Differential inclusions and piecewise models in biochemical and gene regulatory networks

Differensial inklusjoner og stykkvise modeller i biokjemiske og genregulatoriske nettverk

Philosophiae Doctor (PhD) Thesis

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Abstract

The simplification of a complex system is a widely accepted way of its modeling, the inevitable drawback of which is the "resolution reduction", i.e., the loss of information inherent to the real-world processes. In this thesis I want to address the "resolution reduction" issue for some well-elaborated simplifications in systems biology. Broadly speaking, the current work is about determining and justifying mathematically the criteria of eligibility of the simplified frameworks.

The work presented in this thesis is aimed at studying how the theory of differential inclusions can be applied to some open mathematical problems stemming from biology. These problems are motivated by two basic simplification paradigms in systems biology at the micro level: the Boolean-like formalism and the power-law formalism. The Boolean-like formalism is widely used for describing gene regulatory networks. Roughly speaking, it consists in replacing smooth, yet inconvenient, steep sigmoidal nonlinearities with step functions. The power-law formalism assumes that unknown or numerically obtained relationships within biochemical reaction networks can be described by sums of power monomials. Note that both of these formalisms, in the form we consider them in the present work, lead to piecewise models. These models based on discontinuous differential equations can be treated in a rigorous mathematical way using the theory of differential inclusions, which was originally developed within theoretical and applied mathematics. Its application to systems biology has not yet been completely developed.

For the Boolean-like formalism in gene regulatory networks (Paper I, Paper II) we present a rigorous analysis of the simplified model based on differential inclusions; a mathematical justification for the similarities between the "real-world" model (actually also representing a simplification of the real world processes) and the simplified model.

For the power-law formalism in biochemical reaction networks we introduce an algorithm for automated piecewise power-law approximations (Paper III). The algorithm solves the important problem of automated partition in piecewise models. We also obtain analytical results on the convergence and well-posedness of the approximations generated by this algorithm (Paper IV).

In Paper V the study of differential inclusions is extended to its generalization - the theory of functional differential inclusions, which covers also the models with delay effects. Delay effects are well-know phenomena in biological processes, e.g., time delays in gene expression, but are often omitted in modeling for the sake of simplicity. Here we focus mainly on analytical techniques and prove some basic theoretical results.

Sammendrag

Forenkling av et komplekst system er utbredt og akseptert innen numerisk modellering, tross den uunngåelige ulempen med reduksjon av oppløsning, dvs. tap av informasjon iboende den virkelige verden. I denne avhandlingen ønsker jeg å se på problemstillingen ved reduksjon av oppløsning innenfor noen godt utdypede forenklinger innen systembiologi. Dette arbeidet går ut på å fastsette og begrunne matematiske kriterier som ligger til grunne for forenklede rammeverk.

Arbeidet som presenteres i denne avhandlingen har som mål å studere hvordan teorien om differensial-inklusjoner kan anvendes i enkelte åpne matematiske problem som stammer fra biologi. Disse problemene er motivert av to grunnleggende forenklings-paradigmer i systembiologi på mikronivå: Boolean-lignende formalisme og power-law formalisme. Boolean-lignende formalisme er mye brukt for å beskrive gen-regulatoriske nettverk. Grovt sett består den i å erstatte glatte, men upraktiske, bratte sigmoidale ulineariteter med trinnfunksjoner. Power-law formalismen antar at ukjente eller numerisk oppnådde relasjoner innen biokjemiske reaksjonsnettverk kan beskrives av en sum av power- monomialer. Begge disse formalismene, i den form vi ser på dem i dette arbeidet, fører til stykkevise modeller. Disse modellene, basert på ikke-kontinuerlige differensiallikninger, kan behandles på en rigorøs matematisk måte ved å ta i bruk teorien om differensial-inklusjoner, som opprinnelig ble utviklet innenfor teoretisk og anvendt matematikk. Denne teoriens anvendelse inne system-biologi er ikke enda fullt utviklet.

For Boolean-formalismen i gen-regulatoriske nettverk (artikkel I og artikkel II) presenteres en rigorøs analyse av den forenklede idealiserte modell; en matematisk begrunnelse for likhetene mellom modellen av den reelle verden (som også representerer en forenkling av den virkelige prosessen) og modellen av den idealiserte verden.

For power-law fornalismen innen biokjemiske reaksjonsnettverk introduseres en algoritme for automatisert deling i stykkevise power-law tilnærminger (artikkel III). Algoritmen løser det viktige problemet med automatisert deling i stykkevise modeller. Vi oppnådde også analytiske resultat for konvergens og velformulerhet av tilnærmingene generert av denne algoritmen (artikkel IV).

I artikkel V er studien av differensial-inklusjoner utvidet til en generalisering - teorien for funksjonelle differensial-inklusjoner - som også dekker modellene med forsinkelseseffekter. Forsinkelseseffekter er et velkjent fenomen i biologiske prosesser, for eksempel tidsforskyvning i gen-uttrykk, men blir ofte neglisjert i modellering for enkelhets skyld. Her har vi hovedsakelig fokusert på analytiske teknikker og på å bevise noen grunnelggende teoretiske resultat.

List of Papers

The thesis is based on the following papers:

Paper I

A. Machina and A. Ponosov, Filippov solutions in the analysis of piecewise linear models describing gene regulatory networks. *Submitted to Nonlinear Analysis: Theory, Methods & Applications.*

Paper II

A. Machina and A. Ponosov, Stability of stationary solutions of piecewise affine differential equations describing gene regulatory networks. *Submitted to Journal of Mathematical Analysis and Applications.*

Paper III

A. Machina, A. Ponosov, E.O. Voit, Automated piecewise power-law modeling of biological systems. *Article in press, Journal of Biotechnology*, doi:10.-1016/j.jbiotec.2009.12.016.

Paper IV

A. Machina, A. Ponosov, and A. Sorribas, Convergence properties of piecewise power-law approximations to kinetic processes in Systems Biology models. *Submitted to Journal of Mathematical Biology.*

Paper V

A. Machina, A. Bulgakov, and A. Grigorenko, Generalized Solutions of Functional Differential Inclusions. *Abstract and Applied Analysis*, Volume 2008, Article ID 829701, 35 pages, doi:10.1155/2008/829701.

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Chapter 1

Introduction

1.1 Background

Systems biology is a rapidly developing branch of theoretical biology, and it has already posed a lot of unsolved and difficult mathematical problems. The scope of the present work is to study important mathematical questions stemming from systems biology. This gives the research an explicit cross-disciplinary character. However, the focus is mainly on solving open mathematical problems and applying new mathematical theories to the study of theoretical properties of complex biological systems. The present work is only partly about what one calls mathematical modelling in biology. Rather, the emphasis is put on mathematical justification of some practical modelling frameworks that already exist. I believe that our conclusions may give a better understanding of why and when certain biological formalisms work, which should help systems biologists to understand why a rigorous mathematical analysis can be useful.

In genetic and molecular biology it is widely accepted that no analysis is possible without a considerable simplification of the underlying model. This is just due to a huge amount of equations or parameters involved. The focus of the work presented in this thesis is on the two known and well-elaborated simplifications in systems biology: the formalism based on switched systems with Boolean-like response functions and the power-law formalism (in this work we address to the piecewise power-law formalism). These formalisms were developed for simplifying and studying complex biological models at the micro level: gene regulatory networks (GRNs) and biochemical reaction networks (BRNs), respectively. The common feature of these formalisms is that both of them lead to piecewise models, i.e. discontinuous right-hand sides of the differential equations describing biological networks. The theory of differential inclusions is able to deal with systems of discontinuous differential equations

in a rigorous mathematical way. When using functional differential inclusions, the study can be generalized by incorporating delay effects into the models.

Using various approaches, including the theory of differential inclusions, approximation theory, the theory of functional differential inclusions, the research has focused on

- The theory of differential inclusions in the analysis of GRN systems (Paper I, Paper II).
- Piecewise power-law models in BRNs and differential inclusions (Paper III, Paper IV).
- Generalization of non-delay differential inclusions to functional differential inclusions (Paper V).

A more detailed outline of these top ics, including backgrounds and summaries of the papers, can be found in Section 1.2, Section 1.3, and Section 1.4.

1.2 Switchings in Gene Regulatory Networks: differential inclusions

1.2.1 Piecewise linear equations and steep sigmoid formalism

The regulation of gene expression is achieved through gene regulatory systems structured by networks of interactions between DNA,RNA, proteins, and small molecules.

There are several different frameworks used for modelling gene regulatory networks (reviewed by de Jong (16)). The simplest dynamical models – Boolean network models – were used already in 1960's by Kauffman (18). The basic assumption is that a gene is either considered active (ON) or inactive (OFF). However, these models have a descriptive character and cannot model complex dynamical behavior. Being the most widespread formalism to model dynamical systems in science, ordinary differential equations have been widely used to analyze gene regulatory systems. The basic equation is given by

$$\frac{dx_i}{dt} = F_i(Z) - G_i(Z)x_i, \qquad i = 1, ..., n, \tag{1.1}$$

where the gene products regulate their own production by Boolean-like regulatory functions. The production and relative degradation rate functions F_i and G_i depend on a vector $Z = (Z_1, ..., Z_n)$ of steeply sloped threshold functions,

so-called sigmoids. The functions F_i and G_i are often algebraic equivalents of Boolean functions. It is also assumed that F_i and G_i are affine functions in each $Z_i = Z_i(x_i)$.

The system with sigmoids, which are genuinely nonlinear, can however be too complicated to be studied theoretically and even numerically, as the number of the system's variables may be huge. To simplify the functional form of the equations it is common to replace sigmoids with step functions, which converts the original smooth system into a switched system with discontinuous right-hand sides. The main benefit is that, except for the threshold hyperplanes, the resulting equations are of favourable linear form. The disadvantage is that the equations are not defined everywhere in phase space. Recent works (14; 17) use an approach based on the Filippov theory (13) to define the solutions on the threshold hyperplanes. This approach involves extending piecewise linear discontinuous differential equation to piecewise linear differential inclusion. In addition to clarifying the definition of the vector field and its solutions in the *singular domains* (domains, where at least one variable has a threshold value), the differential inclusion approach enables the definition and computation of all the equilibria, including those that lie in singular domains.

Alternatively, the functions Z_i are continuous, but steep sigmoidal functions. The resulting equations are then defined in the whole phase space. In this steep sigmoid formalism singular stationary points were studied by means of the implicit function theorem in (20; 21). To analyse the solution flow a method based on singular perturbation analysis was introduced in (22). This method is based on certain simplifying features in the limit when the sigmoids approach step functions.

Both approaches have properties that facilitate analysis of the system under study, including determining steady states, analysing stability and computing trajectories.

However, there does not exist a systematic comparison of the two approaches. Paper I and Paper II are aimed to fill partly the gap between the two approaches, which were developing independently. Besides, I want to look at the Filippov approach a little bit more systematically, giving a detailed mathematical justification of the technics used in the Filippov framework.

The behavior of the systems described by (1.1) can be easily characterized in the *regular domains* (domains, where none of the variables assumes its threshold value). Developing approach within the Filippov framework for analysing the behavior of the system in singular domains is the prime aim of Paper I and Paper II.

1.2.2 Filippov solutions: stationary solutions and their stability

Section 1.2.1 gives the background for Paper I. Paper II is a follow-up of Paper I.

Paper I: Filippov solutions in the analysis of piecewise linear models describing gene regulatory networks

To overcome the difficulty of describing the dynamics of the system (1.1) near singular stationary points (belonging to the discontinuity set of the system) we use the concept of Filippov solutions. It consists in replacing discontinuous differential equations with differential inclusions. The concept of the Filippov solution can be defined in three different ways (in (14) only one of the definitions is used). But we prove that two of the definitions (where the right-hand sides are convex though constructed in different ways) are in fact equivalent in the case of the gene regulatory networks, while the third gives a different inclusion with a non-convex right-hand side.

We study some basic properties of Filippov solutions of the systems in question putting emphasis on global existence and continuous dependence on parameters. In particular, these results can be used to justify similarities between the "real-world" model based on smooth interactions (sigmoids) and the idealized model based on step-like interactions.

Uniqueness and non-uniqueness of Filippov solutions in the singular domains was also among our interests. For instance, we show that the solution is unique in so-called black walls ("attracting" singular domains of codimension 1), while white walls ("repelling" singular domains of codimension 1) usually give rise to infinitely many Filippov solutions.

Stationary solutions are of special interest in this work. Here we compare the two approaches mentioned in Section 1.2.1. Roughly speaking we show that the main difference between them amounts to the difference between non-equivalent definitions of the Filippov solutions. In the case of a non-convex right-hand side we get stationary points in the sense of steep sigmoid framework, while in the case of a convex right-hand side we obtain stationary points in the sense of Filippov. Although the second approach gives more stationary points than the first one, we show that the Filippov stationary points that are limits of convergent sequences of stationary points of smooth systems (as the steepness of sigmoids increases infinitely) are indeed the Fillipov stationary solutions in the sense of definition with non-convex right-hand sides. We call such stationary solutions Filippov stationary solutions in the narrow sense.

Most of the results (valid actually for any finite dimension n) are illustrated by 2-dimensional examples.

Paper II: Stability of the Filippov solutions in the analysis of piecewise linear models describing gene regulatory networks

This is a follow-up of Paper I, where Filippov singular stationary solutions were introduced without investigating their stability.

The aim of this work is to provide a stability analysis for GRN systems of the form (1.1). We put emphasis on the Filippov approach and focus on the singular domains, as the regular stationary points are know to be asymptotically stable. Following our previous research (Paper I) we consider Filippov stationary solutions in the narrow sense, which are in fact limits of the solutions to smooth "real-world" models. For the stability analysis of such points we justify the reduction principle. This principle consists in reducing the dimension of the system to the singular variables only and investing the stability of the homogeneous differential inclusion, generated by the latter reduced system (the dimension is thus equal to the number of singular variables). The study of the stability of homogeneous inclusions is well elaborated in (13).

Based on the proposed method we developed an algorithm able to investigate the stability of any given SSP. The algorithm is based on the reduction principle, i.e. restricting ourselves to the singular variables only and consists simply in determining the signs of the parameters of the given equations. This procedure seems to be numerically advantageous.

1.3 Piecewise power-law formalism in biochemical reaction networks

1.3.1 Systems biology and power-law approximations

Power-law (PL) formalism is widely used in the hot research area of systems biology related to mathematical modelling of biochemical reaction networks. It is one of so-called canonical representations for the reaction rates, besides other candidates such as Michaelis-Menten and Hill rate laws, their generalizations, etc. PL approximations led to development of a Biochemical Systems Theory framework with the two canonical models: S-system model and Generalized Mass Action (GMA) model. Mathematically, PL formalism consists in representation of a dynamic system in terms of differential equations with the right-hand sides being sums of products (monomials) of elementary power

functions with arbitrary real exponents, both negative and positive. In the simplest case, there are are only two terms representing production and degradation. These systems are denoted S-systems and are given by

$$\frac{dx_i}{dt} = \alpha_i \prod_{j=1}^{n+m} x_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} x_j^{h_{ij}} = V_i^+(x) - V_i^-(x), \qquad i = 1, ..., n. \tag{1.2}$$

Here x_i is the concentration of the given chemical species, index i $(i = 1, ..., n)$ refers to dependent variables, while higher indices $(n + 1, ..., n + m)$ refer to independent variables. The non-negative influx and efflux V_i^+ and V_i^- may possibly consist of sums of other functions describing different contributions to the production or degradation of x_i (GMA model).

A good description of this theory is provided in (26). The exponents $g_{ij} \in \mathbb{R}$ and $h_{ij} \in \mathbb{R}$ are called kinetic orders and describe the quantitative effect of x_j on the production or degradation of x_i, respectively. The multipliers $\alpha_i > 0$ and $\beta_i > 0$ are rate constants. This modelling approach has mainly been applied in metabolic systems, but may also provide good description of gene regulatory networks (24; 25).

Consider a power-law approximation of a given function $V(x)$

$$V(x) \approx \gamma \prod_{j=1}^{n+m} x_j^{f_j}. \tag{1.3}$$

By introducing logarithmic transformation of the variables $y = \ln x$ and taking the logarithm of both sides, the right-hand side of (1.3) can easily be transformed to linearity. Coefficients of the linear expression, representing the kinetic orders and the rate constant, can be interpreted as the first order Taylor series approximation of the function V in log space. It is clear that power-law functions based on this Taylor approximation are local representations. In (15) a least-squares minimization over an operating interval is used to provide a way for defining the power-law approximation to rate laws $V(x)$. In general, even the model of an operating interval can have low accuracy if, for example, saturation is present or the operating domain is too big. A piecewise power-law representation provides a logical extension to a single power law over an operating domain. For univariate functions, it is relatively easy to determine such representations. However, for multivariate functions, the suitable determination of a piecewise power-law representation becomes difficult. Our goal (Paper III) is the following: given metabolic time series data corresponding to an unknown, univariate or multivariate function, compute a piecewise power-law representation that is suitable in a sense that it fits the

data within an acceptable error while consisting of the smallest possible number of pieces. The problem of a piecewise power-law regression, as posed here, is not straightforward, because, given a set of samples of a flux V, one has to compute both a partitioning into regions in the input space and the behavior of the unknown function V over each of them. Because of the mixed nature of the problem, classical approximation techniques cannot be directly applied, and it is instead necessary to develop a specific, customized method. The principles of such a method were introduced a few years ago for linear systems, where the regions in the space of variables are polyhedra and the behavior of the function V in each region is approximated by a linear expression (7; 9).

1.3.2 Piecewise models: differential inclusions and convergence of approximations

Section 1.3.1 gives the background for Paper III.

Paper III: Automated piecewise power-law modeling of biological systems

In Paper III we further develop an approximating algorithm for a piecewise power-law regression over an input domain. The result of the algorithm is an automated partitioning (optimal in some sense) of the input domain and the approximation of the unknown function with power-law functions over each of the sub-domains of partition.

Our algorithm is based essentially on the method developed in (7; 8; 9; 10; 11; 12) for a similar but simpler problem, where the regions in the space of variables are polyhedra and the behavior of the function V in each region is approximated by a linear expression. It is in fact a machine learning method based on Artificial Neural Networks. For this method a free MatLab toolbox, the Hybrid Identification Toolbox (HIT), has been developed.

In order to utilize the mentioned above method, we propose to perform the logarithmic transformation, as in log space power-law functions become linear. After we obtain a polyhedral partition in log space a classical regression based on least squares minimization criterium can be implemented: either linear in log space (giving a power-law representation back in cartesian coordinates) or power-law in Caretesian space.

The results of the paper include testing of the proposed algorithm on artificial datasets, where data points are uniformly spread over operating intervals. The Hill functions of one and two variables are used to generate the datasets.

Thus, the proposed algorithm resolves the main difficulty in reconstructing piecewise power-law representations, namely the simultaneous subdivision

of the variable space and the optimized estimation of parameters within each subdivision. Interestingly, this dual task is solved automatically and requires only a few settings of operational parameters, which however is not a problem. The number of sub-domains, S, can either be predetermined, increased sequentially, or estimated with an adaptive algorithm (see discussion in (12)), and the number of neighboring points for each local regression (parameter c) can be tuned through cross-validation with a built-in option of the HIT software in Matlab. Theoretically, the proposed software permits arbitrarily accurate representations of univariate or multivariate processes. In reality, however, the method is limited by the number of data points and their representation of the manifold on which they lie.

By its nature, the proposed method usually leads to representations with gaps or discontinuities at the boundaries between sub-domains. These discontinuities come in two types. First, the illustrative examples identify gaps in the operating domain. These gaps are entirely due to the choice of a fast pattern-recognition algorithm by the software and can be avoided with more complex and much slower MatLab built-in solvers.

The second type of discontinuity results from the fact that the algorithm does not require the power-law representations to be continuous on the boundaries of sub-domains. These discontinuities require more serious analysis. Note that approximations are only an intermediate step in practical modelling, being involved in higher level models described by differential equations (e.g. S-systems, GMA models). Thus, considered approximations generate piecewise models which require an advanced mathematical theory. For example, there arise problems of describing steady states and analysing their stability (thus linking Paper III and Paper IV to Paper II), optimization problems (i.e. maximization of an objective functional on the trajectories of the given systems), and other problems of a higher level. How to interpret these problems if the right hand sides of the equations are piecewise is not so clear, therefore a new formalization, so called *SC formalism* (see Paper IV), is used in modelling. This formalism provides an analytical resolution of the problems but is in principle nonlinear even in log-log space.

The theory of differential inclusions is an alternative approach to address this problem. In Paper III, Appendix we discuss means of addressing this situation based on differential inclusions and Filippovs theory (13).

Characterization of the convergence of the approximating solutions is an important problem for both the Filippov approach and the SC formalism. The major difficulty of this characterization is the mean-square convergence of the approximations in the piecewise power-law regression, which is distinct from

the standard uniform convergence used in the theory of differential equations and inclusions. However, this is the topic of our next paper.

Paper IV: Convergence properties of piecewise power-law approximations to kinetic processes in Systems Biology models

In this paper we address a problem of convergence of approximations obtained from two versions of the piecewise power-law representation generated by the algorithm from Paper III. Here we consider these two versions in more details. The difference between them amounts to whether we use the least squares minimization criteria for obtaining parameters in Cartesian or in Log space, provided though that in both cases the partition of the input domain is optimal in Log space. In Log space the criterium becomes simply a linear regression with a guaranteed existence of the unique solution, though the error structure of the problem is distorted because of the logarithmic transformation. As a partial remedy, it is therefore advantageous to apply a power-law regression in Cartesian space, giving a better least squares error. We discuss the advantages and drawbacks of the these two regressions and show that nonlinear regression problem is not always well-posed, as illustrated in one of our examples.

Further we study the most important case of the mean square (L^2) convergence in the most general setting, while the uniform convergence is proven in a special case of scalar functions. Uniform convergence is important if one wants to incorporate the Filippov method in the analysis of models obtained by piecewise approximation. It is well-known (see e. g. the monograph (13) or the appendix in the Paper III) that the the convergence of so called "Filippov solutions" is only guaranteed if the the approximating functions converge uniformly.

We also discuss advantages and drawbacks of piecewise power-law representations from the theoretical and practical point of view. When speaking of how to use piecewise approximations in modelling, the emphasis is put on the so-called SC representation which has a strong biological motivation. Illustrative examples are an essential part of the paper.

1.4 Functional differential inclusions

1.4.1 Volterra functional differential inclusions

The piecewise approach used in the Section 1.2 is built mathematically on the notion of differential inclusion. The efficiency of this method for differential

inclusions without delays is studied in Paper I and Paper II. However in the delay case, when a model in some complex way depends on the past (for example integral dependence), the Filippov theory is not applicable. In particular, this is relevant for an inclusion with nonconvex right-hand side. Note, that in Paper I we introduced three different definitions of an inclusion and the one with a nonconvex right-hand side is of special interest for the real-world models.

An appropriate mathematical tool to investigate phenomena with delays is provided by the theory of functional-differential equations. Thus, Paper V is aimed to describe the most general class of functional differential inclusions that have some basic properties (existence of the solution, its continuation, asymptotic properties of approximate solutions, etc.). This class of functional differential inclusions can serve as the theoretical basis for the future theory of both piecewise models in GRNs (Paper I, Paper II) and piecewise power-law models in BRNs (Paper III, Paper IV). However the practical application of the main results of Paper V is beyond the scope of this thesis and will be a matter of the future research.

The background for Paper V can be summarized as follows.

We consider functional differential inclusions with Volterra-Tikhonov (or simply Volterra) type multivalued mappings. Inclusions with Volterra operator are sometimes called *inclusions with after-effect* or *inclusions with delay*.

Consider the initial value problem for a functional differential inclusion with a Volterra multivalued mapping. Let us assume that this mapping is not necessarily decomposable in $L_1^n[a,b]$. Some mathematical models can naturally be described by such an inclusion. For instance, so do certain mathematical models of sophisticated multicomponent systems of automatic control, where, due to the failure of some devices, objects are controlled by different control laws (different right-hand sides). The control of an object must be guaranteed in spite of the fact that failures (switchings from one control law to another) may take place any time. Therefore, the mathematical models should treat all available trajectories (states) corresponding to all switchings. The so-called generalized solutions make up the set of all such trajectories.

However, some recent studies (3; 4; 5; 6) confirm once again V. M. Tikhomirov's conjecture that decomposability is the specific feature of the space $L_1^n[a,b]$ and plays the same role as the concept of convexity in Banach spaces. If a multi-valued mapping is not necessarily decomposable, then the methods known for multi-valued mappings cannot be applied even to the solvability

problem. Furthermore, in this case the equality between the set of quasi-solutions of the inclusion and the solution set of the inclusion with the decomposable hull of the right-hand side fails. This equality for the ordinary differential inclusions was proved by T. Wazewski (see (27)). As a result, we have that fundamental properties of the solution sets (the density principle and "bang-bang" principle) do not hold any more (see (1; 2; 19)).

The concept of a generalized solution (solution of the inclusion with the decomposable hull in the right-hand side) should therefore be introduced and its properties should be studied.

1.4.2 Generalized solutions of functional differential inclusions

Section 1.4.1 gives the background for Paper V.

Paper V: Generalized solutions of functional differential inclusions

In Paper V we consider the initial value problem for a functional differential inclusion with a Volterra multivalued mapping that is not necessarily decomposable in $L_1^n[a,b]$. First, we introduce the concept of the decomposable hull of a set in $L_1^n[a,b]$. The notion of decomposability was introduced by Rockafellar (23) in 1968 and since then decomposable sets became a main tool in nonconvex analysis. They are in a sense a substitute of convexity and many properties of convex sets have counterparts for decomposable sets.

We construct the decomposable hull and the closed decomposable hull of the right-hand sides of the inclusions and study the topological properties of these sets. Using some of these properties we obtain Huasdorff continuity (Hausdorf lower semicontinuity, Hausdorff upper semicontinuity) conditions for the closed decomposable hull of the multivalued mapping.

Next, using the notion of the closed decomposable hull, we introduce the concept of a general solution of a functional differential inclusion with a Volterra multivalued mapping. We have proved that standard results on local existence and continuation of a generalized solution remain true. We study the topological properties of generalized solutions. In particular, we obtained estimates for closeness of generalized solutions to a given absolutely continuous function. These estimates allow us, by means of trial-and-error method, to determine an approximate solution as well as to provide estimates for its accuracy. Besides we have proved that the set of generalized quasisolutions coincides with the solution set of the convexified inclusion. This implies the density principle for

the generalized solutions, i.e. that the set of all generalized solutions is dense in the solution set of the convexified inclusion.

Finally, we consider generalized approximate solutions (generalized δ-solutions) and their asymptotic properties. In the present paper we introduce various definitions of generalized approximate solutions of a functional differential inclusion. The main difference of our definitions from the one given in (13) is that the values of a multi-valued mapping are not convexified. Therefore, the topological properties of the sets of generalized approximate solutions are studied and the stability criterium for the generalized approximate solutions (based on the density principle) is proved.

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Paper I

Filippov solutions in the analysis of piecewise linear models describing gene regulatory networks☆

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Abstract

We study some properties of piecewise-linear differential systems describing gene regulatory networks, where the dynamics are governed by sigmoid-type nonlinearities which are close to or coincide with the step functions. To overcome the difficulty of describing the dynamics of the system near singular stationary points (belonging to the discontinuity set of the system) we use the concept of Filippov solutions. It consists in replacing discontinuous differential equations with differential inclusions. The global existence and some other basic properties of the Filippov solutions such as continuous dependence on parameters are studied. We also study the uniqueness and non-uniqueness of the Fillipov solutions in singular domains. The concept of Filippov stationary point is extensively exploited in the paper. We compare two ways of defining the singular stationary points: one is based on the Fillipov theory and the other consists in replacing step functions with steep sigmoids and investigating the smooth systems thus obtained. The results are illustrated by a number of examples.

Keywords: gene regulatory networks, sigmoid-type functions, differential inclusions, Filippov solutions, singular stationary points
MSC: 34K21, 34A60, 92D10

1. Introduction

An important feature of genetic networks as well as of many other complex biological systems is the presence of thresholds causing switch-like interactions between genes. Such interactions can be described by the so-called "sigmoids", smooth monotone functions assuming the values between 0 and 1 and rapidly increasing around the threshold. The resulting nonlinear system can however be too complicated to be studied theoretically and even numerically, as the number of the system's variables may be huge. To simplify the functional form of the equations it is common to replace sigmoids with step functions, which converts the original smooth system into a switching system with discontinuous right-hand sides. Such a replacement can only be considered admissible if the dynamics of the "idealized" (i.e. switching) systems do mimic the dynamics of the original smooth system. In [1] and [2] it is observed that in many cases the qualitative behavior of the

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solutions does not change under such replacements. This analysis was continued in papers [3, 4, 5, 6, 7], where a special emphasis was put on the behavior of solutions around steady states (equilibrium concentrations) lying close to one or more threshold values. Such states are of interest as they represent homeostatic states in the model. However, if we use the idealized model based on discontinuous right-hand sides, we should first be able to define the very notion of the homeostatic states (which in the limit may end up in the discontinuity set) and to describe an efficient way to identify such states without any additional information from the smooth system.

Basically, there are two ways of solving this problem. The first one is based on the implicit function theorem and goes back to papers [5, 6]. Another approach utilizes the concept of differential inclusions and the so-called "Filippov solutions" [8, 9]. Both approaches have their advantages and disadvantages. For instance, in the second approach we may obtain steady states that are not limits of the proper steady states coming from the smooth model. On the other hand, the results obtained in the framework of the first approach can be too restrictive. However, as far as we know in the available literature there is no attempt to compare these two approaches from the mathematical point of view.

The present paper is aimed to fill partly the gap between the two approaches, which were developing independently. Singular stationary points were studied by means of the implicit function theorem in [5, 6] (1994,1998). To analyse the solution flow a method based on singular perturbation analysis was introduced in [4] (2005). At the same time an alternative approach (based on the Filippov framework) capable of dealing with both of these problems was suggested in [8, 9] (2002,2004). The possibility to study both the stationary properties and the dynamical behavior of discontinuous systems is a big advantage of the latter approach. However to the best of our knowledge there does not exist a complete mathematical comparison between the two approaches. Another objective of this paper is to give a detailed mathematical justification of the method based on the Filippov framework.

Below we want to look at the Filippov approach a little bit more systematically starting with the very concept of the Filippov solution which can be defined in three different ways (in [8] only one of the definitions is used). This is done in Section 3. We prove that two of the definitions (where the right-hand sides are convex though constructed in different ways) are in fact equivalent in the case of the gene regulatory networks, while the third provides a different inclusion with a non-convex right-hand side, thus giving a different set of stationary solutions. However, it is the latter definition that covers the homeostatic states in the model, while the first two may produce stationary solutions of quite a different nature (see a more detailed description of these solutions below).

Then we study some basic properties of Filippov solutions of the systems in question putting emphasis on global existence and continuous dependence on parameters. In particular, these results can be used to justify similarities between the "real-world" model based on smooth interactions (sigmoids) and the idealized model based on step-like interactions. This is done in Section 4.

In Section 5 we study the uniqueness and non-uniqueness of Filippov solutions in the singular domains (i. e. in the set of discontinuity points of the right-hand side). For

instance, we show that the solution is unique in black and transparent walls (see e.g. [4]), while white walls usually give rise to infinitely many Filippov solutions. Walls are segments of switching hyperplanes of codimension 1. Walls could be of three types: black (attract trajectories), white (repel trajectories), or transparent (are passed by trajectories).

Stationary solutions are discussed in Section 6. Here we compare the two approaches mentioned above. Roughly speaking we show that the main difference between them amounts to the difference between non-equivalent definitions of the Filippov solutions. In the case of a non-convex right-hand side we get stationary points in the sense of [4], while in the case of a convex right-hand side we obtain stationary points in the sense of [8]. Although the second approach gives more stationary points than the first one, we show that the Filippov stationary points that are limits of convergent sequences of stationary points of smooth systems (as the steepness of sigmoids increases infinitely) are indeed the Fillipov solutions in the sense of definition with non-convex right-hand sides. In Section 6 we also introduce some examples of stationary points in the sense of [8], which at the same time are not stationary points in the sense of [4].

In real world models each variable can have several thresholds. But in the present paper we are interested only in local properties of the solutions. In this case we can assume without loss of generality that every variable has only one threshold. We admit this simplification throughout the whole paper for the sake of simplicity and convenience of notation. However all the results remain true for the models with multiple thresholds. This concerns also the theorem on global existence of a Filippov solution (see Theorem 2, Section 4), where a global solution can be obtained by simply gluing together local solutions.

2. Description of the mathematical framework

Consider a system of n genes with the gene product concentration x_j. The gene products regulate their own production by Boolean-like regulatory functions. Mestl et al. [3] studied the following model of system of differential equations with switch-like nonlinearities

$$\dot{x}_j = f_j(x, Z) = F_j(Z) - G_j(Z)x_j, \qquad j = 1, ..., n, \tag{1}$$

where $x \in \mathbb{X}^n = \mathbb{R}^n_+$, Z is an n-dimensional vector of switching functions $Z_i(x_i) : \mathbb{R} \to [0, 1]$, $i = 1, ..., n$, the production rate function $F_j \geq 0$ and the relative degradation rate $G_j > 0$ are multilinear polynomials, i.e. affine functions with respect to each Z_i.

Remark 1. An affine (sometimes called also linear) function has the form $aZ_i + b$. According to our assumption, which seems to be sufficient for gene regulatory networks (see [2, 5]), both F and G are affine in this sense with respect to each Z_i. □

For $q > 0$ $Z_i = \Sigma(x_i, \theta_i, q_i)$ is a sigmoid function, q_i is a steepness parameter, and θ_i is the threshold. Suppose that $q_i = q$ for any $i = 1, 2, ..., n$. Sigmoids are smooth monotone functions assuming the values between 0 and 1 and rapidly increasing around the threshold. As $q \to 0$, then $\Sigma(x_i, \theta_i, q)$ approaches the unit step or the shifted Heaviside function with the threshold θ_i.

If $q = 0$, then F_j,G_j are piecewise constant positive functions whose values change, as the variables x_j cross the thresholds $x_j = \theta_j$.

From mathematical point of view, (1) in the limit ($q = 0$) becomes a differential system with discontinuous right-hand sides. One of our goals in this work is to show that the concept of Filippov solutions (see [10], Chapter 2 §4) can clarify the study of such systems, in particular the behavior in the threshold planes and their intersections.

In the vector notation (1) rewrites as

$$\dot{x} = f(x, Z) = F(Z) - G(Z)x, \tag{2}$$

where $x \in \mathbb{X}^n = \mathbb{R}^n_+$, $F = (F_1, \ldots, F_n)$ and $G = \mathrm{diag}\,(G_1, \ldots, G_n)$ (the diagonal matrix with the entries G_j).

In the case of step functions the function f is piecewise linear in $\mathbb{R}^n_+$ and $Z_i = \Sigma(x_i, \theta_i, 0)$ is given by

$$\Sigma(x_i, \theta_i, 0) = \begin{cases} 0 & \text{if} \quad x_i < \theta_i, \\ 1 & \text{if} \quad x_i > \theta_i. \end{cases} \tag{3}$$

Without loss of generality we may put $Z_i = \Sigma(\theta_i, \theta_i, 0) = 1/2$.

According to the assumptions on functions F and G we have that

$$0 \le F_j(Z) \le \overline{F}_j, \qquad 0 < \sigma_j \le G_j(Z) \le \overline{G}_j, \qquad Z_i \in [0, 1],\ i, j = 1, ..., n, \tag{4}$$

where $\overline{F}_j$, $\overline{G}_j$, σ_j are constants. Therefore the dynamical properties of models of the form (2) can be analyzed in the n-dimensional phase space box $\Omega = \Omega_1 \times \ldots \times \Omega_n$, where every Ω_j, $1 \le j \le n$, is defined as

$$\Omega_j = \{x_j \in \mathbb{R}_+ \mid 0 \le x_j \le \mathrm{max}_j\}. \tag{5}$$

max_j is a parameter denoting a maximum concentration for the protein. It will be shown in Section 4 that if we choose

$$\mathrm{max}_j > \overline{F}_j/\sigma_j,$$

then trajectories starting inside Ω will remain in it and trajectories starting outside the space box Ω will eventually enter it.

The threshold hyperplanes $x_j = \theta_j$ divide Ω into 2^n open, rectangular domains called *boxes* or *regular domains*. Thus, $\mathcal{B}$ is a box if there is no j such that $x_j = \theta_i$, i.e none of the variables assumes the threshold value. A segment of a hyperplane of codimension k separating two adjacent boxes is customarily called a *singular* domain (or a *wall* in the case of codimension 1). $\mathcal{B}$ is a singular domain if for at least one j, $1 \le j \le n$, it holds that $x_j = \theta_j$.

A more precise definition of boxes and singular domains were given in [4]. Let $N = \{1, \ldots, n\}$. Let R be an ordered subset of N, and S the ordered complement $N \setminus R$, such that $R \cup S = N$ and $R \cap S = \emptyset$. The symbols R and S stand for *regular* and *singular* corrdinates, respectively. For example y_S stands for an $|S|$-dimensional vector ($|S|$ is the number of elements in S) consisting of singular coordinates of an n-dimensional vector y. Similar for y_R.

A box is an open domain in $\mathbb{X}^n$ where all B_j have specified values.

Definition 1. Let a Boolean vector $B = [B_1, \ldots, B_n]$ be given. To B is associated the box $\mathcal{B}(B) = \{x \in \mathbb{X}^n \mid Z(x) = B\}$.

B_R is a Boolean vector of length $|R|$ ($|R|$ is the number of elements in R) consisting of regular coordinates of B.

Definition 2. Let $S \neq \emptyset$ and B_R be given. If $S \subset N$, then a singular domain is given by $\mathcal{SD}(S, B_R) = \{x \in \mathbb{X}^n \mid x_S = \theta_S,\ Z_R(x) = B_R\}$. The order (codimension) of $\mathcal{SD}(S, B_R)$ is the number $\sigma = |S|$ of elements in S.

For example, in 4-dimensional space $\mathcal{SD}(\{1,3\},[01]) = \{x \in \mathbb{X}^4 \mid x_1 = \theta_1,\, x_3 = \theta_3,\, x_2 < \theta_2\,,\, x_4 > \theta_4\,\}$, $S = \{1,3\}$, $R = \{2,4\}$, $B_R = [01]$ ($Z_2(x_2) = 0$, $Z_4(x_4) = 1$)

The behavior of systems described by (2) can be easily characterized in the regular domains. See Appendix A for the details. It what follows we focus on singular domains only.

Singular domains of codimension 1, customarily called walls, can be of three kinds:

- If trajectories travel through the wall, then the wall is transparent.
- If trajectories hit the wall from either side, then the wall is black.
- It trajectories depart from the wall on both sides, then the wall is white.

Example 1. Consider the following system

$$\begin{aligned} \dot{x}_1 &= k_1\left(Z_1 Z_2 + (1 - Z_1)(1 - Z_2)\right) - \gamma_1 x_1, \\ \dot{x}_2 &= k_2(1 - Z_1) - \gamma_2 x_2. \end{aligned} \tag{6}$$

This is a special case of (2).

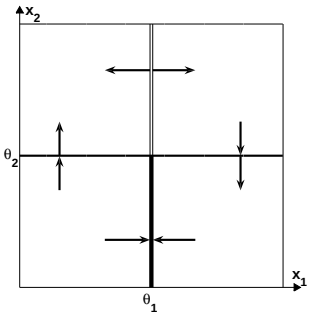

Figure 1. The qualitative flow of (6) in the boxes for $q = 0$ and for small q. The parameter values are $k_1 = k_1 = 1$, $\theta_1 = \theta_2 = 1$, $\gamma_1 = \gamma_2 = 1/2$. The wall $\mathcal{SD}(\{1\}, 0)$ is black, the wall $\mathcal{SD}(\{1\}, 1)$ is white, the two others walls: $\mathcal{SD}(\{2\}, 0)$ and $\mathcal{SD}(\{2\}, 1)$ are transparent. $\square$

In the case when a wall $\mathcal{W}$ is black, there is no indication of how a solution can be continued. Near the wall solutions are approaching it from both sides as t increases, and none of them can leave $\mathcal{W}$. A solution which passes through a point of the wall $\mathcal{W}$ at $t = t_0$ will therefore remain in $\mathcal{W}$ for $t > t_0$ until it reaches the boundary of $\mathcal{W}$. If $\mathcal{W}$ is white, then a solution which passes through a point of the wall $\mathcal{W}$ at $t = t_0$ may either go off $\mathcal{W}$ into one of the adjacent boxes separated by $\mathcal{W}$ or remain in $\mathcal{W}$ for $t > t_0$. In the latter case the solution may go off $\mathcal{W}$ at any moment. In white walls the motion is therefore unstable. A more complex behavior can occur in an intersection of two or more threshold hyperplanes, and a solution can be singular in this case also.

Point attractors can also exist in black walls or in an intersection of threshold hyperplanes, even though the equations are not defined there. Such a stable point is called a *singular stationary point*, abbreviated SSP [11].

3. The concept of Filippov solutions

To provide the existence and the possibility for solutions to be continued in both black and white walls, it is necessary to define the right-hand side of system (2) at these points of discontinuity. A way to achieve this is to exploit the definitions suggested by A.F. Filippov in [10].

Most of the known definitions of solution may be presented as follows. For each point x a set $\mathcal{F}(x)$ in n-dimensional space is specified. If at the point x a function f is continuous, the set $\mathcal{F}(x)$ consists of one point which coincides with the value of the function f at this point. If x is a discontinuity point of the function f, the set $\mathcal{F}(x)$ is given in some other way. A *Filippov solution* of the equation (2) is called a solution of the differential inclusion

$$\dot{x} \in \mathcal{F}(x), \tag{7}$$

that is, an absolutely continuous vector-valued function $x(t)$ defined on an interval I for which $\dot{x}(t) \in \mathcal{F}(x(t))$ almost everywhere on I.

Below we adjust the definitions from [10] to the case of the switching system (2) using the notation from Section 2.

Definition 3. [[10], Chapter 2, §4, 2, definition a)] Let $\mathcal{SD}(S, B_R)$ be a singular domain. For any Boolean vector B_S corresponding to one of the regular domains adjacent to $\mathcal{SD}(S, B_R)$ and any $x \in \mathcal{SD}(S, B_R)$ put $P(B_S, x) = (p_1, ..., p_n)$,

$$p_i = F_i(B_S, B_R) - G_i(B_S, B_R)x_i, \qquad i = 1, ..., n. \tag{8}$$

For each $x \in \mathcal{SD}(S, B_R)$ we put

$$\mathcal{F}(x) = co\{P(B_S, x) \mid B_S \in \{0, 1\}^S\},$$

i.e. $P(B_S, x)$ stands for the values of the function $F(Z) - G(Z)x$, where $Z_R \equiv B_R$ is fixed and $Z_S \equiv B_S$ runs through the set $\{0, 1\}^S$. The number of such points $P(B_S, x)$ is $2^{|S|}$.

