$

$$ {}^2w(t) = e^{-\alpha t}(\alpha t \cdot {}^1w(0) + {}^2w(0)) + \alpha^2 \int_0^t (t-s)e^{-\alpha(t-s)} x(s)ds. $$

From (3.7) and (3.8) we also deduce

$$ {}^1w(0) = \alpha \int_{-\infty}^0 e^{\alpha s} \cdot \varphi(s)ds, \quad {}^2w(0) = -\alpha^2 \int_{-\infty}^0 s e^{\alpha s} \cdot \varphi(s)ds. $$

Evidently, this yields

$$ {}^1w(t) = \int_{-\infty}^0 {}^1K(t-s)\varphi(s)ds + \int_0^t {}^1K(t-s)x(s)ds, $$

$$ {}^2w(t) = \int_{-\infty}^0 {}^2K(t-s)\varphi(s)ds + \int_0^t {}^2K(t-s)x(s)ds, $$

so that ${}^1v(t) = {}^0c\,x(t) + {}^1c \cdot {}^1w(t) + {}^2c \cdot {}^2w(t) = (\Re x)(t)$. In the case ${}^2c = 0$ (the weak generic delay kernel) ${}^1c > 0$ since the system is supplied with delay effect. System (3.5) then reads

$$ \begin{gathered} \dot{x} = F(Z) - G(Z)x \\ {}^1\dot{v} = {}^0c\,(F(Z) - G(Z)x) + \alpha x - \alpha \cdot {}^1v. \end{gathered} \tag{3.9} $$

The initial conditions in this case become

$$ \begin{gathered} x(0) = \varphi(0) \\ {}^1v(0) = {}^0c\,\varphi(0) + {}^1c\alpha \int_{-\infty}^0 e^{\alpha s}\varphi(s)ds \end{gathered} \tag{3.10} $$

Consider ${}^1w = ({}^1v - {}^0cx)({}^1c)^{-1}$ and using (3.5) we get ${}^1\dot{w} = -\alpha \cdot {}^1w + \alpha x$. Similarly to the first case we have that ${}^1v(t) = {}^0c\,x(t) + {}^1c \cdot {}^1w(t) = (\Re x)(t)$, and we obtain the result.

Remark 3.1. We can formally obtain (3.9), (3.10) from (3.5), (3.7) if we simply put ${}^2c = 0$ in the system and in the initial conditions (3.7). Indeed, this will give ${}^2v(t) \equiv 0$ and hence (3.9) and (3.10). By this, ${}^2c = 0$ is a particular case of the general situation.

Remark 3.2. In Section 1 we observed that the assumption ${}^1v(t) \equiv x(t)$ for all $t \geq 0$ corresponds to the non-delay case. It is easy to see that the "tricked" system (3.5) provides in this case two copies of the same non-delay equation.

Subsection 3.2. The second step consists in describing the modified linear chain trick for a quite arbitrary nonlinear delay equation. To simplify the notation, this step is performed for the scalar case, only.

The following scalar nonlinear delay differential equation is considered:

$$\dot{x}(t) = f(t, x(t), (\Re x)(t)), \quad t > 0 \tag{3.11}$$

with the initial condition

$$x(\tau) = \varphi(\tau), \quad \tau \leq 0. \tag{3.12}$$

The function $f(\cdot, \cdot, \cdot) : [0, \infty) \times \mathbb{R}^2 \to \mathbb{R}$ has three properties.

- (C1) The function $f(\cdot, u, v)$ is measurable for any $u, v \in \mathbb{R}$.
- (C2) The function $f(\cdot, 0, 0)$ is bounded: $|f(t, 0, 0)| \leq C$ $(t \geq 0)$ for some constant C.
- (C3) The function f is Lipschitz: There exists a constant L such that

$$|f(t, {}^1u, {}^1v) - f(t, {}^2u, {}^2v)| \leq L(|{}^1u - {}^2u| + |{}^1v - {}^2v|) \tag{3.13}$$

  for all $t \geq 0$, ${}^iu, {}^iv \in \mathbb{R}$.

Note that these three conditions imply that $|f(t, u, v)| \leq L(|u| + |v|) + C$ for any $t \geq 0$ and $u, v \in \mathbb{R}$.

The initial function φ is bounded and measurable. The integral operator $\Re$ is assumed to be

$$(\Re x)(t) = \int_{-\infty}^{t} K(t - s)x(s)ds, \quad t > 0, \tag{3.14}$$

where

$$K(u) = \sum_{\nu=1}^{p} {}^{\nu}c \cdot {}^{\nu}K(u)\,, \tag{3.15}$$

$${}^{\nu}K(u) = \frac{\alpha^{\nu} \cdot u^{\nu-1}}{(\nu - 1)!} e^{-\alpha u}. \tag{3.16}$$

The coefficients ${}^{\nu}c$ are real numbers, and it is also assumed that $\alpha > 0$.

Note that the operator (3.14) is a particular case of the operator (1.2) with ${}^0c = 0$. If the initial function is defined on a finite interval $[-H, 0]$, then one can put $x(\tau) = 0$ for $\tau < -H$.

The functions ${}^{\nu}K$ have the following properties:

$$\begin{gathered} {}^{\nu}K(\infty) = 0, \\ {}^{\nu}K(0) = 0, \quad (\nu \geq 2.) \\ {}^1K(0) = \alpha\,. \end{gathered} \tag{3.17}$$

It is also straightforward to show that

$$\begin{gathered} \frac{d}{du}\,{}^{\nu}K(u) = \alpha \cdot {}^{\nu-1}K(u) - \alpha \cdot {}^{\nu}K(u) \quad (\nu \geq 2) \\ \frac{d}{du}\,{}^{\nu}K(u) = -\alpha \cdot {}^{\nu}K(u) \quad (\nu = 1). \end{gathered} \tag{3.18}$$

The classical linear chain trick (see e.g. [5]) rewritten in the vector form would give

$$ {}^{\nu}w(t) = \int_{-\infty}^{t} {}^{\nu}K(t-s)x(s)ds \quad (\nu = 1, 2, \dots, p) \tag{3.19}$$

yields

$$(\Re x)(t) = \int_{-\infty}^{t} \sum_{\nu=1}^{p} {}^{\nu}c \cdot {}^{\nu}K(t-s)x(s)ds = \sum_{\nu=1}^{p} {}^{\nu}c \cdot {}^{\nu}w(t), \tag{3.20}$$

so that

$$\dot{x}(t) = f(t, x(t), \sum_{\nu=1}^{p} {}^{\nu}c \cdot {}^{\nu}w(t)) = f(t, x(t), lw(t)), \tag{3.21}$$

where

$$l = ({}^{1}c, {}^{2}c, \dots, {}^{p}c), \tag{3.22}$$

the coefficients ${}^{\nu}c$ being identical with the coefficients in (3.15).

On the other hand, for $\nu \geq 2$ the functions ${}^{\nu}w$ satisfy

$$\frac{d}{dt} {}^{\nu}w(t) = \alpha \cdot {}^{\nu-1}w(t) - \alpha \cdot {}^{\nu}w(t),$$

while for $\nu = 1$ one has

$${}^{1}\dot{w}(t) = -\alpha \cdot {}^{1}w(t) + \alpha x(t).$$

This gives the following system of ordinary differential equations:

$$\dot{w}(t) = Aw(t) + \pi x(t), \quad t \geq 0, \tag{3.23}$$

where

$$A = \begin{pmatrix} -\alpha & 0 & 0 & \dots & 0 \\ \alpha & -\alpha & 0 & \dots & 0 \\ 0 & \alpha & -\alpha & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & \alpha & -\alpha \end{pmatrix} \quad \text{and} \quad \pi = \begin{pmatrix} \alpha \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{3.24}$$

Clearly, the system of ordinary differential equations (3.21), (3.23) is equivalent to the delay differential equation (3.11), (3.14).

The initial condition (3.12) can be rewritten in terms of the new functions as follows:

$${}^{\nu}w(0) = \int_{-\infty}^{0} {}^{\nu}K(-\tau)\varphi(\tau)d\tau = (-1)^{\nu-1} \frac{\alpha^{\nu}}{(\nu-1)!} \int_{-\infty}^{0} \tau^{\nu-1} \cdot e^{\alpha\tau}\varphi(\tau)d\tau, \tag{3.25}$$

$\nu = 1, \dots, p$. As before, $x(0) = \varphi(0)$.

The initial conditions (3.25) can be represented in a vector form as well (see e.g. [11]):

$$w(0) = \int_{-\infty}^{0} e^{A(-\tau)}\pi\varphi(\tau)d\tau. \tag{3.26}$$

As we already have mentioned, this classical version of the linear chain trick is not directly suitable for gene regulatory networks as the regulatory functions Z_i depend only on one variable, while the "trick" gives a sum of the form (3.20). That is why we use a modification of the linear chain trick, which is a particular case of the general reduction scheme introduced in [7]. First of all, let us observe that the solution to the auxiliary system (3.23) can be represented as follows:

$$\begin{aligned} w(t) &= e^{At}w(0) + \int_0^t e^{A(t-s)}\pi x(s)ds \\ &= e^{At}\int_{-\infty}^0 e^{A(-\tau)}\pi\varphi(\tau)d\tau + \int_0^t e^{A(t-s)}\pi x(s)ds \\ &= \int_{-\infty}^t e^{A(t-s)}\pi x(s)ds, \end{aligned} \tag{3.27}$$

as $x(s) = \varphi(s)$ for $s \le 0$. Thus,

$$(\Re x)(t) = \int_{-\infty}^t \Big(\sum_{\nu=1}^p {}^{\nu}c \cdot {}^{\nu}w\Big)ds = l\int_{-\infty}^t e^{A(t-s)}\pi x(s)ds. \tag{3.28}$$

This formula is a starting point for a modification of the linear chain trick which is used in this paper. Below we generalize (in a matrix form) the procedure described in Subsection 3.1.

Let us put

$${}^1v = \sum_{\nu=1}^p {}^{\nu}c \cdot {}^{\nu}w, \quad {}^{\nu}v = \sum_{j=1}^{p-\nu+1} {}^{j+\nu-1}c \cdot {}^{j}w \quad (\nu = 2, \dots, p).$$

Formally, the auxiliary system of the same form as in (3.23) is exploited. However, the matrix A, the solution $w(t)$, the functionals π and l will be changed to $\tilde{A} = A^T$,

$$v(t) = \int_{-\infty}^t e^{\tilde{A}(t-s)}\tilde{\pi}x(s)ds, \tag{3.29}$$

$$\tilde{\pi}x = \alpha x \begin{pmatrix} {}^1c \\ {}^2c \\ \vdots \\ {}^pc \end{pmatrix} \tag{3.30}$$

and $\tilde{l} = (1, 0, \dots, 0, 0)$, respectively.

It is claimed, in other words, that System (3.11) with Condition (3.12) is equivalent to the following system of ordinary differential equations:

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), {}^1v(t)) \\ \dot{v} &= \tilde{A}\cdot v + \tilde{\pi}x(t) \end{aligned} \tag{3.31}$$

with the initial conditions $x(0) = \varphi(0)$ and

$$v(0) = \int_{-\infty}^0 e^{\tilde{A}(-\tau)}\tilde{\pi}\varphi(\tau)d\tau. \tag{3.32}$$

Note that, unlike the right-hand side in the classical linear chain trick (see (3.21)), the right-hand side in (3.31) depends only on two state variables: x and ${}^1v$. This is crucial for applications which are of interest in this paper.

To prove (3.31), one needs to show that the representation (3.28) holds true if A, π and l are replaced by $\tilde{A}$, $\tilde{\pi}$ and $\tilde{l}$, respectively. This is done by writing down the fundamental matrix of the corresponding homogeneous system:

$$Y(t) = e^{-\alpha t} \begin{pmatrix} 1 & \alpha t & \frac{(\alpha t)^2}{2!} & \dots & \frac{(\alpha t)^{p-1}}{(p-1)!} \\ 0 & 1 & \alpha t & \dots & \frac{(\alpha t)^{p-2}}{(p-2)!} \\ 0 & 0 & 1 & \dots & \vdots \\ \vdots & \vdots & \ddots & \ddots & \alpha t \\ 0 & 0 & \dots & 0 & 1 \end{pmatrix}. \tag{3.33}$$

Then a direct calculation proves the result. A similar argument gives (3.32).

Remark 3.3. Assume that $v(t)$ is a solution to $\dot{v} = \tilde{A} \cdot v + \tilde{\pi} x(t)$, A, $\tilde{\pi}$ are given by (3.24) and (3.30), respectively. If now ${}^{\nu}c \geq 0$ for $\nu = 1, \dots p$, ${}^{\nu}v(0) \geq 0$ for $\nu = 1, \dots p$, and $x(t) \geq 0$ for all $t \geq 0$, then ${}^{\nu}v(t) \geq 0$ for all $t \geq 0, \nu = 1, \dots, p$, as well. It follows easily from the representation formula for the solution $v(t)$ and the formula (3.33) for the fundamental matrix.

Subsection 3.3. Finally, let us now go back to the general delay system (1.1). To simplify the notation we will write Z for $(Z_1, \dots, Z_m)$. Below we use the formulas obtained in the second part of the section.

First of all let us observe that the delay operators are now slightly different from those studied in the previous part of the section: one term is added, namely ${}^0c_i x_i$. However, this is not a big problem: we will replace ${}^1v$ by the input variable $y = {}^0c\, x + {}^1v$ arriving, as we will see, at a slightly different system of ordinary differential equations. Indeed, differentiating y gives

$$\dot{y} = {}^0c\,\dot{x} + {}^1\dot{v} = {}^0c f(t, x, y) - \alpha \cdot {}^1w + \alpha \cdot {}^2w + \alpha \cdot {}^1c\, x = {}^0c f(t, x, y) - \alpha y + \alpha \cdot {}^2w + \alpha x({}^0c + {}^1c).$$

For the sake of notations simplicity we still want y coincide with the first coordinate ${}^1v$ of the vector instead of v, so that we actually assume that ${}^1v = {}^0cx + \text{"}old\text{"}\,{}^1v$, so that $y = {}^1v$.

For (1.1) this results in the following system of ordinary differential equations:

$$\begin{gathered} \dot{x_i}(t) = F_i(Z) - G_i(Z) x_i(t) \\ \dot{v_i}(t) = A_i v_i(t) + \Pi_i(x_i(t)) \quad t > 0 \\ Z_k = \Sigma(y_{i(k)}, \theta_k, q_k), \quad y_i = {}^1v_i \quad (i = 1, \dots, n), \end{gathered} \tag{3.34}$$

where

$$A_i = \begin{pmatrix} -\alpha_i & \alpha_i & 0 & \dots & 0 \\ 0 & -\alpha_i & \alpha_i & \dots & 0 \\ 0 & 0 & -\alpha_i & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 0 & -\alpha_i \end{pmatrix}, \quad v_i = \begin{pmatrix} {}^1v_i \\ {}^2v_i \\ \vdots \\ {}^pv_i \end{pmatrix}, \tag{3.35}$$

and

$$\Pi_i(x_i) := \alpha_i x_i \pi_i + {}^0c_i f_i(Z, x_i) \tag{3.36}$$

with

$$\pi_i := \begin{pmatrix} {}^0c_i + {}^1c_i \\ {}^2c_i \\ \vdots \\ {}^pc_i \end{pmatrix}, \quad f_i(Z, x_i) := \begin{pmatrix} F_i(Z) - G_i(Z) x_i \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{3.37}$$

Recall that, according to the assumptions on System (1.1), F_i, G_i are real functions which are affine in each Z_k and which satisfy $F_i \geq 0, G_i \geq \delta > 0$ for $0 \leq Z_k \leq 1$.

Note that the notation in (3.34) is chosen in such a way that the first coordinate ${}^1v_i$ always coincides with the i-th input variable y_i. For the sake of simplicity the notation ${}^1v_i$ in (3.34) will be kept in the sequel.

If we assume that $Z_k = \text{const}$ $(i = 1, \dots n)$. Then System (3.34) becomes affine:

$$\begin{gathered} \dot{x}_i(t) = \psi_i - \gamma_i x_i(t) \\ \dot{v}_i(t) = A_i v_i(t) + \bar{\Pi}_i(x_i(t)), \quad t > 0, \quad i = 1, \dots, n, \end{gathered} \tag{3.38}$$

where $y_i = {}^1v_i$, $\psi_i \geq 0, \gamma_i > 0$, and

$$\bar{\Pi}_i(x_i) := \alpha_i x_i \begin{pmatrix} {}^0c_i + {}^1c_i \\ {}^2c_i \\ \vdots \\ {}^pc_i \end{pmatrix} + {}^0c_i \begin{pmatrix} \psi_i - \gamma x_i \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{3.39}$$

4. Some definitions

In this section we give a summary of some general notation and definitions related to geometric properties of System (3.34) in the limit case $(q_k = 0,\ k = 1, \dots, m)$. The notation and similar definitions in the non-delay case were introduced in the paper [8]. According to the idea described in the previous section System (3.34) replaces the delay system (1.1). The system of ordinary differential equations (3.34) is more general than the system studied in [8] and may have different properties as well. By this reason, some definitions from [8] have to be revised.

We start with the notation which we adopt from [8]. In what follows, it is assumed that

- $M := \{1, \dots, m\}$, $J := \{1, \dots, j\}$, $N := \{1, \dots, n\}$, $n \leq j$, $m \leq j$ (i. e. $N \subset J, M \subset J$);
- $R := M - S$ for a given $S \subset M$;
- A^B consists of all functions $v : B \to A$;
- $a_R := (a_r)_{r \in R}$ $(a_R \in A^R)$, $a_S := (a_s)_{s \in S}$ $(a_S \in A^S)$;

The following system of ordinary differential equations, generalizing System (1.1) in the limit case $(q_k = 0,\ k = 1, \dots, m)$, is used in this section

$$\dot{u}(t) = \Phi(Z, u(t)), \quad t > 0, \tag{4.1}$$

where $u = (u_1, \dots u_j)$, $Z = (Z_1, \dots Z_m)$, $Z_k = \Sigma(u_{i(k)}, \theta_k, 0)$ for $k \in M$ (i.e. Z_k is the unit step function with the threshold $\theta_k > 0$), $i(k)$ is a function from M to N. The function $\Phi_j : [0,1]^M \times \mathbb{R}^J \to \mathbb{R}^J$ is continuously differentiable in $Z \in [0,1]^M$ for all $u \in \mathbb{R}^J$ and affine in each vector variable $u \in \mathbb{R}^J$ for all $Z \in [0,1]^M$.

These assumptions are e. g. fulfilled for System (3.34) where u_i coincides with x_i for $i \in N$ and with one of the auxiliary variables ${}^\nu v_i$ (appropriately numbered) for $i \in J - N$. In fact, it is the only example which is of interest in this paper. However, System (4.1) is used to keep the notation under control.

The assumptions imposed on System (4.1) are needed for the following reason: if one replaces the step functions $\Sigma(u_{i(k)}, \theta_k, 0)$ with the sigmoid functions $\Sigma(u_{i(k)}, \theta_k, q_k)$ $(q_k \in (0, q^0))$, satisfying Assumptions 2.1-2.4 from Section 2, then for any $u^0 \in \mathbb{R}^J$ there exists a unique (local) solution $u(t)$ to (4.1) satisfying $u(0) = u^0$.

As $q_k > 0$, the function $\Sigma(u_{i(k)}, \theta_k, q_k)$ is smooth w.r.t. $u_{i(k)}$ for all $k \in M$, so that the unique solution does exist.

Assume again that all $q_k = 0$. Then the right-hand side of System (4.1) can be discontinuous, namely, if one or several $u_{i(k)}$ $(i \in N)$ assume their threshold values $u_{i(k)} = \theta_k$.

We associate a Boolean variable B_k to each Z_k by $B_k = 0$ if $u_{i(k)} < \theta_k$ and $B_k = 1$ if $u_{i(k)} > \theta_k$.

Let Θ denote the set $\{u \in \mathbb{R}^J : \exists k \in M : u_{i(k)} = \theta_k\}$. This set contains all discontinuity points of the vector-function

$$f(\Sigma(u_{i(k)}, \theta_k, 0)_{k\in M}, (u_i)_{i\in J})$$

and is equal to the space $\mathbb{R}$ minus a finite number of open, disjoint subsets of $\mathbb{R}^J$. Inside each of these subsets one has $Z_k = B_k$, where $B_k = 0$ or $B_k = 1$ for all $k \in M$, so that System (4.1) becomes affine:

$$\dot{u}(t) = \Phi(B, u(t)) := A_B u(t) + f_B, \quad t > 0, \tag{4.2}$$

where $B := (B_k)_{k\in M}$ is a constant Boolean vector. The set of all Boolean vectors $B = (B_1, \dots, B_m)$ (where $B_k = 0$ or 1) will be denoted by $\{0, 1\}^M$.

Thus, if the initial value of a possible solution belongs to one of these subsets, then the local existence and uniqueness result can be easily proved. The global existence problem is, however, more complicated (see e. g. [8]). This problem is not addressed here: global existence in the case of smooth response functions and local existence outside the discontinuity set in the case of the step functions are sufficient for our purposes.

System (4.1) is studied below under the assumption $q_k = 0$, $k \in M$, so that $Z_k = \Sigma(u_{i(k)}, \theta_k, 0)$. Assume that $u_{i(k)}$ has thresholds θ_k, θ_l, such as $\theta_k, \neq \theta_l$ if $k \neq l$.

The next three definitions can be found in [8].

Definition 4.1. Given a Boolean vector $B \in \{0, 1\}^M$, the set $\mathcal{B}(B)$, which consists of all $u \in \mathbb{R}^J$, where $(Z_k(u_{i(k)}))_{k\in M} = B$, is called *a regular domain* (or a box).

Remark 4.2. If some variables u_i have more than 1 threshold, then some Boolean vectors can generate empty boxes. The necessary and sufficient condition for $\mathcal{B}(B)$ to be non-empty reads as follows: $i(k) = i(l)$ & $\theta_k > \theta_l \Rightarrow B_k \leq B_l$. This is because $\Sigma(u_{i(k)}, \theta_k, 0) \leq \Sigma(u_{i(l)}, \theta_l, 0)$.

Any box is an open subset of the space $\mathbb{R}^J$, as $\Sigma(\theta_k, \theta_k, 0) = 0.5$ (according to Assumption 2.2) excludes the value $u_{i(k)} = \theta_k$. Only the variables $u_1, \dots, u_n$ can have (one or more) thresholds, the other have no threshold at all. In the system (3.34), these variables correspond to those that are different from any y_i $(i \in N)$, i.e. either to x_i (if x_i is "delayed" and thus different from y_i), or to one of the auxiliary variables ${}^\nu v_i$ with $\nu \geq 2$.

Definition 4.3. Given a subset $S \subset M, S \neq \emptyset$ and a Boolean vector $B_R \in \{0, 1\}^R$, where $R = M - S$, the set $\mathcal{SD}(\theta_S, B_R)$, which consists of all $u \in \mathbb{R}^J$, where $B_r = Z_r(u_{i(r)})$ $(r \in R)$ and $u_{i(s)} = \theta_s$ $s \in S$, is called *a singular domain*.

Remark 4.4. Again, if some variables u_i have more than 1 threshold, then some subsets S can generate empty singular domains. The necessary and sufficient conditions for $\mathcal{SD}(\theta_S, B_R)$ to be non-empty are as follows:

(1) $i(k) = i(l),\ k, l \in R,\ \&\ \theta_k > \theta_l\ \Rightarrow B_k \le B_l$,
(2) $i(k) = i(l),\ k, l \in S\ \Rightarrow k = l$ (this is because any point can only belong to one threshold for each variable u_i),
(3) $i(k) = i(l),\ k \in R,\ l \in S\ \&\ \theta_k > \theta_l\ \Rightarrow B_k = 0$,
(4) $i(k) = i(l),\ k \in R,\ l \in S\ \&\ \theta_k < \theta_l\ \Rightarrow B_k = 1$.

Any $\mathcal{SD}(\theta_S, B_R)$ is an open subset of the linear manifold $\{u_N : u_{i(s)} = \theta_s, s \in S\}$. The boxes are separated by singular (switching) domains. A singular domain can be described by its singular variables $u_{i(s)}(s \in S)$ which have threshold values in $\mathcal{SD}$ and by its regular variables $u_{i(r)}(r \in R)$. The variables $u_{i(r)}(r \in R)$ never obtain their threshold values in $\mathcal{SD}$.

Definition 4.5. Given a number $\mu \in M$ and a Boolean vector $B_R \in \{0,1\}^R$, where $R = M \backslash \{\mu\}$, the singular domain $\mathcal{SD}(\theta_\mu, B_R)$ is called *a wall*.

In other words, a wall is a singular domain of codimention 1. It is always open being also nonempty since $i(k) \ne i(\mu)$ for all $k \in M \backslash \{\mu\}$ (Remark 4.4).

Example 4.6. Consider variables u_1 with the thresholds θ_1, θ_2 ($\theta_1 < \theta_2$) and u_2 with the threshold θ_3. The phase space is then the union of six boxes, seven walls and two singular domains of codimension 2.

Let us consider boxes. For the first box we have $u_1 < \theta_1, u_1 < \theta_2$ and $u_2 > \theta_3$, the corresponding boolean vector is $\{0, 0, 1\}$. Similarly we obtain five other boxes corresponding to the following boolean vectors $\{1, 0, 1\}$, $\{1, 1, 1\}$, $\{0, 0, 0\}$, $\{1, 0, 0\}$, $\{1, 1, 0\}$(see Figure 3). But for example the boolean vectors $\{0, 1, 0\}$, $\{0, 1, 1\}$ generate empty boxes.

To describe walls between two adjacent boxes we should replace the only boolean variable which is different for the two boxes. The wall between boxes $B(1, 0, 1)$ and $B(1, 1, 1)$ is denoted by $\mathcal{SD}(1, \theta_2, 1)$. For this wall one has $u_1 > \theta_1$, $u_1 = \theta_2$ and $u_2 > \theta_3$. In addition, we have the following walls $\mathcal{SD}(\theta_1, 0, 1)$, $\mathcal{SD}(0, 0, \theta_3)$, $\mathcal{SD}(\theta_1, 0, 0)$, $\mathcal{SD}(1, 0, \theta_3)$, $\mathcal{SD}(1, \theta_2, 0)$ and $\mathcal{SD}(1, 1, \theta_3)$. The singular domains of codimension 2 are the limit points for four boxes. They are $u_1 = \theta_1, u_2 = \theta_3$ and $u_1 = \theta_2, u_2 = \theta_3$. But the subsets $\mathcal{SD}(\theta_1, 1, 1)$, $\mathcal{SD}(0, \theta_2, 0)$ generate empty singular domains.

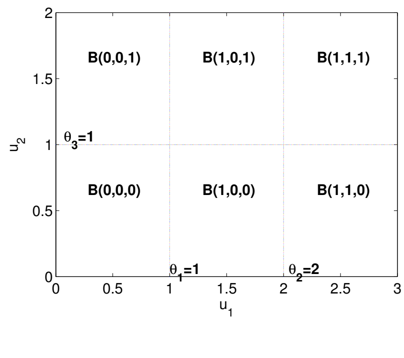

FIGURE 3.

System (4.1) can be regarded, at least in some situations, as a switching dynamical system. Inside any regular domain, it is an affine system of differential equations. Switching between domains can only occur if a trajectory hits a singular domain, usually a wall. But as it is demonstrated in [8], sliding modes can press trajectories into singular domains of lower dimensions as well. It is also shown in [8] that in such cases the dynamics cannot be described by a simple indication of how the system switches between the regular domains.

In the non-delay case walls can be either attractive ("black"), expelling ("white") or "transparent" (see [9]). In the delay case, walls can also be of a mixed type. That is why the properties of "blackness", "whiteness" and "transparency" can now only be described locally, i.e. without using the focal points as in the non-delay case (see [8]).

Consider the wall $\mathcal{SD}(\theta_\mu, B_R)$ which lies between the box $\mathcal{B}(B^0)$, where $Z_\mu = 0$, and the box $\mathcal{B}(B^1)$, where $Z_\mu = 1$. This gives two different systems (4.2): for $B = B^0$ and $B = B^1$, respectively. Let P be a point in a wall $\mathcal{SD}(\theta_\mu, B_R)$ and $u(t, \nu, P)$ be the solution to (4.2) with $B = B^\nu$, which satisfies $u(0, \nu, P) = P$ ($\nu = 0, 1$). Denote by $\dot{u}_\mu(0, Z, P)$ component of number μ (which is orthogonal to the wall $\theta = \theta_\mu$) of the velocity vector $\dot{u}_\mu(t, Z, P)$ at P for $t = 0$ ($Z = 0$ or 1).

Definition 4.7. A point $P \in \mathcal{SD}(\theta_\mu, B_R)$ is called

- "black" if $\dot{u}_\mu(0, 1, P) < 0$ and $\dot{u}_\mu(0, 0, P) > 0$;
- "white" if $\dot{u}_\mu(0, 1, P) > 0$ and $\dot{u}_\mu(0, 0, P) < 0$;
- "transparent" if $\dot{u}_\mu(0, 1, P) < 0$ and $\dot{u}_\mu(0, 0, P) < 0$, or if $\dot{u}_\mu(0, 1, P) > 0$ and $\dot{u}_\mu(0, 0, P) > 0$.

Definition 4.8. We say that a wall $\mathcal{SD}(\theta_\mu, B_R)$ is black (white, transparent) if any point in it, except for a nowhere dense set, is black (white, transparent).

Exceptional points correspond to the trajectories that are not transversal to the hyperplane $u_\mu = \theta_\mu$, i. e. where $\dot{u}_\mu = 0$.

Clearly, at any transparent point the solution to (4.1) can be extended to some neighborhood of this point. Thus, at transparent points System (4.1) can be characterized as a switching dynamical system. However, at black points the system is of a more complicated nature (see [8]).

5. Stationary points

We are studying the system of ordinary differential equations (3.34), which is equivalent to the delay system (1.1). The definitions from the previous section are now applied to (3.34) without further comments.

A very important advantage of the logoid nonlinearities, satisfying Assumptions 2.1-2.4, unlike more general sigmoid nonlinearities, satisfying Assumptions 2.1-2.3, is the localization principle. Roughly speaking we may remove all regular variables in the stability analysis, because they did not influence local properties of solutions around stationary points. This principle is of particular importance for delay systems (which are non-local). On the other hand, the localization principle helps to simplify both notation and proofs.

It is easy to define stationary points for this system if $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ are all smooth ($q_k > 0$). However, in this case the stability analysis and computer simulations may be cumbersome and time-consuming. To simplify the model, one uses the step functions $Z_k = \Sigma(y_{i(k)}, \theta_k, 0)$ and the corresponding limit system. The latter becomes, however, discontinuous if at least one y_i assumes one of its threshold values. If a stationary point of the limit system does not belong to the discontinuity set, then the analysis of the dynamics of the perturbed smooth systems ($q_k > 0,\ k = 1, \dots, m$) is almost trivial (see below). If, however, a (well defined) stationary point of the perturbed system approaches the discontinuity set of the limit system, the corresponding dynamics may be subject to irregularities, and on the other hand, an independent and verifiable definition of a (stable and unstable) stationary point of the limit system should be given. The natural idea is to replace the step functions $Z_k = \Sigma(y_{i(k)}, \theta_k, 0))$ with smooth functions $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ ($q_k > 0$, $k = 1, \dots, m$), which leads to the following formal definition.

Definition 5.1. A point $\hat{P}$ is called a stationary point for System (3.34) with $Z_k = \Sigma(y_{i(k)}, \theta_k, 0)$ ($k \in M$) if for any set of functions $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ ($k \in M$), satisfying Assumptions 2.1-2.4 from Section 2, there exist a number $\varepsilon > 0$ and points $P(q)$, $q = (q_1, \dots, q_m)$, $q_k \in (0, \varepsilon)$ ($k \in M$) such that

- $P(q)$ is a stationary point for System (3.34) with $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ ($k \in M$);
- $P(q) \to \hat{P}$ as $q \to 0$ (i.e. to the zero vector).

If the limit point $\hat{P}$ does not belong to the discontinuity set of System (3.34), i.e. if $y_{i(k)} \neq \theta_k$ ($k \in M$), then $\hat{P}$ simply becomes a conventional stationary point for the limit system.

To see it, we assume that $Z = B$ at $\hat{P}$ for some Boolean vector B. Then the coordinates of $\hat{P}$ satisfy

$$\begin{gathered} F_i(B) - G_i(B)x_i = 0 \quad (i \in N) \\ A_i v_i + \Pi_i(x_i) = 0. \end{gathered} \tag{5.1}$$

Here neither the delay operator $\Re$, nor the logoids $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ ($k \in M$, $q_k > 0$), satisfying Assumptions 2.1-2.4 from Section 2, influence the position of the stationary point.

Conversely, due to Assumption 2.4 we have that $Z_k = B_k$ at $\hat{P}$ for sufficiently small $q_k > 0$ and any $k \in M$. This is because $\hat{P}$ lies at a positive distance from the discontinuity set of the system. The smooth version of System (3.34) in the vicinity of $\hat{P}$ will just be equal to the limit system, so that $P(q) = \hat{P}$ for sufficiently small q.

Thus obtained $\hat{P}$ is called *regular stationary point* (RSP) (see [4], [9]). It is also easy to calculate this point (and by this also $P(q)$):

$$\begin{gathered} \hat{x}_i = F_i(B)G_i^{-1}(B), \\ \hat{v}_i = -(A_i)^{-1}\Pi_i(\hat{x}_i) \quad (i \in N) \end{gathered} \tag{5.2}$$

(the matrix A_i is given by (3.35) therefore it's invertible).

The situation is, however, different if $\hat{P}$ belongs to the discontinuity set. Such a $\hat{P}$ is called *singular stationary point* (SSP)(see [4], [9]). In this case we can only get rid of regular variables.

In quite a similar way, we can define the notion of a stable stationary point (see e.g. [6]).

Definition 5.2. A stationary point $\hat{P}$ for (3.34) with $Z_k = \Sigma(y_{i(k)}, \theta_k, 0)$ ($k \in M$) is called asymptotically stable if for any set of functions $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ ($k \in M$), satisfying Assumptions 2.1-2.4 from Section 2, there exist a number $\varepsilon > 0$ and points $P(q)$, $q = (q_1, \dots, q_m)$, $q_k \in (0, \varepsilon)$ ($k \in M$) such that

- $P(q)$ is a asymptotically stable stationary point for System (3.34) with $Z_k = \Sigma(y_{i(k)}, \theta_k, q_k)$ $(k \in M)$;
- $P(q) \to \hat{P}$ as $q \to 0$ (i.e. to the zero vector).

In what follows, a crucial role will be played by the Jacoby matrix $\frac{\partial}{\partial Z_S} F_S(Z) - \frac{\partial}{\partial Z_S} G_S(Z) y_{i(S)}$. The entry in the s-th row and the σ-th column of this matrix amounts $\frac{\partial}{\partial Z_\sigma} F_{i(s)}(Z) - \frac{\partial}{\partial Z_\sigma} G_{i(s)}(Z) y_{i(s)}$. In other words,

$$\begin{aligned} J_S(Z_S, B_R, y_{i(S)}) &= \frac{\partial}{\partial Z_S} F_S(Z_S, B_R) - \frac{\partial}{\partial Z_S} G_S(Z_S, B_R) y_{i(S)} \\ &= \Big[\frac{\partial}{\partial Z_\sigma} F_{i(s)}(Z_S, B_R) - \frac{\partial}{\partial Z_\sigma} G_{i(s)}(Z_S, B_R) y_{i(s)}\Big]_{s,\sigma \in S}. \end{aligned} \tag{5.3}$$

Using Remark 4.4 it is easy to see that if the singular domain $\mathcal{SD}(\theta_S, B_R)$ is not empty, then this Jacoby matrix is an $|S| \times |S|$-matrix.

Below we will use Proposition 7.4 from the paper [11]:

Proposition 5.3 ([11]). *Given arbitrary $i \in N$, $x_i, y_i \in \mathbb{R}$, the system*

$$\begin{gathered} A_i v_i + \alpha_i x_i \pi_i = 0 \\ {}^1 v_i = y_i, \end{gathered}$$

where A_i and π_i are defined by (3.35) and (3.36), respectively, has a solution ${}^1v_i, {}^2v_i, \dots, {}^pv_i$ if and only if $x_i = y_i$. In this case the solution is unique.

Theorem 5.4. *Assume that for some $S \subset M$ the system of algebraic equations*

$$\begin{gathered} F_{i(S)}(Z_S, B_R) - G_{i(S)}(Z_S, B_R)\theta_{i(S)} = 0, \\ F_{i(R)}(Z_S, B_R) - G_{i(R)}(Z_S, B_R) y_{i(R)} = 0 \end{gathered} \tag{5.4}$$

with the constraints

$$\begin{gathered} 0 < Z_s < 1 \quad (s \in S) \\ Z_r(y_{i(r)}) = B_r \quad (r \in R) \end{gathered} \tag{5.5}$$

has a solution $\hat{Z}_S := (\hat{Z}_s)_{s \in S}$, $\hat{y}_{i(R)} := (\hat{y}_{i(r)})_{r \in R}$, which, in addition, satisfies

$$\det J_S(\hat{Z}_S, B_R, \theta_S) \neq 0. \tag{5.6}$$

Then there exists a stationary point $\hat{P} \in \mathcal{SD}(\theta_S, B_R)$ for System (3.34). This point is independent of the choice of the delay operators $\Re_i$ given by (1.2).

Proof. The case of a box is formally included in the above theorem if we put $S = \emptyset$, but this case was already studied at the beginning of the section. Thus, we may restrict ourselves to the case of a singular domain. Let S be a nonempty subset of the set M.

First of all, we explain how to calculate the coordinates of the point $\hat{P}$. We put

(1) $\hat{x}_{i(r)} = \hat{y}_{i(r)}$, $Z_r(\hat{y}_{i(r)}) = B_r$ $(r \in R)$;
(2) $\hat{x}_s = \hat{y}_s = \theta_s$ $(s \in S)$.

The auxiliary coordinates can be obtained from the system

$$\begin{gathered} A_i v_i + \alpha_i \hat{x}_i \pi_i = 0 \\ {}^1 v_i = \hat{y}_i. \end{gathered} \tag{5.7}$$

This system satisfies the assumptions of Proposition 5.3, which gives a unique solution $\hat{v}_i$ to (5.7).

By this it is also shown that $\hat{P}$ belongs to the singular domain $\mathcal{SD}(\theta_S, B_R)$, this domain is nonempty and therefore satisfies the conditions listed in Remark 4.4. Let us also notice that according to this remark the mapping $s \mapsto i(s)$ is a bijection on the set S. Renumbering we may always assume that $i(s) = s$ for all $s \in S \subset N$.

In the sequel we write $F_S = (F_s)_{s\in S}$ and $G_S = \operatorname{diag}[G_s]_{s\in S}$, which is a diagonal matrix. Similarly, $F_R = (F_{i(r)})_{r\in R}$ and $G_R = \operatorname{diag}[G_{i(r)}]_{r\in R}$ (as variables y_i can have more than one thresholds, the mapping $r \mapsto i(r)$ is not necessarily bijective on R, nor is $r = i(r)$).

The idea of the proof (suggested in [11]) can be described as follows. First of all, we replace the step functions $Z_s = \Sigma(y_s, \theta_s, 0)$ by the smooth sigmoid functions $\Sigma(y_s, \theta_s, q_s)$, $q_s > 0$. Then, using the inverse sigmoid functions, we arrive at a system of functional equations w.r.t. Z_s which is resolved by the implicit function theorem. This gives the values of Z_s depending on the vector parameter $q = q_s$ ($q_s \geq 0$). Then we restore, step by step, the other variables, namely $y(q)$, $x(q)$ and finally, ${}^{\nu}v_i(q)$. All of them depend continuously on the parameter q. Letting q_s go to zero gives SSP in the wall $\mathcal{SD}(\theta_S, B_R)$.

To implement this idea we rewrite the stationarity conditions for the variables y_S in the matrix form. It gives

$$F_S(Z_S, B_R) - G_S(Z_S, B_R)y_S = 0, \tag{5.8}$$

which is an equation in $\mathbb{R}^S$. Originally, i. e. in (5.4), it was assumed that $y_S = \theta_S$. If the step functions are replaced by smooth sigmoid functions, then this equality may be violated. However, we may assume without loss of generality that the regular variables satisfy $Z_R = B_R$ for sufficiently small q (see Assumption 2.4).

Let $Z_S = \Sigma(y_S, \theta_S, q) := (\Sigma(y_s, \theta_s, q_s))_{s\in S}$, where $q_s > 0$. Due to Assumption 2.1 from Section 2 the inverse function $y_S = \Sigma^{-1}(Z_S, \theta_S, q)$ is continuously differentiable with respect to $Z_s \in (0,1)$, $s \in S$. Putting it into (5.8) produces

$$F_S(Z_S, B_R) - G_S(Z_S, B_R)\Sigma^{-1}(Z_S, \theta_S, q) = 0. \tag{5.9}$$

The Jacoby matrix of the left-hand side with respect to Z_S is equal to

$$\begin{aligned}&\frac{\partial}{\partial Z_S}F_S(Z_S, B_R) - \frac{\partial}{\partial Z_S}\big(G_S(Z_S, B_R)\big)\Sigma^{-1}(Z_S, \theta_S, q)\\ &- G_S(Z_S, B_R)\frac{\partial}{\partial Z_S}\big(\Sigma^{-1}(Z_S, \theta_S, q)\big).\end{aligned} \tag{5.10}$$

According to Assumptions 2.1-2.2 from Section 2 and assumptions on F, G listed in Introduction, this is a continuous function w.r.t. (Z_S, q), if $0 < Z_s < 1, 0 < q_s < q^0$. We let now q go to zero (i.e. to the zero-vector) and observe that for any Z_s, $0 < Z_s < 1$, $s \in S$ the last Jacoby matrix in (5.10) goes to the zero matrix in view of Assumption 2.3 from Section 2, while $\Sigma^{-1}(Z_S, \theta_S, q) \to \theta_S$ due to Proposition 2.5 part(1). In both cases the convergence is uniform on compact subsets of the set $\{Z_S : 0 < Z_s < 1, s \in S\}$. Thus, the Jacoby matrix becomes

$$\frac{\partial}{\partial Z_S}F_S(Z_S, B_R) - \frac{\partial}{\partial Z_S}G_S(Z_S, B_R)\theta_S \tag{5.11}$$

in the limit. The uniform convergence of the Jacoby matrix (on compact subsets of the set $\{Z_S : 0 < Z_s < 1, s \in S\}$) as $q_s \to 0$ implies that the left-hand side of Equation (5.9) is, in fact, continuous in (Z_S, q) and continuously differentiable w.r.t. Z_S on the set $0 < Z_s < 1$, $0 \leq q_s < q^0$ ($s \in S$). Remember that the solution $\hat{Z}_S$ of System (5.4) satisfies the constraints $0 < Z_s < 1$, too. Moreover, at $Z_S = \hat{Z}_S$, $q = 0$ and according to (5.3), the matrix, given by (5.11), is equal to $J_S(\hat{Z}_S, B_R, \theta_S)$. This matrix is invertible by (5.6). This allows for using the implicit function theorem yielding a continuous (in q) vector function $Z_S(q)$, where $0 \le q_s < \varepsilon$ for all $s \in S$ and some $\varepsilon > 0$. This function satisfies $0 < \hat{Z}_s < 1$ for all $s \in S$.

Now, put

$$\begin{gathered} x_s(q) = y_s(q) = \Sigma^{-1}(Z_S(q), \theta_s, q_s) \quad (s \in S) \\ x_{i(r)}(q) = y_{i(r)}(q) = F_{i(r)}(Z_S(q), B_R) G^{-1}_{i(r)}(Z_S(q), B_R) \quad (r \in R) \end{gathered} \tag{5.12}$$

and for an arbitrary $i \in N$ consider the following system for the auxiliary variables v_i:

$$\begin{gathered} A_i v_i + \Pi_i x_i(q) = 0 \\ {}^1 v_i = y_i(q), \end{gathered} \tag{5.13}$$

where

$$\Pi_i(x_i(q)) := \alpha_i x_i(q) \pi_i + {}^0 c_i f_i(Z_S(q), B_R, x_i(q))$$

and

$$f_i(Z_S(q), B_R, x_i(q)) = (F_i(Z_S(q), B_R) - G_i(Z_S(q), B_R) x_i(q), 0, \dots 0)^T.$$

By construction, $F_i(Z_S(q), B_R) - G_i(Z_S(q), B_R) x_i(q) = 0$ for all $i \in N$, so that

$$\begin{gathered} A_i v_i + \alpha_i x_i(q) \pi_i = 0 \\ {}^1 v_i = y_i(q). \end{gathered} \tag{5.14}$$

Applying again Proposition 5.3 gives the only solution $v_i(q)$ to (5.14).