A Filippov solution of the equation (2) is a solution of the inclusion (7) with $\mathcal{F}(x)$ so constructed.

At continuity points of the function f the set $\mathcal{F}(x)$ consists of one point $f(x)$, and the Filippov solution satisfies equation (2) in the usual sense. Therefore inside regular domains Filippov solutions coincide with solutions to ordinary differential equations (ODE).

If the point $x \in \mathcal{SD}(S, B_R)$ lies on the boundaries of cross-section of two or several regular domains (boxes) $\mathcal{B}(B_S, B_R)$ (the number of such boxes $k = 2^{|S|}$), the set $\mathcal{F}(x)$ is a segment, a convex polygon, or a polyhedron with vertices $P^j(B_S, x)$, $j = 1, ..., k$, whose coordinates $p_i^j(B_S, x)$,$i = 1, ..., n$, are given by (8).

All the points $P^j(x)$, $j = 1, \ldots, k$, are contained in $\mathcal{F}(x)$, but it is not necessary that all of them be vertices. In other words $\mathcal{F}(x) = co\{P^1, \ldots, P^k\}$.

Such a construction of the set $\mathcal{F}(x)$ is used in [8]. Consider another and more general definition.

Definition 4. [[10], Chapter 2, §4, 2, definition c)] Consider the system (2). For each discontinuity point $x \in \mathcal{SD}(S, B_R)$ let $\mathbb{Z}_j(x) \equiv [0, 1]$, $j \in S$, and $\mathbb{Z}_S(x) \equiv [0, 1]^{|S|} = [0, 1] \times [0, 1] \times ... \times [0, 1]$. At the points where $Z_j(x)$ is continuous the set $\mathbb{Z}_j(x)$,$j \in S$, consists only of one point $Z_j(x) \in \{0, 1\}$. Let

$$\mathcal{F}_1(x) = \{F(\mathbb{Z}_S, B_R) - G(\mathbb{Z}_S, B_R)x\} \tag{9}$$

be the set of all values of the function $f(x, Z_S, Z_R = B_R)$, where x and B_R are fixed and Z_j,$j \in S$, independently run over the sets $\mathbb{Z}_j$,$j \in S$, respectively. Filippov solutions of the differential equation (2) are defined as solutions of the differential inclusion

$$\dot{x} \in \mathcal{F}_2(x),$$

where $\mathcal{F}_2(x) = \overline{co}\mathcal{F}_1(x)$.

There exists one more definition.

Definition 5. [[10], Chapter 2, §4, 2, definition b)] Filippov solutions of the differential equation (2) can be defined as solutions of the differential inclusion

$$\dot{x} \in \mathcal{F}_1(x),$$

where $\mathcal{F}_1(x)$ is from Definition 4. In what follows, such solutions will be called *Filippov solutions in the narrow sense.*

Motion along a singular domain $\mathcal{W}$ of codimension k, $1 \leq k \leq m$, may only occur with the velocity

$$\dot{x} \in K(x), \tag{10}$$

where $K(x)$ is the intersection of the set $\mathcal{F}(x)$ (or $\mathcal{F}_1(x)$, $\mathcal{F}_2(x)$) with the $(n - k)$-dimensional hyperplane containing $\mathcal{W}$.

If the function f in (2) is nonlinear in variables $Z_1, \ldots, Z_n$, then the set $K(x)$ consists of more than one point and the velocity along W is not determined in a unique way.

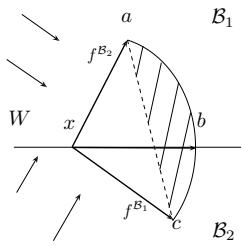

Figure 2. A sketchy view of the three possible definitions for the right-hand side of (7). $\mathcal{B}_1$, $\mathcal{B}_2$ stand for the two regular domains separated by the singular domain $\mathcal{W}$ and associated to Boolean vectors B_1, B_2. $f^{\mathcal{B}_1}$ and $f^{\mathcal{B}_2}$ stand for the values of the function $f(x, Z)$, where $Z = B_1$ and $Z = B_2$, respectively.

Any Filippov solution in the sense of Definition 3 is a Filippov solution in the sense of Definition 4 (in Figure 2 the set $\mathcal{F}$ is the chord ac, $\mathcal{F}_1$ is the arc abc, and $\mathcal{F}_2$ is the cross-hatched segment). The converse does not hold in general, but still holds if f in (2) is linear in $Z_1, \ldots, Z_n$ (see [10], Chapter 2 §4 2). In our case we assume that F and G are affine functions with respect to each of the components Z_j, i.e. f admits nonlinear terms such as $Z_1 Z_2$, but does not admit terms such as Z_1^2. Thus, the equivalence of the two definitions does not follow from the above result. However, it is possible to show that in this case both definitions are equivalent as well.

Remark 2. Since we show later in this chapter that $\mathcal{F}(x) = \mathcal{F}_2(x)$, solutions in the sense of Definition 3 and Definition 4 will be both called Filippov solutions. □

Example 2.

$$\begin{aligned} \dot{x}_1 &= Z_1 - x_1, \\ \dot{x}_2 &= Z_2 - x_2 \\ \dot{x}_3 &= Z_1 Z_2 - Z_3 x_3 \end{aligned} \tag{11}$$

We assume that $\theta_1 = 1$, $\theta_2 = 1$, $\theta_3 = 1/2$ and consider the point $(1, 1, 1)$ located in the singular domain $\mathcal{SD}(1, 2, [1]) = \{x_1 = \theta_1,\, x_2 = \theta_2,\, x_3 > \theta_3\}$ of codimension 2.

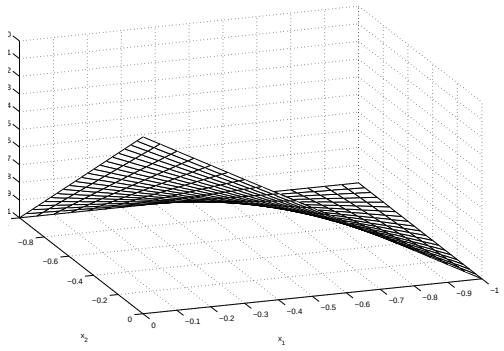

Figure 3. The surface represents the set $\mathcal{F}_1(x)$ for the system (11) constructed at the point $x = (1, 1, 1)$. The set $\mathcal{F}_2(x) = \overline{co}\mathcal{F}_1(x)$ coincides with the set $\mathcal{F}(x) = co\{f_1 = (-1, -1, -1), f_2 = (0, -1, -1), f_3 = (-1, 0, -1), f_4 = (0, 0, 0)\}$. Both of them (the set $\mathcal{F}_2$ and $\mathcal{F}$) are the pyramid with the vertices at f_1, f_2, f_3, f_4. $\square$

Let us prove the following general fact.

Lemma 1. *Let $g : \mathbb{R}^m \to \mathbb{R}^n$,$g = g(Z)$, $Z \in \mathbb{Z}^m \equiv [0, 1]^m$, be an affine function with respect to each variable Z_i, $i = 1, ..., m$. Let B be a Boolean vector of dimension m. The set of all such vectors we denote by $\mathbb{B}^m$. Then*

$$co\, g(\mathbb{Z}^m) = co\, g(\mathbb{B}^m). \tag{12}$$

Proof. The proof is by induction over the dimension m.

If $m = 1$, then $g(Z) = AZ + B$, $A, B \in \mathbb{R}^n$. This function is linear and the proof is trivial.

Suppose now that (12) holds for $m = k - 1$, i.e. for any affine (with respect to each variable) function $g : \mathbb{R}^{k-1} \to \mathbb{R}^n$ the equality (12) is satisfied.

Then for $Z_1 = 0$ and $Z_1 = 1$, by the inductive assumption, we have

$$co\, g(0, \mathbb{Z}^{k-1}) = co\, g(0, \mathbb{B}^{k-1}) \subset co\, g(\mathbb{B}^k),$$

$$co\, g(1, \mathbb{Z}^{k-1}) = co\, g(1, \mathbb{B}^{k-1}) \subset co\, g(\mathbb{B}^k).$$

Let us prove now that for any $Z^0 \in \mathbb{Z}^k$ $g(Z^0) \in co\, g(\mathbb{B}^k)$. Let $Z^0 = (Z_1^0, ..., Z_k^0)$. Since g is an affine function with respect to Z_1, we have

$$g(Z_1, Z_2, ..., Z_k) = Z_1 g_1(Z_2, ..., Z_k) + g_2(Z_2, ..., Z_k).$$

Therefore since

$$g(1, Z_2^0, ..., Z_k^0) = g_1(Z_2^0, ..., Z_k^0) + g_2(Z_2^0, ..., Z_k^0),$$
$$g(0, Z_2^0, ..., Z_k^0) = g_2(Z_2^0, ..., Z_k^0),$$

we have

$$g(Z_1^0, Z_2^0, ..., Z_k^0) = Z_1^0 g_1(Z_2^0, ..., Z_k^0) + g_2(Z_2^0, ..., Z_k^0) =$$
$$Z_1^0 g(1, Z_2^0, ..., Z_k^0) + (1 - Z_1^0) g(0, Z_2^0, ..., Z_k^0).$$

Since $0 \le Z_1^0 \le 1$ and $g(0, Z_2^0, ..., Z_k^0), g(1, Z_2^0, ..., Z_k^0) \in co\, g(\mathbb{B}^k)$, we see that $g(Z_1^0, Z_2^0, ..., Z_k^0) \in co\, g(\mathbb{B}^k)$ as well. This means that $g(\mathbb{Z}^k) \subset co\, g(\mathbb{B}^k)$ and consequently $co\, g(\mathbb{Z}^k) \subset co\, g(\mathbb{B}^k)$.

The opposite inclusion is obvious since $\mathbb{B}^k \subset \mathbb{Z}^k$.

Hence $co\, g(\mathbb{Z}^k) = co\, g(\mathbb{B}^k)$ and the proof is complete. $\square$

Theorem 1. *Let F and G in (2) be affine functions with respect to the variables $Z_1, \ldots, Z_n$. Then Definition 3 and Definition 4 are equivalent, i.e. $\mathcal{F}(x) = \mathcal{F}_2(x)$.*

Proof. It follows from Lemma 1 applied to any singular domain $\mathcal{S}D(S, B_R)$ and from the equality $g(Z_S) = f(Z_S, B_R) - G(Z_S, B_R)\theta_S$. $\square$

Remark 3. Note that if $m > 1$ in Lemma 1, then it is not always true that g(convex set)=convex set. Indeed, in Example 2 the set $g(\mathbb{Z}^2) = \mathcal{F}_1$ (the surface in Figure 4) is non-convex. $\square$

The following example shows that the presence of nonlinear terms such as Z_1^2 may lead to $\mathcal{F}(x) \neq \mathcal{F}_2(x)$ ($\mathcal{F}(x) \subset \mathcal{F}_2(x)$).

Example 3.

$$\begin{aligned} \dot{x}_1 &= 0.5Z_1 + Z_2 + 0.5Z_1^2 - x_1, \\ \dot{x}_2 &= Z_2^2 - x_2. \end{aligned} \tag{13}$$

We assume that $\theta_1 = 1$ and $\theta_2 = 1$.

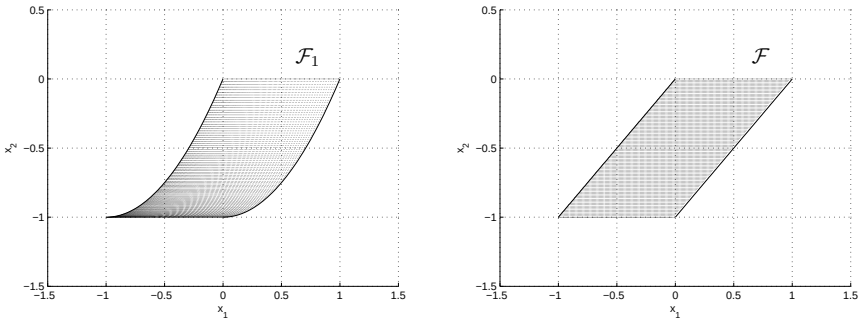

Figure 4. For the system (13) the sets $\mathcal{F}_1(x)$ and $\mathcal{F}(x)$ constructed at the point $x = (\theta_1, \theta_2)$. The set $\mathcal{F}_2(x) = \overline{co}\mathcal{F}_1(x)$ does not coincide with the set $\mathcal{F}(x) = co\{f_1 = (-1,-1), f_2 = (0,-1), f_3 = (1,0), f_4 = (0,0)\}$. $\square$

4. The existence and properties of Filippov solutions

Consider the initial value problem for the differential inclusion

$$\dot{x} \in \mathcal{F}(x), \qquad x(t_0) = x^0. \tag{14}$$

with the right-hand side $\mathcal{F}$ from Definition 3.

Let us recall some basic notations. For two compact nonempty subsets A, B of a metric space put $\beta(A,B) = \sup\limits_{a \in A} \rho(a,B)$. The function $\alpha(A,B) = \max\{\beta(A,B), \beta(B,A)\}$ is a metric and is called the Hausdorff metric. A function $\mathcal{F}(x)$ is called *β-continuous* (or Hausdorff upper semicontinuous) at x if $\beta(\mathcal{F}(x'), \mathcal{F}(x)) \to 0$ as $x' \to x$. A function $\mathcal{F}(x)$ is called β-continuous (or Hausdorff upper semicontinuous) on a domain Ω if it is β-continuous (or Hausdorff upper semicontinuous) at each point of this domain.

Definition 6. A vector function $y(t)$ is called a δ-solution (approximate solution within accuracy δ) of the inclusion (14) with β-continuous $\mathcal{F}(x)$ if y is absolutely continuous and almost everywhere

$$\dot{y}(t) \in \mathcal{F}_\delta(y(t)), \quad \mathcal{F}_\delta(y) \equiv [\mathrm{co}\mathcal{F}(y^\delta)]^\delta.$$

Here we denote by M^δ the closed δ-neighborhood of M and by $\mathcal{F}(y^\delta)$ the union of the sets $\mathcal{F}(y_1)$ for all $y_1 \in y^\delta$.

Let Ω be the closed bonded domain given by (5). According to [10] we say that a multivalued function $\mathcal{F}$ satisfies the *basic conditions* in Ω if for any $x \in \Omega$ the set $\mathcal{F}$ is nonempty, bounded, closed, convex and the function $\mathcal{F}$ is β-continuous.

Since the multivalued function $\mathcal{F}(x)$ in (14) satisfies basic conditions in Ω, the following theorem holds.

Theorem 2. *Consider (14) under assumptions on functions F and G listed in Section 2. Then*

A. *At least one Filippov solution of (14) passes through any internal point (t_0, x^0) of the domain Ω.*

B. *Let $x(t) = (x_1(t), ..., x_n(t))$ be a Filippov solution of (14). If $x_i(t_0) = x_i^0 > 0$ for all $i = 1, ..., n$, then $x_i(t) > 0$, for all $t \geq t_0$, $i = 1, ..., n$. If in addition $x_i^0 \leq \overline{F}_i/\sigma_i$,$i = 1, ..., n$, ($\overline{F}_i, \sigma_i$ are the constants from inequalities (4)), then $x_i(t) \leq \overline{F}_i/\sigma_i$ for all $t \geq t_0$, $i = 1, ..., n$. Such a Filippov solution is defined for all $t \geq t_0$.*

C. *All the Filippov solutions are uniformly continuous on any finite time interval $a \leq t \leq b$.*

D. *The limit of a uniformly convergent sequence of Filippov solutions (or δ_k-solutions, where $\delta_k \to 0$), $a \leq t \leq b$, is a Filippov solution as well.*

E. *For $a \leq t \leq b$ consider all the Filippov solutions with a given initial condition $x(t_0) = x^0$ (or with all possible initial conditions $x^0 \in \mathcal{A}$, $\mathcal{A}$ is a given compact set). The set of points belonging to the graphs of these Filippov solutions (the segment of the Filippov solution funnel) is bounded and closed. The set of these Filippov solutions is compact in $C[a, b]$.*

F. *If $\mathcal{A}$ in Proposition E is a connected compact set, then the solution set is connected in $C[a, b]$. The section of the solution funnel by any plane $t = t_1 \in [a, b]$ is a connected compact set.*

Proof. The function $\mathcal{F}$ in (14) is β-continuous (see Lemma 3 in [10], Chapter 2 §6). Therefore, due to the construction of the set $\mathcal{F}$ in Definition 3, the function $\mathcal{F}$ satisfies the basic conditions. The existence of a local Filippov solution then follows from Theorem 1 and 2 in [10], Chapter 2 §7. The assertions C–F of the theorem also hold due to [10], Chapter 2 §7.4.

Let us prove now the assertion B. First let us note that if a Filippov solution $x_i(t)$, $i = 1, ..., n$, of the problem (14) is non negative for some t, then for these t

$$-\overline{G}_i x_i(t) \leq \dot{x}_i(t) \leq \overline{F}_i - \sigma_i x_i(t). \tag{15}$$

This is obvious for regular domains (see (4)). Let us show the validity of (15) for a singular domain $\mathcal{W}$. Motion along $\mathcal{W}$ may only occur with the velocity $\dot{x} \in K(x)$ (see (10)). Any element $\dot{x}$ of $K(x)$ has the form

$$\dot{x} = \alpha^1(x)P^1 + \alpha^2(x)P^2 + ... + \alpha^k(x)P^k, \tag{16}$$

where the vectors $\alpha^j(x)$,$j = 1, ..., k$ (k is the number of the boxes), are such that $\sum_{j=1}^{k} \alpha_i^j(x) = 1$,$i = 1, ..., n$. Points P^j are determined in Definition 3 and are given by $P^j = \beta^j - \Gamma^j x$,

where $\Gamma^j = \mathrm{diag}\,(\gamma_1^j, \ldots, \gamma_n^j)$ (the diagonal matrix with the entries γ_i^j),$j = 1, ..., k$. Here β^j, γ^j are constant vectors inside each box. Hence (16) transforms to

$$\dot{x} = \sum_{j=1}^{k} \alpha^j(x)\beta^j - \sum_{j=1}^{k} \alpha^j(x)\Gamma^j x,$$

Since $0 \le \beta_i^j \le \overline{F}_i$, $\sigma_i \le \gamma_i^j \le \overline{G}_i$, and $x_i(t) \ge 0$, we have, due to $\sum\limits_{j=1}^{k} \alpha_i^j(x) = 1$, the validity of (15).

Let us show now that if we choose $x_i(t_0) = x_i^0 > 0$ for all $i = 1, ..., n$, then $x_i(t)$ satisfying (14) satisfies $x_i(t) > 0$ for all $t \ge t_0$, $i = 1, ..., n$. Assume the converse. Then there exists $m \in \{1, ..., n\}$ and $t^* < \infty$ such that $x_m(t^*) = 0$. Let t^* be the first moment of time when $x_m(t)$ becomes zero, i.e. $x_m(t^*) = 0$ but $x_m(t) > 0$ for all $t_0 \le t < t^*$. Obviously $t^* > t_0$ due to the continuity of $x(t)$. Any Filippov solution of the problem (14) has the form

$$x_m(t) = x_m^0 + \int_{t_0}^{t} g_m(x(s))ds, \qquad m \in \{1, ..., n\}, \tag{17}$$

where $g_m \in \{f \in L^1[t_0, t] : f(s) \in \mathcal{F}_m(x(s)) \text{ for a. e. } s \in [t_0, t]\}$. Since for $t \in [t_0, t^*]$ $x_m(t) > 0$, we have, due to (15),

$$x_m(t^*) = x_m^0 + \int_{t_0}^{t^*} g_m(x(s))ds \ge x_m^0 + \int_{t_0}^{t^*} (-\overline{G}_m x_m)ds.$$

By the theorem on integral inequalities, $x_m(t) \ge \underline{x}_m(t)$, $t \in [t_0, t^*]$, where $\underline{x}_m(t) = x_m^0 e^{-\overline{G}_m(t-t_0)} > 0$ is the solution of the problem

$$\dot{\underline{x}}_m(t) = -\overline{G}_m \underline{x}_m(t), \qquad \underline{x}_m(t_0) = x_m^0.$$

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

Let us show now that if we choose $x_i(t_0) = x_i^0 \le \overline{F}_i/\sigma_i$ and $x_i^0 > 0$, $i = 1, ..., n$, then $x_i(t)$ satisfying (14) also satisfies $x_i(t) \le \overline{F}_i/\sigma_i$ for all $t \ge t_0$. In a similar way, since $x_i(t) \ge 0$ and due to (15),(17), we have

$$x_i(t) = x_i^0 + \int_{t_0}^{t} g_i(x(s))ds \le x_i^0 + \int_{t_0}^{t} (\overline{F}_i - \sigma_i x_i(s))ds.$$

Due to the theorem on integral inequalities we obtain $x_i(t) \le \overline{x}_i(t)$, where $\overline{x}_i(t) \ge 0$ is the solution of the following initial value problem

$$\dot{\overline{x}}_i(t) = \overline{F}_i - \sigma_i \overline{x}_i(t), \qquad \overline{x}_i(t_0) = x_i^0. \tag{18}$$

The solution of (18) is given by

$$\overline{x}_i(t) = \overline{F}_i/\sigma_i + (x_i^0 - \overline{F}_i/\sigma_i)e^{-\sigma_i(t-t_0)}.$$

We denote $t - t_0 = \Delta t > 0$ and since $x_i^0 \le \overline{F}_i/\sigma_i$, we have

$$\overline{x}_i(t) = \overline{F}_i/\sigma_i + (x_i^0 - \overline{F}_i/\sigma_i)e^{-\sigma_i \Delta t} \le \overline{F}_i/\sigma_i.$$

Therefore $x_i(t) \le \overline{x}_i(t) \le \overline{F}_i/\sigma_i$ for all $t \ge t_0$ and we have the global existence of a Filippov solution in positive direction.

The proof of the theorem is complete. $\square$

Remark 4. If a trajectory starts in Ω (defined in Section 2), it will remain inside, while trajectories starting outside will eventually enter Ω. For $x_i^0 \le \overline{F}_i/\sigma_i$ this follows from the theorem. If $x_i^0 > \overline{F}_i/\sigma_i$, then $x_i(t) \le \overline{F}_i/\sigma_i + (x_i^0 - \overline{F}_i/\sigma_i)e^{-\sigma_i \Delta t}$. Since the right-hand side of the latest inequality goes to $\overline{F}_i/\sigma_i$ as $t \to \infty$, we have that $x(t) \le \overline{F}_i/\sigma_i + \varepsilon$ for any $\varepsilon < 0$ and $t > t^*(\varepsilon)$. $\square$

Below we adjust some theorems from [10] (Chapter 2 §8) on dependence of a Fillipov solution on initial data and on the right-hand side of the equation to the case of switching system (14).

Let a multivalued function $\mathcal{F}$ be defined in a certain ε_0-neighborhood D_0 of the set D and let $\mathcal{F}^*$ be defined in the set D. Then for $0 < \delta\sqrt{2} < \varepsilon_0$ the set $\mathcal{F}(x^\delta)$ is well-defined. This set is the union of the sets $\mathcal{F}(x_1)$ for all $x_1 \in x^\delta$. We say that $d_D(\mathcal{F}^*, \mathcal{F}) \le \delta$ if and only if for all $x \in D$

$$\mathcal{F}^*(x) \in [co\mathcal{F}(x^\delta)]^\delta.$$

Theorem 3. *[[10], Chapter 2 §8, Theorem 1] For $a \le t \le b$ and $x_0 \in \Omega$ consider all the Filippov solutions of the problem (14). Let $\mathcal{F}$, $\mathcal{F}^*$ be the multivalued functions describing two different right-hand sides of (14). Then for any $\varepsilon > 0$ there exists $\delta > 0$ such that for any x_0^* and $\mathcal{F}^*(x)$ satisfying the following conditions*

$$|x_0^* - x^0| \le \delta, \qquad d_\Omega(\mathcal{F}^*, \mathcal{F}) \le \delta,$$

every Filippov solution of the problem

$$\dot{x}^* \in \mathcal{F}^*(x^*), \qquad x^*(t_0^*) = x_0^*, \tag{19}$$

exists for $a \le t \le b$ and its deviation from some Filippov solution of the problem (14) does not exceed ε. $\square$

This means that every Filippov solution $x^*(t)$ of the problem (19) either exists on $[a, b]$, or may be extended to the entire segment $[a, b]$, and there exists a Filippov solution $x(t)$ of the problem (14) such that

$$\max_{a \le t \le b} |x^*(t) - x(t)| \le \varepsilon.$$

Let $f(x)$ and $f^*(x)$ be piecewise continuous in domain Ω vector functions defined in Section 2. We say that $d^0(f^*, f) \le \delta$ if and only if for each continuity point x of the function f^* there exists a continuity point x' of the function f such that

$$|x' - x| \le \delta, \qquad |f(x') - f^*(x)| \le \delta. \tag{20}$$

Notice that from (20) it does not necessarily follow that the deviation of the values of the functions f and f^* in discontinuity sets does not exceed δ.

Theorem 4. *[[10], Chapter 2 §8, Theorem 2] For $a \le t \le b$ and $x_0 \in \Omega$ consider all the Filippov solutions of the problem (14). Let f, f^* be functions describing two different right-hand sides of the equation (2). Suppose also that f, f^* correspond to multivalued functions $\mathcal{F}$, $\mathcal{F}^*$, respectively. Then for any $\varepsilon > 0$ there exists $\delta > 0$ such that for any x_0^* and $f^*(x)$ satisfying the following conditions*

$$|x_0^* - x^0| \le \delta, \qquad d^0(f^*, f) \le \delta,$$

every Filippov solution of the problem

$$\dot{x}^* \in \mathcal{F}^*(x^*), \qquad x^*(t_0^*) = x_0^*,$$

exists for $a \le t \le b$ and its deviation from some Filippov solution of the problem (14) does not exceed ε. $\square$

The next corollary provides a more explicit version of Theorem 4. It asserts that solutions of the perturbed problem (14) approach solutions of the original problem (14) for sufficiently small perturbations of the initial value, the threshold value, and the functions F and G in (2).

Corollary 1. *For $a \le t \le b$ and $x_0 \in \Omega$ consider all the Filippov solutions of the problem (14). Let $F(Z)$,$G(Z)$,$F^*(Z)$,$G^*(Z)$, where $Z_i = \Sigma(x_i, \theta_i, 0)$,$i = 1, ..., n$, be the functions on two different right-hand sides of the equation (2) satisfying the properties listed in Section 2. Suppose also that $\mathcal{F}$ and $\mathcal{F}^*$ are the multivalued functions from Definition 3 corresponding to $F(Z)$,$G(Z)$ and $F^*(Z^*)$,$G^*(Z^*)$, respectively, where $Z_i^* = \Sigma(x_i, \theta_i^*, 0)$,$i = 1, ..., n$. Then for any $\varepsilon > 0$ there exists $\delta > 0$ such that for any x_0^*, θ^*, $F^*(Z)$, and $G^*(Z)$ satisfying the following conditions*

$$|x_0^* - x^0| \le \delta, \quad |\theta - \theta^*| \le \delta_1 \le \delta,$$

$$\max_{Z \in \{0,1\}^n} |F^*(Z) - F(Z)| \le \delta_2 \le \delta, \quad \max_{Z \in \{0,1\}^n} |G^*(Z) - G(Z)| \le \delta_3 \le \delta \tag{21}$$

every Filippov solution of the problem

$$\dot{x}^* \in \mathcal{F}^*(x^*), \qquad x^*(t_0^*) = x_0^*,$$

exists for $a \le t \le b$ and its deviation from some Filippov solution of the problem (14) does not exceed ε.

Proof. By Theorem 4, all we need is to show that $d^0(f^*, f) \le \delta$, where $f(x, Z) = F(Z) - G(Z)x$, $f^*(x, Z^*) = F^*(Z^*) - G^*(Z^*)x$.

Let $x_i \ne \theta_i^*$,$i = 1, ..., n$, be a continuity point of the function $f_i^*(x_i, Z_i^*) = F_i^*(Z_i^*) - G_i^*(Z_i^*)x_i$. We can assume without loss of generality that $\theta_i \le \theta_i^*$. Due to the definition of the function Z (see (3)), there exists $x_i' \notin [\theta_i, \theta_i^*]$ such that $|x_i' - x_i| \le \delta_1 \le \delta$ and $Z_i(x_i') = Z_i^*(x_i) = \hat{Z}_i \in \{0, 1\}$. Obviously, this x_i' is a continuity point of the function f_i. Consider $|f_i(x_i', Z_i(x_i')) - f_i^*(x_i, Z_i^*(x_i))| \le |F_i(\hat{Z}_i) - F_i^*(\hat{Z}_i)| + |G_i(\hat{Z}_i)x_i' - G_i^*(\hat{Z}_i)x_i| \le \delta + |G(\hat{Z}_i)x_i' - G_i^*(\hat{Z}_i)x_i'| + |G_i^*(\hat{Z}_i)x_i' - G_i^*(\hat{Z}_i)x_i|$. By (21), (5), (4) and due to $|x' - x| \le \delta$, we obtain

$$|f_i(x_i', Z_i(x_i')) - f_i^*(x_i, Z_i^*(x_i))| \le \delta + \delta \max + \overline{G}\delta.$$

If we choose δ_1, δ_2, δ_3 sufficiently small, then the latter inequality implies $d^0(f^*, f) \le \delta$, and the proof is complete. $\square$

Finally, we prove that solutions of the smooth system (2) (including sigmoids rather than step functions) approach a certain Filippov solution as the steepness parameter q goes to 0.

Corollary 2. *For $x_0 \in \Omega$ consider all the Filippov solutions of the problem (14) for $a \le t \le b$. Let $f^* = f(x, Z^*) = F(Z^*) - G(Z^*)x$ be the vector function on the right-hand side of the equation (2) with a steep sigmoid $Z_i^* = \Sigma(x_i, \theta_i, q)$,$i = 1, ..., n$, $q > 0$. Then for any $\varepsilon > 0$ there exists $\delta > 0$ such that for any x_0^*, q satisfying the following conditions*

$$|x_0^* - x^0| \le \delta, \quad q \le \delta,$$

every solution of the problem

$$\dot{x}^* = f^*(x^*), \qquad x^*(t_0^*) = x_0^*$$

exists for $a \le t \le b$ and its deviation from some Filippov solution of the problem (14) does not exceed ε.

Proof. Due to Theorem 3, it is sufficient to show that $d_\Omega(f^*, \mathcal{F}) \le \delta$. Let $\tilde{x} \in \Omega$ be such that $\tilde{x}_i \ne \theta_i$,$i = 1, ..., n$. Then $\mathcal{F}_i(\tilde{x}) = f_i(\tilde{x}_i, Z(\tilde{x}_i))$, where f_i is a vector function defined by (2). Due to the properties of a sigmoid function Z^* (it approaches the step function as $q \to 0$), $Z_i^*(\tilde{x}_i) \to Z_i(\tilde{x}_i)$ as $q \to 0$. Therefore, by continuity of the functions F and G, $F_i(Z_i^*(\tilde{x}_i)) \to F_i(Z_i(\tilde{x}_i))$ and $G_i(Z_i^*(\tilde{x}_i)) \to G_i(Z_i(\tilde{x}_i))$ as $q \to 0$. Then for a sufficiently small q we have $|f_i^*(\tilde{x}_i) - f_i(\tilde{x}_i)| \le |F_i(Z_i^*(\tilde{x}_i)) - F_i(Z_i(\tilde{x}_i))| + |G_i(Z_i^*(\tilde{x}_i))\tilde{x}_i - G_i(Z_i(\tilde{x}_i))\tilde{x}_i| \le \delta$. Therefore $f_i^*(\tilde{x}_i) = f_i(\tilde{x}_i, Z_i^*) \subset (f_i(\tilde{x}_i, Z_i))^\delta \equiv (\mathcal{F}_i(\tilde{x}_i))^\delta \subset [co\mathcal{F}_i(\tilde{x}_i^\delta)]^\delta$, i.e. $d_\Omega(f_i^*, \mathcal{F}_i) \le \delta$ provided $\tilde{x}_i \ne \theta_i$.

Suppose now that $x_i = \theta_i$,$i \in S$. Due to the properties of a sigmoid function Z^*, $Z_i^*(\theta_i) \to 1/2$ as $q \to 0$. By construction of the set $\mathcal{F}_i$, $f_i(\theta_i, 1/2) \in \mathcal{F}_i(\theta_i)$. Due to the continuity of f_i with respect to Z_i, $f_i^*(\theta_i) = f_i(\theta_i, Z_i^*(\theta_i)) \to f_i(\theta_i, 1/2)$ as $q \to 0$. Hence for a sufficiently small q $\rho(f_i^*(\theta_i), \mathcal{F}_i(\theta_i)) \le \delta$. Therefore $f_i^*(\theta_i) \subset (\mathcal{F}_i(\theta_i))^\delta \subset [co\mathcal{F}_i(\theta_i^\delta)]^\delta$, i.e. $d_\Omega(f_i^*, \mathcal{F}_i) \le \delta$ for $x_i = \theta_i$. $\square$

5. The uniqueness and non-uniqueness of Filippov solutions in singular domains

We consider the Filippov solutions. In regular domains we have the uniqueness (both right and left) of a Filippov solution due to the continuity of df/dx.

The theorems below follow directly from [10], Chapter 2 §10.

Theorem 5. *If a Filippov solution hits a transparent wall at some point, then this solution travels through this wall into the adjacent box. This solution is unique at least until it hits another singular domain.*

Consider an arbitrary transparent wall $x_i = \theta_i$. It is a singular domain $\mathcal{S}D(\{i\}, B_R)$ of codimension 1. Let $\mathcal{B}^1$, $\mathcal{B}^2$ be the two adjacent boxes separated by this wall and corresponding to $x_i > \theta_i$ and $x_i < \theta_i$, respectively. Let B^1, B^2 be the corresponding Boolean vectors.

Within the box $\mathcal{B}^1$ the motion is given by

$$\dot{x}_j = F_j(B^1) - G_j(B^1)x_j = f_j^1(x_j), \qquad j = 1, ..., n, \tag{22}$$

and within the box $\mathcal{B}^2$

$$\dot{x}_j = F_j(B^2) - G_j(B^2)x_j = f_j^2(x_j), \qquad j = 1, ..., n, \tag{23}$$

where F_j, G_j reduce to some constants within each of the two boxes.

The Filippov solution $x(t)$ starting at $x^0 = x(t_0)$ inside the box $\mathcal{B}^1$ is described by

$$x_j(t) = \Phi_j^1 + (x_j^0 - \Phi_j^1)\exp\left[-G_j(B^1)(t - t_0)\right],$$

where $\Phi_j^1 = F_j(B^1)/G_j(B^1)$. If it hits the transparent wall $x_i = \theta_i$ at some finite $t^* > t_0$, then this solution travels through this wall into the box $\mathcal{B}^2$ and its motion is described by

$$x_j(t) = \Phi_j^2 + (x_j^* - \Phi_j^2)\exp\left[-G_j(B^2)(t - t^*)\right],$$

where $\Phi_j^2 = F_j(B^2)/G_j(B^2)$, $x^* = x(t^*)$. This solution is unique.

Theorem 6. *Each point of a black wall is hit by exactly one Filippov solution coming from one of the boxes separated by this wall and by exactly one Filippov solution coming from the adjacent box. Any solution starting in a black wall is unique at least until it hits an intersection of walls.*

We will now determine the velocity of the motion along a black wall and show the non-uniqueness of Filippov solutions in white walls.

Remark 5. [Chapter 2 §4.2 a) in [10]] In the case of the black wall $x_i = \theta_i$ Filippov solutions do not leave the wall. They will stay in this wall at least for a while until they hit another wall and will satisfy, due to [10], the equation $\dot{x}_j = f_j^0(x_j)$,$j = 1, ..., n$,$j \neq i$, where

$$f_j^0 = \alpha f_j^1 + (1 - \alpha)f_j^2, \qquad \alpha = \frac{f_i^2}{f_i^2 - f_i^1}, \qquad 0 \leq \alpha \leq 1. \tag{24}$$

Here f_j^1, f_j^2, $j = 1, ..., n$, are defined by (22), (23), respectively. For the black wall $x_i = \theta_i$ separating the boxes $\mathcal{B}^1$, $\mathcal{B}^2$ α is given by

$$\alpha = \frac{F_i(B^2) - G_i(B^2)\theta_i}{F_i(B^2) - F_i(B^1) - (G_i(B^2) - G_i(B^1))\theta_i}. \tag{25}$$

□

Remark 6. Situation with white walls is different. Let us show that there we have infinitely many Filippov solutions.

Consider equation

$$\dot{x} = F(Z) - G(Z)x \tag{26}$$

on the interval $t \in [0, T]$. We assume that $x_1 = \theta_1$ is the white wall, $Z_R = B_R$. This is the case if $F_1(0, B_R) - G_1(0, B_R)\theta_1 < 0$ and $F_1(1, B_R) - G_1(1, B_R)\theta_1 > 0$ or, in other words, there exists $Z_1^* \in (0, 1)$ such that

$$F_1(Z_1^*, B_R) - G_1(Z_1^*, B_R)\theta_1 = 0. \tag{27}$$

Let us find all the Filippov solutions of the inclusion

$$\dot{x} \in \mathcal{F}(x) \tag{28}$$

with the initial condition $x(0) = x^0 = (\theta_1, x_2, ..., x_n)$, $x_i \neq \theta_i$, $i = 2, ..., n$. The right-hand side $\mathcal{F}$ is determined in Definition 3, $Z_i = \Sigma(x_i, \theta_i, 0)$.

We start with the coordinate x_1. Due to $x_1(0) = \theta_1$, we have for $t = 0$

$$\dot{x}_1(0) \in \mathcal{F}(x(0)) = \mathrm{co}\{F_1(0, B_R) - G_1(0, B_R)\theta_1; F_1(1, B_R) - G_1(1, B_R)\theta_1\}. \tag{29}$$

Since F_1,G_1 are affine functions with respect to Z_1, (29) can be rewritten as

$$\dot{x}_1(0) \in \mathcal{F}(\theta_1) = \{F_1(Z_1, B_R) - G_1(Z_1, B_R)\theta_1 \mid \quad 0 \leq Z_1 \leq 1\}.$$

Due to (27), $0 \in \mathcal{F}(\theta_1)$. Therefore it might happen that $\dot{x}_1(t) = 0$ for some $t \geq 0$. Let $\alpha = \inf\{t \geq 0 : \dot{x}_1(t) \neq 0\}$. Then for any $t \in [0, \alpha)\dot{x}_1(t) = 0$, i.e. $x_1(t) = \theta_1$ for all $t \in [0, \alpha)$. Due to the continuity of the Filippov solution, $x_1(t) = \theta_1$ for all $t \in [0, \alpha]$. Let t_0 be such that $t_0 > \alpha$ and $\dot{x}_1(t_0) \neq 0$. Let, for example, $\dot{x}_1(t_0) > 0$. Without loss of generality we can assume that $\dot{x}_1(t) > 0$ for all $\alpha < t \leq t_0$. Then $x_1(t) > \theta_1$ for $\alpha < t \leq t_0$ and hence

$$\dot{x}_1(t) = F_1(1, B_R) - G_1(1, B_R)x_1 \quad \text{for} \quad \alpha < t \leq t_0.$$

Therefore any Filippov solution has the form

$$x_1(t) = \begin{cases} \theta_1, & 0 \leq t \leq \alpha, \\ \frac{F_1(1,B_R)}{G_1(1,B_R)} + (\theta_1 - \frac{F_1(1,B_R)}{G_1(1,B_R)})e^{-G(1,B_R)(t-\alpha)}, & \alpha < t \leq t_0. \end{cases} \tag{30}$$

The similar formula is valid for $\dot{x}_1(t_0) < 0$

$$x_1(t) = \begin{cases} \theta_1, & 0 \leq t \leq \alpha, \\ \frac{F_1(0,B_R)}{G_1(0,B_R)} + (\theta_1 - \frac{F_1(0,B_R)}{G_1(0,B_R)})e^{-G(0,B_R)(t-\alpha)}, & \alpha < t \leq t_0. \end{cases} \tag{31}$$

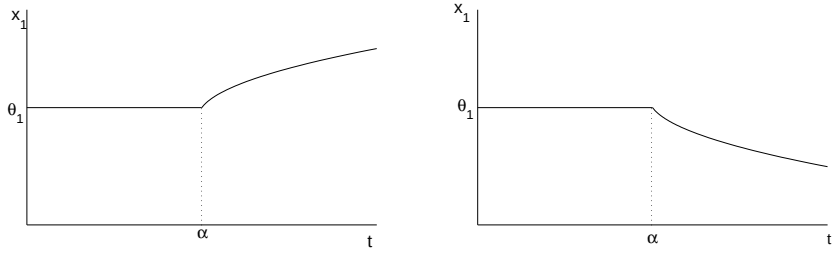

Figure 5. The sketchy view of a Filippov solution in both cases.

Since α may be chosen arbitrarily on the interval $[0, T]$, we have infinitely many Filippov solutions (at least for the first coordinate).

Now we add one more coordinate, say x_2.

$$\dot{x}_2(t) \in \mathcal{F}(x(t)) = \mathrm{co}\{F_2(0, B_R) - G_2(0, B_R)x_2(t); F_2(1, B_R) - G_2(1, B_R)x_2(t)\},$$

where $x_2(0) \neq \theta_2$ and $x_1(t) = \theta_1$.

Or

$$\dot{x}_2(t) \in \mathcal{F}(x(t)) = \{F_2(Z_1, B_R) - G_2(Z_1, B_R)x_2(t) \,|\quad 0 \leq Z_1 \leq 1\}, \tag{32}$$

where $x_1(t) = \theta_1$ and $x_2(t) - \theta_2$ does not change the sign (which holds at least in a vicinity of $t = 0$). The problem (32) has at least one Filippov solution in a vicinity of $t = 0$. The same applies to the coordinates x_3, x_4, etc.

Thus, there exist infinitely many $\alpha > 0$ such that (30)(or (31)) and (32) represent the Filippov solutions of (26) for $i = 1$ and $i \geq 2$ respectively. In fact, there are no other Filippov solutions close to the white wall, due to the argument just presented. □

Summarizing, we have the uniqueness of a Filippov solution in black and transparent walls and non-uniqueness in white walls.

Example 4. Consider the following example from [4].

$$\begin{aligned} \dot{x}_1 &= Z_1 + Z_2 - 2Z_1Z_2 - \gamma_1 x_1, \\ \dot{x}_2 &= 1 - Z_1Z_2 - \gamma_2 x_2. \end{aligned} \tag{33}$$

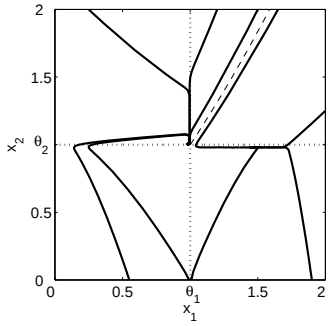

Figure 6. Some trajectories of (33) for the steep model with $q = 0.01$. Parameter values: $\gamma_1 = 0.6$, $\gamma_2 = 0.9$, $\theta_1 = \theta_2 = 1$.