By this, all the coordinates of the stationary point $P(q)$ for $q_s > 0$, $s \in S$ are calculated. Let now $q \to 0$. It is already shown that $Z_S(q) \to \hat{Z}_S$. Using again Proposition 2.5 part(1) gives

$$\hat{y}_S := \lim_{q \to 0} y_s(q) = \lim_{q \to 0} \Sigma^{-1}(Z_S(q), \theta_S, q) = \theta_S.$$

This and (5.12) justify also the equalities

$$\begin{gathered} \hat{x}_S := \lim_{q \to 0} x_S(q) = \lim_{q \to 0} y_S(q) = \theta_S, \\ \hat{y}_{i(R)} := \lim_{q \to 0} y_{i(R)}(q) = \lim_{q \to 0} x_{i(R)}(q) := \hat{x}_{i(R)}. \end{gathered}$$

Finally, $v_i(q) \to \hat{v}_i$ which solves Equation (5.7), where $\hat{x}_i = \hat{y}_i$ for all $i \in N$. By this, it is shown that the point $\hat{P}$, constructed at the very beginning of the proof, is the limit point for $P(q)$, $q \to 0$, the latter being stationary points for System (3.34) with $Z_s = \Sigma(y_s, \theta_s, q_s)$ ($q_s > 0$, $s \in S$). The proof is complete. □

Let Γ be a parameter space for System (5.4)-(5.5); i.e., Γ is the set of all polynomial coefficients F_i, G_i and thresholds θ_i such that

(1) $F_i > 0$, $G_i > 0$ for $0 < Z_k < 1$ and $\theta_k > 0$ ($k \in M$),

(2) $\theta_i > 0$.

The functions F_i, G_i are continuous in Z_k and θ_k. Therefore, if the number of parameters equals p, then Γ is an open subset of the space R^p.

Consider the subset $\Gamma_S \subset \Gamma$ (S is a fixed subset of M, B_R is a fixed Boolean vector, corresponding to the singular domain $\mathcal{SD}(\theta_S, B_R)$), such that there exists at least one solution to System (5.4)-(5.5). By $\Gamma^0_S \subset \Gamma_S$ we denote the set where $\det J_S(\hat{Z}_S, B_R, \theta_S) = 0$.

Theorem 5.5. *If $\mathcal{SD}(\theta_S, B_R) \neq \emptyset$, then $\Gamma_S - \Gamma_S^0$ is an open and dense subset of Γ_S.*

Proof. First let us prove that $\Gamma_S - \Gamma_S^0$ is open in Γ_S. Suppose we have (5.6) for some $\gamma_0 \in \Gamma_S$. Take $\gamma \in \Gamma_S$ to be sufficiently close to γ_0.

Using the implicit function theorem for the first equation of System (5.4), we observe that for any γ, which is sufficiently close to γ_0, the equation is solvable in the vicinity of $\hat{Z}_S$. Moreover, the condition (5.6) and the first condition in (5.5) are fulfilled. Let us denote this solution by $\hat{Z}_S(\gamma)$. Using the second equation in (5.4) we obtain $\hat{y}_{i(R)}(\gamma)$ from the formula

$$\hat{y}_{i(r)}(\gamma) = \frac{F_{i(r)}(\hat{Z}_S(\gamma), B_R)}{G_{i(r)}(\hat{Z}_S(\gamma), B_R)}.$$

The function $\hat{y}_{i(r)}(\gamma)$ is continuous in γ (we can use a smaller neighborhood of γ_0 if needed), therefore the second condition in (5.5) is fulfilled also. Thus, $\Gamma_S - \Gamma_S^0$ is open in Γ_S.

Now we will show that $\Gamma_S - \Gamma_S^0$ is dense in Γ_S. Let $\gamma_1 \in \Gamma_S$, $\hat{Z}_S$ be the corresponding solution of the first equation of System (5.4). Suppose that the condition (5.6) is not fulfilled for $\hat{Z}_S$ and that there exists a vicinity $\mathfrak{O}$ of γ_1 such that $\det J_S = 0$ for any $\gamma \in \mathfrak{O}$ and for any solution of System (5.4)-(5.5).

Put $\xi_s = Z_s - \hat{Z}_s$ $(s \in S)$. It follows from Remark 4.4 that $\mathcal{SD}(\theta_S, B_R) \neq 0$, so that i is an bijective function on S. It can be assumed that $i(s) = s$ for all $s \in S$ and $S = \{1, \dots, |S|\}$. Then the system

$$f_s(\xi_s) = F_s(\xi_s, B_R) - G_s(\xi_s, B_R)\theta_{i(s)} = 0$$

has a zero solution $\hat{\xi}_s$ $(s \in S)$. The first member of equation is an affine polynomial in $\hat{\xi}_s$ $(s \in S)$, i.e.

$$f_s(\xi_1, \dots, \xi_{|S|}) = a_{1s}\xi_1 + a_{2s}\xi_2 + \dots + a_{ss}\xi_s + \sum_{p \geq 2} A_{s_1 \dots s_p}\xi_{s_1} \dots \xi_{s_p}.$$

Obviously, $\det J_S(0, B_R, \theta_S) = \det(a_{ij})_{i,j \in S} = 0$.

Consider the perturbed coefficients $a_{ij} + \varepsilon_{ij}$ $(\varepsilon_{ij} \neq 0)$. In this case, $\hat{\xi}_s = 0$ is still a solution with the Jacoby matrix $J_{S,\varepsilon}(0, B_R, \theta_S) = (a_{ij} + \varepsilon_{ij})_{i,j \in S}$. We assumed before that $\det J_{S,\varepsilon} = 0$ for any sufficiently small ε_{ij} $(i, j \in S)$. However, it is well-known that in each neighborhood of a singular $n \times n$-matrix there exists a nonsingular matrix. This contradiction proves the theorem. □

Remark 5.6. Condition (5.6) guarantees the uniqueness of the solution $(\hat{Z}_S, \hat{y}_{i(R)})$ in its vicinity.

In a similar way, we define the notion of a stable stationary point (see e.g. [6]).

Remark 5.7. The coordinates $\hat{x}_i, \hat{y}_i, {}^\nu\hat{v}_i$ $(i \in N, \nu = 1, \dots, p)$ of the stationary point $\hat{P}$ for System (3.34) with $Z_i = \Sigma(y_i, \theta_i, 0)$ $(i \in N)$ satisfy

(1) $\hat{x}_{i(r)} = \hat{y}_{i(r)}$, $Z_r(\hat{y}_{i(r)}) = B_r$ $(r \in R)$;
(2) $\hat{x}_s = \hat{y}_s = \theta_s$ $(s \in S)$;
(3) $A_i\hat{v}_i + \alpha_i\pi_i\hat{x}_i = 0$ $(i \in N)$.

Example 5.8. Consider the delay equation

$$\dot{x} = 2 - 2Z - x$$
$$Z = \Sigma(y, 1, q)$$
$$y(t) = {}^0cx(t) + {}^1c\int_{-\infty}^{t} {}^1K(t-s)x(s)ds.$$

Assume that ${}^0c \geq 0$, ${}^0c + {}^1c = 1$, $q \geq 0$, $\Sigma(y, 1, q)$ is the logoid function, given in Example 2.7, and ${}^1K(u)$ is the weak generic delay kernel given by (1.5).

Using the non-delay representation (3.34), we obtain the system:

$$\dot{x} = 2 - 2Z - x$$
$${}^1\dot{v} = {}^0c\,(2 - 2Z - x) + \alpha x - \alpha \cdot {}^1v$$
$$Z = \Sigma(y, 1, q).$$

Let us apply Theorem 5.4 to this system. Solving the equation $2 - 2Z - 1 = 0$, corresponding to (5.4), we obtain $\hat{Z}_S = 0.5$, where we also have $\det J_S = -2 \neq 0$. Thus, the point $\hat{P}(1, 1)$ is SSP.

The coordinates of points $P(q)(x_k, y_k)$ can be found from the system

$$2 - 2\frac{(0.5 + \frac{y_k - 1}{2\delta(q_k)})^{\frac{1}{q_k}}}{(0.5 + \frac{y_k - 1}{2\delta(q_k)})^{\frac{1}{q_k}} + (0.5 - \frac{y_k - 1}{2\delta(q_k)})^{\frac{1}{q_k}}} - y_k = 0,$$
$$x_k = y_k,$$

where $q_k \in (0, \varepsilon)$ $(k \in M)$. Assume that $\delta(q_k) = q_k$. The relation between q_k and y_k is shown in Figure 4.

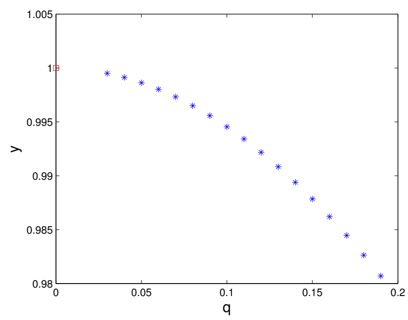

FIGURE 4.

Example 5.9. Consider the system

$$\dot{x_1} = Z_1 - Z_1Z_2 - \gamma_1 x_1$$
$$\dot{x_2} = 1 - Z_1Z_2 - \gamma_2 x_2$$
$$y_1 = x_1$$
$$y_2 = \int_{-\infty}^{t} {}^1K(t-s)x_2(s)ds,$$

where γ_1, γ_2, are positive parameters, $Z_i = \Sigma(x_i, \theta_i, q)$, $(q \geq 0)$, $(i = 1, 2)$ are logoid functions, given in Example 2.7. Assume that the thresholds $\theta_1 = \theta_2 = 1$ and the parameters $\gamma_1 = 0.6$, $\gamma_2 = 0.9$.

The model has four walls $\mathcal{SD}(1, \theta_2)$, $\mathcal{SD}(\theta_1, 1)$, $\mathcal{SD}(\theta_1, 0)$ and $\mathcal{SD}(0, \theta_2)$. Let us apply Theorem 5.4 to this system. For the first wall $\mathcal{SD}(1, \theta_2)$ System (5.4) will be

$$\begin{gathered} F_2(Z_2, 1) - G_2(Z_2, 1)\theta_2 = 0 \\ F_1(Z_2, 1) - G_1(Z_2, 1)\hat{y}_1 = 0, \end{gathered}$$

or

$$\begin{gathered} 1 - \hat{Z}_2 - 0.9\,\theta_2 = 0 \\ 1 - \hat{Z}_2 - 0.6\,\hat{y}_1 = 0. \end{gathered}$$

The solution $\hat{y}_1 = 1.5, \hat{Z}_2 = 0.1$ satisfies the constraints (5.5).

For $\mathcal{SD}(\theta_1, 1)$ System (5.4) becomes

$$\begin{gathered} 1 - \hat{Z}_1 - 0.9\,\hat{y}_2 = 0 \\ 1 - \hat{Z}_1 - 0.6\,\theta_1 = 0, \end{gathered}$$

but the solution $\hat{y}_2 = 0.6, \hat{Z}_1 = 0.4$ does not belong to this wall. The same conclusion holds for the singular domains $\mathcal{SD}(\theta_1, 0)$ and $\mathcal{SD}(0, \theta_2)$.

The Jacoby determinant (5.3) for the wall $\mathcal{SD}(1, \theta_2)$ will be

$$\det J_2(\hat{Z}_2, \theta_2) = \det\Big(\frac{\partial}{\partial Z_2} F_2(Z_2, 1) - \frac{\partial}{\partial Z_2} G_2(Z_2, 1) y_2\Big) = -1 \neq 0.$$

This means that, the system has one stationary point $\hat{P} \in \mathcal{SD}(1, \theta_2)$ for $q = 0$ (and thus stationary points for small $q > 0$) with the coordinates $x_1 = y_1 = 1.5$, $x_2 = y_2 = 1$.

6. Stability analysis and the localization principle

We study System (1.1) with the delay operator (1.2). According to our method, System (1.1) is replaced with System (3.34), which includes more variables. We should therefore justify that stability properties of (1.1) and (3.34) are the same.

We start with the formal definition of stability (instability) using the delay equation (3.11) and System (3.31). Equation (3.11) and System (3.31) are generalizations of (1.1) and (3.34), respectively.

Assume that $x(t) = 0$ is a solution of Equation (3.11) for $t \geq 0$. Obviously, $x(t) = 0,\ v(t) = 0$ will be a zero solution of System (3.31) for $t \geq 0$.

Definition 6.1. The zero solution of (3.11) is called exponentially stable if there exist $M > 0$, $\kappa > 0$, $\delta > 0$ such that

$$|x(t)| \leq M e^{-\kappa t} \sup_{\tau \leq 0} |\varphi(\tau)| \quad (t > 0) \tag{6.1}$$

for any measurable function $\varphi(\tau), \tau \leq 0$, which is the initial function for $x(t)$ (see (3.11)) satisfying the estimate

$$\sup_{\tau \leq 0} |\varphi(\tau)| < \delta.$$

Definition 6.2. The zero solution of (3.31) is called exponentially stable if there exist $M > 0$, $\kappa > 0$, $\delta > 0$ such that

$$|x(t)| + |v(t)| \le Me^{-\kappa t}(|x(0)| + |v(0)|) \quad (t > 0) \tag{6.2}$$

where $|x(0)| < \delta$, $|v(0)| < \delta$.

Definition 6.3. The zero solution of (3.11) is stable if for any $\varepsilon > 0$ there exists $\delta > 0$ such that

$$\sup_{t>0} |x(t)| < \varepsilon \tag{6.3}$$

as soon as

$$\sup_{\tau \le 0} |\varphi(\tau)| < \delta,$$

where $\varphi(\tau)$ is the initial function for $x(t)$.

Definition 6.4. The zero solution of (3.31) is stable if for any $\varepsilon > 0$ there exists $\delta > 0$ such that

$$|x(t)| + |v(t)| < \varepsilon \tag{6.4}$$

as soon as $|x(0)| < \delta$, $|v(0)| < \delta$.

Theorem 6.5. *Suppose that $x(t) = 0$ is a solution of Equation (3.11), where f satisfies the conditions (C1)-(C3) from Subsection 3.2 and $\Re$ is given by (3.14)-(3.16). Then the exponential stability (instability) of $x(t) = 0$ is equivalent to the exponential stability (instability) of the zero solution of System (3.31), where A, $\tilde{\pi}$ are given by (3.24) and (3.30), respectively.*

Proof. First we consider the case of exponential stability. Assume that the solution $(x(t), v(t))$ of (3.31) satisfies (6.2). The matrix A is stable ($\operatorname{Re}\lambda \le -\kappa_1$ for all eigenvalues of the matrix A, ($\kappa_1 > 0$)). Then we have

$$\|e^{At}\| \le Ne^{-\kappa_1 t} \ \ (t \ge 0). \tag{6.5}$$

Put $\delta_1 = \frac{\delta\kappa_1}{\|\tilde{\pi}\| N}$, where $\delta > 0$, such as we have (6.2) while $|x(0)| < \delta$, $|v(0)| < \delta$. If

$$\sup_{\tau \le 0} |\varphi(\tau)| \le \delta_1,$$

then (3.31) gives

$$\begin{aligned} |x(t)| \le |x(t)| + |v(t)| &\le Me^{-\kappa t}(|x(0)| + |v(0)|) \\ &\le Me^{-\kappa t}(|\varphi(0)| + \frac{N\|\tilde{\pi}\|}{\kappa_1} \sup_{\tau \le 0} |\varphi(\tau)|) \\ &= \bar{M}e^{-\kappa t} \sup_{\tau \le 0} |\varphi(\tau)|, \end{aligned}$$

since $x(0) = \varphi(0)$, $|x(0)| < \delta$, $|v(0)| < \delta$ and

$$|v(0)| \le \frac{N\|\tilde{\pi}\|}{\kappa_1} \sup_{\tau \le 0} |\varphi(0)|.$$

Therefore, the solution $x(t)$ of (3.31) satisfies (6.1).

Now assume that we have the estimate (6.1) for the solution $x(t)$. Using (3.29) we obtain

$$\begin{aligned}
&|x(t)| + |v(t)| \\
&\le Me^{-\kappa t} \sup_{\tau \le 0} |\varphi(\tau)| + |e^{A^T t} v(0)| + \Big| \int_0^t e^{A^T (t-s)} \tilde{\pi} x(s) ds \Big| \\
&\le Me^{-\kappa t} \sup_{\tau \le 0} |\varphi(\tau)| + Ne^{-\kappa_1 t} |v(0)| + \int_0^t e^{-\kappa_1 (t-s)} \|\tilde{\pi}\| M e^{-\kappa s} ds \cdot \sup_{\tau \le 0} |\varphi(\tau)| \\
&\le Me^{-\kappa t} \sup_{\tau \le 0} |\varphi(\tau)| + \frac{\|\tilde{\pi}\| M}{|\kappa - \kappa_1|} |e^{-\kappa_1 t} - e^{-\kappa t}| \sup_{\tau \le 0} |\varphi(\tau)| + Ne^{-\kappa_1 t} |v(0)|.
\end{aligned}$$

(we may assume that $\kappa \neq \kappa_1$, otherwise we can use a smaller κ_1). Taking $\bar{\kappa} = \min\{\kappa, \kappa_1\} > 0$ we arrive at

$$|x(t)| + |v(t)| \le \bar{M} e^{-\bar{\kappa} t} \sup_{\tau \le 0} |\varphi(\tau)| + Ne^{-\kappa_1 t} |v(0)|.$$

The last estimate holds for any φ which gives the solution $x(t)$ of Equation (3.11). However, another φ may give the same solution $x(t)$, $t \ge 0$. Let us use this fact.

Equation (3.11) and System (3.31) are equivalent. Thus, $\varphi_1(\tau)$ and $\varphi_2(\tau)$ give the same solution $x(t)$ of Equation (3.11) if and only if $\varphi_1(0) = \varphi_2(0)$ $(= x(0))$ and $\int_0^\infty e^{\tilde{A}\tau} \varphi_1(-\tau) d\tau = \int_0^\infty e^{\tilde{A}\tau} \varphi_2(-\tau) d\tau$ $(= v(0))$, as the pair $(x(0), v(0))$ completely determines the solution of System (3.31).

Let $\varphi(\tau)$ is equal to a constant vector φ_0 on the interval $(-\infty, 0)$ and $\varphi(0) = x(0)$. Also assume that φ_0 satisfies the equation

$$v(0) = \int_0^\infty e^{\tilde{A}\tau} \tilde{\pi} \varphi_0 d\tau = \bar{A} \tilde{\pi} \varphi_0,$$

where $\bar{A} = \int_0^\infty e^{\tilde{A}\tau} d\tau$.

According to (3.32), all eigenvalues of the matrix A are equal to $\int_0^\infty e^{-\alpha t} dt = \frac{1}{\alpha} \neq 0$. Thus, $\bar{A}$ is an invertible matrix. Let $\tilde{\pi}^\sharp$ be a left inverse matrix to $\tilde{\pi}$. Assume that $\varphi_0 = \pi^\sharp \bar{A}^{-1} v(0)$, so that

$$\begin{aligned}
\sup_{s \le 0} |\varphi(s)| &= \max\{|\varphi_0|; |x(0)|\} \\
&\le \max\{\|\pi^\sharp\| \cdot \|\bar{A}^{-1}\| \cdot |v(0)|; |x(0)|\} \\
&\le c_1(|v(0)| + |x(0)|).
\end{aligned}$$

Substituting φ just defined we obtain

$$\begin{aligned}
|x(t)| + |v(t)| &\le \bar{M} e^{-\bar{\kappa} t} c_1(|v(0)| + |x(0)|) + Ne^{-\kappa t} |v(0)| \\
&\le M_2 e^{-\bar{\kappa} t} (|v(0)| + |x(0)|), \quad t \ge 0
\end{aligned}$$

for sufficiently small $|v(0)|$ and $|x(0)|$. This gives the estimate (6.2).

Continuing the proof of the theorem we look now at the property of instability. If the zero solution $x(t)$ of System (3.11) is unstable then, obviously, the zero solution of System (3.31) is unstable as well, since $x(t)$ is part of this solution.

Assume that the zero solution of System (3.31) is unstable. Suppose that this solution is stable in the first component, i.e. the relation (6.3) is satisfied. From

(3.29) and (6.5) we obtain

$$\begin{aligned}|v(t)| &\le Ne^{-\kappa t}|v(0)| + \int_0^t Ne^{-\kappa_1(t-s)}\|\tilde\pi\|\varepsilon ds\\ &\le Ne^{-\kappa t}|v(0)| + \frac{\varepsilon\|\tilde\pi\|N}{\kappa_1}(1-e^{-\kappa_1 t})\\ &< Ne^{-\kappa t}|v(0)| + \frac{\varepsilon\|\tilde\pi\|N}{\kappa_1}\end{aligned}$$

for

$$\sup_{\tau\le 0}|\varphi(\tau)| < \delta.$$

Letting $\varepsilon_1 > 0$ be fixed, let us choose ε such that $\frac{\varepsilon\|\tilde\pi\|N}{\kappa_1} < \frac{\varepsilon_1}{2}$ and construct δ such that the estimate (6.3) holds for this ε. Moreover, assume that $\delta < \frac{\varepsilon}{2N}$. Now for any $v(0)$ and $x(0)$, satisfying $|x(0)| < \delta$ and $|v(0)| < \delta$, we get $|v(t)| < \varepsilon_1$ for all $t > 0$. It means that the zero solution is stable in both components. This contradiction completes the proof. □

Let us now formulate a stability result for System (1.1) with Z_k given by the logoid function ($k = 1,\dots,m$). Let $S \subset M$ and B_R be fixed. We are looking for SSP in the singular domain $\mathcal{SD}(S, B_R)$. Assume that the conditions of Theorem 5.4 are fulfilled, i.e. there exists an isolated stationary point $\hat P \in \mathcal{SD}(S, B_R)$.

Consider the reduced system

$$\begin{gathered}\dot{\mathbf{x}}_s = \mathbf{F}_s(\mathbf{Z}_s) - \mathbf{G}_s(\mathbf{Z}_s)\mathbf{x}_s\\ \mathbf{Z}_s = \Sigma(\mathbf{y}_s, \theta_s, q_s)\\ \mathbf{y}_s(t) = (\Re_s x_s)(t), \quad (s\in S),\end{gathered} \tag{6.6}$$

where $\mathbf{F}_s(\mathbf{Z}_s) = F_{i(s)}(Z_s, B_R)$, $\mathbf{G}_s(\mathbf{Z}_s) = G_{i(s)}(Z_s, B_R)$.

Theorem 6.6 (localization principle)**.** *Suppose that the conditions of Theorem 5.4 are fulfilled. Then System (6.6) has an isolated stationary point* $\hat{\mathbf{P}}$*. The point* $\hat{\mathbf{P}}$ *is asymptotically stable (unstable) if and only if* $\hat P$ *is asymptotically stable (unstable) for System* (1.1)*.*

Proof. We use Theorem 5.4, where we put $S = N$, $R = \emptyset$, $i(s) = s$, $\hat{\mathbf{Z}}_\mathbf{s} = \hat Z_s$ and obtain a condition of existence of SSP for System (6.6). According to Theorem 6.5, it is equivalent to study stability properties of this point for System (1.1) and for System (3.34).

According to Proposition 7.4 from the paper [11] , we have that $\hat x_i = \hat y_i$ for a stationary point. Therefore, $x_i(q)$ is close to $y_i(q)$ for a small q. Then $\Sigma(y_{i(r)}, \theta_r, q_r) = B_r$ for all $r \in R$ and System (3.34) becomes quasi-triangular:

$$\begin{gathered}\dot\xi = A(\xi),\\ \dot\eta = B(\xi,\eta),\end{gathered} \tag{6.7}$$

where $\xi = (x_S, v_S)^T$, $\eta = (x_{i(R)}, v_{i(R)})^T$,

$$A(\xi) = (F_S(Z_S, B_R) - G_S(Z_S, B_R)x_S; A_S v_S + \Pi_S(x_S))^T,$$

$$B(\xi,\eta) = (F_{i(R)}(Z_S, B_R) - G_{i(R)}(Z_S, B_R)x_{i(R)}; A_{i(R)}v_{i(R)} + \Pi_{i(R)}(x_{i(R)}))^T.$$

Clearly, the first equation coincides with System (6.6). Assume that the stationary point $\hat{\mathbf{P}}$ for (6.6) is asymptotically stable. According to Theorem 5.4 the stationary point $\hat{P}$ of System (6.7) is $\hat{P} = (\hat{\mathbf{P}}, \hat{Q})$, where $\hat{Q}$ is a coordinate vector corresponding to η.

Since System (6.6) is asymptotically stable and the matrix A is differentiable, the zero solution of the linearized equation is asymptotically stable, as well. Let us linearize the whole System (6.7) around the stationary point $\hat{P}$. Clearly, the Jacoby matrix there will be quasi-triangular. This implies that it is sufficient to check stability properties of the second quasi-diagonal matrix. It is, however, easy to see that this matrix coincides with the stable matrix $A_{i(R)}$ given by (3.35).

Thus, the whole matrix A is stable too, so that the solution $\hat{P}$ of System (6.7) is asymptotically stable, i.e. the stationary solution of System (1.1) is asymptotically stable, as well (in fact, exponential stable).

If the stationary solution of (6.6) is unstable then the stationary solution of (6.7) is unstable a fortiori. □

Example 6.7. Consider the system from Example 5.8. The reduced system in the wall $\mathcal{SD}(1, \theta_2)$ will be

$$
\begin{aligned}
\dot{x_1} &= 1 - Z_2 - 0.6x_1, \\
\dot{x_2} &= 1 - Z_2 - 0.9x_2, \\
y_2 &= \int_{-\infty}^{t} {}^1K(t-s)x_2(s)ds.
\end{aligned}
$$

Using Theorem 5.4 to find a stationary point, we obtain the following system:

$$
\begin{aligned}
1 - \hat{Z}_2 - 0.9\,\theta_2 &= 0 \\
1 - \hat{Z}_2 - 0.6\,\hat{y}_1 &= 0.
\end{aligned}
$$

Solving this system, we get the same solution $\hat{y}_1 = 1.5$, $\hat{Z}_2 = 0.1$ as in Example 5.8.

Remark 6.8. The reduced system for System (3.34) is given by

$$
\begin{aligned}
\dot{\mathbf{x}}_s(t) &= \mathbf{F}_s(\mathbf{Z}_s) - \mathbf{G}_s(\mathbf{Z}_s)\mathbf{x}_s(t) \\
\dot{\mathbf{v}}_s(t) &= A_s\mathbf{v}_s(t) + \mathbf{\Pi}_s(\mathbf{x}_s(t)), \quad t > 0 \\
\mathbf{Z}_s &= \Sigma(\mathbf{y}_s, \theta_s, q_s), \quad \mathbf{y}_s = {}^1\mathbf{v}_s \quad ,
\end{aligned}
\tag{6.8}
$$

where $\mathbf{x}_s = x_{i(s)}$, $\mathbf{v}_s = v_{i(s)}$, $\mathbf{F}_s(\mathbf{Z}_s) = F_{i(s)}(Z_s, B_R)$, $\mathbf{G}_s(\mathbf{Z}_s) = G_{i(s)}(Z_s, B_R)$ $(i = 1, \dots, n,\ s = 1, \dots, \sigma,\ \sigma = |S|)$.

Notice that this reduced system is equal to the reduced system (6.6). Then the Jacoby matrix for System (6.6) will be

$$
J := \begin{pmatrix}
XX & XV_1 & XV_2 & XV_3 & \dots & XV_\sigma \\
V_1X & V_1V_1 & V_1V_2 & V_1V_3 & \dots & V_1V_\sigma \\
V_3X & V_3V_1 & V_3V_2 & V_3V_3 & \dots & V_3V_\sigma \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
V_\sigma X & V_\sigma V_1 & V_\sigma V_2 & V_\sigma V_3 & \dots & V_\sigma V_\sigma
\end{pmatrix},
\tag{6.9}
$$

where

$$
XX := \begin{pmatrix}
-g_1 & 0 & 0 & \dots & 0 \\
0 & -g_2 & 0 & \dots & 0 \\
0 & 0 & -g_3 & \dots & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & 0\dots & -g_\sigma
\end{pmatrix},
$$

$$V_jV_j := \begin{pmatrix} -\alpha_j + {}^0c_jJ_j & \alpha_j & 0 & \dots & 0 \\ 0 & -\alpha_j & \alpha_j & \dots & 0 \\ 0 & 0 & -\alpha_j & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0\dots & -\alpha_j \end{pmatrix},$$

$V_jV_k = \emptyset$ if $j \neq k$ $(j,k = 1,\dots,\sigma)$,

$$XV_1 := \begin{pmatrix} J_1 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0\dots & 0 \end{pmatrix}, \quad XV_2 := \begin{pmatrix} 0 & 0 & 0 & \dots & 0 \\ 0 & J_2 & 0 & \dots & 0 \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0\dots & 0 \end{pmatrix}, \dots,$$

$$XV_\sigma := \begin{pmatrix} 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & \dots & 0 \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0\dots & J_\sigma \end{pmatrix}, \quad V_1X := \begin{pmatrix} a_1 & 0 & 0 & \dots & 0 \\ \alpha_1\,{}^2c_1 & 0 & 0 & \dots & 0 \\ \alpha_1\,{}^3c_1 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \alpha_1\,{}^pc_1 & 0 & 0 & 0\dots & 0 \end{pmatrix},$$

$$V_2X := \begin{pmatrix} 0 & a_2 & 0 & \dots & 0 \\ 0 & \alpha_2\,{}^2c_2 & 0 & \dots & 0 \\ 0 & \alpha_2\,{}^3c_2 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \alpha_2\,{}^pc_2 & 0 & 0\dots & 0 \end{pmatrix}, \dots, V_\sigma X := \begin{pmatrix} 0 & 0 & 0 & \dots & a_\sigma \\ 0 & 0 & 0 & \dots & \alpha_\sigma\,{}^2c_\sigma \\ 0 & 0 & 0 & \dots & \alpha_\sigma\,{}^3c_\sigma \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0\dots & \alpha_\sigma\,{}^pc_\sigma \end{pmatrix},$$

$J_s = (\frac{\partial}{\partial \mathbf{Z}_s}\mathbf{F}_s(\mathbf{Z}_s) - \mathbf{x}_s\frac{\partial}{\partial \mathbf{Z}_s}\mathbf{G}_s(\mathbf{Z}_s))\frac{\partial \mathbf{Z}_s}{\partial y_s}$, $a_s = \alpha_s({}^0c_s + {}^1c_s) - \mathbf{G}_s(\mathbf{Z}_s){}^0c_s$, $g_s = \mathbf{G}_s(Z_s)$, $(s = 1,\dots,\sigma,\ \ \sigma = |S|)$.

7. Stability analysis of SSP in the black wall

In Section 4 we mentioned that the system can have 3 types singular domains (white, black and transparent). In this section we study a stable singular points therefore we will focus only on stationary points in the black wall.

In the non-delay case any regular stationary point is always asymptotically stable as soon as it exists. This is due to the assumptions $G_i > 0$. Stability of the matrix $J_S(Z_S, B_R, \theta_S)$ (see (5.3)) provides, then, asymptotic stability of singular stationary points (see e.g. [10] for delays).

Including delays leads to more involved stability conditions. We study here Equation (3.1)

$$\begin{gathered} \dot{x}(t) = F(Z) - G(Z)x(t) \\ Z = \Sigma(y,\theta,q) \\ y(t) = (\Re x)(t) \quad (t \geq 0) \end{gathered}$$

with the delay operator given by (3.2)

$$(\Re x)(t) = {}^0cx(t) + \int_{-\infty}^{t} K(t-s)x(s)ds, \quad t \geq 0,$$

where $K(u) = {}^1c \cdot {}^1K(u) + {}^2c \cdot {}^2K(u)$, ${}^\nu c \geq 0$ $(\nu = 0,1,2)$, ${}^0c + {}^1c + {}^2c = 1$.

According to the localization principle presented in the previous section the stability analysis below is, in fact, valid for an arbitrary number of genes x_i, where only one gene x becomes activated (i.e. y assumes its threshold value) at any time. Applying the generalized linear chain trick, we arrive at System (3.5)

$$\begin{aligned}\dot{x} &= F(Z) - G(Z)x\\ {}^1\dot{v} &= {}^0c\,(F(Z) - G(Z)x) + \alpha x({}^0c + {}^1c) - \alpha\cdot{}^1v + \alpha\cdot{}^2v\\ {}^2\dot{v} &= \alpha\cdot{}^2c\,x - \alpha\cdot{}^2v,\end{aligned}$$

where $Z = \Sigma(y, \theta, q)$. The equivalence of Systems (3.1) and (3.5) is a particular case of equivalence of Systems (1.1) and (3.34) (or, in general, Systems (3.11) and (3.34)).We first present two theorems.

Theorem 7.1. *Let ${}^0c > 0$ in (3.2) and let the equation*

$$F(Z) - G(Z)\theta = 0 \tag{7.1}$$

have a solution ${}^0Z$ satisfying $0 < {}^0Z < 1$.

Then the point $\hat{P}({}^0x, {}^0({}^1v), {}^0({}^2v))$, where ${}^0x = {}^0({}^1v) = \theta$, ${}^0({}^2v) = {}^2c\,\theta$, will be asymptotically stable if $D < 0$, and unstable if $D > 0$, where

$$D = F'(Z) - G'(Z)\theta \tag{7.2}$$

is independent of Z (as both F and G are affine).

Proof. In the course of the proof we keep fixed an arbitrary logoid function $Z = \Sigma(y, \theta, q)$, $q > 0$, satisfying Assumptions 2.1-2.4. Let $P(q)(x(q), {}^1v(q), {}^2v(q))$ be the corresponding approximating stationary points from Definition 5.2, which converge to $\hat{P}$ as $q \to 0$. (Below $y(q)$ replaces ${}^1v(q)$ to simplify the notation.) Then

$$Z(q) := \Sigma(y(q), \theta, q) \to \Sigma({}^0y, \theta, 0) := \hat{Z}$$

due to Assumption 2.1. As $P(q)$ is a stationary point for (3.1) with $Z = \Sigma(y, \theta, q)$ for sufficiently small $q > 0$, we have $F(Z(q)) - G(Z(q))x(q) = 0$. Letting $q \to +0$, we obtain the equality $F(\hat{Z}) - G(\hat{Z})\theta = 0$. From the assumptions of the theorem it follows, however, that $F({}^0Z) - G({}^0Z)\theta = 0$. As the functions $F(Z)$ and $G(Z)$ are affine in Z, the function $F(Z) - G(Z)\theta$ is affine as well and, moreover, it is not constant because $\det D \neq 0$. This implies that $\hat{Z} = {}^0Z$. In particular,

$$Z(q) = \Sigma(y(q), \theta, q) \to {}^0Z \quad (q \to 0). \tag{7.3}$$

According to Definition 5.2, we have to look at the Jacoby matrix $J(q)$ of the smooth system (3.1) with $Z = \Sigma(y, \theta, q)$, $q > 0$, evaluated at the stationary point $P(q)$. Evidently,

$$J(q) := \begin{pmatrix} -g(q) & D(q)d(q) & 0\\ \alpha({}^0c + {}^1c) - {}^0cg(q) & -\alpha + {}^0cD(q)d(q) & \alpha\\ \alpha\,{}^2c & 0 & -\alpha \end{pmatrix}, \tag{7.4}$$

where we, to simplify the notation, put

$$g(q) := G(Z(q)), \quad D(q) := F'(Z(q)) - G'(Z(q))x(q), \quad d(q) := \frac{\partial\Sigma}{\partial y}(y(q), \theta, q). \tag{7.5}$$

Clearly,

$$g(q) \to G({}^0Z), \quad D(q) \to D, \quad d(q) \to +\infty \tag{7.6}$$

as $q \to 0$.

The challenge is to study spectral properties of the matrix $J(q)$ as $q \to 0$. This is done in the paper [12]. The final result says that if $D < 0$, then the matrix $J(q)$ is stable for small positive q, and if $D > 0$, then the matrix $J(q)$ is unstable for small positive q. This completes the proof of the theorem. □

Theorem 7.2. *Let* ${}^0c = 0$ *in (3.2) and let the equation (7.1) have a solution* ${}^0Z$ *satisfying* $0 <{}^0Z < 1$.

Then the point $\hat{P}({}^0x, {}^0({}^1v), {}^0({}^2v))$, *where* ${}^0x = {}^0({}^1v) = \theta$, ${}^0({}^2v) = {}^2c\,\theta$, *has the following properties*

1. *If* $D > 0$, *then* $\hat{P}$ *is unstable.*
2. *If* $D < 0$, ${}^1c = 0$, *then* $\hat{P}$ *is unstable.*
3. *If* $D < 0$, ${}^1c \neq 0$ *and* $G({}^0Z) < \alpha({}^1c)^{-1}(1 - 2\,{}^1c)$, *then* $\hat{P}$ *is unstable.*
4. *If* $D < 0$, ${}^1c \neq 0$ *and* $G({}^0Z) > \alpha({}^1c)^{-1}(1 - 2\,{}^1c)$, *then* $\hat{P}$ *is asymptotically stable spiral point.*

Here D *is again given by (7.2).*

Proof. Setting ${}^0c = 0$ in (7.4) produces

$$J(q) = \begin{pmatrix} -g(q) & D(q)d(q) & 0 \\ \alpha \cdot {}^1c & -\alpha & \alpha \\ \alpha \cdot {}^2c & 0 & -\alpha \end{pmatrix}, \tag{7.7}$$

which has no limit as $q \to 0$.

The asymptotical analysis of the matrix $J(q)$ yields the following (see [12]): if $D < 0$, ${}^1c \neq 0$ and $\alpha({}^1c)^{-1}(1 - 2\,{}^1c) < G({}^0Z)$, then the matrix $J(q)$ is stable for small positive q. If one of the above inequalities changes, then the matrix $J(q)$ is unstable for small positive q. This gives the result described in the theorem. □

The two theorems are used to study System (1.1), where $\Re$ is given by (3.2).

Corollary 7.3. *Assume that* ${}^0c > 0$ *in (3.2) and that for some finite sequence* B_i $(i = 2, \dots n)$ *consisting of* 0 *or* 1 *the system*

$$\begin{gathered} F_1(Z_1, B_R) - G_1(Z_1, B_R)\theta_1 = 0 \\ 0 < Z_1 < 1 \\ \Sigma(x_i, \theta_1, 0) = B_i \quad (i \geq 2) \end{gathered} \tag{7.8}$$

has a solution ${}^0Z_1$, ${}^0x_i$ $(i \geq 2)$.

Then the point $\hat{P} = ({}^0x_1, \dots, {}^0x_n, {}^0({}^1v), {}^0({}^2v))$, *where* ${}^0x_1 = {}^0({}^1v) = \theta_1$ *and* ${}^0({}^2v) = {}^2c\,\theta_1$, *is an asymptotically stable SSP for System (3.34) with* $Z_i = \Sigma(y_i, \theta_i, 0)$ $(i = 1, \dots, n)$ *if* $\bar{D} < 0$. *If* $\bar{D} > 0$, *then SSP* $\hat{P}$ *is unstable.* $\bar{D}$ *is given by*

$$\bar{D} = \frac{\partial}{\partial Z_1} F_1(Z_1, B_R) - \frac{\partial}{\partial Z_1} G_1(Z_1, B_R).$$

Corollary 7.4. *Assume that* ${}^0c = 0$ *in (3.2) and that for some finite sequence* B_i $(i = 2, \dots n)$ *consisting of* 0 *or* 1 *the system (7.8) has a solution* ${}^0Z_1$, ${}^0x_i$ $(i \geq 2)$.

Then the point $\hat{P} = ({}^0x_1, \dots, {}^0x_n, {}^0({}^1v), {}^0({}^2v))$, *where* ${}^0x_1 = {}^0({}^1v) = \theta_1$ *and* ${}^0({}^2v) = {}^2c\,\theta_1$ *is an unstable SSP for System (3.34) with* $Z_i = \Sigma(y_i, \theta_i, 0)$ $(i = 1, \dots, n)$ *in the following cases:*

1. *If* $\bar{D} > 0$.
2. *If* $\bar{D} < 0$, ${}^1c = 0$.

(3) *If* $\bar{D} < 0$, ${}^1c \neq 0$ *and* $G({}^0Z_1) < \alpha({}^1c)^{-1}(1 - 2\,{}^1c)$.

If $\bar{D} < 0$, ${}^1c \neq 0$ *and* $G({}^0Z_1) > \alpha({}^1c)^{-1}(1 - 2\,{}^1c)$, *then* $\hat{P}$ *is an asymptotically stable SSP.*

The proof of Corollaries 7.3 and 7.4 is followed from Theorems 6.6, 7.1 and 7.2.

Let consider now a more general case. We study System (3.1) with the delay operator

$$(\Re x)(t) = {}^0c x(t) + \int_{-\infty}^{t} K(t-s)x(s)ds, \quad t \geq 0, \tag{7.9}$$

where

$$K(u) = \sum_{\nu=1}^{n} {}^{\nu}c \cdot {}^{\nu}K(u)\,, \tag{7.10}$$

$${}^{\nu}K(u) = \frac{\alpha^{\nu} \cdot u^{\nu-1}}{(\nu-1)!} e^{-\alpha u}\,. \tag{7.11}$$

The coefficients ${}^{\nu}c$ $(\nu = 0, \dots, n)$ are real nonnegative numbers satisfying $\sum_{\nu=0}^{n} {}^{\nu}c = 1$. It is also assumed that $\alpha > 0$. Let us put

$${}^{\nu}w(t) = \int_{-\infty}^{t} {}^{\nu}K(t-s)x(s)ds, \tag{7.12}$$

where $t \geq 0$.

Below we summarize the ideas we presented in Section 3. Let us put

$${}^1v = {}^0cx + \sum_{\nu=1}^{n} {}^{\nu}c \cdot {}^{\nu}w, \quad {}^{\nu}v = \sum_{j=1}^{n-\nu+1} {}^{j+\nu-1}c \cdot {}^{j}w \quad (\nu = 2, \dots, n). \tag{7.13}$$

In particular, ${}^nv = {}^nc \cdot {}^1w$. Then

$$\begin{gathered} \dot{x}(t) = F(Z) - G(Z)x(t) \\ \dot{\mathbf{v}}(t) = A\mathbf{v}(t) + \Pi(x(t)), \quad t > 0 \\ Z = \Sigma(y, \theta, q), \quad y = {}^1v, \end{gathered} \tag{7.14}$$

where

$$A = \begin{pmatrix} -\alpha & \alpha & 0 & \dots & 0 \\ 0 & -\alpha & \alpha & \dots & 0 \\ 0 & 0 & -\alpha & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 0 & -\alpha \end{pmatrix}, \mathbf{v} = \begin{pmatrix} {}^1v \\ {}^2v \\ \vdots \\ {}^nv \end{pmatrix}, \tag{7.15}$$

and

$$\mathbf{\Pi}(x) := \alpha x \pi + {}^0c\, \mathbf{f}(Z, x) \tag{7.16}$$

with

$$\pi = \begin{pmatrix} {}^0c + {}^1c \\ {}^2c \\ \vdots \\ {}^nc \end{pmatrix}, \quad \mathbf{f}(Z, x) := \begin{pmatrix} F(Z) - G(Z)x \\ 0 \\ \vdots \\ 0 \end{pmatrix}. \tag{7.17}$$

In this case we get the system of ordinary differential equations:

$$\begin{aligned}
\dot{x} &= F(Z) - G(Z)x \\
{}^1\dot{v} &= {}^0c\,(F(Z) - G(Z)x) + \alpha x({}^0c + {}^1c) - \alpha\cdot{}^1v + \alpha\cdot{}^2v \\
{}^2\dot{v} &= \alpha\cdot{}^2cx - \alpha\cdot{}^2v + \alpha\cdot{}^3v \\
{}^3\dot{v} &= \alpha\cdot{}^3cx - \alpha\cdot{}^3v + \alpha\cdot{}^4v, \\
&\dots \\
{}^{n-1}\dot{v} &= \alpha\cdot{}^{n-1}c\,x - \alpha\cdot{}^{n-1}v + \alpha\cdot{}^nv, \\
{}^n\dot{v} &= \alpha\cdot{}^ncx - \alpha\cdot{}^nv,
\end{aligned} \tag{7.18}$$

where $Z = \Sigma(y, \theta, q)$. In this case, $\sum_{k=0}^{n} {}^kc = 1$. This system is equivalent to (3.1).

Consider the Jacoby matrix of System (7.18) to study the asymptotical stability of System (3.1). The $(n+1)\times(n+1)$ Jacoby matrix of the system (7.18) reads

$$J(q) := \begin{pmatrix}
-g(q) & D(q)d(q) & 0 & 0 & 0 & \dots & 0 & 0 \\
\alpha({}^0c + {}^1c) - {}^0cg(q) & -\alpha + {}^0cD(q)d(q) & \alpha & 0 & 0 & \dots & 0 & 0 \\
\alpha\cdot{}^2c & 0 & -\alpha & \alpha & 0 & \dots & 0 & 0 \\
\alpha\cdot{}^3c & 0 & 0 & -\alpha & \alpha & \dots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
\alpha\cdot{}^{n-1}c & 0 & 0 & 0 & 0 & \dots & -\alpha & \alpha \\
\alpha\cdot{}^nc & 0 & 0 & 0 & 0 & \dots & 0 & -\alpha
\end{pmatrix}, \tag{7.19}$$

where $g(q)$, $D(q)$, $d(q)$ are given by (7.5).

Let us introduce the property (AS):

$$(\exists\varepsilon > 0)\ (\forall q \in (0,\varepsilon)),\ J(q) \text{ is stable }.$$

For study this property we will use the Routh-Hurwitz condition.

Proposition 7.5. *Let the equation (7.1) have a solution* ${}^0Z$ *satisfying* $0 < {}^0Z < 1$ *and* $D \neq 0$. *Then the point* $\hat{P}({}^0x, {}^0({}^1v), \dots, {}^0({}^nv))$, *where* ${}^0x = {}^0\,({}^1v) = \theta$, ${}^0({}^iv) = (1 - \sum_{k=0}^{i-1} {}^kc)\theta$, $(i = 2, \dots, n)$ *is SSP for System (3.1) with operator* $\Re$ *given by (7.9)-(7.12). The point* $\hat{P}$ *is stable if and only if the property (AS) is true.*

The Routh-Hurwitz condition. Let

$$P(\lambda) = \lambda^{n+1} + A_1\lambda^n + A_2\lambda^{n-1} + \dots A_n\lambda + A_{n+1} \tag{7.20}$$

be the characteristic polynomial of the matrix $J(q)$ given by (7.19) multiplied by $(-1)^{n+1}$, i.e. $(-1)^{n+1}\det(J(q) - \lambda I)$. Let

$$R(q) := \begin{pmatrix}
A_1 & 1 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 & 0 \\
A_3 & A_2 & A_1 & 0 & 0 & \dots & 0 & 0 & 0 & 0 & 0 \\
A_5 & A_4 & A_3 & A_2 & A_1 & \dots & 0 & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & 0 & 0 & \dots & A_{n+1} & A_n & A_{n-1} & A_{n-2} & A_{n-3} \\
0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 & A_{n-3} & A_{n-2} & A_{n-1} \\
0 & 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 & A_{n+1}
\end{pmatrix} \tag{7.21}$$

be its Hurwitz matrix. A necessary and sufficient condition for $J(q)$ to be stable is that all principle leading minors of this matrix are strictly positive, i.e.

$$\Delta_k > 0, \quad k = 1, 2, \dots, n+1 \tag{7.22}$$

Remark 7.6. It is well-known that A_k is a sum C_n^k of all principle leading minors of order k of the matrix $J(q)$ multiplied by $(-1)^k$. In particular, $A_1 = -\operatorname{tr} J(q)$, $A_{n+1} = (-1)^{n+1} \det J(q)$.

For example, for $n = 1$,

$$R(q) = \begin{pmatrix} A_1 & 1 \\ 0 & A_2 \end{pmatrix} = \begin{pmatrix} -\operatorname{tr} J(q) & 1 \\ 0 & \det J(q) \end{pmatrix},$$
$$\Delta_1 = -\operatorname{tr} J(q), \quad \Delta_2 = A_1 A_2 = -\operatorname{tr} J(q) \cdot \det J(q).$$

Thus, condition (7.22) becomes the well-known criterion of stability for a two dimensional matrix : $\operatorname{tr} J(q) < 0$, $\det J(q) > 0$.

Theorem 7.7. *$D < 0$ is necessary for (AS). In particular, if $D > 0$ then $\hat{P}$ is unstable.*

Proof. According to the Routh-Hurwitz condition, if the matrix $J(q)$ is stable then $\Delta_1 = A_1 > 0$. By calculation we get

$$A_1(q) = -\operatorname{tr} J(q) = g(q) -{}^0c \cdot \det J(q) d(q) + n\alpha.$$

From this formula and the condition (7.5) we obtain

$$\operatorname{sgn}(A_1(q)) = -\operatorname{sgn}(\det J(q)) = -\operatorname{sgn}(D)$$

for all small $q > 0$. Therefore, $\Delta_1 > 0$ if and only if $D < 0$ for all small $q > 0$. □

For $n, k = 0, 1, 2, \dots$ we put

$$C_n^k = \frac{n!}{k!(n-k)!} \quad \text{if} \quad k \le n; \qquad C_n^k = 0 \quad \text{if} \quad k > n.$$

Lemma 7.8. *The coefficients of the characteristic polynomial $P(\lambda)$ for the equation* (7.20) *will be*

$$A_k = C_n^k \alpha^k + C_n^{k-1} \alpha^{k-1} g(q) - \alpha^{k-1} d(q) \det J(q) \sum_{j=1}^{k} C_{n+1-j}^{k-j} \cdot{}^{j-1}c, \tag{7.23}$$

$k = 1, 2, \dots, n+1$*; in particular,*

$$A_1 = n\alpha + g(q) - d(q) \det J(q)^0 c,$$
$$A_2 = C_n^2 \alpha^2 + n\alpha g(q) - \alpha d(q) \det J(q)(n \cdot{}^0c + {}^1c),$$
$$A_{n+1} = \alpha^n g(q) - \alpha^n d(q) \det J(q) \sum_{j=0}^{n} {}^jc = \alpha^n g(q) - \alpha^n d(q) \det J(q).$$

The proof of the above lemma is performed by direct calculation of $P(\lambda) = \det(\lambda I - J(q))$. It is omitted.

Assume that the operator in System (3.1) is given by

$$(\Re x)(t) = {}^0c x(t) + \int_{-\infty}^{t} K(t-s) x(s) ds, \quad t \ge 0,$$

where $K(u) = \sum_{\nu=1}^{n} {}^{\nu}c \cdot {}^{\nu}K(u)$, $\sum_{\nu=0}^{n} {}^{\nu}c = 1$, $(\nu = 0, \dots, n)$.

The analytical formulas for $n = 2, 3, 4, 5$ can be obtained with the help of Mathematica. The results for the case $n = 2$ are shown in Theorems 7.1 and 7.2.

For $n = 3$ the Jacoby matrix is

$$J(q) := \begin{pmatrix} -g(q) & D(q)d(q) & 0 & 0 \\ \alpha({}^0c + {}^1c) - {}^0c g(q) & -\alpha + {}^0c D(q)d(q) & \alpha & 0 \\ \alpha \cdot {}^2c & 0 & -\alpha & \alpha \\ \alpha \cdot {}^3c & 0 & 0 & -\alpha \end{pmatrix}, \tag{7.24}$$

where $g(q)$, $D(q)$, $d(q)$ are given by (7.5).

Proposition 7.9. *If*

(1) ${}^0c > 0$, $D < 0$ *and* $9\,{}^0c^2 + {}^1c\,(2\,{}^1c + {}^2c) + {}^0c\,(9\,{}^1c + 3\,{}^2c - 1) > 0$ *or*
(2) ${}^0c = 0$, $D < 0$ *and* $\alpha({}^1c - {}^2c) + {}^1c\, G({}^0Z) > 0$,

then the point $\hat{P}$ *is asymptotically stable.*

For $n = 4$ the Jacoby matrix

$$J(q) := \begin{pmatrix} -G({}^0Z) & D(q)d(q) & 0 & 0 & 0 \\ \alpha({}^0c + {}^1c) - {}^0c g(q) & -\alpha + {}^0c D(q)d(q) & \alpha & 0 & 0 \\ \alpha \cdot {}^2c & 0 & -\alpha & \alpha & 0 \\ \alpha \cdot {}^3c & 0 & 0 & -\alpha & \alpha \\ \alpha \cdot {}^4c & 0 & 0 & 0 & -\alpha \end{pmatrix}, \tag{7.25}$$

where $g(q)$, $D(q)$, $d(q)$ are given by (7.5).

Proposition 7.10. *If*

(1) ${}^0c > 0$, $D < 0$, $20\,{}^0c^2 + {}^1c\,(3\,{}^1c + {}^2c) + {}^0c\,(15\,{}^1c + 2\,{}^2c - {}^3c) > 0$ *and* $80\,{}^0c^3 + 8\,{}^0c^2\,(15\,{}^1c + 6\,{}^2c + 2\,{}^3c - 2) + {}^1c\,(9\,{}^1c^2 + {}^2c\,(2\,{}^2c + {}^3c) + {}^1c\,(9\,{}^2c + 3\,{}^3c - 1)) + {}^0c\,(57\,{}^1c^2 + 4\,{}^2c^2 - {}^3c^2 + 4\,{}^1c\,(10\,{}^2c + 3\,{}^3c - 2)) > 0$ *or*
(2) ${}^0c = 0$, $D < 0$, $\alpha({}^1c - {}^2c) + {}^1c G({}^0Z) > 0$ *and*
$9\,{}^1c^2 + {}^2c\,(2\,{}^2c + {}^3c) + {}^1c\,(9\,{}^2c + 3\,{}^3c - 1) > 0$,

then the point $\hat{P}$ *is asymptotically stable.*

For $n = 5$

$$J(q) := \begin{pmatrix} -G({}^0Z) & D(q)d(q) & 0 & 0 & 0 & 0 \\ \alpha({}^0c + {}^1c) - {}^0c g(q) & -\alpha + {}^0c D(q)d(q) & \alpha & 0 & 0 & 0 \\ \alpha \cdot {}^2c & 0 & -\alpha & \alpha & 0 & 0 \\ \alpha \cdot {}^3c & 0 & 0 & -\alpha & \alpha & 0 \\ \alpha \cdot {}^4c & 0 & 0 & 0 & -\alpha & \alpha \\ \alpha \cdot {}^5c & 0 & 0 & 0 & 0 & -\alpha \end{pmatrix}, \tag{7.26}$$

where $g(q)$, $D(q)$, $d(q)$ are given by (7.5).

Proposition 7.11. *If*

(1) ${}^0c > 0$, $D < 0$, $40\,{}^0c^2 + {}^1c\,(4\,{}^1c + {}^2c) + {}^0c\,(24\,{}^1c + 2\,{}^2c - {}^3c) > 0$, $275\,{}^0c^3 + {}^0c\,(139\,{}^1c^2 + (2\,{}^2c - {}^3c)(3\,{}^2c + {}^3c) + {}^1c\,(64\,{}^2c - 2\,{}^3c - 10\,{}^4c + 1)) + {}^1c\,(20\,{}^1c^2 + {}^2c(3\,{}^2c + {}^3c) + {}^1c\,(15\,{}^2c + 2\,{}^3c - {}^4c)) + 5\,{}^0c^2\,(66\,{}^1c + 13\,{}^2c - 4\,{}^3c - 5\,{}^4c + 1) > 0$ *and* $1375\,{}^0c^4 + 50\,{}^0c^2\,(55\,{}^1c + 23\,{}^2c + 9\,{}^3c + 3\,{}^4c - 7) + {}^0c^2\,(2015\,{}^1c^2 + 225\,{}^2c^2 + 30\,{}^3c - 45\,{}^3c^2 - 1 + 5\,{}^2c\,(13\,{}^3c - 2\,{}^4c - 6) + 10\,{}^4c - 70\,{}^3c\,{}^4c - 25\,{}^4c^2 + 10\,{}^1c\,(157\,{}^2c + 57\,{}^3c + 18\,{}^4c - 35)) + {}^1c\,(80\,{}^1c^3 + 8\,{}^1c^2\,(15\,{}^2c + 6\,{}^3c + 2\,{}^4c - 2) + {}^2c\,(9\,{}^2c^2 + {}^3c\,(2\,{}^3c + {}^4c) + {}^2c\,(9\,{}^3c + 3\,{}^4c - 1)) + {}^1c\,(57\,{}^2c^2 + 4\,{}^3c^2 - {}^4c^2 + 4\,{}^2c\,(10\,{}^3c + 3\,{}^4c - 2))) + {}^0c\,(656\,{}^1c^3 + 2\,{}^1c^2\,(374\,{}^2c + 140\,{}^3c + 47\,{}^4c - 64) + (2\,{}^2c - {}^3c)(9\,{}^2c^2 + {}^3c\,(2\,{}^3c + {}^4c) + {}^2c\,(9\,{}^3c + 3\,{}^4c - 1)) + {}^1$

$c\,(231\,{}^2c^2 + {}^2c\,(123\,{}^3c + 34\,{}^4c - 36) + 2\,(4\,{}^3c - 4\,{}^3c^2 + {}^4c - 11\,{}^3c\,{}^4c - 5\,{}^4c^2))) > 0$
or

(2) ${}^0c = 0$, $D < 0$, $\alpha({}^1c - {}^2c) + {}^1c\,G({}^0Z) > 0$, $20\,{}^1c^2 + {}^2c\,(3\,{}^2c + {}^3c) + {}^1c\,(15\,{}^2c + 2\,{}^3c - {}^4c) > 0$ *and* $80\,{}^1c^3 + 8\,{}^1c^2\,(15\,{}^2c + 6\,{}^3c + 2\,{}^4c - 2) + {}^2c(9\,{}^2c^2 + {}^3c\,(2\,{}^3c + {}^4c) + {}^2c\,(9\,{}^3c + 3\,{}^4c - 1)) + {}^1c\,(57\,{}^2c^2 + 4\,{}^3c^2 - {}^4c^2 + 4\,{}^2c\,(10\,{}^3c + 3\,{}^4c - 2)) > 0$, $G({}^0Z) > 0$,

then the point $\hat{P}$ is asymptotically stable.

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Singular perturbation analysis and gene regulatory networks with delay

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ABSTRACT

The problem of how the dynamics of the smooth gene networks is related to the simplified dynamics of the Boolean networks is studied. The emphasis is put on the gene regulatory networks with delay. Asymptotic analysis which is applied in the paper goes back to Tikhonov's theory of singular perturbed differential equations and a modified algorithm of reducing delay equations to ordinary differential equations. A number of illustrative examples complements the theory which is offered in the paper.

1. Introduction

A gene regulatory network is a part of the interaction system of genes and proteins. The network is responsible for providing a cell in the organism with the right amount of the proteins necessary for development of the embryo or maintaining life functions of the organism. All these processes take place under varying internal and external conditions. When trying to understand the role and functioning of the gene regulatory network, the first step is to assemble the components of the network and the interactions between them.

There are different ways of modeling the gene regulatory network. The simplest dynamic models – Boolean network models – were used already in the 1960's by Stuart Kauffman (see e.g. the review article [1]). In a Boolean approach, a binary description takes only the genetic activity into account; i.e. gene "on" $\equiv 1$ and gene "off" $\equiv 0$. These models have a descriptive character and cannot model complex dynamic behavior. Differential equations allow for a more detailed description of network dynamics by explicitly modeling the concentration changes of molecules over time. The basic equations for the differential equations models are:

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = F_i(Z) - G_i(Z)x_i, \quad i = 1, \dots, n. \tag{1}$$

The production and relative degradation rate functions F_i and G_i depend on a vector Z of steeply sloped threshold functions. The most popular and simple approach of the threshold functions is similar to the Boolean network approach. The threshold functions Z_i, $i = 1, \dots, n$ are approximated by step functions. Regarding the thresholds in the state space, Eq. (1) changes into a piecewise linear system. The dynamics of the obtained system can be described very easily between such thresholds, but not in the switching domains. This approximation leads to the following problems:

(1) to analyze stationary points of the system and
(2) to define continuous solutions at discontinuity points.

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The solution to the first problem in the non-delay case can be found in [2,3] (see also references therein). The delay case is extensively studied in [4]. The second problem in the non-delay case was studied in [5] by applying singular perturbation analysis and combining two motions $\mathbb{X}^n$ and $\mathbb{Z}^n$. It was shown that the solution for steep sigmoids approaches the limit solution uniformly, in any finite time interval (when the sigmoids approach the step functions). But the model proposed in [5] does not take into account a time delay in cellular systems. However, analysis of real gene expression data shows a considerable number of time-delayed interactions suggesting that time delay is essential in gene regulation. Therefore, time-delay may have a great effect on the dynamics of the system and presents one of the critical factors that should be considered in the reconstruction of gene regulatory networks.

The present work is a generalization of [5]. The inclusion of delay effects into the system for gene regulatory network leads to unexpected and interesting results. The goal of this paper is to formalize the singular perturbation analysis for the case of systems with delay and to obtain an analog of Tikhonov's theorem giving sufficient conditions for determining the limit system for the delay case.

To explain the approach let us consider Eq. (1). Assume that $Z = (Z_1, \dots, Z_n)$, where any Z_i is the Hill function given by

$$Z_i = \Sigma(x_i, \theta_i, q_i) = \begin{cases} \dfrac{x_i^{1/q_i}}{x_i^{1/q_i} + \theta_i^{1/q_i}} & \text{if } x_i \geq 0 \\ 0 & \text{if } x_i < 0 \end{cases} \tag{2}$$

with the steepness parameter $q_i > 0$ and the threshold value $\theta_i > 0$, $i = 1, \dots, n$. Suppose that $q_i = q$ for any $i = 1, \dots, n$ and let q go to 0. Then each Z_i, $i = 1, \dots, n$ approaches the step function and the right-hand side of Eq. (1) becomes discontinuous. The threshold lines $x_i = \theta_i$ divide the plane into regions, called regular domains or boxes. Inside each regular domain Z_i are equal to 0 or 1 and the differential equation describing the motion inside the domain is linear, so that it can be easily solved. In switching domains, called singular domains or walls, the system is not defined. To find solutions we apply the singular perturbation analysis to (1) in any of singular domains.

Assume that $x_1 = \theta_1$ and consider the corresponding singular domain $\{x_1 = \theta_1,\ x_i \neq \theta_i,\ i = 2, \dots, n\}$. The variable x_1 is singular, that is the right-hand side of (1) is discontinuous at $x_1 = \theta_1$ and $q = 0$. To obtain an equation describing the motion in this domain we substitute this variable by Z_1. This simple transformation is a starting point for singular perturbation analysis. Z_1 is assumed to be the Hill function given by (2), so that we get

$$x_1 = \Sigma^{-1}(Z_1, \theta_1, q) = \theta_1 \left(\frac{Z_1}{1 - Z_1} \right)^q$$

and

$$\frac{dx_1}{dZ_1} = \theta_1 q \left(\frac{Z_1}{1 - Z_1} \right)^{q-1} \frac{1}{(1 - Z_1)^2} = \frac{q x_1}{Z_1(1 - Z_1)}. \tag{3}$$

Note that if $q \to 0$, then $x_1 \to \theta_1$.

From (3) we obtain

$$\frac{dZ_1}{dx_1} = \frac{Z_1(1 - Z_1)}{q x_1}$$

and Eq. (1) is transformed to

$$\begin{aligned} q\dot{Z}_1 &= \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q)} (F_1(Z) - G_1(Z)\Sigma^{-1}(Z_1, \theta_1, q)), \\ \dot{x}_i &= F_i(Z) - G_i(Z)x_i, \quad i = 2, \dots, n \end{aligned} \tag{4}$$

where $q > 0$. This equation describes trajectories around the singular domain. In terms of singular perturbation analysis Eq. (4) with the corresponding initial conditions is called the full initial value problem.

The stretching transformation $\tau = t/q$ takes the full initial value problem into the boundary layer system

$$\begin{aligned} Z_1' &= \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q)} (F_1(Z) - G_1(Z)\Sigma^{-1}(Z_1, \theta_1, q)), \\ x_i' &= q(F_i(Z) - G_i(Z)x_i), \quad i = 2, \dots, n, \end{aligned} \tag{5}$$

where prime denotes differentiation with respect to τ.

By letting $q \to 0$ in (5) we get the following system which describes the limit solution in the singular domain in slow time τ

$$\begin{aligned} Z_1' &= \frac{Z_1(1 - Z_1)}{\theta} (F_1(Z) - G_1(Z)\theta), \\ x_i' &= 0, \quad i = 2, \dots, n. \end{aligned} \tag{6}$$

To apply Tikhonov's theorem we let q go to 0 in (4). It gives us the system

$$\frac{Z_1(1-Z_1)}{\theta_1}(F_1(Z_1,B_R)-G_1(Z_1,B_R)\theta_1)=0,$$
$$\dot{x}_i=F_i(Z_1,B_R)-G_i(Z_1,B_R)x_i,\quad i=2,\dots,n,$$

where $B_R=(B_2,\dots,B_n)$ is a corresponding Boolean vector (see Section 4 for more details). The last equation can be explicitly solved and gives us the limit solution of Eq. (4) in the singular domain. Notice that the system must be provided with sufficient conditions for using Tikhonov's theorem (see Theorem 14, Appendix B).

Assume now that two variables x_1 and x_2 are singular. Then similarly to the case described above we get the system

$$Z_1'=\frac{Z_1(1-Z_1)}{\theta_1}(F_1(Z)-G_1(Z)\theta_1),$$
$$Z_2'=\frac{Z_2(1-Z_2)}{\theta_2}(F_2(Z)-G_2(Z)\theta_2)$$

describing the behavior of trajectories in the singular domain $\{x_1=\theta_1,x_2=\theta_2\}$ for the slow time τ. Combining the trajectories' motions expressed in the regular and singular variables gives us the whole picture of solutions' behavior.

The paper is organized in the following way. In Section 2 we formulate the main problem and point out the assumptions. For studying the delay case we use a modified linear chain trick method (Section 3). This method helps us to remove the delays from the model and obtain an equivalent system of ordinary differential equations. Section 4 contains a summary of definitions and notation related to geometrical properties of the system used in the paper. In Sections 5 and 6 we consider two particular cases of singular perturbation analysis for a scalar equation and for walls, respectively. The main result of the paper Theorem 9 is presented in Section 7 and is based on Tikhonov's theorem which can be found in Appendix B. Sufficient conditions, which guarantee the existence of solutions and ensure the fact that solutions of the smooth problem go to the limit solution for delay problems, are given in Sections 5–7 for scalar equations, walls and for general cases, respectively. For a better understanding of the problem, we discuss the example from [5] in Appendix A in detail. In Section 8 we introduce the delay effect into this example and study how it influences the trajectories' behavior. The presented graphs of motion in $\mathbb{X}^2$ and $\mathbb{Z}^2$ show a big difference between non-delay and delay cases.

2. Problem formulation

We study the delay system

$$\begin{aligned}&\dot{x}_i(t)=F_i(Z_1,\dots,Z_m)-G_i(Z_1,\dots,Z_m)x_i(t)\\&Z_k=\Sigma(y_{i(k)},\theta_k,q_k)\\&y_i(t)=(\Re_i x_i)(t),\quad t\ge 0,\quad i=1,\dots,n,\ k=1,\dots,m.\end{aligned}\tag{7}$$

This system describes a gene regulatory network with autoregulation [2–7], where changes in one or more genes happen slower than in the others, which causes delay effects in some of the variables.

The functions F_i, G_i are affine in each Z_k and satisfy

$$F_i(Z_1,\dots,Z_m)\ge 0,\qquad G_i(Z_1,\dots,Z_m)>0$$

for $0\le Z_k\le 1$, $k=1,\dots,m$. F_i and G_i stand for the production rate and the relative degradation rate of the product of gene i, respectively, and $x_i(t)$ denotes the gene product concentration. The input variables y_i endow Eqs. (7) with feedbacks which, in general, are described by nonlinear Volterra ("delay") operators $\Re_i$ depending on the gene concentration $x_i(t)$. The delay effects in the model arise from the time required to complete transcription, translation and diffusion to the place of action of a protein [8].

If $\Re_i$ is the identity operator, then $x_i=y_i$ and x_i is a non-delay variable. Non-delay regulatory networks, where $x_i=y_i$ for all $i=1,\dots,n$ in their general form (i.e. where both production and degradation are regulated) were introduced in [2].

As in [4] we assume $\Re_i$ to be integral operators of the form

$$(\Re_i x_i)(t)={}^0cx_i(t)+\int_{-\infty}^{t}K_i(t-s)x_i(s)\mathrm{d}s,\quad t\ge 0,\ i=1,\dots,n,\tag{8}$$

where

$$K_i(u)=\sum_{\nu=1}^{p}{}^{\nu}c_i{}^{\nu}K_i(u),$$
$${}^{\nu}K_i(u)=\frac{\alpha_i^{\nu}u^{\nu-1}}{(\nu-1)!}\mathrm{e}^{-\alpha_i u},\quad i=1,\dots,n,p=1,\dots,n.$$

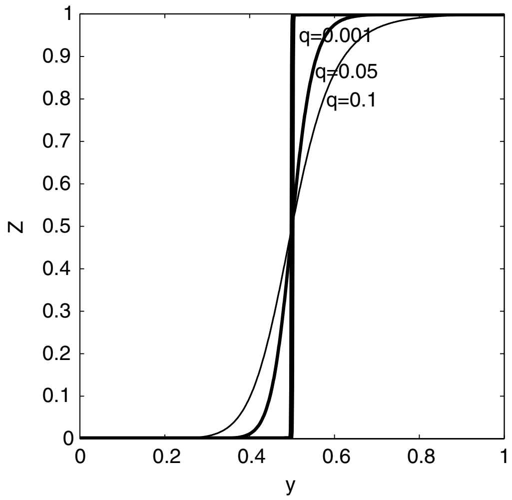

Fig. 1. The Hill function for $q = 0.1, 0.05, 0.001$ and $\theta = 0.5$.

The coefficients ${}^{\nu}c_i$ ($\nu = 0, \dots, p, i = 1, \dots, n$) are real nonnegative numbers satisfying

$$\sum_{\nu=0}^{p} {}^{\nu}c_i = 1$$

for any $i = 1, \dots, n$. It is also assumed that $\alpha_i > 0$ for all $i = 1, \dots, n$.

The "response functions" Z_k express the effect of the different transcription factors regulating the expression of the gene. Each $Z_k = Z_k(y_{i(k)})$, $0 \le Z_k \le 1$ for $y_{i(k)} \ge 0$ is a smooth function depending on exactly one input variable $y_{i(k)}$ and on two other parameters; i.e. the threshold value θ_k and the steepness value $q_k > 0$. If $q_k = 0$ then Z_k becomes the unit step function. A gene may have an arbitrary number of thresholds. This is expressed in the dependence $i = i(k)$. If different k correspond to the same i, then gene $i(k)$ has more than one threshold. If some i does not correspond to any k, then gene $i(k)$ has no threshold.

Below is an example of the response function (the so-called Hill function) which is used in this paper. In fact, the main results admit more general response functions, for example those axiomatized in the paper [5]. However, we will restrict ourselves, as do many people who deal with modeling of gene regulatory network, only to the case of the Hill function which gives a good fit to the experimental measurements of reaction rates [9].

Let $\theta > 0$, $q > 0$. *The Hill function* (Fig. 1) is given by

$$\Sigma(y, \theta, q) := \begin{cases} 0 & \text{if } y < 0 \\ \dfrac{y^{1/q}}{y^{1/q} + \theta^{1/q}} & \text{if } y \ge 0. \end{cases} \tag{9}$$

The Hill function satisfies the following properties (see [10]):

(1) $\Sigma(y, \theta, q)$ is continuous in $(y, q) \in \mathbb{R} \times (0, 1)$ for all $\theta > 0$, continuously differentiable with respect to $y > 0$ for all $\theta > 0$, $0 < q < 1$, and $\frac{\partial}{\partial y}\Sigma(y, \theta, q) > 0$ on the set $\{y > 0 : 0 < \Sigma(y, \theta, q) < 1\}$;
(2) $\Sigma(y, \theta, q)$ satisfies

$$\Sigma(\theta, \theta, q) = 0.5, \qquad \Sigma(0, \theta, q) = 0, \qquad \Sigma(+\infty, \theta, q) = 1$$

for all $\theta > 0$, $0 < q < 1$;
(3) For all $\theta > 0$, $\frac{\partial}{\partial Z}\Sigma^{-1}(Z, \theta, q) \to 0$ uniformly on compact subsets of the interval $Z \in (0, 1)$ as $q \to 0$;
(4) If $q \to 0$, then $\Sigma^{-1}(Z, \theta, q) \to \theta$ uniformly on all compact subsets of the interval $Z \in (0, 1)$ and for every $\theta > 0$;
(5) If $q \to 0$, then $\Sigma(y, \theta, q)$ tends to 1 ($\forall y > \theta$), to 0 ($\forall y < \theta$) and is equal to 0.5 (if $y = \theta$) for all $\theta > 0$;
(6) For any sequence (y_n, θ, q_n) such as $q_n \to 0$ and $\Sigma(y_n, \theta, q_n) \to Z^*$ for some $0 < Z^* < 1$ we have $\frac{\partial \Sigma}{\partial y}(y_n, \theta, q_n) \to +\infty$.

3. The modified linear chain trick

A method to study (7) with the operator $\Re_i$ given by (8), being well-known in the literature, is usually called "the linear chain trick" (LCT) [11]. However, a direct application of LCT in its standard form is not suitable for our purposes, because we want Z_i to depend on y_i, only. A modification of LCT is described in [4].

In fact, our modified linear chain trick is a particular case of the so-called "W-transform", which is widely used in the theory of functional differential equations [12,13].

Consider Eq. (7) with the operator $\Re_i$ given by (8). Assume that this system is equipped with the initial conditions

$$x_i(\tau) = \varphi_i(\tau), \quad \tau < 0,\ i = 1, \dots, n, \tag{10}$$

where $\varphi_i(\tau)$ are bounded and measurable. The application of the modified linear chain trick method helps us to remove the delay from the system and obtain an equivalent system of ordinary differential equations. We use the vector substitution (which is a version of W-substitution)

$$v_i(t) = \alpha_i \int_{-\infty}^{t} Y_i(t-s)\pi_i x_i(s)\mathrm{d}s + {}^0c_i x_i e_1, \quad i = 1, \dots, n, \tag{11}$$

where

$$v_i = \begin{pmatrix} {}^1v_i \\ {}^2v_i \\ \vdots \\ {}^pv_i \end{pmatrix}, \qquad \pi_i = \begin{pmatrix} {}^1c_i \\ {}^2c_i \\ \vdots \\ {}^pc_i \end{pmatrix}, \qquad e_1 = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}$$

and

$$Y_i(t) = \mathrm{e}^{-\alpha_i t} \begin{pmatrix} 1 & \alpha_i t & \dfrac{(\alpha_i t)^2}{2!} & \dots & \dfrac{(\alpha_i t)^{p-1}}{(p-1)!} \\ 0 & 1 & \alpha_i t & \dots & \dfrac{(\alpha_i t)^{p-2}}{(p-2)!} \\ 0 & 0 & 1 & \dots & \vdots \\ \vdots & \vdots & \ddots & \ddots & \alpha_i t \\ 0 & 0 & \dots & 0 & 1 \end{pmatrix}$$

is a fundamental matrix of the system $\dot{y} = A_i y$ with

$$A_i = \begin{pmatrix} -\alpha_i & \alpha_i & 0 & \dots & 0 \\ 0 & -\alpha_i & \alpha_i & \dots & 0 \\ 0 & 0 & -\alpha_i & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 0 & -\alpha_i \end{pmatrix}.$$

Then we obtain that Eq. (7) is equivalent to the following system of ordinary differential equations [4]

$$\begin{aligned} &\dot{x}_i(t) = F_i(Z_1, \dots, Z_m) - G_i(Z_1, \dots, Z_m)x_i(t) \\ &\dot{v}_i(t) = A_i v_i(t) + \Pi_i(x_i(t)), \quad t > 0 \\ &Z_k = \Sigma(y_{i(k)}, \theta_k, q_k), \qquad y_i = {}^1v_i, \quad i = 1, \dots, n, \end{aligned} \tag{12}$$

where

$$\Pi_i(x_i(t)) := \alpha_i x_i(t)\pi_i + {}^0c_i f_i(Z, x_i(t))$$

with

$$\pi_i := \begin{pmatrix} {}^0c_i + {}^1c_i \\ {}^2c_i \\ \vdots \\ {}^pc_i \end{pmatrix}, \qquad f_i(Z, x_i(t)) := \begin{pmatrix} F_i(Z) - G_i(Z)x_i(t) \\ 0 \\ \vdots \\ 0 \end{pmatrix}$$

and A_i, v_i defined above.

Now we look at the initial conditions (10), which should be rewritten in terms of the new variables. Using the substitution (11) we obtain

$$\begin{aligned} &x_i(0) = \varphi_i(0), \\ &v_i(0) = \int_{-\infty}^{0} Y_i(-\tau)\pi_i\varphi_i(\tau)\mathrm{d}\tau + {}^0c_i\varphi_i(0)e_1. \end{aligned} \tag{13}$$

In [4] it is shown that the initial delay problem (7), (10) is equivalent to the initial value problem of ordinary differential equations (12) and (13).

Remark 1. Note that instead of the vector substitution (11) we can use the new modified variables

$$ {}^1v_i = {}^0c_i x_i + \sum_{\nu=1}^{p} {}^\nu c_i\, {}^\nu w_i \quad \text{and} \quad {}^\nu v_i = \sum_{j=1}^{p-\nu+1} {}^{j+\nu-1}c_i\, {}^j w_i, \quad \nu = 2, \dots, p, $$

where

$$ {}^\nu w_i(t) = \int_{-\infty}^{t} {}^\nu K_i(t-s) x_i(s) \mathrm{d}s, \quad \nu = 1, \dots, p,\ i = 1, \dots, n. $$

4. Regular and singular domains

In this section we give a summary of some general notation and definitions related to geometric properties of system (12) in the limit case $q_k = 0,\ k = 1, \dots, m$.

We start with the notation which we adopt from [5]. In what follows, it is assumed that

- $J := \{1, \dots, j\},\ M := \{1, \dots, m\},\ N := \{1, \dots, n\},\ m \le j,\ n \le j$, i.e. $M \subset J,\ N \subset J$;
- $R := M - S$ for a given $S \subset M$;
- Y^X consists of all functions $v : X \to Y$; X and Y are arbitrary sets;
- $y_R := (y_r)_{r\in R},\ y_R \in Y^R,\ y_S := (y_s)_{s\in S},\ y_S \in Y^S$.

The following system of ordinary differential equations, generalizing system (12) in the limit case $q_k = 0,\ k = 1, \dots, m$, is used in this section

$$ \dot{u}(t) = \Psi(Z, u(t)), \quad t > 0, \tag{14} $$

where $u = (u_1, \dots, u_j)$, $\Psi = (\Psi_1, \dots, \Psi_j)$, $Z = (Z_1, \dots, Z_m)$, $Z_k = \Sigma(u_{i(k)}, \theta_k, 0)$ for $k \in M$, i.e. Z_k is the unit step function with the threshold $\theta_k > 0$, $i(k)$ is a function from M to N. The function $\Psi_j : [0, 1]^M \times \mathbb{R}^J \to \mathbb{R}^J$ is continuously differentiable in $Z \in [0, 1]^M$ for all $u \in \mathbb{R}^J$ and affine in each vector variable $u \in \mathbb{R}^J$ for all $Z \in [0, 1]^M$.

Remind that all $q_k = 0$. Then the right-hand side of (14) can be discontinuous, namely, if one or several $u_{i(k)}$, $k \in M$ assume their threshold values $u_{i(k)} = \theta_k$.

We associate a Boolean variable B_k to each Z_k by $B_k = 0$ if $u_{i(k)} < \theta_k$ and $B_k = 1$ if $u_{i(k)} > \theta_k$.

Let Θ denote the set $\{u \in \mathbb{R}^J : \exists k \in M : u_{i(k)} = \theta_k\}$. This set contains all discontinuity points of the vector-function

$$ \Psi(\Sigma(u_{i(k)}, \theta_k, 0)_{k\in M}, (u_i)_{i\in J}) $$

and is equal to the space $\mathbb{R}$ minus a finite number of open, disjoint subsets of $\mathbb{R}^J$. Inside each of these subsets one has $Z_k = B_k$, where $B_k = 0$ or $B_k = 1$ for all $k \in M$, so that Eq. (14) becomes affine

$$ \dot{u}(t) = \Psi(B, u(t)) := A(B)u(t) + f(B), \quad t > 0, \tag{15} $$

where $B = (B_k)_{k\in M}$ is a constant Boolean vector, $A(B)$ is a constant matrix and $f(B)$ is a constant vector corresponding to the box B. The set of all Boolean vectors $B = (B_1, \dots, B_m)$, where $B_k = 0$ or 1, will be denoted by $\{0, 1\}^M$.

Definition 2. The set $\mathcal{B}(B)$, which consists of all $u \in \mathbb{R}^J$, where $(Z_k(u_{i(k)}))_{k\in M} = B$, is called a regular domain or *a box*.

The set $\mathcal{SD}(\theta_S, B_R)$, which consists of all $u \in \mathbb{R}^J$, where $Z_r(u_{i(r)}) = B_r,\ r \in R$ and $u_{i(s)} = \theta_s,\ s \in S$ $(S \ne \emptyset)$ is called *a singular domain*.

The singular domain $\mathcal{SD}(\theta_\mu, B_R)$, where a number $\mu \in M$, $R = M \setminus \{\mu\}$ is called *a wall*.

Consider the wall $\mathcal{SD}(\theta_\mu, B_R)$ which lies between the box $\mathcal{B}(B^0)$, where $Z_\mu = 0$, and the box $\mathcal{B}(B^1)$, where $Z_\mu = 1$. This gives two different systems (15) for $B = B^0$ and $B = B^1$, respectively. Let P be a point in a wall $\mathcal{SD}(\theta_\mu, B_R)$ and $u(t, \nu, P)$ be the solution to (15) with $B = B^\nu$, which satisfies $u(t_0, \nu, P) = P$, $\nu = 0, 1$. Denote by $\dot{u}_\mu(t_0, Z, P)$ component of number μ (which is orthogonal to the wall $\mathcal{SD}(\theta_\mu, B_R)$) of the velocity vector $\dot{u}_\mu(t, Z, P)$ at P for $t = t_0$, $Z = 0$ or 1.

Definition 3. A point $P \in \mathcal{SD}(\theta_\mu, B_R)$ is called

"*black*" if $\dot{u}_\mu(t_0, 1, P) < 0$ and $\dot{u}_\mu(t_0, 0, P) > 0$;
"*white*" if $\dot{u}_\mu(t_0, 1, P) > 0$ and $\dot{u}_\mu(t_0, 0, P) < 0$;
"*transparent*" if $\dot{u}_\mu(t_0, 1, P) < 0$ and $\dot{u}_\mu(t_0, 0, P) < 0$, or if $\dot{u}_\mu(t_0, 1, P) > 0$ and $\dot{u}_\mu(t_0, 0, P) > 0$.

We say that a wall $\mathcal{SD}(\theta_\mu, B_R)$ is black (white, transparent) if any point in it, except for a nowhere dense set, is black (white, transparent).

In the non-delay case walls can be either attractive ("black"), expelling ("white") or "transparent" (see [6]). In the delay case, walls can also be of a mixed type.

In what follows, the variables u_i will be specified as either x_i, y_i or v_i.

5. Singular perturbation analysis for a scalar equation

We consider a scalar equation, which is a particular case of Eqs. (7)

$$\begin{aligned} &\dot{x}(t) = F(Z) - G(Z)x(t) \\ &Z = \Sigma(y, \theta, q) \\ &y(t) = (\Re x)(t), \quad t \geq 0 \end{aligned} \tag{16}$$

with the initial condition

$$x(t_0, q) = x^0(q),$$

where the functions $F(Z) \geq 0, G(Z) > 0$ for $Z \in [0, 1]$ are affine; $\Sigma(y, \theta, q)$ is the Hill function if $q > 0$ and the step function if $q = 0$. The integral operator is given by

$$(\Re x)(t) = {}^0c x(t) + \int_{-\infty}^{t} K(t-s)x(s)\mathrm{d}s, \quad t \geq 0, \tag{17}$$

where

$$\begin{aligned} &K(u) = \sum_{\nu=1}^{p} {}^{\nu}c\, {}^{\nu}K(u), \\ &{}^{\nu}K(u) = \frac{\alpha^{\nu}\, u^{\nu-1}}{(\nu-1)!}\mathrm{e}^{-\alpha u}. \end{aligned}$$

The coefficients ${}^{\nu}c$ are real nonnegative numbers satisfying $\Sigma_{\nu=0}^{p}\, {}^{\nu}c = 1$. Finally, it is also assumed that $\alpha > 0$.

Example 4 (*[11]*).

$$\begin{aligned} &{}^1K(u) = \alpha \mathrm{e}^{-\alpha u}, \quad \alpha > 0 \text{ is the weak generic delay kernel,} \\ &{}^2K(u) = \alpha^2\, u\mathrm{e}^{-\alpha u}, \quad \alpha > 0 \text{ is the strong generic delay kernel.} \end{aligned} \tag{18}$$

If ${}^0c = 1$ in (17), then $x = y$ and Eq. (16) does not contain a delay. Then $x = y = \Sigma^{-1}(Z, \theta, q)$ for $q > 0$.

In order to let q go to 0 we replace x (which causes a jump in Z when x crosses the threshold value $x = \theta$) with $Z = \Sigma(x, \theta, q)$ and apply the singular perturbation analysis. The procedure is similar to the method described in the Introduction.

Since Z is assumed to be the Hill function, then replacing x with Z gives us

$$q\dot{Z} = \frac{Z(1-Z)}{\Sigma^{-1}(Z, \theta, q)}(F(Z) - G(Z)\Sigma^{-1}(Z, \theta, q)) \tag{19}$$

with the initial condition $Z(t_0, q) = Z^0(q)$, where we assume that the convergence of the initial values $x(t_0, q)$ for Eq. (16) implies the convergence of $Z(t_0, q)$ as $q \to 0$.

By letting $q \to 0$ we get

$$\frac{Z(1-Z)}{\theta}(F(Z) - G(Z)\theta) = 0. \tag{20}$$

The equation $F(Z) - G(Z)\theta = 0$ is affine therefore it has a unique solution $\hat{Z}$.

If $\hat{Z} \notin [0, 1]$, then exactly one of the other solutions $Z = 0$ or $Z = 1$ is a stable stationary point for (20). In this case $F(1) - G(1)\theta$ and $F(0) - G(0)\theta$ have the same sign and $x = \theta$ is transparent (Definition 3). Geometrically it means that solutions cross the threshold value (Figs. 2a,b, 3a,b). This case is not interesting for us now, since it does not require the singular perturbation analysis.

If $\hat{Z} \in (0, 1)$ and $\hat{Z}$ is unstable, then $Z = 0$ and $Z = 1$ are both stable and the wall is white.

Finally, if the solution $\hat{Z} \in (0, 1)$ is stable. It means that $F(1) - G(1)\theta < 0$ and $F(0) - G(0)\theta > 0$, then $x = \theta$ is black or attractive (Figs. 2c, 3c) and the solution $\hat{Z}$ becomes an asymptotically stable point for the associated problem

$$\tilde{Z}' = \frac{\tilde{Z}(1-\tilde{Z})}{\theta}(F(\tilde{Z}) - G(\tilde{Z})\theta)$$

with the attractor basin (0, 1), where $\tilde{Z}' = \frac{\mathrm{d}\tilde{Z}}{\mathrm{d}\tau}$, $\tau = \frac{t}{q}$. Thus, by Tikhonov's theorem (Theorem 14, Appendix B) the solution $Z(t, q)$ of (19) with $Z(0, q) \in (0, 1)$ will tend to $\hat{Z}$ uniformly on any $[\sigma, T]$ $(\sigma > 0)$.

Now we study the delay case in more detail. We assume that ${}^0c < 1$; i.e. at least one ${}^{\nu}c \neq 0$, $\nu = 1, \ldots, p$. Therefore, $x \neq y$.

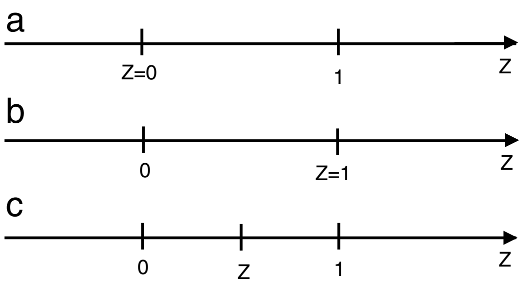

Fig. 2.

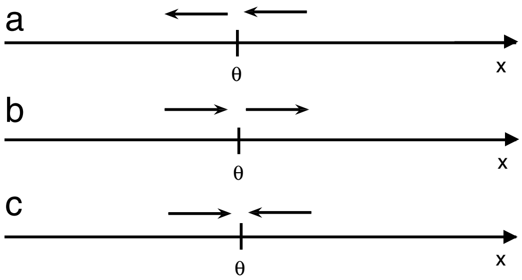

Fig. 3.

Using the modified linear chain trick [4] we get that Eq. (16) is equivalent to the system

$$\begin{aligned} \dot{x} &= F(Z) - G(Z)x \\ \dot{y} &= -\alpha y + \alpha\, {}^2v + \alpha x({}^0c + {}^1c) + {}^0c(F(Z) - G(Z)x) \\ \dot{v}^- &= A^- v^- + \Pi^-(x) \\ Z &= \Sigma(y, \theta, q), \quad y = {}^1v, \end{aligned} \tag{21}$$

where

$$v^- = \begin{pmatrix} {}^2v \\ {}^3v \\ \vdots \\ {}^pv \end{pmatrix}, \qquad A^- = \underbrace{\begin{pmatrix} -\alpha & \alpha & \dots & 0 \\ 0 & -\alpha & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & 0 & -\alpha \end{pmatrix}}_{p-1} \quad \text{and} \quad \Pi^- = \begin{pmatrix} {}^2c \\ {}^3c \\ \vdots \\ {}^pc \end{pmatrix}$$

with the initial values

$$\begin{aligned} x(t_0, q) &= x^0(q) \\ y(t_0, q) &= y^0(q) \\ v^-(t_0, q) &= v^0(q). \end{aligned} \tag{22}$$

Eqs. (21) are a particular case of (12).
Since Z is assumed to be the Hill function, then replacing y with Z gives us

$$\begin{aligned} \dot{x} &= F(Z) - G(Z)x \\ q\dot{Z} &= \frac{Z(1-Z)}{\Sigma^{-1}(Z, \theta, q)}[-\alpha \Sigma^{-1}(Z, \theta, q) + \alpha\, {}^2v + \alpha x({}^0c + {}^1c) + {}^0c(F(Z) - G(Z)x)] \\ \dot{v}^- &= A^- v^- + \Pi^-(x), \quad q > 0 \end{aligned} \tag{23}$$

with the initial values

$$\begin{aligned} x(t_0, q) &= x^0(q) \\ v^-(t_0, q) &= v^0(q) \\ Z(t_0, q) &= Z^0(q), \end{aligned}$$

where we assume that the convergence of the initial values (22) implies the convergence of $Z(t_0, q)$ as $q \to 0$. To be able to apply Tikhonov's theorem (see Appendix B) we let $q \to 0$ (the conditions of the theorem are verified below).