This model has two black walls $\mathcal{SD}(1, [1])$ ($x_1 = \theta_1$, $x_2 > \theta_2$) and $\mathcal{SD}(2, [1])$ ($x_2 = \theta_2$, $x_1 > \theta_1$). The single point $x_1 = \theta_1$,$x_2 = \theta_2$ is the singular domain $\mathcal{SD}(1, 2)$ of codimension 2.

Any Filippov solution that starts inside the box $\mathcal{B}([11])$ and hits one of these black walls stays there and, due to Theorem 6, is unique unless it reaches the intesection of the walls.

In the wall $\mathcal{SD}(1, [1])$, by Remark 5, the equations of motion are given by

$$\begin{aligned} x_1(t) &= \theta_1 \\ x_2(t) &= 2/3 + (x_2^0 - 2/3)e^{-0.9(t-t_0)}. \end{aligned}$$

Since $x_2(t) \to 2/3 < \theta_2$, any Filippov solution that hits the black wall $\mathcal{SD}(1, [1])$ remains in this wall, is unique (unless it reaches the intersection of the walls) and converges to the point $x_1 = \theta_1$,$x_2 = \theta_2$.

Similarly, for the black wall $\mathcal{SD}(2,[1])$ we have

$$x_1(t) = 3/2 + (x_1^0 - 3/2)e^{-0.6(t-t_0)},$$
$$x_2 = \theta_2.$$

Thus, any Filippov solution that hits the black wall $\mathcal{SD}(2,[1])$ remains in this wall, is unique and converges to the point $x_1 = 3/2$, $x_2 = \theta_2$.

Consider now the intersection of these black walls, i.e. the point $x_1 = \theta_1$,$x_2 = \theta_2$. We will show that a Filippov solution that passes through this point is not unique.

First notice that $\{(x_1^0, x_2^0) \,|\, x_1^0 \geq \theta_1, x_2^0 \geq (x_1^0)^{3/2}\}$ (the area above the dotted line inside one of the boxes in Figure 6) is the set of all initial conditions such that the Filippov solution starting at these points at $t_0 = 0$ reaches the point (θ_1, θ_2) at some $t^* > t_0$. The point (θ_1, θ_2) is also reached in a finite time by any Filippov solution coming from the box $\{x_1 < \theta_1, x_2 > \theta_2\}$.

Then, by the definition of a Filippov solution, for $t > t^*$ the Filippov solution "splits" into two parts, i.e. either it stays forever an the point $(1,1)$, or stays at $(1,1)$ for an arbitrary yet a finite period of time and then converges along the black wall $\mathcal{SD}(2,[1])$ to the point $(3/2,1)$. Since the Filippov solution may stay at $(1,1)$ for any arbitrary period of time, we have infinitely many Filippov solutions. In Figure 6 the area in the box $\mathcal{B}([11])$ above the dotted line represents the initial conditions for such non-unique solutions. □

6. Stationary points

In this section we will compare two approaches to identify stationary points to (2): one is based on the method from [4] and another utilizes the Filippov method [10].

We will show that the main difference between these approaches amounts to the difference between non-equivalent definitions of the Filippov solutions. In the case of a non-convex right-hand side (the set $\mathcal{F}_1(x)$, Definition 5) we get stationary points in the sense of [4], while in the case of a convex right-hand side (the set $\mathcal{F}(x)$, Definition 3) we obtain stationary points in the sense of [8]. Although the second approach gives more stationary points than the first one, we will show (Theorems 9) that the Filippov stationary points that are limits of convergent sequences of stationary points of smooth systems ($q \to 0$) are indeed the Fillipov solutions in the sense of definition with non-convex right-hand sides, i.e. Filippov solutions in the narrow sense. We also introduce Example 5 of stationary points in the sense of [8], which at the same time are not stationary points in the sense of [4].

Definition 7. A point x^0 is called a Filippov stationary point of (2) if $0 \in \mathcal{F}(x^0)$, where $\mathcal{F}(x)$ is from Definition 3.

Remark 7. If $0 \in \mathcal{F}_1(x^0)$, where $\mathcal{F}_1(x)$ is from Definition 4, then we will call x^0 a Filippov stationary point in the narrow sense. As we show below, the difference between non-equivalent definitions of the Filippov solution represents the two approaches: one based on [4] (Filippov solutions in the narrow sense) and another based on [8] (Filippov solutions). □

If x^0 is located inside a regular domain $\mathcal{B}$ determined by a Boolean vector B, then $\mathcal{F}(x^0) = F(B) - G(B)x^0$ and we have the definition of a conventional stationary point. The position of such regular stationary points (RSPs [14]) is given by $\Phi_i = F_i(B)/G_i(B)$ (i.e. by the focal points [13]), $i = 1, ..., n$. All RSPs are asymptotically stable. In the sequel we consider singular stationary points (SSPs), only.

The following definition gives a formal description of SSP in the sense of [4].

Definition 8. A point $x^0 \in \mathcal{SD}(\theta_S, B_R)$ is called a singular stationary point (SSP) for the system (2), $Z_s = \Sigma(x_s, \theta_s, 0)(s \in S)$, if for any set of steep sigmoid functions $\Sigma(x_s, \theta_s, q)$ $(s \in S)$ there exist a number $\varepsilon > 0$ and points x^q, where $q \in (0, \varepsilon)$, such that

- The point x^q is a stationary point for the system (2) with $Z_s = \Sigma(x_s, \theta_s, q)$ $(s \in S)$;
- $x^q \to x^0$ as $q \to +0$ $(s \in S)$.

Due to Theorem 4 in [4], this is the case if

A) $\det(\partial f_S/\partial Z_S) \neq 0$ and

B) There exists $0 < Z_S^* < 1$, where Z_S^* is obtained from the system

$$\begin{aligned} 0 &= F_S(Z_S^*, B_R) - G_S(Z_S^*, B_R)\theta_S, \\ 0 &= F_R(Z_S^*, B_R) - G_R(Z_S^*, B_R)x_R^0. \end{aligned}$$

This means that a soulution in the sense of [4] is actually a Filippov solution in the narrow case.

The condition A) guarantees, by the implicit function theorem, the existence of stationary solutions for small $q > 0$ and the condition B) indicates that $x^0 \in \mathcal{SD}(\theta_S, B_R)$ is indeed a stationary point of the simplified equations with step functions.

For the more detailed explanation of such solutions we refer the reader to [4]. Briefly, gene regulatory equations with steep but not infinitely steep sigmoids are considered. The method introduced was based on certain simplifying features in the limit when sigmoids approach step function (this is not the same as replacing sigmoids with step functions) and singular perturbation technics were used to analyse the behavior near the thresholds.

We will show below (Theorem 9) that a Filippov stationary solution x^* satisfying $0 \in \mathcal{F}(x^*) \backslash \mathcal{F}_1(x^*)$, i.e. a Filippov stationary solution that is not a Filippov stationary solution in the narrow sense, is not covered by Definition 8. To give an illustration of what can happen to such a stationary solution for small $q > 0$ let us consider the following example.

Example 5. Consider the system

$$\begin{aligned} \dot{x}_1 &= 1.65 - Z_1 + 2Z_2 - 2Z_1Z_2 - \gamma_1 x_1, \\ \dot{x}_2 &= 2.25 + Z_1 - Z_2 - Z_1Z_2 - \gamma_2 x_2. \end{aligned} \tag{34}$$

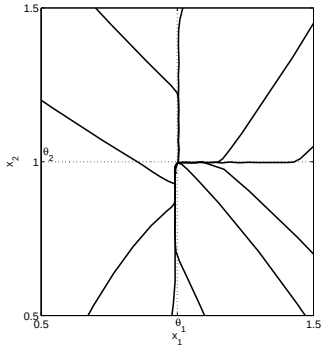

Figure 7. Some trajectories of (34) for the steep model with $q = 0.01$. Parameter values: $\gamma_1 = 1.5$, $\gamma_2 = 2.5$, $\theta_1 = \theta_2 = 1$.

According to Section 5, the Filippov solution in the black wall $\mathcal{SD}(1,[1]) = \{x_1 = \theta_1, x_2 > \theta_2\}$ has the form

$$\begin{aligned} x_1 &= \theta_1 \\ x_2 &= 0.5 + (x_2^0 - 0.5)e^{-2.5(t-t_0)}. \end{aligned}$$

We see that $x_2(t) \to 0.5$ as $t \to \infty$. In the black wall $\mathcal{SD}(2,[1]) = \{x_2 = \theta_2, x_1 > \theta_1\}$ the Filippov solution is given by

$$\begin{aligned} x_1 &= 13/30 + (x_1^0 - 13/30)e^{-1.5(t-t_0)} \\ x_2 &= \theta_2 \end{aligned}$$

and therefore $x_1(t) \to 13/30$ as $t \to \infty$. In the black wall $\mathcal{SD}(1,[0]) = \{x_1 = \theta_1, x_2 < \theta_2\}$ the Filippov solution has the form

$$\begin{aligned} x_1 &= \theta_1 \\ x_2 &= 0.96 + (x_2^0 - 0.96)e^{-2.5(t-t_0)}. \end{aligned}$$

Therefore $x_2(t) \to 0.96$ as $t \to \infty$.

It can be easily checked that $0 \in \mathcal{F}(x^0)$, where $x^0 = (1,1)$. Here

$$\mathcal{F}(x^0) = co\{P^{00}(x^0), P^{01}(x^0), P^{10}(x^0), P^{11}(x^0)\},$$

where $P^{00}(x^0) = \begin{pmatrix} 1.65 - 1.5x_1^0 \\ 2.25 - 2.5x_2^0 \end{pmatrix}$, $P^{01}(x^0) = \begin{pmatrix} 3.65 - 1.5x_1^0 \\ 1.25 - 2.5x_2^0 \end{pmatrix}$, $P^{10}(x^0) = \begin{pmatrix} 0.65 - 1.5x_1^0 \\ 3.25 - 2.5x_2^0 \end{pmatrix}$, $P^{11}(x^0) = \begin{pmatrix} 0.65 - 1.5x_1^0 \\ 1.25 - 2.5x_2^0 \end{pmatrix}$.

Thus $(1,1)$ is a Filippov stationary point of the system (34). Another Filippov stationary point is $(1, 0.96)$

The Filippov stationary point $(1,1)$ cannot be obtained using the method described in [4] because stationarity conditions here

$$\begin{aligned} &1.65 - Z_1 + 2Z_2 - 2Z_1Z_2 - 1.5 = 0, \\ &2.25 + Z_1 - Z_2 - Z_1Z_2 - 2.5 = 0 \end{aligned}$$

do not give real solutions (the condition B) is not fulfilled). Indeed, for $x^0 = (1,1)$ $0 \in \mathcal{F}(x^0)$ but $0 \notin \mathcal{F}_1(x^0)$

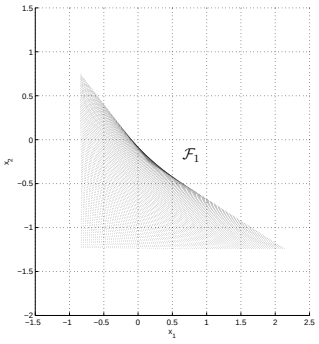

Figure 8. For the system (34) the set $\mathcal{F}_1$ constructed at the point (θ_1, θ_2) does not coincide with the set $\mathcal{F} = \overline{co}\mathcal{F}_1$. Here we have $0 \notin \mathcal{F}_1(x^0)$ and $0 \in \mathcal{F}(x^0)$.

The behavior of the Filippov solution near the point $(1,1)$ is as follows. A trajectory hitting one of the black walls $x_1 = \theta_1$, $x_2 > \theta_2$ or $x_2 = \theta_2$, $x_1 > \theta_1$ will reach the point (θ_1, θ_2) after a finite period of time and then it may either stay at this point forever, or stay there for any arbitrary yet finite period of time and then converge along $\mathcal{SD}(1,[0])$ to the other Filippov stationary point $(1, 0.96)$. Again we have the non-uniqueness of Filippov solutions. Numerical analysis for the considered above system (34) illustrates the behavior of solutions of steep sigmoid model for small $q > 0$ near the Filippov stationary points x^0 satisfying $0 \in \mathcal{F}(x^0) \backslash \mathcal{F}_1(x^0)$.

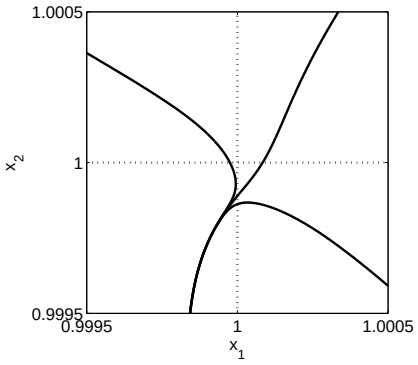

Figure 9. The behavior of some trajectories of the system (34) near the Filippov stationary point $(1,1)$, steepness parameter $q = 0.0001$.

Since $(1,1)$ is not a stationary point in the narrow sense, this point cannot be a limit of stationary points of steep sigmoid systems. Solutions of steep model then turn about this point and then converge towards the SSP $x^1 = (1, 0.96)$ located in the black wall $\mathcal{SD}(1,[0])$ and satisfying $0 \in \mathcal{F}_1(x^1)$. $\square$

Theorem 7. *Any SSP of (2) obtained by the method from [4] is a Filippov stationary point.*

PROOF. Since $x^q(t) = x^q$ is the solution of $\dot{x}^q = F(Z) - G(Z)x^q = 0$ with the steep sigmoid $Z_i = \Sigma(x_i^q, \theta_i, q)$,$q > 0$, we have, due to Corollary 2, that this solution converges uniformly on any interval to a certain Filippov solution of the inclusion $\dot{x} \in \mathcal{F}(x)$. On the other hand $x^q \to x^0$ as $q \to 0$ and hence x^0 is a Filippov solution of $\dot{x} \in \mathcal{F}(x)$ on any interval and therefore for all x. Since x^0 is a constant, $0 \in \mathcal{F}(x^0)$ and x^0 is a Filippov stationary point of (2). □

The converse does not hold in general, but still holds for black and white walls. We consider only black walls bellow, as SSP in white walls are never stable and are therefore of low interest.

Theorem 8. *Any Filippov stationary point of system (2) located in a black wall is a SSP in the sense of [4].*

PROOF. Let $x^0 \in \mathcal{SD}(s, B_R)$, $s \in S$, be a Filippov stationary point. Without loss of generality we may assume that $x^0 \in \mathcal{SD}(1, B_R)$, and let $\mathcal{SD}(1, B_R)$ be a black wall.

Since F and G are affine functions with respect to Z_1, we have that $\mathcal{F}(x) = \mathcal{F}_1(x)$, where the sets $\mathcal{F}$,$\mathcal{F}_1$ are given in Definition 3, Definition 4. Due to the uniqueness of a Filippov solution in a black wall, there exists $Z_1^* \in (0, 1)$ such that for the Filippov stationary solution x^0 we have

$$0 = F_1(Z_1^*, B_R) - G_1(Z_1^*, B_R)\theta_1,$$
$$0 = F_R(Z_1^*, B_R) - G_R(Z_1^*, B_R)x_R^0.$$

Let

$$\frac{\partial F_1}{\partial Z_1} - \frac{\partial G_1}{\partial Z_1}\theta_1 \neq 0.$$

This inequality holds for a black wall. Then, by [4], there exists x^q (for sufficiently small q) such that

$$0 = F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1^q,$$
$$0 = F_R(Z_1, B_R) - G_R(Z_1, B_R)x_R^q$$

and $x^q \to x^0$ as $q \to 0$. We have the definition of a stationary solution in the sense of [4]. □

Below we compare the two classes of stationary solutions to (2): the stationary solutions in the sense of [4] and the Filippov stationary solutions in the narrow sense.

Theorem 9. *For the system (2) consider a Filippov stationary point x^*. Suppose, moreover, that x^* is a stationary point of (2) in the sense of [4]. Then x^* is in fact a Filippov stationary solution in the narrow sense.*

PROOF. We assume that x_i^* is a Filippov stationary point that is a limit of stationary points for small $q > 0$, $i = 1, ..., n$, i.e. there exists a sequence $x^q \to x^*$ as $q \to 0$, such that $F(Z^q) - G(Z^q)x^q = 0$. Here $Z^q = (Z_1^q, ..., Z_n^q)$, $Z_i^q = \Sigma(x_i^q, \theta_i, q)$. Due to $0 \leq Z_i^q \leq 1$ and the properties of a sigmoid function, we may assume without loss of generality (for example considering subsequences q_k if required) that $Z_i^{q_k} \to Z_i^* \in [0, 1]$ $(i = 1, ..., n)$ as $q_k \to 0$ (for any sequence $q_k \to 0$). Due to the continuity of F and G, we obtain $F(Z^*) - G(Z^*)x^* = 0$. Since $0 \leq Z_i^* \leq 1$, we have that x^* is indeed a Filippov solution in the sense that $0 \in \mathcal{F}_1(x^*)$, where $\mathcal{F}_1$ is defined by (9) (see Definition 4). □

The following examples illustrate the fact that not every Filippov stationary point in the narrow sense can be obtained by the method from [4].

Example 6. Consider the system

$$\begin{aligned} \dot{x}_1 &= 1 + Z_2 - \gamma_1 x_1, \\ \dot{x}_2 &= 2 - Z_1 Z_2 - \gamma_2 x_2. \end{aligned} \tag{35}$$

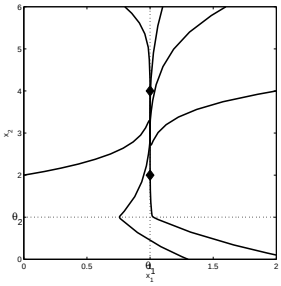

Figure 10. Some trajectories to (35) for the steep model with $q = 0.01$. Parameter values: $\gamma_1 = 2$, $\gamma_2 = 0.5$, $\theta_1 = \theta_2 = 1$. Diamonds mark the stationary points Φ^{01} and Φ^{11}.

The focal points $\Phi^{01} = (1, 4)$ and $\Phi^{11} = (1, 2)$ of the boxes $\mathcal{B}([01])$ and $\mathcal{B}([11])$ respectively are located in the singular domain $\mathcal{SD}(1, [1])$. At a point $x \in \mathcal{SD}(1, [1])$

$$\mathcal{F}_1(x) = \left\{ \begin{pmatrix} 0 \\ 2 - \mathbb{Z}_1 - 0.5x_2 \end{pmatrix}, \quad \mathbb{Z}_1 = [0, 1] \right\}.$$

Due to $0 \in \mathcal{F}_1(x)$ for $x = (1, 2)$ and $x = (1, 4)$, the points $\Phi^{01} = (1, 4)$ and $\Phi^{11} = (1, 2)$ are stationary points of (35) in the narrow sense. Since $\det(\partial f_1/\partial Z_1) = 0$ at Φ^{01} and Φ^{11} (f is the right-hand side of (35)), these stationary points cannot be obtained by method from [4] as the condition A) is not fulfilled.

Using Definition 5, it can be shown that a Filippov solution starting at the point x^0, $x_1^0 = 1$, $x_2^0 \geq 4$ converges along $\mathcal{SD}(1, [1])$ to $\Phi^{01} = (1, 4)$. Some Filippov solutions reach this point only for $t \to \infty$ and others reach it during a finite period of time. In the latter case after passing this point Filippov solutions may either change direction and return back to $\Phi^{01} = (1, 4)$ at any moment of time or continue motion towards $\Phi^{11} = (1, 2)$. "Switchings" of the direction of the motion may occur any time and we have infinitely many Filippov solutions. □

Example 7. Consider the system

$$\begin{aligned} \dot{x}_1 &= 1 + Z_1 + Z_2 - 2Z_1 Z_2 - \gamma_1 x_1, \\ \dot{x}_2 &= 1 + Z_1 + Z_2 - 2Z_1 Z_2 - \gamma_2 x_2. \end{aligned} \tag{36}$$

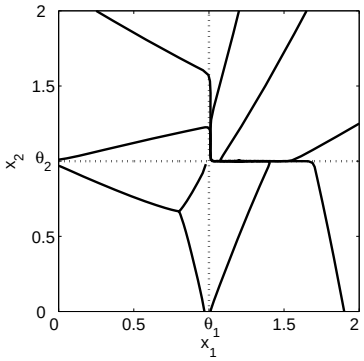

Figure 11. Some trajectories of (36) for the steep model with $q = 0.01$. Parameter values: $\gamma_1 = 1.25$, $\gamma_2 = 1.25$, $\theta_1 = \theta_2 = 1$.

This system has two black walls $\mathcal{SD}(1,[1])$ ($x_1 = \theta_1$, $x_2 > \theta_2$) and $\mathcal{SD}(2,[1])$ ($x_2 = \theta_2$, $x_1 > \theta_1$). The single point $x_1 = \theta_1$,$x_2 = \theta_2$ is the singular domain $\mathcal{SD}(1,2)$ of codimension 2. We want to find stationary points that are hidden in black walls or the intersection of the walls.

According to Section 5, Filippov solution in the black wall $\mathcal{SD}(1,[1])$ has the form

$$\begin{aligned} x_1 &= \theta_1 \\ x_2 &= 1 + (x_2^0 - 1)e^{-1.25(t-t_0)}. \end{aligned}$$

We have that $x_2(t) \to 1$ as $t \to \infty$. In the black wall $\mathcal{SD}(2,[1])$ the Filippov solution is given by

$$\begin{aligned} x_1 &= 1 + (x_1^0 - 1)e^{-1.25(t-t_0)} \\ x_2 &= \theta_2. \end{aligned}$$

and here $x_1(t) \to 1$ as $t \to \infty$.

Using the method based on the Filippov theory presented in Section 5, we can show that $x^0 = (\theta_1, \theta_2)$ is a Filippov stationary point of (36) in the narrow sense. To do this, we need to prove that $0 \in \mathcal{F}_1(x^0)$. As

$$\mathcal{F}(x) = \begin{pmatrix} 1 + \mathbb{Z}_1 + \mathbb{Z}_2 - 2\mathbb{Z}_1\mathbb{Z}_2 - \gamma_1 x_1 \\ 1 + \mathbb{Z}_1 + \mathbb{Z}_2 - 2\mathbb{Z}_1\mathbb{Z}_2 - \gamma_1 x_2 \end{pmatrix}, \quad \mathbb{Z} = [0,1]^2,$$

it is easy to check that $0 \in \mathcal{F}_1(x^0)$ for $x^0 = (\theta_1, \theta_2)$. Therefore $x^0 = (\theta_1, \theta_2)$ is a Filippov stationary point of (36) in the narrow sense.

On the other hand this Filippov stationary point cannot be obtained by the method from [4]. This is due to the equality $\det(\partial f_S / \partial Z_S) = 0$. Thus, the condition A) is not fulfilled. Here f is the right-hand side of (36). $\square$

The following system represents another interesting case when uniform convergence for solutions of steep sigmoid systems cannot be shown by the method from [4] but still follows from the method of Filippov.

Example 8. Consider the system

$$\begin{aligned} \dot{x}_1 &= 3 - 2Z_2 - Z_1 Z_2 - x_1, \\ \dot{x}_2 &= 2Z_1 - x_2. \end{aligned} \tag{37}$$

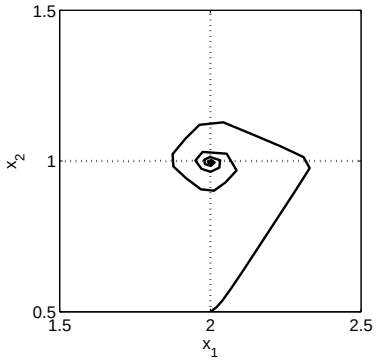

Figure 12. Some trajectories of (37) for the steep model with $q = 0.01$. Parameter values: $\theta_1 = 2$, $\theta_2 = 1$.

The system was presented by Edwards [12]. Solutions cycle through boxes and transparent walls approaching the SSP $(2, 1)$. Solutions of (37) with step switching functions, i.e. Filippov solutions, reach this point after an infinite number of cycles, but in finite time, let say $[0, T]$. The Main Result from [4] on uniform convergence of solutions of steep sigmoid systems does not hold here for a finite time interval $[0, T_1]$, where $T_1 \geq T$. However, uniform convergence on any finite interval for solutions x^q of steep sigmoid systems can still be shown using the Filippov theory (see Corollary 2). Note that the Filippov solution in this 2-dimensional example is unique. □

The example above can be generalized to the n-dimensional case for a point P belonging to a switching domain $\mathcal{SD}(S, B_R)$ of codimension $|S| \geq 2$.

Proposition 1. *Consider a point $P \in \mathcal{SD}(S, B_R)$, where $|S| \geq 2$. Suppose that in a vicinity of P Filippov solutions of (2) pass infinitely often through switching hyperplanes $x_K = \theta_K$, $K \subset S$, $2 \leq |K| \leq |S|$, when converging to P in finite time $[0, T]$. Then, as $q \to 0$, the trajectory x^q of the system (2) with steep sigmoid converges uniformly on any finite interval $a \leq t \leq b$ to a certain Filippov solution of (2).*

Proof. Indeed, it follows from Corollary 2 that solutions x^q of steep sigmoid systems convergence to a certain Filippov solution of (2) uniformly on any finite interval. □

Remark 8. Note that the results of Proposition 1 cannot be obtained using the method from [4]. The Main Result there does not hold when a trajectory passes through infinite sequence of regular and switching domains. □

Conclusions and discussions

The main results of the paper provide a mathematical justification for the similarities between the "real-world" model based on smooth interactions (sigmoids) and the idealized model based on step-like interactions. Putting emphasis on the Filippov approach and focusing on singular domains mainly, we have introduced three different ways to define Filippov solutions, unlike [8] where only one of the definitions is used. We have studied the global existence and some other basic properties of the Filippov solutions as well as their uniqueness and non-uniqueness. We have proved that two of the definitions (where the right-hand sides are convex though constructed in different ways) are in fact equivalent in the case of the gene regulatory networks, while the third provides a different inclusion with a non-convex right-hand side. We have shown that the latter definition, which stays for Filippov solutions in the narrow sense, covers stationary solutions in the sense of [4], while the first two may produce stationary solutions of quite a different nature.

We have proved that the Filippov stationary points satisfying $0 \in \mathcal{F}(x^*) \backslash \mathcal{F}_1(x^*)$ (i.e. stationary points not in the narrow sense) cannot be the limits of proper stationary points of the approximating smooth systems, where the step functions are replaced with sufficiently steep sigmoids (see [4, 5, 6] for details). Numerical analysis in this 2-dimensional case shows that trajectories of the smooth systems just pass through these points before converging to another stationary point. Therefore, an interpretation of such points is not obvious. Filippov stationary points which are not stationary points in the sense of [4] but are the limits of more complicated dynamics may still exist. For instance, the approximating smooth systems may possess invariant measures, the support of which shrinks into a singleton (being a Filippov stationary point, but not a stationary point in the sense of [4]), as the steepness parameters approach zero. Neither the existence of such invariant measures is shown, nor their absence proved yet.

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Appendix A. Behavior of systems in regular domains

The behavior of the systems described by (2) can be easily characterized in the regular domains. Within each box $\mathcal{B}$ the rates $F_j(Z)$ and $G_j(Z)$ reduce to the constants $\beta_j(\mathcal{B})$ and $\gamma_j(\mathcal{B})$, respectively. These constants may be different in different boxes. Thus, x_j is governed by the locally valid linear differential equation

$$\dot{x}_j = \beta_j - \gamma_j x_j, \qquad j = 1, \ldots, n. \tag{38}$$

In a single box $\mathcal{B}$ the solution $x(t)$ of (38) satisfying $x(t_0) = x^0$ is

$$x_j(t) = \Phi_j + (x_j^0 - \Phi_j) \exp\left[-\gamma_j(t - t_0)\right],$$

where $\Phi_j = \beta_j/\gamma_j$. When $t \to \infty$, $x_j(t) \to \Phi_j$. We shall call $\Phi(\mathcal{B}) = [\Phi_1, \ldots, \Phi_n]$ the *focal point* [13] of $\mathcal{B}$ because all trajectories in $\mathcal{B}$ head towards this point attractor until one of the coordinates x_j assumes the threshold value θ_j. If $\Phi(\mathcal{B}) \in \mathcal{B}$, then $\Phi(\mathcal{B})$ becomes a stable point of the system and an attractor for all trajectories in $\mathcal{B}$. It is called a *regular stationary point*, abbreviated RSP [14]. In [15] focal points and regular stationary point are called *virtual* and *admissible equilibria* respectively. If $\Phi(\mathcal{B}) \notin \mathcal{B}$, any trajectory passing through $\mathcal{B}$ will eventually hit one of the singular domains.

Paper II

Stability of stationary solutions of piecewise affine differential equations describing gene regulatory networks[☆]

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Abstract

We study stability properties of a class of piecewise affine systems of ordinary differential equations arising in the modeling of gene regulatory networks. Our method goes back to the concept of a Filippov stationary solution (in the narrow sense) to a differential inclusion corresponding to the system in question. The main result of the paper justifies a reduction principle in the stability analysis enabling to omit the variables that are not singular, i.e. that stay away from the discontinuity set of the system. We suggest also "the first approximation method" to study asymptotic stability of stationary solutions based on calculating the principal part of the system, which is 0-homogeneous rather than linear. This leads to an efficient algorithm of how to check asymptotic stability without calculating the eigenvalues of the system's Jacobian. In Appendix we discuss and compare two other concepts of stationary solutions to the system in question.

Keywords: gene regulatory network, differential inclusion, Filippov solution, singular stationary point, stability analysis
MSC: 34D20, 34A60, 92D10

1. Introduction

The regulation of gene expression occurs through networks of regulatory interactions between DNA, RNA, proteins and small molecules, so-called *gene regulatory networks* (GRNs). There are different ways of modelling gene regulatory networks. A class of piecewise affine (PWA) systems of differential equations, originally proposed by Glass and Kauffman [3], is well suited to qualitative analysis and has been widely used in modelling gene regulatory networks. The variables in these models stand for concentrations of proteins encoded by genes, while the differential equations describe the regulatory interactions in the network by means of step functions. The use of step functions is motivated by the presence of thresholds causing switch-like interactions between genes. The dynamics of the obtained system can be easily described between such thresholds, but the vector field for the PWA systems of differential equations is undefined when one of the variables assumes a threshold value.

[☆] This document is a collaborative effort.

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In the present work we focus on stability analysis of PWA systems. Equilibria of the PWA systems that lie in *regular domains*, i.e. outside the discontinuity set of the right-hand side (called in the sequel *singular domains*), are always asymptotically stable (see e. g. [8]). A method of studying the stability of equilibria in singular domains, i. e. of (*singular stationary point* - SSP) was suggested by E. Plahte et al. in [6, 8, 9]. The crucial step in the approach consisted in replacing the step functions with continuous *response functions*, the so-called *logoids*, which gave the opportunity to linearize the system around the perturbed stationary point, study stability properties for the perturbed system and then observe that going back to the step function does not influence the stability properties of the perturbed Jacobians. Strictly speaking, this method studies stability properties of stationary points of the perturbed systems, rather than the stability of SSP in the original PWA model. In particular, this may, in principle, cause the situation when the basins of attractions of the perturbed steady states would shrink into a singleton in the limit, so that the given SSP in fact may become unstable.

On the other hand, the recent works [4, 1] exploit another approach to define and analyze the solutions inside the singular domains, namely the one based on the Filippov theory [2]. According to this approach the given PWA system is replaced with a PWA differential inclusion. In order to analyze the dynamics of the system the phase space is divided into pieces (regular domains) bounded by the threshold hyperplanes and their intersections (singular domains). For any singular domain a multivalued function can be defined giving a differential inclusion which enables us to define solutions and calculate all possible equilibria for the original PWA system, including all SSP.

The stability analysis for SSP, which is based on the Filippov theory, was first considered in the paper [1]. In this pioneer work the conditions that guarantee stability of the so-called *focal sets* (i.e. set-valued equilibria in singular domains) were found and justified. However, this method offers only limited opportunities in the case when one wants to verify whether a *given* SSP is stable or not.

With the present paper we will try to develop the stability analysis of PWA systems in the spirit of the papers [6, 8, 9], i.e. we wish to analyze stability properties of a *given* SSP. On the other hand, our method is based on the Filippov theory, so that we will study stability properties of SSP itself, and not of its approximations as in [6, 8, 9]. Thus, our approach cannot be based on the Jacobians. Instead, we use the so-called 0-*homogeneous* differential inclusions described in [2]. We suggest an efficient algorithm to determine stability of a given SSP based on this approach. This algorithm replaces the conventional analysis of eigenvalues, which in many situations may cause difficult numerical problems.

Compared to the Filippov-like approach from [1], one of the main advantages of the stability analysis suggested by E. Plahte et al. is the justification of the so-called *reduction principle*. Roughly speaking it means that stability properties of an SSP are governed by the reduced Jacobian which is just evaluated for the singular part of the system, thus living apart all the regular variables (i.e. those which are not close to their respective thresholds). This can only be justified if the response functions in the model are of the *logoid* shape. A logoid $Z_i = Z_i(x_i, \theta_i)$ assumes the values 0 and 1 as long as x_i is outside a δ-neighborhood of the threshold θ_i. When passing through this neighborhood, the logoid rapidly increases from 0 to 1 thus following the step function. When δ tends to zero, the

logoid approaches this step function.

In our paper we justify this important principle within the PWA model, i.e. without referring to particular smooth perturbations.

The only case which is not covered by our method, but which is possible to treat with the help of Plahte's logoid approach, is the situation of the *bouncing ball* when the trajectories cross singular domains infinitely many times before they reach the equilibrium. We conjectured that in the PWA systems describing GRN such a behavior always imply asymptotic stability of the (only) limit point, but we did not manage to prove this conjecture.

2. Preliminaries

Consider a system of n genes with the gene product concentration x_j. The gene products regulate their own production by Boolean-like regulatory functions. Mestl et al. [6] studied the following model of system of differential equations with switch-like nonlinearities

$$\dot{x}_j = f_j(x, Z) = F_j(Z) - G_j(Z)x_j, \qquad j = 1, ..., n, \tag{1}$$

where $x \in \mathbb{X}^n = \mathbb{R}^n_+$, Z is an n-dimensional vector of switching functions $Z_i : \mathbb{R}_+ \to \{0, 1\}$, $i = 1, ..., n$, (i. e. $Z_i = Z_i(x_i)$); the production rate function $F_j \geq 0$ and the relative degradation rate $G_j > 0$ are multilinear polynomials, i.e. affine functions with respect to each Z_i.

Clearly, (1) is a system of differential equations with discontinuous right-hand sides. Our work is aimed to apply the Filippov theory of differential inclusions (see [2]) to study stability of the stationary points located in the discontinuity set of the system (1).

According to the assumptions on the functions F and G we have that

$$0 \leq F_j(Z) \leq \overline{F}_j, \qquad 0 < \sigma_j \leq G_j(Z) \leq \overline{G}_j, \qquad Z_i \in [0, 1],\ i, j = 1, ..., n, \tag{2}$$

where $\overline{F}_j$, $\overline{G}_j$, σ_j are constants. Therefore the dynamical properties of (1) can be analyzed within the n-dimensional phase space box $\Omega = \Omega_1 \times \ldots \times \Omega_n$, where every Ω_j, $1 \leq j \leq n$, is defined as

$$\Omega_j = \{x_j \in \mathbb{R}_+ \mid 0 \leq x_j \leq \max_j\}. \tag{3}$$

$\max_j$ is a parameter denoting a maximum concentration for the protein.

The threshold hyperplanes $x_j = \theta_j$ divide Ω into 2^n open, rectangular domains called *boxes* or *regular domains*. Thus, $\mathcal{B}$ is a box if there is no j such that $x_j = \theta_i$, i.e none of the variables assumes the threshold value. A segment of a hyperplane of codimension k separating two adjacent boxes is called a *singular* domain (or a *wall* in the case of codimension 1). $\mathcal{B}$ is a singular domain if for at least one j, $1 \leq j \leq n$, it holds that $x_j = \theta_j$.

A more formalized definition of boxes and singular domains was suggested in [7]. Let $N = \{1, \ldots, n\}$. Let R be an ordered subset of N, and S the ordered complement $N \setminus R$, such that $R \cup S = N$ and $R \cap S = \emptyset$. The symbols R and S stand for the sets of *regular* and *singular* coordinates, respectively. For example y_S stands for an $|S|$-dimensional vector ($|S|$ is the number of elements in S) consisting of the singular coordinates of an n-dimensional vector y. A similar description applies to y_R.

Definition 1. Let a Boolean vector $B = (B_1, \ldots, B_n)$ be given. To B is associated the box $\mathcal{B}(B) = \{x \in \mathbb{X}^n \mid Z(x) = B\}$.

B_R is a Boolean vector of length $|R|$ ($|R|$ is the number of elements in R) consisting of regular coordinates of B.

Definition 2. Let $S \neq \emptyset$ and B_R be given. If $S \subset N$, then a singular domain is given by $\mathcal{SD}(S, B_R) = \{x \in \mathbb{X}^n \mid x_S = \theta_S,\ Z_R(x) = B_R\}$. The order (codimension) of $\mathcal{SD}(S, B_R)$ is the number $\sigma = |S|$ of elements in S.

For example, in 4-dimensional space $\mathcal{SD}(\{1,3\},[01]) = \{x \in \mathbb{X}^4 \mid x_1 = \theta_1,\, x_3 = \theta_3,\, x_2 < \theta_2\,,\, x_4 > \theta_4\,\}$, $S = \{1,3\}$, $R = \{2,4\}$, $B_R = [01]$ ($Z_2(x_2) = 0$, $Z_4(x_4) = 1$)

Singular domains of codimension 1, sometimes called walls, can be of three kinds:

- If trajectories travel through the wall, then the wall is transparent.
- If trajectories hit the wall from either side, then the wall is black.
- It trajectories depart from the wall on both sides, then the wall is white.

Point attractors in black walls or in an intersection of threshold hyperplanes, are called *singular stationary points*, abbreviated SSP [10].

Definition 3. [[2], Chapter 2, §4, 2, definition a)] Let $\mathcal{SD}(S, B_R)$ be a singular domain. For any Boolean vector B_S corresponding to one of the regular domains adjacent to $\mathcal{SD}(S, B_R)$ and any $x \in \mathcal{SD}(S, B_R)$ put $P(B_S, x) = (p_1, ..., p_n)$,

$$p_i = F_i(B_S, B_R) - G_i(B_S, B_R)x_i, \qquad i = 1, ..., n. \tag{4}$$

For each $x \in \mathcal{SD}(S, B_R)$ we put

$$\mathcal{F}(x) = co\{P(B_S, x) \mid B_S \in \{0,1\}^S\},$$

i.e. $P(B_S, x)$ stands for the values of the function $F(Z) - G(Z)x$, where $Z_R \equiv B_R$ is fixed and $Z_S \equiv B_S$ runs through the set $\{0,1\}^S$. The number of such points $P(B_S, x)$ is $2^{|S|}$.

A Filippov solution of the equation (1) is a solution of the inclusion

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

with $\mathcal{F}(x)$ so constructed.

At the continuity points of the function f the set $\mathcal{F}(x)$ consists of one point $f(x)$, and the Filippov solution satisfies equation (1) in the usual sense. Therefore inside regular domains Filippov solutions coincide with solutions to ordinary differential equations (ODE).

If the point $x \in \mathcal{SD}(S, B_R)$ lies on the boundaries of cross-section of two or several regular domains (boxes) $\mathcal{B}(B_S, B_R)$ (the number of such boxes $k = 2^{|S|}$), the set $\mathcal{F}(x)$ is

a segment, a convex polygon, or a polyhedron with vertices $P^j(B_S, x)$, $j = 1, ..., k$, whose coordinates $p_i^j(B_S, x)$,$i = 1, ..., n$, are given by (4).

All the points $P^j(x)$, $j = 1, \ldots, k$, are contained in $\mathcal{F}(x)$, but it is not necessary that all of them be vertices. In other words $\mathcal{F}(x) = co\{P^1, \ldots, P^k\}$.

Such a construction of the set $\mathcal{F}(x)$ is used in [4]. Consider an alternative definition of an inclusion describing systems with discontinuous right-hand sides in the Filippov theory.

Definition 4. [[2], Chapter 2, §4, 2, definition c)] Consider the system (1). For each discontinuity point $x \in \mathcal{SD}(S, B_R)$ let $\mathbb{Z}_j(x) \equiv [0, 1]$, $j \in S$, and $\mathbb{Z}_S(x) \equiv [0, 1]^{|S|} = [0, 1] \times [0, 1] \times ... \times [0, 1]$. At the points where $Z_j(x)$ is continuous the set $\mathbb{Z}_j(x)$,$j \in S$, consists only of one point $Z_j(x) \in \{0, 1\}$. Let

$$\mathcal{F}_1(x) = \{F(\mathbb{Z}_S, B_R) - G(\mathbb{Z}_S, B_R)x\} \equiv f(x, \mathbb{Z}_S, B_R) \tag{6}$$

be the set of all values of the function $f(x, Z_S, Z_R = B_R)$, where x and B_R are fixed and Z_j,$j \in S$, independently run over the sets $\mathbb{Z}_j$,$j \in S$, respectively.

The alternative Filippov solutions of the differential equation (1) can be then defined as solutions of the differential inclusion

$$\dot{x} \in \mathcal{F}_2(x),$$

where $\mathcal{F}_2(x) = \mathrm{co}\mathcal{F}_1(x)$.

Normally, Definitions 3 and 4 yield different solution sets. However, it can be shown (unpublished) that for the PWA system (1) one always has the equality $\mathcal{F}(x) = \mathcal{F}_2(x)$, so that the two above definitions of a Filippov solution in fact are equivalent in our case. That is why we will in the sequel use the notation $\mathcal{F}(x)$ for the multivalued function corresponding to the right-hand side of the system (1).

There exists one more definition of a Filippov solution, which also will be used in the sequel.

Definition 5. [[2], Chapter 2, §4, 2, definition b)] Filippov solutions of the differential equation (1) can be defined as solutions of the differential inclusion

$$\dot{x} \in \mathcal{F}_1(x),$$

where $\mathcal{F}_1(x)$ is given by (6). In what follows, such solutions will be called *Filippov solutions in the narrow sense.*

Let us recall some basic notation. For two compact nonempty subsets A, B of a metric space put $\beta(A, B) = \sup_{a \in A} \rho(a, B)$. The function $\alpha(A, B) = \max\{\beta(A, B), \beta(B, A)\}$ is a metric and is called the Hausdorff metric. A function $\mathcal{F}(x)$ is called *β-continuous* (or Hausdorff upper semicontinuous) at x if $\beta(\mathcal{F}(x'), \mathcal{F}(x)) \to 0$ as $x' \to x$. A function $\mathcal{F}(x)$ is called β-continuous (or Hausdorff upper semicontinuous) on a domain Ω if it is β-continuous (or Hausdorff upper semicontinuous) at each point of this domain.