Then (23) takes on the following form

$$\begin{aligned} \dot{x} &= F(Z) - G(Z)x \\ 0 &= \frac{Z(1-Z)}{\theta}[-\alpha\theta + \alpha\, {}^2v + \alpha x({}^0c + {}^1c) + {}^0c(F(Z) - G(Z)x)] \\ \dot{v}^- &= A^- v^- + \Pi^-(x). \end{aligned} \tag{24}$$

Consider the equation

$$0 = \frac{Z(1-Z)}{\theta}[-\alpha\theta + \alpha\, {}^2v + \alpha x({}^0c + {}^1c) + {}^0c(F(Z) - G(Z)x)],$$

which defines a stationary solution $\hat{Z}$.

Unlike the non-delay case, different points in the wall can have different properties depending on the choice of x and v^- in (21). Denoting $\Phi_d(Z, x, {}^2v) = -\alpha\theta + \alpha\, {}^2v + \alpha x({}^0c + {}^1c) + {}^0c(F(Z) - G(Z)x)$ we have the following conditions of blackness of the point (x, θ, v^-)

$$\begin{aligned} &\Phi_d(1, x, {}^2v) < 0, \\ &\Phi_d(0, x, {}^2v) > 0. \end{aligned}$$

This system gives us the unique solution $\hat{Z} \in (0, 1)$ (case c), which is asymptotically stable for the associated problem

$$\tilde{Z}' = \frac{\tilde{Z}(1-\tilde{Z})}{\theta}\Phi_d(\tilde{Z}, x, {}^2v).$$

The solution $(x(t, q), Z(t, q), v^-(t, q))$ of (23) tends to the solution $(x(t, 0), Z(t, 0), v^-(t, 0))$ of (24) in the following sense

$x(t, q) \to x(t, 0)$ and $v^-(t, q) \to v^-(t, 0)$ uniformly on $[0, T]$ as $q \to 0$,
$Z(t, q) \to \hat{Z} = \hat{Z}(x(t, 0), v^-(t, 0))$ uniformly on all $[\sigma, T]$ $(\sigma > 0)$ as $q \to 0$, where $\hat{Z}$ is a unique solution of (24).

Example 5. Consider the delay equation

$$\begin{aligned} \dot{x} &= 2 - 2Z - x, \\ Z &= \Sigma(y, 1, q), \\ y(t) &= {}^0cx(t) + {}^1c \int_{-\infty}^{t} {}^1K(t-s)x(s)\mathrm{d}s. \end{aligned} \tag{25}$$

Assume that ${}^0c \geq 0$, ${}^0c + {}^1c = 1$, $q > 0$, $\Sigma(y, 1, q)$ is the Hill function given by (9) and ${}^1K(u)$ is the weak generic delay kernel given by (18). Applying the modified linear chain trick to (25) gives us the equivalent system of ordinary differential equations

$$\begin{aligned} \dot{x} &= 2 - 2Z - x \\ \dot{y} &= \alpha x - \alpha y + {}^0c(2 - 2Z - x), \\ Z &= \Sigma(y, 1, q). \end{aligned} \tag{26}$$

The trajectories of (26) for $\alpha = 0.1$, $q = 0.01$ and ${}^0c = 1$ (non-delay case), ${}^0c = 0.2$, ${}^0c = 0$ (delay is present) are shown in Figs. 4–6, respectively.

Description of Figs. 4–6.

This example illustrates how the type of the wall $y = \theta = 1$ depends on the coefficient ${}^0c$. The wall $y = 1$ is black in the non-delay case and it does not change its character in the vicinity of $(1, 1)$ when we add the delay effect into the system. However, in this case the wall $y = 1$ changes its type from black to transparent at $x = 1 \pm {}^0c(\alpha - {}^0c)^{-1}$ (see Definition 3). If ${}^0c = 0$, then the wall is transparent. Notice that the stationary point $(1, 1)$ is always black (attractive).

The sliding modes can arise only along a black wall or a black part of a wall. Therefore the case ${}^0c = 0$, when the wall is transparent does not require the singular perturbation analysis.

Let us now apply the singular perturbation analysis for the case illustrated in Fig. 5. Consider the system

$$\begin{aligned} \dot{x} &= 2 - 2Z - x \\ \dot{y} &= 0.4 - 0.4Z - 0.1x - 0.1y, \end{aligned} \tag{27}$$

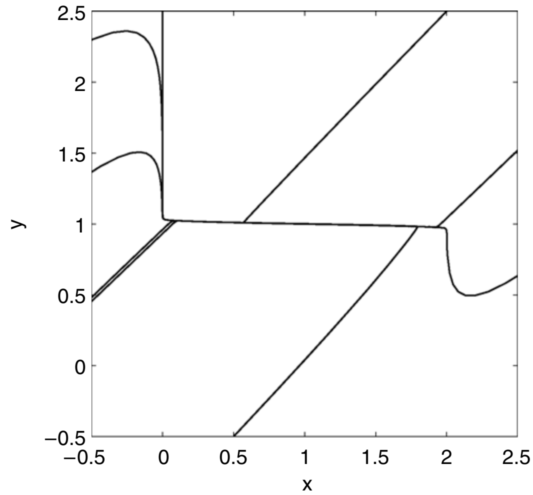

Fig. 4. The trajectories of (26) for $\alpha = 0.1$, $q = 0.01$ and ${}^0c = 1$.

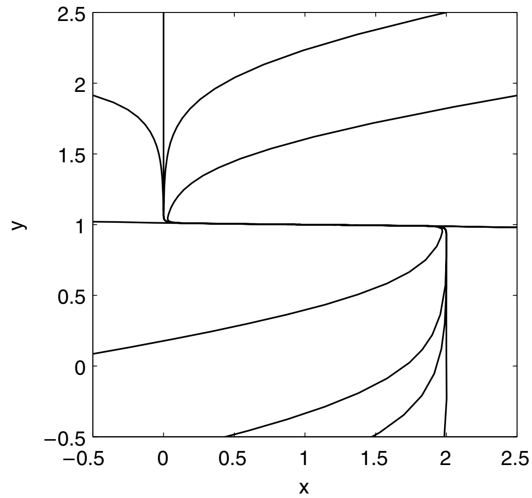

Fig. 5. The trajectories of (26) for $\alpha = 0.1$, $q = 0.01$ and ${}^0c = 0.2$.

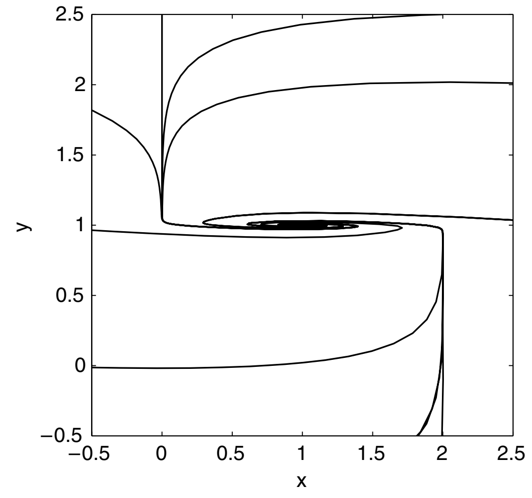

Fig. 6. The trajectories of (26) for $\alpha = 0.1$, $q = 0.01$ and ${}^0c = 0$.

which is a particular case of (26) for ${}^0c = 0.2$, $\alpha = 0.1$ and defines smooth solutions for $q > 0$. Assume that Eq. (27) is equipped with the initial conditions

$$x(t_0, q) = 2, \quad y(t_0, q) = y^0(q) > 0.$$

The first initial condition $x(t_0, q) = 2$ guarantees the fact that solutions hit the wall $y = 1$ in its black part.

The variable y is singular, Z is the Hill function, therefore the changing of variables gives us

$$\begin{aligned} &\dot{x} = 2 - 2Z - x \\ &q\dot{Z} = \frac{Z(1-Z)}{\Sigma^{-1}(Z,1,q)}(0.4 - 0.4Z - 0.1x - 0.1\Sigma^{-1}(Z,1,q)) \end{aligned} \tag{28}$$

with the initial conditions

$$x(t_0, q) = 2, \qquad Z(t_0, q) = Z^0(q), \quad 0 < Z^0(q) < 1,$$

where it is assumed that we have the convergence of the Z variable as $q \to 0$.

Let $q \to 0$. Then $y(t, q)$ reaches the value $y = 1$ for infinitesimal time and we get the system

$$\begin{aligned} &\dot{x} = 2 - 2Z - x \\ &Z(1-Z)(0.3 - 0.4Z - 0.1x) = 0 \end{aligned} \tag{29}$$

under the initial conditions

$$x(t_0, 0) = 2.$$

The solution of the second equation $\hat{Z} = 0.25$ is an asymptotically stable, uniformly with respect to x, solution of the associated problem

$$\tilde{Z}' = \tilde{Z}(1-\tilde{Z})(0.3 - 0.4\tilde{Z} - 0.1x) \tag{30}$$

with the attractor basin (0, 1), and the limit solution of (27) will be given by

$$\dot{x} = 1.5 - x, \quad x(t_0, 0) = 2.$$

The smooth solutions of (27) approach this limit solution. Fig. 5 does not show clearly the dynamics in the wall $y = 1$, but we can get it by using the analytical expression for the limit solution.

6. Singular perturbation analysis for walls

In this section and Section 7 we do not refer to the delay system (7) assuming that we already have the equivalent system of ordinary differential equation (12) obtained by applying the modified linear chain trick method from Section 3 to (7).

In this section we study the situation where exactly one of the variables y_i, $i = 1, \ldots, n$ in (12) approaches one of its threshold values θ_k, while the others stay away from their thresholds. Renumbering we can always assume that the singular variable is y_1 with the threshold value θ_1. The other variables are then "regular". In the limit (i.e. as $\bar{q} \to \bar{0}$) we obtain that $y_1 = \theta_1$ and $Z_k(y_k) = 1$ or 0 for $k \geq 2$.

First of all, we rewrite system (12) in the form

$$\begin{aligned} &\dot{x}_i = F_i(Z_1, \ldots, Z_m) - G_i(Z_1, \ldots, Z_m)x_i \\ &{}^1\dot{v}_i = -\alpha_i\,{}^1v_i + \alpha_i\,{}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(Z_1, \ldots, Z_m) - G_i(Z_1, \ldots, Z_m)x_i) \\ &{}^2\dot{v}_i = -\alpha_i\,{}^2v_i + \alpha_i\,{}^3v_i + \alpha_i x_i\,{}^2c_i \\ &{}^3\dot{v}_i = -\alpha_i\,{}^3v_i + \alpha_i{}^4v_i + \alpha_i x_i\,{}^3c_i \\ &\ldots \\ &{}^p\dot{v}_i = -\alpha_i{}^pv_i + \alpha_i x_i{}^pc_i \\ &Z_k = \Sigma(y_{i(k)}, \theta_k, q_k), \qquad y_i = {}^1v_i, \quad i = 1, \ldots, n,\ k = 1, \ldots, m. \end{aligned}$$

Assume that (12) is equipped with the initial conditions

$$x(t_0, \bar{q}) = x^0(\bar{q}), \qquad v(t_0, \bar{q}) = v^0(\bar{q}) \tag{31}$$

and consider the wall

$$\mathcal{SD}(\theta_1, B_R) = \{(x, v) : \{y_1 = \theta_1\},\ Z_k(y_k) = B_k,\ k \geq 2\}, \tag{32}$$

where $x = (x_1, \ldots, x_n)$, $v = (v_1, \ldots, v_n)$, B_k is a Boolean variable associating to each Z_k by $B_k = 0$ if $y_k < \theta_k$ and $B_k = 1$ if $y_k > \theta_k$. The wall W can contain different parts: attractive (i.e. black), expelling (i.e. white) or transparent. Assume that W is a black part of the wall and the limit initial point belongs to W; i.e.

$$(x^0(\bar{q}), v^0(\bar{q})) \to (x^0(\bar{0}), v^0(\bar{0})) \in W, \quad \bar{q} = (q_1, \ldots, q_m)$$

as $\bar{q} \to \bar{0}$. In particular, $y_1^0(\bar{0}) = {}^1v_1^0(\bar{0}) = \theta_1$.

We want to find the conditions when the solutions of the smooth problem (12), (31) uniformly converge to the solution of the limit system for $\bar{q} = \bar{0}$. To do this we will use the singular perturbation analysis.

Consider the wall W given by (32) with the singular variable y_1. If the singular variable y_1 has no delay then $y_1 = x_1$ and we consider the equation $\dot{x}_1 = F_1(Z_1, \dots, Z_m) - G_1(Z_1, \dots, Z_m)x_1$. Denote

$$\Phi_o^r(Z_1, Z_R, x_1, \bar{q}) = F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1$$

and

$$\Phi_o^s(Z_1, Z_R, \bar{q}) = F_1(Z_1, Z_R) - G_1(Z_1, Z_R)\Sigma^{-1}(Z_1, \theta_1, q_1),$$

where $Z_R = (Z_2, \dots, Z_m)$, $\bar{q} = (q_1, \dots, q_m)$.

If the singular variable is delayed, then we have that $y_1 = {}^1v_1$ and work with the equation

$${}^1\dot{v}_1 = -\alpha_1\, {}^1v_1 + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, \dots, Z_m) - G_1(Z_1, \dots, Z_m)x_1).$$

Denote

$$\Phi_d^r(Z_1, Z_R, x_1, {}^1v_1, {}^2v_1, \bar{q}) = -\alpha_1\, {}^1v_1 + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1)$$

and

$$\Phi_d^s(Z_1, Z_R, x_1, {}^2v_1, \bar{q}) = -\alpha_1 \Sigma^{-1}(Z_1, \theta_1, q_1) + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1),$$

where $Z_R = (Z_2, \dots, Z_m)$, $\bar{q} = (q_1, \dots, q_m)$. We use these complicated notations for Φ_d^r and Φ_d^s because it will allow us later on to unify the analysis for both delay and non-delay cases.

According to the singular perturbation analysis described in the Introduction, we replace y_1 with Z_1. Since Z_k are assumed to be the Hill functions, the equation for y_1 will be replaced with

$$q_1\dot{Z}_1 = \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}\Phi_o^s(Z_1, Z_R, \bar{q})$$

or

$$q_1\dot{Z}_1 = \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}\Phi_d^s(Z_1, Z_R, x_1, {}^2v_1, \bar{q})$$

in the non-delay and delay cases, respectively. Then the equation of motion in W will be given by either
(1) if the singular variable y_1 has no delay

$$\begin{aligned}
q_1\dot{Z}_1 &= \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}(F_1(Z_1, Z_R) - G_1(Z_1, Z_R)\Sigma^{-1}(Z_1, \theta_1, q_1))\\
\dot{x}_j &= F_j(Z_1, Z_R) - G_j(Z_1, Z_R)x_j,\\
{}^1\dot{v}_i &= -\alpha_i\, {}^1v_i + \alpha_i\, {}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(Z_1, Z_R) - G_i(Z_1, Z_R)x_i)\\
{}^2\dot{v}_i &= -\alpha_i\, {}^2v_i + \alpha_i\, {}^3v_i + \alpha_i x_i\, {}^2c_i\\
{}^3\dot{v}_i &= -\alpha_i\, {}^3v_i + \alpha_i\, {}^4v_i + \alpha_i x_i\, {}^3c_i\\
&\vdots\\
{}^p\dot{v}_i &= -\alpha_i\, {}^pv_i + \alpha_i x_i\, {}^pc_i,\\
i &= 1, \dots, n,\ j = 2, \dots, n
\end{aligned}$$

or
(2) if y_1 is "delayed"

$$\begin{aligned}
q_1\dot{Z}_1 &= \frac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}(-\alpha_1\Sigma^{-1}(Z_1, \theta_1, q_1) + \alpha_1{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1))\\
\dot{x}_i &= F_i(Z_1, Z_R) - G_i(Z_1, Z_R)x_i,\\
{}^1\dot{v}_j &= -\alpha_j{}^1v_j + \alpha_j\, {}^2v_j + \alpha_j x_j({}^0c_j + {}^1c_j) + {}^0c_j(F_j(Z_1, Z_R) - G_j(Z_1, Z_R)x_j)\\
{}^2\dot{v}_i &= -\alpha_i{}^2v_i + \alpha_i\, {}^3v_i + \alpha_i x_i\, {}^2c_i\\
{}^3\dot{v}_i &= -\alpha_i{}^3v_i + \alpha_i{}^4v_i + \alpha_i x_i\, {}^3c_i\\
&\vdots\\
{}^p\dot{v}_i &= -\alpha_i{}^pv_i + \alpha_i x_i\, {}^pc_i, \quad i = 1, \dots, n,\ j = 2, \dots, n.
\end{aligned}$$

For convenience we rewrite the systems as

$$
\begin{aligned}
&q_1\dot{Z}_1 = \frac{Z_1(1-Z_1)}{\Sigma^{-1}(Z_1,\theta_1,q_1)}\Phi(\bar{q})\\
&\dot{x}_1 = \bar{\Phi}(\bar{q})\\
&\dot{x}_i = F_i(Z_1,Z_R) - G_i(Z_1,Z_R)x_i\\
&{}^1\dot{v}_i = -\alpha_i\,{}^1v_i + \alpha_i\,{}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(Z_1,Z_R) - G_i(Z_1,Z_R)x_i)\\
&\dot{v}_i^-(t) = A_i^- v_i^- + \alpha_i x_i \Pi_i^-(x_i), \quad i = 2,\dots,n,
\end{aligned} \tag{33}
$$

where

$$
A_i^- = \underbrace{\begin{pmatrix} -\alpha_i & \alpha_i & \dots & 0\\ 0 & -\alpha_i & \dots & 0\\ \vdots & \ddots & \ddots & \vdots\\ 0 & \dots & 0 & -\alpha_i \end{pmatrix}}_{p-1}, \qquad v_i^- = \begin{pmatrix} {}^2v_i\\ {}^3v_i\\ \vdots\\ {}^pv_i \end{pmatrix} \quad \text{and} \quad \Pi_i^- = \begin{pmatrix} {}^2c_i\\ {}^3c_i\\ \vdots\\ {}^pc_i \end{pmatrix}. \tag{34}
$$

Remark that for the non-delay case

$$x_1 = {}^1v_1, \qquad \Phi(\bar{q}) = \Phi_o^s(Z_1,Z_R,\bar{q}), \qquad \bar{\Phi}(\bar{q}) = \Phi_d^r(Z_1,Z_R,x_1,{}^1v_1,{}^2v_1,\bar{q}).$$

In the delay case

$$\Phi(\bar{q}) = \Phi_d^s(Z_1,Z_R,x_1,{}^2v_1,\bar{q}), \qquad \bar{\Phi}(\bar{q}) = \Phi_o^r(Z_1,Z_R,x_1,\bar{q}).$$

Consider Eq. (33) with the initial conditions

$$
\begin{aligned}
&x(t_0,\bar{q}) = x_{r_1}(t_0,\bar{q}) = x^0(\bar{q})\\
&v(t_0,\bar{q}) = v_{r_2}(t_0,\bar{q}) = v^0(\bar{q})\\
&Z_1(t_0,q_1) = Z^0(q_1).
\end{aligned} \tag{35}
$$

Assume that the convergence of the initial values in (31) implies the convergence of the Z_1 variable in (35) as $q_1 \to 0$.

In (35) $r_1 = 2,\dots,n$ and $r_2 = 1,\dots,n$ if the singular variable does not have a delay. If the singular variable is delayed, then $r_1 = 1,\dots,n$ and $v_{r_2} = (v_{1,R}, v_2,\dots,v_n)$, v_i $(i \geq 2)$ are as before in (34), $v_{1,R} = ({}^2v_1, {}^3v_1,\dots,{}^pv_1)$ and $Z_1(q_1) = \Sigma(y_1,\theta_1,q_1)$.

Let $\bar{q}$ go to $\bar{0}$ and consider the corresponding reduced system for Eqs. (33)

$$
\begin{aligned}
&\frac{Z_1(1-Z_1)}{\theta_1}\Phi(\bar{0}) = 0\\
&\dot{x}_1 = \bar{\Phi}(\bar{0})\\
&\dot{x}_i = F_i(Z_1,B_R) - G_i(Z_1,B_R)x_i\\
&{}^1\dot{v}_i = -\alpha_i\,{}^1v_i + \alpha_i\,{}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(Z_1,B_R) - G_i(Z_1,B_R)x_i)\\
&\dot{v}_i^-(t) = A_i^- v_i^- + \alpha_i x_i \Pi_i^-(x_i), \quad i = 2,\dots,n,
\end{aligned} \tag{36}
$$

where $B_R = (B_2,\dots,B_m)$, A_i^-, v_i^- and Π_i^- are given by (34) and with the initial conditions

$$x(t_0,\bar{0}) = x^0(\bar{0}), \qquad v(t_0,\bar{0}) = v^0(\bar{0}),$$

where it is assumed that

$$
\begin{aligned}
&x^0(\bar{0}) = \lim_{\bar{q}\to\bar{0}} x^0(\bar{q})\\
&v^0(\bar{0}) = \lim_{\bar{q}\to\bar{0}} v^0(\bar{q})\\
&(x^0(\bar{0}), v^0(\bar{0})) \in W.
\end{aligned}
$$

Remark that for the non-delay case

$$
\begin{aligned}
&\Phi(\bar{0}) = \Phi_o^s(Z_1,B_R,\bar{0}) = F_1(Z_1,B_R) - G_1(Z_1,B_R)\theta_1\\
&\bar{\Phi}(\bar{0}) = \Phi_d^r(Z_1,B_R,x_1,{}^1v_1,{}^2v_1,\bar{0}) = -\alpha_1\,{}^1v_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1,B_R) - G_1(Z_1,B_R)x_1)
\end{aligned}
$$

and in the delay case

$$\Phi(\bar{0}) = \Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0}) = -\alpha_1\,\theta_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1),$$
$$\bar{\Phi}(\bar{0}) = \Phi_o^r(Z_1, B_R, x_1, \bar{0}) = F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1.$$

Since the sliding modes can arise only along the black part of the wall we need to find the conditions which provide this. To this end, we work with the equation for the singular variable.

If the singular variable has no delay, then $x_1 = \theta_1$ and according to Definition 3, the conditions of blackness are given by

$$\Phi_o^s(1, B_R, \bar{0}) < 0$$
$$\Phi_o^s(0, B_R, \bar{0}) > 0$$

or

$$F_1(1, B_R) - G_1(1, B_R)\theta_1 < 0$$
$$F_1(0, B_R) - G_1(0, B_R)\theta_1 > 0. \tag{37}$$

If the singular variable is delayed, then we have that ${}^1v_1 = \theta_1$ and the conditions of blackness will be given by

$$\Phi_d^s(1, B_R, x_1, {}^2v_1, \bar{0}) < 0$$
$$\Phi_d^s(0, B_R, x_1, {}^2v_1, \bar{0}) > 0$$

or

$$-\alpha_1\,\theta_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(1, B_R) - G_1(1, B_R)x_1) < 0$$
$$-\alpha_1\,\theta_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(0, B_R) - G_1(0, B_R)x_1) > 0. \tag{38}$$

Clearly, if ${}^0c_1 = 0$ then $\Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0})$ does not change the sign. Therefore the necessary condition for a wall to be black is ${}^0c_1 \neq 0$.

Consider Eq. (36) and denote by $\hat{Z}_1$, $0 < \hat{Z}_1 < 1$ a unique solution of the equation

$$\Phi(\bar{0}) = 0.$$

Remark that if $\Phi(\bar{0}) = \Phi_o^s(Z_1, B_R, \bar{0})$, then $\hat{Z}_1 = const$ and if $\Phi(\bar{0}) = \Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0})$, then $\hat{Z}_1$ is a function of x_1 and ${}^2v_1$, in the non-delay and delay cases, respectively.

Theorem 6. *Assume that the condition (38) or the condition (37) is satisfied for ${}^0c_1 < 0$ (the delayed case) and ${}^0c_1 = 0$ (the non-delay case), respectively. Then there exists $T_0 > t_0$ such that*

$$\lim_{\bar{q}\to\bar{0}} x(t, \bar{q}) = x(t, \bar{0}),$$
$$\lim_{\bar{q}\to\bar{0}} v(t, \bar{q}) = v(t, \bar{0}), \quad t \in [t_0, T_0], \tag{39}$$

the convergence is uniform in $t \in [t_0, T_0]$, where $x(t, \bar{q})$, $v(t, \bar{q})$ are solutions of (33) and $x(t, \bar{0})$, $v(t, \bar{0})$ are a limit solution and satisfy the system

$$\dot{x}_1 = \bar{\Phi}(\bar{0})$$
$$\dot{x}_i = F_i(\hat{Z}_1, B_R) - G_i(\hat{Z}_1, B_R)x_i$$
$${}^1\dot{v}_i = -\alpha_i\,{}^1v_i + \alpha_i\,{}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(\hat{Z}_1, B_R) - G_i(\hat{Z}_1, B_R)x_i) \tag{40}$$
$$\dot{v}_i^-(t) = A_i^- v_i^- + \alpha_i x_i \Pi_i^-(x_i), \quad i = 2, \ldots, n$$

with the initial conditions (35) and A_i^-, v_i^-, Π_i^- given by (34).

Moreover, we have

$$\lim_{q_1\to 0} Z_1(t, q_1) = \hat{Z}_1, \qquad \sigma \le t \le T_0,$$

the convergence is uniform on any $[\sigma, T_0]$, $\sigma > t_0$.

Proof. To prove the theorem we need to show that Tikhonov's theorem (see Appendix B) can be applied to the system for $\Phi(\bar{0}) = \Phi_o^s(Z_1, B_R, \bar{0})$ (non-delay case) and $\Phi(\bar{0}) = \Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0})$ (the case when the delay is present).

Let us look at the more difficult case $\Phi(\bar{0}) = \Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0})$. For the proof we have to check the following conditions:

(1) *Isolated root condition.*

The first equation of (36) has an isolated root $\hat{Z}_1$ with respect to Z_1.

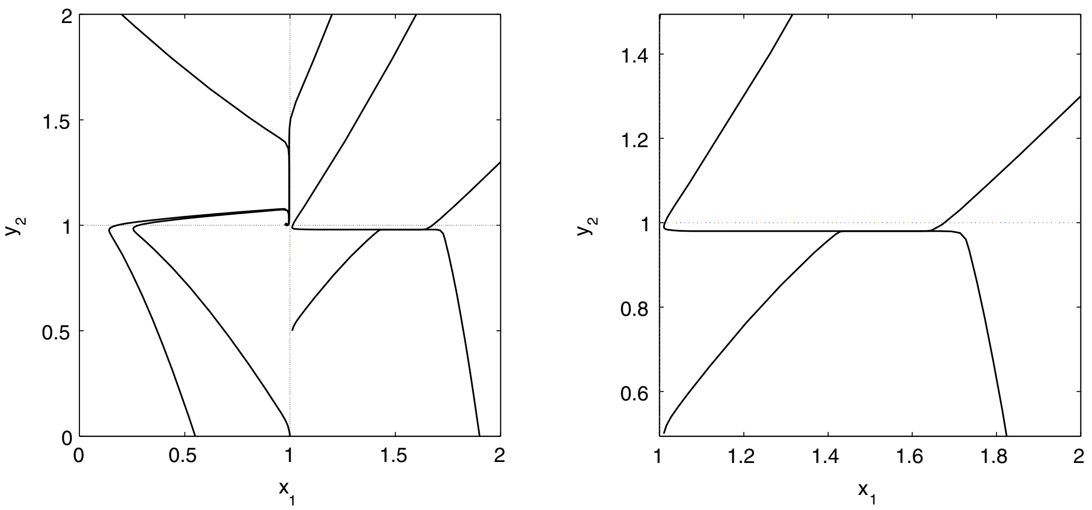

Fig. 7. The trajectories of (42) for $q = 0.01$, ${}^0c = 1$.

(2) *Associated problem. Lyapunov stability condition.*
For the associated problem

$$\tilde{Z}_1' = \frac{\tilde{Z}_1(1-\tilde{Z}_1)}{\theta_1}\Phi_d^s(\tilde{Z}_1, B_R, x_1, {}^2v_1, \bar{0}), \tag{41}$$

where $\tilde{Z}_1' = \frac{\partial \tilde{Z}_1}{\partial \tau}$, $\tau = \frac{t}{q}$ is the stretching transformation, the root $\hat{Z}_1$ is an equilibrium point. Moreover, this point is asymptotically stable in the sense of Lyapunov, uniformly in $(x_1, {}^2v_1) \in K$, where K is any compact subset of a set $M \subset \mathbb{R}^2$ of all solutions $(x_1, {}^2v_1)$ of Eq. (38).
(3) *The domain of attraction condition.*
The initial values should belong to the domain of attraction of the root $\hat{Z}_1$.
Let us now check that these assumptions are satisfied.
The condition (1) is ensured by (38) and linearity of $\Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0})$ in the first variable. Moreover, $0 < \hat{Z}_1 < 1$.
Let us look at the condition (2). The function $\Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0})$ is linear in Z_1 (see assumptions on F_i, G_i) therefore, as in (1) for any $(x_1, {}^2v_1)$ there exists a unique solution $\hat{Z}_1(x_1, {}^2v_1)$, $0 < \hat{Z}_1(x_1, {}^2v_1) < 1$ satisfying the equation $\Phi_d^s(Z_1, B_R, x_1, {}^2v_1, \bar{0}) = 0$. According to (38), the derivative of function Φ_d^s changes from minus to plus at $\hat{Z}_1$, therefore the solution is an asymptotically stable stationary point of the problem (41) in the Lyapunov sense. Moreover, the solution $\hat{Z}_1(x_1, {}^2v_1)$ is uniformly stable in $(x_1, {}^2v_1) \in K \subset M$. The conditions 1 and 2 are thus satisfied.
For $t = t_0$ and $\bar{q} = \bar{0}$ we have $(x^0(\bar{0}), v^0(\bar{0})) \in W$ therefore $(x_1^0(\bar{0}), {}^2v_1^0(\bar{0})) \in M$. Solving the equation $\Phi_d^s(Z_1, B_R, x_1^0(\bar{0}), {}^2v_1^0(\bar{0}), \bar{0}) = 0$ we see again that Z_1 belongs to the domain of attraction, as soon as $(x_1^0(\bar{0}), v_1^0(\bar{0})) \in M$. Therefore the conditions (1)–(3) are verified and we can apply Tikhonov's theorem to any interval $[t_0, T_0]$, where $(x_1, {}^2v_1) \in K$.
The proof for $\Phi_0^s(Z_1, B_R, \bar{0})$ is similar. The theorem is proved.

Theorem 6 gives us an opportunity to extend the solution along a black part of a wall. Moreover this extension is unique and satisfies (40). Also, according to the formulas (39), we get the convergence of smooth solutions to the limit solutions as $\bar{q} \to \bar{0}$.

Example 7. Consider the system

$$\begin{aligned}
\dot{x}_1 &= Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1\\
\dot{x}_2 &= 1 - Z_1Z_2 - 0.9x_2\\
Z_i &= \Sigma(y_i, 1, q_i), \quad i = 1, 2\\
y_1 &= x_1\\
y_2(t) &= {}^0c x_2(t) + {}^1c\int_{-\infty}^{t} {}^1K(t-s)x_2(s)\mathrm{d}s.
\end{aligned} \tag{42}$$

Assume that ${}^0c \geq 0$, ${}^0c + {}^1c = 1$, $q_i \geq 0$, $\Sigma(y_i, 1, q_i)$, $i = 1, 2$ is the Hill function given by (9) and ${}^1K(u)$ is the weak generic delay kernel given by (18).

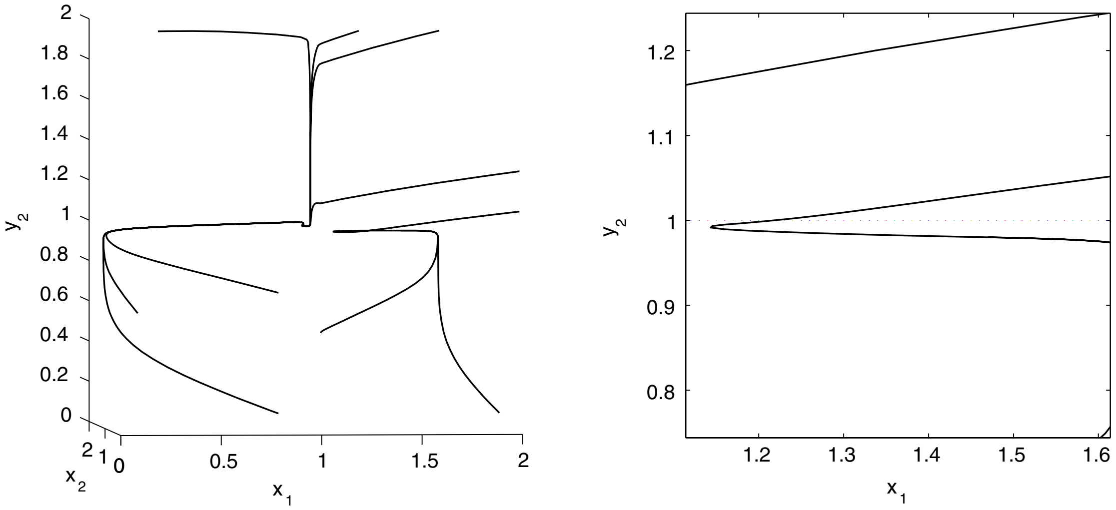

Fig. 8. The trajectories of (42) for $q = 0.01$, ${}^0c = 0.2$, $x_2^0 = 0.4$.

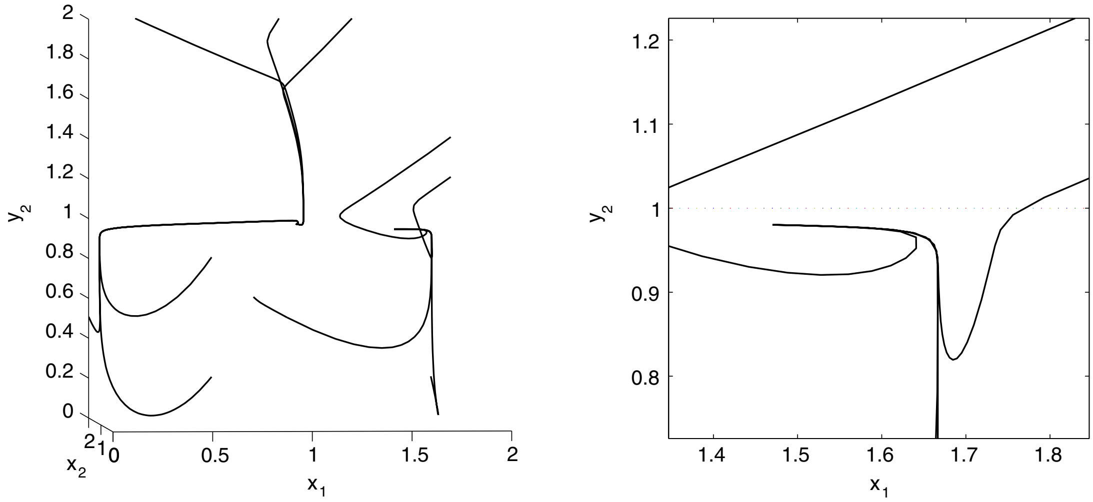

Fig. 9. The trajectories of (42) for $q = 0.01$, ${}^0c = 0.2$, $x_2^0 = 5$.

The trajectories of (42) are shown in Figs. 8–10 for the corresponding values of parameters, where the left graphs display the general behavior of trajectories of (42), and the right graphs describe parts of the wall $\mathcal{SD}(\theta_2, 1) : \{x_1 > \theta_1,\ y_2 = \theta_2\}$ that are of interest for us. Fig. 7 illustrates the non-delay case.

Description of Figs. 7–10

Fig. 7 illustrates the non-delay case, the wall $\mathcal{SD}(\theta_2, 1)$ is black. With adding the delay effect the situation changes. According to the conditions of blackness (38), we get the system

$$-\alpha_2 + \alpha_2 x_2 + {}^0c(-0.9x_2) < 0$$
$$-\alpha_2 + \alpha_2 x_2 + {}^0c(1 - 0.9x_2) > 0.$$

Assume that $\alpha_2 = 0.1$, ${}^0c = 0.2$. Then we get that only the part $-1.25 < x_2 < 1.25$ of the wall is black and the rest is transparent. So if a trajectory hits the wall in the black part (as in Fig. 8), then a solution does not leave this wall and goes to a stationary point. If a trajectory hits the wall in the transparent part (as in Fig. 9), then it crosses the wall a finite many times until it approaches the black part. Afterwards the behavior of the solution is the same as in the previous case. The case $c_0 = 0$ is shown in Fig. 10, the wall $\mathcal{SD}(\theta_2, 1)$ is always transparent, independently of x_2.

The sliding modes can arise only along a black wall or a black part of a wall. Therefore the case ${}^0c = 0$, when the wall is transparent, does not require the singular perturbation analysis.

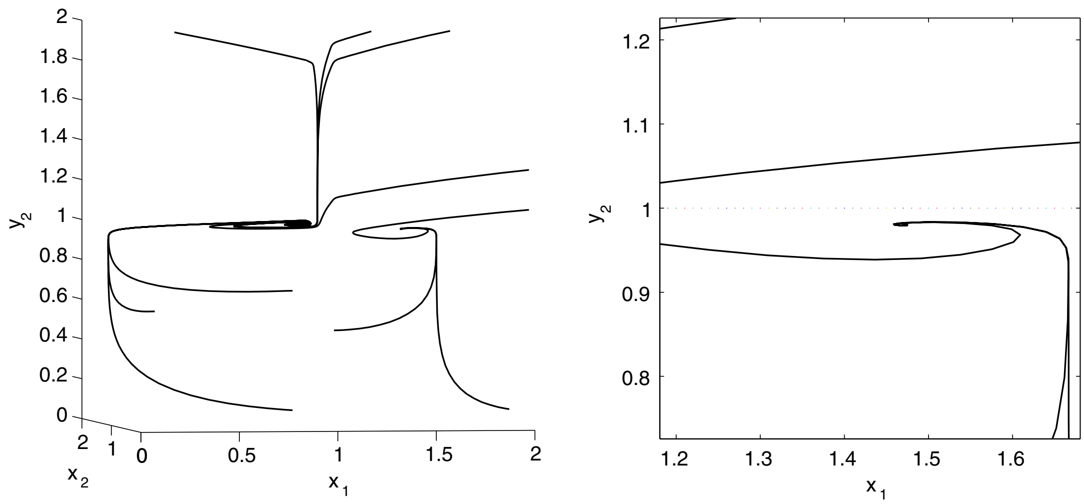

Fig. 10. The trajectories of (42) for $q = 0.01$, ${}^0c = 0$, $x_2^0 = 0.4$.

Let us apply the singular perturbation analysis in the case illustrated in Fig. 8. Consider the system

$$\begin{aligned}\dot{x_1} &= Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1\\ \dot{x_2} &= 1 - Z_1Z_2 - 0.9x_2\\ \dot{y_2} &= -0.1y_2 + 0.1x_2 + 0.2(1 - Z_1Z_2 - 0.9x_2)\end{aligned} \tag{43}$$

which defines smooth solutions for ${}^0c = 0.2$, $\alpha = 0.1$ and $q > 0$ (Fig. 8). Assume that Eq. (43) is equipped with the initial conditions

$$x_1(t_0, q) = x_1^0(q), \qquad x_2(t_0, q) = 0.4, \qquad y_2(t_0, q) = y_2^0(q) > 0.$$

These conditions guarantee the fact that solutions hit the wall in its black part.

Consider the wall $\mathcal{SD}(\theta_2, 1)$, the variable y_2 is singular. Change of variables in (43) gives us

$$\begin{aligned}\dot{x_1} &= Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1\\ \dot{x_2} &= 1 - Z_1Z_2 - 0.9x_2\\ q_2\dot{Z_2} &= \frac{Z_2(1 - Z_2)}{\Sigma^{-1}(Z_2, \theta_2, q_2)}(-0.1\Sigma^{-1}(Z_2, \theta_2, q_2) + 0.1x_2 + 0.2(1 - Z_1Z_2 - 0.9x_2))\end{aligned} \tag{44}$$

with the initial conditions

$$x_1(t_0, q) = x_1^0(q), \qquad x_2(t_0, q) = 0.4, \qquad Z_2(t_0, q) = Z_2^0(q), \quad 0 < Z_2^0(q) < 1,$$

where we assume that the convergence of the Z_2 variable as $q \to 0$ is the case.

Let $q \to 0$. Then $y_2(t, q)$ reaches the value $y_2 = \theta_2$ after infinitesimal time and we get the system

$$\begin{aligned}\dot{x_1} &= 1 - Z_2 - 0.6x_1\\ \dot{x_2} &= 1 - Z_2 - 0.9x_2\\ &\frac{Z_2(1 - Z_2)}{\theta_2}(-0.1\theta_2 + 0.1x_2 + 0.2(1 - Z_2 - 0.9x_2)) = 0\end{aligned} \tag{45}$$

with the initial condition

$$x_1(t_0, 0) = x_1^0(0), \qquad x_2(t_0, 0) = 0.4, \qquad y_2(t_0, 0) = \theta_2.$$

The solution of the third equation in (45) $\hat{Z}_2 = 0.34$ is an asymptotically stable, uniformly in x_2, solution of the associated problem

$$\tilde{Z}_2' = \frac{\tilde{Z}_2(1 - \tilde{Z}_2)}{\theta}(-0.1\theta_2 + 0.1x_2 + 0.2(1 - \tilde{Z}_2 - 0.9x_2))$$

with the attractor basin (0, 1). By the direct substitution $\hat{Z}_2 = 0.34$ in (44) we obtain that the limit solution of (43) in the wall is given by

$$\dot{x_1} = 0.66 - 0.6x_1$$
$$\dot{x_2} = 0.66 - 0.9x_2$$
$$y_2 = \theta_2, \quad x_1(t_0, 0) = x_1^0(0), \quad x_2(t_0, 0) = 0.4.$$

The smooth solutions of (43) approach this limit solution.

7. Singular perturbation analysis, the general case

In this section we treat the case of arbitrarily many singular variables letting the variables y_s, $s \in S$ approach their threshold values θ_k. Renumbering we can gassume that the singular variables are the first $|S|$ variables $y_1, \dots, y_{|S|}$. The other $|R|$ variables are regular. Assume that the steepness parameters q_s, $s \in S$ are equal for all singular variables (this is essential for singular perturbation analysis; see e.g. [5]); i.e. $q_s = q$ for all $s \in S$ and q_r, $r \in R$ can be different. Denote $\bar{q} = (q_S, q_R)$.

Consider system (12) equipped with the initial conditions

$$x(t_0, \bar{q}) = x^0(\bar{q}), \qquad v(t_0, \bar{q}) = v^0(\bar{q}). \tag{46}$$

We want to find conditions under which the solutions of the problem (12), (46) with $q_i > 0$, $i \in M$ uniformly converge to the solution of the limit system for $\bar{q} = \bar{0}$. To do this we use the singular perturbation analysis.

Denote

$$\Phi_o^r(Z_S, Z_R, x_r, \bar{q}) = F_r(Z_S, Z_R) - G_r(Z_S, Z_R)x_r,$$
$$\Phi_o^s(Z_S, Z_R, \bar{q}) = F_s(Z_S, Z_R) - G_s(Z_S, Z_R)\Sigma^{-1}(Z_s, \theta_s, q_s)$$

and

$$\Phi_d^r(Z_S, Z_R, x_r, {}^1v_r, {}^2v_r, \bar{q}) = -\alpha_r\, {}^1v_r + \alpha_r\, {}^2v_r + \alpha_r x_r({}^0c_r + {}^1c_r) + {}^0c_r(F_r(Z_S, Z_R) - G_r(Z_S, Z_R)x_r),$$
$$\Phi_d^s(Z_S, Z_R, x_s, {}^2v_s, \bar{q}) = -\alpha_s\Sigma^{-1}(Z_s, \theta_s, q_s) + \alpha_s\, {}^2v_s + \alpha_s x_s({}^0c_s + {}^1c_s) + {}^0c_s(F_s(Z_S, Z_R) - G_s(Z_S, Z_R)x_s).$$

Consider the singular domain $\mathcal{SD}(\theta_S, B_R)$. The equation of the motion in $\mathcal{SD}(\theta_S, B_R)$ will be given by

$$\begin{aligned} q_s\dot{Z}_s &= \frac{Z_s(1 - Z_s)}{\Sigma^{-1}(Z_s, \theta_s, q_s)}\Phi(\bar{q}) \\ \dot{x}_r &= \bar{\Phi}_o(\bar{q}) \\ {}^1\dot{v}_r &= \bar{\Phi}_d(\bar{q}) \\ \dot{v}_i^-(t) &= A_i^- v_i^- + \alpha_i x_i \Pi_i^-(x_i), \quad i = 2, \dots, n,\ s \in S,\ r \in R, \end{aligned} \tag{47}$$

where

$$A_i^- = \underbrace{\begin{pmatrix} -\alpha_i & \alpha_i & \dots & 0 \\ 0 & -\alpha_i & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \dots & 0 & -\alpha_i \end{pmatrix}}_{p-1}, \qquad v_i^- = \begin{pmatrix} {}^2v_i \\ {}^3v_i \\ \vdots \\ {}^pv_i \end{pmatrix} \quad \text{and} \quad \Pi_i^- = \begin{pmatrix} {}^2c_i \\ {}^3c_i \\ \vdots \\ {}^pc_i \end{pmatrix}. \tag{48}$$

Note that
(1) if all singular variables $y_1, \dots, y_{|S|}$ are without delay, then

$$\Phi(\bar{q}) = \Phi_o^s(Z_S, Z_R, \bar{q}), \quad s = 1, \dots, |S|,$$
$$\bar{\Phi}_o(\bar{q}) = \Phi_o^r(Z_S, Z_R, x_r, \bar{q}), \quad r = |S| + 1, \dots, n,$$
$$\bar{\Phi}_d(\bar{q}) = \Phi_d^r(Z_S, Z_R, x_r, {}^1v_r, {}^2v_r, \bar{q}), \quad r = 1, \dots, n.$$

(2) if all singular variables $y_1, \dots, y_{|S|}$ are delayed, then

$$\Phi(\bar{q}) = \Phi_d^s(Z_S, Z_R, x_s, {}^2v_s, \bar{q}), \quad s = 1, \dots, |S|,$$
$$\bar{\Phi}_o(\bar{q}) = \Phi_o^r(Z_S, Z_R, x_r, \bar{q}), \quad r = 1, \dots, n,$$
$$\bar{\Phi}_d(\bar{q}) = \Phi_d^r(Z_S, Z_R, x_r, {}^1v_r, {}^2v_r, \bar{q}), \quad r = |S| + 1, \dots, n.$$

(3) if $y_1, \ldots, y_c$, $c < |S|$ do not have delays and $y_{c+1}, \ldots, y_{|S|}$ are delayed, then

$$\Phi(\bar{q}) = \begin{cases} \Phi_o^s(Z_S, Z_R, \bar{q}) & \text{if } s = 1, \ldots, c \\ \Phi_d^s(Z_S, Z_R, x_s, {}^2v_s, \bar{q}) & \text{if } s = c+1, \ldots, |S|, \end{cases}$$

$$\bar{\Phi}_o(\bar{q}) = \Phi_o^r(Z_S, Z_R, x_r, \bar{q}), \quad r = c+1, \ldots, n,$$
$$\bar{\Phi}_d(\bar{q}) = \Phi_d^r(Z_S, Z_R, x_r, {}^1v_r, {}^2v_r, \bar{q}), \quad r = 1, \ldots, c; |S|+1, \ldots, n.$$

Consider Eq. (47) with the initial conditions

$$\begin{aligned} &x(t_0, \bar{q}) = x_{r_1}(t_0, \bar{q}) = x^0(\bar{q}), \\ &v(t_0, \bar{q}) = v_{r_2}(t_0, \bar{q}) = v^0(\bar{q}), \\ &Z_S(t_0, \bar{q}) = Z^0(\bar{q}). \end{aligned} \tag{49}$$

Assume that the convergence of the initial values in (46) implies the convergence of the Z_S variable in (49) as $\bar{q} \to \bar{0}$ and remark that

in the case (1) $r_1 = |S|+1, \ldots, n$ and $r_2 = 1, .., n$;
in the case (2) $r_1 = 1, \ldots, n$; $v_{r_2} = (v_{1,R}, v_2, \ldots, v_n)$, v_i, $i \geq 2$ are the same as in (48), $v_{1,R} = ({}^{|S|+1}v_1, \ldots, {}^p v_1)$;
in the case (3) $r_1 = c+1, \ldots, n$; $v_{r_2} = (v_{1,R}, v_2, \ldots, v_n)$, v_i, $i \geq 2$ are the same as in (48), $v_{1,R} = ({}^1v_1, \ldots, {}^c v_1, {}^{|S|+1}v_1, \ldots, {}^p v_1)$.

The corresponding reduced system for $\bar{q} = \bar{0}$ is

$$\begin{aligned} &\frac{Z_s(1-Z_s)}{\theta_s}\Phi(\bar{0}) = 0 \\ &\dot{x}_r = \bar{\Phi}_o(\bar{0}) \\ &{}^1\dot{v}_r = \bar{\Phi}_d(\bar{0}) \\ &\dot{v}_i^-(t) = A_i^- v_i^- + \alpha_i x_i \Pi_i^-(x_i) \quad i = 2, \ldots, n,\ s \in S,\ r \in R, \end{aligned} \tag{50}$$

where A_i^-, v_i^- and Π_i^- are given by (48) and with the initial conditions

$$x(t_0, \bar{0}) = x^0(\bar{0}), \qquad v(t_0, \bar{0}) = v^0(\bar{0}). \tag{51}$$

Remark that

(1) if all singular variables $y_1, \ldots, y_{|S|}$ are without delay, then

$$\begin{aligned} \Phi(\bar{0}) &= \Phi_o^s(Z_S, B_R, \bar{0}) = F_s(Z_S, B_R) - G_s(Z_S, B_R)\theta_s, \quad s = 1, \ldots, |S|, \\ \bar{\Phi}_o(\bar{0}) &= \Phi_o^r(Z_S, B_R, x_r, \bar{0}) = F_r(Z_S, B_R) - G_r(Z_S, B_R)x_r, \quad r = |S|+1, \ldots, n, \\ \bar{\Phi}_d(\bar{0}) &= \Phi_d^r(Z_S, B_R, x_r, {}^1v_r, {}^2v_r, \bar{0}) \\ &= -\alpha_r {}^1v_r + \alpha_r {}^2v_r + \alpha_r x_r({}^0c_r + {}^1c_r) + {}^0c_r(F_r(Z_S, B_R) - G_r(Z_S, B_R)x_r), \quad r = 1, \ldots, n, \\ B_R &= (B_{|S|+1}, \ldots, B_n). \end{aligned}$$

(2) if all singular variables $y_1, \ldots, y_{|S|}$ are delayed, then

$$\begin{aligned} \Phi(\bar{0}) &= \Phi_d^s(Z_S, B_R, x_s, {}^2v_s, \bar{0}) = -\alpha_s\theta_s + \alpha_s {}^2v_s + \alpha_s x_s({}^0c_s + {}^1c_s) + {}^0c_s(F_s(Z_S, B_R) - G_s(Z_S, B_R)x_s), \quad s = 1, \ldots, |S|, \\ \bar{\Phi}_o(\bar{0}) &= \Phi_o^r(Z_S, B_R, x_r, \bar{0}) = F_r(Z_S, B_R) - G_r(Z_S, B_R)x_r, \quad r = 1, \ldots, n, \\ \bar{\Phi}_d(\bar{0}) &= \Phi_d^r(Z_S, B_R, x_r, {}^1v_r, {}^2v_r, \bar{0}) \\ &= -\alpha_r {}^1v_r + \alpha_r {}^2v_r + \alpha_r x_r({}^0c_r + {}^1c_r) + {}^0c_r(F_r(Z_S, B_R) - G_r(Z_S, B_R)x_r), \quad r = |S|+1, \ldots, n, \\ B_R &= (B_{|S|+1}, \ldots, B_n). \end{aligned}$$

(3) if $y_1, \ldots, y_c$, $c < |S|$ do not have delays and $y_{c+1}, \ldots, y_{|S|}$ are delayed, then

$$\Phi(\bar{0}) = \begin{cases} \Phi_o^s(Z_S, B_R, \bar{0}) & \text{if } s = 1, \ldots, c \\ \Phi_d^s(Z_S, B_R, x_s, {}^2v_s, \bar{0}) & \text{if } s = c+1, \ldots, |S|, \end{cases}$$

where

$$\begin{aligned} &\Phi_o^s(Z_S, B_R, \bar{0}) = F_s(Z_S, B_R) - G_s(Z_S, B_R)\theta_s, \quad s = 1, \ldots, c, \\ &\Phi_d^s(Z_S, B_R, x_s, {}^2v_s, \bar{0}) = -\alpha_s\theta_s + \alpha_s {}^2v_s + \alpha_s x_s({}^0c_s + {}^1c_s) + {}^0c_s(F_s(Z_S, B_R) - G_s(Z_S, B_R)x_s), \quad s = c+1, \ldots, |S|, \\ &\bar{\Phi}_o(\bar{0}) = \Phi_o^r(Z_S, B_R, x_r, \bar{0}) = F_r(Z_S, B_R) - G_r(Z_S, B_R)x_r, \quad r = c+1, \ldots, n, \\ &\bar{\Phi}_d(\bar{0}) = \Phi_d^r(Z_S, B_R, x_r, {}^1v_r, {}^2v_r, \bar{0}) = -\alpha_r {}^1v_r + \alpha_r {}^2v_r + \alpha_r x_r({}^0c_r + {}^1c_r) + {}^0c_r(F_r(Z_S, B_R) - G_r(Z_S, B_R)x_r), \\ &\qquad r = 1, \ldots, c, |S|+1, \ldots, n,\ B_R = (B_{|S|+1}, \ldots, B_n). \end{aligned}$$

Assumption 8. Assume that

$$\lim_{\bar{q}\to\bar{0}} x^0(\bar{q}) = x^0(\bar{0})$$
$$\lim_{\bar{q}\to\bar{0}} v^0(\bar{q}) = v^0(\bar{0})$$

and $(x^0(\bar{0}), v^0(\bar{0})) \in \mathcal{SD}(\theta_S, B_R)$.

Consider (50) and denote by $\hat{Z}_S$, $0 < \hat{Z}_s < 1$, $s \in S$ a unique solution of the equation

$$\Phi(\bar{0}) = 0.$$

Recall that $\Phi(\bar{0})$ depends on the following set of parameters

$\{Z_1, \dots, Z_{|S|}\}$ in the case (1),
$\{Z_1, \dots, Z_{|S|}, x_1, \dots, x_{|S|}, {}^2v_1, \dots, {}^2v_{|S|}\}$ in the case (2) and
$\{Z_1, \dots, Z_{|S|}, x_{c+1}, \dots, x_{|S|}, {}^2v_{c+1}, \dots, {}^2v_{|S|}\}$ in the case (3).

Denote by $S_o = \{1, \dots, c\}$ and $S_d = \{c+1, \dots, |S|\}$. Then we get that $\Phi(\bar{0}) = \Phi(Z_S, \bar{0})$, $\Phi(\bar{0}) = \Phi(Z_S, x_{S_o}, x_{S_d}, {}^2v_{S_o}, {}^2v_{S_d}, \bar{0})$ and $\Phi(\bar{0}) = \Phi(Z_S, x_{S_d}, {}^2v_{S_d}, \bar{0})$ for (1), (2) and (3) cases, respectively.

Theorem 9. *Let Assumption 8 be fulfilled. Assume that there exists a point $\hat{P}(\hat{Z}_S, \hat{x}_{S_d}, {}^2\hat{v}_{S_d}) \in (0,1)^{|S|} \times \mathbb{R}^{2(|S|-c)}$, where the Jacobi matrix with respect to $\tilde{Z}_S$ for the associated problem*

$$\tilde{Z}_s' = \frac{\tilde{Z}_s(1-\tilde{Z}_s)}{\theta_s}\Phi(\bar{0}), \quad s \in S \tag{52}$$

is stable; i.e. $\mathcal{R}e\,\lambda_i < 0$ for all eigenvalues λ_i of the Jacobi matrix.

Then there exists $T_0 > t_0$ and open bounded subsets $V_1 \in (0,1)^{|S|}$ and $V_2 \in \mathbb{R}^{2(|S|-c)}$, $\hat{P} \in V_1 \times V_2$, for which the following statements are true

$$\lim_{\bar{q}\to\bar{0}} x(t,\bar{q}) = x(t,\bar{0}),$$
$$\lim_{\bar{q}\to\bar{0}} v(t,\bar{q}) = v(t,\bar{0}), \quad t \in [t_0, T_0],$$

the convergence is uniform in $t \in [t_0, T_0]$, provided that the additional assumptions are put on the initial data $Z^0(\bar{q}) \in V_1$ for $0 < q_i < \delta$ and $(x^0_{S_d}(\bar{q}), v^0_{S_d}(\bar{q})) \in [V_2]$, where $[V_2]$ is the closure of V_2.

The limit solution $x(t,\bar{0})$, $v(t,\bar{0})$ satisfies the system

$$\dot{x}_r = \bar{\Phi}_o(\bar{0})$$
$${}^1\dot{v}_r = \bar{\Phi}_d(\bar{0})$$
$$\dot{v}_i^-(t) = A_i^- v_i^- + \alpha_i x_i \Pi_i^-(x_i), \quad i = 2, \dots, n, \; r \in R$$

with the initial conditions (51) and A_i^-, v_i^-, Π_i^- given by (48).

Moreover, we have

$$\lim_{q_s\to 0} Z_s(t, q_s) = \hat{Z}_s, \quad \sigma \le t \le T_0, \; s \in S,$$

the convergence is uniform on any $[\sigma, T_0]$, $\sigma > t_0$.

Remark 10. If in Theorem 9 $c = |S|$ ($c = 0$) then we get the case when all singular variables are non-delayed (case 1) (delayed (case 2)), respectively.

Proof of Theorem 9. To simplify the notation we put $\mu = (x_{S_d}, {}^2v_{S_d}) \in \mathbb{R}^{2(|S|-c)}$ and $\hat{\mu} = (\hat{x}_{S_d}, {}^2\hat{v}_{S_d})$. Let us first construct the set V_2. As it is known, at the point $\hat{P}$ we have a stable derivative $\hat{J}$ (the Jacobi matrix), and then the implicit function theorem yields a closed neighborhood $[V_2]$, where V_2 is an open and bounded subset of $\mathbb{R}^{2(|S|-c)}$ containing $\hat{\mu}$, and a continuous function $\hat{Z}_S^{\mu}$, $\mu \in [V_2]$ such that $P^{\mu} = P(\hat{Z}_S^{\mu}, \mu)$ is an isolated stationary point of (52) that satisfies $P(\hat{Z}_S^{\hat{\mu}}, \hat{\mu}) = \hat{P}$.

Moreover, Lyapunov's lemma (Theorem 8.7.2, [14]) states the matrix equation $\hat{J}^T V + V\hat{J} = -I$, where I is the identity matrix, has a positive definite matrix solution V. Denoting by $J(\tilde{Z}_S, \mu)$ the Jacobi matrix at a point $P(\tilde{Z}_S, \mu) \in (0,1)^{|S|} \times \mathbb{R}^{2(|S|-c)}$ observe that the symmetric matrix $-(J^T(\tilde{Z}_S, \mu)V + VJ(\tilde{Z}_S, \mu))$ will still be positive definite in the vicinity of $\hat{P}$. Without loss of generality we may assume that this is satisfied for any $\mu \in [V_2]$ and any $\tilde{Z}_S \in [V_1]$, where V_1 is some open and bounded neighborhood of $\hat{Z}_S$ containing $\hat{Z}_S^{\mu}$, $\mu \in [V_2]$.

Now we are ready to check the three assumptions of Tikhonov's theorem.
(1) *Isolated root condition.*
For any $\mu \in [V_2]$ the stationary point $P(\hat{Z}_S^{\mu}, \mu)$ is isolated by the construction.
(2) *Associated problem. Lyapunov stability condition.*
Consider the quadratic Lyapunov function $L^{\mu}(\tilde{Z}_S) = (\tilde{Z}_S - \hat{Z}_S^{\mu})^T V(\tilde{Z}_S - \hat{Z}_S^{\mu})$. As the Jacobi matrix $J(\tilde{Z}_S, \mu)$ is stable for $\tilde{Z}_S \in [V_1]$, $\mu \in [V_2]$ due to Lyapunov's lemma mentioned above, then the derivative of L^{μ} along solutions of (52) satisfies

$$\frac{d}{dt} L^{\mu}(\tilde{Z}_S) \leq -m|\tilde{Z}_S|^2, \quad \tilde{Z}_S \in [V_1] \tag{53}$$

for some $m > 0$ which is independent of $\mu \in [V_2]$ (because $L^{\mu}(\tilde{Z}_S)$ is continuous in $(\tilde{Z}_S, \mu) \in [V_1] \times [V_2]$, $[V_1] \times [V_2]$ is compact). This gives the uniform asymptotic stability of $\tilde{Z}_S^{\mu}$ with respect to $\mu \in [V_2]$.
(3) *The domain of attraction condition.*
We simply observe that as (53) is satisfied for all $\tilde{Z}_S \in [V_1]$, then LaSalle's principle (Theorem A.2, [15]) guarantees that $[V_1]$ belongs to the domain of attraction of $\tilde{Z}_S^{\mu}$.
Finally, we observe that, according to our assumptions on convergence of the initial values (49), all the conditions of Tikhonov's theorem are verified, and the proof of Theorem 9 is completed.

8. Examples

In Sections 6–8 we give a mathematical justification of the simplified analysis of the system describing gene regulatory networks with delay. We study the situations where exactly one of the variables y_i ($i = 1, \ldots, n$) (Sections 5 and 6) or arbitrary many variables y_i ($i = 1, \ldots, |S|$) approach their threshold values. Examples 5 and 7 illustrate the case where exactly one variable is singular and we apply the singular perturbation analysis to the domain of the first order. Following the logic of the paper we now want to look at the solutions' behavior in the singular domain of the order greater than 1. Theorem 9 gives us the theoretical grounds for application of singular perturbation analysis to singular domains of higher order. The case when few variables approach their thresholds is more complicated. At the same time, analysis of this situation can give us more information that can be of great importance for obtaining the whole picture of the trajectories' behavior.

For a better understanding we suggest the reader to start with a non-delay example from [5] presented in Appendix A. In this section we introduce delay into this example and consider a singular domain of the second order. All technical details are omitted; we focus on comparison of delay and non-delay cases and observe how introducing the delay influences the solutions' behavior.

Let us start with the case when the variable x_1 is delayed. Consider the system

$$\begin{aligned}
\dot{x}_1 &= Z_1 + Z_2 - 2Z_1Z_2 - \gamma_1 x_1 \\
\dot{x}_2 &= 1 - Z_1Z_2 - \gamma_2 x_2 \\
Z_i &= \Sigma(y_i, \theta_i, q_i), \quad i = 1, 2 \\
y_1(t) &= {}^0c x_1(t) + {}^1c \int_{-\infty}^{t} {}^1K(t-s)x_1(s)\mathrm{d}s.
\end{aligned}$$

Assume that $\gamma_1 = 0.6, \gamma_2 = 0.9, Z_i = \Sigma(y_i, \theta_i, q_i), i = 1, 2$ is the Hill function given by (9), the threshold values $\theta_1 = \theta_2 = 1$ and ${}^0c > 0, {}^0c + {}^1c = 1, q_i \geq 0, i = 1, 2, {}^1K(u)$ is the weak generic delay kernel given by (18).

To remove the delay from the system we apply the modified linear chain trick and get the equivalent system

$$\begin{aligned}
\dot{x}_1 &= Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1 \\
\dot{y}_1 &= -\alpha y_1 + \alpha x_1 + {}^0c(Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1) \\
\dot{x}_2 &= 1 - Z_1Z_2 - 0.9x_2 \\
x_2 &= y_2.
\end{aligned} \tag{54}$$

Assume that $\alpha = 0.1, {}^0c = 0.2$ and $q_1 = q_2 = q$. Images of some trajectories of Eq. (54) for $q = 0.01$ with the initial values $x_1^0 = 0.1$ and $x_1^0 = 10$ are shown in Figs. 11a and 12a, respectively. We look only at the Y_1X_2 plane; it is more convenient for a future comparison of the delay and non-delay cases.

Consider the singular domain of the second order; i.e. the point (θ_1, θ_2) of intersection of the threshold lines. Letting $q \to 0$ we get that the equations of motion in $\mathbb{Z}^2$ are

$$\begin{aligned}
Z_1' &= \frac{Z_1(1-Z_1)}{\theta_1}(-\alpha\theta_1 + \alpha x_1 + {}^0c(Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1)) \\
Z_2' &= \frac{Z_2(1-Z_2)}{\theta_2}(1 - Z_1Z_2 - 0.9\theta_2)
\end{aligned} \tag{55}$$

with the same parameters' values as in (54).

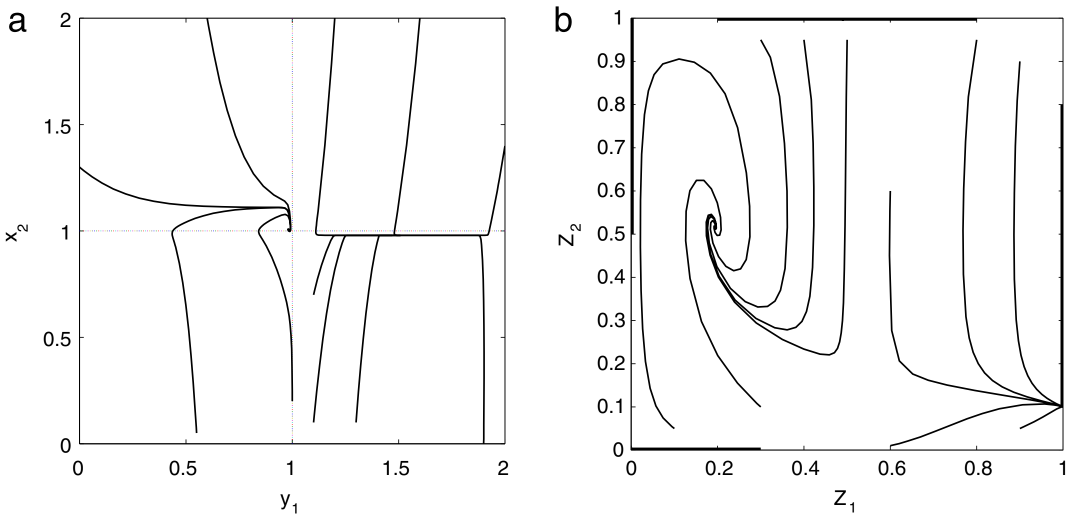

Fig. 11. The trajectories of (54) for $q = 0.01, x_1^0 = 0.1$ (a) and of (55) for $q = 0.01, x_1^0 = 0.1$ (b).

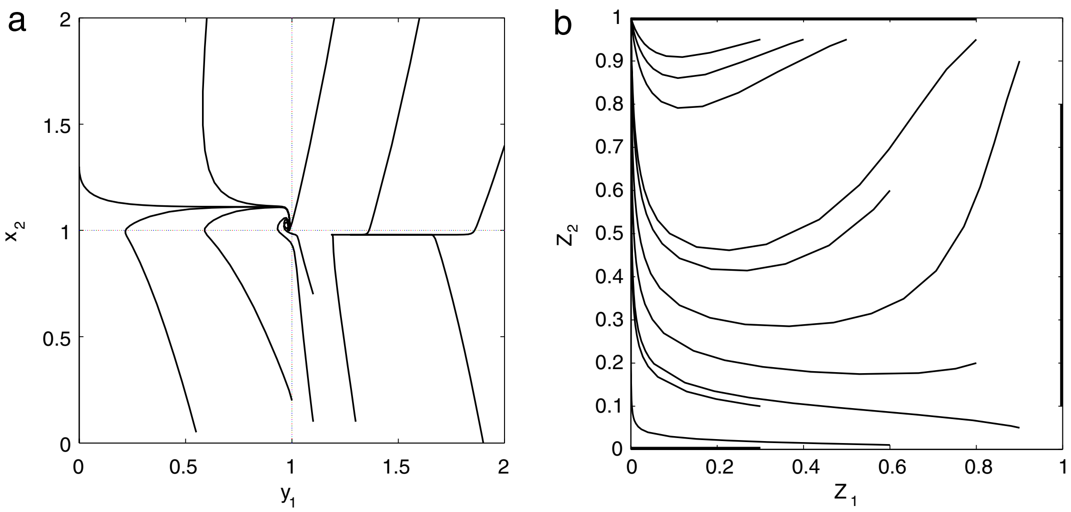

Fig. 12. The trajectories of (54) for $q = 0.01, x_1^0 = 10$ (a) and of (55) for $q = 0, x_1^0 = 10$ (b).

Figs. 11b and 12b show the trajectories of (55) in $\mathbb{Z}^2$ plane for $x_1^0 = 0.1$ and $x_1^0 = 10$, respectively.

Description of Figs. 11 and 12.

Depending on the initial value x_1^0, system (55) has two interior stationary points (if $0 < x_1^0 < 4$) or does not have interior stationary points at all (if $x_1^0 > 4$).

If the initial value $x_1^0 = 0.1$ (Fig. 11), then the behavior of trajectories in $\mathbb{X}^2$ and $\mathbb{Z}^2$ planes is similar to the non-delay case (see Appendix A).

If $x_1^0 = 10$ (Fig. 12), then we get new results. Let us concentrate on the main differences. The walls $\mathcal{SD}(\theta_1, 0)$ and $\mathcal{SD}(\theta_1, 1)$ did change their types and are transparent now. Note that the wall $\mathcal{SD}(\theta_1, 0)$ is white if $-5 < x_1^0 < 5$ and otherwise it's transparent. $\mathcal{SD}(\theta_2, 1)$ is still black, but there are no stable stationary points belonging to the wall. This implies that the point $(1, 1)$ of intersection of threshold lines is a unique attractive point. Any trajectory in $\mathbb{X}^2$ approaches it by sliding along the black wall $\mathcal{SD}(\theta_2, 1)$ or by crossing one of the transparent walls $\mathcal{SD}(\theta_1, 0)$, $\mathcal{SD}(\theta_1, 1)$ or $\mathcal{SD}(\theta_2, 0)$ depending on a starting point.

Assume now the delay effect in the second variable x_2. Then we get the system

$$\begin{aligned}
\dot{x_1} &= Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1 \\
\dot{x_2} &= 1 - Z_1Z_2 - 0.9x_2 \\
\dot{y_2} &= -\alpha y_2 + \alpha x_2 + {}^0c(1 - Z_1Z_2 - 0.9x_2) \\
x_1 &= y_1
\end{aligned} \qquad (56)$$

with the same parameters' values as in (54).

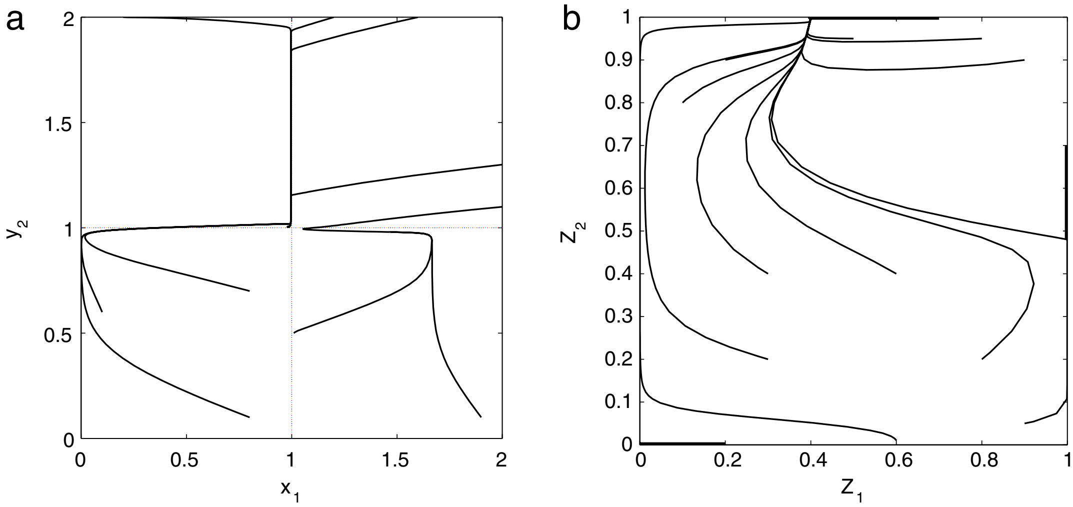

Fig. 13. The trajectories of (56) for $q = 0.01, x_2^0 = 0.05$ (a) and of (57) for $q = 0, x_2^0 = 0.05$ (b).

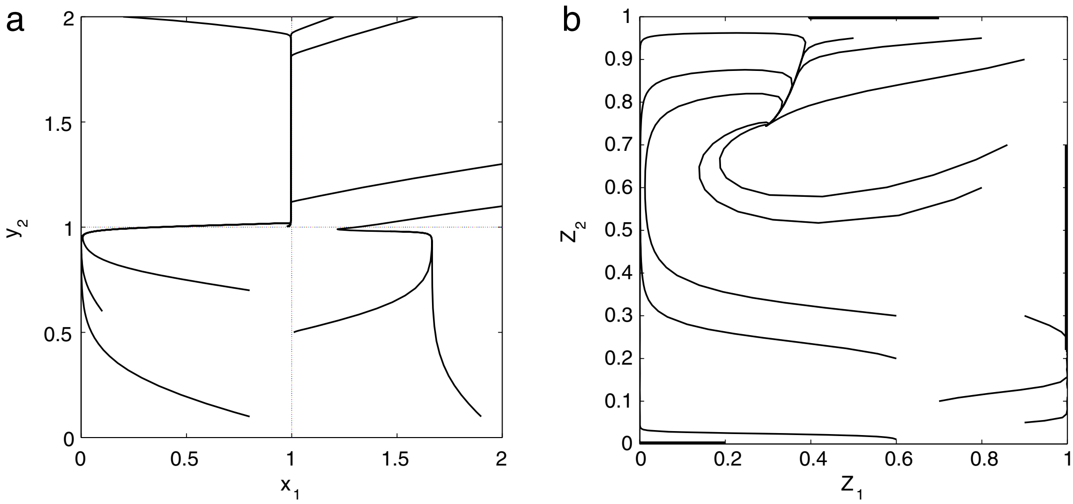

Fig. 14. The trajectories of (56) for $q = 0.01, x_2^0 = 0.7$ (a) and of (57) for $q = 0, x_2^0 = 0.7$ (b).

When $q \to 0$ the equations of motion in $\mathbb{Z}^2$ are

$$\begin{aligned} Z_1' &= \frac{Z_1(1-Z_1)}{\theta_1}(Z_1 + Z_2 - 2Z_1Z_2 - 0.6\theta_1) \\ Z_2' &= \frac{Z_2(1-Z_2)}{\theta_2}(-\alpha\theta_2 + \alpha x_2 + {}^0c(1 - Z_1Z_2 - 0.9x_2)). \end{aligned} \tag{57}$$

Figs. 13a, 14a, 15a, and 13b, 14b, 15b show the trajectories of Eqs. (56) and (57) in $\mathbb{X}^2$ (X_1Y_2) and $\mathbb{Z}^2$ planes, respectively, with the different initial values for x_2^0.

Description of Figs. 13–15.

If the initial value $0.25 < x_2^0 < 1.25$, then system (57) has two interior stationary points. Otherwise there are no such points at all.

Consider the case $x_2^0 = 0.05$ (Fig. 13). All walls are of the same type as in the non-delay case. But there are no stable stationary points in the black wall $\mathcal{SD}(\theta_2, 1)$. Moreover, the point with the coordinates $x_1 = \theta_1, y_2 = 1.16$ belonging to the black wall $\mathcal{SD}(\theta_1, 1)$ is a stable point. Therefore all trajectories in the $\mathbb{X}^2$ plane approach this point.

The case $x_2^0 = 0.7$ (Fig. 14) is similar to the non-delay case (Appendix A).

If the initial value $x_2^0 = 10$ (Fig. 15), then the wall $\mathcal{SD}(\theta_2, 1)$ becomes transparent and trajectories cross this wall. Note that $\mathcal{SD}(\theta_2, 1)$ is transparent for $x_2^0 > 1.25$ and black for $x_2^0 < 1.25$. Due to this fact, after the intersection the trajectories' behavior changes (as a result of a new starting point), the wall becomes attractive, trajectories approach the wall and slide along to the point (1, 1). The wall $\mathcal{SD}(\theta_1, 1)$ is still black but does not contain a stable point; therefore the intersection of the threshold lines is a unique stable point and all trajectories approach it.

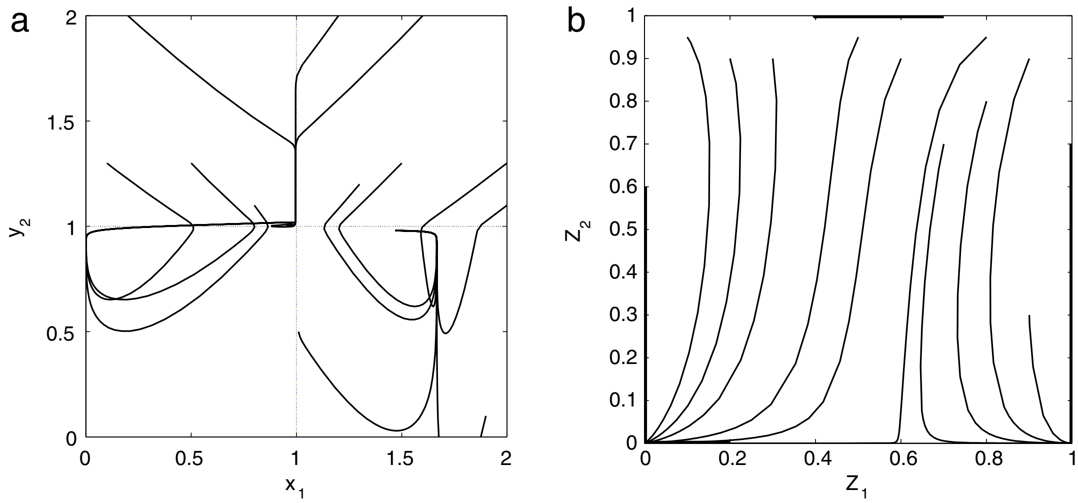

Fig. 15. The trajectories of (56) for $q = 0.01, x_2^0 = 10$ (a) and of (57) for $q = 0, x_2^0 = 10$ (b).

The analysis of the examples shows that it is not sufficient to obtain information only from the $\mathbb{Z}^2$ or $\mathbb{X}^2$ planes. To get the whole picture of trajectories' behavior we have to analyze both planes.

9. Conclusion

The main result of the paper provides a mathematical justification of the simplified analysis of gene regulatory networks in the presence of delays. The emphasis is put on sliding modes along one or more thresholds, which requires singular perturbation analysis. We know that the dynamics of the genes can only be understood if one combines the dynamics in two time scales: slow and fast. We study the cases where the input variables are delayed, not delayed, and combinations thereof. We discover some effects which one does not observe in the non-delay case. The theoretical studies are supplied with numerous examples illustrating different kinds of genes' dynamics.

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Appendix A

Let us consider the system of two genes x_1 and x_2 studied in [5]

$$\begin{aligned} \dot{x_1} &= Z_1 + Z_2 - 2Z_1Z_2 - \gamma_1 x_1, \\ \dot{x_2} &= 1 - Z_1Z_2 - \gamma_2 x_2, \end{aligned} \tag{58}$$

where $\gamma_1 = 0.6, \gamma_2 = 0.9$ are the relative degradation rates. Thus, only the production terms are regulated by the switching functions $Z_i = \Sigma(x_i, \theta_i, q_i)$ $(i = 1, 2)$, which are assumed to be the Hill-functions given by (9). Suppose that the threshold values are $\theta_1 = \theta_2 = 1$ (dotted lines in Fig. 16a) and $q_1 = q_2 = q \geq 0$.

This model has two black walls $\mathcal{SD}(\theta_1, 1) = \{x_1 = \theta_1, x_2 > \theta_2\}$ and $\mathcal{SD}(\theta_2, 1) = \{x_1 > \theta_1, x_2 = \theta_2\}$, one white wall $\mathcal{SD}(\theta_1, 0) = \{x_1 = \theta_1, x_2 < \theta_2\}$ and the wall $\mathcal{SD}(\theta_2, 0) = \{x_1 < \theta_1, x_2 = \theta_2\}$ is transparent. Some trajectories of Eq. (58) for $q = 0.01$ are shown in Fig. 16a.

When $q \to 0$ the equations of motion in the singular domain $\mathbb{Z}^2$ (the point of intersection of threshold lines) are

$$\begin{aligned} Z_1' &= \frac{Z_1(1 - Z_1)}{\theta_1}(Z_1 + Z_2 - 2Z_1Z_2 - \gamma_1\theta_1), \\ Z_2' &= \frac{Z_2(1 - Z_2)}{\theta_2}(1 - Z_1Z_2 - \gamma_2\theta_2). \end{aligned} \tag{59}$$

Fig. 16b shows the heteroclinic trajectories; i.e. images of trajectories in $\mathbb{X}^2$, in $\mathbb{Z}^2$ with the same parameter values as in Fig. 16a, but for $q = 0$.

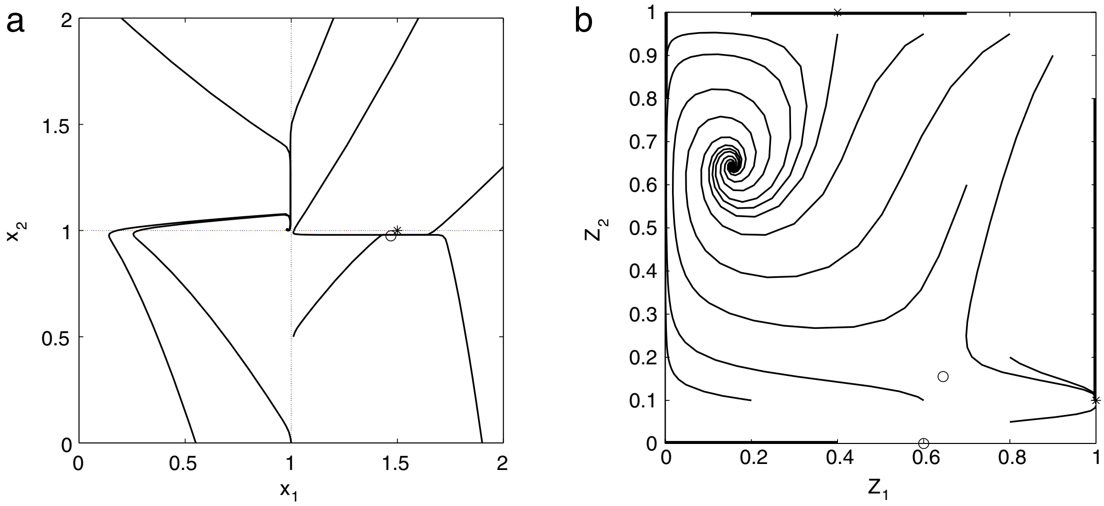

Fig. 16. The trajectories of (58) for $q = 0.01$ (a) and of (59) for $q = 0$ (b).

Description of Fig. 16.

Now we would like to compare the motions in $\mathbb{X}^2$ and $\mathbb{Z}^2$ to get a whole picture of trajectories' behavior for Eq. (58). Notice that the walls $\mathcal{SD}(\theta_1, 1)$, $\mathcal{SD}(\theta_1, 0)$, $\mathcal{SD}(\theta_2, 1)$ and $\mathcal{SD}(\theta_2, 0)$ in $\mathbb{X}^2$ correspond to the upper horizontal edge, the lower horizontal edge, the right vertical edge and the left vertical edge in $\mathbb{Z}^2$, respectively.

Eq. (59) has two interior stationary points $(1/(4+\sqrt{6}), (4+\sqrt{6})/10)$ and $(1/(4-\sqrt{6}), (4-\sqrt{6})/10)$, three stationary points belonging to the edges $(1, 0.1)$; $(0.6, 0)$ and $(0.4, 1)$. Moreover, all four vertices are stationary points as well. But only two of them $(1/(4+\sqrt{6}), (4+\sqrt{6})/10)$ and $(1, 0.1)$ (marked by an asterisk in Fig. 16b) are stable. Depending on the starting point, a trajectory in $\mathbb{Z}^2$ approaches one of these stable points. The unstable point $(1/(4-\sqrt{6}), (4-\sqrt{6})/10)$ between them plays a dividing role. In $\mathbb{X}^2$ this point characterizes a separatrix in the box $\mathcal{B}(1, 1)$.

The stable point $(1, 0.1)$ in $\mathbb{Z}^2$ means that the wall $\mathcal{SD}(\theta_2, 1)$ in $\mathbb{X}^2$ is black. Moreover, this shows that there exists a stable stationary point. An additional analysis of this wall in the $\mathbb{X}^2$ plane gives coordinates of this point. For the limit case $q = 0$ it is the point $x_1 = 1.5, x_2 = \theta_2 = 1$ marked by an asterisk in Fig. 16a. For the case $q = 0.01$ the stable point marked by a circle approaches the horizontal black wall. The interior and stable (in $\mathbb{Z}^2$) point $(1/(4+\sqrt{6}), (4+\sqrt{6})/10)$ indicates that the point $(1, 1)$ of intersection of the two threshold lines is stable in $\mathbb{X}^2$.

The point $(0.4, 1)$ is not stable in $\mathbb{Z}^2$, but it is stable in the edge $\{Z_2 = 1\}$, that means that the wall $\mathcal{SD}(\theta_1, 1)$ in the $\mathbb{X}^2$ plane is black. We cannot say anything about the existence of stable points in this wall by looking only at the $\mathbb{Z}^2$ plane. We need to return to $\mathbb{X}^2$. In this case an additional stability analysis of the wall does not give any stable point. To summarize the what is stated above, let us look at the $\mathbb{X}^2$ plane and consider any trajectory starting in the box $\mathcal{B}(1, 1)$. Depending on the initial point, the trajectory hits the horizontal black wall and approaches the stable stationary point in this wall or hits the vertical black wall and slides along this wall towards to the point $(1, 1)$. In both cases the trajectory stops and never leaves the point which is reached.

Let us now go back to the $\mathbb{Z}^2$ plane and consider the other stationary points. The point $(0.6, 0)$ is unstable (also in the edge $\{Z_2 = 0\}$), it means that the wall $\mathcal{SD}(\theta_1, 0)$ in $\mathbb{X}^2$ is white and all trajectories are repulsed from this wall towards $\mathcal{SD}(\theta_2, 0)$ or $\mathcal{SD}(\theta_2, 1)$ depending on a starting point of a trajectory. Finally consider the edge $\{Z_1 = 0\}$. There are no stationary points except for the vertices in this wall. The point $(0, 0)$ is unstable and $(0, 1)$ is stable in this wall. It indicates that the wall $\mathcal{SD}(\theta_2, 0)$ in $\mathbb{X}^2$ is transparent and trajectories cross it from the box $\mathcal{B}(0, 0)$ towards the box $\mathcal{B}(0, 1)$.

Appendix B

Let us consider the initial value problem

$$\begin{aligned} \epsilon \frac{dz}{dt} &= F(z, y) \\ \frac{dy}{dt} &= f(z, y), \quad 0 \le t \le T, \end{aligned} \tag{60}$$

$$z(0, \epsilon) = z^0, \qquad y(0, \epsilon) = y^0. \tag{61}$$

Here $\epsilon > 0$, z and y are vector functions of arbitrary dimensions M and m, respectively. We assume that the functions $F(z, y)$ and $f(z, y)$ are continuous together with their derivatives with respect to z and y in some domain G. Denote by $z(t, \epsilon)$ and $y(t, \epsilon)$ the solution of (60), (61).

Setting $\varepsilon = 0$, we obtain

$$0 = F(\bar{z}, \bar{y})$$
$$\frac{d\bar{y}}{dt} = f(\bar{z}, \bar{y}). \tag{62}$$

We will call (62) the reduced system. The initial condition for this system is

$$\bar{y}(0) = y^0. \tag{63}$$

Denote by $\bar{z}(t, \epsilon)$ and $\bar{y}(t, \epsilon)$ the solution of (62), (63).

Let us formulate the conditions for the passage limit.

Assumption 11 (*Isolated Root Condition*). Let the equation $F(\bar{z}, \bar{y}) = 0$ have an isolated root with respect to $\bar{z} : \bar{z}(\bar{y}) = \varphi(\bar{y}), \bar{y} \in K$ (K is some compact set) and suppose the problem (62), (63) has a unique solution corresponding to this root.

Assumption 12 (*Associated Problem. Lyapunov Stability Condition*). Let the stationary point of the associated system

$$\frac{d\tilde{z}}{d\tau} = F(\tilde{z}, y), \quad \tau \geq 0 \tag{64}$$

be asymptotically stable in the sense of Lyapunov, uniformly in $y \in D$ as $\tau \to \infty$.