Following [2], we say that a multivalued function $\mathcal{G}$ satisfies the *basic conditions* in Ω if for any $x \in \Omega$ the set $\mathcal{G}$ is nonempty, bounded, closed, convex and the function $\mathcal{G}$ is β-continuous. It could be shown that for the systems (1) $\mathcal{F}(x) = \mathcal{F}_2(x)$ and each of these functions satisfies basic conditions.

Definition 6. A point x^0 is called a Filippov stationary point of (1) if $0 \in \mathcal{F}(x^0)$, where $\mathcal{F}(x)$ is from Definition 3.

Definition 7. If $0 \in \mathcal{F}_1(x^0)$, where $\mathcal{F}_1(x)$ is given by (6), then we will call x^0 a Filippov stationary point in the narrow sense.

3. The Filippov theory and stability in the first approximation.

Assume that the step functions Z_i in (1) are all replaced with sequences of certain smooth response functions (for instance with the logoids), which converge to the step function. Assume further that any smooth system in the sequence has a stationary point, and the sequence (or a subsequence) of these stationary points converge to some point P^0. In Appendix it is shown that P^0 will be a Filippov stationary solutions to (1) in the narrow sense. This motivates us to disregard other stationary solutions, as those have no biological interpretation. That is why in this paper we only consider the Filippov stationary solutions in the narrow sense, i.e. those satisfying Definition 7.

The main result of this section justifies the reduction principle which says that stability of a Filippov stationary solution in the narrow sense is only determined by the singular variables of the system (1). Moreover, we will show that the singular part of the inclusion can be replaced with its "first approximation" in the sense of homogeneous inclusions of order 0 (or piecewise constant inclusions, in other words). These two results considerably simplify the stability analysis of stationary solutions in the sense of Filippov.

Below we consider an arbitrary Filippov stationary point in the narrow sense, which will be denoted by $P^0 = (\theta_S, x_R^0)$ and which by this will be assumed to be located in a singular domain $\mathcal{SD}(S, B_R)$.

After separating regular and singular variables the system (1) can be rewritten as

$$\begin{aligned} \dot{x}_S &= F_S(Z_S, Z_R) - G_S(Z_S, Z_R)x_S, \\ \dot{x}_R &= F_R(Z_S, Z_R) - G_R(Z_S, Z_R)x_R. \end{aligned} \tag{7}$$

In the singular domain $\mathcal{SD}(S, B_R)$ the latter system can be specified as follows:

$$\begin{aligned} \dot{x}_S &= F_S(h_S(x_S - \theta_S), B_R) - G_S(h_S(x_S - \theta_S), B_R)x_S, \\ \dot{x}_R &= F_R(h_S(x_S - \theta_S), B_R) - G_R(h_S(x_S - \theta_S), B_R)x_R, \end{aligned} \tag{8}$$

where h_S is a vector of the Heaviside step functions, B_R is a Boolean vector.

Let us introduce a new variable $y \in \mathbb{R}^{|S|}$ by setting

$$x_S - \theta_S = y_S,$$

which translates the singular coordinates of the SSP P^0 to the origin

$$\begin{aligned} \dot{y}_S &= F_S(h_S(y_S), B_R) - G_S(h_S(y_S), B_R)(y_S + \theta_S), \\ \dot{x}_R &= F_R(h_S(y_S), B_R) - G_R(h_S(y_S), B_R)x_R. \end{aligned} \tag{9}$$

For the discontinuous system (9) we denote $u = (y_S, x_R)$ and consider the corresponding differential inclusion

$$\dot{u} \in \mathcal{F}(u) \tag{10}$$

with the right-hand side $\mathcal{F}$ obtained via Definition 3. Let $\mathcal{F}_S$ and $\mathcal{F}_R$ be the projections of the set $\mathcal{F}$ onto the subspace of the singular and regular coordinates, respectively. Then every solution $u = (y_S, x_R)$ of the inclusion (10) will satisfy the system

$$\dot{y}_S \in \mathcal{F}_S(y_S) \tag{11}$$

$$\dot{x}_R \in \mathcal{F}_R(y_S, x_R). \tag{12}$$

The converse does not hold true, in general. For the solutions $(y_S(t), x_R(t)) = (0, x_R(t))$ lying in $\mathcal{SD}(S, B_R)$ the functions $x_R(t)$ represent solutions of the inclusion

$$\dot{x}_R \in \mathcal{F}^0(x_R), \qquad \mathcal{F}^0(x_R) = \mathcal{F}(y_S, x_R) \cap \mathcal{SD}(S, B_R) \qquad \text{where } (y_S, x_R) = (0, x_R) \tag{13}$$

It will be shown later (Section 3.2) that the stability of the singular part of the systems (9) guarantees the stability of the whole system. Thus, the focus of our study will be put on the singular variables, so that we start with considering the reduced system

$$\dot{y}_S = F_S(h_S(y_S), B_R) - G_S(h_S(y_S), B_R)(y_S + \theta_S). \tag{14}$$

To investigate stability of the zero solution of the system (14) we will replace this system, or more precisely the corresponding differential inclusion, with its "first approximation" around the stationary point, which in this particular case will be a differential inclusion with a homogeneous (of order 0) right-hand side. The latter should capture the local stability properties of the former, exactly in the same manner as the Jacobian captures the local stability properties of a smooth system.

3.1. 0-homogeneous inclusions and their stability

Definition 8. A multivalued function $\mathcal{H}(z)$ is called homogeneous of order α if $\mathcal{H}(cz) \equiv c^\alpha \mathcal{H}(z)$ for all $c > 0$.

The corresponding differential inclusion

$$\dot{z} \in \mathcal{H}(z), \qquad \mathcal{H}(cz) \equiv c^\alpha \mathcal{H}(z), \quad c > 0 \tag{15}$$

will be called homogeneous (of order α) as well.

In what follows we consider homogeneous functions of order 0. We call such functions 0-*homogeneous*. For instance, any step function with discontinuity at the origin is 0-homogeneous.

Let us introduce a discontinuous system which stands for the "first approximation" to the system (14) around the Filippov stationary point $y_S = 0$. This system is given by

$$\dot{y}_S = F_S(h_S(y_S), B_R) - G_S(h_S(y_S), B_R)\theta_S, \tag{16}$$

or by the corresponding differential inclusion

$$\dot{y}_S \in \mathcal{H}_S(y_S). \tag{17}$$

with the right-hand side $\mathcal{H}_S$ obtained via Definition 3 (or Definition 4).

Clearly, the inclusion (17) is 0-homogeneous.

Below we will show that the stability properties of the zero solution of the system (14) can be deduced from the corresponding stability properties of its 0-homogeneous counterpart. That is why we will now focus on a stability criterium for the homogeneous inclusions.

The following theorem reformulates Theorem 6, [2], Chapter 3, 15 in terms of the systems we are interested in and provides a verifiable stability condition for 0-homogeneous inclusions with piecewise constant right-hand sides. It could be applied to differential inclusions in the sense of Definition 3 or Definition 4.

Given $\mathcal{SD}(S, B_R)$, consider further the space $\mathbb{R}^l$ ($l = |S| \leq n$) of singular coordinates y_S. Let $\mathcal{SD}_p^m$ $m = 1, ..., l-1$; $p = 1, ..., p_m$, denote m-dimensional singular domains in $\mathbb{R}^l$ that separate the space $\mathbb{R}^l$ into regular boxes $\mathcal{B}_p^l$ $p = 1, ..., 2^l$, with a vertex $y = 0$.

Theorem 1. *Consider the multi-valued 0-homogeneous function $\mathcal{H}_S(y_S)$ from (17), which depends on y_S in none of the regular boxes $\mathcal{B}_p^l$ and on none of the singular domains $\mathcal{SD}_p^m$, i.e., $\mathcal{H}(y_S) = H_p^m$ for $y \in \mathcal{SD}_p^m$, $m = 1, ..., l-1$, $p = 1, ..., p_m$, and $\mathcal{H}(y_S) = H_p^l$ for $y \in \mathcal{B}_p^l$, $p = 1, ..., 2^l$. Let the solutions of the inclusion $\dot{y}_S \in \mathcal{H}_S(y_S)$ be unable to pass from one singular domain $\mathcal{SD}_p^m$ or regular box $\mathcal{B}_p^l$ into another singular domain or regular box infinitely many times. The function $y_S(t) \equiv 0$ is an asymptotically stable solution if and only if for each $\mathcal{SD}_p^m$ (respectively $\mathcal{B}_p^l$,) none of the vectors from the set H_p^m (respectively H_p^l) lie in $\mathcal{SD}_p^m$ (respectively $\mathcal{B}_p^l$) or on its boundary $\partial\mathcal{SD}_p^m$ (respectively $\partial\mathcal{B}_p^l$).*

Remark 1. Note that according to the proof presented in [2], Chapter 3, §15 2, the solutions in the above theorem actually reach the zero point after a finite time. This observation will be crucial in the next subsection.

Definition 9. Let a multi-valued function $\mathcal{H}(z)$ be 0-homogeneous. We say $d_0(\mathcal{F}, \mathcal{H}) \leq \delta$ for $|z| \leq \rho_0$ if for each $\rho \in (0, \rho_0]$ the graph of the function $\mathcal{F}(\rho\omega)$ considered as a function of ω,$|\omega| = 1$, is contained in the δ-neighborhood of the graph of the function $\mathcal{H}(\omega)$ and $\mathcal{F}(0) \subset \mathcal{H}(0)^\delta$.

The next theorem essentially reformulates a result from [2] (Theorem 7, Chapter 3, §15 3) in terms that are convenient for our purposes.

Theorem 2. *If the inclusion (17) has an asymptotically stable zero solution, then so does the inclusion (11).*

Proof. By [2] (Theorem 7, Chapter 3, §15 3), we need to show that there exists $\delta(\rho) \to 0$ ($\rho \to 0$) such that for every fixed $\rho \leq \rho_0$ we have $d_0(\mathcal{F}_S(y_S), \mathcal{H}_S(y_S)) \leq \delta(\rho)$ for $|y_S| \leq \rho$. Here the functions $\mathcal{H}_S(y_S)$, $\mathcal{F}_S(y_S)$ are from (17),(11) respectively. First, let $\tilde{\mathcal{H}}_S(y_S)$, $\tilde{\mathcal{F}}_S(y_S)$ be the functions defined by (16),(14) with $h_S(y_S) = [0,1]^{|S|} \equiv \{h_S \mid 0 \leq h_s \leq 1,\ \forall s \in S\}$, i.e. $\mathcal{H}_S(y_S) = \overline{co}\tilde{\mathcal{H}}_S(y_S)$, $\mathcal{F}_S(y_S) = \overline{co}\tilde{\mathcal{F}}_S(y_S)$.

Following Definition 9, we fix ρ_0 and consider for each $\rho \in (0, \rho_0]$ the Euclidean distance $\rho_{euc}(u_S, \tilde{\mathcal{H}}(\omega_S))$, where $u_S \in \tilde{\mathcal{F}}_S(\rho\omega_S)$, $|\omega_S| = 1$. We assume first that $\rho\omega_S$ is a discontinuity point of (14). Let $u_S \in \tilde{\mathcal{F}}_S(\rho\omega_S)$ correspond to some $h^u_S \in [0,1]^{|S|}$, i.e.

$$u_S = F_S(h^u_S(\rho\omega_S), B_R) - G_S(h^u_S(\rho\omega_S), B_R)(\rho\omega_S + \theta_S) = \tilde{F}^u_S - \tilde{G}^u_S(\rho\omega_S + \theta_S),$$

where $\tilde{F}^u_S$, $\tilde{G}^u_S$ are constants. Then the set $\tilde{\mathcal{H}}_S(\omega_S)$ contains the point $\tilde{F}^u_S - \tilde{G}^u_S\theta_S$. Therefore $\rho_{euc}(u_S, \tilde{\mathcal{H}}(\omega_S)) \leq |-G_S\rho\omega_S| \leq \bar{G}\rho|\omega_S| = \bar{G}\rho$, where $\bar{G} = \max\limits_j \bar{G}_j$. Since $u_S \in \tilde{\mathcal{F}}_S(\rho\omega_S)$ is arbitrary, $\tilde{\mathcal{F}}_S(\rho\omega_S) \subset (\tilde{\mathcal{H}}_S(\omega_S))^{\bar{G}\rho}$. Due to the properties of a convex set, $\mathcal{F}_S = \overline{co}\tilde{\mathcal{F}}_S \subset \overline{co}((\tilde{\mathcal{H}}_S)^{\bar{G}\rho}) = (\mathcal{H}_S)^{\bar{G}\rho}$. The validity of this embedding for a continuity point $\rho\omega_S$ is straightforward. Thus the graph of the function $\mathcal{F}(\rho\omega)$ considered as a function of ω,$|\omega| = 1$, is contained in the δ-neighborhood of the graph of the function $\mathcal{H}(\omega)$.

Since $\mathcal{F}_S(0) \equiv \mathcal{H}_S(0)$, we put $\delta(\rho) = \bar{G}\rho \to 0$ ($\rho \to 0$) and we have that $d_0(\mathcal{F}_S(y_S), \mathcal{H}_S(y_S)) \leq \delta(\rho)$ for $|y_S| \leq \rho$. Thus, by [2] (Theorem 7, Chapter 3, §15 3), the statement of the theorem holds true. □

3.2. The reduction principle in stability analysis of Filippov stationary solutions

In this subsection we prove that stability of the singular component of a Filippov stationary solution in the narrow sense ensures the stability of the other, i.e. regular component. This result justifies the reduction principle for the discontinuous systems (9). This principle (in other terms) appeared in the papers [6, 8, 9] as a main simplification tool in the stability analysis of gene regulatory networks.

We start with the following "first approximation" system in a small neighborhood of the singular domain $\mathcal{SD}(S, B_R)$

$$\begin{aligned} \dot{y}_S &= F_S(h_S(y_S), B_R) - G_S(h_S(y_S), B_R)\theta_S \equiv f_S(0, h_S(y_S)) = \hat{f}_S(h_S(y_S)) \\ \dot{x}_R &= F_R(h_S(y_S), B_R) - G_R(h_S(y_S), B_R)x_R \equiv f_R(x_R, h_S(y_S)). \end{aligned} \tag{18}$$

Our first objective is to justify the reduction principle for the system (18).

We put two requirements on the system in question, which are formulated in terms of the singular part of the system (inclusion), i. e. for the differential inclusion

$$\dot{y}_S \in \mathrm{co}\hat{f}_S(\mathbb{Z}_S) \tag{19}$$

with the right-hand side obtained via Definition 3

Assumption 1. $0 \in co\hat{f}_S(\mathbb{Z}_S)$ *if and only if* $0 \in \hat{f}_S(\mathbb{Z}_S)$ *and the latter inclusion has finitely many solutions.*

This ensures that the zero solution can only be Filippov stationary solution in the narrow sense (as we do not consider other types of stationary solutions - see the discussion at the beginning of Section 3).

Assumption 2. *The inclusion (19) satisfies the assumptions of Theorem 1.*

This implies that the zero solution $y_S^0 = 0$ of the reduced system is asymptotically stable.

For the system (18) we consider the corresponding differential inclusion obtained by Definition 3

$$\begin{pmatrix} \dot{y}_S \\ \dot{x}_R \end{pmatrix} \in \mathrm{co} \begin{pmatrix} \hat{f}_S(\mathbb{Z}_S) \\ f_R(x_R, \mathbb{Z}_S) \end{pmatrix} \tag{20}$$

The following theorem provides the reduction principle for the discontinuous system (18) and the corresponding differential inclusion (20).

Theorem 3. *Assume that (y_S^0, x_R^0), where $y_S^0 = 0$ is a Filippov stationary solution in the narrow sense of the inclusion (20). If Assumptions 1 and 2 are fulfilled, then (y_S^0, x_R^0) is asymptotically stable.*

Proof. By Assumption 2, $y_S^0(t) = 0$ is an asymptotically stable solution of (19). According to Remark 1 any solution of (19) become zero after a finite time T, i. e. $y_S(t) = 0 = y_S^0(t)$ for all $t \geq T$. Let us fix any such a solution. The inclusion (20) becomes then

$$\begin{pmatrix} 0 \\ \dot{x}_R \end{pmatrix} \in \mathrm{co} \begin{pmatrix} \hat{f}_S(\mathbb{Z}_S) \\ f_R(x_R, \mathbb{Z}_S) \end{pmatrix} \quad \text{for } t > T, \tag{21}$$

or in other words, $0 = \sum_{l \in L(t)} \mu_l(t) \hat{f}_S(Z_S^l(t))$ and $\dot{x}_R(t) = \sum_{l \in L(t)} \mu_l(t) f_R(x_R, \mathbb{Z}_S^l(t))$ where for any $t > T$ the set of natural numbers $L(t)$ is finite, $\mu_l(t) \geq 0$, $\sum_{l \in L(t)} \mu_l(t) = 1$, $0 \leq Z_S^l(t) \leq 1$.

By Assumption 1 the inclusions $0 \in \mathrm{co}\hat{f}_S(\mathbb{Z}_S)$ and $0 \in \hat{f}_S(\mathbb{Z}_S)$ are equivalent. In terms of $\mu_l(t)$ and $Z_S^l(t)$ this means that there exist a finite number of values $Z_S^{(k)} \in [0, 1]$, $k = 0, 1, ..., N$, and a finite partition $I^{(k)}$, $k = 0, 1, ..., N$, of the interval $[T, \infty)$ such that (after a renumbering if necessary) $\mu_k(t) = 1$ and $Z_S^k(t) = Z_S^{(k)}$ as soon as $t \in I^{(k)}$.

In other words,

$$\begin{aligned} &F_S(Z_S^{(k)}, B_R) - G_S(Z_S^{(k)}, B_R)\theta_S = 0, \\ &\dot{x}_R = F_S(Z_S^{(k)}, B_R) - G_S(Z_S^{(k)}, B_R)x_R, \end{aligned} \qquad \text{if } t \in I^{(k)}. \tag{22}$$

Next we use the piecewise continuous substitution

$$y_R(t) = x_R(t) - x_R^{(k)}, \qquad \text{if } t \in I^{(k)}, \quad t \geq t,$$

where $x_R^{(k)}$ is such that

$$F_R(Z_S^{(k)}, B_R) - G_R(Z_S^{(k)}, B_R)x_R^{(k)} = 0, \qquad \text{if } t \in I^{(k)}.$$

Then the second equation in (22) can be rewritten as

$$\dot{y}_R = F_R(Z_S^{(k)}, B_R) - G_R(Z_S^{(k)}, B_R)x_R^{(k)} - G_R(Z_S^{(k)}, B_R)y_R = -G_R(Z_S^{(k)}, B_R)y_R$$

As $G_R \geq m > 0$, by GronwallBellman inequality,

$$|y_R(t)| \leq Ce^{-mt}, \qquad t \geq T.$$

In other words,

$$|x_R(t) - x_R^{(k)}| \le Ce^{-mt}, \qquad t \in I^{(k)},\ k = 1, ..., N. \tag{23}$$

This holds in particular for the stationary solution (y_S^0, x_R^0), so that

$$|x_R^0 - x_R^{(k)}| \le Ce^{-mt}, \qquad t \in I^{(k)},\ k = 1, ..., N. \tag{24}$$

Using (23) and (24) results in the estimate $|x_R(t) - x_R^0| \le 2Ce^{-mt}$, $t \ge T$, which proves asymptotic stability of the stationary solution (y_S^0, x_R^0) to (20). $\square$

Combining Theorem 3 with Theorem 9, [2], Chapter 3, §15 yields the reduction principle for the main system (8).

Theorem 4. *Let $P^0 \in \mathcal{SD}(S, B_R)$ be a Filippov stationary solution in the narrow sense for the system (8). Under Assumptions 1 and 2 this solution will be locally asymptotically stable.*

3.3. Stability of SSPs in black walls

Here we consider an example, where we apply the proposed above method (based mainly on Assumption 1 and Assumption 2) to study the stability of a differential inclusions. We consider the case of a black wall.

Example 1. Let us show that any Filippov stationary solution $P^0 = (\theta_s, x_R^0)$ located in a black wall $\mathcal{SD}(s, B_R)$ is locally asymptotically stable.

Without loss of generality we may assume that $x_1 = \theta_1$ for the black wall $\mathcal{SD}(s, B_R)$. In a black wall any Filippov stationary point is a Filippov stationary point in the narrow sense and therefore Assumption 1 is fulfilled.

Following Assumption 2 (and thus Theorem 1) we restrict ourselves to the space of singular variables only, i.e. the x_1 axis.

By introducing a new variable

$$x_1 - \theta_1 = y_1,$$

we get "the first approximation" equation for y_1

$$\dot{y}_1 = F_1(h_1(y_1), B_R) - G_1(h_1(y_1), B_R)\theta_1,$$

and the corresponding 0-homogeneous differential inclusion $\dot{y}_1 \in \mathcal{H}_1(y_1)$ with the right-hand side from Definition 3.

The vertex $y_1 = 0$ separates the y_1 axis into two regular boxes $\mathcal{B}_1^1 : \{y_1 < 0\}$ and $\mathcal{B}_2^1 : \{y_1 > 0\}$. Consider $\mathcal{H}(y) = H_1^1$ for $y \in \mathcal{B}_1^1$, i.e. $h(y_1) = 0$,

$$H_1^1 = F_1(0, B) - G_1(0, B)\theta_1.$$

and $\mathcal{H}(y) = H_2^1$ for $y \in \mathcal{B}_2^1$, i.e. $h(y_1) = 1$,

$$H_2^1 = F_1(1, B) - G_1(1, B)\theta_1.$$

Since the wall is black, we have the following inequalities

$$F_1(0,B) - G_1(0,B)\theta_1 > 0,$$
$$F_1(1,B) - G_1(1,B)\theta_1 < 0$$

indicating that $H_1^1 \notin \mathcal{B}_1^1$ and $H_2^1 \notin \mathcal{B}_2^1$.

By Theorem 1 and Theorem 4, the SSP (θ_1, x_R^0) is asymptotically stable.

□

4. Algorithm for stability analysis of SSPs based on the Filippov theory

As a practical application to Theorem 4 we propose an algorithm for stability analysis of SSPs and consider some examples, where we apply the proposed algorithm.

Algorithm

Let $P^0 = (\theta_S, x_R^0)$ be a Filippov stationary solution in the narrow sense located in a singular domain $\mathcal{SD}(S, B_R)$. Let $h_R(x_R(0) - \theta_R) = B_R$.

Step 1 Introduce the new variable $y \in \mathbb{R}^l$, $l = |S|$.

$$x_S - \theta_S = y_S$$

to translate the singular coordinates of P^0 to the origin. Write down the following equations for the singular variables only

$$\dot{y}_S = F_S(h_S(y_S), B_R) - G_S(h_S(y_S), B_R)\theta_S. \tag{25}$$

Step 2 List all the regular domains $\mathcal{B}_p^l$, $p = 1, ..., 2^l$ and singular m-dimensional domains $\mathcal{SD}_p^m$, $m = 1, ..., l-1$, $p = 1, ..., p_m$ adjacent to the point $y_S = 0$ in $\mathbb{R}^l$. For example, $\mathcal{B}_{p_0}^l : \{y_1 > 0, y_2 < 0, ..., y_l > 0\}$, $\mathcal{SD}_{p_0}^2 : \{y_1 = 0, y_2 = 0, y_3 > 0, ..., y_l < 0\}$.

Step 3 For each of the regular domains $\mathcal{B}_p^l$, $p = 1, ..., 2^l$, calculate $H_p^l = F_S(B^p, B_R) - G_S(B^p, B_R)\theta_S$, where B^p is a Boolean vector of length $|S| = l$ associated to the regular domain $\mathcal{B}_p^l$. For example, $H_{p_0}^l = F_S([10...1], B_R) - G_S([10...1], B_R)\theta_S$.

Check the condition $H_p^l \notin \mathcal{B}_p^l$, which simply means to compare with 0 the coordinates of the vector H_p^l. Violation of this condition implies instability of P^0. Otherwise proceed to the next step.

Step 4 For each of the singular domains $\mathcal{SD}_p^m$, $m = 1, ..., l-1$, $p = 1, ..., p_m$, consider the set

$$H_p^m = \overline{co}\{F_S((B)_i, B_R) - G_S((B)_i, B_R)\theta_S \mid i = 1, 2, 3, ..., 2^{l-m}\},$$

where $(B)_i$, $i = 1, 2, 3, ..., 2^{l-m}$, are the Boolean vectors of length $|S| = l$ associated to all the regular domains in $\mathbb{R}^l$ adjacent to $\mathcal{SD}_p^m$.

Thus $H_p^m = \{\sum_{i=1}^{2^{l-m}} \alpha_i \left(F_S((B)_i, B_R) - G_S((B)_i, B_R)\theta_S\right) \mid \sum_{i=1}^{2^{l-m}} \alpha_i = 1,\ 0 \le \alpha_i \le 1\}$.

For each $m = 1, ..., l-1$, $p = 1, ..., p_m$ check that none of the vectors from the set H_p^m lie in $\mathcal{SD}_p^m$ (or in $\partial\mathcal{SD}_p^m$). To do this one will need to solve the following system of linear equations and inequalities

$$\begin{cases} \sum\limits_{i=1}^{2^{l-m}} \alpha_i \left(F_S((B)_i, B_R) - G_S((B)_i, B_R)\theta_S\right) = b, \quad b \in \mathcal{SD}_p^m, \quad (\text{or } b \in \partial\mathcal{SD}_p^m) \\ \sum\limits_{i=1}^{2^{l-m}} \alpha_i = 1, \\ 0 \le \alpha_i \le 1 \end{cases} \tag{26}$$

with the unknown $(\alpha_1, ..., \alpha_{2^{l-m}})$ and $(b_1, ..., b_l)$.

If the solution set of (26) is empty, then the SSP P^0 is asymptotically stable. Otherwise it is unstable.

End

4.1. Examples

Example 2. Consider the following example from [7].

$$\begin{aligned} \dot{x}_1 &= Z_1 + Z_2 - 2Z_1Z_2 - \gamma_1 x_1, \\ \dot{x}_2 &= 1 - Z_1Z_2 - \gamma_2 x_2. \end{aligned} \tag{27}$$

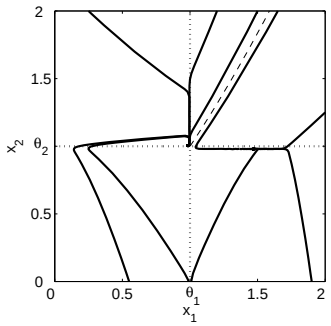

Figure 1. Some trajectories of (27) for the steep model with $q = 0.01$. Parameter values: $\gamma_1 = 0.6$, $\gamma_2 = 0.9$, $\theta_1 = \theta_2 = 1$.

This model has two black walls $\mathcal{SD}(1, [1])$ ($x_1 = \theta_1$, $x_2 > \theta_2$) and $\mathcal{SD}(2, [1])$ ($x_2 = \theta_2$, $x_1 > \theta_1$). The single point $x_1 = \theta_1$,$x_2 = \theta_2$ is the singular domain $\mathcal{SD}(1, 2)$ of codimension 2. It can be shown that this system possesses two SSPs: $(3/2, \theta_2)$ and (θ_1, θ_2). The point $(3/2, \theta_2)$ is located in a black wall and is therefore asymptotically stable. Let us investigate the stability of (θ_1, θ_2).

We introduce the new variables

$$\begin{aligned} x_1 - \theta_1 &= y_1, \\ x_2 - \theta_2 &= y_2, \end{aligned}$$

and consider the following system

$$\begin{aligned}\dot{y}_1 &= h_1(y_1) + h_2(y_2) - 2h_1(y_1)h_2(y_2) - \gamma_1\theta_1,\\ \dot{y}_2 &= 1 - h_1(y_1)h_2(y_2) - \gamma_2\theta_2.\end{aligned}$$

and its corresponding 0-homogeneous differential inclusion $\dot{y} \in \mathcal{H}(y)$ with the right-hand side from Definition 3.

Following the algorithm we consider in the space of new variable y four 2-dimensional regular boxes $\mathcal{B}_1^2 : \{y_1 < 0,\ y_2 < 0\}$, $\mathcal{B}_2^2 : \{y_1 > 0,\ y_2 < 0\}$, $\mathcal{B}_3^2 : \{y_1 < 0,\ y_2 > 0\}$, $\mathcal{B}_4^2 : \{y_1 > 0,\ y_2 > 0\}$ and four 1-dimensional singular domains $\mathcal{SD}_1^1 : \{y_1 = 0,\ y_2 > 0\}$, $\mathcal{SD}_2^1 : \{y_2 = 0,\ y_1 > 0\}$, $\mathcal{SD}_3^1 : \{y_1 = 0,\ y_2 < 0\}$, $\mathcal{SD}_4^1 : \{y_2 = 0,\ y_1 < 0\}$. Then for the regular boxes we have $H_1^2 = \begin{pmatrix} -0.6 \\ 0.1 \end{pmatrix} \notin \mathcal{B}_1^2$, $H_2^2 = \begin{pmatrix} 0.4 \\ 0.1 \end{pmatrix} \notin \mathcal{B}_2^2$, $H_3^2 = \begin{pmatrix} 0.4 \\ 0.1 \end{pmatrix} \notin \mathcal{B}_3^2$, $H_4^2 = \begin{pmatrix} -0.6 \\ -0.9 \end{pmatrix} \notin \mathcal{B}_4^2$.

For singular domains, by Definition 3, we have $H_1^1 = \overline{co}\{\begin{pmatrix} 0.4 - h \\ 0.1 - h \end{pmatrix} \mid h \in \{0, 1\}\} = \{\alpha \begin{pmatrix} 0.4 \\ 0.1 \end{pmatrix} + (1 - \alpha) \begin{pmatrix} -0.6 \\ -0.9 \end{pmatrix},\ 0 \le \alpha \le 1\} = \{H_1^1(\alpha)\}$. It is easy to check that there does not exist α, $0 \le \alpha \le 1$, such that $H_1^1(\alpha) \in \mathcal{SD}_1^1$.

But for $H_2^1 = \overline{co}\{\begin{pmatrix} 0.4 - h \\ 0.1 - h \end{pmatrix} \mid h \in \{0, 1\}\} = \{\alpha \begin{pmatrix} 0.4 \\ 0.1 \end{pmatrix} + (1 - \alpha) \begin{pmatrix} -0.6 \\ -0.9 \end{pmatrix},\ 0 \le \alpha \le 1\} = \{H_2^1(\alpha)\}$ there exists $\alpha = 0.9$ so that $H_2^1(0.9) = \begin{pmatrix} 0.3 \\ 0 \end{pmatrix} \in \mathcal{SD}_2^1$. Then it follows from Theorem 1 that the SSP (θ_1, θ_2) is unstable. $\square$

Example 3. Consider the system

$$\begin{aligned}\dot{x}_1 &= 1.65 - Z_1 + 2Z_2 - 2Z_1Z_2 - \gamma_1 x_1,\\ \dot{x}_2 &= 2.25 + Z_1 - Z_2 - Z_1Z_2 - \gamma_2 x_2.\end{aligned} \tag{28}$$

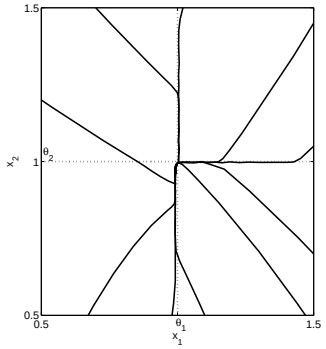

Figure. Some trajectories of (28) for the steep model with $q = 0.01$. Parameter values: $\gamma_1 = 1.5$, $\gamma_2 = 2.3$, $\theta_1 = \theta_2 = 1$.

This model has three black walls $\mathcal{SD}(1, [1])$ $(x_1 = \theta_1,\ x_2 > \theta_2)$, $\mathcal{SD}(2, [1])$ $(x_2 = \theta_2,\ x_1 > \theta_1)$, and $\mathcal{SD}(1, [0])(x_1 = \theta_1,\ x_2 < \theta_2)$. The single point $P^0 = (\theta_1, \theta_2)$ is actually a

Filippov stationary point in the narrow sense, i.e. in the sense of Definition 7. Let us investigate the stability of (θ_1, θ_2).

We introduce the new variables

$$x_1 - \theta_1 = y_1,$$
$$x_2 - \theta_2 = y_2$$

and consider the following system

$$\dot{y}_1 = 1.65 - h_1(y_1) + 2h_2(y_2) - 2h_1(y_1)h_2(y_2) - \gamma_1\theta_1,$$
$$\dot{y}_2 = 2.25 + h_1(y_1) - h_2(y_2) - h_1(y_1)h_2(y_2) - \gamma_2\theta_2.$$

and its corresponding 0-homogeneous differential inclusion $\dot{y} \in \mathcal{H}(y)$ with the right-hand side from Definition 3.

Following the algorithm we consider in the space of new variable y four 2-dimensional regular boxes $\mathcal{B}_1^2 : \{y_1 < 0,\, y_2 < 0\}$, $\mathcal{B}_2^2 : \{y_1 > 0,\, y_2 < 0\}$, $\mathcal{B}_3^2 : \{y_1 < 0,\, y_2 > 0\}$, $\mathcal{B}_4^2 : \{y_1 > 0,\, y_2 > 0\}$ and four 1-dimensional singular domains $\mathcal{SD}_1^1 : \{y_1 = 0,\, y_2 > 0\}$, $\mathcal{SD}_2^1 : \{y_2 = 0,\, y_1 > 0\}$, $\mathcal{SD}_3^1 : \{y_1 = 0,\, y_2 < 0\}$, $\mathcal{SD}_4^1 : \{y_2 = 0,\, y_1 < 0\}$. Then for the regular boxes we have $H_1^2 = \begin{pmatrix} 0.15 \\ -0.05 \end{pmatrix} \notin \mathcal{B}_1^2$, $H_2^2 = \begin{pmatrix} -0.85 \\ 0.95 \end{pmatrix} \notin \mathcal{B}_2^2$, $H_3^2 = \begin{pmatrix} 2.15 \\ -1.05 \end{pmatrix} \notin \mathcal{B}_3^2$, $H_4^2 = \begin{pmatrix} -0.85 \\ -1.05 \end{pmatrix} \notin \mathcal{B}_4^2$.

For singular domains, by Definition 3, we have $H_1^1 = \overline{co}\{\begin{pmatrix} 0.15 - 3h \\ -1.05 \end{pmatrix} \mid h \in \{0,1\}\} = \{\alpha \begin{pmatrix} 0.15 \\ -1.05 \end{pmatrix} + (1-\alpha)\begin{pmatrix} -2.85 \\ -1.05 \end{pmatrix},\, 0 \le \alpha \le 1\} = \{\begin{pmatrix} 3\alpha - 2.85 \\ -1.05 \end{pmatrix},\, 0 \le \alpha \le 1\} = \{H_1^1(\alpha)\}$. It is easy to check that there does not exist α, $0 \le \alpha \le 1$, such that $H_1^1(\alpha) \in \mathcal{SD}_1^1$. For example using the angle between vectors and the inner product: $\frac{(H_1^1(\alpha), d_1^1)}{|H_1^1(\alpha)||d_1^1|} \neq 1$, where $d_1^1 = (0, d)$, $d > 0$.

$H_2^1 = \overline{co}\{\begin{pmatrix} -0.85 - h \\ 0.95 - 2h \end{pmatrix} \mid h \in \{0,1\}\} = \{\alpha \begin{pmatrix} -0.85 \\ 0.95 \end{pmatrix} + (1-\alpha)\begin{pmatrix} -1.85 \\ -1.05 \end{pmatrix},\, 0 \le \alpha \le 1\} = \{H_2^1(\alpha)\}$. It is easy to check that there does not exist α, $0 \le \alpha \le 1$, such that $H_2^1(\alpha) \in \mathcal{SD}_2^1$.

$H_3^1 = \overline{co}\{\begin{pmatrix} 0.15 - h \\ -0.05 + h \end{pmatrix} \mid h \in \{0,1\}\} = \{\alpha \begin{pmatrix} 0.15 \\ -0.05 \end{pmatrix} + (1-\alpha)\begin{pmatrix} -0.85 \\ 0.95 \end{pmatrix},\, 0 \le \alpha \le 1\} = \{H_3^1(\alpha)\}$. It is easy to check that there does not exist α, $0 \le \alpha \le 1$, such that $H_3^1(\alpha) \in \mathcal{SD}_3^1$.

$H_4^1 = \overline{co}\{\begin{pmatrix} 0.15 + 2h \\ -0.05 - h \end{pmatrix} \mid h \in \{0,1\}\} = \{\alpha \begin{pmatrix} 0.15 \\ -0.05 \end{pmatrix} + (1-\alpha)\begin{pmatrix} 2.15 \\ -1.05 \end{pmatrix},\, 0 \le \alpha \le 1\} = \{H_4^1(\alpha)\}$. It is easy to check that there does not exist α, $0 \le \alpha \le 1$, such that $H_4^1(\alpha) \in \mathcal{SD}_4^1$.

Thus, the SSP (θ_1, θ_2) is locally asymptotically stable. $\square$

Conclusions

The main results of the paper provide a stability analysis for differential systems with discontinuous right-hand sides arising from gene regulatory networks. Putting emphasis

on the Filippov approach and focusing on singular domains mainly, we have developed an algorithm enabling to investigate the stability of any given stationary solution which is located in the discontinuity set of the system. The algorithm is based on the reduction principle which is justified in the paper and which relies upon the analysis of only those variables which are close to their respective threshold values ("singular variables"). The algorithm of checking local asymptotic stability consists in determining the signs of certain parameters of the given equations, rather than in calculating the eigenvalues of the Jacobian. Therefore, the suggested algorithm seems to be numerically advantageous. We restricted ourselves to the case of Filippov stationary solutions in the narrow sense (that are defined without convexifying the right-hand side of the corresponding inclusion), because only these stationary solutions can be obtained as limits of the stationary solutions to the smooth perturbations of the given discontinuous system.

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Appendix: Stationary solutions revisited

In the Appendix we want to discuss connections of the concept of the Filippov stationary solutions in the narrow sense with two other definitions of stationary solutions to the PWA systems.

The definition below gives a formal description of a singular stationary point (SSP) in the sense of E. Plahte et al. [8].

Definition 10. A point $P^0 \in \mathcal{SD}(\theta_S, B_R)$ is called a singular stationary point (SSP) for system (7) $Z_s = \Sigma(x_s, \theta_s, 0)(s \in S)$ if for any set of logoid functions $\Sigma(x_s, \theta_s, q)$, $s \in S$, there exists a number $\varepsilon > 0$ and points P^q, where $q \in (0, \varepsilon)$, such that

- The point P^q is a stationary point for system (7) with $Z_s = \Sigma(x_s, \theta_s, q)$ $(s \in S)$;
- $P^q \to P^0$ as $q \to +0$ $(s \in S)$.

Due to Theorem 4 in [7], this is the case if $\det(\partial f_S/\partial Z_S) \neq 0$ and $0 < Z_S^* < 1$, where Z_S^* is the solution of the stationary conditions

$$\begin{aligned} 0 &= F_S(Z_S^*, B_R) - G_S(Z_S^*, B_R)\theta_S, \\ 0 &= F_R(Z_S^*, B_R) - G_R(Z_S^*, B_R)x_R^0. \end{aligned} \tag{29}$$

Theorem 5. *Any SSP of Eq. (7) obtained by method of E. Plahte et al. [8, 7] is a Filippov stationary point in the narrow sense.*

Proof. Since $x(t) = x^q$ is the solution of $\dot{x} = F(Z) - G(Z)x^q = 0$ with a logoid $Z_i = \Sigma(x_i, \theta_i, q)$,$q > 0$, this solution converges uniformly on any interval to a certain solution of the inclusion $\dot{x} \in \mathcal{F}(x)$. On the other hand $x^q \to x^0$ as $q \to 0$ and hence x^0 is the solution of $\dot{x} \in \mathcal{F}(x)$ on any interval and therefore for all x. Since x^0 is a constant, $0 \in \mathcal{F}(x^0)$ and x^0 is a Filippov stationary point of Eq. (7). $\square$

The converse in general probably doesn't hold but still holds for black walls.

Theorem 6. *Any Filippov stationary point of Eq. (7) located on a black wall is a SSP in the sense of E. Plahte et al. [7] as well.*

Proof. Let $x^0 \in \mathcal{SD}(s, B_R)$, $s \in S$, be a Filippov stationary point. Without loss of generality we may assume that $x^0 \in \mathcal{SD}(1, B_R)$, and let $\mathcal{SD}(1, B_R)$ be a black wall. As functions are affine with respect to Z_1 the Filippov solution is unique in the black wall, as there exists only one $Z_1^* \in [0, 1]$ such that for the Filippov stationary solution x^0 we have

$$\begin{aligned} 0 &= F_1(Z_1^*, B_R) - G_1(Z_1^*, B_R)\theta_1, \\ 0 &= F_R(Z_1^*, B_R) - G_R(Z_1^*, B_R)x_R^0. \end{aligned} \tag{30}$$

Let

$$\frac{\partial F_1}{\partial Z_1} - \frac{\partial G_1}{\partial Z_1}\theta_1 \neq 0. \tag{31}$$

This equality holds for a black wall. Then, the implicit function theorem used in [7], gives x^q (for sufficiently small q) such that

$$\begin{array}{l} 0 = F_1(Z_1, B_R) - G_1(Z_1, B_R)x_1^q, \\ 0 = F_R(Z_1, B_R) - G_R(Z_1, B_R)x_R^q \end{array} \tag{32}$$

and $x^q \to x^0$ as $q \to 0$. We have obtained a stationary solution in the sense of E. Plahte et al. $\square$

Let us now consider an example showing that not every Filippov stationary solution is a solution in the narrow sense, i.e. that the inclusion $0 \in \mathcal{F}(x)\backslash\mathcal{F}_1(x)$ may have constant solutions $x = x^*$.

Example 4. Let

$$\begin{array}{l} \dot{x}_1 = 1.65 - Z_1 + 2Z_2 - 2Z_1Z_2 - \gamma_1 x_1, \\ \dot{x}_2 = 2.25 + Z_1 - Z_2 - Z_1Z_2 - \gamma_2 x_2. \end{array} \tag{33}$$

The parameter values are: $\gamma_1 = 1.5$, $\gamma_2 = 2.5$, $\theta_1 = \theta_2 = 1$.

It is straightforward to check that $0 \in \mathcal{F}(1,1)$, where

$$\mathcal{F}(x) = co\{P^{00}(x), P^{01}(x), P^{10}(x), P^{11}(x)\}.$$

Here $P^{00}(x) = \begin{pmatrix} 1.65 - 1.5x_1 \\ 2.25 - 2.5x_2 \end{pmatrix}$, $P^{01}(x) = \begin{pmatrix} 3.65 - 1.5x_1 \\ 1.25 - 2.5x_2 \end{pmatrix}$, $P^{10}(x) = \begin{pmatrix} 0.65 - 1.5x_1 \\ 3.25 - 2.5x_2 \end{pmatrix}$, $P^{11}(x) = \begin{pmatrix} 0.65 - 1.5x_1 \\ 1.25 - 2.5x_2 \end{pmatrix}$.