There might exist several roots of the equation $F(\bar{z}, \bar{y}) = 0$ that satisfy Assumption 12. To make the final choice of the root, consider the associated system (64) for the initial parameters $y = y^0$

$$\frac{d\tilde{z}}{d\tau} = F(\tilde{z}, y^0) \tag{65}$$

with the initial condition

$$\tilde{z}(0) = z^0. \tag{66}$$

Assumption 13 (*The Domain of Attraction*). Let the solution $\tilde{z}(\tau)$ of the problem (65), (66) exist for $\tau \geq 0$ and tend to the stationary point $\varphi(y^0)$ as $\tau \to \infty$.

Theorem 14 (*Tikhonov's Theorem [16]*). *Under Assumptions 11–13 and for a sufficiently small ϵ, the problem (60), (61) has a unique solution $z(t, \epsilon), y(t, \epsilon)$ such that the following limiting equalities hold*

$$\lim_{\epsilon \to 0} y(t, \epsilon) = \bar{y}(t) \quad \text{for } 0 \leq t \leq T$$
$$\lim_{\epsilon \to 0} z(t, \epsilon) = \bar{z}(t) \quad \text{for } 0 < \delta \leq t \leq T$$

(the convergence is uniform for any $\delta > 0$).

Remark 15 (*[17]*). The result of Theorem 14 holds true for systems of the form

$$\epsilon \frac{dz}{dt} = F(z, y, \epsilon)$$
$$\frac{dy}{dt} = f(z, y, \epsilon),$$

where $F(z, y, \epsilon)$, $f(z, y, \epsilon)$ are continuous in all variables and $F(\tilde{z}, y^0)$, $f(z, y)$ are replaced by $F(\tilde{z}, y^0, 0)$, $f(z, y, 0)$, respectively.

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Paper III

Stochastically perturbed gene regulatory networks

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Abstract

We propose an analytic stochastic modeling approach which incorporates intrinsic noise effects directly into a well established continuous and deterministic formalism for describing gene regulatory networks characterized by steep gene regulatory functions. The stochastic effects are assumed to take the form of constant white noises whose diffusion coefficients solely depend on the steepness parameters of the smooth regulatory functions. The basic technical tool consists in replacing the smooth functions by much simpler step functions. The dynamics of the resulting piecewise linear system can then be described explicitly between the thresholds. The singularities that arise around discontinuities are handled by use of a uniform version of the stochastic Tikhonov theorem in singular perturbation analysis suggested by Yu. Kabanov and Yu. Pergamentshchikov.

Key words: stochastic differential equations, delay effect, singular perturbation analysis, gene regulation
MSC: 60H10, 60H30, 34K50

1 Introduction

The development of gene regulatory network (GRN) models of the form

$$\dot{x}_i(t) = F_i(Z) - G_i(Z)x_i(t), \quad i = 1, \dots, n. \tag{1}$$

where the production and relative degradation rate functions F_i and G_i depend on a vector Z of steeply sloped response functions (or gene regulatory functions) Z_i, has been motivated by the empirical fact that steep dose-response

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relationships seem to be an ubiquitous feature of GRNs [1]-[3]. A further motivation has been that this structure makes it possible to obtain analytical insights on the behaviour of GRNs that are beyond reach with a standard ordinary differential equation description (see e.g. [1]-[3]). To get a more analytically tractable mathematical structure, one normally replace the smooth response functions Z_i by step functions and obtain a piecewise linear system. The dynamics of such system can be described explicitly between the thresholds (also called singular or switching domains). Inside the singular domains one can use singular perturbation analysis to define continuous extensions of solutions which are close to the solutions of (1) provided that the response functions are close to the step functions (see [1] for more details).

Guided by the fact that time delays out of necessity is a characteristic of real GRNs [4], [5], the effects of introducing delays into (1) were extensively studied by [6] and [7] by use of the system:

$$\begin{aligned} \dot{x}_i(t) &= F_i(Z) - G_i(Z)x_i(t) \\ Z_i &= \Sigma(y_i, \theta_i, q_i) \\ y_i(t) &= (\Re_i x_i)(t), \quad t \geq 0, \;\; i = 1, \ldots, n, \end{aligned} \tag{2}$$

where the operators $\Re_i$ are bounded linear Volterra operators of the form

$$(\Re_i x_i)(t) = {}^0\!c_i x_i(t) + \int_{-\infty}^{t} K_i(t-s)x_i(s)ds, \quad t \geq 0, \;\; i = 1, \ldots, n.$$

(for more details see Section 4). A similar simplification procedure is implemented in the case of the delay system (2), where in addition the modified linear chain trick is invoked to convert the delay system into a larger system of ordinary differential equations (see [6], [7]). This framework allows an analytical assessment of when the dynamics of a network model is sensitive to time delays and when it is not.

Because GRNs have been shown to be inherently stochastic [8], [9], [10], a natural further extension is to introduce stochasticity into (1) and (2) to provide an analytical framework for assessing under which conditions a stochastic description needs to be invoked to properly describe the dynamics of systems with and without delays.

Here we show that it is indeed possible to incorporate stochastic effects directly into these equation structures. We do this by adding to the right hand sides of Systems (1) and (2) constant white noises whose diffusion coefficients depend on the steepness parameters q_i of the smooth response functions, only. We prove that in the limit (i. e. as $q_i \to 0$) the stochastic dynamics approaches uniformly the deterministic dynamics of the corresponding piecewise linear, deterministic systems. The main challenge here is, exactly as in the case of

Systems (1) and (2), to be able to deal with the singularities that arise in the limit around discontinuities of the right hand sides. We make use of an approach that goes back to Yu. Kabanov and Yu. Pergamentshchikov who suggested a uniform version of the stochastic Tikhonov theorem in singular perturbation analysis. In the case of System (2) this technique is combined with the modified linear chain trick, exactly as in the deterministic case.

One outcome of this new formalism is that it provides an analytical explanation of why a deterministic model (with or without delay) provide a good approximation to a stochastic model in the case when the activation occurs much faster than the other processes.

Although System (1) is a particular case of System (2), we have chosen to treat them separately. Detailed proofs are offered in the non-delay case, as this explains the main ideas and techniques in a more refined way and without additional, and sometimes cumbersome, notation which is necessary to formalize the delay model. Because the delay case is very similar to the non-delay one we only outline the needed adjustments of the proofs. We have also chosen to study the situation when exactly one variable approaches its threshold value at a time, i.e. we only consider the case of singular domains of codimension 1 ("the walls"). A general case of codimension greater that 1 is not considered in this paper, partly because we did not want to overload the paper with too many technicalities, partly because in many cases it does not represent a severe restriction.

The paper is organized as follows: In Section 2 we formulate the main problem in the non-delay case and list major assumptions applied to the right hand sides of the system. Section 3 provides a detailed analysis of two main cases that could occur in the limit. In the first case we get the so-called "transparent wall" in the limit. The solutions just travels through such a wall, and the challenge is to study convergence of the solutions in a vicinity of it. The second case gives us the so-called "black wall" which are hit by the solutions from either side. To be able to reconstruct the behavior of the limit solutions along the black wall we need to apply a certain change of variables and the stochastic Tikhonov theorem. In Section 4 we introduce stochastically perturbed GRN with delay and give a short overview of the modified linear chain trick to be applied in Section 5. Section 5 relies heavily on the technique developed in Section 3. We again consider the case of transparent and black walls and justify the convergence of solutions in the delay case by exploiting the stochastic Tikhonov theorem. In Appendix A we formulate some known results from the theory of stochastic differential equations that may ease the reading of the paper, while Appendix B contains the version of the stochastic Tikhonov theorem, which is due to Yu. Kabanov and Yu. Pergamentshchikov.

2 Formulation of the problem in the non-delay case

Consider the system

$$\begin{aligned} \dot{x}_i &= F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i + \sigma_i(q_i)\dot{\mathcal{B}}_i \\ Z_i &= \Sigma(x_i, \theta_i, q_i), \quad q_i \geq 0, \; i = 1, \ldots, n \end{aligned} \tag{3}$$

with the initial conditions

$$x(t_0, \bar{q}) = x^0(\bar{q}). \tag{4}$$

Here $\mathcal{B} = (\mathcal{B}_1, \ldots, \mathcal{B}_n)$ represents the n-dimensional Brownian motion, and $\sigma = (\sigma_1, \ldots, \sigma_n)$ is a vector of small parameters. The functions F_i and G_i stand for the production rate and the relative degradation rate of the product of gene i, respectively, and x_i denotes the gene product concentration. The functions F_i, G_i are affine in each Z_i and satisfy

$$F_i(Z_1, \ldots, Z_n) \geq 0, \quad G_i(Z_1, \ldots, Z_n) > 0$$

for $0 \leq Z_i \leq 1$, $i = 1, \ldots, n$. The response functions Z_i express the effect of the different transcription factors regulating the expression of the gene. Each $Z_i = \Sigma_i(x_i, \theta_i, q_i)$ is a smooth function depending on exactly one input variable x_i and on two other parameters, i.e. the threshold value θ_i and the steepness value $q_i > 0$. In this paper we restrict ourselves, as do many people who deal with modeling of GRN, to the case when $Z_i = \Sigma_i(x_i, \theta_i, q_i)$ are assumed to be the Hill functions given by

$$\Sigma_i(x_i, \theta_i, q_i) := \begin{cases} 0 & \text{if} \quad x_i < 0 \\ \frac{x_i^{1/q_i}}{x_i^{1/q_i} + \theta_i^{1/q_i}} & \text{if} \quad x_i \geq 0 \end{cases} \tag{5}$$

for $q_i > 0$. If $q_i = 0$ then Z_i become unit step functions (Fig.1).

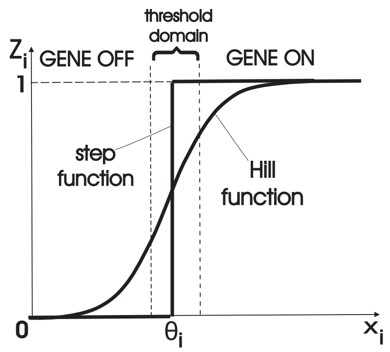

Fig. 1

For $q_i > 0$, $i = 1, \ldots, n$, the functions $F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i$ and $\sigma_i(q_i)$ in the right hand side of System (3) are smooth, therefore locally Lipschitz. Since all response functions Z_i are bounded ($0 \leq Z_i \leq 1$) then $|F_i| \leq M_i$

and $0 < \delta \leq G_i \leq M_i$. The functions x_i are not bounded therefore the right hand side of System (3) grows linearly. Thus, by the existence and uniqueness theorem for stochastic differential equations (see Appendix A) there exists a unique solution for (3) for $q_i > 0$, $i = 1, \ldots, n$.

When q_i go to 0, $i = 1, \ldots, n$ all threshold functions Z_i tend to the step functions. Assume that $\sigma_i(q_i) \to 0$ as $q_i \to 0$. Thus, regarding the thresholds in the state space, System (3) changes into a deterministic piecewise linear system. The dynamics of the obtained system can be described very easily between such thresholds, but not in the singular domains. To define solutions in the singular domains in the deterministic case E. Plahte and S. Kjøglum made use of the singular perturbation analysis in each of the domains (see [1]). It was shown that the solution for steep sigmoids ($q_i > 0$) approaches the limit solution ($q_i = 0$) uniformly, in any finite time interval (when the sigmoids approach the step functions). Our main goal is to show that this is also the case for System (3), i.e. the convergence of the stochastically perturbed solutions with $q_i > 0$ to the limit solution with $q_i = 0$. We restrict ourselves to the case where only one of the variables approaches its threshold. The case where several variables approach their respective thresholds will be studied elsewhere.

3 Analysis in the non-delay case

Let $q_i \to 0$, $i = 1, \ldots, n$, and consider the situation where exactly one of the variables x_i in (3) approaches its threshold value θ_i, while the others stay away from their thresholds. Renumbering we can always assume that the singular variable is x_1 with the threshold value θ_1. The other variables are then per definition regular ([6]). In the limit, i.e. as $q_i \to 0$, $i = 1, \ldots, n$, we obtain that $x_1 = \theta_1$ and $Z_i(x_i) = 1$ or 0 for $i = 2, \ldots, n$. Denote this singular domain as

$$\mathcal{SD}(\theta_1, B_R) = \{(x_1, \ldots, x_n) : x_1 = \theta_1,\ Z_i(x_i) = B_i,\ i \geq 2\},$$

where B_i is a corresponding Boolean vector associated to each Z_i by $B_i = 0$ if $x_i < \theta_i$ and $B_i = 1$ if $x_i > \theta_i$.

We consider below two kinds of walls: the transparent ones, when the trajectories travel through them, and the black ones, when the trajectories hit them from either side. Third case of white (repelling) walls [1] requires no additional analysis in the stochastic setting.

3.1 The case of transparent walls

We assume that

A1 The singular domain $\mathcal{SD}(\theta_1, B_R)$ is transparent such that $F_1(0, B_R) - G_1(0, B_R)\theta_1$ and $F_1(1, B_R) - G_1(1, B_R)\theta_1$ have the same sign.

For the sake of simplicity, we consider below the situation when both these expressions are negative, what means that trajectories go from the regular domain $\mathcal{R}(1, B_R) = \{(x_1, \ldots, x_n) : x_1 > \theta_1,\ Z_i(x_i) = B_i,\ i \geq 2\}$ to the regular domain $\mathcal{R}(0, B_R) = \{(x_1, \ldots, x_n) : x_1 < \theta_1,\ Z_i(x_i) = B_i,\ i \geq 2\}$. Assume that the limit initial point $x^0(\bar{0}) \in \mathcal{R}(1, B_R)$.

Denote by $x(t, \bar{q}) = (x_1(t, \bar{q}), \ldots, x_n(t, \bar{q}))$, $\bar{q} = (q_1, \ldots, q_n)$ the solution of the stochastically perturbed system (3) and by $x(t, \bar{0}) = (x_1(t, \bar{0}), \ldots, x_n(t, \bar{0}))$ the solution of the limit system

$$\begin{aligned} \dot{x}_i &= F_i(1, B_R) - G_i(1, B_R)x_i \text{ if } x(t, \bar{0}) \in \mathcal{R}(1, B_R) \\ \dot{x}_i &= F_i(0, B_R) - G_i(0, B_R)x_i \text{ if } x(t, \bar{0}) \in \mathcal{R}(0, B_R) \end{aligned} \tag{6}$$

on the interval $[t_0, T]$. Here $\bar{0}$ is the null-vector.

Theorem 1 *Under Assumption A1*

$$\lim_{\bar{q} \to \bar{0}} \mathbb{E} \sup_{[t_0, T]} |x(t, \bar{q}) - x(t, \bar{0})|^2 = 0.$$

Proof.

Assume that the solution $x(t, \bar{0})$ crosses the singular domain $\mathcal{SD}(\theta_1, B_R)$ at the time t_1, i.e. $x_1(t_1, 0) > \theta_1$ for $t < t_1$ and $x_1(t_1, 0) < \theta_1$ for $t > t_1$. Take any $\sigma > 0$ and let us first compare the solutions $x(t, \bar{q})$ and $x(t, \bar{0})$ on the intervals $[t_0, t_1 - \sigma]$ and $[t_1 + \sigma, T]$.

Denote $\delta_1 = \min_{t_0 \leq t \leq t_1 - \sigma} |x_1(t, 0) - \theta_1|$ and $\delta_r = \min_{t_0 \leq t \leq t_1 - \sigma} |x_r(t, 0) - \theta_r|$, $r = 2, \ldots, n$. Since $t = t_1$ is the instant when the solution $x(t, \bar{0})$ crosses $\mathcal{SD}(\theta_1, B_R)$ for the first time, then $\delta_1 > 0$. The coordinates $x_r(t, \bar{0})$ do not leave the regular domain corresponding to B_R. Therefore $\delta_r > 0$. By properties of the Hill function it is easy to check that $Z_1(x_1, \theta_1, q_1) \to 0$ uniformly on $0 \leq x_1 \leq \theta_1 - \delta_1$ and $Z_r(x_r, \theta_r, q_r) \to 0$ uniformly on $|x_r - \theta_r| \geq \delta_r$, $r = 2, \ldots, n$. Therefore the right hand sides of System (3) converge to $F_i(0, B_R) - G_i(0, B_R)x_i$ as $q_i \to 0$, $i = 1, \ldots, n$. Moreover, the partial derivatives with respect to all x_i converge uniformly in the domain $\{0 \leq x_1 \leq \theta_1 - \delta_1,\ |x_r - \theta_r| \geq \delta_r,\ r = 2, \ldots, n\}$. Thus, by the theorem on the continuous dependence of the solutions of stochastic differential equations [14], the solutions $x(t,\bar{q})$ of the problem (3), (4) converge to the limit solution $x(t,\bar{0})$, which satisfies the second equation of (6) with the same initial conditions, in the following sense

$$\lim_{\bar{q}\to\bar{0}} \mathbb{E} \sup_{[t_0,t_1-\sigma]} |x(t,\bar{q}) - x(t,\bar{0})|^2 = 0. \tag{7}$$

In a similar way it can be shown that

$$\lim_{\bar{q}\to\bar{0}} \mathbb{E} \sup_{[t_1+\sigma,T]} |x(t,\bar{q}) - x(t,\bar{0})|^2 = 0. \tag{8}$$

The right hand side of the limit system becomes discontinuous when the solution $x(t,\bar{0})$ hits the threshold line $x_1 = \theta_1$. Therefore in a vicinity of the point $t = t_1$ the theorem on the continuous dependence of the solutions of stochastic differential equations can not be applied. Moreover, the derivatives of the right hand side of (3) go to infinity as $\bar{q} \to \bar{0}$. Thus, the vicinity of $t = t_1$ requires an additional analysis. We need to prove that

$$\mathbb{E} \sup_{|t-t_1|\le\sigma} |x(t,\bar{q}) - x(t,\bar{0})|^2 = 0.$$

It is sufficient to show the convergence in each of the coordinates x_i, $i = 1,\ldots,n$. To do this let us estimate the following difference

$$\begin{aligned}
&\mathbb{E} \sup_{|t-t_1|\le\sigma} |x_i(t,q_i) - x_i(t,0)|^2 = \mathbb{E} \sup_{|t-t_1|\le\sigma} |\int_{t_0}^{t} ([F_i(Z_i(x_i(s,q_i))) - F_i(0,B_R)] - \\
&[G_i(Z_i(x_i(s,q_i)))x_i(s,q_i) - G_i(0,B_R)x_i(s,0)])ds + \int_{t_0}^{t} \sigma_i(q_i)d\mathcal{B}_i(s)|^2 \le \\
&2\,\mathbb{E} \sup_{|t-t_1|\le\sigma} |\int_{t_0}^{t_1-\sigma} ([F_i(Z_i(x_i(s,q_i))) - F_i(0,B_R)] - [G_i(Z_i(x_i(s,q_i)))x_i(s,q_i) - \\
&G_i(0,B_R)x_i(s,0)])ds + \int_{t_0}^{t_1-\sigma} \sigma_i(q_i)d\mathcal{B}_i(s)|^2 + 2\,\mathbb{E} \sup_{|t-t_1|\le\sigma} |\int_{t_1-\sigma}^{t} ([F_i(Z_i(x_i(s,q_i))) - \\
&F_i(0,B_R)] - [G_i(Z_i(x_i(s,q_i)))x_i(s,q_i) - G_i(0,B_R)x_i(s,0)])ds + \\
&\int_{t_1-\sigma}^{t} \sigma_i(q_i)d\mathcal{B}_i(s)|^2 = 2I_1 + 2I_2
\end{aligned} \tag{9}$$

We have proved before the convergence of solutions on the interval $[t_0, t_1 - \sigma]$. Therefore $I_1 \to 0$ as $q_i \to 0$, $i = 1,\ldots,n$. Now we want to show that

$$I_2 = \mathbb{E} \sup_{|t-t_1|\le\sigma} |\int_{t_1-\sigma}^{t} ([F_i(Z_i(x_i(s,q_i))) - F_i(0,B_R)] - [G_i(Z_i(x_i(s,q_i)))x_i(s,q_i) -$$

$G_i(0, B_R)x_i(s,0)])ds + \int\limits_{t_1-\sigma}^{t} \sigma_i(q_i)d\mathcal{B}_i(s)|^2$ is bounded.

By the linear growth in $x_i(s, q_i)$ and $x_i(s, 0)$ there exist positive constants C_1 and C_2 such that

$$I_2 \leq \mathbb{E} \sup_{|t-t_1|\leq\sigma} \int\limits_{t_1-\sigma}^{t} [C_1 + C_2(|x_i(s, q_i)|^2 + |x_i(s, 0)|^2)]ds +$$

$$\mathbb{E} \sup_{|t-t_1|\leq\sigma} \left(\int\limits_{t_1-\sigma}^{t} \sigma_i(q_i)d\mathcal{B}_i(s)\right)^2 \leq \text{by Doob's inequality and Itô isometry}$$

$$\leq \mathbb{E} \sup_{|t-t_1|\leq\sigma} \int\limits_{t_1-\sigma}^{t} [C_1 + C_2(|x_i(s, q_i)|^2 + |x_i(s, 0)|^2)]ds + 4 \int\limits_{t_1-\sigma}^{t_1+\sigma} \sigma_i^2(q_i)ds.$$

From the existence and uniqueness theorem for stochastic differential equations (see [11]) we know that the solutions of System (3) satisfy

$$\mathbb{E}\left[\int\limits_{t_1-\sigma}^{t_1+\sigma} |x_i(t, q_i)|^2 dt\right] \leq L_1.$$

Let us now show that $x_i(t, 0)$, $i = 1, \dots, n$, are bounded on $[t_1 - \sigma, t_1 + \sigma]$. From (6) we have

$$|\dot{x}_i(t, 0)| \leq F_i(0, B_R) \text{ if } t \in [t_1 - \sigma, t_1],$$
$$|\dot{x}_i(t, 0)| \leq F_i(1, B_R) \text{ if } t \in [t_1, t_1 + \sigma].$$

By Lagrange's mean value theorem

$|x_i(t, 0)| \leq |\dot{x}_i(c_1, 0)|\sigma + |x_i(t_1 - \sigma, 0)|$ for $t_1 - \sigma \leq t < t_1$, $c_1 \in [t_1 - \sigma, t]$ and

$|x_i(t, 0)| \leq |\dot{x}_i(c_2, 0)|\sigma + |x_i(t_1 + \sigma, 0)|$ for $t_1 \leq t < t_1 + \sigma$, $c_2 \in [t, t_1 + \sigma]$.

Therefore

$$|x_i(t, 0)| \leq \max\{F_i(0, B_R), F_i(1, B_R)\}\, \sigma + \max\{|x_i(t_1 - \sigma, 0)|, |x_i(t_1 + \sigma, 0)|\}$$
$$\leq L_2\sigma + L_3$$

and

$$I_2 \leq (C_1 + C_2L_1 + L_2\sigma + L_3 + 4 \max_i \sigma_i^2(q_i))2\sigma.$$

Let us now go back to the formula (9). Assume that $\epsilon > 0$ is given. For this ϵ choose $\sigma > 0$ such that $I_2 < \epsilon/2$ and $q^* > 0$ such that $I_1 < \epsilon/2$ for all $0 < q_i < q^*$. Then

$$\mathbb{E} \sup_{|t-t_1|\leq\sigma} |x_i(t, q_i) - x_i(t, 0)|^2 < \epsilon \quad \text{for } 0 < q_i < q^*.$$

From (7), (8) it follows that there exists $0 < q^{**} < q^*$ such that

$$\mathbb{E} \sup_{\substack{|t - t_1| > \sigma \\ t \in [t_0, T]}} |x_i(t, q_i) - x_i(t, 0)|^2 < \epsilon \quad \text{for } 0 < q_i < q^{**}.$$

The last two estimations give

$$\mathbb{E} \sup_{t \in [t_0, T]} |x_i(t, q_i) - x_i(t, 0)|^2 < \epsilon \quad \text{for } 0 < q_i < q^{**}.$$

The theorem is proved.

3.2 The case of black walls and singular perturbation analysis

For a further simplification of the notation we want to distinguish the singular variable from the regular variables. Throughout this subsection we use the lower index 1 in all notations corresponding to the singular variable, i.e. x_1, F_1, G_1, Z_1, θ_1, q_1, $\mathcal{B}_1$, σ_1 and the lower index R for the vectors, corresponding to the regular variables, while its components we specify with the lower index r. In our case $x_R = (x_2, \ldots, x_n)^T$, $F_R = (F_2, \ldots, F_n)$, G_R is a diagonal $(n-1) \times (n-1)$ matrix with the diagonal elements $G_2, \ldots, G_n$, $Z_R = (Z_2, \ldots, Z_n)$, $\theta_R = (\theta_2, \ldots, \theta_n)$, $q_R = (q_2, \ldots, q_n)$, $\mathcal{B}_R = (\mathcal{B}_2, \ldots, \mathcal{B}_n)^T$, $\sigma_R(q_R) = (\sigma_2(q_2), \ldots, \sigma_n(q_n))$.

Using this new notation System (3) can be rewritten as

$$\begin{aligned} \dot{x}_1 &= F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1 + \sigma_1(q_1)\dot{\mathcal{B}}_1 \\ \dot{x}_R &= F_R(Z_1, Z_R) - G_R(Z_1, Z_R)x_R + \sigma_R(q_R)\dot{\mathcal{B}}_R \end{aligned} \tag{10}$$

with the initial conditions

$$\begin{aligned} &(x_1(t_0), x_R(t_0)) \in \mathcal{SD}(\theta_1, B_R), \text{ i.e.} \\ &x_1(t_0) = \theta_1, \quad x_R(t_0) = x_R^0, \text{ where } Z_i(x_R^0) = B_R. \end{aligned}$$

To obtain an equation describing the motion in the singular domain $\mathcal{SD}(\theta, B_R)$ we substitute the singular variable x_1 by Z_1. This simple transformation is a starting point for the singular perturbation analysis.

Below we calculate dZ_1 using the Itô formula. For the sake of simplification of notation we skip the lower index 1. Z is assumed to be the Hill function given by (5), so that we get

$$x = \Sigma^{-1}(Z, \theta, q) = \theta \left(\frac{Z}{1-Z} \right)^q .$$

In the deterministic case

$$\frac{dZ}{dt} = \frac{dZ}{dx}\frac{dx}{dt} \quad \text{and} \quad dZ = \frac{Z(1-Z)}{qx} dx.$$

In the stochastic case we use Itô's formula

$$df(X) = f'(X)dX + \frac{f''(X)}{2!}(dX)^2. \tag{11}$$

Then we get

$$dZ = d\Sigma(x, \theta, q) = \Sigma'(x, \theta, q)dx + \frac{1}{2}\Sigma''(x, \theta, q)(dx)^2$$

where

$$\begin{aligned}
&\Sigma'(x, \theta, q) = \frac{Z(1-Z)}{q\Sigma^{-1}(Z, \theta, q)}, \\
&\Sigma''(x, \theta, q) = \left(\frac{Z(1-Z)}{q\Sigma^{-1}(Z, \theta, q)} \right)' = \frac{Z(1-Z)(1-2Z-q)}{q^2(\Sigma^{-1}(Z, \theta, q))^2}, \\
&dx = (F(Z, Z_R) - G(Z, Z_R)x)dt + \sigma(q)d\mathcal{B}, \\
&(dx)^2 = ((F(Z, Z_R) - G(Z, Z_R)x)dt + \sigma(q)d\mathcal{B})^2 = ((F(Z, Z_R) - G(Z, Z_R)x)^2 \cdot \\
&(dt)^2 + 2((F(Z, Z_R) - G(Z, Z_R)x)\sigma(t)dtd\mathcal{B} + \sigma^2(t)(d\mathcal{B})^2 = \sigma^2(q)dt,
\end{aligned}$$

since

$$\begin{aligned}
&(dt)^2 = 0 \quad \text{since} \quad (\triangle t)^2 \sim o(\triangle t), \\
&dtd\mathcal{B} = 0 \quad \text{since} \quad \triangle t \triangle \mathcal{B} \approx (\triangle t)^{3/2} \sim o(\triangle t), \\
&(d\mathcal{B})^2 = dt \quad \text{since} \quad (\triangle \mathcal{B})^2 \approx \triangle t \quad \text{(see [11])}.
\end{aligned}$$

Then System (10) takes the form

$$\begin{aligned}
&q_1 \dot{Z}_1 = \frac{Z_1(1-Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}[F_1(Z_1, Z_R) - G_1(Z_1, Z_R)\Sigma^{-1}(Z_1, \theta_1, q_1) + \\
&\frac{1-2Z_1-q_1}{2q_1\Sigma^{-1}(Z_1, \theta_1, q_1)}\sigma_1^2(q_1)] + \frac{Z_1(1-Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}\sigma_1(q_1)\dot{\mathcal{B}}_1, \\
&\dot{x}_R = F_R(Z_1, Z_R) - G_R(Z_1, Z_R)x_R + \sigma_R(q_R)\dot{\mathcal{B}}_R, \quad q_i \geq 0, \ i = 1, \ldots, n
\end{aligned} \tag{12}$$

with the initial conditions

$$\begin{aligned}
&x_R(t_0) = x_R^0, \\
&Z(t_0) = 0.5
\end{aligned} \tag{13}$$

(since $Z = \Sigma(\theta, \theta, q) = 0.5$ for $q > 0$).

We assume that:

A2 The singular domain $\mathcal{SD}(\theta_1, B_R)$ is black such that

$$\begin{cases} F_1(1, B_R) - G_1(1, B_R)\theta_1 < 0 \\ F_1(0, B_R) - G_1(0, B_R)\theta_1 > 0. \end{cases} \tag{14}$$

A3 The diffusion coefficient $\sigma_1(q_1)$ satisfies

$$\sigma_1(q_1) = o\left(\sqrt{\left|\frac{q_1}{\ln q_1}\right|}\right) \quad \text{as } q_1 \to 0$$

and all diffusion coefficients of the regular variables

$$\sigma_i(q_i) \to 0 \quad \text{as } q_i \to 0, \quad i \in R.$$

Let us now verify for the problem (12)-(13) the assumptions in the stochastic Tikhonov theorem listed in Appendix B.

Verification of B1.

First let us prove the continuity of right hand side of Systems (12) in (q_1, Z_1, x_R), $q_1 \in [0, q']$, $q' < 1$, $Z_1 \in [0, 1]$, $x_r \in [0, \infty)$, $r \in R$. Obviously it is continuous in all x_r everywhere.

To show the continuity in two other variables we start with the term $\dfrac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}$. If $Z_1 \in (0, 1)$ then only the point $q_1 \to 0$ is a problematic point. But in this case $\Sigma^{-1}(Z_1, \theta_1, q_1) \to \theta_1 > 0$ and we get the continuity at this point.

If $Z_1 = 0$ ($Z_1 = 1$), then $\Sigma^{-1}(Z_1, \theta_1, q_1) \to -\infty$ $(+\infty)$ by definition and $\dfrac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)} \to 0$. Therefore $\dfrac{Z_1(1 - Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}$ is continuous on $[0, 1] \times [0, q']$, $q' < 1$.

The next term is $\dfrac{Z_1(Z_1 - 1)(1 - 2Z_1 - q_1)}{q_1[\Sigma^{-1}(Z_1, \theta_1, q_1)]^2}\sigma_1^2(q_1)$.

Since $\dfrac{\sigma_1^2(q_1)|\ln(q_1)|}{q_1} \to 0$ (by A3) and $|\ln(q_1)| \to \infty$ as $q_1 \to 0$ then $\sigma_1^2(q_1) = o\left(\dfrac{q_1}{|\ln(q_1)|}\right)$ and $\dfrac{\sigma_1^2(q_1)}{q_1} \to 0$ as $q_1 \to 0$.

$$[\Sigma^{-1}(Z_1,\theta_1,q_1)]^2 = \left[\theta_1\left(\frac{Z_1}{1-Z_1}\right)^{q_1}\right]^2 = \theta_1^2\left(\frac{Z_1}{1-Z_1}\right)^{2q_1} = \Sigma^{-1}(Z_1,\theta_1^2,2q_1).$$

Therefore $\dfrac{Z_1(Z_1-1)}{[\Sigma^{-1}(Z_1,\theta_1,q_1)]^2} = \dfrac{Z_1(Z_1-1)}{\Sigma^{-1}(Z_1,\theta_1^2,2q_1)}$ is continuous on $[0,1]\times[0,q'/2]$, $q'<1$.

Evidently the terms $(1-q_1-2Z_1)$, $(F_1(Z_1,Z_R)-G_1(Z_1,Z_R)\Sigma^{-1}(Z_1,\theta_1,q_1))$ and the right hand side of equations corresponding to the slow variables are continuous in all variables (q_1,Z_1,x_R). The continuity is proved.

We have shown before the linear growth and locally Lipschitz conditions in (Z_1,x_R) of RHS of System (3). By similar arguments we obtain that RHS of System (12) satisfies these conditions.

Verification of B2.

By the assumptions all diffusion coefficients $\sigma_1(q_1)$ and $\sigma_R(q_R)$ go to 0 as $q_1\to 0$ and $q_R\to\bar{0}$. The wall $\mathcal{SD}(\theta_1,B_R)$ is assumed to be black then the equation

$$\frac{Z_1(1-Z_1)}{\theta_1}(F_1(Z_1,B_R)-G_1(Z_1,B_R)\theta_1)=0$$

has the solution $Z_1=\hat{Z}_1\in(0,1)$ satisfying B2.

Verification of B3.

Since in the limit all noises disappeared, we have the same associated problem as in the deterministic case

$$\tilde{Z}_1' = \frac{\tilde{Z}_1(1-\tilde{Z}_1)}{\theta_1}(F_1(\tilde{Z}_1,B_R)-G_1(\tilde{Z}_1,B_R)\theta_1), \tag{15}$$

where $\tilde{Z}_1'=\frac{d\tilde{Z}_1}{d\tau}$, $\tau=t/q$ is the stretching transformation. Denote the right hand side by $A(0,\tilde{Z}_1)$. Since $\tilde{Z}_1$ is the one variable in this equation we can rewrite it as following:

$$A(0,\tilde{Z}_1)=\frac{\tilde{Z}_1(1-\tilde{Z}_1)}{\theta_1}(M\,\tilde{Z}_1+N).$$

The wall $\mathcal{SD}(\theta_1,B_R)$ is assumed to be black then according to (14) the equilibrium point $\hat{Z}_1$ is a stable point for (15).

From (14) we get $N>0$, $M+N<0$ and $M<0$, therefore

$$A_{\tilde{Z}_1}(0,\hat{Z}_1)=\frac{\hat{Z}_1(1-\hat{Z}_1)}{\theta_1}M<0.$$

We take $k_N = \dfrac{\hat{Z}_1(1-\hat{Z}_1)}{\theta_1}M$, then

$$u^\star A_{\tilde{Z}_1}(0,\hat{Z}_1)u \le -k_N|u|^2 \quad \forall u \in \mathbb{R}^n.$$

Verification of B4.

The attraction domain of the root $\hat{Z}_1$ for the equation $\dfrac{Z_1(1-Z_1)}{\theta_1}(F_1(Z_1,B_R) - G_1(Z_1,B_R)\theta_1) = 0$ is the open interval $(0,1)$ and the initial value $Z_1^0(0)$ belongs to this interval.

We have proved the following:

Theorem 2 *Under Assumptions A2, A3*

$$P - \lim_{q_R \to \bar{0}} \sup_{0\le t\le T} |x_R(t,q_R) - x_R(t,\bar{0})| \to 0$$
$$P - \lim_{q_1 \to 0} \sup_{\delta\le t\le T} |Z_1(x_1,\theta_1,q_1) - \hat{Z}_1| \to 0 \quad 0 < \delta \le T,$$

where $x_R(t,q)$ is a stochastically perturbed solution of (12); $x_R(t,0)$ is the limit solution satisfied the system

$$\dot{x}_R = F_R(\hat{Z}_1,B_R) - G_R(\hat{Z}_1,B_R)x_R$$

with the initial conditions $x_R(t_0) = x_R^0$.

Let us consider how we can determine the interval of convergence $[0,T]$. We know that $x_R(t,q_R) \to x_R(t,\bar{0})$ as $q_R \to \bar{0}$ as long as $x_R(t,\bar{0})$ is a solution of the equation

$$\dot{x}_R = F_R(\hat{Z}_1,Z_R) - G_R(\hat{Z}_1,Z_R)x_R.$$

In other words it holds as long as the solution $x_R(t,\bar{0})$ belongs to the singular domain $\mathcal{SD}(\theta,B_R)$. Therefore we need to find the time T when the solution leaves the domain. The following example shows how to do this.

Example 1 *Consider the system*

$$\dot{x}_1 = Z_1 + Z_2 - 2Z_1Z_2 - 0.6x_1$$
$$\dot{x}_2 = 1 - Z_1Z_2 - 0.9x_2,$$

where $Z_i = \Sigma(x_i,1,q)$, $i = 1,2$ are the Hill functions, under the initial conditions

$$x_1(0,q) = x_1^0(q), \quad x_2(0,q) = x_2^0(q).$$

Consider the singular domain $\mathcal{SD}(\theta_1, 1) = \{(x_1, x_2) : x_1 = \theta_1, x_2 > 1\}$ *which is black. Assume that the limit initial point* $(x_1^0(0), x_2^0(0))$ *belongs to it. To determine the solution in* $\mathcal{SD}(\theta_1, 1)$ *we change the singular variable* x_1 *with* Z_1*. It gives us*

$$
\begin{aligned}
q\dot{Z}_1 &= \tfrac{Z_1(1-Z_1)}{\Sigma^{-1}(Z_1,1,q)}(Z_1 + Z_2 - 2Z_1Z_2 - 0.6\Sigma^{-1}(Z_1, 1, q)) \\
\dot{x_2} &= 1 - Z_1Z_2 - 0.9x_2 \\
Z_2 &= \Sigma(x_2, 1, q).
\end{aligned}
$$

Let $q \to 0$*. Then* $Z_2 \to 1$*,* $\Sigma^{-1}(Z_1, 1, q) \to 1$ *and we get the system*

$$
\begin{aligned}
0 &= \tfrac{Z_1(1-Z_1)}{1}(1 - Z_1 - 0.6) \\
\dot{x_2} &= 1 - Z_1 - 0.9x_2,
\end{aligned}
$$

which describes the limit solution in $\mathcal{SD}(\theta_1, 1)$*. The solution* $x_2(t, 0)$ *belongs to this singular domain as long as* $x_2(t, 0) \geq 1$*. From the first equation* $\hat{Z} = 0.4 \in (0, 1)$ *is a stable point. Therefore the equation*

$$
\begin{aligned}
\dot{x_2} &= 0.6 - 0.9x_2 \\
x_2(0, 0) &> 1, \quad x_2(T, 0) = 1
\end{aligned}
\tag{16}
$$

describes the interval of convergence. From (16) we get that $T = \frac{1}{0.9}\ln(3x_2^0(0) - 2)$*, the interval depends on the initial value* $x_2^0(0)$*.*

4 Formulation of the problem in the delay case

We study the delay system

$$
\begin{aligned}
\dot{x}_i(t) &= F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i(t) + \sigma_i(q_i)\dot{\mathcal{B}}_i \\
Z_i &= \Sigma(y_i, \theta_i, q_i) \\
y_i(t) &= (\Re_i x_i)(t), \quad t \geq 0, \;\; i = 1, \ldots, n.
\end{aligned}
\tag{17}
$$

This system describes a GRN with autoregulation [1], [2], where changes in one or more genes happen slower than in the others, which causes delay effects in some of the variables.

We assume that the components of this delay system, that were present in the non-delay case, have the same properties. Unlike the non-delay system the input variables y_i endow System (17) with time-lags. In general, these variables are described by nonlinear Volterra ("delay") operators $\Re_i$ depending on the gene concentration $x_i(t)$.

If $\Re_i$ is the identity operator, then $x_i = y_i$ and x_i is a non-delay variable.

As in [6] we assume $\Re_i$ to be integral operators of the form

$$(\Re_i x_i)(t) = {}^0c_i x_i(t) + \int_{-\infty}^{t} K_i(t-s)x_i(s)ds, \quad t \geq 0, \;\; i = 1, \ldots, n,$$

where

$$K_i(u) = \sum_{\nu=1}^{p} {}^{\nu}c_i \; {}^{\nu}K_i(u)\,,$$
$${}^{\nu}K_i(u) = \frac{(\alpha_i)^{\nu}\, u^{\nu-1}}{(\nu-1)!} e^{-\alpha_i u}, \;\; i = 1, \ldots, n, \;\; p = 1, \ldots, n.$$

The coefficients ${}^{\nu}c_i$ are real nonnegative numbers satisfying

$$\sum_{\nu=0}^{p} {}^{\nu}c_i = 1.$$

It is also assumed that $\alpha_i > 0$.

To study System (17) we first want to remove the delay from the system. To do this we apply the modified linear chain trick method, which is described in [6]. The main idea is to introduce the new modified variables

$${}^1v_i = {}^0c_i x_i + \sum_{\nu=1}^{p} {}^{\nu}c_i \; {}^{\nu}w_i \quad \text{and} \quad {}^{\nu}v_i = \sum_{j=1}^{p-\nu+1} {}^{j+\nu-1}c_i \; {}^{j}w_i,$$

where

$${}^{\nu}w_i(t) = \int_{-\infty}^{t} {}^{\nu}K_i(t-s)x_i(s)ds, \quad \nu = 1, \ldots, p, \;\; i = 1, \ldots, n.$$

Then we obtain that System (17) is equivalent to the following non-delay system

$$\begin{aligned}
&\dot{x}_i = F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i + \sigma_i(q_i)\dot{\mathcal{B}}_i \\
&{}^1\dot{v}_i = -\alpha_i \; {}^1v_i + \alpha_i \; {}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(Z_1, \ldots, Z_n) - G_i(Z_1, \ldots, Z_n)x_i + \\
&\sigma_i(q_i)\dot{\mathcal{B}}_i) \\
&{}^2\dot{v}_i = -\alpha_i \; {}^2v_i + \alpha_i \; {}^3v_i + \alpha_i x_i \; {}^2c_i \\
&\ldots \\
&{}^p\dot{v}_i = -\alpha_i \, {}^pv_i + \alpha_i x_i \; {}^pc_i \\
&Z_i = \Sigma(y_i, \theta_i, q_i), \quad y_i = {}^1v_i, \quad i = 1, \ldots, n.
\end{aligned} \tag{18}$$

By the same arguments as in the non-delay case, for $q_i > 0$, $i = 1, \ldots, n$, the right hand side of System (18) satisfies the linear growth and local Lipschitz conditions, therefore by Theorem 5 (Appendix A) there exists a unique solution for (18) for $q_i > 0$, $i = 1, \ldots, n$.

If q_i go to 0, $i = 1, \ldots, n$, then all threshold functions Z_i are replaced with the step functions. The system thus obtained becomes solvable in any its domain of continuity, but the main problem in this case is to put the solutions together. The paper [7] suggests a framework of how to apply singular perturbation analysis to genetic models with delay and how to trace the solutions in the discontinuity sets of the right-hand sides of the simplified systems. But all analysis was done only for the deterministic case. The case of stochastically perturbed genetic models with delay has not been studied before. Our goal is to give a justification of the passage to the limit from the original complex stochastic model (18) to the simplified solvable model in the presence of delay. As in the non-delay case we consider the situation of exactly one singular variable.

5 Analysis in the delay case

Let $q_i \to 0$, $i = 1, \ldots, n$ and consider the situation where exactly one of the variables in (18) approaches its threshold value. Moreover we suppose that this singular variable is delayed. Renumbering we can always assume that the singular variable is ${}^1v_1 = y_1$ with the threshold value θ_1. Then in the limit, i.e. as $q_i \to 0$ we obtain that ${}^1v_1 = \theta_1$ and $Z_i(y_i) = 1$ or 0 for $i = 2, \ldots, n$. Denote this singular domain as

$$\mathcal{SD}(\theta_1, B_R) = \{(x, v) : {}^1v_1 = \theta_1,\ Z_i(y_i) = B_i,\ i = 2, \ldots, n\},$$

where $x = (x_1, \ldots, x_n)$, $v = (v_1, \ldots, v_n)$ with $v_i = ({}^1v_i, \ldots, {}^pv_i)$, and B_i is a corresponding Boolean vector, $i = 1, \ldots, n$.

In the non-delay case walls can be either black (attractive), white (expelling) or transparent. In the delay case walls can also be of a mixed type (see [7]). We consider two cases: $\mathcal{SD}(\theta_1, B_R)$ is a transparent wall (a transparent part of the wall) and a black wall (a black part of the wall) in Subsections 5.1 and 5.2, respectively. The third case of white walls does not require additional analysis in the stochastic setting, therefore it is not of interest to us.

5.1 Transparent walls

We assume that

A4 The singular domain $\mathcal{SD}(\theta_1, B_R)$ is transparent such that

$$-\alpha_1\, \theta_1 + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(0, B_R) - G_1(0, B_R)x_1)$$

and

$$-\alpha_1\, \theta_1 + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(1, B_R) - G_1(1, B_R)x_1)$$

have the same sign.

For the sake of simplicity, we consider below the situation when both these expressions are negative, what means that trajectories go from the regular domain $\mathcal{R}(1, B_R) = \{(x, v) : {}^1v_1 > \theta_1,\ Z_i(y_i) = B_i,\ i \geq 2\}$ to the regular domain $\mathcal{R}(0, B_R) = \{(x, v) : {}^1v_1 < \theta_1,\ Z_i(y_i) = B_i,\ i \geq 2\}$. Assume that the limit initial point $(x^0, v^0) \in \mathcal{R}(1, B_R)$, where $x^0 = (x_1(t_0), \ldots, x_n(t_0))$, $v^0 = (v_1(t_0), \ldots, v_n(t_0))$ with $v_i(t_0) = ({}^1v_i(t_0), \ldots, {}^pv_i(t_0))$, $i = 1, \ldots, n$.

Denote by $x(t, \bar{q}) = (x_1(t, \bar{q}), \ldots, x_n(t, \bar{q}))$, $v(t, \bar{q}) = (v_1(t, \bar{q}), \ldots, v_n(t, \bar{q}))$, $\bar{q} = (q_1, \ldots, q_n)$, the solution of the stochastically perturbed system (18) and by $x(t, \bar{0}) = (x_1(t, \bar{0}), \ldots, x_n(t, \bar{0}))$, $v(t, \bar{0}) = (v_1(t, \bar{0}), \ldots, v_n(t, \bar{0}))$ the solution of the limit system given by

$$\begin{array}{l}
\begin{cases}
\dot{x}_i = F_i(1, B_R) - G_i(1, B_R)x_i \\
{}^1\dot{v}_i = -\alpha_i\, {}^1v_i + \alpha_i\, {}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(1, B_R) - G_i(1, B_R)x_i) \\
{}^2\dot{v}_i = -\alpha_i\, {}^2v_i + \alpha_i\, {}^3v_i + \alpha_i x_i\, {}^2c_i \\
\ldots \\
{}^p\dot{v}_i = -\alpha_i\, {}^pv_i + \alpha_i x_i\, {}^pc_i
\end{cases} \\
\text{if } (x(t, \bar{0}), v(t, \bar{0})) \in \mathcal{R}(1, B_R) \\
\text{and} \\
\begin{cases}
\dot{x}_i = F_i(0, B_R) - G_i(0, B_R)x_i \\
{}^1\dot{v}_i = -\alpha_i\, {}^1v_i + \alpha_i\, {}^2v_i + \alpha_i x_i({}^0c_i + {}^1c_i) + {}^0c_i(F_i(0, B_R) - G_i(0, B_R)x_i) \\
{}^2\dot{v}_i = -\alpha_i\, {}^2v_i + \alpha_i\, {}^3v_i + \alpha_i x_i\, {}^2c_i \\
\ldots \\
{}^p\dot{v}_i = -\alpha_i\, {}^pv_i + \alpha_i x_i\, {}^pc_i
\end{cases}
\end{array} \qquad (19)$$

if $(x(t, \bar{0}), v(t, \bar{0})) \in \mathcal{R}(0, B_R)$, $i = 1, \ldots, n$, on the interval $[t_0, T]$.

Theorem 3 *Under Assumption A4*

$$\lim_{\bar{q}\to\bar{0}} \mathbb{E} \sup_{[t_0,T]} |x(t,\bar{q}) - x(t,\bar{0})|^2 = 0$$
$$\lim_{\bar{q}\to\bar{0}} \mathbb{E} \sup_{[t_0,T]} |v(t,\bar{q}) - v(t,\bar{0})|^2 = 0.$$

Proof.

The proof is similar to the proof in the non-delay case therefore we omit a good many details. Assume that the solution $(x(t,\bar{0}), v(t,\bar{0}))$ crosses the singular domain $\mathcal{SD}(\theta_1, B_R)$ at the time t_1, i.e. ${}^1v_1(t_1,\bar{0}) > \theta_1$ for $t < t_1$ and ${}^1v_1(t_1,\bar{0}) < \theta_1$ for $t > t_1$. Take any $\sigma > 0$. On the intervals $[t_0, t_1 - \sigma]$ and $[t_1 + \sigma, T]$ the x_i and ${}^jv_i$ components of the stochastically perturbed solutions of (18) converge to the corresponding components of the limit solution given by (19) by the same arguments as in the non-delay case, i.e. we have

$$\begin{aligned} &\mathbb{E} \sup_{\substack{|t-t_1|>\sigma \\ t\in[t_0,T]}} |x_i(t,\bar{q}) - x_i(t,\bar{0})|^2 < \epsilon, \\ &\mathbb{E} \sup_{\substack{|t-t_1|>\sigma \\ t\in[t_0,T]}} |{}^jv_i(t,\bar{q}) - {}^jv_i(t,\bar{0})|^2 < \epsilon, \end{aligned} \tag{20}$$

where $i, j = 1, \ldots, n$.

Now we look what happens in a vicinity of the point t_1. The difference for the x_i components, $i = 1, \ldots, n$, is the same as in the non-delay case. Therefore there exists $\tilde{q} > 0$ such that

$$\mathbb{E} \sup_{|t-t_1|\le\sigma} |x_i(t,\bar{q}) - x_i(t,\bar{0})|^2 < \epsilon \quad \text{for } 0 < q_i < \tilde{q},\ \ i = 1, \ldots, n. \tag{21}$$

Since ${}^jv_i(t,\bar{q})$, $i = 1, \ldots, n$, $j = 2, \ldots, n$, does not depend on any of Z_i therefore $|{}^jv_i(t,\bar{q}) - {}^jv_i(t,\bar{0})| = 0$ and

$$\mathbb{E} \sup_{|t-t_1|\le\sigma} |{}^jv_i(t,\bar{q}) - {}^jv_i(t,\bar{0})|^2 = 0, \quad i = 1, \ldots, n,\ \ j = 2, \ldots, n. \tag{22}$$

At last we look at the ${}^1v_i$ components, $i = 1, \ldots, n$.

$$|{}^1v_i(t,\bar{q}) - {}^1v_i(t,\bar{0})| = {}^0c_i |x_i(t,\bar{q}) - x_i(t,\bar{0})|,$$

where $0 \le {}^0c_i \le 1$. Therefore there exists q^{**} such that

$$\mathbb{E} \sup_{|t-t_1|\le\sigma} |{}^1v_i(t,\bar{q}) - {}^1v_i(t,\bar{0})|^2 < \epsilon \quad \text{for } 0 < q_i < q^{**},\ \ i = 1, \ldots, n. \tag{23}$$

Estimations (20)-(23) prove the theorem.

5.2 Black walls and singular perturbation analysis

Consider System (18) equipped with the initial conditions

$$x(t_0) = x^0,\ \ v(t_0) = v^0,\ \ (x^0, v^0) \in \mathcal{SD}(\theta_1, B_R),$$

where $x = (x_1, \dots, x_n)$, $v = (v_1, \dots, v_n)$ with $v_i = ({}^1v_i, \dots, {}^pv_i)$, $i = 1, \dots, n$.

We assume that:

A5 $\mathcal{SD}(\theta_1, B_R)$ is black (or a black part of the wall) such that

$$\begin{cases} -\alpha_1\,\theta_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(1, B_R) - G_1(1, B_R)x_1) < 0 \\ -\alpha_1\,\theta_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(0, B_R) - G_1(0, B_R)x_1) > 0, \end{cases} \tag{24}$$

where ${}^0c_1 \neq 0$.

Assume also that the diffusion coefficients $\sigma_1(q_1)$ and $\sigma_i(q_i)$, $i = 2, \dots, n$ satisfy the assumption A3.

According to the singular perturbation analysis we replace ${}^1v_1$ with Z_1. Using the formula (11) to calculate dZ_1, we get the following system describing the trajectories' behavior in $\mathcal{SD}(\theta_1, B_R)$

$$\begin{aligned} & q_1\dot{Z}_1 = \frac{Z_1(1-Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}(-\alpha_1\Sigma^{-1}(Z_1, \theta_1, q_1) + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + \\ & {}^0c_1(F_1(Z_1, Z_R) - G_1(Z_1, Z_R)x_1) + \frac{Z_1(1-Z_1)(1-2Z_1-q_1)}{2q_1(\Sigma^{-1}(Z_1, \theta_1, q_1))^2}\ {}^0c_1^2\,\sigma_1^2(q_1) + \\ & \frac{Z_1(1-Z_1)}{\Sigma^{-1}(Z_1, \theta_1, q_1)}\ {}^0c_1\sigma_1(q_1)\dot{\mathcal{B}}_1 \\ & \dot{x}_i = F_i(Z_1, Z_R) - G_i(Z_1, Z_R)x_i + \sigma_i(q_i)\dot{\mathcal{B}}_i \\ & {}^1\dot{v}_j = -\alpha_j\,{}^1v_j + \alpha_j\,{}^2v_j + \alpha_j x_j({}^0c_j + {}^1c_j) + {}^0c_j(F_j(Z_1, Z_R) - G_j(Z_1, Z_R)x_j) + \\ & {}^0c_j\sigma_j(q_j)\dot{\mathcal{B}}_j \\ & {}^2\dot{v}_i = -\alpha_i\,{}^2v_i + \alpha_i\,{}^3v_i + \alpha_i x_i\,{}^2c_i \\ & {}^3\dot{v}_i = -\alpha_i\,{}^3v_i + \alpha_i\,{}^4v_i + \alpha_i x_i\,{}^3c_i \\ & \vdots \\ & {}^p\dot{v}_i = -\alpha_i\,{}^pv_i + \alpha_i x_i\,{}^pc_i, \quad i = 1, \dots, n,\ j = 2, \dots, n. \end{aligned} \tag{25}$$

with the initial conditions

$$x(t_0) = x^0, \ \ Z(t_0) = 0.5$$
$$V(t_0) = V^0, \tag{26}$$

where $x = (x_1, \ldots, x_n)$, $V = (v_{1,R}, v_2, \ldots, v_n)$ with $v_{1,R} = ({}^2v_1, {}^3v_1, \ldots, {}^pv_1)$, $v_j = ({}^1v_j, \ldots, {}^pv_j), j = 2, \ldots, n$.

Now we need to show that under the assumptions A3 - A5 all conditions of the stochastic Tikhonov theorem listed in Appendix B are fulfilled for the problem (25)-(26).

Verification of B1.

The proof of the facts that the right hand side of (25) is continuous in Z_1, q_i, x_i and ${}^pv_i$ and satisfies the linear growth and locally Lipschitz conditions in x_i and ${}^pv_i$ is similar to the non-delay case.

Verification of B2.

By the assumption the diffusion coefficient $\sigma_1(q_1)$ goes to 0 as $q_1 \to 0$. Then we get that the first equation in (25) takes the form

$$\frac{Z_1(1-Z_1)}{\theta_1}[-\alpha_1\theta_1 + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1] = 0.$$

The function in the square brackets is linear in Z_1, moreover the wall $\mathcal{SD}(\theta_1, B_R)$ is assumed to be black. Therefore this equation has the solution

$\hat{Z}_1 = \hat{Z}_1(x_1, {}^2v_1) \in (0, 1)$ satisfying B2.

Verification of B3.

Since in the limit all noises disappeared, we have the same associated problem as in the deterministic case

$$\tilde{Z}_1' = \frac{\tilde{Z}_1(1-\tilde{Z}_1)}{\theta_1}[-\alpha_1\theta_1 + \alpha_1\, {}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(\tilde{Z}_1, B_R) - G_1(\tilde{Z}_1, B_R)x_1],$$

where $\tilde{Z}_1' = \partial Z_1 / \partial \tau$, $\tau = t/q_1$ is the stretching transformation.

The Lyapunov stability of the solution of the associated problem follows from the linearity of the function in the square brackets and the condition of blackness (24).

Verification of B4.

For $t = 0$ and $\bar{q} = \bar{0}$ we have $(x^0(\bar{0}), v^0(\bar{0})) \in \mathcal{SD}(\theta_1, B_R)$ therefore

$(x_1^0(\bar{0}), {}^2v_1^0(\bar{0})) \in M$, where $M \subset \mathbb{R}^2$ is a set of all solutions $(x_1, {}^2v_1)$ of System (24). Solving the equation

$$-\alpha_1\theta_1 + \alpha_1\,{}^2v_1 + \alpha_1 x_1({}^0c_1 + {}^1c_1) + {}^0c_1(F_1(\tilde{Z}_1, B_R) - G_1(\tilde{Z}_1, B_R)x_1 = 0$$

we see that Z_1 belongs to the domain of attraction, as soon as $(x^0(\bar{0}), v^0(\bar{0})) \in \mathcal{SD}(\theta_1, B_R)$.

Therefore the following theorem is fulfilled.

Theorem 4 *Under Assumptions A3,A5*

$$P - \lim_{\bar{q}\to\bar{0}} \sup_{0\le t\le T} |x(t,\bar{q}) - x(t,\bar{0})| \to 0$$
$$P - \lim_{\bar{q}\to\bar{0}} \sup_{0\le t\le T} |v(t,\bar{q}) - v(t,\bar{0})| \to 0$$
$$P - \lim_{q_1\to 0} \sup_{\delta\le t\le T} |Z_1(y_1,\theta_1,q_1) - \hat{Z}| \to 0, \quad 0 < \delta \le T,$$

where $x(t,\bar{q})$, $v(t,\bar{q})$ is a stochastically perturbed solutions of (25) and $x(t,\bar{0})$, $v(t,\bar{0})$ is a limit solution satisfied the system

$$\begin{aligned}
&\dot{x}_i = F_i(\hat{Z}_1, B_R) - G_i(\hat{Z}_1, B_R)x_i\\
&{}^1\dot{v}_j = -\alpha_j\,{}^1v_j + \alpha_j\,{}^2v_j + \alpha_j x_j({}^0c_j + {}^1c_j) + {}^0c_j(F_j(\hat{Z}_1, B_R) - G_j(\hat{Z}_1, B_R)x_j)\\
&{}^2\dot{v}_i = -\alpha_i\,{}^2v_i + \alpha_i\,{}^3v_i + \alpha_i x_i\,{}^2c_i\\
&{}^3\dot{v}_i = -\alpha_i\,{}^3v_i + \alpha_i\,{}^4v_i + \alpha_i x_i\,{}^3c_i\\
&\vdots\\
&{}^p\dot{v}_i = -\alpha_i\,{}^pv_i + \alpha_i x_i\,{}^pc_i, \quad i = 1,\dots,n,\ j = 2,\dots,n.
\end{aligned}$$

with the initial conditions (26).

6 Appendix A

Let us briefly review the basic definitions and notations of probability theory and stochastic equations [11], [12], which are used in this paper.

Definition 1 *Let $\mathcal{B}_t(\omega)$ be n-dimensional Brownian motion. Then we define $\mathcal{F}_t = \mathcal{F}_t^{(n)}$ to be the σ-algebra generated by the random variables $\mathcal{B}_s(\cdot)$, $s \le t$. In other words, $\mathcal{F}_t$ is the smallest σ-algebra containing all sets of the form*

$$\{\omega; \mathcal{B}_{t_1}(\omega) \in F_1, \dots, \mathcal{B}_{t_k}(\omega) \in F_k\},$$

where $t_j \le t$ and $F_j \subset \mathbb{R}^n$ are Borel sets, $j \le k$, $k = 1, 2, \dots$.

Definition 2 *A real valued function* $X : \Omega \to \mathbb{R}$ *is said to be* $\mathcal{F}$*-measurable if*

$$\{\omega : X(\omega) \leq a\} \in \mathcal{F} \quad \forall a \in \mathbb{R}.$$

Definition 3 *Let* $\{\mathcal{F}_t\}_{t\geq 0}$ *be an increasing family of* σ*-algebras of subsets of* Ω*. A process* $g(t,\omega) : [0,\infty) \times \Omega \to \mathbb{R}^n$ *is called* $\mathcal{F}_t$*-adapted if for each* $t \geq 0$ *the function* $\omega \to g(t,\omega)$ *is* $\mathcal{F}_t$*-measurable.*

Definition 4 *Let* $\mathcal{V} = \mathcal{V}(S,T)$ *be a class of functions* $f(t,\omega) : [0,\infty) \times \Omega \to \mathbb{R}^n$ *such that*

- $(t,\omega) \to f(t,\omega)$ *is* $\mathcal{B} \times \mathcal{F}$*-measurable, where* $\mathcal{B}$ *denotes the Borel* σ*-algebra on* $[0,\infty)$*,*
- $f(t,\omega)$ *is* $\mathcal{F}_t$*-adapted,*
- $E\left[\int\limits_S^T |f(t,\omega)|^2 dt\right] < \infty.$

For the function $f \in \mathcal{V}$ we define the Itô integral by

$$I_{[f]}(\omega) = \int\limits_S^T f(t,\omega)d\mathcal{B}_t(\omega).$$

Definition 5 *A filtration (on* $(\Omega,\mathcal{F})$*) is a family* $\mathcal{M} = \{\mathcal{M}_t\}_{t\geq 0}$ *of* σ*-algebras* $\mathcal{M}_t \subset \mathcal{F}$ *such that* $0 \leq s < t \Rightarrow \mathcal{M}_s \subset \mathcal{M}_t$*.*

Let $(\Omega,\mathcal{F},P)$ be a complete probability space with the Brownian motion $\mathcal{B}(t) = (\mathcal{B}_1,\ldots,\mathcal{B}_m)^T$, $t \geq 0$, and a filtration $\{\mathcal{F}_t\}_{t\geq 0}$. Let x_0 be an $\mathcal{F}_{t_0}$-measurable $\mathbb{R}^n$-valued random variables such that $E|x_0|^2 < \infty$. Let $f : \mathbb{R}^n \times [t_0,T] \to \mathbb{R}^n$ and $g : \mathbb{R}^n \times [t_0,T] \to \mathbb{R}^{n\times m}$ be both Borel measurable.

Consider the n-dimensional stochastic differential equation of Itô type

$$dx(t) = f(x(t),t)dt + g(x(t),t)d\mathcal{B}(t) \quad \text{on } t_0 \leq t \leq T \tag{27}$$

with the initial value $x(t_0) = x_0$. This equation is equivalent to the following stochastic integral equation

$$x(t) = x_0 + \int\limits_{t_0}^{t} f(x(s),s)ds + \int\limits_{t_0}^{t} g(x(s),s)d\mathcal{B}(s) \quad \text{on } t_0 \leq t \leq T. \tag{28}$$

Definition 6 *An* $\mathbb{R}^n$*-valued stochastic process* $\{x(t)\}_{t_0\leq t\leq T}$ *is called a solution of (28) if it has the following properties:*

- $x(t)$ *is continuous and* $\mathcal{F}_t$*-adapted,*
- $f(x(t),t) \in \mathcal{L}^1([t_0,T];\mathbb{R}^n)$ *and* $\{g(x(t),t)\} \in \mathcal{L}^2([t_0,T];\mathbb{R}^{n\times n})$*,*
  where $\mathcal{L}^p([a,b];\mathbb{R}^n)$ *is the family of* $\mathbb{R}^n$*-valued* $\mathcal{F}_t$*-adapted processes* $\{h(t)\}_{a\leq t\leq b}$

such that $\int_a^b |h(t)|^p dt < \infty$ *a.s.*,

- *System (27) holds for every* $t \in [t_0, T]$ *with probability* 1.

Definition 7 *We say that the function* $h : [0,T] \times E_1 \to E_2$*, where* E_1*,* E_2 *are Euclidian spaces, satisfies the linear growth and local Lipschitz conditions in* x *if:*

- *there is a constant* L *such that*

$$|h(t,x)| \leq L(1+|x|) \quad \forall t \in [0,T],\ x \in E_1,$$

- *for any* $N > 0$ *there is a constant* L_N *such that*

$$|h(t,x_1) - h(t,x_2)| \leq L_N|x_1 - x_2| \quad \forall t \in [0,T],\ x_i \in E_1,\ |x_i| \leq N.$$

Theorem 5 [12] *Assume that the functions* $f(x(t),t)$*,* $g(x(t),t)$ *satisfy the linear growth and local Lipschitz conditions in* (x,t)*. Then there exists a unique solution* $x(t)$ *to System (28) in* $\mathcal{M}^2([t_0,T];\mathbb{R}^n)$*, where* $\mathcal{M}^2([a,b];\mathbb{R}^n)$ *is the family of processes* $\{h(t)\}_{a \leq t \leq b}$ *in* $\mathcal{L}^2([a,b];\mathbb{R}^n)$ *such that* $E\int_a^b |h(t)|^2 dt < \infty$*.*

7 Appendix B

Consider in $\mathbb{R}^k \times \mathbb{R}^n$ the system of stochastic differential equations

$$\begin{aligned} dx(t,q) &= a(q,x(t,q),y(t,q)) + b(q,x(t,q),y(t,q))d\mathcal{B}^x(t), \quad x(0) = x_0, \\ qdy(t,q) &= A(q,x(t,q),y(t,q)) + B(q,x(t,q),y(t,q))d\mathcal{B}^y(t),\ y(0) = y_0, \end{aligned}$$

where $\mathcal{B}^x(t)$, $\mathcal{B}^y(t)$ are independent Brownian motions, $B(q,x(t,q),y(t,q)) = \sigma(q)B_0(q,x(t,q),y(t,q))$, x_0 and y_0 are constants.

Definition 8 *Let* X *and* X_k*,* $k \geq 1$*, be* $\mathbb{R}^n$*-valued random variables.*
If for every $\epsilon > 0$*,* $P\{\omega : |X_k(\omega) - X(\omega)| > \epsilon\} \to 0$ *as* $k \to \infty$*, then* X_k *is said to converge to* X *stochastically or in probability, i.e.*

$$P - \lim_{k\to\infty} \|X_k(\omega) - X(\omega)\| = 0.$$

We introduce the following assumptions:

B1 The functions a, A, b and B_0 are continuous in all variables (q,x,y) and satisfy the linear growth and local Lipschitz conditions in (x,y).

B2 Isolated root condition.

There is a function $\varphi : \mathbb{R}^k \to \mathbb{R}^n$ satisfying the linear growth and local Lipschitz conditions in x such that

$$A(0, x, \varphi(x)) = 0, \quad \forall x \in \mathbb{R}^k.$$

B3 Associated problem. Lyapunov stability condition.

The derivative A_y exists, it is a continuous function on the set $\mathbb{R}^k \times \mathbb{R}^n$ and for any $N > 0$ there exists a constant $k_N > 0$ such that for every $x \in \mathbb{R}^k$ with $|x| \le N$

$$z^\star A_y(0, x, \varphi(x))z \le -k_N|z|^2 \quad \forall z \in \mathbb{R}^n.$$

B4 The domain of attraction.

The solution of the problem

$$\tilde{y}'_\tau = A(0, x_0, \tilde{y}_\tau), \quad \tilde{y}_0 = y_0,$$

tends to $\varphi(x_0)$ as $\tau \to \infty$: $\lim\limits_{\tau\to\infty} \tilde{y}_\tau = \varphi(x_0)$, where $\tau = t/q$ is the stretching transformation.

Assumption B4 means that the initial value y_0 belongs to the domain of influence of the root $\varphi(x_0)$ of the equation $A(0, x_0, y) = 0$.

B5 The function

$$\sigma(q) = o\left(\sqrt{\left|\frac{q}{\ln q}\right|}\right) \quad \text{as } q \to 0.$$

Theorem 6 [13] *Under Assumptions B1-B5*

$$P - \lim_{q\to 0} \|x(t, q) - x(t, 0)\| = 0 \quad t \in [0, T],$$
$$P - \lim_{q\to 0} \|y(t, q) - y(t, 0)\| = 0 \quad t \in [\delta, T],$$

where $0 < \delta \le T$.

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Paper IV

Functional differential inclusions generated by functional differential equations with discontinuities

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Abstract

Given a functional differential equation with a discontinuity, a construction of its extension in the shape of a functional differential inclusion is offered. This construction can be regarded as a generalization of the famous Filippov approach to study ordinary differential equations with discontinuities. Some basic properties of the solutions of the introduced functional differential inclusions are studied. The developed approach is applied to analysis of gene regulatory networks with general delays.

Key words: multivalued operators, Filippov's theory, delay, gene regulatory networks
MSC: 34K09, 45D05, 46N60

1 Introduction

The theory of differential and integral inclusions is a popular and well-developed branch of modern mathematics [1]-[5]. It is well-known that one of the ways of obtaining differential inclusions is Filippov's theory of discontinuous differential equations [1]. This approach is widely used in many applications. One of the recent examples is the Boolean analysis of gene regulatory networks [6]-[8].

On the other hand, it is well-known too that delay effects are an important issue in genetic models. In the papers [9], [10] a way of incorporating delays into the Boolean analysis of gene regulatory networks is suggested, this approach is based on the studies of singular perturbations (Tikhonov's theory). However, it only covers very special types of delays, namely distributed delays where the corresponding integral operators are finite dimensional, i. e. their kernel are finite sums of special functions. The reason for that is a special technique suggested in these papers, which is based upon a special substitution (a modified linear chain trick) converting a given delay equation to a system of ordinary differential equations. This analysis may be suitable for certain biological applications, yet a simple case of a constant delay is not covered by this method.

The aim of the present paper is two-fold. On one hand, we suggest an analogue of Filippov's theory for functional differential equations, on the other, we show how this analogue can be applied to gene regulatory networks. We stress that our method covers very general discontinuous functional differential equations and in particular, very general Boolean genetic models with delay.

As gene networks serve as the main motivation for our approach, let us look at their mathematical aspects in more detail.

An important feature of gene regulatory networks is the presence of thresholds causing switch-like interactions between genes. Such interactions can be described by smooth monotone functions rapidly increasing in a vicinity of their thresholds. The resulting smooth nonlinear system can however be too complicated to be studied theoretically and even numerically, as the resulting system may contain thousands of variables. To simplify the functional form of the equations it is common to represent interactions by the step functions, which gives a system of differential equations with discontinuous right-hand sides. Such a representation can only be considered mathematically rigorous if the dynamics of the simplified system is closed to the dynamics of the original smooth system. Some important justification results in the non-delay case are obtained in the papers [11], [12], [13], [14], where the emphasis is put on stability of the steady states and reconstruction of the trajectories in the discontinuity set of the network. A biological motivation for these studies can be also found in these papers.

However, a drawback of the analysis just mentioned is that it treats the asymptotic study of steady states and the reconstruction of the limit solutions separately, because two different techniques are applied. For instance, it is not possible to conclude from the results obtained in these papers whether the limit solutions tend to the limit steady states.

A way to put together the asymptotic stability analysis and reconstruction of the limit trajectories was suggested in [7]. This approach exploits the concepts of differential inclusions and the Filippov solutions.

Certainly, this second approach also has its disadvantages. For instance, using it one may obtain steady states that are not limits of the proper steady states coming from the smooth model. Yet, a clear advantage of this approach is its more universal character and possibility to complete the asymptotic analysis around steady states of the network.

Unlike the papers [9] and [10] based on the first approach, the present paper follows the second approach, i. e. the one based on multivalued mappings. Yet, the classical Filippov theory treats only the non-delay case. As we are interested in incorporating very general delays into a discontinuous system of differential equations, we use the language of Volterra operators and functional differential equations (see e.g. [15]). In order to implement the central idea of Filippov's theory, we suggest a formal procedure of obtaining a functional differential inclusion from a general discontinuous functional differential equation. This gives us a possibility to define an analogue of a Filippov solution for discontinuous functional differential equations and finally to apply the developed theory to gene regulatory networks with general delays.

The paper is organized as follows.

In Section 2 we study families of functional differential inclusions that are discontinuous in one parameter. In the gene network setting this means that only one gene concentration approaches its threshold value (the case of a wall - see [9]). We show how such a family gives rise to a well-defined functional differential inclusion. We study also basic properties of the resulting inclusions such as local existence, uniqueness of (Filippov) solutions and their continuous dependence on parameters (like the threshold value itself). We demonstrate as well how the existence of global solutions can be obtained.

The key property which enables us to prove the announced results is the compactness of the constructed multivalued mappings in the weak topology of the Lebesgue space L_1^n.

In Section 3 we apply the results of the previous section to the case of one singular variable in a gene regulatory network with delay. At the beginning of this section a short yet comprehensive overview of the relevant terminology is offered.

In Section 4 we generalize the central results of Section 2 to the case of simultaneous discontinuity in several parameters. This section contains the main results of the paper related to its first aim - development of an analogue of Filippov's theory for general functional differential equations. But as we show, this general case can in fact be deduced from the special case studied in Section 2. In particular, we do not need to repeat the whole analysis developed in Section 2 with all its technicalities.

Finally, the case of arbitrary many singular variables in a gene regulatory network with general delays is treated in Section 5. This section contains the central results of the paper related to its second aim, i. e. a justification of the Boolean analysis of a gene regulatory network with a general delay.

2 Operators discontinuous in one parameter

Throughout the paper we use the following notation. The space $\mathbb{R}^n$ consists of all n–dimensional column vectors and the norm $|\cdot|$ in this space is kept fixed. For a normed space $\mathbb{X}$ with the norm $\|\cdot\|_{\mathbb{X}}$, let $B_{\mathbb{X}}[x,\delta]$ be the closed ball in the space $\mathbb{X}$ with the center at $x \in \mathbb{X}$ and of radius $\delta > 0$. We denote by $\mathbb{C}^n[a,b]$ the space of continuous functions $x : [a,b] \to \mathbb{R}^n$ with the norm $\|x\|_{\mathbb{C}^n[a,b]} = \max\{|x(t)| : t \in [a,b]\}$, $\mathbb{L}_1^n(\mathcal{U})$ the space of all integrable functions $x : \mathcal{U} \to \mathbb{R}^n$ and $\mathbb{K}$ an arbitrary metric space. For $n = 1$ we will write $\mathbb{C}[a,b]$ and $\mathbb{L}_1[a,b]$. For $U \subset \mathbb{X}$ we denote by $\Omega(U)$ the set of all nonempty convex subsets of U. We say that a set $\Phi \subset \mathbb{L}_1^n[a,b]$ is dominated by an integrable function if there exists a function $\varphi_\Phi \in \mathbb{L}_1[a,b]$ such that for each $x \in \Phi$ and almost all $t \in [a,b]$ one has $|x(t)| \leqslant \varphi_\Phi(t)$.

Definition 1 *A mapping $\tilde{P} : \mathbb{C}^n[a,b] \to \Omega(\mathbb{L}_1^n[a,b])$ is called a (multivalued) Volterra operator (see[15]), if for any $a < \tau \le b$ the equality $x = y$ on $[a,\tau]$ implies $\tilde{P}(x)|_\tau = \tilde{P}(y)|_\tau$, where $\tilde{P}(z)|_\tau$ is the set of all functions from $\tilde{P}(z)$ restricted to $[a,\tau]$.*

As a particular case, we obtain the standard definition of a single-valued Volterra operator $P : \mathbb{C}^n[a,b] \to \mathbb{L}_1^n[a,b]$.

In this paper we study the functional differential equation

$$\dot{x} = P(q, x, \lambda), \tag{1}$$

where the single-valued operator P satisfies Property $\mathcal{A}$ which is described in the next definition.

Definition 2 *We say that a continuous mapping*

$$P : (0,1] \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$$

has Property $\mathcal{A}$ if this mapping satisfies the following conditions:

1) for any bounded sets $U \subset \mathbb{C}^n[a,b]$ and $E \subset \mathbb{K}$ the image $P((0,1] \times U \times E)$ is dominated by an integrable function, *2) for any $q \in (0,1]$ and $\lambda \in \mathbb{K}$ the operator $P(q,\cdot,\lambda)$ is Volterra.*

Notice that if the mapping $P(\cdot,\cdot,\cdot)$ has Property $\mathcal{A}$ then the operator $P(\cdot,\cdot,\cdot)$ is not necessarily defined or continuous for $q = 0$. For such an operator $P(\cdot,\cdot,\cdot)$ we construct a multi-valued mapping which is defined for $q = 0$ and which is closed in the space $\mathbb{L}_1^n[a,b]$ equipped with the weak topology.

We define a multivalued mapping $\widetilde{P}(0,\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{L}_1^n[a,b])$, which extends the single-valued mapping P, by putting

$$\widetilde{P}(0,x,\lambda) = \bigcap_{\delta \in (0,1]} \overline{\mathrm{co}} P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta]). \quad (2)$$

Lemma 1 *The mapping $\widetilde{P}(0,\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{L}_1^n[a,b])$ given by (2) is closed and compact in the weak topology of $\mathbb{L}_1^n[a,b]$.*

Proof.

Assume that $x_i \to x$ in $\mathbb{C}^n[a,b]$, $\lambda_i \to \lambda$ in $\mathbb{K}$ as $i \to \infty$ and $z_i \to z$, $z_i \in \widetilde{P}(0,x_i,\lambda_i)$ weakly in $\mathbb{L}_1^n[a,b]$ as $i \to \infty$. Let us show that $z \in \widetilde{P}(0,x,\lambda)$. Assume that for some $\delta \in (0,1]$ and $q \in (0,\delta)$ there exists a number i_0 such that $B_{\mathbb{C}^n[a,b]}[x_i,q] \subset B_{\mathbb{C}^n[a,b]}[x,\delta]$ and $B_{\mathbb{K}}[\lambda_i,q] \subset B_{\mathbb{K}}[\lambda,\delta]$ for $i \geq i_0$. Then

$$P((0,q] \times B_{\mathbb{C}^n[a,b]}[x_i,q] \times B_{\mathbb{K}}[\lambda_i,q]) \subset P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$$

and therefore

$$\overline{\mathrm{co}} P((0,q] \times B_{\mathbb{C}^n[a,b]}[x_i,q] \times B_{\mathbb{K}}[\lambda_i,q]) \subset \overline{\mathrm{co}} P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta]) \quad (3)$$

for each $i \geq i_0$.

From the definition of $\widetilde{P}(0,\cdot,\cdot)$, it follows that $\widetilde{P}(0,x_i,\lambda_i) \subset \overline{\mathrm{co}} P((0,q] \times B_{\mathbb{C}^n[a,b]}[x_i,q] \times B_{\mathbb{K}}[\lambda_i,q])$. Using this and (3) we get

$$z_i \in \overline{\mathrm{co}} P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$$

for each $i \geq i_0$.

Since the set $\overline{\mathrm{co}} P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$ is closed in the weak topology of the space $\mathbb{L}_1^n[a,b]$ we obtain that $z \in \overline{\mathrm{co}} P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$. We see that the latter relation holds for all $\delta \in (0,1]$, so that $z \in \widetilde{P}(0,x,\lambda)$.

From the definition of the mapping $\widetilde{P}(0,\cdot,\cdot)$ and Property $\mathcal{A}$ of the operator P, it follows that for any bounded sets $U \subset \mathbb{C}^n[a,b]$ and $E \subset \mathbb{K}$ the image $\widetilde{P}(0,U,E)$ is dominated by an integrable function. Therefore $\widetilde{P}(0,\cdot,\cdot)$ is compact in the weak topology of $\mathbb{L}_1^n[a,b]$. The proof is complete.

Below we let $(B_{\mathbb{C}^n[a,b]}[x,\delta])|_\tau$ denote the set of the restrictions (to the interval $[0,\tau]$) of all functions from $B_{\mathbb{C}^n[a,b]}[x,\delta]$, where $\tau \in (a,b)$. In other words, for each $\tau \in (a,b)$ the set $(B_{\mathbb{C}^n[a,b]}[x,\delta])|_\tau$ is the closed ball in the space $\mathbb{C}^n[a,\tau]$ with the center $x|_\tau$ and the radius δ. Here $x|_\tau$ is the restriction of x to $[a,\tau]$. Evidently, if $P(\cdot,\cdot,\cdot)$ is a (single-valued) Volterra operator in the second variable, then the mapping $\widetilde{P}(0,\cdot,\cdot)$ is a (multivalued) Volterra operator as well.

In what follows we consider the following initial value problem for the functional differential inclusion (1) depending on a parameter $\lambda \in \mathbb{K}$

$$\dot{x} \in \widetilde{P}(0,x,\lambda), \quad x(a) = x_0. \tag{4}$$

For any $\tau \in (a,b]$ we define a continuous mapping $V_\tau : \mathbb{C}^n[a,\tau] \to \mathbb{C}^n[a,b]$ by

$$(V_\tau x) = \begin{cases} x(t) \text{ if } t \in [a,\tau] \\ x(\tau) \text{ if } t \in (\tau,b]. \end{cases} \tag{5}$$

Definition 3 *We say that an absolutely continuous function $x{:}[a,\tau] \to \mathbb{R}^n$ is a solution of the problem (4) on the interval $[a,\tau]$, if x satisfies the inclusion $\dot{x} \in (\widetilde{P}(0,V_\tau x,\lambda))|_\tau$ and the initial condition $x(a) = x_0$, where the continuous mapping $V_\tau : \mathbb{C}^n[a,\tau] \to \mathbb{C}^n[a,b]$ given by (5).*

A function $x : [a,c) \to \mathbb{R}^n$ which is absolutely continuous on every interval $[a,\tau] \subset [a,c)$, $c \in (a,b]$, is called a solution of the problem (4) on the interval $[a,c)$ if for each $\tau \in (a,c)$ the restriction of x to $[a,\tau]$ is a solution of the problem (4) on the interval $[a,\tau]$.

A solution $x : [a,c) \to \mathbb{R}^n$ of the problem (4) on the interval $[a,c)$ is said to be nonextendable if there is no solution y of the problem (4) on any larger interval $[a,\tau]$ (here $\tau \in (c,b]$ if $c < b$ and $\tau = b$ if $c = b$) such that $x(t) = y(t)$ for each $t \in [a,c)$.

Remark 1 *The above defined solution of the functional differential inclusion (4) can be called a Filippov solution of the discontinuous functional differential equation (1). A similar terminology is widely used in the theory of differential equations with discontinuous right hand sides.*

Let mappings $\Lambda : \mathbb{L}_1^n[a,b] \to \mathbb{C}^n[a,b]$ and $\Phi(0,\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{C}^n[a,b])$ be given by

$$(\Lambda z)(t) = \int_a^t z(s)ds, t \in [a,b], \qquad \Phi(0,x,\lambda) = x_0 + \Lambda\widetilde{P}(0,x,\lambda). \tag{6}$$

For each $\tau \in (a,b]$ let us define the operator $\Phi_\tau(0,\cdot,\cdot) : \mathbb{C}^n[a,\tau] \times \mathbb{K} \to \Omega(\mathbb{C}^n[a,\tau])$ by

$$\Phi_\tau(0,x,\lambda) = (\Phi(0,V_\tau x,\lambda))|_\tau, \tag{7}$$

where the continuous operator $V_\tau : \mathbb{C}^n[a,\tau] \to \mathbb{C}^n[a,b]$ and the mapping $\Phi(0,\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{C}^n[a,b])$ are given by (5) and (6), respectively.

Lemma 2 *For each $\tau \in (a,b]$ the mapping $\Phi_\tau(0,\cdot,\cdot)$ given by the formula (7) satisfies the following conditions:*

1) $\Phi_\tau(0,\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{C}^n[a,\tau])$ is a compact and closed operator,

2) for each $\lambda \in \mathbb{K}$, $\tau,\nu \in (a,b]$ $(\tau < \nu)$ and for any $x \in \mathbb{C}^n[a,\tau]$, $y \in \mathbb{C}^n[a,\nu]$ satisfying $x = y|_\tau$, we have $\Phi_\tau(0,x,\lambda) = (\Phi_\nu(0,y,\lambda))|_\tau$.

Proof. Let $\tau \in (a,b]$, $x_i \to x$ in $\mathbb{C}^n[a,b]$ and $\lambda_i \to \lambda$ in $\mathbb{K}$ as $i \to \infty$. Assume that $y_i \to y$, $y_i \in \Phi_\tau(0,x_i,\lambda_i)$ in $\mathbb{C}^n[a,\tau]$ as $i \to \infty$. We want to show that $y \in \Phi_\tau(0,x,\lambda)$. Let $h_i \in \widetilde{P}(0,V_\tau x_i,\lambda_i)$ be such that $y_i(t) = x_0 + (\Lambda h_i)(t)$, $i \in \mathbb{N}$, for each $t \in [a,\tau]$. The sequence h_i, $i \in \mathbb{N}$, is dominated by an integrable function, so that there exists $h \in \mathbb{L}_1^n[a,b]$ such that $h_i \to h$ weakly in $\mathbb{L}_1^n[a,b]$ as $i \to \infty$ and $y_i = x_0 + (\Lambda h_i)|_\tau \to x_0 + (\Lambda h)|_\tau = y$ in $\mathbb{C}^n[a,b]$ as $i \to \infty$. Then, according to Lemma 1, we have that $h \in \widetilde{P}(0,V_\tau x,\lambda)$ and therefore $y \in \Phi_\tau(0,x,\lambda)$.

From Lemma 1 we obtain that the operator $\Phi_\tau(0,\cdot,\cdot)$ is compact. The second condition follows from the definition of the mappings $\Phi_\tau(0,\cdot,\cdot)$, $\tau \in (a,b]$, and the fact that the mapping $\widetilde{P}(0,\cdot,\cdot)$ is Volterra in the second variable. Lemma is proved.

From (7) it follows that the solutions of the inclusion

$$x \in \Phi_\tau(0,x,\lambda)$$

coincide with the solutions of the problem (4) on the interval $[a,\tau]$. From this and the results of the paper [15] we directly deduce the following theorems.

Theorem 1 *There exists $\tau \in (a,b]$ such that the solution of the problem (4) is defined on the interval $[a,\tau]$.*

Theorem 2 *The solution $x : [a,c) \to \mathbb{R}^n$ of the problem (4) admits an extension to a larger interval if and only if $\overline{\lim\limits_{t\to c-0}} \, |x(t)| < \infty$.*

Corollary 1 *The solution $x : [a,c) \to \mathbb{R}^n$ of the problem (4) is a nonextendable solution if and only if $\overline{\lim\limits_{t\to c-0}} |x(t)| = \infty$.*

Theorem 3 *If y is the solution of the problem (4) on the interval $[a,\tau]$, $\tau \in (a,b)$, then there exists a nonextendable solution x of (4) defined on $[a,c)$,*

$c \in (\tau, b]$ *or on* $[a, b]$ *such that* $x(t) = y(t)$ *for each* $t \in [a, \tau]$.

Let $H(x_0, \lambda, \tau)$, $\lambda \in \mathbb{K}$ be the set of all local solutions of the problem (4) on $[a, \tau]$, $\tau \in (a, b]$. We say that $H(x_0, \lambda, \tau)$ is a priori bounded if there exists a number $r > 0$ such that for each $\tau \in (a, b]$ there is no solution $y \in H(x_0, \lambda, \tau)$ such that $\|y\|_{\mathbb{C}^n[a,\tau]} > r$.

Theorems 1–3 yield the following result.

Theorem 4 *Let the set of all local solutions of the problem (4) be a priori bounded. Then* $H(x_0, \lambda, \tau) \neq \emptyset$ *for each* $\tau \in (a, b]$ *and there exists a number* $r > 0$ *such that the inequality* $\|y\|_{\mathbb{C}^n[a,\tau]} \leq r$ *holds for all* $\tau \in (a, b]$, $y \in H(x_0, \lambda, \tau)$, $\lambda \in \mathbb{K}$.

Theorem 5 *If* $\lambda_i \to \lambda$ *in* $\mathbb{K}$ *as* $i \to \infty$ *and* $x_i \to x$, $x_i \in H(x_0, \lambda_i, \tau), \tau \in (a, b]$ *in* $\mathbb{C}^n[a, \tau]$ *then* $x \in H(x_0, \lambda, \tau)$.

Proof.

Assume that $h_i \in \widetilde{P}(0, V_\tau x_i, \lambda_i)$, $i \in \mathbb{N}$, satisfy the equality $x_i(t) = x_0 + (\Lambda h_i)(t)$ for each $t \in [a, \tau]$. The sequence h_i, $i \in \mathbb{N}$, is dominated by an integrable function, therefore there exists $h \in \mathbb{L}_1^n[a, b]$ such that $h_i \to h$ weakly in $\mathbb{L}_1^n[a, b]$ as $i \to \infty$. From Lemma 2 it follows that $h \in \widetilde{P}(0, V_\tau x, \lambda)$. If $\Lambda h_i \to \Lambda h$ in $\mathbb{C}^n[a, b]$ as $i \to \infty$, then $x(t) = x_0 + (\Lambda h)(t)$ for all $t \in [a, \tau]$. Therefore $x \in H(x_0, \lambda, \tau)$. The proof is complete.

Corollary 2 *For each* $\tau \in (a, b]$ *the set* $H(x_0, \lambda, \tau)$ *is closed in* $\mathbb{C}^n[a, \tau]$.

Definition 4 *A mapping* M *from an ordered set* $\mathcal{D}$ *into an ordered set* $\mathcal{P}$ *such that for any* $a, b \in \mathcal{D}$, $a \leq b$ *we have* $M(a) \leq M(b)$, *is called monotone.*

Below $|\cdot|$ stands for the operator $x(\cdot) \to |x(\cdot)|$ from $\mathbb{C}^n[a, b]$ to $C_+^n[a, b]$.