On the other hand, the stationary point $(1,1)$ is not the stationary point in the narrow sense (and hence not SSP in the sense of E. Plahte et al., as the system

$$\begin{array}{l} 1.65 - Z_1 + 2Z_2 - 2Z_1Z_2 - 1.5 = 0, \\ 2.25 + Z_1 - Z_2 - Z_1Z_2 - 2.5 = 0 \end{array} \tag{34}$$

does not have real solutions.

The question then arises as to how to interpret Filippov stationary solutions that are not solutions in the narrow sense and therefore not limits of proper stationary solutions of approximating equations. Below we suggest that such solutions may come from invariant measures of the solution flows of approximating equations. If these measures shrink into the singleton in the limit, then this limit must belong to the convex hull $\mathcal{F}$ of the set $\mathcal{F}_1$, but not necessarily to $\mathcal{F}_1$ itself. $\square$

Theorem 7. *Let A_q, $q > 0$, be the the sequence of compact sets that converges in the Hausdorff metric to the point x^* as $q \to 0$. Suppose that the set A_q remains invariant with respect to the solution flow $U(t, x, q)$, $t \geq 0$, $x \in X$, of the system*

$$\dot{x}_i = f_i(x_i, q) = F_i(\Sigma(x_i, \theta_i, q)) - G_i(\Sigma(x_i, \theta_i, q))x_i, \quad i = 1, ..., n,$$

with the logoid functions Σ, i.e.

$$U(t, A_q, q) \subset A_q, \quad \forall t \geq 0, \quad 0 < q < q_0.$$

Then x^* is a Filippov stationary solution to the differential inclusion (5).

Proof.

By the Krylov-Bogolubov theorem (see e.g. [5]), the solution flow $U(t,x,q)$ has an invariant probability measure μ_q and $\mu_q(A_q)=1$, $(0<q<q_0)$. Due to the convergence of A_q, we can assume that $A_q \subset A$, $0<q<q_0$, A is a compact set.

By the definition of a solution flow, we have that

$$U(t,x,q)-U(0,x,q)=\int_0^t f(U(s,x,q),q)ds.$$

Integrating this equality with respect to μ_q, yields, due to $U(0,x,q)=x$, the following equality:

$$\int_X U(t,x,q)\mu_q(dx)-\int_X x\mu_q(dx)=\int_0^t ds\int_X f(U(s,x,q),q)\mu_q(dx). \tag{35}$$

By the definition of an invariant measure we get

$$\int_X g(x)\mu_q(dx)=\int_X g(U(t,x,q))\mu_q(dx)$$

for any continuous function g.

Hence choosing $g(x)=x$ in the latter equality gives the left hand side of (35) which is equal to 0. Therefore if we change, by Fubini's theorem, the order of the integration in (35), then we obtain, due to continuity of $f(x,q)$ and the invariance of the measure μ_q with respect to $U(t,x,q)$, that

$$t\int_X f(x,q)\mu_q(dx)=0, \quad 0<q<q_0.$$

Thus,

$$\int_X f(x,q)\mu_q(dx)=0, \quad 0<q<q_0. \tag{36}$$

Since the function $f(x,q)$ becomes discontinuous for $q=0$, we cannot interchange the limit and the integration in (36). Therefore we will act in the the following way. For any $\varepsilon>0$ we choose q_ε such that for $0<q<q_\varepsilon$ we have $f(x,q)\in\mathcal{F}_1^\varepsilon(x) \quad \forall x\in A$, where $\mathcal{F}_1^\varepsilon(x)$ is the ε-neighborhood of $\mathcal{F}_1$.

Hence

$$0\in\int_X \mathcal{F}_1^\varepsilon(x)\mu_q(dx).$$

Moreover, since $\operatorname{supp}\mu_q$ converges to x^*, we may assume without loss of generality (by taking a smaller q_ε if required) that $\operatorname{supp}\mu_q\in B[x^*,\varepsilon]$ ($B[x^*,\varepsilon]$ is the closed ε-vicinity of x^*) for $0<q<q_\varepsilon$. Therefore

$$0\in\int_{B[x^*,\varepsilon]} \mathcal{F}_1^\varepsilon(x)\mu_q(dx).$$

Due to the mean value theorem for multivalued functions (see [2]), there exists $x^\varepsilon \in B[x^*, \varepsilon]$ such that

$$0 \in \overline{co}\mathcal{F}_1^\varepsilon(x^\varepsilon).$$

As $\overline{co}\mathcal{F}_1^\varepsilon(x^\varepsilon) = \mathcal{F}_1^\varepsilon(x^\varepsilon)$ (see [2]), we obtain that

$$0 \in \mathcal{F}_2^\varepsilon(x^\varepsilon).$$

Since $\varepsilon > 0$ is arbitrarily small and $\mathcal{F}_1$ is upper semicontinuous (see [2]), we conclude that $0 \in \mathcal{F}_2(x^*)$. This implies that x^* is a Filippov stationary solution to the differential inclusion (5). The theorem is proved. Let us only remark that it is the mean value theorem for multivalued functions that yields the convex hull of $\mathcal{F}_1$, i.e $\mathcal{F}$, and not $\mathcal{F}_1$ itself. $\square$

Paper III

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Automated piecewise power-law modeling of biological systems

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ABSTRACT

Recent trends suggest that future biotechnology will increasingly rely on mathematical models of the biological systems under investigation. In particular, metabolic engineering will make wider use of metabolic pathway models in stoichiometric or fully kinetic format. A significant obstacle to the use of pathway models is the identification of suitable process descriptions and their parameters. We recently showed that, at least under favorable conditions, Dynamic Flux Estimation (DFE) permits the numerical characterization of fluxes from sets of metabolic time series data. However, DFE does not prescribe how to convert these numerical results into functional representations. In some cases, Michaelis–Menten rate laws or canonical formats are well suited, in which case the estimation of parameter values is easy. However, in other cases, appropriate functional forms are not evident, and exhaustive searches among all possible candidate models are not feasible. We show here how piecewise power-law functions of one or more variables offer an effective default solution for the almost unbiased representation of uni- and multivariate time series data. The results of an automated algorithm for their determination are piecewise power-law fits, whose accuracy is only limited by the available data. The individual power-law pieces may lead to discontinuities at break points or boundaries between sub-domains. In many practical applications, these boundary gaps do not cause problems. Potential smoothing techniques, based on differential inclusions and Filippov's theory, are discussed in Appendix A.

1. Introduction

Enormous advances in molecular biology, engineering and computer science have propelled the computational analysis of biological systems into the center of systems biology, and it is becoming feasible to use systems biological methods like pathway analysis in biotechnology and, especially, metabolic engineering. The main challenge for practical applications of computational systems biology is currently the process of making the computational models fit the dynamic responses of biological systems. This challenge consists of two related sub-tasks. The first is the determination of suitable functions that are capable of describing the observed dynamics with sufficient accuracy, and the second is the identification of parameter values that render a good numerical fit between observed and modeled responses. Although these two sub-tasks are clearly dependent on each other, they are different in character. While the second task of parameter identification is primarily a technical issue, which may be difficult, but which one might expect to be solvable with brute force, if not with elegance, the task of determining appropriate functions exceeds the realm of pure computation and requires insight into the biological phenomenon under investigation, numerous assumptions and simplifications, which cannot always be validated, and some degree of ingenuity in finding or inventing functional forms that fit the need. The reason that this sub-task is complicated is that nature has not provided us with guidelines for selecting these functions, and that it is usually not feasible to reduce biological processes to elemental physical processes for which mathematical descriptions are available (Voit, 2008).

Many models of biochemical systems in the past used functional forms that were chosen from a default repertoire of candidates, which included Michaelis–Menten and Hill rate laws, their generalizations toward several substrates, inhibitors and other modulators (Schulz, 1994), or so-called *canonical* representations like power-law (Voit, 1991) and lin-log functions (Heijnen, 2005). However, it is becoming increasingly evident that the standard rate functions are not always applicable and that they, like canonical representations, are simply too inaccurate for reliable extrapolations of the model to new experimental conditions.

In an attempt to respond to these challenges, we recently proposed Dynamic Flux Estimation as a useful tool for estimating

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metabolic pathway systems (Goel et al., 2008). This method consists of two phases, of which the first is entirely model free, while the second requires the choice of a mathematical representation of all involved fluxes. More specifically, the first phase consists of solving a linear system of fluxes in such a manner that the change in each variable pool at each time point is the numerical result of fluxes entering and exiting the pool. Under ideal conditions, this solution can be obtained with straightforward methods of linear algebra; in other cases, additional biological information, complementing the observed metabolic time series, is needed (Voit et al., 2009). In either case, the solution of the first phase of DFE consists of a set of points characterizing the dynamic profile of each flux over the observed time interval. This solution allows inspection of each flux either plotted against time or against its contributing metabolites and modulators. However, since the representation is not functional, it does not allow simulations of new scenarios or extrapolations to untested conditions.

The key goal of the second phase is the conversion of these numerical representations into functional forms, which subsequently permit simulations, extrapolations, and other manipulations and analyses with the model. If the numerical representation of a flux exhibits a simple trend, a function like a Michaelis–Menten or Hill rate law, or even a simple power-law representation, may serve as an adequate model. Indeed, the arsenal of traditional biochemical process descriptions is essentially unlimited (Schulz, 1994), yet it may still be insufficient. For instance, Peskov et al. (2008) recently proposed a representation of the phosphofructokinase reaction in *Escherichia coli* that by far exceeds the complexity of any traditional rate laws. In cases where the typical candidates of biochemistry fail, there is no guidance as to what other functional forms might yield satisfactory flux fits. Without an evident functional format, one might try to exhaust a set of more complex candidate functions, but it is clear that it is logistically difficult and computationally very expensive to execute such a search.

As an alternative with minimal bias, we propose here the use of univariate or multivariate piecewise power-law functions. It is known that such functions with sufficiently many pieces are capable of modeling unknown data trends with arbitrary accuracy. It is also known that even single power-law functions are often reasonable descriptions of biological processes *in vivo*, in most cases outperforming linear and other simple functions. Thus, the search for a moderately small number of pieces, each described with a power-law function, appears to be quite natural. One might wonder whether this inference of piecewise representations really qualifies as model identification. Two arguments seem to provide affirmative answers. First, if the piecewise representation is sufficiently accurate, it may serve as an extrapolation tool that is likely much better than a single-pieced representation. Furthermore, once suitable pieces have been identified, it might at least in principle be possible to reverse-engineer a single function that provides a collective, smooth representation of all individual pieces and, thus, the data describing the process.

If the numerical flux representation depends on only one variable, the determination of suitable breakpoints and fitting intervals may be accomplished by inspection. However, this is no longer feasible if the flux depends on multiple variables. In the following we describe an algorithm, adapted from a method for piecewise linear systems analysis, that automatically dissects the flux-variable space into suitable segments within which the flux is represented with a product of power-law functions. The algorithm works well for fluxes that depend on a single variable or on a larger number of variables. It allows the specification of the number of desired segments or iteratively increases this number until an acceptable residual error is reached. The resulting piecewise representation is a direct generalization of models within the widely used modeling framework of Biochemical Systems Theory (Savageau, 1976; Voit, 2000) and introduces minimal bias due to the choice of functional forms.

2. Problem statement

We consider a system of the form

$$\dot{x}_i = V_i^+(x_1, x_2, \ldots, x_{n+m}) - V_i^-(x_1, x_2, \ldots, x_{n+m}), \quad (1)$$

where index i ($i = 1, \ldots, n$) refers to dependent variables, while higher indices ($n+1, \ldots, n+m$) refer to independent variables. The non-negative influx and efflux functions V_i^+ and V_i^- may possibly consist of sums of other functions describing different contributions to the production or degradation of x_i.

Once the functions V_i^+ and V_i^- are specified, simulations with the model in Eq. (1) are easily performed, and many methods are available for mathematical analyses of features such as local stability or parameter sensitivities at the system's steady states. However, before such analyses are feasible, it is necessary to specify the functions in the model. As discussed in Section 1, this specification consists of two parts, namely the determination of the mathematical structure of the functions and the identification of suitable parameter values.

It is by now widely recognized that the estimation of parameter values from time series data is much simplified if the data are first smoothed, because smoothing permits the computation of slopes at any desired number of points along the time trajectory of any of the system variables (Vilela et al., 2007). The slopes, in turn, can be used as a set of substitutes for the differentials on the left-hand side of each differential equation at k time points ($S_i(t_k) \approx \dot{x}_i(t_k)$) (Voit and Savageau, 1982; Varah, 1982). This procedure has two significant advantages. First, the differential equations no longer have to be integrated numerically, which usually requires substantial computational effort, often consuming between 95% and close to 100% of the entire estimation time (Voit and Almeida, 2004). Second, the slope substitution in effect decouples the system of differential equations and permits parameter estimation one equation at a time, thus facilitating simpler sequential or parallel execution. Many applications of these methods have been analyzed in the fields of genomics and metabolic pathway analysis (Chou and Voit, 2009). The latter is particularly well suited because pathways not only have a well-defined connectivity but also entail conservation of mass at nodes and within the entire system. Most comments in the following therefore refer to metabolic pathway systems, even though other biological systems are not categorically excluded.

While the slope substitution and decoupling method has found plenty of applicability (Chou and Voit, 2009) and was shown to be statistically sound (Brunel, 2008), it still requires in most cases the estimation of parameters in sets of nonlinear (algebraic) equations. This estimation is not always trivial. Indeed it is common that evolutionary or regression algorithms are unable to find the global optimum within a reasonable time, while global estimation methods, such as branch-and-bound methods, are computationally expensive and sometimes difficult to implement (Guillen-Gosalbez and Sorribas, 2009; Polisetty et al., 2006). A second common issue is that entire ensembles of solutions may model the data with similar residual errors, thus causing model identification problems (Gutenkunst et al., 2007a,b; Raue et al., 2009). These ensembles may form more or less elliptical regions whose center is the optimal solution, but it is also possible that distinctly different solution sets are indistinguishable with respect to the residual error. Finally, a less-recognized issue is the compensation of errors among different terms within an equation, among sets of equations, or even within a single term (Raue et al., 2009; Goel, 2009). In the simplest case, two parameters p and q may always appear in the same combination, such as p/q, which precludes their individual identification. In other

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cases, conserved quantities are much more complex and difficult to detect and characterize. Error compensation is a hideous problem: the fit to one or a few training datasets may be quite good, because a badly estimated parameter in one term is compensated by an incorrect parameter in a different term. However, if the resulting model is used for extrapolations to new conditions, the compensation may no longer hold and the model fit becomes unacceptable.

Dynamic Flux Estimation (DFE) addresses this issue of error compensation (Goel, 2009). DFE begins with a model-free estimation phase, where a linear system of fluxes is constructed at each time point. These fluxes correspond to the functions affecting the dynamics of each variable (as in Eq. (1)), but only their values are taken at one point at a time, and a functional specification is not required. Thus, at time point t_k, equations of the following type are constructed:

$$\dot{x}_i(t_k) = Influx_1(t_k) + Influx_2(t_k) + \cdots - Efflux_1(t_k) - Efflux_2(t_k) - \cdots. \quad (2)$$

Under ideal conditions (see Goel et al., 2008), the collection of all these linear equations for all variables can be solved directly with method of linear algebra, and the result is a set of points characterizing the dynamic profiles of all fluxes in the system. In other words, one obtains model-free representations of all fluxes as discrete time series. For example, if $Efflux_2$ in Eq. (2) depends on variables x_3 and x_6 and if we rename this flux for simplicity as V, one obtains a dataset of the form $\{x_3(t_k), x_6(t_k), V(t_k);\ k = 1, \ldots, K\}$. From this result, one obtains an impression of V as a function of time and/or as a function of x_3 and x_6.

The second phase of DFE is model based. Here, the task is to assign functional forms to the flux profiles that were obtained in the first phase. Ideally, such a function should perfectly match the plot of the flux versus time and also versus its alleged substrates and modulators. If a suitable functional form is known or can be assumed with some justification, this matching step is easily accomplished with a nonlinear regression algorithm. However, if no such form is known, it is unclear how to proceed.

A possible default candidate is a power-law representation of the form

$$V_i = \gamma_i \prod_{j=1}^{n} x_j^{f_{ij}}, \quad (3)$$

where the rate constant γ_i is non-negative and the kinetic orders f_{ij} are real numbers. These representations were proposed as useful approximations for metabolic systems 40 years ago and have been the method of choice in many applications. They form the basis of a modeling framework that is now widely recognized as *Biochemical Systems Theory* (BST; Voit, 1991, 2000; Savageau, 1969a,b, 1970, 1976; Torres and Voit, 2002). Power-law representations are intriguing because they are nonlinear and cover an enormously rich repertoire of functional responses when they are embedded in differential equations (Savageau and Voit, 1987), yet individually permit a simple logarithmic transformation to linearity. It was clear from the beginning of BST and its roots in Taylor approximation theory that power-law functions are local representations that are useful for modeling the dynamics of variables operating within a moderate range about their normal states, but that they may incur unacceptable errors if one tries to fit complex functional shapes that extend over wide ranges of variation in the involved metabolites and modulators.

Because power-law functions can be seen as linearizations in logarithmic space, their range of applicability may be extended in two ways. First, higher order terms could be considered in order to improve the accuracy of approximation (Cascante et al., 1991). However, while theoretically reasonable, this strategy leads to convoluted representations that are rather inconvenient for further analyses and modeling purposes. As an alternative, one may consider piecewise representations. For univariate functions, it is relatively easy to determine such representations, and they have been used, for instance, in the analysis of gene circuits (Savageau, 2001, 2002). However, for multivariate functions, the suitable determination of a piecewise power-law representation becomes difficult. In the following, we present an algorithm that automatically identifies appropriate piecewise power-law representations.

Thus, our goal is the following: given metabolic time series data corresponding to an unknown, univariate or multivariate function, compute a piecewise power-law representation that is suitable in a sense that it fits the data within an acceptable error while consisting of the smallest possible number of pieces. The problem of a piecewise power-law regression, as posed here, is not straightforward, because, given a set of samples of a flux V, which is possibly affected by noise, one has to compute both a partitioning into regions in the space of metabolites and the behavior of the unknown function V over each of them. Because of the "mixed nature" of the problem, classical approximation techniques cannot be directly applied, and it is instead necessary to develop a specific, customized method. The principles of such a method were introduced a few years ago for linear systems, where the regions in the space of variables are polyhedra and the behavior of the function V in each region is approximated by a linear expression (Ferrari-Trecate and Muselli, 2002; Ferrari-Trecate et al., 2001a).

3. Methods

3.1. An algorithm for piecewise linear regression

Ferrari-Trecate and Muselli (2002) and Ferrari-Trecate et al. (2001a) introduced a machine learning method for piecewise linear regression based on Artificial Neural Networks (ANNs). The solution of such a machine learning problem involves the reconstruction of an unknown function $W: X \to Y$ from a finite set M of samples of W (the so-called *training set*), which is possibly corrupted by noise. Upon training, the result is tested against a set of data that was not used during training and is typically called the *validation set*. ANNs may be applied to two groups of such problems according to the range of values assumed by the output Y. For Boolean-like output (0 or 1; on or off) or for output with a limited number of elements, one speaks of a classification problem, while output coded by a continuous variable requires the solution of a regression task. The identification of an optimal partition that is of interest in (Ferrari-Trecate and Muselli, 2002; Ferrari-Trecate et al., 2001a), as well as here, lies right at the border between classification and regression, because the input space X has to be subdivided into a small number of disjoint regions and the behavior of the unknown, continuous function W over each of these regions has to be generated. Thus, the method proposed in Ferrari-Trecate and Muselli (2002) and Ferrari-Trecate et al. (2001a) combines local estimation, clustering in weight space, multi-categorical classification, and linear regression, which we will substitute by power-law regression. The original method may be summarized as follows.

Let X be a polyhedron in the n-dimensional space $\Re_+^n \setminus \{0\}$ and let $\{X_s\}_{s=1}^S$ be a polyhedral partition of X, *i.e.*, $X_i \cap X_j = \emptyset$ for every i, $j = 1, \ldots, S$ and $\bigcup_{i=1}^S X_i = X$. The target of piecewise linear regression is to reconstruct an unknown function $f: X \to \Re_+$ assuming linear behavior in each region X_s:

$$f(x) = z_s = w_{s0} + \sum_{j=1}^{n} w_{sj} x_j, \quad (4)$$

when only a training set M containing m samples (x_k, y_k), $k = 1, \ldots, m$ is available. The output y_k gives an evaluation of $f(x_k)$ subject to noise in $x_k \in X$, and the region X_s to which x_k belongs is not known in

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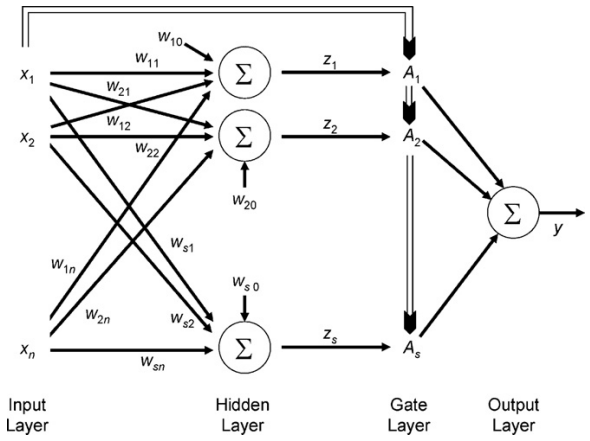

Fig. 1. Diagram of a neural network realizing a piecewise linear function (adapted from Ferrari-Trecate and Muselli, 2002; Ferrari-Trecate et al., 2001a).

advance. Scalar weights $w_{s0}, w_{s1}, \ldots, w_{sn}$, for $s = 1, \ldots, S$, uniquely characterize the function f, and their estimation is the target of the piecewise linear regression problem. For notational purposes, the weights are collected in a vector w_s. Since the regions X_s are polyhedral, they can be defined by a set of l_s linear inequalities of the type:

$$a_{sj0} + \sum_{k=1}^{n} a_{sjk} x_k \leq 0. \tag{5}$$

The scalars a_{sjk}, for $j = 1, \ldots, l_s$ and $k = 0, 1, \ldots, n$, can be collected in a matrix A_s whose estimation thus becomes the target of the reconstruction process for every $s = 1, \ldots, S$. Discontinuities are allowed and indeed are often present at the boundaries between two regions X_s.

Following (Ferrari-Trecate and Muselli, 2002; Ferrari-Trecate et al., 2001a), a neural network realizing a piecewise linear function f of this kind can be modeled as shown in Fig. 1.

As previously noted, the solution of the piecewise linear regression requires a combination of classification and regression: the classification aims at finding matrices A_s to be inserted into the gate layer of the neural network, whereas the latter provides the weight vector w_s as input to the hidden layer connections (Fig. 1).

Ferrari-Trecate and Muselli (2002) and Ferrari-Trecate et al. (2001a) solved the problem in four steps that correspond to specific tasks and are outlined below.

1. Local regression
   For every $k = 1, \ldots, m$ do the following:
   1a. Form the set C_k containing the pair (x_k, y_k) and the samples $(x, y) \in M$ associated with $c - 1$ nearest neighbors x to x_k.
   1b. Perform linear regression to obtain the weight vector v_k of a linear unit fitting the samples in C_k.
2. Clustering
   Perform a clustering process in the space $\Re^{n+1}$ to subdivide the set of weight vectors v_k into S groups V_s.
3. Classification
   Build a new training set M' containing the m pairs (x_k, s_k), where V_{s_k} is the cluster containing v_k. Train a multi-categorical classification method to produce the matrices A_s for the regions X_s.
4. Regression
   For every $s = 1, \ldots, S$ perform linear regression on the samples $(x, y) \in M$ with $x \in X_s$ to obtain the weight vector w_s for the s^{th} unit in the hidden layer.

In the following, we are interested in power-law functions rather than linear functions and, correspondingly, use either linear regression in log space or power-law regression. In order to make the necessary alterations to the linear method as clear as possible, Table 1 shows, side by side, the steps in the different procedures.

In broad strokes, the linear and power-law methods are structured as follows (excluding self-evident log-transformations):

1. Associate to each data point a local linear model (Step 1);
2. Aggregate local models with similar features into clusters (Step 2);
3. Classify data points corresponding to local models in the same cluster and estimate the regions (Step 3);
4. Estimate the parameter vectors (Step 4).

Each step faces distinct challenges and assumptions, which may be summarized as follows:

1. Step 1 requires the specification of the number of neighboring points c, which is needed for each local regression. The bigger the number c, the bigger is the number of mixed points (*i.e.*, points providing spurious information about the true model). For this reason, one should like to keep c as low as possible. At the same time, one needs to choose c large enough to counteract the effects of noise on the accuracy of the local models. Thus, the choice of c is a trade-off.
2. The goal of Step 2 is to determine S clusters. This is accomplished via *clustering algorithms*, that require S as an input. In some cases, the number of desired clusters is given *a priori*. However, if S is not known, it may theoretically be estimated from the dataset. According to Ferrari-Trecate et al. (2003), this can be done by adopting clustering algorithms where the number of clusters is not fixed *a priori* but automatically estimated (Fritzke, 1997).
3. At Step 3 each cluster is expected to collect all local models with similar features, data points are classified, and sub-model datasets are built accordingly. The regions $\{X_s\}_{s=1}^{S}$ can be found by resorting to *pattern-recognition* algorithms. The main disadvantage is that the fastest pattern-recognition algorithms may leave gaps in the input domain X, when the dimension of X is greater than one. More precise algorithms that do not leave holes are available, but they are considerably slower and require more memory. Specifically, for the identification of a small number of pieces with a large number of data points, the fast Proximal Support Vector Classification (PSVC) algorithm is recommended, and results are obtained within seconds or minutes on a standard PC. However, if the dimension of the problem is greater than one, it is not guaranteed that the union of regions will cover the input domain. To avoid gaps, one may use Multi-category Robust Linear Programming (MRLP), if access to professional Linear Programming (LP) and Quadratic Programming (QP) solvers like CPLEX is available.
4. Conceptually, this is the easiest step. The data points in each region $\{X_s\}_{s=1}^{S}$ can be used for estimating the parameter vectors of the linear (or, respectively, power-law) regression. It is apparent that X_s must contain enough data points to perform both the local regressions and the estimation of scalar parameters composing a parameter vector. If a cluster contains few points, it is discarded and the number of modes is reduced.

3.2. Piecewise Power-Law Regression

Given the general strategy in the previous section and in Table 1, it is now relatively straightforward to adapt the original linear method to power-law models. This adaptation begins with a logarithmic transformation of the data. In logarithmic coordinates,

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Table 1
Steps toward piecewise linear and piecewise power-law models.

Method	Original linear method	Piecewise power-law model based on linear regression	Piecewise power-law model based on power-law regression
		Logarithmic transformation	
		Local regression (Step 1) Clustering (Step 2) Classification (Step 3)	
	Linear regression (Step 4)	Linear regression	Inverse-logarithmic transformation
		Inverse-logarithmic transformation	Power-law regression
Key features	Output is a piecewise linear approximation to a function. The sum of squared errors is E1.	Output is a piecewise power-law approximation with the sum of squared errors E2 < E1 (provided the unknown function is nonlinear).	Output is a piecewise power-law approximation with the sum of squared errors E3 < E2 < E1 (provided the unknown function is nonlinear).

the piecewise power-law function becomes piecewise linear, and we therefore implement the first three steps of local regression, clustering, and classification of the above algorithm with the log-transformed data. This transition allows us to obtain a polyhedral partition of the input domain in logarithmic space. Implementation of Step 4 (linear regression) yields the weight parameters in Eq. (4) for the data in logarithmic coordinates. These parameters are the rate constant and the kinetic orders of the target representation in piecewise power-law format. When we apply the inverse-logarithmic transformation, the polyhedral partition that is produced by the algorithm for logarithmic data becomes a partition of the initial input domain that is bounded by nonlinear surfaces given by

$$a_{sj0} + \sum_{k=1}^{n} a_{sjk} \ln x_k \leq 0, \tag{6}$$

where the coefficients a_{sjk} ($k = 0, 1, \ldots, n$; $s = 1, \ldots, S$) were obtained in the classification Step 3 of the algorithm. In this manner we obtain a piecewise power-law approximation to an unknown function, where sub-domains of the partition are defined by Eq. (6).

The procedure has all the advantages of linear regression. However, because the logarithmic transformation distorts the error structure of the problem, the least squares error for the resulting piecewise power-law is in general less accurate than the corresponding error obtained by power-law regression of the original data. As a partial remedy, it is therefore advantageous to modify Step 4 of the algorithm by applying a power-law regression to the original data over each of the S regions in Eq. (6). Even though the regression is now nonlinear, the increase in computational difficulty is modest, due to the partition in small pieces. In other words, the partition of the initial domain localizes the process of approximation to sub-domains, thereby reducing the risk of failure of the power-law regression. While this modification reduces error distortion to some degree, it does not affect Steps 1-3, in which the boundaries of the domains are determined. As a consequence, the domains are optimal in log space but not necessarily in Cartesian space and, for instance, result in better fits for small values of metabolite concentrations, which become more pronounced in the logarithmic representation. Expressed differently, the method is optimized toward relative, rather than absolute errors, which in many cases in biology is actually an advantage. We will see the consequences of this distortion in the first example of Section 4. The same example demonstrates that the distortion becomes less significant as the algorithm uses higher numbers of segments.

The modified algorithm thus proceeds as follows. Let X be the image of X in the n-dimensional logarithmic space R^n and let $\{X_s\}_{s=1}^{S}$ be a polyhedral partition of X, *i.e.*, $X_i \cap X_j = \emptyset$ for every $i, j = 1, \ldots, S$ and $\bigcup_{i=1}^{S} X_i = X$. Let M be the image of M in logarithmic space R^n.

1. Logarithmic transformation
   Transform the data points (x_k, y_k) $(k = 1, \ldots, m)$ logarithmically to $x_k = \ln x_k$, $y_k = \ln y_k$.
2. Local regression
   For every $k = 1, \ldots, m$ do the following:
   2a. Form the set C_k containing the pair (x_k, y_k) and the samples $(x, y) \in M$ associated with $c - 1$ nearest neighbors x to x_k.
   2b. Perform a linear regression to obtain the weight vector v_k of a linear unit fitting the samples in C_k.
3. Clustering
   Perform a clustering process in the space R^{n+1} to subdivide the set of weight vectors v_k into S groups V_s.
4. Classification
   Build a new training set M' containing the m pairs (x_k, s_k), where V_{s_k} is the cluster containing v_k. Train a multi-categorical classification method to produce the matrices A_s for the polyhedral regions X_s.
5. Inverse-logarithmic transformation
   Exponentially transform the data back to Cartesian space: $x_k = \exp(x_k)$, $y_k = \exp(y_k)$. Utilize matrices A_s to obtain the partition of the input domain given by Eq. (6).
6. Regression
   For every $s = 1, \ldots, S$ perform power-law regression on the samples $(x, y) \in M$ with $x \in X_s$ to obtain the rate constant and the kinetic orders for each sub-domain given by Eq. (6).

3.3. Implementation as MatLab toolbox

The Hybrid Identification Toolbox (HIT) is a free MatLab toolbox for regression with piecewise linear maps. HIT implements the clustering-based algorithms described in (Ferrari-Trecate et al., 2001b, 2003; Ferrari-Trecate and Muselli, 2003; Ferrari-Trecate and Schinkel, 2003). In addition, HIT provides facilities for plotting and validating the identified models. HIT uses routines of the MPT toolbox (Kvasnica et al., 2004) for handling polytopes and solving Linear Programming (LP) and Quadratic Programming (QP) problems. These toolboxes can be used to implement the first four steps of the modified algorithm, which produce the partition of the input domain. As soon as the partitioning is known, one can perform a power-law regression, using MatLab or other software.

One of the default assumptions of the algorithm is that the number of sub-domains S in the target solution is given. However, this may not always be desirable. For instance, one may want to create a minimal partition that satisfies a maximally acceptable error. If S is unknown, it may be estimated from the dataset. According to

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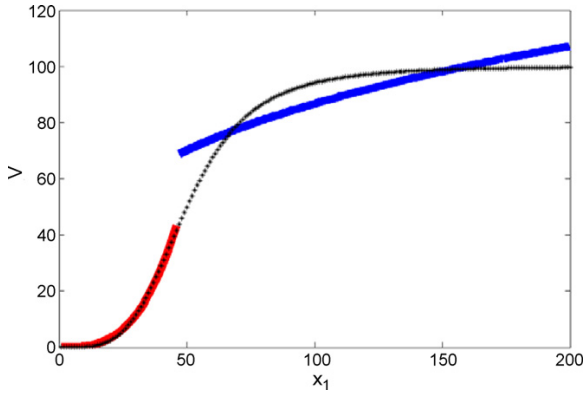

Fig. 2. Two-piece power-law fit to the Hill function in Eq. (7). See text for explanations.

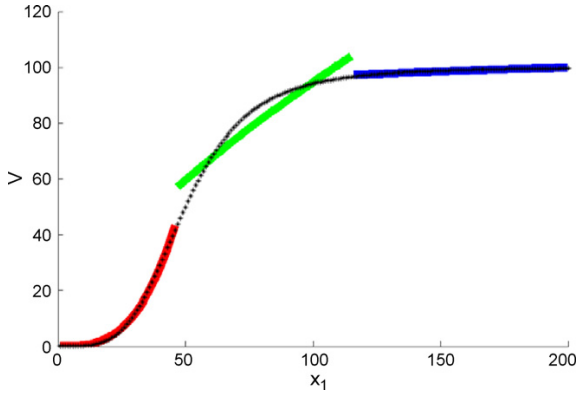

Fig. 3. An improved fit is obtained if the interval of higher concentrations from the previous fit (Fig. 2) is automatically split into two. The new breakpoint is $x_1 = 117$ and the residual error is SSE = 1849.

Ferrari-Trecate et al. (2003), this can be done by adopting clustering algorithms where the number of clusters is not fixed *a priori* and is automatically estimated (Fritzke, 1997). As a simple alternative, one may run the algorithm with increasing values for S until an acceptable solution is reached. This strategy is quite reasonable because the algorithm is fairly fast on a standard PC. An example is presented in Section 4.

Another parameter to be specified is the number c of nearest neighbors (see 2.a of the modified algorithm). HIT provides facilities for the selection of S and c through cross-validation. For details about tuning the parameter c the reader is referred to Ferrari-Trecate et al. (2003).

4. Results

4.1. Piecewise power-law regression of a univariate function

For reasons of easy illustration and visualization, it is beneficial to study the algorithm for modeling a univariate function. It is known that a single power-law function cannot model S-shaped dynamics well, and we therefore use as a base function the Hill rate law

$$V(x_1) = \frac{V_m x_1^h}{K_m^h + x_1^h} \tag{7}$$

with arbitrarily chosen Hill coefficient $h = 4$, maximal velocity $V_m = 100$, and Michaelis constant $K_m = 50$. The artificial dataset consists of 200 points that are uniformly spread out over the interval [1, 200].

As a first illustration, we specify the number of sub-domains as $S = 2$. The result of the algorithm is a good fit for small values of x_1 and a less appealing fit for large values (Fig. 2). The breakpoint at $x_1 = 47$ is obtained directly by the algorithm, and the sum of squared errors in this case is SSE = 7056. Inspection makes it clear that the interval of lower values of V is better represented than the interval containing higher values of V. The imbalance is due to the fact that the partitioning algorithm works on logarithms of the data and therefore on relative errors, which are more pronounced for small concentrations x_1.

One may proceed in two ways. Either, one may specify $S = 3$ and redo the analysis. Or, one may retain the fit for the interval [0, 47] and compute a two-piece approximation of the remaining interval [47, 200]. The result of the latter strategy is a good representation of high values [117, 200] and a reasonable representation of the center interval (Fig. 3). The residual error is now SSE = 1849, which roughly corresponds to a 70% error reduction. A third application of the algorithm to this center interval leads to a four-piece representation with a much reduced error of SSE = 196 (Fig. 4).

An obvious question is the minimally required number of data points. While the question itself is important and valid, its answer is surprisingly complicated, because it depends on a number of factors, including the complexity of the function, the complexity in relation to the noise in the data, and the desired smoothness. For instance, the identification of an exponential function without much noise may only require three or four data points, while a damped oscillation or a more complicated function may need dozens or more points, even if the noise level is low. Another factor influencing the minimum number of data points is their spatial distribution. If many data points are clustered within a small domain, they do not convey much information. Similarly, if many time courses are available but represent only a small portion of the possible space of values of the variables, not much is gained from additional, similar data.

As an example, Fig. 5 shows fits to the Hill function (Eq. (7); compare with Figs. 2–4) obtained with 50, 20, and 10 error-free points, respectively.

4.2. Piecewise power-law regression of a multivariate function

As a more complicated example, suppose we had analyzed N time series with K time points each from a metabolic pathway

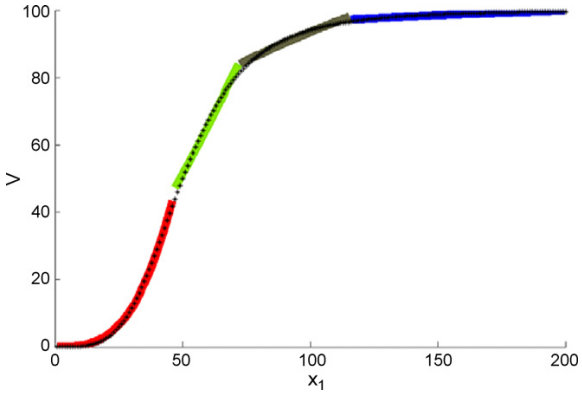

Fig. 4. A much improved fit is obtained if the former center interval (Fig. 3) is further split into two. The new residual error is SSE = 196.

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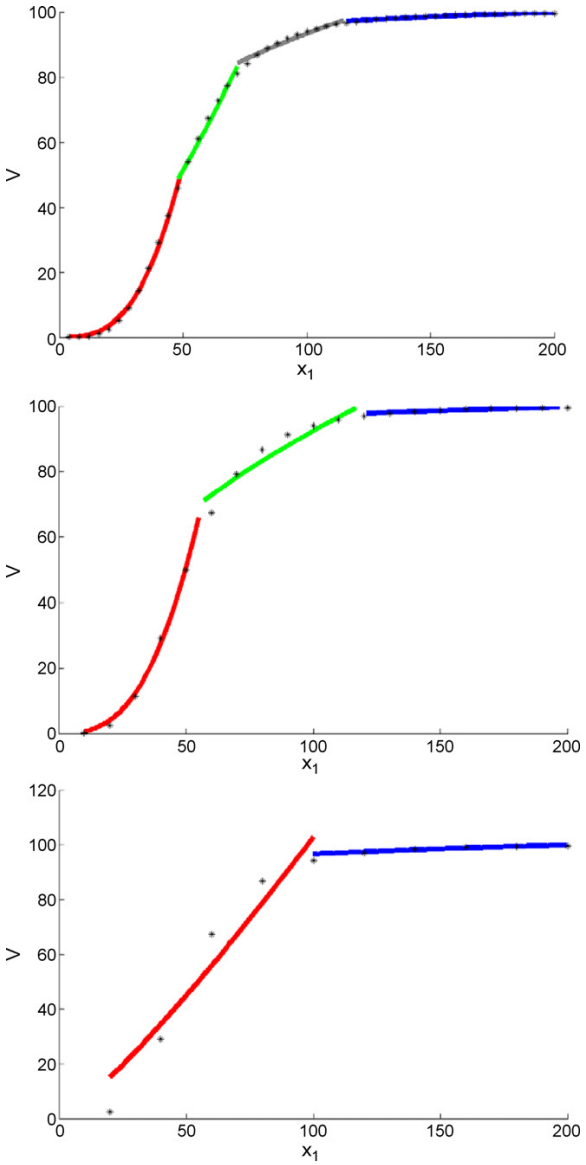

Fig. 5. Piecewise power-law fits to the Hill function in Eq. (7) when smaller numbers of data points are available than in Figs. 2–4. Reducing the number of data points to 50 (top panel) does not alter the earlier results much. If the number of data points is further reduced to 20 (center panel), four pieces can no longer be estimated, and the best option is a representation with three pieces. Finally, only 2 pieces are possible for a dataset containing 10 points (bottom panel).

system involving some number of metabolites. The differences between the N time series may be the result of different initial conditions, such as different amounts of substrate input. Under the action of the pathway system, each metabolite exhibits some time trend, which is affected directly or indirectly by some or all of the other variables. Suppose we had analyzed the data with DFE and that one of the processes in the system, V, was known to depend *directly* only on two of the system variables, x_1 and x_2, which themselves were affected by other variables. The result of the DFE analysis that is pertinent here would then consist of N data sets $\{x_1(t_k), x_2(t_k), V(t_k)\}_n$ $(k = 1, \ldots, K;\ n = 1, \ldots, N)$. The true function V, which we however pretend not to know, is a two-variable

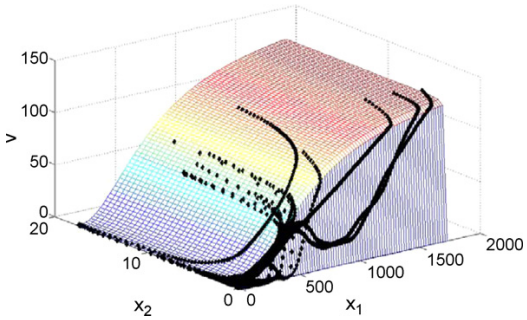

Fig. 6. Different datasets correspond to points that form trend lines lying on the surface given by Eq. (8). The shape and location of the trend lines depend, for instance, on the initial conditions of the pathway model, in which x_1 and x_2 are just two of several metabolites.

Hill function of the form

$$V(x_1, x_2) = \frac{V_m x_1^h x_2^h}{(K_{m1}^h + x_1^h)(K_{m2}^h + x_2^h)} \tag{8}$$

with the arbitrarily chosen Hill coefficient $h = 2$ for both components, a maximal velocity $V_m = 150$, and Michaelis constants $K_{m1} = 600$ and $K_{m2} = 0.1$.

Each dataset corresponds to a single time course and forms a dotted trend line on the three-dimensional surface that is given by Eq. (8) in the space of x_1, x_2, and V (Fig. 6). In reality this surface is unknown. Even with 13 complete datasets, the observed data constitute a rather sparse sample of the surface, demonstrating how difficult the quest for the minimal number of necessary data is (Fig. 6). In our example, the data are noise free, but noise is no hindrance to the partitioning and approximation method and is therefore ignored here for clarity.

The operating domain for the algorithm is specified as $\Omega = [\min(x_1), \max(x_1)] \times [\min(x_2), \max(x_2)]$. Fitting the data with a single two-variable power-law over the entire domain Ω yields an SSE of 180625 (results not shown). In order to reduce SSE, we execute the piecewise power-law method for two sub-domains ($S = 2$). The resulting representations in log space and Cartesian space are shown in Figs. 7 and 8. The residual error in this case is SSE = 101761

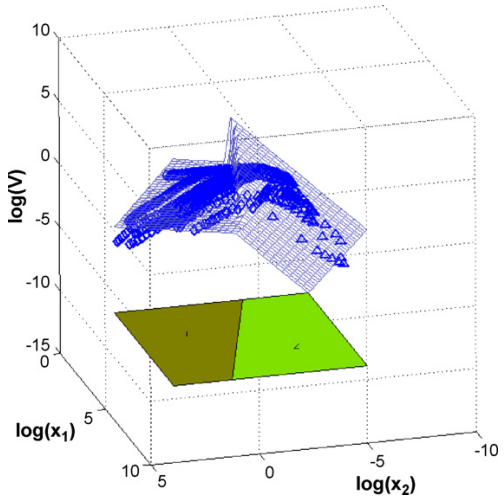

Fig. 7. Two-domain power-law representation for 13 datasets sampling the space (x_1, x_2, V) as trend lines (see text for explanations). The representation shown is in logarithmic coordinates. See Fig. 8 for a Cartesian representation.

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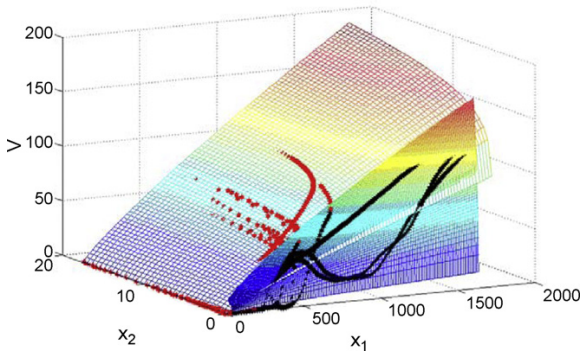

Fig. 8. Two-domain power-law representation for 13 datasets sampling the space (x_1, x_2, V) as trend lines (see text for explanations). In contrast to Fig. 7, the representation here is in Cartesian coordinates.

which corresponds to a reduction of about 40% over the single power-law fit.

As the next illustration we increase the number of sub-domains to $S = 4$. This higher resolution reduces SSE to 30976, which corresponds to about 80% of the single-domain fit, but one notes that the algorithm begins to suffer from an insufficient number of data points in some of the sub-domains. The results in log space and Cartesian space are shown in Figs. 9 and 10. One also notes the gaps in representation. These gaps are caused by MatLab's fast Proximal Support Vector Classification pattern-recognition algorithm for reconstructing the regions. If it is necessary to fill these gaps, a slower method such as Multi-category Robust Linear Programming (MRLP) must be employed.

It is not easy to judge the quality of approximation from these global plots. It is therefore useful to show how well individual time courses ($x_1(t_k)$, $x_2(t_k)$, $V(t_k)$) are represented by the four-piece power-law representation. Six examples are given in Fig. 11, where the black symbols represent the original data, while corresponding piecewise approximations are shown in different colors. One can see that the approximation quality depends on the particular dataset as well as the concentrations of x_1 and x_2.

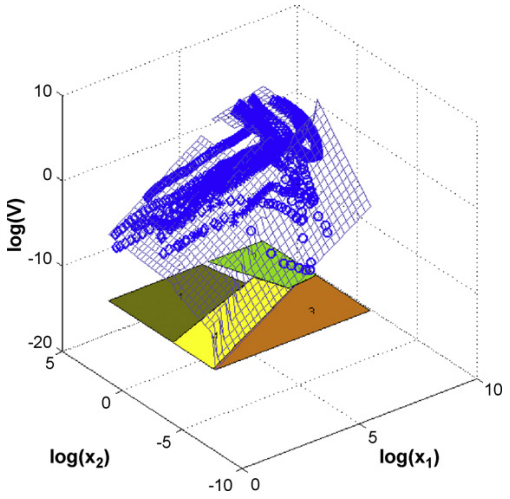

Fig. 9. Four-domain power-law representation for 13 datasets sampling the space (x_1, x_2, V) as trend lines (blue symbols; see text for explanations). The corresponding representation in Cartesian space is shown in Fig. 10. The fit with four pieces is significantly improved over a fit with two pieces (Fig. 7), with the SSE being reduced from 101761 to 30976.

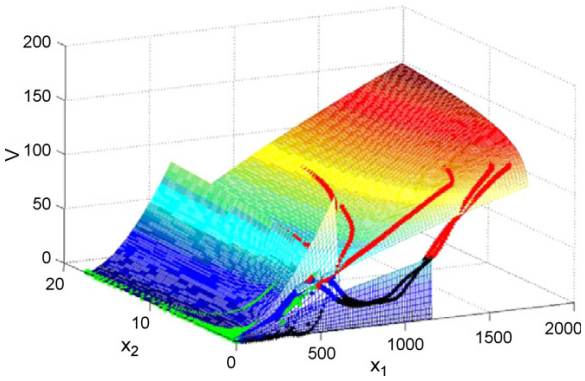

Fig. 10. Four-domain power-law representation for 13 datasets sampling the space (x_1, x_2, V) as trend lines. The corresponding representation in log space is shown in Fig. 9. The fit with four pieces is much better than the corresponding fit with two pieces (Fig. 8).

The algorithm is not limited to two dimensions and can, in principle, be applied to any number of dependent variables. Such examples are difficult to visualize and require rich datasets. Nonetheless, if such data are given, the algorithm performs the classification and piecewise representation quite quickly.

5. Discussion

Until about a decade ago, biomathematical modeling was in some sense easier, because the comparatively poor quality of data allowed for substantial latitude. For instance, even rather crude approximations were often still considered consistent with the modeled data, due to large experimental error bands. Recent developments in molecular and high-throughput biology have changed this situation. It is now feasible to measure comprehensive metabolic time series, sometimes even *in vivo* (Neves et al., 2000), and the resulting data are often so good and plentiful that inferior model descriptions can no longer survive and that it quickly becomes evident when the deviations between model and data are systematic, rather than statistic. Furthermore, methods like Dynamic Flux Estimation (DFE; Goel et al., 2008) reach beyond standard fitting routines by identifying individual flux representations and their dependency not only just on time but also on its contributing metabolites and modulators. While a significant step forward, this result leads to a new challenge, namely the identification of specific functional forms matching the inferred numerical flux profile. Experience in our lab indicates that these profiles are often much more complicated than previously assumed and that simple Michaelis–Menten, Hill, or power-law functions are sometimes, but not always, capable of representing them appropriately (Goel, 2009). This insight, in turn, suggests the need for either an intensified, yet targeted search for suitable local representations of metabolic processes, or an expansion of the simple canonical approximations that in the past were found to be useful defaults.

In this article we have discussed the second of the two options. Specifically, we showed how piecewise power-law representations for unknown functional relationships between fluxes and metabolites can automatically be constructed with a customized adaptation of software that had been proposed for piecewise linear systems analysis (Ferrari-Trecate and Muselli, 2002; Ferrari-Trecate et al., 2001a). This expansion is directly in line with Biochemical Systems Theory (Voit, 1991, 2000; Savageau, 1976; Torres and Voit, 2002) and the next logical step beyond piecewise definitions of single power-law functions (*e.g.*, Savageau, 2001, 2002).

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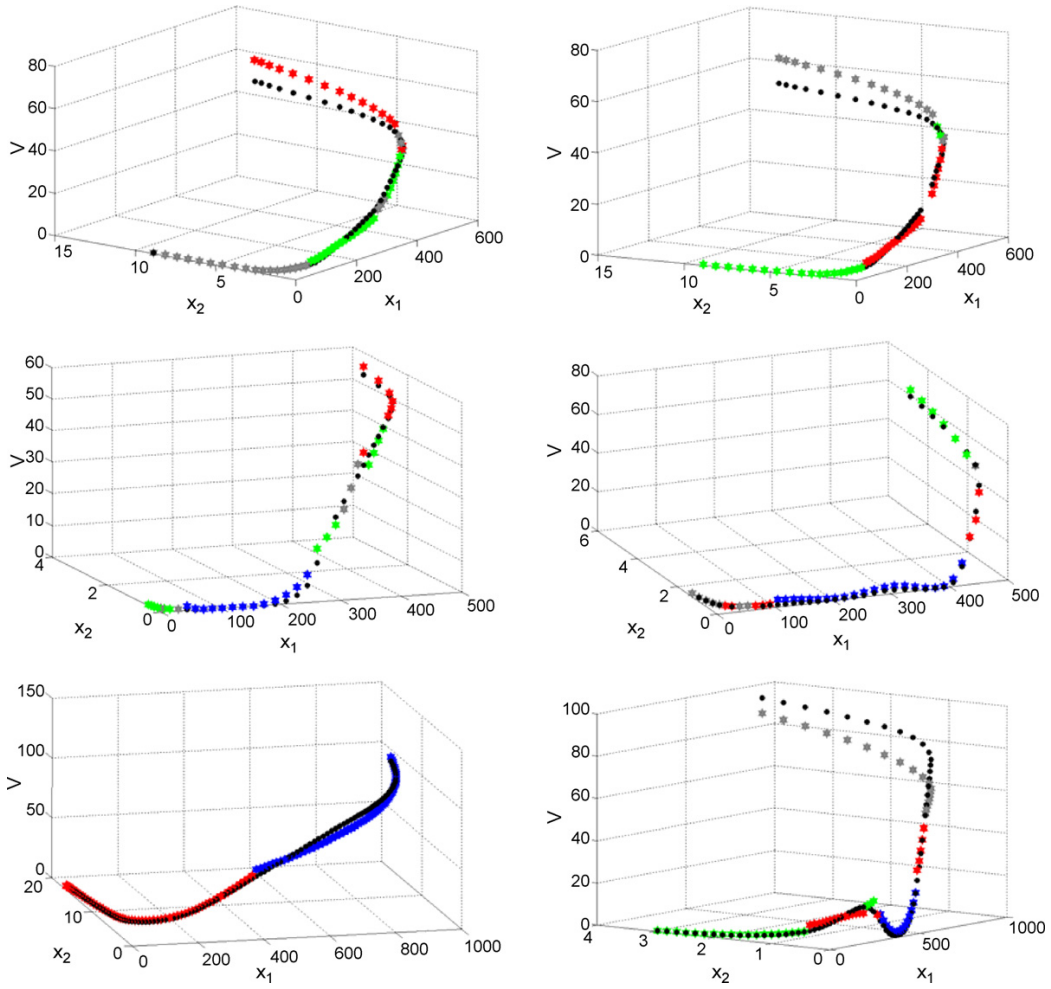

Fig. 11. Comparison of individual time trends in V as a function of its substrates x_1 and x_2. Depending on the particular dataset, the shape of V is quite different, and so is the quality of the piecewise power-law approximations. Error-free data are shown as black symbols and pieces of approximation in different colors.

The proposed algorithm resolves the main difficulty in reconstructing piecewise power-law representations, namely the simultaneous (integer-valued) subdivision of the variable space and the optimized (real-valued) estimation of parameters within each subdivision. Interestingly, this dual task is solved automatically and requires only a few settings of operational parameters, which however is not a problem. The number of clusters, S, can either be predetermined, increased sequentially, or estimated with an adaptive algorithm (Fritzke, 1997), and the number of neighboring points for each local regression (parameter c) can be tuned through cross-validation with a built-in option of the HIT software in Matlab (Ferrari-Trecate et al., 2003).

Theoretically, the proposed software permits arbitrarily accurate representations of univariate or multivariate processes. In reality, however, the method is limited by the number of data points and their representation of the manifold on which they lie. Metabolic time series that correspond to trend lines within a narrow sub-manifold constitute limited samples that may allow the inference of the sub-manifold, but not of the entire manifold, which might be of interest for extrapolation studies. Obviously, the method is also limited by the complexity of the manifold itself. If this manifold is smooth and monotonic, a few sub-domains with their own power-law models might be sufficient. By contrast, a ragged manifold will require many more sub-domains and quickly lead to situations where the data samples are no longer representative and sufficiently comprehensive.

By its nature, the proposed method usually leads to representations with gaps or discontinuities at the boundaries between sub-domains. These discontinuities come in two types. First, the illustrative examples identify gaps in the operating domain. These gaps are entirely due to the choice of a fast pattern-recognition algorithm by the software and can be circumvented with more complex and much slower methods. The second type of discontinuity results from the fact that the algorithm does not require the power-law representations to be continuous on the boundaries of sub-domains. In most practical applications, these discontinuities will be of no major concern. However, if the discontinuities are indeed undesirable, inspection of the collection of pieces might suggest a suitable nonlinear function that could capture the entire range of variation in variables. If so, this candidate function can be reverse-engineered and parameterized from the pieces, and the result is smooth throughout. In this sense, the proposed method is indeed a means for model identification, even if it is somewhat indirect. As an alternative, Appendix A discusses means of addressing

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this situation based on differential inclusions and Filippov's theory (Filippov, 1985).

While issues such as discontinuities should be investigated further, the proposed piecewise power-law representation, as it is described here, offers a welcome and relatively unbiased alternative to a potentially unlimited search for suitable functions.

Acknowledgments

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Appendix A.

The proposed piecewise power-law regression method naturally leads to discontinuities between neighboring sub-domains. In many cases, these jumps may not cause problems: one simply defines variables within sub-domains and uses one of the boundary values. Nevertheless, the question arises of whether it is possible in principle to define continuous solutions. A general answer is not trivial and requires concepts from Filippov's theory and differential inclusions (Filippov, 1985). These concepts are sketched out in the following.

Let us consider the generic vector equation

$$\dot{x} = f(x) \equiv V^+(x) - V^-(x), \tag{A1}$$

where $x = (x_1, x_2, \ldots, x_n)$ belongs to the open operating domain Ω whose closure $\bar{\Omega}$ is contained in the set $\Re^n_+ = \left\{(x_1, x_2, \ldots, x_n)\right\}, x_j > 0, j = 1, 2, \ldots, n$. Assume that after having performed the piecewise power-law regression we arrived at the following result: the influx (or efflux) function $V^+(x)$ (or $V^-(x)$) is approximated by $V^+ = \gamma^+ \prod_{j=1}^n x_j^{f_{ij}^+}$ if $x \in \Omega_i^+$ (or by $V^- = \gamma^- \prod_{j=1}^n x_j^{f_{ij}^-}$ if $x \in \Omega_i^-$), where the closures $\bar{\Omega}_i^\pm$ of the disjoint open subsets $\Omega_i^\pm \subset \Omega^\pm, i \in I^\pm$ satisfy $\bigcup_{i \in I^\pm} \bar{\Omega}_i^\pm \supset \Omega^\pm$. In other words, the open sets $\Omega_i^\pm$ constitute a partition of the set $\Omega^\pm$, which does not contain gaps as they appeared in Fig. 9; that is, we assume that the regression algorithm automatically removes possible gaps from the partition.

The approximation leads to the following vector equation

$$\dot{x} = \hat{f}(x) \equiv \hat{V}^+(x) - \hat{V}^-(x), \tag{A2}$$

where the functions $\hat{V}^\pm(x)$ are defined as follows

$$\hat{V}^\pm(x) = V_i^\pm(x) \equiv \gamma_i^\pm \prod_{j=1}^n x_j^{f_{ij}^\pm} \quad \text{if } x = (x_1, x_2, \ldots, x_n) \in \Omega_i^\pm, \quad i \in I^\pm.$$

This representation simply formalizes the fact that we merged different pieces of the functions $\hat{V}^\pm(x)$ that are defined differently over different operating sub-domains. As any of these pieces is an output of the automatically performed regression procedure, the functions $\hat{V}^\pm(x)$ may be discontinuous on the borders of the operating sub-domains, *i.e.*, on the sets $\Omega^\pm \backslash \bigcup_{i \in I^\pm} \Omega_i^\pm$, respectively. One also notes that the regression does not guarantee that the partitions $\Omega_i^\pm, i \in I^\pm$, coincide. This implies that the discontinuity set of the function $\hat{f}(x)$ in (A2) may be as big as the union of the respective discontinuity sets of the functions $\hat{V}^\pm(x)$. Hence the solutions of the vector equation (A2) are only well defined in any of the open subsets $\Omega_i^+ \cap \Omega_k^-$ provided that this subset is non-empty. More precisely, we are able to define mathematically and find (theoretically or numerically) a piece $x_{ij}(t)$ of the entire solution of the vector equation (A2) for time points t, where $x_{ik}(t) \in \Omega_i^+ \cap \Omega_k^-$. In this case, the solution satisfies the equation having the following power-law representation:

$$\dot{x} = \gamma_i^+ \prod_{j=1}^n x_j^{f_{ij}^+} - \gamma_k^- \prod_{j=1}^n x_j^{f_{kj}^-}. \tag{A3}$$

This representation is valid only for separate pieces of the entire trajectory, namely for those satisfying $x_{ik}(t) \in \Omega_i^+ \cap \Omega_k^-$.

Now the natural question arises of whether and how it is possible to join these pieces. The resulting trajectory should be continuous, being an approximation to the continuous solution $x(t)$ of the vector equation (A1). But unlike $x(t)$, this approximation may be non-smooth outside the subsets $\Omega_i^+ \cap \Omega_k^-$, as the right-hand side of the approximating vector equation (A2) is discontinuous there. An answer to the question of how to "glue together" the different pieces is not always trivial, even if we sacrifice the property of smoothness. In fact, it requires a more thorough treatment than we presented before.

We observe first that the solution to (A3) is not unique, because it still requires an initial value and an initial time. Assume that we know how to find any of these solutions and that we are able to check for which values of t the solutions belong to the sub-domain $\Omega_i^+ \cap \Omega_k^-$. We know as well that joining the pieces of the solution should produce a continuous function. Let us first consider the case where this problem can be easily solved. Assume that we have two adjacent sub-domains $G_1 = \Omega_{i1}^+ \cap \Omega_{k1}^-$ and $G_2 = \Omega_{i2}^+ \cap \Omega_{k2}^-$ having Γ as the common piece of the boundary. Assume further that the piece of the solution which belongs to G_1 hits Γ at some point χ at some time point t_0. In this case we may try to define a natural extension of the solution by solving the corresponding vector equation (A3) in G_2 under the additional initial value condition $x(t_0) = \chi$. If the resulting solution proceeds into the sub-domain G_2, then our problem is solved, at least as long as the solution belongs to G_2 for $t > t_0$. By definition, this solution is continuous in both G_1 and G_2, but its derivative may have a jump at $t = t_0$. This kind of solutions is well known in the theory of switching systems. Sometimes one calls the set Γ the *transparent* piece of the boundary, because the solution just travels through Γ like a ray of light.

However, this is not the only scenario. Assume, for instance, that the solution to the corresponding Eq. (A3) satisfying the initial condition $x(t_0) = \chi$ *does not* belong to G_2 for $t > t_0$. In other words, the solutions of the respective equations in the sub-domains G_1 and G_2 approach $\chi \in \Gamma$ from both sides, which means that the point χ is attractive. From the mathematical point of view both solutions stop at χ, but we know that this cannot be true, as no solution of the original vector equation (A1) can stop. Again, from the theory of switching systems it is known that such χ gives rise to so-called "sliding motions" along the piece Γ, which in this case is called "black." This situation is generic in a sense that it cannot be destroyed by small, even smooth, perturbations. In our setting such a situation would mean that the solutions cannot simply be joined at χ. To obtain a proper solution we need to trace the sliding motion along Γ which however cannot be constructed directly from the representation (A3). The solution may still leave Γ after some time, entering G_2 at some point χ_1 at time t_1, so that we will be able to calculate it as the solution of the corresponding Eq. (A3) subject to the initial condition $x(t_1) = \chi_1 (t > t_1)$ and provided that we know how to calculate t_1 and χ_1. The latter is only possible if

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we know exactly the behavior of the solution along Γ, which is a non-trivial problem in its own. Thus, the main disadvantage of the piecewise power-law regression method lies in the properties of the approximating solutions in the vicinity of the boundaries between the operating sub-domains. This disadvantage balances the considerable appeal of this method, namely that the power-law representation (A3) is often very efficient and fits biological data well.

The question therefore arises as to how to construct approximating solutions in the discontinuity set of vector equation (A2). A natural way to do this consists of using smooth approximations of Eq. (A2), which replace the right-hand side $\hat{f}(x)$ with a continuous approximation. However, such a replacement makes it impossible to exploit the representation in (A3) and thus removes the advantage of using the power-law formalism. In addition, one is left with very steep nonlinearities which are often difficult to handle.

An alternative approach goes back to Filippov's theory and is based upon differential inclusions, *i.e.*, differential equations with multi-valued right-hand sides. This approach enables us to define continuous trajectories of the approximating solutions without sacrificing the local power-law representations. The price we have to pay is non-uniqueness of the solutions themselves. The following offers a brief explanation for this phenomenon, based on ideas from Chapter 2 of Filippov's monograph (Filippov, 1985).

Assume that a point $x \in \Omega$ is a limit point for the sub-domains $G_m = \Omega_{im}^{+} \cap \Omega_{km}^{-}$ ($m = 1, 2, \ldots, M$), but not for any other sub-domain $G = \Omega_i^{+} \cap \Omega_k^{-}$, *i.e.*, $x \in \bar{G}_m$ ($m = 1, 2, \ldots, M$), but $x \notin \bar{G}$ for any other sub-domain. Inside each G_m the vector equation (A2) can be represented as in (A3):

$$\dot{x} = f(x, m) \equiv \gamma_{im}^{+} \prod_{j=1}^{n} x_j^{f_{ijm}^{+}} - \gamma_{km}^{-} \prod_{j=1}^{n} x_j^{f_{kjm}^{-}}. \tag{A4}$$

Let $F(x)$ be the least convex subset of $\Re^n$ containing all vectors $f(x, m)$ ($m = 1, 2, \ldots, M$), *i.e.*, $F(x) = co\{f(x, m) | m = 1, 2, \ldots, M\}$, and let us consider the following differential inclusion:

$$\dot{x} \in F(x) \tag{A5}$$

in the operating domain Ω. A solution to the inclusion (A5) on an interval $[a, b]$ is an absolutely continuous function $x(t)$, $t \in [a, b]$ which satisfies $\dot{x}(t) \in F(x(t))$ almost everywhere on $[a, b]$.

According to Filippov's theory, the initial value problem $x(t_0) = x_0$ has a solution for some $t > t_0$ provided that $x_0 \in \Omega$. The solution either exists for all $t > t_0$, or it blows up at some instant t_1: $x(t) \to \infty$ as $t \to t_1$. However, this solution is not unique in general.

If x belongs to some sub-domain, *i.e.*, if $x \in \Omega_i^{+} \cap \Omega_k^{-}$, then by definition $F(x) = \gamma_i^{+} \prod_{j=1}^{n} x_j^{f_{ij}^{+}} - \gamma_k^{-} \prod_{j=1}^{n} x_j^{f_{kj}^{-}}$ and we obtain the power-law representation (A3). This means that inside any $\Omega_i^{+} \cap \Omega_k^{-}$ the solutions of (A5) coincide with the solutions of (A3). But the inclusion (A5) gives us much more information about the solutions: it states how to join the separate pieces without losing control over continuity. Thus, any solution of the inclusion (A5) may be viewed as a continuous approximation of the solution to the vector equation (A1). Moreover, this approximating solution coincides with the solutions of Eq. (A3) on the respective sub-domains. Thus, we have solved (at least theoretically) the problem of how to define solutions of collections of differential equations obtained with piecewise power-law regression.

The approximations thus defined may be non-unique. To see why this is so, let us go back to the conventional method of calculating approximating solutions by replacing the right-hand side $\hat{f}(x)$ with its smooth approximations $\hat{f}_\alpha(x)$ where the parameter α indicates how good the approximation $\hat{f}_\alpha(x)$ is, *i.e.*, $\hat{f}_\alpha(x) \to \hat{f}(x)$ as $\alpha \to 0$. The smoothness of $\hat{f}_\alpha(x)$ guarantees the existence of a unique solution $x_\alpha(t)$ of the initial value problem $\dot{x} = \hat{f}_\alpha(x), x(a) = x_0$, say, on the interval $[a, b]$. According to Filippov's theory, the set $\{x_\alpha\}$ is compact in the topology of the uniform convergence on $[a, b]$, and any converging subsequence $\{x_{\alpha_\nu}\}$ approaches one of the solutions $x(t)$ of the differential inclusion (A5) satisfying the same initial condition $x(a) = x_0$. However, different approximations may give different limit solutions, so that non-uniqueness of the Filippov solutions means simply non-uniqueness of approximating solutions in the piecewise power-law regression algorithm. The latter is in turn the result of a very special shape of the approximation (A2): we know how the solutions look like inside any of the operating sub-domains $\Omega_i^{+} \cap \Omega_k^{-}$ due to the power-law representation (A3). However, between the operating sub-domains the behavior of the approximating trajectories becomes more uncertain, which is reflected in the possible non-uniqueness of the solutions outside these sub-domains.

In summary, the paper prescribes how to obtain piecewise power-law representations, even in high-dimensional spaces, but the problem of constructing *smooth* approximating solutions numerically is not solved. Some algorithms based on singular perturbation analysis may be useful for this purpose and can be found in (Plahte and Kjoglum, 2005). Similarly, characterization of the convergence of the approximating solutions, *i.e.*, the solutions of the differential inclusion (A5) to the solutions of the vector equation (A1), is beyond the scope of this paper. The major difficulty of this characterization is the mean-square convergence of the approximations in the piecewise power-law regression, which is distinct from the standard uniform convergence used in the theory of differential equations and inclusions. It is likely that additional assumptions on the influx and efflux functions $V^{+}(x)$ and $V^{-}(x)$ are needed in order to prove convergence of the approximating solutions.

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Paper IV

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Convergence properties of piecewise power-law approximations to kinetic processes in Systems Biology models

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Abstract We address a problem of convergence of approximations obtained from two versions of the piecewise power-law representation arisen in Systems Biology. The most important case of the mean square (L^2) convergence is analyzed in detail, but the uniform convergence is studied as well. Advantages and drawbacks of piecewise power-law representations from the theoretical and practical point of view are discussed, and some ideas of how to use piecewise approximations are suggested, where the emphasis is put on the so-called "Saturable and Cooperative (SC) Formalism", as the latter has a strong biological motivation. Illustrating examples show the practical utility of the methods.

Keywords power-law representation · piecewise approximation · least-squares minimization · mean square and uniform convergence · saturable and cooperative formalism

Mathematics Subject Classification (2000) 40A30 · 41A65 · 42C45 · 65D15

1 Introduction

Mathematical representation of kinetic processes, i.e. enzymatic catalyzed reactions that are part of complex metabolic networks, is a challenge for obtaining useful models in Systems Biology. Although mechanistic descriptions provide a detailed account of the underlying processes, a close form for the rate of the process can be obtained only under specific simplifying assumptions. Thus, classical enzyme rate-laws are approximations to the actual dynamic processes that are associated to each step of the mechanism. The validity of these rate-laws in conditions other than those corresponding to the assumptions used in their derivation is open to question (Savageau 1993, 1995). At the best, the previous strategy produces mathematical representations with a case-dependent mathematical structure that, in general, are too much complicated for modeling purposes. Furthermore, in most cases the involved parameters are difficult to identify with a reasonable experimental effort.

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An alternative that may help obtaining useful models is to use mathematical approximations that lead to canonical representations and simplify the modeling task and the estimation of parameters from experimental data. Of course, by doing that we pay an additional price of accuracy that will now be restricted to a given range around an operating point. The Power-Law Formalism (Savageau 1969a,b, 1970) is one of these alternative representations. It is based on a Taylor series linear approximation of the actual function in the Logarithmic ("log-log") space (Alves et al 2008). As a result, an unknown kinetic function that depends on n variables can be approximated at a given operating point $(x_{1_0}, .., x_{n_0})$ as:

$$v_r(x_1, .., x_n) = \gamma_r \prod_{j=1}^{n} X_j^{f_{rj}}, \tag{1}$$

where γ_r and f_{rj} are the apparent rate-constant and kinetic-orders defined as:

$$f_{rj} = \left(\frac{\partial v_r}{\partial X_j}\right)_0 \frac{X_{j_0}}{v_{r_0}}, \tag{2}$$

and

$$\gamma_r = v_{r_0} \prod_{j=1}^{n} X_{j_0}^{-f_{rj}}. \tag{3}$$

The Power-Law Formalism has been successfully applied to a wide number of problems. His main advantage is that the models are systematic and relatively easy to analyze. In practice, power-law representations can be derived in different ways: (1) As a local approximation at a given operating point (Savageau 1969a,b, 1970); (2) Using a piecewise representation that takes into account a different power-law in different regions (Savageau 1969a, 2002); (iii) As a result of fitting experimental data that encompasses a given range of values (Hernández-Bermejo et al 2000; Chou and Voit 2009); and (iv) As an exact representation through recasting a non-linear model into a power-law form (Savageau and Voit 1987). Each of these alternatives has its advantages and drawbacks. When it comes to numerical models, recasting and piecewise representations may have advantages. However, recasting can only be used if we know the actual function. This precludes using this technique in many cases. Piecewise representations can be obtained either by qualitative modeling or from actual data (Machina et al 2010).

Power-law models are particularly well suited for analyzing design principles in biological networks (Savageau 1975b,a, 1977, 2002). In this kind of problems, alternative designs for a given network are analyzed to identify the functional advantages linked to specific designs when compared to the alternatives. The concept of design space helps in discussing the possible phenotypes associate to parameter values by identifying boundaries between qualitatively different regions (Savageau et al 2009). In this case, piecewise representation of the target system helps in the process.

Piecewise representations are appealing as they may cover the whole variation of the rate as a function of the underlying metabolites while maintaining in each subregion a simple power-law representation. In this way, we can keep track of cooperativity and saturation for each of the involved variable. Following similar arguments as those used for developing the Power-Law Formalism, an alternative representation that has been recently suggested is the Saturable and Cooperative (SC) Formalism (Sorribas et al 2007), which results from Taylor series approximation of an unknown function in a space of generalized-inverses (see (Sorribas et al 2007) for details). The SC representation includes saturation and cooperativity and may serve as both a complement and an alternative to the piecewise representation.

In this paper we shall explore the convergence of piecewise power-law representations to kinetic functions that can exhibit cooperativity and saturation. Also we shall briefly discuss the practical utility of the obtained representations and its connection to SC representations.

2 Description of the mathematical framework

Let us consider a system of the form

$$\dot{x_i} = \sum_{r=1}^{p} \mu_{ir} v_r(x_1, .., x_{n+m}), \tag{4}$$

where index $i\,(i = 1, ..., n)$ refers to dependent variables, while higher indices $(n+1, ..., n+m)$ refer to independent variables. The function $v_r(x_1, .., x_{n+m})$ accounts for the rate of a given process, while μ_{ir} is a stoichiometric factor that accounts for the number of molecules of x_i produced, i.e. $\mu_{ir} = 1, 2, ...$ or $\mu_{ir} = -1, -2, ...$

Once the functions v_r are specified, simulations with the model in Eq. (4), representing a complex biological system, are easily performed, and many methods are available for mathematical analyses of features such as local stability or parameter sensitivities at the systems steady states. However, before such analyses are feasible, it is necessary to specify the functions in the model.

For simply shaped flux profiles $v_r(x)$, a possible candidate is a power-law (PL) representation of the form

$$v_r^{\mathrm{PL}}(x_1, x_2, ..., x_{n+m}) = \gamma_r \prod_{j=1}^{n+m} x_j^{f_{rj}}, \tag{5}$$

where the rate constants γ_r are non-negative and the kinetic-orders f_{rj} are real numbers.

For the sake of notational convenience, as we will intend to approximate any of the functions v_r, we put $m = 0$ and omit the index r in the calculations, so that

$$v^{\mathrm{PL}}(x_1, x_2, ..., x_n) = \gamma \prod_{j=1}^{n} x_j^{f_j}, \tag{6}$$

Power-law representations are intensively exploited in approximations because they are non-linear and cover a rich repertoire of functional responses when they are embedded in differential equations (4), yet individually permit a simple logarithmic transformation to linearity.

Applying the logarithmic transformation to the power-law representation v^{PL} of the function $v(x)$, we obtain

$$\begin{aligned} &y_j = \log x_j, \quad j = 1, ..., n, \\ &v^{\mathrm{PL}}(x_1, x_2, ..., x_n) = \exp(f_1 y_1 + ... + f_n y_n + c), \\ &v(x_1, x_2, ..., x_n) = \exp(\psi(y_1, y_2, ..., y_n)), \end{aligned} \tag{7}$$

where $c = \log(\gamma)$. In the classical formulation of the Power-Law Formalism the sum $f_1 y_1 + ... + f_n y_n + c$ can be interpreted as the first order Taylor series approximation of the actual, in general non linear, function $\psi(y)$.

Although Taylor-based power-law representation can be adequate for many applications, it might be desirable to give an approximation of the function over a range which cannot be covered by its approximation in a single operating point. We would look for a method that, without leaving the Power-Law Formalism, would lead to a better representation of the behavior of the target function within the selected range.

In (Hernández-Bermejo et al 2000) a least-squares (LS) minimization is used to provide a way for defining the power-law approximation to rate laws $v(x_1, ..., x_n)$. Minimization is constrained within the operating domain $\Omega \in \mathbb{R}_+^n \setminus \{0\}$ in such a way that the following integral achieves a minimum:

$$\int_{\Omega} \left[v(x_1, ..., x_n) - \gamma \prod_{j=1}^{n} x_j^{f_j} \right]^2 dx_1 ... dx_n \to \min . \tag{8}$$

Thus, the problem amounts to determining the set of LS kinetic-orders f_j and the LS rate constant γ.

The advantage of a model with operating domains is obvious if the actual dynamics of the system should be considered over the entire range. This new formulation is more consistent, as it was shown in (Hernández-Bermejo et al 2000), with the results that can be obtained by fitting experimental data. In practice, data fitting from dynamic data may proceed in a quite different way, thus producing a power-law model that, overall, describes the available data according to specific criteria (see (Chou and Voit 2009) for a review). In any case, the resulting power-law functions are no longer local representations in the sense of the original definition.

3 Piecewise power-law approximation

In general, even the model with operating domains can have low accuracy. For example, if the operating domain is wide, the target function can run through saturation and cooperativity. In that case, power-law approximations cannot capture these features at the same time (see the examples in Section 6). A piecewise power-law (PWPL) representation provides a logical extension to a single power-law over an operating domain (Savageau 2002).

The problem of a piecewise power-law regression is not straightforward, because, given a function $v : \Omega \to \mathbb{R}_+$, one has to compute both a partitioning into sub-domains and an approximation to v within each of the sub-domains.

Because of the mixed nature of the problem, classical approximation techniques cannot be directly applied, and it is instead necessary to use a specific, customized method. The principles of such a method were introduced a few years ago for the simplest situation, where the regions in the space of variables are polyhedra and the behavior of an unknown function in each region is approximated by a linear expression (Ferrari-Trecate and Muselli 2002; Ferrari-Trecate et al 2001).

The adaption to power-law functions begins with a logarithmic transformation of the data. In the logarithmic coordinates, a piecewise power-law function becomes piecewise linear (PWL). Thus, one can implement the algorithm of the piecewise linear regression from (Ferrari-Trecate and Muselli 2002; Ferrari-Trecate et al 2001) to the logarithmic data and obtain an optimal polyhedral partition of the input domain in the Logarithmic space and the best piecewise linear approximation.

Let Δ be a polyhedral domain in the Logarithmic space $\mathbb{R}^n$ and $\Psi(y) = \log(v(x))$, so that $\Psi : \Delta \to \mathbb{R}$.

Let also the number N of the sub-domains be fixed. Partitions $\{\Delta_s\}_{s=1}^N$ of Δ are assumed to be polyhedral as well. The target of piecewise linear regression from (Ferrari-Trecate and Muselli 2002; Ferrari-Trecate et al 2001) is to determine a polyhedral partition $\{\Delta_s\}_{s=1}^N$ and a piecewise linear function

$$\psi^{\mathrm{PWL}}(y) = \psi_s(y) = w_{s0} + \sum_{j=1}^{n} w_{sj} y_j, \quad y \in \Delta_s \tag{9}$$

(thus assuming its linear behavior in each region Δ_s) which minimize the functional

$$\begin{array}{l} \int\limits_{\Delta} \left[\Psi(y_1, ..., y_n) - \psi(y_1, ..., y_n))\right]^2 dy_1 ... dy_n = \\ \sum_{s=1}^{N} \int\limits_{\Delta_s} \left[\Psi(y_1, ..., y_n) - \psi_s(y_1, ..., y_n))\right]^2 dy_1 ... dy_n \\ \to \min \end{array} \tag{10}$$

The minimum is taken over all polyhedral partitions $\{\Delta_s\}_{s=1}^N$ of Δ and all piecewise linear approximations ψ_s $(s = 1, ..., N)$.

Scalar weights $w_{s0}, w_{s1}, ..., w_{sn}$, for $s = 1, ..., N$ uniquely characterize the function ψ in Δ_s. For notational purposes, the weights can be collected in a vector w_s. Since the regions Δ_s are polyhedral, they can be defined by a set of linear inequalities of the type:

$$a_{sj0} + \sum_{k=1}^{n} a_{sjk} y_k \leq 0. \tag{11}$$

The scalars a_{sjk} for $j = 1, ..., l_s$ and $k = 0, 1, ..., n$ can be collected in a matrix A_s whose estimation also was the target of the reconstruction process for every $s = 1, ..., N$. Discontinuities are allowed and indeed are often present at the boundaries between two regions Δ_s.

As long as the partition is known, one can perform a linear regression over each of the subdomains Δ_s and thus find the piecewise linear function $\psi^{\mathrm{PWL}}(y)$. The construction of the optimal partition is based on a special clustering algorithm. The details can be found in (Ferrari-Trecate and Muselli 2002; Ferrari-Trecate et al 2001) (see also (Machina et al 2010).

When we apply the inverse logarithmic transformation, the polyhedral partition that is produced by the algorithm for logarithmic data becomes a partition of the initial input domain by nonlinear surfaces given by

$$a_{sj0} + \sum_{k=1}^{n} a_{sjk} \log x_k \leq 0, \tag{12}$$

where the coefficients a_{sjk}, $k = 0, 1, ...n$, $s = 1, ..., N$ are known and obtained by the algorithm. The inverse logarithmic transformation

$$v^{\mathrm{PWPL}}(x) = \exp(\psi^{\mathrm{PWL}}(y))$$

defines a piecewise power-law approximation to an unknown function $v(x)$, where sub-domains of the partition are defined by (12).

The procedure has all the advantages of the linear regression. However, because the logarithmic transformation distorts the error structure of the problem, the least squares error for the resulting piecewise power-law is in general less accurate than the corresponding error for a power-law regression of the original data. As a partial remedy, it is therefore advantageous to apply a power-law regression to the original data over each of the N regions in (12). Even though the regression is now nonlinear, the increase in difficulty is modest, due to the partition in small pieces. In other words, the partition of the initial domain localizes the process of approximation to sub-domains, thereby reducing the risk of failure of the power-law regression. While this modification reduces error distortion to some degree, it does not affect that part of the algorithm, in which the boundaries of the domains are determined. As a consequence, the domains are optimal in the Logarithmic space but not necessarily in the Cartesian space. The distortion constitutes the price one has to pay for the automated nature of the segmentation process. It may be undesirable, but becomes less influential as the algorithm uses higher numbers of segments.

In the next section we discuss advantages and disadvantages of both approaches.

3.1 Least squares criteria in the Cartesian and Logarithmic spaces

Here we will discuss two different ways to obtain a piecewise power-law approximation when a partition of the input domain is known. The partition is defined by (11) in the Logarithmic space (respectively, by (12) in the Cartesian space) and, according to the algorithm in (Ferrari-Trecate and Muselli 2002; Ferrari-Trecate et al 2001), is optimal in the Logarithmic space.

Let Δ be a polyhedron in the Logarithmic space R^n. Suppose that Δ is the image of the domain Ω in the Cartesian space $R^n_+ \setminus \{0\}$. Let (11) define a partition $\{\Delta_s\}_{s=1}^N$ of Δ, $\Delta_s \cap \Delta_j = \emptyset$ for every $s, j = 1, ..., N$ and $\bigcup_{s=1}^N \Delta_s = \Delta$. Let $\{\Omega_s\}_{s=1}^N$ be the corresponding partition of Ω in the Cartesian space $R^n_+ \setminus \{0\}$.

Let $v : \Omega \to R_+$ and let the function $\psi : \Delta \to R$ be given by $\psi(y) = \log v(x)$, $y = \log x$.

Since the partition is optimal in the Logarithmic space, it is natural to complete the approximation procedure in the logarithmic coordinates. Then, over each of the sub-domains Δ_s a power law function is represented in the linear form (see (7)) and its coefficients can be obtained from the least squares minimization criterion

$$\int_{\Delta_s} \left[\psi(y_1, ..., y_n) - (f_1 y_1 + f_2 y_2 + ... + f_n y_n + c)\right]^2 dy_1 ... dy_n \to \min, \tag{13}$$

where the constant c is defined in (7).

Another approach is as follows: using the optimal partition in the Logarithmic space one performs the inverse logarithmic transformation to find a power-law approximation to the original function in the Cartesian space over each of Ω_s, i.e. using the following minimization criterion:

$$\int_{\Omega_s} \left[v(x_1, ..., x_n) - \gamma \prod_{j=1}^{n} x_j^{f_j} \right]^2 dx_1 ... dx_n \to \min . \tag{14}$$

The main advantage of the criterion (13) is its linearity that provides the uniqueness of the solution and also makes the process of finding the solution computationally cheap, as it is based on explicit matrix formulas. On the other hand the use of the logarithmic transformation requires caution. The influences of the data values will change, as will the error structure of the model.

Obviously, the criterion (14) gives better approximation in terms of the LS error in the Cartesian space. However, a nonlinear regression algorithm should be used in this case, which is less

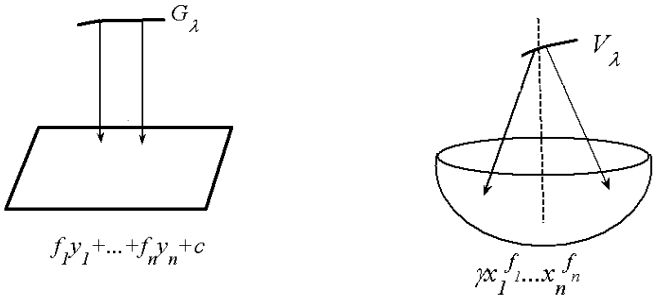

Fig. 1 Convex vs. nonconvex projection sets

advantageous, especially when the number of the estimated parameters is big. In addition, the nonlinear regression may have other drawbacks, one of which is ill-posedness.

Below we show that the nonlinear regression in the case of the minimization criterion (14) is indeed ill-posed.

Hence both criteria have their strong and weak sides, so that the choice between them must be undertaken by modeling considerations.

Now let us consider an example when the minimization problem (14) is ill-posed.

Example 1 Let us assume that $v(x)$ is only known with a certain accuracy, as it is often the case. Mathematically, we will describe this situation by letting v depend on a (small) parameter λ, i.e. $v = v_\lambda(x)$ (and so becomes the function $\psi = \psi_\lambda(y)$ as well). But it turns out, as we will show below, that for certain values of λ small perturbations may cause a "jump" in the corresponding power-law representation, i.e. while functions $v_\lambda(x)$ remain close to each other, the least-squares minimization criterion (14) may produce the power-law representations that are very different.