Lemma 3 *Let* $M : [0, 1] \times \mathbb{C}_+^1[a, b] \times \mathbb{K} \to \mathbb{L}_+^1[a, b]$ *be a continuous mapping satisfying the following conditions:*

1) for any $\varkappa \in [0, 1]$, $\lambda \in \mathbb{K}$ *the operator* $M(\varkappa, \cdot, \lambda)$ *is Volterra and monotone,*

2) for any $\varkappa \in (0, 1]$, $t \in (a, b]$, $x \in \mathbb{C}^n[a, b]$ *and* $\lambda \in \mathbb{K}$

$$\|P(\varkappa, x, \lambda)\|_{\mathbb{L}_1^n[a,t]} \leq \|M(\varkappa, |x|, \lambda)\|_{\mathbb{L}_1[a,t]}. \tag{8}$$

Then for any $t \in (a, b]$, $x \in \mathbb{C}^n[a, b]$, $\lambda \in \mathbb{K}$ *and* $y \in \widetilde{P}(0, x, \lambda)$ *we have*

$$\|y\|_{\mathbb{L}_1^n[a,t]} \leq \|M(0, |x|, \lambda)\|_{\mathbb{L}_1[a,t]},$$

where the mapping $\widetilde{P}(0, \cdot, \cdot) : \mathbb{C}^n[a, b] \times \mathbb{K} \to \Omega(\mathbb{L}_1^n[a, b])$ *is given by (2).*

Proof.

Let $t \in (a,b]$, $x \in \mathbb{C}^n[a,b]$, $\lambda \in \mathbb{K}$ be fixed. Taking $\delta \in (0,1]$, we assume that $P(\varkappa, w, \sigma) \in P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$. Using that $M(\varkappa,\cdot,\lambda)$ is monotone and applying the inequality (8) we obtain

$$\|P(\varkappa, w, \sigma)\|_{\mathbb{L}_1^n[a,t]} \le \|M(\varkappa, |x|+\delta, \sigma)\|_{\mathbb{L}_1[a,t]}. \tag{9}$$

Let $w \in \operatorname{co}P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$. Then there exist $\nu_i \ge 0$, $\varkappa_i \in (0,\delta]$, $w_i \in B_{\mathbb{C}^n[a,b]}[x,\delta]$, $\sigma_i \in B_{\mathbb{K}}[\lambda,\delta]$, $i=1,2,\ldots,m$, such that $\sum\limits_{i=1}^{m} \nu_i = 1$ and $w = \sum\limits_{i=1}^{m} \nu_i P(\lambda_i, w_i, \sigma_i)$. According to the inequality (9) we have

$$\|w\|_{\mathbb{L}_1^n[a,t]} \le \sum_{i=1}^{m} \nu_i \|M(\varkappa_i, |x|+q, \sigma_i)\|_{\mathbb{L}_1[a,t]}. \tag{10}$$

Denote

$$O(\delta,x,\lambda) = \overline{\operatorname{co}}\{\|M(\varkappa, |x|+\delta, \sigma)\|_{\mathbb{L}_1^1[a,t]} : \varkappa \in [0,\delta], \sigma \in B_{\mathbb{K}}[\lambda,\delta]\} \tag{11}$$

and

$$\|O(\delta,x,\lambda)\| = \max_{r \in O(\delta,x,\lambda)} r. \tag{12}$$

From (10), (11), (12) it follows that

$$\|w\|_{\mathbb{L}_1^n[a,t]} \le \|O(\delta,x,\lambda)\| \tag{13}$$

for all $w \in \overline{\operatorname{co}}P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$. Using (11), (12) and the continuity of the operator $M(\cdot,\cdot,\lambda)$ we get

$$\lim_{\delta \to +0} \|O(\delta,x,\lambda)\| = \|M(0,|x|,\lambda)\|_{\mathbb{L}_1[a,t]}. \tag{14}$$

Now let $y \in \widetilde{P}(0,x,\lambda)$. From the definition of $\widetilde{P}(\cdot,\cdot,\cdot)$ it follows that $y \in \overline{\operatorname{co}}P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta])$ for all $\delta \in (0,1]$. From (13) we obtain $\|y\|_{\mathbb{L}_1^n[a,t]}\| \le \|O(\delta,x,\lambda)\|$ for all $\delta \in (0,1]$. Letting $\delta \to +0$ in the last inequality and using (14), we obtain the result.

Definition 5 *We say that a continuous mapping $P : (0,1] \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ has Property $\mathcal{B}$ if this mapping has Property $\mathcal{A}$ and there exists a continuous mapping $M : [0,1] \times \mathbb{C}_+^1[a,b] \times \mathbb{K} \to \mathbb{L}_+^1[a,b]$ satisfying conditions 1), 2) of Lemma 3, and the problem*

$$\dot{y} = M(0,y,\lambda), y(a) = |x_0|, \lambda \in \mathbb{K} \tag{15}$$

has an upper solution, where x_0 is the initial value in the problem (4).

Theorem 6 *Let a continuous mapping $P : (0,1] \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ have Property $\mathcal{B}$. Then for every solution of the problem (4) we have $|x(t)| \le \xi(t)$ for each $t \in [a,b]$, where $\xi(\cdot)$ is the upper solution to (15).*

PROOF.

Let an operator $\Theta : \mathbb{L}_1^n[a,b] \to \mathbb{D}^1[a,b]$ be given by

$$(\Theta z)(t) = |x_0| + \int_a^t |z(s)| ds.$$

Let x be the solution to (4). From Lemma 3 it follows that

$$\|\dot{x}\|_{\mathbb{L}_1^n[a,t]} \le \|M(0,|x|,\lambda)\|_{\mathbb{L}_1[a,t]} \tag{16}$$

for all $t \in (a,b]$. We have that $|x(t)| \le (\Theta\dot{x})(t)$ for all $t \in [a,b]$. Using this, the inequality (16) and the assumption that the operator $M(\cdot,\cdot,\cdot)$ is monotone in the second variable, we obtain

$$(\Theta\dot{x})(t) \le |x_0| + \int_a^t M(0,\Theta\dot{x},\lambda)(s) ds \tag{17}$$

for all $t \in [a,b]$. Denote

$$(\Theta\dot{x})(t) \le |x_0| + \int_a^t M(0,\Theta\dot{x},\lambda)(s) ds. \tag{18}$$

From (17) we see that

$$(\Theta\dot{x})(t) \le v(t) \tag{19}$$

for all $t \in [a,b]$. Differentiating (18) we get

$$\dot{v}(t) = M(0,\Theta\dot{x},\lambda)(t).$$

Using (19) and the assumption that the operator $M(\cdot,\cdot,\cdot)$ is monotone in the second variable we obtain

$$\dot{v}(t) \le M(0,v,x)(t), \quad v(a) = |x_0|.$$

Applying the theorem on differential inequalities for monotone operators, we get $|x(t)| \le \xi(t)$ for all $t \in [a,b]$ (see [15]).

From Theorems 4 and 5, we obtain the following corollary.

Corollary 3 *Let the mapping $P : (0,1] \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ have Property B. Then for all $\tau \in (a,b]$ we have that $H(x_0,\lambda,\tau) \ne 0$ and any solution $x \in H(x_0,\lambda,\tau)$ admits an extension to the entire interval $[a,b]$.*

3 Gene regulatory networks with delay, the scalar case

Let us apply the developed theory to analysis of gene regulatory networks with general delays. The latter is given by

$$
\begin{aligned}
&\dot{x}_1 = F_1(Z_1, Z_2, \ldots, Z_n) - G_1(Z_1, Z_2, \ldots, Z_n)x_1 \\
&\dot{x}_2 = F_2(Z_1, Z_2, \ldots, Z_n) - G_2(Z_1, Z_2, \ldots, Z_n)x_2 \\
&\ldots \\
&\dot{x}_n = F_n(Z_1, Z_2, \ldots, Z_n) - G_n(Z_1, Z_2, \ldots, Z_n)x_n \\
&Z_i = \sum(y_i, \theta_i, q_i) \\
&y_i(t) = (\tilde{\mathcal{R}}_i x_i)(t), \;\; t \in (-\infty, b], \;\; i = 1, 2, \ldots n
\end{aligned}
\tag{20}
$$

with the initial conditions

$$
x_i(s) = \varphi_i(s), \;\; s \le a, \;\; i = 1, 2, \ldots, n, \tag{21}
$$

where x_i denotes the gene product concentration and the functions F_i and G_i stand for the production and relative degradation rate of the product of the gene i, respectively. The input variable y_i is described by nonlinear Volterra (delay) operator and endows the system with time-lags. Assume that System (20) satisfies the following assumptions.

Assumption 1 *F_i, G_i are affine functions in each Z_i and satisfy*

$$
F_i(Z_1, Z_2, \ldots, Z_n) \ge 0, \quad G_i(Z_1, Z_2, \ldots, Z_n) \ge \delta > 0
$$

for $0 \le Z_i \le 1$.

Assumption 2 *The continuous operator $\tilde{\mathcal{R}}_i : \mathbb{C}(-\infty, b] \to \mathbb{C}[a, b]$ can be rewritten in the following way*

$$
(\tilde{\mathcal{R}}_i x)(t) = \psi_i(t) + (\mathcal{R}_i x)(t), \tag{22}
$$

where $\psi_i \in \mathbb{C}[a, b]$ and $\mathcal{R}_i : \mathbb{C}[a, b] \to \mathbb{C}[a, b]$ is a linear, bounded and Volterra operator.

Assumption 3 *Each $Z_i = \Sigma(y_i, \theta_i, q_i)$ is continuous in $(y_i, q_i) \in \mathbb{C}[a, b] \times (0, 1)$ for any $\theta_i \in \mathbb{R}$, continuously differentiable w.r.t. $y_i \in \mathbb{C}[a, b]$ for all $(\theta_i, q_i) \in \mathbb{R} \times (0, 1)$, and $\frac{\partial}{\partial y_i}\Sigma(y_i, \theta_i, q_i) > 0$ on the set $\{y_i \in \mathbb{C}[a, b] : \;\; 0 < \Sigma(y_i, \theta_i, q_i) < 1\}$.*

Assumption 4 *Each $Z_i = \Sigma(y_i, \theta_i, q_i)$ satisfies*

$$
\Sigma(\theta_i, \theta_i, q_i) = 0.5, \quad \Sigma(0, \theta_i, q_i) = 0, \quad \Sigma(+\infty, \theta_i, q_i) = 1
$$

for all $(\theta_i, q_i) \in \mathbb{R} \times (0,1)$.

Assumption 5 $\frac{\partial}{\partial Z_i}\Sigma^{-1}(Z_i, \theta_i, q_i) \to 0$ *uniformly on any compact subset of the interval* $(0,1)$ *as* $q_i \to 0$ *for all* $\theta_i \in \mathbb{R}$, *and* $\Sigma^{-1}(Z_i, \theta_i, q_i) \to \theta_i$ *pointwise as* $q_i \to 0$ *for all* $Z_i \in (0,1)$ *and* $\theta_i \in \mathbb{R}$.

In a "real-world" gene regulatory network a number of genes is rather large, so that a theoretical or a computer-based analysis of such networks can be complicated. The most common simplification consists in replacing the smooth response functions Z_i with much simpler step functions obtained when $q_i \to 0$. This operation splits the system into a number of affine scalar delay systems. It is usually not difficult to describe the dynamics of each of these systems explicitly. However, coupled together these systems can produce some complicated effects, especially when trajectories approach a domain where a switching from one system to another occurs. It may be quite a challenge to describe the behavior of the solutions in a vicinity of such switching (usually called "singular") domains.

We continue with some definitions and notation related to geometrical properties of the gene network studied in this paper. We associate a Boolean variable B_i to each $Z_i(y_i)$ by $B_i = 0$ if $y_i < \theta_i$ and $B_i = 1$ if $y_i > \theta_i$.

Definition 6

The set $\mathcal{B}(B)$, *which consists of all* $x \in \mathbb{C}^n[a,b]$, *where* $Z_i = B_i$ *for all* $i = 1, \dots, n$, *is called a regular domain or a box.*

The set $\mathcal{SD}(\theta_S, B_R)$, *which consists of all* $x \in \mathbb{C}^n[a,b]$, *where* $y_i = \theta_i$ *for* $i \in S$, *i.e.* $i = 1, \dots s$, *and* $Z_i(y_i) = B_i$ *for* $i \in R$, *i.e.* $i = s, \dots, n$, $s < n$, *is called a singular domain.*

Singular domains of codimension 1 ("walls") can be classified into three groups, depending on a behavior of solutions in their vicinity:

- attractive or "black" walls, the trajectories hit them from either side;
- repelling or "white" walls, the trajectories depart from them on both sides;
- transparent walls, the trajectories travel through them.

Let us give the mathematical description of these types of singular domains. Consider the singular domain $\mathcal{SD}(\theta_\mu, B_R)$ of codimension 1 (i.e. a wall) which lies between the box $\mathcal{B}(B^0)$, where $Z_\mu = 0$, and the box $\mathcal{B}(B^1)$, where $Z_\mu = 1$. This gives two different systems for B^0 and B^1. Let P be a point in the singular domain $\mathcal{SD}(\theta_\mu, B_R)$ and $u(t, \nu, P)$ be the solution with $B = B^\nu$, which satisfies $u(t_0, \nu, P) = P$, $\nu = 0, 1$. Denote by $\dot{u}_\mu(t_0, Z, P)$ component of number μ (which is orthogonal to $\mathcal{SD}(\theta_\mu, B_R)$) of the velocity vector $\dot{u}_\mu(t, Z, P)$ at P for $t = t_0$, $Z = 0$ or 1.

Definition 7 A point $P \in \mathcal{SD}(\theta_\mu, B_R)$ is called

- "black" if $\dot{u}_\mu(t_0, 1, P) < 0$ and $\dot{u}_\mu(t_0, 0, P) > 0$;
- "white" if $\dot{u}_\mu(t_0, 1, P) > 0$ and $\dot{u}_\mu(t_0, 0, P) < 0$;
- "transparent" if $\dot{u}_\mu(t_0, 1, P) < 0$ and $\dot{u}_\mu(t_0, 0, P) < 0$, or if $\dot{u}_\mu(t_0, 1, P) > 0$ and $\dot{u}_\mu(t_0, 0, P) > 0$.

We say that a part of a wall $\mathcal{SD}(\theta_\mu, B_R)$ is black (white, transparent) if any point in it, except for a nowhere dense set, is black (white, transparent). In the non delay case walls are either black, white or transparent [11]. In the delay case, they can also be of a mixed type [9].

Returning to the problem (20)-(21) let us consider the case, when exactly one of the variables y_i approaches its threshold value θ_i, while the others stay away from their thresholds. The general case when all variables may approach their respective thresholds will be studied later in Section 5. Renumbering we can always assume that the singular variable is y_1 with the threshold value θ_1. Denote this singular domain by $\mathcal{SD}(\theta_1, B_R)$. In the limit, i.e. as all $q_i \to 0$, we obtain that $y_1 = \theta_1$ and $Z_i(y_i) = B_i$, $i \geq 2$, where B_i is a corresponding Boolean vector. The system describing trajectories' behavior in $\mathcal{SD}(\theta_1, B_R)$ then will be given by

$$\begin{aligned} \dot{x} &= F(Z_1, B_R) - G(Z_1, B_R)x \\ Z_1 &= \Sigma(y_1, \theta_1, q_1) \\ y_1(t) &= (\mathcal{R}x_1)(t), \ \ t \in [-\infty, b), \end{aligned} \tag{23}$$

where $x = \mathrm{col}(x_1, x_2, \ldots, x_n)$, $F(Z_1, B_R) = \mathrm{col}(F_1(Z_1, B_R),\ F_2(Z_1, B_R), \ldots, F_n(Z_1, B_R))$ and $G(Z_1, B_R)$ is a diagonal $n \times n$-matrix with the diagonal elements $G_1(Z_1, B_R)$, $G_2(Z_1, B_R), \ldots, G_n(Z_1, B_R)$.

The right hand side of (23) is discontinuous at the point $q_1 = 0$. Now we want to apply the theory developed in the previous section for describing solutions of (23) in the singular domain $\mathcal{SD}(\theta_1, B_R)$. For this end we introduce a parameterized mapping Γ_{θ_1, q_1} depending on θ_1, q_1 and given by

$$\Gamma_{\theta_1, q_1}(x, \mathcal{R}x_1, t) = F(\mathcal{R}x_1, \theta_1, q_1, t) - G(\mathcal{R}x_1, \theta_1, q_1, t)x.$$

Then the problem (20)-(21) can be rewritten as

$$\dot{x}(t) = \Gamma_{\theta_1, q_1}(x, \mathcal{R}x_1, t).$$

Let us introduce the superposition (Nemytskii) operator $\mathcal{N}_{\theta_1, q_1} : \mathbb{C}^n[a, b] \times \mathbb{C}[a, b] \to \mathbb{C}^n[a, b]$ by setting

$$\mathcal{N}_{\theta_1, q_1}(x, \mathcal{R}x_1)(t) = \Gamma_{\theta_1, q_1}(x, \mathcal{R}x_1, t)$$

and define the operator $P : (0, 1] \times \mathbb{C}^n[a, b] \times \mathbb{R} \to \mathbb{C}^n[a, b]$ by

$$P(q_1, x, \theta_1) \equiv \mathcal{N}_{\theta_1, q_1}(x, \mathcal{R}x_1). \tag{24}$$

The next step is to construct a multivalued operator $\widetilde{P}(0, x, \theta_1) : \mathbb{C}^n[a, b] \times \mathbb{K} \to \Omega(\mathbb{L}_1^n[a, b])$, which is defined in (2) in its most general shape, for the case of our specific problem.

For the sake of simplicity we assume below that the threshold value θ_1 is fixed, i.e. the operators $P(q_1, x) : (0, 1] \times \mathbb{C}^n[a, b] \to \mathbb{C}^n[a, b]$ and $\widetilde{P}(0, x) : \mathbb{C}^n[a, b] \to \Omega(\mathbb{L}_1^n[a, b])$ do not depend on this parameter.

Theorem 7 *If the singular variable y_1 never approaches its threshold value θ_1, i.e. the solution never crosses the singular domain $\mathcal{SD}(\theta_1, B_R)$. Then the operator $\tilde{P}(0, x)$ is a single valued operator given by either*

$$\tilde{P}(0, x) = F(0, B_R) - G(0, B_R)x \quad \textit{if} \quad y_1 < \theta_1$$

or

$$\tilde{P}(0, x) = F(1, B_R) - G(1, B_R)x \quad \textit{if} \quad y_1 > \theta_1.$$

If the singular variable y_1 approaches its threshold value at the time t^* and leaves it at once, i.e. $y_1 = \theta_1$ only for $t = t^*$ (what means that the point $(x_1(t^*), x_2(t^*), \ldots, x_n(t^*))$ is transparent). Then the operator $\tilde{P}(0, x)$ is a single-valued operator defined by either

$$\tilde{P}(0, x) = \begin{cases} F(0, B_R) - G(0, B_R)x \textit{ for } t \leq t^* \\ F(1, B_R) - G(1, B_R)x \textit{ for } t > t^* \end{cases}$$

or

$$\tilde{P}(0, x) = \begin{cases} F(1, B_R) - G(1, B_R)x \textit{ for } t \leq t^* \\ F(0, B_R) - G(0, B_R)x \textit{ for } t > t^*. \end{cases}$$

If the singular variable y_1 approaches its threshold value at the time t^* and never leaves, i.e. $y_1 = \theta_1$ for $t \geq t^*$ (what means that the point $(x_1(t^*), x_2(t^*), \ldots, x_n(t^*))$ is black). Then the operator $\tilde{P}(0, x)$ is a multivalued operator defined by either

$$\tilde{P}(0, x) = \begin{cases} F(0, B_R) - G(0, B_R)x & \textit{for } t < t^* \\ \overline{co}\{F(Z_1, B_R) - G(Z_1, B_R)x \mid 0 \leq Z_1 \leq 1\} & \textit{for } t \geq t^* \end{cases}$$

or

$$\tilde{P}(0, x) = \begin{cases} F(1, B_R) - G(1, B_R)x & \textit{for } t < t^* \\ \overline{co}\{F(Z_1, B_R) - G(Z_1, B_R)x \mid 0 \leq Z_1 \leq 1\} & \textit{for } t \geq t^*. \end{cases}$$

Proof.

The first two cases are obvious. We assume now that

$$\begin{cases} y_1 < \theta_1 \text{ for } t < t^* \\ y_1 = \theta_1 \text{ for } t \geq t^*, \end{cases}$$

i.e. y_1 approaches θ_1 from the left at the time t^*.

Since $y_1 < \theta_1$ for $t < t^*$, then $Z_1 = 0$ and $\tilde{P}(0, x)$ is a single-valued operator given by

$$\tilde{P}(0, x) = F(0, B_R) - G(0, B_R)x \quad \text{for} \quad t < t^*.$$

Now we want to construct $\tilde{P}(0, x)$ for $t \geq t^*$. By the formula (2)

$$\widetilde{P}(0, x) = \bigcap_{\delta \in (0,1]} \overline{\text{co}} P((0, \delta] \times B_{\mathbb{C}^n[a,b]}[x, \delta]).$$

Choose any $\delta \in (0, 1]$ and for this δ take $q_1 \in (0, \delta]$ and $X = (X_1, \dots, X_n) \in \{B_{\mathbb{C}^n[a,b]}[x, \delta] : |X_1(t) - x_1(t)| < \delta, \ \dots, \ |X_n(t) - x_n(t)| < \delta\}$ for $t \leq t^*$.

Substituting X into (24), we get

$$P(q_1, X) = \mathcal{N}_{q_1}(X, \mathcal{R}X_1) = F(Z_1(y_1(X_1)), B_R) - G(Z_1(y_1(X_1)), B_R)X,$$

where $Z_1(y_1(X_1)) = Z_1(\mathcal{R}X_1, \theta_1, q_1)$.

Since y_1 approaches its threshold value θ_1 at the time t^* and never leaves this point, then $|y_1(X_1) - \theta_1| < \sigma$ for all $t \leq t^*$. Now we want to find the range of the function $Z_1 = \Sigma(y_1(X_1), \theta_1, q_1)$ while $y_1(X_1)$ and q_1 vary over the intervals $(\theta_1 - \sigma, \theta_1 + \sigma)$ and $(0, \delta]$, respectively. Let us look at the particular case when the response function is the Hill function given by $Z_1 = \Sigma(y_1, \theta_1, q_1) = \frac{y_1^{q_1}}{y_1^{q_1} + \theta_1^{q_1}}$.

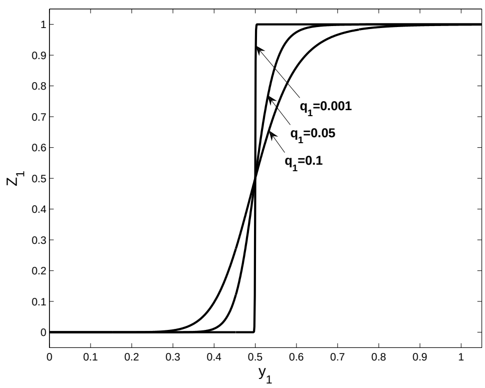

Fig. 1.

$Z_1 = \Sigma(y_1, \theta_1, q_1) = \frac{y_1^{q_1}}{y_1^{q_1} + \theta_1^{q_1}}$ is the Hill function, $\theta_1 = 0.5$ and $q_1 = 0.1$, 0.05, 0.001.

Fig. 1 illustrates how the range of the Hill function changes in the vicinity of the threshold as the steepness parameter gets closer to 0. Therefore for $y_1 \in (\theta_1 - \sigma, \theta_1 + \sigma)$ and $q_1 \in (0,1]$ the range of Z_1 is the whole interval $[0,1]$. Assumptions 3-5 put on Z_1 allow us to conclude that $Z_1 \in [0,1]$ for any response function Z_1 satisfied these assumptions. Thus,

$$\widetilde{P}(0,x) = \bigcap_{\delta \in (0,1]} \overline{\text{co}} P((0,\delta] \times B_{\mathbb{C}^n[a,b]}[x,\delta]) = \overline{\text{co}}\{F(Z_1,B_R) - G(Z_1,B_R)x \mid 0 \le Z_1 \le 1\}$$

for $t \geq t^*$.

The proof for the case

$$\begin{cases} y_1 > \theta_1 \text{ for } t < t^* \\ y_1 = \theta_1 \text{ for } t \geq t^*. \end{cases}$$

is similar. The theorem is proved.

Remark 2 *The time t^* in Theorem 7 can be found explicitly for any specified $x_1(t)$ from the equation $y_1(x_1(t^*)) = \theta_1$.*

Remark 3 *The mapping $P(q_1,x) : (0,1] \times \mathbb{C}^n[a,b] \to \mathbb{C}^n[a,b]$ satisfies Properties A and B.*

Remark 4 *For any solution of the problem*

$$\dot{x} \in \widetilde{P}(0,x), \quad x(a) = \varphi(a),$$

with $\widetilde{P}(0,x)$ constructed in Theorem 7, we have that $|x(t)| \leq \xi^*(t)$, where $\xi^*(\cdot)$ is an upper solution of the problem

$$\dot{y} = C_1 + C_2 y, \;\; y(a) = |\varphi(a)|.$$

C_1 and C_2 are upper bounds of $|F(Z_1,B_R)|$ and $\|G(Z_1,B_R)\|$, respectively.

We do not provide a proof of the statements in Remarks 3, 4 in this section. We will prove these results in Section 4 under more general assumptions.

4 Operators discontinuous in several parameters

All properties formulated in Section 2 for the mapping $P : (0,1] \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$, also hold for an operator, which is discontinuous w.r.t. several parameters, i.e. for an operator defined on $\underbrace{(0,1] \times (0,1] \times \ldots \times (0,1]}_{m} \times \mathbb{C}^n[a,b] \times \mathbb{K}$. We write $P^m : (0,1] \times (0,1] \times \ldots \times (0,1] \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ for such an operator.

Below we show that the limit operator $\tilde{P}^m(\bar{0},\cdot,\cdot):\mathbb{C}^n[a,b]\times\mathbb{K}\to\Omega(\mathbb{L}_1^n[a,b])$ constructed from $P^m(\cdot,\cdot,\cdot)$ is independent of the way the parameters approach 0. In other words, we prove that for any $x\in\mathbb{C}^n[a,b]$ and $\lambda\in\mathbb{K}$

$$\bigcap_{\delta\in(0,1]}\overline{\text{co}}P^m((0,\delta]\times\ldots\times(0,\delta]\times B_{\mathbb{C}^n[a,b]}[x,\delta]\times B_{\mathbb{K}}[\lambda,\delta])= \tag{25}$$

$$\bigcap_{\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda\in(0,1]}\overline{\text{co}}P^m((0,\delta_1]\times\ldots\times(0,\delta_m]\times B_{\mathbb{C}^n[a,b]}[x,\delta_x]\times B_{\mathbb{K}}(\lambda,\delta_\lambda]).$$

Let A_1 and A_2 be the left and right hand side of (25), respectively. First of all we show that $A_1\subset A_2$. Let $\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda\in(0,1]$ and $\delta<\min\{\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda\}$. Then we have

$$P^m((0,\delta]\times\ldots\times(0,\delta]\times B_{\mathbb{C}^n[a,b]}[x,\delta]\times B_{\mathbb{K}}[\lambda,\delta])\subset$$
$$P^m((0,\delta_1]\times\ldots\times(0,\delta_m]\times B_{\mathbb{C}^n[a,b]}[x,\delta_x]\times B_{\mathbb{K}}[\lambda,\delta_\lambda]).$$

Therefore

$$\begin{aligned}&\overline{\text{co}}P^m((0,\delta]\times\ldots\times(0,\delta]\times B_{\mathbb{C}^n[a,b]}[x,\delta]\times B_{\mathbb{K}}[\lambda,\delta])\subset\\&\overline{\text{co}}P((0,\delta_1]\times\ldots\times(0,\delta_m]\times B_{\mathbb{C}^n[a,b]}[x,\delta_x]\times B_{\mathbb{K}}(\lambda,\delta_\lambda]).\end{aligned} \tag{26}$$

From the definition of the set A_1, it follows that

$$A_1\subset\overline{\text{co}}P^m((0,\delta]\times\ldots\times(0,\delta]\times B_{\mathbb{C}^n[a,b]}[x,\delta]\times B_{\mathbb{K}}[\lambda,\delta]).$$

Therefore for any $\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda\in(0,1]$ from (26) we get that

$$A_1\subset\overline{\text{co}}P^m((0,\delta_1]\times\ldots\times(0,\delta_m]\times B_{\mathbb{C}^n[a,b]}[x,\delta_x]\times B_{\mathbb{K}}(\lambda,\delta_\lambda])$$

so that $A_1\subset A_2$.

Now let us show that $A_2\subset A_1$. Pick $\delta\in(0,1]$ and choose $\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda\in(0,1]$ such that $\max\{\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda\}<\delta$. For the selected $\delta_1,\ldots,\delta_m,\delta_x,\delta_\lambda$ we have the inclusion

$$\begin{aligned}&\overline{\text{co}}P^m((0,\delta_1]\times\ldots\times(0,\delta_m]\times B_{\mathbb{C}^n[a,b]}[x,\delta_x]\times B_{\mathbb{K}}(\lambda,\delta_\lambda])\subset\\&\overline{\text{co}}P^m((0,\delta]\times\ldots\times(0,\delta]\times B_{\mathbb{C}^n[a,b]}[x,\delta]\times B_{\mathbb{K}}[\lambda,\delta]).\end{aligned} \tag{27}$$

Since

$$A_2\subset\overline{\text{co}}P^m((0,\delta_1]\times\ldots\times(0,\delta_m]\times B_{\mathbb{C}^n[a,b]}[x,\delta_x]\times B_{\mathbb{K}}(\lambda,\delta_\lambda]),$$

then from (27) we get that

$$A_2\subset\overline{\text{co}}P^m((0,\delta]\times\ldots\times(0,\delta]\times B_{\mathbb{C}^n[a,b]}[x,\delta]\times B_{\mathbb{K}}[\lambda,\delta])$$

for each $\delta \in (0,1]$. Therefore $A_2 \subset A_1$, and we obtain the equality (25).

Due to the above discussion we can define the mapping $\tilde{P}^m(\bar{0},\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{L}_1^n[a,b])$ by setting

$$\tilde{P}^m(\bar{0},x,\lambda) = \bigcap_{\delta\in(0,1]} \overline{\mathrm{co}} P^m((0,\delta]^m \times B_{\mathbb{C}^n[a,b]}[x,\delta] \times B_{\mathbb{K}}[\lambda,\delta]) \qquad (28)$$

and the mappings

$$\Phi^m(\bar{0},\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{C}^n[a,b])$$
$$\Phi^m_\tau(\bar{0},\cdot,\cdot) : \mathbb{C}^n[a,\tau] \times \mathbb{K} \to \Omega(\mathbb{C}^n[a,\tau]), \quad \tau \in (a,b],$$

by

$$\Phi^m(\bar{0},x,\lambda) = x_0 + \Lambda\tilde{P}^m(\bar{0},x,\lambda)$$
$$\Phi^m_\tau(\bar{0},x,\lambda) = (\Phi(\bar{0},V_\tau x,\lambda))|_\tau.$$

The initial value problem for the limit functional differential inclusion in this case is defined as

$$\dot{x} \in \tilde{P}^m(\bar{0},x,\lambda), x(a) = x_0. \qquad (29)$$

Lemma 3, which gives the estimates for solutions of the initial value problem to the limit functional differential inclusion, can be formulated in the following way.

Lemma 4 *Let there exist a continuous mapping* $M^m : [0,1]^m \times \mathbb{C}^1_+[a,b] \times \mathbb{K} \to \mathbb{L}^1_+[a,b]$ *satisfying the conditions:*

1) for each vector $\varkappa \in [0,1]^m, \lambda \in \mathbb{K}$ *the operator* $M(\varkappa,\cdot,\cdot)$ *is Volterra and monotone,*

2) for all $\varkappa \in [0,1]^m$, $t \in (a,b]$, $x \in \mathbb{C}^n[a,b]$, $\lambda \in \mathbb{K}$

$$\| P^m(\varkappa,x,\lambda) \|_{\mathbb{L}_1^n[a,t]} \leq \| M^m(\varkappa,|x|,\lambda) \|_{\mathbb{L}_1[a,t]} .$$

Then

$$\| y \|_{\mathbb{L}_1^n[a,t]} \leq \| M^m(\bar{0},|x|,\lambda) \|_{\mathbb{L}_1[a,t]}$$

for any $t \in (a,b]$, $x \in \mathbb{C}^n[a,b]$, $\lambda \in \mathbb{K}$, $y \in \tilde{P}^m(\bar{0},x,\lambda)$, *where* $\tilde{P}^m(\bar{0},\cdot,\cdot) : \mathbb{C}^n[a,b] \times \mathbb{K} \to \Omega(\mathbb{L}_1^n[a,b])$ *is given by (28).*

Let us formulate Properties A^* and B^* for the mapping $P^m : (0,1]^m \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ using Definitions 2 and 5 from Section 2.

Definition 8 *We say that a continuous mapping*

$$P^m : (0,1]^m \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$$

has Property A^* if this mapping satisfies the following conditions:

1) for all bounded sets $U \subset \mathbb{C}^n[a,b]$ and $E \subset \mathbb{K}$ the image $P^m((0,1]^m \times U \times E)$ is dominated by an integrable function,

2) for any $\varkappa \in (0,1]^m, \lambda \in \mathbb{K}$ the operator $P^m(\varkappa, \cdot, \lambda)$ is Volterra.

Definition 9 *We say that a continuous mapping $P^m : (0,1]^m \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ has Property B^* if this mapping has Property A^* and there exists a continuous mapping $M^m : [0,1]^m \times \mathbb{C}_+^1[a,b] \times \mathbb{K} \to \mathbb{L}_+^1[a,b]$ satisfying conditions 1), 2) of Lemma 4, and the problem*

$$\dot{y} = M^m(\bar{0}, y, \lambda), \;\; y(a) = |x_0|, \;\; \lambda \in \mathbb{K} \tag{30}$$

has an upper solution, where x_0 is the initial condition of the problem (29).

Theorem 8 *Let a continuous mapping $P^m : (0,1]^m \times \mathbb{C}^n[a,b] \times \mathbb{K} \to \mathbb{L}_1^n[a,b]$ have Property B^*. Then for any solution of the problem (29) we have that $|x(t)| \leq \xi^*(t)$ for any $t \in [a,b]$, where $\xi^*(\cdot)$ is the upper solution of the problem (30).*

5 Gene regulatory networks with delay, the case of a general dimension

This section is a generalization of the main theoretical results obtained in Section 3. The central results of this section serve as a rigorous justification of the analysis of gene regulatory networks with general delays.

We again consider the problem (20)-(21) under Assumptions 1-5. Unlike Section 3 we assume now that all variables y_i may approach their respective threshold values θ_i, $i = 1, 2, \ldots, n$.

First of all we want to rewrite the problem in a way which is more convenient for our analysis. To this end, we put

$$\theta = \text{col}(\theta_1, \theta_2, \ldots, \theta_n),$$

$$y = \text{col}(y_1, y_2, \ldots, y_n),$$

$$q = (q_1, q_2, \ldots, q_n) \in (0,1]^n.$$

Then

$$
\begin{aligned}
&Z_i(y_i, \theta_i, q_i, t) = \sum(y_i + \psi_i(t), \theta_i, q_i),\\
&F_i(y, \theta, q, t) = F_i(Z_1(y_1, \theta_1, q_1, t),\ Z_2(y_2, \theta_2, q_2, t), \dots, Z_n(y_n, \theta_n, q_n, t)),\\
&G_i(y, \theta, q, t) = G_i(Z_1(y_1, \theta_1, q_1, t),\ Z_2(y_2, \theta_2, q_2, t), \dots, Z_n(y_n, \theta_n, q_n, t)),\ i = 1, 2, \dots, n.
\end{aligned}
$$

Let us also introduce a parameterized mapping $\Gamma_{\theta,q} : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$ depending on θ, q and given by

$$
\Gamma_{\theta,q}(x, y, t) = F(y, \theta, q, t) - G(y, \theta, q, t)x, \tag{31}
$$

where $x = \mathrm{col}(x_1, x_2, \dots, x_n)$, $F(y, \theta, q, t) = \mathrm{col}(F_1(y, \theta, q, t),\ F_2(y, \theta, q, t), \dots,$ $F_n(y, \theta, q, t))$ and $G(y, \theta, q, t)$ is $n \times n$-matrix given by

$$
G(y, \theta, q, t) = \begin{pmatrix} G_1(y, \theta, q, t) & 0 & \dots & 0 \\ 0 & G_2(y, \theta, q, t) & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & G_n(y, \theta, q, t) \end{pmatrix}.
$$

Let $\mathcal{R} : \mathbb{C}^n[a, b] \to \mathbb{C}^n[a, b]$ be a linear, bounded and Volterra operator given by

$$
(\mathcal{R}x)(t) = \mathrm{col}((\mathcal{R}_1 x_1)(t), (\mathcal{R}_2 x_2)(t), \dots, (\mathcal{R}_n x_n)(t)), \tag{32}
$$

where $\mathcal{R}_i : \mathbb{C}[a, b] \to \mathbb{C}[a, b]$, $i = 1, 2, \dots, n$, are linear, bounded and Volterra operators given by (22).

Then the problem (20)-(21) can be rewritten as

$$
\dot{x}(t) = \Gamma_{\theta,q}(x(t), (\mathcal{R}x)(t), t). \tag{33}
$$

We stress, that according to the above assumptions the right hand side of Equation (33) is, in general, discontinuous in $\bar{q} \in (0, 1]^n$ at the point $\bar{0} \in \mathbb{R}^n$.

Following the notation from Section 4 we now construct a mapping P^n : $(0, 1]^n \times \mathbb{C}^n[a, b] \times \mathbb{R}^n \to \mathbb{C}^n[a, b]$ using the right hand side of (33). Then we prove its right hand side Properties A^* and B^* and define the limit functional differential inclusion (29).

Let us define the superposition (Nemytskii) operator $\mathcal{N}_{\theta,q} : \mathbb{C}^n[a, b] \times \mathbb{C}^n[a, b] \to \mathbb{C}^n[a, b]$ by setting

$$
\mathcal{N}_{\theta,q}(x, y)(t) = \Gamma_{\theta,q}(x(t), y(t), t),
$$

where the function $\Gamma_{\theta,q} : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$ is given by (31).

According to Assumption 2, the functions $\sum(y_i + \psi_i(t), \theta_i, q_i)$ are continuous. Therefore $\Gamma_{\theta,q}(x, y, t)$ is continuous in all variables (x, y, t, θ, q).

Hence, the continuous Nemytskii operator $\mathcal{N}_{\theta,q} : \mathbb{C}^n[a, b] \times \mathbb{C}^n[a, b] \to \mathbb{C}^n[a, b]$ continuously depends on a vector $(q, \theta) \in (0, 1]^n \times \mathbb{R}^n$.

Let an operator $P^n : (0, 1]^n \times \mathbb{C}^n[a, b] \times \mathbb{R}^n \to \mathbb{C}^n[a, b]$ be given by

$$P^n(q, x, \theta) \equiv \mathcal{N}_{\theta,q}(x, \mathcal{R}x).$$

Then the initial value problem for the limit functional differential inclusion takes on the following view

$$\dot{x} \in \tilde{P}^n(\bar{0}, x, \theta) \tag{34}$$

under the initial condition

$$x(s) = \varphi(s), \;\; s \le a, \tag{35}$$

where the mapping $\tilde{P}^n(\bar{0}, \cdot, \cdot) : \mathbb{C}^n[a, b] \times \mathbb{R}^n \to \Omega(\mathbb{L}_1^n[a, b])$ is given by

$$\tilde{P}^n(\bar{0}, x, \theta) = \bigcap_{\delta \in (0,1]} \overline{\text{co}} P^n((0, \delta]^n \times B_{\mathbb{C}^n[a,b]}[x, \delta] \times B_{\mathbb{K}}[\theta, \delta]). \tag{36}$$

In Section 4 we proved the following property of the limit operator.

Theorem 9 *The limit operator $\tilde{P}^n(\bar{0}, \cdot, \cdot)$ given by (36) does not depend on the way parameters approach* 0.

Let us show that the operator $P^n(q, x, \theta) \equiv N_{\theta,q}(x, \mathcal{R}x)$ satisfies Properties A^* and B^*.

Since the linear bounded operator $\mathcal{R} : \mathbb{C}^n[a, b] \to \mathbb{C}^n[a, b]$ given by (32) is Volterra, the mapping $P^n(\cdot, \cdot, \cdot)$ is continuous and $P^n(q, \cdot, \theta)$ is Volterra for any $(q, \theta) \in (0, 1]^n \times \mathbb{R}^n$.

We prove now that $P^n(\cdot, \cdot, \cdot)$ satisfies the first condition of Definition 8. According to (31), for each $(q, x, y, \theta, t) \in (0, 1]^n \times \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^n \times [a, b]$ we have that

$$|\Gamma_{\theta,q}(x, y, t)| \le |F(y, \theta, q, t)| + \parallel G(y, \theta, q, t) \parallel \cdot |x|, \tag{37}$$

where $|\cdot|$ is the norm in the space $\mathbb{R}^n$ and $\parallel G(y, \theta, q, t) \parallel$ is the corresponding matrix norm. From Assumption 1 it follows that $F_i(Z_1, Z_2, \ldots, Z_n)$ are bounded. It means that there exists a number $C_1 \ge 0$ such that

$$|F(y, \theta, q, t)| \le C_1 \tag{38}$$

for any $(q, x, y, \theta, t) \in (0, 1]^n \times \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^n \times [a, b]$.

Similarly, there exists a number $C_2 > 0$ such that

$$\| G(y, \theta, q, t) \| \leq C_2 \tag{39}$$

for any $(q, x, y, \theta, t) \in (0,1]^n \times \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^n \times [a, b]$.

From (37), (38), (39) we deduce that

$$|\Gamma_{\theta,q}(x, y, t)| \leq C_1 + C_2|x| \tag{40}$$

for any $(q, x, y, \theta, t) \in (0,1]^n \times \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^n \times [a, b]$.

From the inequality (40) it follows that for any bounded $U \subset \mathbb{C}^n[a, b]$ there exists a constant $\varphi_U \geq 0$ such that

$$|N_{\theta,q}(x, \mathcal{R}x)(t)| \leq \varphi_U$$

for all $t \in [a, b]$.

Thus, we proved that the mapping $P^n(\cdot, \cdot, \cdot)$ given by (5) has Property A^*.

According to (40), the operator $M : \mathbb{C}^1_+[a, b] \to \mathbb{L}^1_+[a, b]$ given by

$$(Mx)(t) = C_1 + C_2x(t)$$

satisfies the conditions 1), 2) of Lemma 4 formulated for the mapping $P^n(\cdot, \cdot, \cdot)$. Since the problem

$$\dot{y} = C_1 + C_2y, \;\; y(a) = |\varphi(a)|,$$

where $\varphi(a) = \mathrm{col}(\varphi_1(a), \varphi_2(a), \ldots, \varphi_n(a)), \varphi_i(a),\; i = 1, 2, \ldots, n$ are values of the initial function (21) at the point a, has a unique solution, then the mapping $P^n : (0, 1]^n \times \mathbb{C}^n[a, b] \times \mathbb{R}^n \to \mathbb{C}^n[a, b]$ has Property B^*.

By this we have proved the following result:

Theorem 10 *Let a continuous mapping $P^n : (0, 1]^n \times \mathbb{C}^n[a, b] \times \mathbb{R}^n \to \mathbb{L}^n_1[a, b]$ have Property B^*. Then for any solution of the problem (34)-(35) for any $t \in [a, b]$ we have that $|x(t)| \leq \xi^*(t)$, where $\xi^*(\cdot)$ is an upper solution of the problem*

$$\dot{y} = C_1 + C_2y, \;\; y(a) = |\varphi(a)|.$$

Theorem 10 gives us the global existence of the solution of the problem (20)-(21) on the interval $[a, \infty)$.

The theorem below is an analog of Theorem 7. We consider the case when all singular variables y_i, $i = 1, \ldots, n$, approach their respective threshold values θ_i, $i = 1, \ldots, n$, at the time t^* and stay in the switching domain $\mathcal{SD}(\theta_S, B_R)$ for all $t > t^*$. For the sake of simplicity we assume that the threshold values

θ_i are fixed, i.e. the operators $P^n(\bar{q}, x) : (0,1]^n \times \mathbb{C}^n[a,b] \to \mathbb{C}^n[a,b]$ and $\tilde{P}^n(\bar{0}, x) : \mathbb{C}^n[a,b] \to \Omega(\mathbb{L}_1^n[a,b])$ do not depend on these parameters.

Theorem 11 *If $y_i = \theta_i$, $i = 1, \ldots, n$, for $t \geq t^*$ (what means that the point is black). Then the operator $\tilde{P}^n(\bar{0}, x)$ is a multivalued operator defined by*

$$\tilde{P}^n(\bar{0}, x) = \overline{co}\{F(Z_S, B_R) - G(Z_S, B_R)x |\ 0 \leq Z_s \leq 1,\ s \in S\} \quad \text{for } t \geq t^*.$$

Depending on the trajectories' behavior before the time $t = t^*$ we construct the operator $\tilde{P}^n(\bar{0}, x)$ for $t < t^*$ similarly to the ways described in Theorem 7.

Remark 5 *The above analysis covers of course the case when only a part of the variables approach their respective threshold. In this case, the limit operator will be single-valued with respect to these variables.*

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