This ill-posedness is caused by the fact that the set $\{\gamma x_1^{f_1}...x_n^{f_n}\}$ from (14) is a non-convex set. Let us remind that given a linear space L, a set $M \in L$ is said to be *convex* if whenever it contains two points x and y, it also contains the segment joining x and y. For example, $\{f_1y_1 + f_2y_2 + ... + f_ny_n + c\}$ from (13) is a vector space and therefore a convex set.

Geometrically, we can think of a LS power-law (respectively, linear) representation of a given function as its projection onto the set of functions of the form $\{\gamma x_1^{f_1}...x_n^{f_n}\}$ (respectively, $\{f_1y_1 + f_2y_2 + ... + f_ny_n + c\}$).

When the projection set is convex, the problem is always well-posed. This is the case with the projection of the parameterized point ψ_λ onto $\{f_1y_1 + f_2y_2 + ... + f_ny_n + c\}$, see Figure 1. This means that for any point its projection onto a convex set is unique and the projections of two points are close to each other if the points are close to each other. Graphically, there is no jump in the projection function of the parameterized point, if the point depends continuously on the parameter λ.

However, if we are dealing with a nonconvex projection set, for example with the set $\{\gamma x_1^{f_1}...x_n^{f_n}\}$, then for certain parameterized sets of points (e.g. for the dotted line in Figure 1) the corresponding projection functions may have jumps around certain critical values of λ.

Let us illustrate this fact analytically considering a specific example. We will consider, only for the sake of simplicity, a function $v(x)$ of one variable

$$\int_L^U (v(x) - \gamma x^f)^2 dx \to \min . \tag{15}$$

Using MATLAB we will also provide some graphical representations.

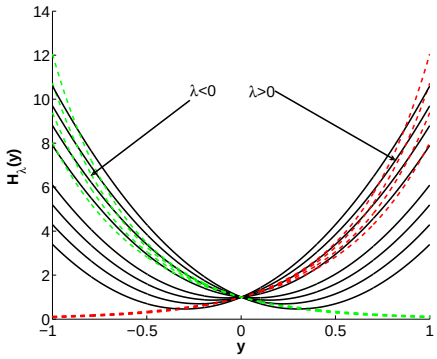

Fig. 2 The continuous lines represent the function $H_\lambda(y)$ for different values of λ and the dotted lines give its LS approximation. Red color corresponds to the values $\lambda > 0$, while green color describes the case $\lambda < 0$

If $v = v_\lambda(x)$, then γ and f that minimize (15) are also functions of λ.

We first consider a simpler problem assuming that $\gamma = \text{const}$, so that after rescaling we may assume that $\gamma = 1$ and rewrite (15) as

$$\int_L^U \left(v_\lambda(x) - x^{f_\lambda}\right)^2 dx \to \min$$

After applying the variable substitution $y = \log x$, $a = \log U$, $b = \log L$, we obtain

$$\int_a^b \left(v_\lambda(e^y) - e^{y f_\lambda}\right)^2 e^y dy \to \min$$

or

$$\int_a^b \left(H_\lambda(y) - e^{\beta_\lambda y}\right)^2 dy \to \min, \tag{16}$$

where $H_\lambda(y) = v_\lambda(e^y)e^{y/2}$, $\beta_\lambda = f_\lambda + 1/2$.

Now, let the operating interval be $[-1, 1]$. Consider the specific function defined as $H_\lambda(y) = 3\lambda y + 6y^2 + 1$ and its LS power-law approximation $e^{\beta(\lambda)y}$.

It is easily seen that the projection function $e^{\beta(\lambda)y}$ is discontinuous in λ (see Figure 2). Figure 3 gives a graphical representation of this discontinuity in λ for one value of y.

Of course, we can always go back to the variable x. The above function becomes then $v_\lambda(x) = \dfrac{3\lambda \log x + 6\log^2 x + 1}{\sqrt{x}}$, the operating interval being given by $[1/e, e]$. But the discontinuity in λ will of course be preserved.

Let us now consider the general scalar case as it is given by the minimization criterion (15). Using the same function $H_\lambda(y)$ as before we in a similar way obtain its LS power-law approximation given by $e^{\beta(\lambda)y + c(\lambda)}$ where $c_\lambda = \log\gamma$, $\gamma = \gamma(\lambda)$. The results of approximations are depicted in Figures 4 and 5. Again, we observe a discontinuity of the projection function in λ.

This example shows that the criterion (8) may produce a LS power-law approximation that is not stable under small perturbations of the parameter λ and by this under small perturbations of the target function, which causes ill-posedness of the minimization problem. We stress also that this effect is generic, i.e. independent of the number of the involved parameters, as the comparison of Figures 2 (resp. Figure 3) and Figure 4 (resp. Figure 5) clearly demonstrates.

4 L^2-convergence of piecewise power-law approximations obtained in the Cartesian and Logarithmic spaces

In this section we continue to analyze mathematical justification of the piecewise power-law model focusing on the convergence properties of the piecewise approximations constructed in (Machina

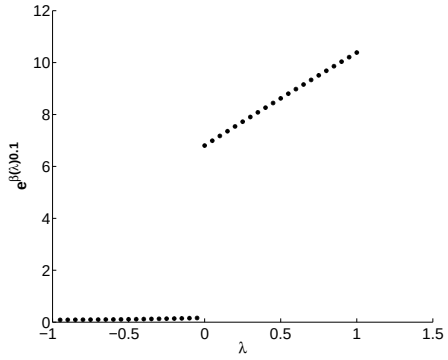

Fig. 3 This graph demonstrates how the LS power-law approximation at $y = 0.1$, i.e $e^{\beta(\lambda)0.1}$, depends on λ. We see that $\beta(\lambda)$ is discontinuous at $\lambda = 0$

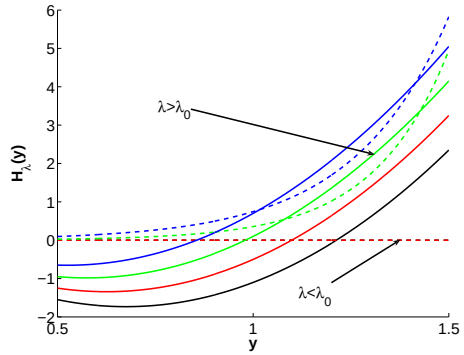

Fig. 4 The continuous lines represent the functions $H_\lambda(y)$ for different values of λ and the dotted lines give its LS approximations within the operating interval $[0.5, 1.5]$. Blue and green colors correspond to the values $\lambda > \lambda_0$, while red and black colors describe the case of $\lambda < \lambda_0$

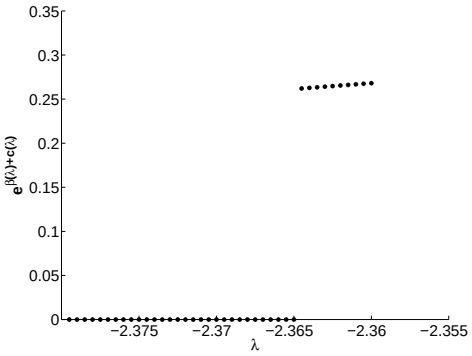

Fig. 5 This graph explains how the LS power-law approximations at $y = 1$, i.e $e^{\beta(\lambda)+c(\lambda)}$, depend on λ. We see that $\beta(\lambda) + c(\lambda)$ is discontinuous at $\lambda_0 \approx -2.365$

et al 2010). The main question can be formulated as follows: do these approximations of a given target function converge to this function when the number of sub-domains in the partitions increases. An important issue to be studied concerns the topology of this convergence, which depends on the overall mathematical model. Since the approximations include minimization in the L^2-metric, we consider first L^2-convergence conditions, while in the next section we will concentrate on the uniform convergence which is topologically stronger.

The main technical challenges stemming from the approximation algorithm can be summarized as follows: 1) the L^2-convergence of the approximations in the logarithmic space may not imply the L^2-convergence of their images in the Cartesian space (and vice versa); 2) it is not evident that

automatic dissection of the operating domain makes the diameters of the sub-domains go to zero even if the number of sub-domains tends to ∞.

We review here some notation. Let $v : \mathbb{R}^n_+ \setminus \{0\} \to \mathbb{R}_+$, and let $\psi : \mathbb{R}^n \to \mathbb{R}$ be given by $\psi(y) = \log v(x)$, $y = \log x$.

Let Ω be a domain in the Cartesian space $\mathbb{R}^n_+ \setminus \{0\}$. We assume Ω to be closed and bounded (i.e. compact) subset of $\mathbb{R}^n$. Let Δ be its image in the Logarithmic space $\mathbb{R}^n$ and $\{\Delta_i^N\}_{i=1}^N$ be a measurable partition of Δ. This means that Δ_i^N are all Borel measurable subsets of $\mathbb{R}^n$, $\Delta_i^N \cap \Delta_j^N = \emptyset$ for every $i, j = 1, ..., N$ and $\bigcup_{i=1}^N \Delta_i^N = \Delta$ for any natural N. The reason why we cannot assume the sub-domains to be closed, is that it would contradict the second assumption of disjointness.

Let $\{\Omega_i^N\}_{i=1}^N$ be the corresponding partition of Ω in the Cartesian space.

We also put $\delta^N = \max\limits_{1 \le i \le N} (\operatorname{diam}(\Delta_i^N))$.

For a given number N of sub-domains we let $v_i^N(x) = \gamma_i^N \prod\limits_{j=1}^n x_j^{f_{ij}^N}$ be the LS power-law approximation to the function v on Ω_i^N, $i = 1, ..., N$. For $x \in \Omega$ we consider a piecewise power-law function $v^N(x) = v_i^N(x)$, whenever $x \in \Omega_i^N$. We put $\psi^N(y) = \log(v^N(x))$.

We also put $\Psi_i^N(y) = c^N + \sum\limits_{j=1}^n f_{ij}^N y_j$, $c^N = \log(\gamma^N)$, being a LS linear approximation to the function ψ on Δ_i^N, $i = 1, ..., N$. For $y \in \Delta$ we consider the piecewise linear function $\Psi^N(y) = \Psi_i^N(y)$, whenever $y \in \Delta_i^N$. We put also $V^N(x) = \exp(\Psi^N(y))$.

The results below provide the L^2-convergence of piecewise power-law approximations whose parameters were obtained either in the Logarithmic space (V^N) or in the Cartesian space (v^N), or in other words, according to the minimization criteria (13) and (14), respectively.

In the first theorem we do not assume that $\{\Delta_i^N\}_{i=1}^N$ is an optimal polyhedral partition in the Logarithmic space obtained by the algorithm described in Machina et al (2010) or briefly in Section 3.

Theorem 1 *Let the target function v be continuous on Ω and $\psi = \log v$. Suppose that for each natural number N the measurable partition $\{\Delta_i^N\}_{i=1}^N$ satisfies the property $\delta^N \to 0$ $(N \to \infty)$. Then for the corresponding LS approximations Ψ^N (in Δ) and v^N (in Ω) we have $\Psi^N \to \psi$, $v^N \to v$ in the respective L^2-norms if $N \to \infty$.*

To prove this theorem we need the following lemma:

Lemma 1 *Let v be continuous on Ω and $\psi = \log v$. Let the measurable partition $\{\Delta_i^N\}_{i=1}^N$ satisfy the property $\delta^N \to 0$ $(N \to \infty)$, $y_i^N \in \Delta_i^N$ and $\theta^N(y) = \psi(y_i^N)$ for all $y \in \Delta_i^N$. Then the functional sequence $\{\theta^N\}$ (resp. $\{\Theta^N\} = \{\exp(\theta^N)\}$) converges to ψ (resp. v), and this convergence is uniform on Δ (resp. Ω).*

Proof. We start first with the convergence in the Logarithmic space. Let us notice that the function $\psi = \log v$ is continuous on Δ and Δ is compact, as it is the image of the compact set Ω under the continuous transformation. That is, the function ψ is uniformly continuous on Δ, so that given an $\varepsilon > 0$ there exists a $\delta > 0$ for which $|y - y'| < \delta$, $y, y' \in \Delta$ implies $|\psi(y) - \psi(y')| < \epsilon$. Let N be chosen in such a way that $\delta^N < \delta$ for all $N \ge N_0$. If $y \in \Delta_i^N$, then we have

$$|\psi(y) - \theta^N(y)| = |\psi(y) - \psi(y_i^N)| < \varepsilon,$$

as $y, y_i^N \in \Delta_i^N$ and $\operatorname{diam} \Delta_i^N < \delta^N < \delta$, which gives uniform convergence of the sequence $\{\theta^N\}$ on Δ.

A similar argument can be applied to the sequence $\{\Theta^N\}$ on Ω if we prove that $\tilde{\delta}^N = \max\limits_{1 \le i \le N} (\operatorname{diam}(\Omega_i^N)) \to 0$ as $N \to \infty$. This fact follows however from the uniform continuity of the inverse logarithmic transformation on the compact set Δ. $\square$

Proof of **Theorem 1.** We use the sequences

$$\{\theta^N\} \quad \text{and} \quad \{\Theta^N\} = \{\exp(\theta^N)\}$$

from the lemma 1, which both converge uniformly and therefore in the L^2-sense in the respective input domains.

Since $\Psi^N(y)$ is the LS piecewise linear approximation in the input domain Δ and $v^N(x)$ is the LS piecewise power-law approximation in the input domain Ω, we have

$$\|\Psi^N - \psi\|_{L^2(\Delta)} \leq \|\theta^N - \psi\|_{L^2(\Delta)} \to 0$$

and

$$\|v^N - v\|_{L^2(\Omega)} \leq \|\Theta^N - \psi\|_{L^2(\Omega)} \to 0$$

as $N \to \infty$. $\square$

In the next theorem we do not assume continuity of the functions and that $\delta^N \to 0$.

Theorem 2 *Let Δ be a polyhedral input domain in $\mathbb{R}^n$, the function ψ be measurable and square integrable (i. e. L^2) and $\{\Delta_i^N\}_{i=1}^N$ be an optimal polyhedral partition in the Logarithmic space obtained by the algorithm described in Machina et al (2010) or briefly in Section 3. Then for the corresponding LS approximations Ψ^N in Δ we have $\Psi^N \to \psi$ in the L^2-norm if $N \to \infty$.*

Proof. For the function ψ there exists a sequence of polyhedral partitions $\{\bar{\Delta}_i\}_{i=1}^N$ of the input domain Δ such that $\bar{\delta} = \max_i(\mathrm{diam}\,(\bar{\Delta}_i)) \to 0$ as $N \to \infty$ and a sequence of piecewise constant functions $\{\bar{\Psi}^N(y)\}$ given by $\bar{\psi}^N(y) = \bar{C}_i^N$, whenever $y \in \bar{\Delta}_i^N$ for which $\bar{\Psi}^N \to \psi$ in the L^2-norm if $N \to \infty$.

For the optimal polyhedral approximation $\Psi^N(y)$ we obtain

$$\|\Psi^N - \psi\|_{L^2(\Delta)} \leq \|\bar{\Psi}^N - \psi\|_{L^2(\Delta)} \to 0$$

as $N \to \infty$. $\square$

In particular, the assumption on ψ is fulfilled if the target function v is measurable and bounded on Ω.

The case of the L^2-convergence of the approximations V^N given as $V^N = \exp(\Psi^N)$ is more involved. The reason for that is that the L^2-convergence of the sequence $\{\Psi^N\}$ does not necessarily imply the L^2-convergence of the sequence $\{\exp(\Psi^N)\}$.

We introduce the following notation. Given a sub-domain Δ_i^N of the input domain Δ we set

$$e_i^N(0, y) = 1, \quad e_i^N(k, y) = y_k - \bar{y}_i^N(k) \ (k = 1, ..., n), \tag{17}$$

where the point $(\bar{y}_i^N(k))_{k=1}^n \in \Delta_i^N$ is the center of mass of the convex set Δ_i^N given by

$$\bar{y}_i^N(k) = \frac{1}{\mathrm{mes}\,\Delta_i^N} \int\limits_{\Delta_i^N} y_k dy, \quad k = 1, ..., n. \tag{18}$$

Let $A_i^N = (a_i^N(kl))$ be the symmetric $n \times n$-matrix with the entries defined as

$$a_i^N(k, l) = \frac{1}{\mathrm{mes}\,\Delta_i^N} \int\limits_{\Delta_i^N} e_i^N(k, y) e_i^N(l, y) dy, \quad k, l = 1, ..., n, \tag{19}$$

Below we fix a matrix norm $\|.\|$. All matrix norms are equivalent. One of the norms is Euclidean, which is defined via the maximal eigenvalues: $\|A\| = \sqrt{\lambda_{max}(A^T A)}$. In the case of symmetric, positive definite matrices (like A_i^N above) we can write that $\|A\| = \lambda_{max}(A)$.

We say that the sequence of partitions $\{\Delta_i^N\}_{i=1}^N$ $(N = 1, 2, ...)$ of Δ satisfies the condition $(\mathbf{\Delta})$ if there exists a constant $c_0 > 0$ such that

$$\mathrm{diam}\Delta_i^N \sqrt{\|(A_i^N)^{-1}\|} \leq c_0.$$

If the chosen norm is Euclidean, then the latter estimate can be rewritten as

$$\frac{\mathrm{diam}\Delta_i^N}{\sqrt{\lambda_i^N}} \leq c_0,$$

where λ_i^N is the least (positive) eigenvalue of the matrix A_i^N $(i = 1, ..., N;\ N = 1, 2, ...)$.

Informally speaking, this property means, that the sub-domains cannot be too different from each other in the shape. As an illustration, let us consider the case of a sequence of rectangular boxes. The result says that ratio between the longest edge and the shortest edge is bounded above, i. e. boxes cannot be "too thin".

Theorem 3 *A sequence of rectangular boxes $\{P^N\}$ satisfies the property $(\mathbf{\Delta})$ if and only if $\sup\limits_{N=1,2,...} \frac{a^N}{b^N} < \infty$, where a^N (resp. b^N) is the length of the least (resp. biggest) edge of the box P^N.*

Proof. We calculate the matrix (19).

We fix N and the Nth rectangular box $P = P^N$ given by

$$\begin{array}{c} y_1^l \le y_1 \le y_1^r, \\ y_2^l \le y_2 \le y_2^r, \\ ... \\ y_n^l \le y_n \le y_n^r. \end{array}$$

Let $\bar{y}_i = \dfrac{y_i^l + y_i^r}{2}$, $i = 1, ..., n$, be the center of mass and $e(i, y) = y_i - \bar{y}_i$.

The substitution

$$y_i = y_i^l + \delta_i z_i, \text{ where } \delta_i = y_i^r - y_i^l, \ z_i \in [0, 1], \ y_i - \bar{y}_i = \delta_i(z_i - 1/2),$$

yields

$$\int\limits_P e(k, y)e(l, y)dy = \int\limits_\Sigma \delta_1...\delta_n\delta_k\delta_l(z_k - 1/2)(z_l - 1/2)dz \quad (1 \le k, l \le n)$$

where $\Sigma = [0, 1] \times [0, 1] \times ... \times [0, 1] \in \mathbb{R}^n$. Since

$$\int\limits_\Sigma (z_k - 1/2)(z_l - 1/2)dz = 0 \quad (k \ne l), \int\limits_\Sigma (z_k - 1/2)^2 dz = \frac{1}{12},$$

and $\operatorname{mes} \Delta_i^N = \delta_1...\delta_n$, the matrix (19) becomes $\operatorname{diag}[\frac{\delta_1^2}{12}, ..., \frac{\delta_n^2}{12}]$. The least eigenvalue of the matrix is equal to $\min\{\frac{\delta_1^2}{12}, ..., \frac{\delta_n^2}{12}\}$, i. e. to $\frac{(a^N)^2}{12}$. The diameter of the box can be estimated above by the constant $\sqrt{n}\, b^N$, which also dominates the asymptotics of the diameter. Therefore the condition $(\mathbf{\Delta})$ is fulfilled for the given sequence of rectangular boxes if and only if the sequence $\{\frac{b^N}{a^N}\}$ is bounded above. $\square$

Lemma 2 *Assume that the target function $v(x)$ is measurable and bounded on Ω and $\psi = \log v$. Assume further that the sequence of partitions $\{\Delta_i^N\}_{i=1}^N$ $(N = 1, 2, ...)$ of Δ satisfies the condition $(\mathbf{\Delta})$. Then the corresponding LS approximations $V^N(x)$ and $\Psi^N(y)$ are uniformly bounded on Ω and Δ, respectively, i.e. there exist constant $C_1 > 0$ and $C_2 > 0$ such that*

$$|V^N(x)| \le C_1 \sup_{x \in \Delta} |v(x)|$$

for all $N = 1, 2, ...$ and all $x \in \Delta$,

$$|\Psi^N(y)| \le C_2 \sup_{y \in \Delta} |\psi(y)|$$

for all $N = 1, 2, ...$ and all $y \in \Delta$.

Proof.

Clearly, $\psi(y)$ is measurable and bounded on Δ. Let $c = \sup\limits_{y \in \Delta} |\psi(y)|$.

Let us fix a sub-domain Δ_i^N. Our aim now is to find estimates for the norms of orthonormal basis functions $\{\tilde{e}_k\}$, $k = 0, ...n$ in the linear subspace of the space $L^2(\Delta_i^N)$ consisting of all linear functions and equipped with the scalar product

$$\xi \cdot \eta = \frac{1}{\operatorname{mes} \Delta_i^N} \int\limits_{\Delta_i^N} \xi(y)\eta(y)dy.$$

One basis is given by the set (17). However, this set is not necessarily orthogonal.

First of all, we choose $\tilde{e}_0 = 1$ and observe that its norm is equal to 1. Using the description (17) of the basis functions $e_i^N(k, y)$ defined via the center of mass we directly deduce from (18)

that $\tilde{e}_0 = 1$ is orthogonal to any linear combination of the other basis functions. The challenge is therefore to estimate the norms of linear combinations $\tilde{e}_k = \sum_{l=1}^{n} \alpha_l e_i^N(l,y)$, where α_l are real numbers.

In the proof below we often omit one of the variables in $e_i^N(l,y)$, that is either l, or y, depending on a particular interpretation of this basis. Writing $e_i^N(y)$ means that we regard it as a vector for each particular y, i. e. $e_i^N(y) = (e_i^N(1,y), ..., e_i^N(n,y))$ (the component $e_i^N(0,y)$ is excluded in further considerations). Omitting y ($e_i^N(l)$) means that we treat $e_i^N(l,y)$ as a function of y for a given l, i.e. as an element of the space $L^2(\Delta_i^N)$.

As $\|\tilde{e}_k\| = 1$, we require the following constraints on the coefficients:

$$\begin{aligned} 1 &= \tfrac{1}{\operatorname{mes}\Delta_i^N} \int\limits_{\Delta_i^N} |\tilde{e}_k(y)|^2 dy = \sum_{k,l=1}^{n} \tfrac{1}{\operatorname{mes}\Delta_i^N} \int\limits_{\Delta_i^N} e_i^N(k,y) e_i^N(l,y) \alpha_l \alpha_k dy \\ &= \alpha^T A_i^N \alpha, \end{aligned} \tag{20}$$

where $\alpha = (\alpha_l)_{l=1}^n$. Therefore,

$$\max_{y\in\Delta_i^N} |\tilde{e}_k(y)| = \max_{y\in\Delta_i^N} |\alpha \cdot e_i^N(y)| \tag{21}$$

(where $|.|$ is the Euclidean norm in $\mathbb{R}^n$ and $a \cdot b$ is the scalar product of two vectors) with the constraint $\alpha^T A_i^N \alpha = 1$.

Diagonalization of the symmetric, positive definite matrix A_i^N with the help of an orthogonal matrix Q gives the matrix containing the eigenvalues $\lambda_k > 0$ of A_i^N on the diagonal. Putting $\beta = Q\alpha$ and using $|Qy| = |y|$, we obtain from (21) that

$$\max_{y\in\Delta_i^N} |\tilde{e}_k(y)| = \max_{y\in\Delta_i^N} |\beta \cdot Q e_i^N(y)|$$

$$\leq |\beta| \max_{y\in\Delta_i^N} |e_i^N(y)| \leq \operatorname{diam}\Delta_i^N \left(\sum_{k=1}^{n} \beta_k^2 \right)^{\frac{1}{2}}$$

with the constraint $\sum_{k=1}^{n} \lambda_k \beta_k^2 = 1$, where the constant $\operatorname{diam}\Delta_i^N$ is evidently an upper estimate for the functions (17) on the sub-domain Δ_i^N. The maximum value of the expression $\left(\sum_{k=1}^{n} \beta_k^2\right)^{\frac{1}{2}}$ under the above constraint is $\frac{1}{\sqrt{\lambda_i^N}}$, where λ_i^N is the minimal eigenvalue of the matrix A_i^N. Due to the condition ($\mathbf{\Delta}$) we get that $\max\limits_{y\in\Delta_i^N} |e_i^N(k,y)| \leq c_0$, where the constant c_0 does not depend on i and N.

The final step in the proof of the lemma uses the explicit representation of the LS approximation Ψ^N:

$$\Psi^N(y) = \sum_{k=0}^{n} \mu_k \tilde{e}_k(y) \quad (y \in \Delta_i^N),$$

where

$$\mu_k = \frac{1}{\operatorname{mes}\Delta_i^N} \int\limits_{\Delta_i^N} \psi(y) \tilde{e}_k(y) dy.$$

Therefore $|\mu_0| \leq c$, $|\mu_k| \leq c c_0$ $(k = 1, ..., n)$ and

$$|\Psi^N(y)| \leq n(1+c)c_0^2 = C_2 \sup_{y\in\Delta} |\psi(y)|.$$

This implies also the uniform boundedness of the approximations $V_i^N(x)$ on Ω. The proof of the lemma is complete. □

Combining the previous results on the L^2-convergence we get the following theorem:

Theorem 4 *Assume that the sequence of partitions* $\{\Delta_i^N\}_{i=1}^N$ *(*$N = 1, 2, ...$*) of* Δ *satisfies the condition* $(\boldsymbol{\Delta})$.

Let, in addition, one of the two following conditions be fulfilled:

1. The target function v *is continuous on* Ω *and for each natural number* N *the measurable partition* $\{\Delta_i^N\}_{i=1}^N$ *has the property* $\delta^N \to 0$ *(*$N \to \infty$*).*

2. The target function v *is measurable and bounded on* Ω*,* Δ *is a polyhedral input domain in* $\mathbb{R}^n$ *and* $\{\Delta_i^N\}_{i=1}^N$ *is the optimal polyhedral partition in the Logarithmic space obtained by the algorithm described in Machina et al (2010) or briefly in Section 3.*

Then the LS power-law approximations V^N *converge to* v *in the* $L^2(\Omega)$*-norm as* $N \to \infty$.

Proof. Using either the theorem 1 or the theorem 2 we obtain the L^2 convergence of the LS approximations Ψ^N to the function $\psi = \log v$. Applying the lemma 2 we obtain the uniform boundedness of the approximations: $|\psi(y)|, |\Psi^N(y)| \le M$ for some M and any $N = 1, 2, ...$ Then we have

$$\|V^N - v\|_{L^2(\Omega)} = \int\limits_{\Omega} |V^N(x) - v(x)|^2 dx$$

$$= \int\limits_{\Delta} |\exp(\Psi^N(y)) - \exp(\psi(y))|^2 \exp(y_1 + ... + y_n) dy \le C \|\Psi^N - \psi\|_{L^2(\Delta)},$$

where $C = \exp(M) \max\limits_{y \in \Delta} \exp(y_1 + ... + y_n)$. The latter estimate is due to the uniform Lipschitz continuity of the function $\exp(u)$ on the interval $[0, M]$: $|\exp(u) - \exp(v)| \le \exp(M)\,|u - v|$.

This estimate proves the L^2-convergence of the LS approximations V^N to the target function v.

□

5 Uniform convergence of approximations

In the previous section the convergence in the L^2-norm on any compact domain was considered, which is the main mathematical result of the paper. However, in many applications it is desirable to consider certain types of convergence in a stronger sense, for instance, the uniform convergence. This may be, for instance, of interest, if we include the obtained approximations into the models based on differential equations, as it is well-known that convergence of (approximations of) solutions is only guaranteed by the uniform convergence of (approximations of) the right-hand sides.

In the case of LS power-law approximations treated in this paper, the situation with the convergence may be even more complicated. As the regression process within each sub-domain is independent of the other sub-domains, the resulting approximating functions may be discontinuous, so that we will need to deal with the solutions of discontinuous differential equations. It is well-known (see e. g. the monograph (Filippov 1998) or the discussion in the paper (Machina et al 2010)) that the continuous solutions can be in such a case defined as the so-called "Filippov solutions" of the corresponding differential inclusions. Again, the convergence of these solutions can only be guaranteed if the approximating right-hand sides converge uniformly. Neither the problem of convergence of the solutions of differential equations, nor the procedure of how to define and treat Filippov solutions in the case of discontinuous approximations is addressed in the paper. Yet, we intend to demonstrate in this section how the uniform convergence of approximations can be proved if needed.

A different type of convergence may require a different type of approximations. Therefore, in the most cases below we will not assume that v^N or Ψ^N are LS approximations (i.e. the best possible approximations in the L^2-norm).

An immediate consequence of the lemma 1 is the following

Theorem 5 *Let* v *be continuous on* Ω *and* $\psi = \log v$*. Let the measurable partition* $\{\Delta_i^N\}_{i=1}^N$ *satisfy the property* $\delta^N \to 0$ *(*$N \to \infty$*). Then there exist piecewise power-law approximations* $\{w^N\}$ *(resp. piecewise linear approximations* $\{\theta^N\}$*) which converge to* v *(resp.* ψ*) uniformly on* Ω *(resp.* Δ*).*

However, these approximations are piecewise constant. Below we treat proper piecewise linear approximations. In the next theorem we assume that the partition consists of sub-domains Δ_i^N satisfying the following property: the closure of Δ_i^N coincides with the closure of its interior (i.e. the closure of Δ_i^N is the closed domain). This is necessary, as we want to differentiate the target function within each of the sub-domains.

Theorem 6 *Let the target function v be a C^1-function (i.e. differentiable with the continuous partial derivatives). Let the sequence of partitions $\{\Delta_i^N\}_{i=1}^N$ $(N = 1, 2, ...)$ of Δ have the property $\delta^N \to 0$ $(N \to \infty)$. Assume, in addition, that for any $i = 1, ..., N$, $N = 1, 2, ...$ there exist points y_i^N, $c_i^N \in \Delta_i^N$ such that the piecewise linear approximations $\Psi^N (= \Psi_i^N$ on $\Delta_i^N)$ satisfy*

$$\begin{aligned} \psi(y_i^N) &= \Psi^N(y_i^N), \\ \nabla\psi(c_i^N) &= \nabla\Psi^N(c_i^N). \end{aligned} \tag{22}$$

Then for the corresponding (not necessarily least-squares) approximations Ψ^N (in Δ) and V^N (in Ω) we have

$$\Psi^N \to \psi, \quad V^N \to v \quad (N \to \infty)$$

uniformly on Δ (resp. on Ω).

Proof. We fix N and consider some arbitrarily chosen sub-domain Δ_i^N. By assumption, for $y \in \Delta_i^N$ we have $\Psi_i^N(y) = \nabla\psi(c_i^N) \cdot (y - y_0) + \psi(y_i^N)$, where $y_i^N, c_i^N \in \Delta_i^N$. On the other hand, the mean value theorem yields $\psi(y) - \psi(y_i^N) = \nabla\psi(c)(y - y_i^N)$ where $c \in \Delta_i^N$ depends on y. Therefore

$$|\Psi_i^N(y) - \psi(y)| \le |\nabla\psi(c) - \nabla\psi(c_i^N)||y - y_i^N|.$$

The uniform continuity of the continuous vector function $\nabla\psi(y)$ on Δ and the property that $\delta^N = \max\limits_{1 \le i \le N} \operatorname{diam} \Delta_i^N \to 0$ $(N \to \infty)$ imply that given an $\varepsilon > 0$ the estimate

$$|\Psi_i^N(y) - \psi(y)| < \varepsilon. \tag{23}$$

holds for sufficiently large N.

Since (23) holds for any $i \in \{1, 2, ..., N\}$, we also obtain that for sufficiently large N $|\Psi^N(y) - \psi(y)| < \varepsilon$, i.e. $\Psi^N \to \psi$ uniformly as $N \to \infty$.

As the proven uniform convergence of the sequence $\{\Psi^N\}$ implies its uniform boundedness, i. e. that for some M we have $|\Psi^N(y)|, |\psi(y)| \le M$ for all $y \in \Delta$, then

$$|V^N(x) - v(x)| = |\exp\Psi^N(y) - \exp\psi(y)| \le C|\Psi^N(y) - \psi(y)|,$$

where $C = \exp M$. This gives the uniform convergence of V^N to v as $N \to \infty$.

□

Our last result shows that the LS approximations converge uniformly in the scalar case. This is due to the fact that in the scalar case the equalities (22) are fulfilled.

Theorem 7 *Let the target function v be continuous on $\Omega = [A, B]$ $(A > B > 0)$ and $\psi = \log v$. Assume that the sequence of partitions $\{\Delta_i^N\}_{i=1}^N$ $(N = 1, 2, ...)$ of $\Delta = [a, b]$ $(a = \log A$, $b = \log B)$ has the property $\delta^N \to 0$ $(N \to \infty)$.*

Then for the corresponding LS approximations Ψ^N (in Δ) and V^N (in Ω) we have

$$\Psi^N \to \psi, \quad V^N \to v \quad (N \to \infty)$$

uniformly on Δ (resp. on Ω).

The proof of the theorem follows directly from the previous theorem and the following lemma:

Lemma 3 *Let a linear function $l : [a, b] \to \mathbb{R}$ be the LS approximation of a C^1 function $\psi : [a, b] \to \mathbb{R}$ on the entire interval $[a, b]$. Then there exist $y_0 \in [a, b]$ and $c \in (a, b)$ such that*

$$\begin{aligned} l(y_0) &= \psi(y_0), \\ l'(c) &= \psi'(c). \end{aligned}$$

PROOF. Let us first prove the existence of y_0. Assume the converse, i.e. that $\theta(y) \neq l(y)$ for all $y \in [a,b]$. Let for instance $\theta(y) - l(y) > 0$ for all $y \in [a,b]$. Put $\varepsilon = \min\limits_{y\in[a,b]} |\theta(y) - l(y)| > 0$. Then the linear function $l_1(y) = l(y) + \varepsilon/2$ satisfies the estimates $l(y) < l_1(y) < \theta(y)$. Therefore

$$\int_a^b (\theta(y) - l(y))^2 dy = \int_a^b (\theta(y) - l_1(y))^2 dy + 2\int_a^b (\theta(y) - l_1(y))\frac{\varepsilon}{2} dy + \int_a^b \frac{\varepsilon^2}{4} dy$$

$$> \int_a^b (\theta(y) - l_1(y))^2 dy.$$

This, however, contradicts the definition of the least squares approximations. The case $\theta(y) - l(y) < 0$ is treated in a similar manner.

Assume now that $l'(y) \neq \theta'(y)$ for all $y \in [a,b]$. We shall prove that in this case the graph of the scalar linear function $l(y)$ intersects the graph of $\theta(y)$ in at least two points from the interval $[a,b]$.

From the first part of the proof we know that at least one intersection point does exist. Assume that there is exactly one point $d \in [a,b]$ such that $l(d) = \theta(d)$. Without loss of generality we may assume that $\Theta'(d) > 0$ where $\Theta(y) = \theta(y) - l(y)$. Since $\Theta(d) = 0$ and $\Theta(y) \neq 0$ for all $y \neq d$, we obtain that $\Theta(y) = \theta(y) - l(y) < 0$ for $y < d$ and $\Theta(y) = \theta(y) - l(y) > 0$ for $y > d$ (one of these sets may be empty). Consider a new linear approximation given by $l_1(y) = l(y) + \delta(y - d)$, where a sufficiently small $\delta > 0$ is chosen in such a way that the graphs of the functions $\theta(y)$ and $l_1(y)$ have still one intersection point in $[a,b]$ (namely, d by construction).

It is easy to see that such a δ does exist. Indeed, in a vicinity U of the point d we have that $\Theta'(y) \neq 0$, so that for small $\delta > 0$ we have $\theta'(y) > l_1'(y)$, $y \in U$ and hence d is the only intersection point of the graphs of the functions $\theta(y)$ and $l_1(y)$ in U. Outside U, i.e. inside the compact set $[a,b]\backslash U$ the continuous function Θ is non-zero, so that $m = \min\limits_{y\in U} \Theta(y) > 0$. Choosing $\delta > 0$ in such a way that $\max\limits_{y\in[a,b]} |l(y) - l_1(y)| < m$ guarantees that the graphs of the functions θ and l_1 meet only in d.

We complete now our analysis of the scalar case observing that for such δ

$$\int_a^b (\theta(y) - l(y))^2 dy > \int_a^b (\theta(y) - l_1(y))^2 dy,$$

simply because the graph of l_1 is closer to the graph of θ, than the graph of l. This contradicts the assumption that l is the LS approximation of θ. We have therefore proved that there exists $c \in [a,b]$ such that $\Theta'(c) = 0$. □

The main results of Sections 5 and 6 provide a mathematical justification of the piecewise power-law approximations in two cases, which are of importance for applications, as both come from the optimal polyhedral partitions of the operating domain in the Logarithmic space. This justification consists in verification of the L^2 convergence of the approximations so obtained. In addition, we notice that the uniform convergence (at least in the one dimensional case) can be proved, if needed, provided that some additional assumptions are put on the functions and the domains. However, the uniform convergence, including convergence of the Filippov solutions of differential inclusions, is beyond the scope of this paper and will be discussed in a separate publication. Instead, we now will concentrate on a more practical solution of how piecewise approximations can be included into differential equations. This approach, which is an alternative to the piecewise continuous representation, is discussed in the next section.

6 Smoothing piecewise representations

In practice, piecewise representations may be difficult to use in a mathematical model. Also, data from experiments may be incomplete, which makes it impossible to derive a complete piecewise representation. At the best, i.e. when enough data points are available, piecewise functions will have discontinuities at the boundary of each subregion. At the worst, data will be available only

in some ranges, leading to piecewise representations that do not cover the full space of metabolite values.

While the limitations of these incompleteness remains to be established in actual problems, it is interesting to consider the problem of smoothing the piecewise representations obtained in a given case. Machina et al. (Machina et al 2010) discussed this problem through the use of Filippov's theory (Filippov 1998). This theory provides a theoretical basis for the model and suggests possible ways of a mathematical justification of the modeling paradigm. However, its straightforward application is difficult and unpractical.

As an alternative, we will discuss a quite different approach known as "the SC Formalism" (Hernández-Bermejo et al 2000), which is defined via the representation

$$v_r = \frac{V_r \prod_{j=1}^{n+m} x_j^{n_{rj}}}{\prod_{j=1}^{n+m} \left(K_{rj}^{n_{rj}} + x_j^{n_{rj}}\right)}, \tag{24}$$

where n_{rj} and K_{rj} are real numbers.

The function in (24) accumulates two important properties widely observed in biological systems: saturation and cooperativity - see (Sorribas et al 2007) for more details. The piecewise power-law representation does not possess these two properties, yet it has other convenient features. In particular, the procedure of calculating the power-law representation is essentially linear and can be automatized. We think therefore that the idea to use piecewise power-law approximations to derive the SC representation may be useful in application. Below we illustrate this idea with a numerical example.

Example 2 Let us consider a target function of the form

$$v = \frac{1}{1 + e^{-\beta_0 - \beta_1 x}} \tag{25}$$

First, we will obtain the approximation of this function over the full range of values of S from 0 to saturation by a piecewise power-law in three segments (Figure 6). As expected, the result is good enough although a discontinuity in the piecewise representation can be observed at the boundary of each subregion. Using the piecewise representation as a target, a SC function can be fitted to the resulting k piecewise representations obtained at each of the (a_k, b_k) regions by minimizing SSE

$$SSE = \sum_k \left(\int_{a_k}^{b_k} \left(\gamma_k x^{f_k} - \frac{V x^n}{K^n + x^n} \right)^2 dx \right) \tag{26}$$

In Figure 6 we show the obtained result compared to the piecewise and the original function. The resulting SC representation smooths the piecewise representation and provides a close approximation to the target function. Of course, if the number of regions in the piecewise representation increases, results are closer to the actual function (Figure 7).

Similar results can be obtained from a piecewise representation derived from data points. In Figure 8 we simulate a case in which data from two experiments are obtained. Here, the piecewise representation provides an approximation to each data set, but a poor extrapolation is obtained outside the data region. The SC Formalism can be used as an all-purpose function for obtaining an approximation to the original function. As shown in Figure 8, the resulting SC representation approximates with reasonable accuracy the target function.

As far as data points include saturation and information on other parts of the rate-substrate curve, results are good and the resulting SC is an excellent approximation to the actual function. Poor data sets may arise if few experiments are available or when the system behavior leads to few variations on the rate-substrate region. In that case, it may be impossible to recover the actual function (Figure 9). This emphasizes the importance of an appropriate experimental design. However, depending on the complexity of the system, identifiability problems may arise even if sufficiently many experiments are at hand (Srinath and Gunawan 2010).

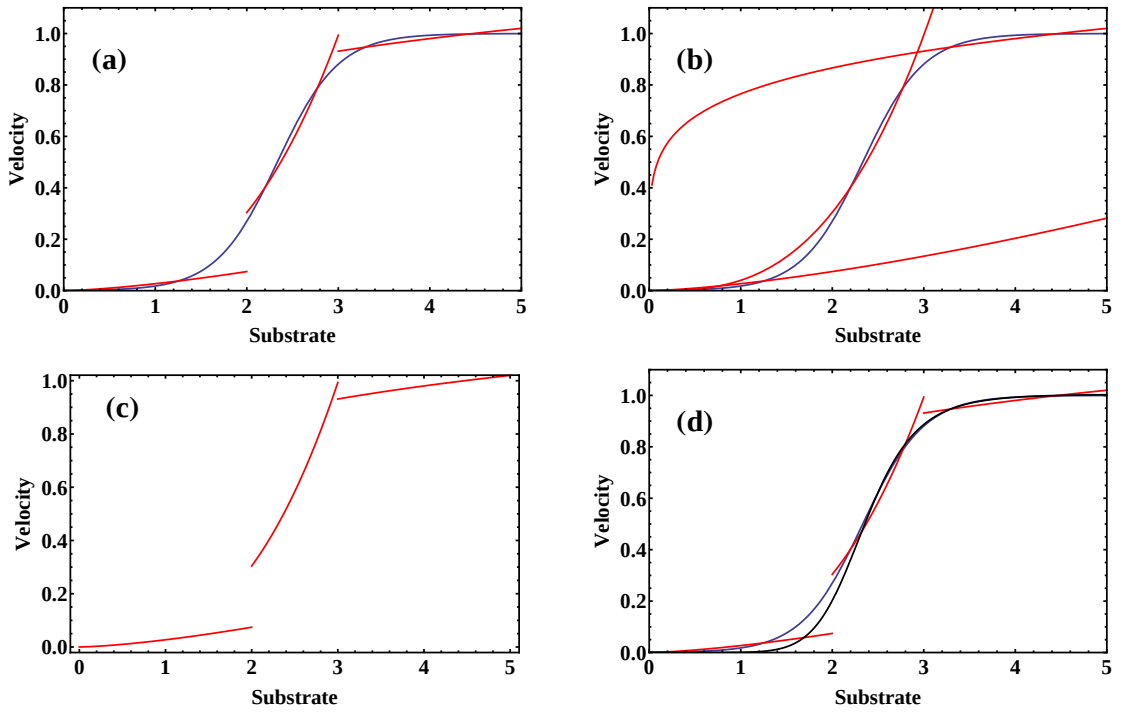

Fig. 6 The piecewise power-law (red) and the resulting SC (black) representations compared to the original function (blues). The number of regions is 3. (a) Piecewise approximation to the original function using the partition (0,2), (2,3), (3,5). (b) Resulting power-law functions fitted within each region. (c) Piecewise representation. (d) SC representation fitted to the piecewise representation

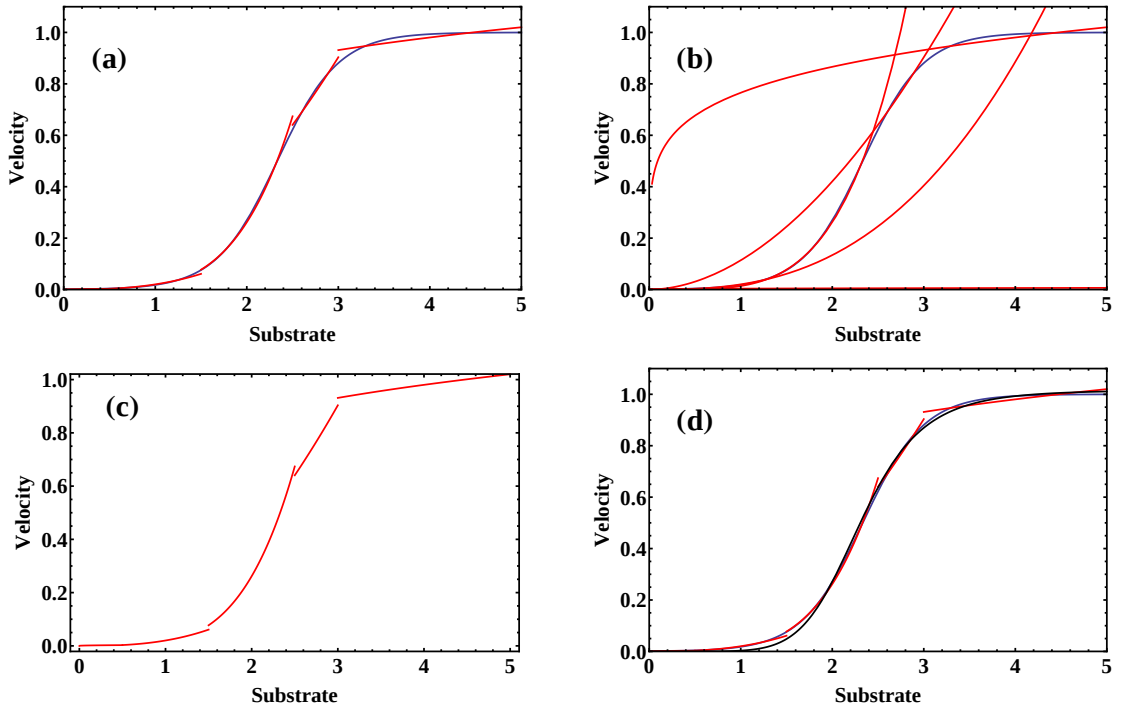

Fig. 7 The piecewise power-law (red) and the resulting SC (black) representations compared to the original function (blue). The number of regions is 4. (a) Piecewise approximation to the original function using the partition (0,1.5), (1.5,2.5), (2.5,3), (3,5). (b) Resulting power-law functions fitted within each region. (c) Piecewise representation. (d) SC representation fitted to the piecewise representation

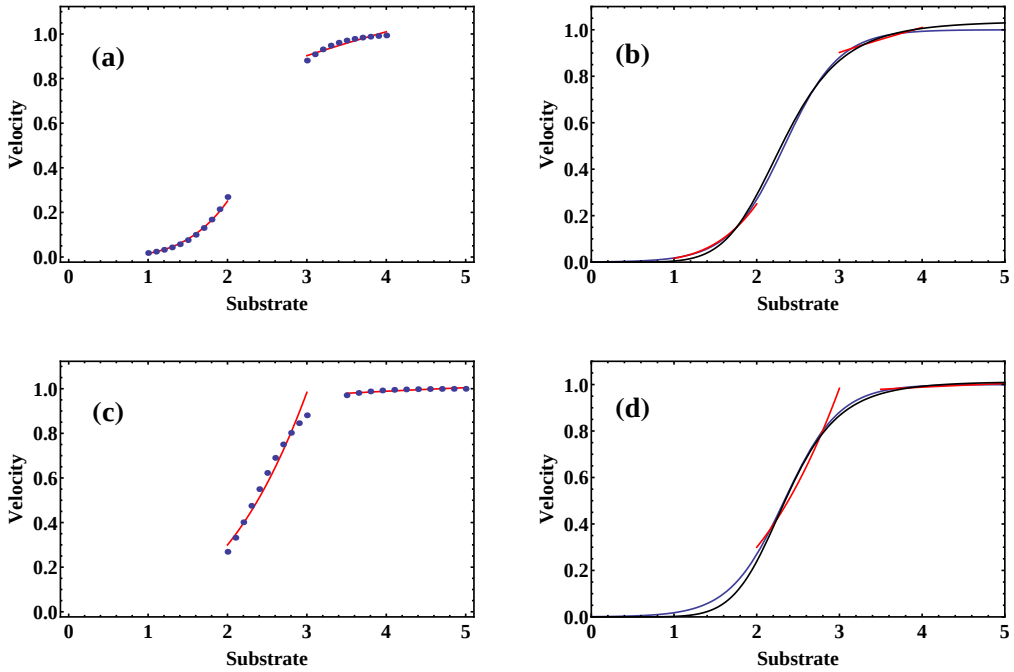

Fig. 8 The piecewise power-law (red) and the resulting SC (black) representations compared to the available data set (dotted). (a) and (c) show two examples of piecewise approximations to each data set. (b) and (d) show the corresponding SC approximations fitted to these regions. The number of regions is 2

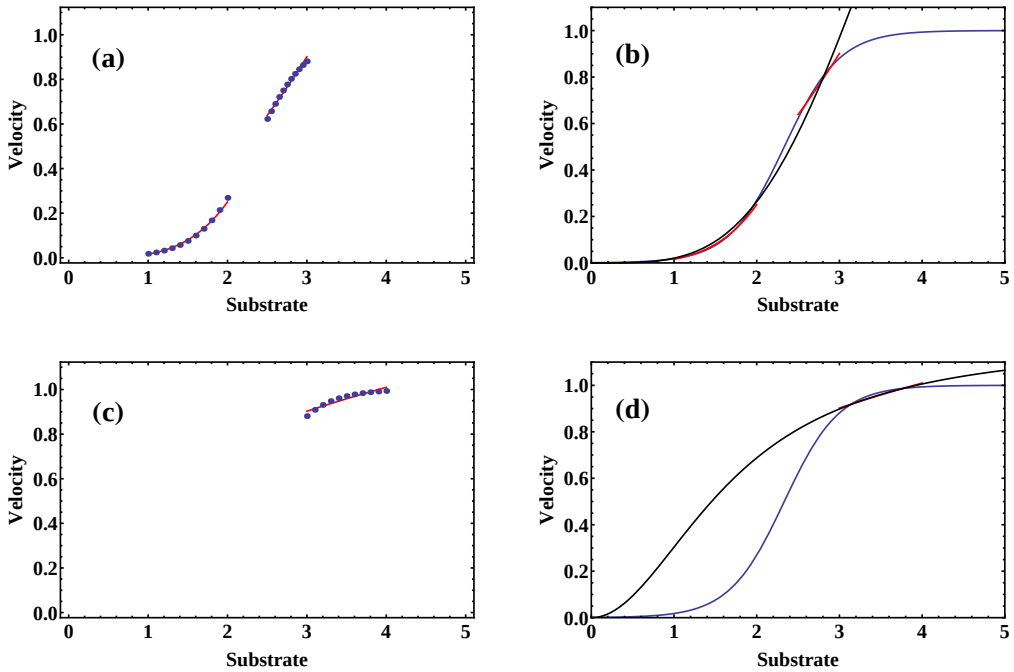

Fig. 9 The piecewise power-law (red) and the resulting SC (black) representations compared to the available data set (dotted). The number of regions is 1 or 2. (a) and (c) show two examples of piecewise approximations to each data set. (b) and (d) show the corresponding SC approximations fitted to these regions

7 Conclusions

Piecewise representations may be very useful as a practical approximation to an unknown function. In the work (Hernández-Bermejo et al 2000), it was shown that piecewise power-law representations can easily fit experimental data that expand well over wide ranges that cannot be covered by a single power-law. In this work, it is shown that these approximations converge to the target function provided that the partitions satisfy some additional assumptions, for instance they are optimal in the sense of (Ferrari-Trecate and Muselli 2002).

Of course, the quality and completeness of the experimental data will determine the appropriateness of the piecewise representation. If the function depends on several variables, it may be difficult to effectively devise experiments that produce data expanding all the potential variable ranges. Thus, at the best one may expect obtaining incomplete piecewise representations according to the available experimental data.

We have demonstrated that the SC representation (Sorribas et al 2007) may be an excellent complement to a piecewise power-law. By taking the piecewise representation as an approximation to an unknown function, a SC function that fits the piecewise representation can be obtained. This SC function smooths the piecewise representation and may provide a practical approximation to the underlying unknown function.

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Paper V

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Research Article

Generalized Solutions of Functional Differential Inclusions

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We consider the initial value problem for a functional differential inclusion with a Volterra multivalued mapping that is not necessarily decomposable in $L_1^n[a,b]$. The concept of the decomposable hull of a set is introduced. Using this concept, we define a generalized solution of such a problem and study its properties. We have proven that standard results on local existence and continuation of a generalized solution remain true. The question on the estimation of a generalized solution with respect to a given absolutely continuous function is studied. The density principle is proven for the generalized solutions. Asymptotic properties of the set of generalized approximate solutions are studied.

1. Introduction

During the last years, mathematicians have been intensively studying (see [1, 2]) perturbed inclusions that are generated by the algebraic sum of the values of two multivalued mappings, one of which is decomposable. Many types of differential inclusions can be represented in this form (ordinary differential, functional differential, etc.). In the above-mentioned papers, the authors investigated the solvability problem for such inclusions. Estimates for the solutions were obtained similar to the estimates, which had been obtained by Filippov for ordinary differential inclusions (see [3, 4]). The concept of quasisolutions is introduced and studied. The density principle and the "bang-bang" principle are proven. In papers [5–8], the perturbed inclusions with internal and external perturbations are considered, and the conjecture that "small" internal and external perturbations can significantly

change the solution set of the perturbed inclusion is proven. Let us remark that, in the cited papers, the proofs of the obtained results essentially depend on the assumption that the multivalued mapping, which generates the algebraic sum of the values, is decomposable. Therefore, these studies once again confirm V. M. Tikhomirov's conjecture that decomposability is a specific feature of the space $L_1^n[a,b]$ and plays the same role as the concept of convexity in Banach spaces. The decomposability is implicitly used in many fields of mathematics: optimization theory, differential inclusions theory, and so forth. If a multivalued mapping is not necessarily decomposable, then the methods known for multivalued mappings cannot even be applied to the solvability problem of the perturbed inclusion. Furthermore, in this case, the equality between the set of quasisolutions of the perturbed inclusion and the solution set of the perturbed inclusion with the decomposable hull of the right-hand side fails. This equality for the ordinary differential inclusions was proven by Ważewski (see [9]). The point is that, in this case, the closure (in the weak topology of $L_1^n[a,b]$) of the set of the values of this multivalued mapping does not coincide with the closed convex hull of this set. As a result, we have that fundamental properties of the solution sets (the density principle and "bang-bang" principle) do not hold any more (see [3, 10–13]). The situation cannot be improved even if the mapping in question is continuous.

In this paper, we consider the initial value problem for a functional differential inclusion with a multivalued mapping. We assume that this mapping is not necessarily decomposable. Some mathematical models can naturally be described by such an inclusion. For instance, so do certain mathematical models of sophisticated multicomponent systems of automatic control (see [14]), where, due to the failure of some devices, objects are controlled by different control laws (different right-hand sides) with the diverse sets of the control admissible values. This means that the object's control law consists of a set of the controlling subsystems. These subsystems may be linear as well as nonlinear. For example, this occurs in the control theory of the hybrid systems (see [15–20]). Due to the failure of a device, the control object switches from one control law to another. The control of an object must be guaranteed in spite of the fact that failures (switchings) may take place any time. Therefore, the mathematical model should treat all available trajectories (states) corresponding to all switchings. The generalized solutions of the inclusion make up the set of all such trajectories. The concept of a generalized solution should be then introduced and its properties should be studied.

We consider a functional differential inclusion with a Volterra-Tikhonov type (in the sequel simply Volterra type) multivalued mapping and we prove that for such an inclusion, the theorem on existence and continuation of a local generalized solution holds true. This justifies one of the requirements, which were formulated in the monograph of Filippov [4] for generalized solutions of differential equations with discontinuous right-hand sides. In the present paper, it is also proven that in the regular case, that is, when a multivalued mapping is decomposable, a generalized solution coincides with an ordinary solution. At the same time, the concept of a generalized solution discussed in the present paper does not satisfy all the requirements that are usually put on generalized (in the sense of the monograph [4]) solutions of differential equations with discontinuous right-hand sides. For instance, the limit of generalized (in the sense of the present paper) solutions is not necessarily a generalized solution itself. The reason for that is that a multivalued mapping that determines a generalized solution (the definition is given below) may not be closed in the weak topology of $\mathbf{L}_1^n[a,b]$, as this mapping is not necessarily convex-valued.

2. Preliminaries

We start with the notation and some definitions. Let X be a normed space with the norm $\|\cdot\|_X$. Let $B_X[x,\varepsilon]$ be the closed ball in the space X with the center at $x \in X$ and of radius $\varepsilon > 0$; if $\varepsilon = 0$, then $B_X[x,0] \equiv x$. Let $U \subset X$. Then $\overline{U}$ is the closure of U, $\operatorname{co} U$ is the convex hull of U; $\overline{\operatorname{co}}\, U \equiv \overline{\operatorname{co} U}$, $\operatorname{ext} U$ is the set of all extreme points of U; $\overline{\operatorname{ext}}\, U = \overline{\operatorname{ext} U}$. Let $\|U\|_X = \sup_{u\in U}\|u\|_X$. Let $U^\varepsilon \equiv \overline{\bigcup_{u\in U} B[u,\varepsilon]}$ if $\varepsilon > 0$ and $U^0 \equiv \overline{U}$.

Let $\rho_X[x;U]$ be the distance from the point $x \in X$ to the set U in the space X; let $h^+_X[U_1;U] \equiv \sup_{x\in U_1}\rho_X[x,U]$ be the Hausdorff semideviation of the set U_1 from the set U; let $h_X[U_1;U] = \max\{h^+_X[U_1;U]; h^+_X[U;U_1]\}$ be the Hausdorff distance between the subsets U_1 and U of X.

We denote by comp $[X]$ (resp., comp $[X^*]$) the set of all nonempty compact subsets of X (resp., the set of all nonempty, bounded, closed in the space X, and relatively compact in the weak topology on the space X subsets of X). Let 2^X be the set of all nonempty bounded subsets of X.

Let $\mathcal{P}$ be a system of subsets of X (a subset of X). We denote by $\Omega(\mathcal{P})$ the set of all nonempty convex subsets of X, belonging to the system $\mathcal{P}$ (the set of all nonempty convex subsets of X, belonging to $\mathcal{P}$).

Let $\mathbb{R}^n$ be the space of all n-dimensional column vectors with the norm $|\cdot|$. We denote by $C^n[a,b]$ (resp., $D^n[a,b]$) the space of continuous (resp., absolutely continuous) functions $x : [a,b] \to \mathbb{R}^n$ with norm $\|x\|_{C^n[a,b]} = \max\{|x(t)| : t \in [a,b]\}$ (resp., $\|x\|_{D^n[a,b]} = |x(a)| + \int_a^b |\dot{x}(s)|\,ds$). Let $\mathcal{U} \subset [a,b]$ be a measurable set $\mu(\mathcal{U}) > 0$ (μ—the Lebesgue measure). We denote by $L^n_p(\mathcal{U})$ the space of all functions $x : \mathcal{U} \to \mathbb{R}^n$ such that $(x(s))^p$ is integrable (if $p < \infty$) and the space of all measurable, essentially bounded (if $p = \infty$) functions $x : \mathcal{U} \to \mathbb{R}^n$ with the norms

$$\|x\|_{L^n_p(\mathcal{U})} = \left(\int_{\mathcal{U}} \left|x(s)\right|^p ds\right)^{1/p}, \qquad \|x\|_{L^n_\infty(\mathcal{U})} = \operatorname*{vraisup}_{s\in\mathcal{U}} \left|x(s)\right|, \tag{2.1}$$

respectively.

Let $\Phi \subset L^n_1[a,b]$. The set Φ is called integrally bounded if there exists a function $\varphi_\Phi \in \mathbf{L}^1_1[a,b]$ such that $|x(t)| \le \varphi_\Phi(t)$ for each $x \in \Phi$ and almost all $t \in [a,b]$. The set Φ is said to be *decomposable* if for each $x, y \in \Phi$ and every measurable set $\mathcal{U} \subset [a,b]$ the inclusion $\chi(\mathcal{U})x + \chi([a,b] \setminus \mathcal{U})y \in \Phi$ holds, where $\chi(V)$ is the characteristic function of the set V. We denote by $Q[\mathbf{L}^n_1[a,b]]$ (resp., $\Pi[L^n_1[a,b]]$) the set of all nonempty, closed, and integrally bounded (resp., nonempty, bounded, closed, and decomposable) subsets of the space $L^n_1[a,b]$.

Let $F : [a,b] \to \text{comp}\,[\mathbb{R}^n]$ be a measurable mapping. Then by definition, $S(F) = \{y \in L^n_1[a,b] : y(t) \in F(t)$ for almost all $t \in [a,b]\}$. By $C^1_+[a,b]$ (resp., $L^1_+[a,b]$), denote the cone of all nonnegative functions of the space $C^1_1[a,b]$ (resp., $L^1_1[a,b]$).

Let $f : P \to Q$ be a mapping between two partially ordered sets P and Q (the partial order of both sets is denoted by $\le$). The mapping f is isotonic if $f(x) \le f(y)$, whenever $x \le y$.

In this paper, the expression "measurability of a single-valued function" is always used in the sense of Lebesgue measurability and "measurability of a multivalued function" in the sense of [21]. Let (T,Σ,μ) be a space with finite positive measure and let F be a multivalued mapping from T to $\mathbb{R}^n$. A set $\{x_\nu(\cdot)\}$ ($\nu \in \mathbb{N}$) of measurable mappings from T to $\mathbb{R}^n$ is said to approximate the multivalued mapping F if the set $\{t \in T \mid x_\nu(t) \in F(t)\}$ is measurable for any $\nu \in \mathbb{N}$, and the set $F(t)$ belongs to the closure of its intersection with the set $\bigcup_{\nu\in\mathbb{N}}\{x_\nu(t)\}$ for

almost all $t \in T$. A multivalued mapping F from T to $\mathbb{R}^n$ is called measurable if there exists a countable set of measurable mappings from T to $\mathbb{R}^n$ that approximates the mapping F.

Further, let us introduce the main characteristic properties of a set that is decomposable.

Lemma 2.1. *Let $\Phi \in \Pi[L_1^n[a,b]]$. Then there exists a function $u \in L_1^1[a,b]$ such that $|\varphi(t)| \leqslant u(t)$ for each function $\varphi \in \Phi$ and almost all $t \in [a,b]$.*

Proof. Let $\varphi_i \in \Phi$, $i = 1,2,\dots$, be a sequence of functions such that

$$\lim_{i\to\infty} \|\varphi_i\|_{L_1^n[a,b]} = \|\Phi\|_{L_1^n[a,b]}. \tag{2.2}$$

Let us show that there exists a sequence of functions $\widetilde{\varphi}_i \in \Phi$, $i = 1,2,\dots$, such that the equality (2.2) holds and

$$|\widetilde{\varphi}_1(t)| \leqslant |\widetilde{\varphi}_2(t)| \leqslant |\widetilde{\varphi}_3(t)| \leqslant \cdots \leqslant |\widetilde{\varphi}_i(t)| \leqslant |\widetilde{\varphi}_{i+1}(t)| \leqslant \cdots \tag{2.3}$$

for almost all $t \in [a,b]$.

Indeed, let $\widetilde{\varphi}_1 = \varphi_1$ and $\widetilde{\varphi}_{i+1} = \chi(\mathcal{U}_i)\widetilde{\varphi}_i + \chi([a,b \setminus \mathcal{U}_i)\varphi_{i+1}$, $i = 1,2,\dots$, where $\mathcal{U}_i = \{t \in [a,b] : |\widetilde{\varphi}_i(t)| \geqslant |\varphi_{i+1}(t)|\}$. Since $\Phi \in \Pi[L_1^n[a,b]]$, we see that the sequence $\widetilde{\varphi}_i \in \Phi$, $i = 1,2,\dots$, has the following properties: for almost all $t \in [a,b]$, the inequalities (2.3) hold and $\|\widetilde{\varphi}_i\|_{L_1^n[a,b]} \geqslant \|\varphi_i\|_{L_1^n[a,b]}$ for each $i = 1,2,\dots$. Hence, from this property and equality (2.2), it follows that the sequence $\widetilde{\varphi}_i$, $i = 1,2,\dots$, satisfies (2.2). Further, we consider a measurable function $u : [a,b] \to [0,\infty)$ defined by

$$u(t) = \lim_{i\to\infty} |\widetilde{\varphi}_i(t)|. \tag{2.4}$$

Since the set Φ is bounded, we see, using Fatou's lemma (see [22]), that $u \in L_1^1[a,b]$. Moreover, by the definition of the function u and due to (2.2),

$$\int_{\mathcal{U}} u(t)dt = \|\Phi\|_{L_1^n(\mathcal{U})} \tag{2.5}$$

for every measurable set $\mathcal{U} \subset [a,b]$. Now, let us show that the function u defined by (2.4) satisfies the assumptions of the lemma. Indeed, if the contrary is true, then there exist a function $\varphi \in \Phi$ and a measurable set $\mathcal{U}_1 \subset [a,b]$ ($\mu(\mathcal{U}_1) > 0$) such that $|\varphi(t)| > u(t)$ for each $t \in \mathcal{U}_1$. This implies that $\int_{\mathcal{U}_1} |\varphi_1(t)|dt > \int_{\mathcal{U}_1} u(t)dt$, which contradicts (2.5). This completes the proof. □

Lemma 2.2. *Let $\Phi \in \Pi[L_1^n[a,b]]$ and $\varphi_i \in \Phi$, $i = 1,2,\dots$, be a sequence that is dense in Φ. Further, let a measurable set $F : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$ be defined by*

$$F(t) = \overline{\{\varphi_i(t),\ i = 1,2,\dots\}}. \tag{2.6}$$

Then $S(F) = \Phi$.

Proof. Since $\varphi_i \in S(F)$ and the sequence φ_i, $i = 1,2,\dots$, is dense in Φ, we have, due to the closedness of the set Φ, the relation $\Phi \subset S(F)$. Let us prove that $S(F) \subset \Phi$. Let $x \in S(F)$. For each k, $i = 1,2,\dots$, put

$$E_i^k = \left\{t \in [a,b] : |x(t) - \varphi_i(t)| \leqslant \frac{1}{k}\right\}, \tag{2.7}$$

which are measurable sets. For $i = 1$, let $\widetilde{E}_1^k = E_1^k$, and for $i = 2,3,\ldots$, let $\widetilde{E}_i^k = E_i^k \setminus \bigcup_{j=1}^{i-1} E_j^k$. Then $\widetilde{E}_i^k \bigcap \widetilde{E}_j^k = \varnothing$ if $i \neq j$. By the definition of the mapping $F : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$, for each $k = 1,2,\ldots$, we have

$$\mu\left(\bigcup_{i=1}^{\infty} \widetilde{E}_i^k\right) = b - a. \tag{2.8}$$

Let $x_k : [a,b] \to \mathbb{R}^n$, $k = 1,2,\ldots$, be a sequence of measurable functions such that

$$x_k(t) = \begin{cases} \varphi_i(t) & \text{if } t \in \widetilde{E}_i^k,\ i = 1,2,\ldots,k, \\ \varphi_1(t) & \text{if } t \in [a,b] \setminus \bigcup_{i=1}^{k} \widetilde{E}_i^k. \end{cases} \tag{2.9}$$

Since the set Φ is decomposable, we see that $x_k \in \Phi$ for each $k = 1,2,\ldots$. Moreover, from Lemma 2.1 and the definition of the set $\widetilde{E}_i^k$, it follows that for the functions x_k, $k = 1,2,\ldots$, we have the estimates

$$\|x - x_k\|_{L_1^n[a,b]} \leqslant \frac{b-a}{k} + 2\int_{[a,b]\setminus\cup_{i=1}^{k}\widetilde{E}_i^k} u(t)dt, \tag{2.10}$$

where u satisfies the assertions of Lemma 2.1. From (2.8) and (2.10), it follows that $x_k \to x$ in $L^n[a,b]$ as $k \to \infty$. Since the set Φ is closed, we have that $x \in \Phi$. Hence $S(F) \subset \Phi$. Thus $S(F) = \Phi$. □

Lemma 2.3. *Let measurable sets $F_i : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$, $i = 1,2,\ldots$, be integrally bounded, then $S(F_1(\cdot)) \subset S(F_2(\cdot))$ if and only if $F_1(t) \subset F_2(t)$ for almost all $t \in [a,b]$.*

Proof. First of all, it is evident that if for almost all $t \in [a,b]$, $F_1(t) \subset F_2(t)$, then $S(F_1(\cdot)) \subset S(F_2(\cdot))$.

Let $S(F_1(\cdot)) \subset S(F_2(\cdot))$ and let $\varphi_i \in L_1^n[a,b]$, $i = 1,2,\ldots$, be a countable set, which is dense in $S(F_1)$ and which approximates $F_1 : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$ (see [21]). Thus $\varphi_i \in S(F_2(\cdot))$ for each $i = 1,2,\ldots$ and by the definition of the set $S(F_2(\cdot))$, we have that $\{\varphi_i(t) : i = 1,2,\ldots\} \subset F_2(t)$ for almost all $t \in [a,b]$. Since the sequence φ_i, $i = 1,2,\ldots$, approximates the map $F_1 : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$, it follows from the previous inclusion that $F_1(t) \subset F_2(t)$ for almost all $t \in [a,b]$. □

Corollary 2.4. *Let $\Phi \in \Pi[L_1^n[a,b]]$ and let $F_i : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$, $i = 1,2$, be measurable sets such that $\Phi = S(F_1) = S(F_2)$. Then $F_1(t) = F_2(t)$ for almost all $t \in [a,b]$.*

Remark 2.5. If $\Phi \in \Pi[L_1^n[a,b]]$, then a measurable set $F : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$, that satisfies $S(F) = \Phi$, uniquely determines the set Φ.

3. Decomposable hull of a set in the space of integrable functions

We introduce the concept of the decomposable hull of a set in the space $\mathbf{L}_1^n[a,b]$. We consider a multivalued mapping that is not necessarily decomposable. For such a mapping, we construct its decomposable hull and investigate topological properties of this hull.

Definition 3.1. Let Φ be a nonempty subset of $\mathbf{L}_1^n[a,b]$. By $\operatorname{dec}\Phi$, we denote the set of all finite combinations

$$y = \chi(\mathcal{U}_1)x_1 + \chi(\mathcal{U}_2)x_2 + \cdots + \chi(\mathcal{U}_m)x_m \tag{3.1}$$

of elements $x_i \in \Phi$, $i = 1,2,\ldots,m$, where the disjoint measurable subsets $\mathcal{U}_i$, $i = 1,2,\ldots,m$, of the segment $[a,b]$ are such that $\bigcup_{i=1}^m \mathcal{U}_i = [a,b]$.

Lemma 3.2. *The set* $\operatorname{dec}\Phi$ *is decomposable for any nonempty set* $\Phi \subset \mathbf{L}_1^n[a,b]$.

Proof. Let $y_1, y_2 \in \operatorname{dec}\Phi$. Let also $\mathcal{U} \subset [a,b]$ be a measurable set. Without loss of generality, it can be assumed that

$$y_i = \chi(\mathcal{U}_1^i)x_1^i + \chi(\mathcal{U}_2^i)x_2^i + \cdots + \chi(\mathcal{U}_m^i)x_m^i, \tag{3.2}$$

where $x_j^i \in \Phi$, $j = 1,2,\ldots,m$, $i = 1,2$, and the measurable disjoint sets $\mathcal{U}_j^i \subset [a,b]$, $j = 1,2,\ldots,m$, $i = 1,2$, are such that $[a,b] = \bigcup_{j=1}^m \mathcal{U}_j^i$, $i = 1,2$, (if the number of summands in (3.2) is not the same, we may use arbitrary functions multiplied by the characteristic functions of the empty sets). Further, from the equality

$$\chi(\mathcal{U})y_1 + \chi([a,b] \setminus \mathcal{U})y_2 = \sum_{i=1}^m \chi(\mathcal{U} \cap \mathcal{U}_i^1)x_i^1 + \sum_{i=1}^m \chi(([a,b] \setminus \mathcal{U}) \cap \mathcal{U}_i^2)x_i^2, \tag{3.3}$$

it follows that $\chi(\mathcal{U})y_1 + \chi([a,b] \setminus \mathcal{U})y_2 \in \operatorname{dec}\Phi$. Hence, the set $\operatorname{dec}\Phi$ is decomposable. □

Remark 3.3. Note that even if a set $\Phi \subset \mathbf{L}_1^n[a,b]$ is bounded, the set $\operatorname{dec}\Phi$ is not necessarily bounded. For example, let us check that

$$\operatorname{dec}\left[B_{\mathbf{L}_p^n[a,b]}[0,1]\right] = \mathbf{L}_p^n[a,b] \quad (p \in [1,\infty)). \tag{3.4}$$

Indeed, let $z \in \mathbf{L}_p^n[a,b]$ and e_i, $i = 1,2,\ldots,m$, be measurable sets with the following properties: $e_i \cap e_j = \varnothing$ if $i \neq j$, $i,j = 1,2,\ldots,m$, $\bigcup_{i=1}^m e_i = [a,b]$; for each $i = 1,2,\ldots,m$, the inequality

$$\int_{e_i} |z(s)|^p ds < 1 \tag{3.5}$$

holds. Then $z_i = \chi(e_i)z \in B_{\mathbf{L}_p^n[a,b]}[0,1]$, $i = 1,2,\ldots,m$, and

$$z = \chi(e_1)z_1 + \chi(e_2)z_2 + \cdots + \chi(e_m)z_m. \tag{3.6}$$

Therefore, $z \in \operatorname{dec}\left[B_{\mathbf{L}_p^n[a,b]}[0,1]\right]$ and consequently, the equality (3.4) holds.

Remark 3.4. From (3.4), it follows that if a set $\Phi \subset \mathbf{L}_1^n[a,b]$ is relatively compact in the weak topology of $\mathbf{L}_1^n[a,b]$, then the set $\operatorname{dec}\Phi$ does not necessarily possess this property.

Remark 3.5. Note that if a set is convex in $\mathbf{L}_1^n[a,b]$, then this set is not necessarily decomposable. The ball $B_{\mathbf{L}_1^n[a,b]}[0,1]$ is an example of such a set.

Remark 3.6. If a set $\Phi \subset \mathbf{L}_1^n[a,b]$ is integrally bounded, then by Lemma 2.2, for the set $\overline{\operatorname{dec}}\,\Phi \in \Pi[\mathbf{L}_1^n[a,b]]$, there exists a measurable and integrally bounded mapping $F_{\overline{\operatorname{dec}}\,\Phi} : [a,b] \to \operatorname{comp}[R^n]$ such that

$$\overline{\operatorname{dec}}\,\Phi = S\big(F_{\overline{\operatorname{dec}}\,\Phi}(\cdot)\big). \tag{3.7}$$

Lemma 3.7. *If a set* $\Phi \subset \mathbf{L}_1^n[a,b]$ *is decomposable, then* $\operatorname{dec}\Phi = \Phi$.

Proof. Evidently, $\Phi \subset \operatorname{dec}\Phi$. We claim that $\operatorname{dec}\Phi \subset \Phi$. The proof is made by induction over m. By the definition of the switching convexity, any expression (3.1) including two elements $x_1, x_2 \in \Phi$ and two measurable sets $\mathcal{U}_1, \mathcal{U}_2 \subset [a,b]$ belongs to Φ.

Suppose now that for $m = k$, the combination of the form (3.1) belongs to Φ. Let $x_1, x_2, \ldots, x_{m+1} \in \Phi$ and let $\mathcal{U}_1, \mathcal{U}_2, \ldots, \mathcal{U}_{m+1} \subset [a,b]$ be disjoint measurable sets such that $[a,b] = \bigcup_{i=1}^{m+1} \mathcal{U}_i$. Let

$$z = \chi(\mathcal{U}_2 \cup \mathcal{U}_1)x_2 + \chi(\mathcal{U}_3)x_3 + \cdots + \chi(\mathcal{U}_{m+1})x_{m+1}. \tag{3.8}$$

By the inductive assumption, $z \in \Phi$ and therefore $\chi(\mathcal{U}_1)x_1 + \chi([a,b] \setminus \mathcal{U}_1)z \in \Phi$. Since

$$\chi([a,b] \setminus \mathcal{U}_1)z = \chi(\mathcal{U}_2)x_2 + \chi(\mathcal{U}_3)x_3 + \cdots + \chi(\mathcal{U}_{m+1})x_{m+1}, \tag{3.9}$$

we have that

$$\chi(\mathcal{U}_1)x_1 + \chi(\mathcal{U}_2)x_2 + \cdots + \chi(\mathcal{U}_{m+1})x_{m+1} \in \Phi. \tag{3.10}$$

Hence $\operatorname{dec}\Phi \subset \Phi$. This concludes the proof. □

Corollary 3.8. *If* $\Phi \subset \mathbf{L}_1^n[a,b]$, *then the set* $\operatorname{dec}\Phi$ *is the minimal set which is decomposable and which contains* Φ.

Proof. Consider any set $U \subset \mathbf{L}_1^n[a,b]$ which is decomposable and which satisfies $\Phi \subset U$. Then, by Lemma 3.7, we have $\Phi \subset \operatorname{dec}\Phi \subset \operatorname{dec}U = U$. □

Lemma 3.9. *If a set* $\Phi \subset \mathbf{L}_1^n[a,b]$ *is convex, then so is the set* $\operatorname{dec}\Phi \in \mathbf{L}_1^n[a,b]$.

Proof. Let $y_1, y_2 \in \operatorname{dec}\Phi$ be given by the formula (3.2). It follows from the convexity of the set $\Phi \subset \mathbf{L}_1^n[a,b]$ and the equality

$$\lambda y_1 + (1-\lambda)y_2 = \sum_{i,j=1}^{m} \chi(\mathcal{U}_i^1 \cap \mathcal{U}_j^2)\big(\lambda x_i^1 + (1-\lambda)x_j^2\big) \tag{3.11}$$

that $\lambda y_1 + (1-\lambda)y_2 \in \operatorname{dec}\Phi$ for any $\lambda \in [0,1]$. Thus, the set $\operatorname{dec}\Phi$ is convex. □

Similar to the definition of the convex hull in a normed space, the set $\operatorname{dec}\Phi$ will, in the sequel, be called the *decomposable hull of the set* Φ *in the space of integrable functions*, or simply the *decomposable hull of the set* Φ. Likewise, $\overline{\operatorname{dec}}\,\Phi$ is addressed as the *closed decomposable hull of the set* Φ.

Remark 3.10. If $\Phi \in Q[\mathbf{L}_1^n[a,b]]$, then the closed decomposable hull of the set Φ (the set $\overline{\operatorname{dec}}\,\Phi$) can be constructed as described in Remark 3.6. To do it, one needs a measurable and integrally bounded (see Remark 3.6) mapping $F_{\overline{\operatorname{dec}}\,\Phi} : [a,b] \to \operatorname{comp}[\mathbb{R}^n]$ that satisfies (3.7). Note that finding this mapping $F_{\overline{\operatorname{dec}}\,\Phi}$ is easier than constructing the set $\overline{\operatorname{dec}}\,\Phi$. At the same time, when one studies the metrical relations between the sets $\Phi_1, \Phi_2 \subset \mathbf{L}_1^n[a,b]$ and their decomposable hulls (see Lemma 3.12), it is more convenient to use Definition 3.1.

Lemma 3.11. *Let $v \in \mathbf{L}_1^n(\mathcal{U})$ $(\mathcal{U} \subset [a,b])$ and let a set $\Phi \subset \mathbf{L}_1^n[a,b]$ be decomposable. Then for any disjoint measurable sets $\mathcal{U}_1, \mathcal{U}_2 \subset \mathcal{U}$ such that $\mathcal{U}_1 \cup \mathcal{U}_2 = \mathcal{U}$, one has*

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}[v;\Phi] = \rho_{\mathbf{L}_1^n(\mathcal{U}_1)}[v;\Phi] + \rho_{\mathbf{L}_1^n(\mathcal{U}_2)}[v;\Phi]. \tag{3.12}$$

Proof. Indeed, let $\varepsilon > 0$ and $y \in \Phi$ satisfy $\|v - y\|_{\mathbf{L}_1^n(\mathcal{U})} < \rho_{\mathbf{L}_1^n(\mathcal{U})}[v;\Phi] + \varepsilon$. It follows from this estimate that

$$\rho_{\mathbf{L}_1^n(\mathcal{U}_1)}[v;\Phi] + \rho_{\mathbf{L}_1^n(\mathcal{U}_2)}[v;\Phi] \leqslant \|v - y\|_{\mathbf{L}_1^n(\mathcal{U}_1)} + \|v - y\|_{\mathbf{L}_1^n(\mathcal{U}_2)} < \rho_{\mathbf{L}_1^n(\mathcal{U})}[v;\Phi] + \varepsilon. \tag{3.13}$$

This yields

$$\rho_{\mathbf{L}_1^n(\mathcal{U}_1)}[v;\Phi] + \rho_{\mathbf{L}_1^n(\mathcal{U}_2)}[v;\Phi] \leqslant \rho_{\mathbf{L}_1^n(\mathcal{U})}[v;\Phi]. \tag{3.14}$$

Further, let us show that the opposite inequality is valid. Let $y_i \in \Phi|_{\mathcal{U}_i}$, $i = 1,2$, where $\Phi|_{\mathcal{U}_i}$ is the set of of all mappings from Φ, restricted to $\mathcal{U}_i$, $i = 1,2$, and suppose that the functions y_i, $i = 1,2$, satisfy

$$\|v - y_i\|_{\mathbf{L}_1^n(\mathcal{U}_i)} < \rho_{\mathbf{L}_1^n(\mathcal{U}_i)}[v;\Phi] + \frac{\varepsilon}{2}, \quad i = 1,2. \tag{3.15}$$

Since the set Φ is decomposable, it follows that the map $y : \mathcal{U} \to \mathbb{R}$ defined by

$$y(t) = \begin{cases} y_1(t) & \text{if } t \in \mathcal{U}_1, \\ y_2(t) & \text{if } t \in \mathcal{U}_2 \end{cases} \tag{3.16}$$

belongs to the set $\Phi|_{\mathcal{U}}$. By (3.15), we have

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}[v;\Phi] \leqslant \|v - y\|_{\mathbf{L}_1^n(\mathcal{U})} < \rho_{\mathbf{L}_1^n(\mathcal{U}_1)}[v;\Phi] + \rho_{\mathbf{L}_1^n(\mathcal{U}_2)}[v;\Phi] + \varepsilon. \tag{3.17}$$

This implies that

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}[v;\Phi] \leqslant \rho_{\mathbf{L}_1^n(\mathcal{U}_1)}[v;\Phi] + \rho_{\mathbf{L}_1^n(\mathcal{U}_2)}[v;\Phi]. \tag{3.18}$$

Comparing (3.14) and (3.18), we obtain (3.12). □

Lemma 3.12. *If $\Phi_1, \Phi_2 \in Q[\mathbf{L}_1^n[a,b]]$ and there exists a function $\omega \in \mathbf{L}_+^1[a,b]$ such that*

$$h^+_{\mathbf{L}_1^n(\mathcal{U})}[\Phi_1;\Phi_2] \leqslant \int_{\mathcal{U}} \omega(s)ds \tag{3.19}$$

for any measurable set $\mathcal{U} \subset [a,b]$, then

$$h^+_{\mathbf{L}_1^n(\mathcal{U})}[\operatorname{dec}\Phi_1;\operatorname{dec}\Phi_2] \leqslant \int_{\mathcal{U}} \omega(s)ds \tag{3.20}$$

for any measurable set $\mathcal{U} \subset [a,b]$.

Proof. Let $\mathcal{U} \subset [a,b]$ be a measurable set, $\mu(\mathcal{U}) > 0$. Let $z \in \operatorname{dec}\Phi_1$ and $z_i \in \Phi_1$, $i = 1,2,\dots,m$. Suppose also that the functions z_i and disjoint measurable sets $\widetilde{e}_i \subset [a,b]$, $i = 1,2,\dots,m$, such that $[a,b] = \bigcup_{i=1}^{m} \widetilde{e}_i$, satisfy the equality

$$z = \chi(\widetilde{e}_1)z_1 + \chi(\widetilde{e}_2)z_2 + \cdots + \chi(\widetilde{e}_m)z_m. \tag{3.21}$$

Further, by z, z_i, $i = 1,2,\dots,m$, we denote the restrictions of these functions to $\mathcal{U}$ and put $e_i = \widetilde{e}_i \cap \mathcal{U}$, $i = 1,2,\dots,m$.

From (3.21) and Lemma 3.11, it follows that

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}\left[z; \operatorname{dec}\Phi_2\right] = \sum_{i=1}^{m} \rho_{\mathbf{L}_1^n(e_i)}\left[z_i; \operatorname{dec}\Phi_2\right] \leqslant \sum_{i=1}^{m} \rho_{\mathbf{L}_1^n(e_i)}\left[z_i; \Phi_2\right]. \tag{3.22}$$

From (3.19), we obtain that

$$\rho_{\mathbf{L}_1^n(e_i)}\left[z_i; \Phi_2\right] \leqslant \int_{e_i} \omega(s)ds \tag{3.23}$$

for each $i = 1,2,\dots,m$.

Therefore, (3.22) and (3.23) imply

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}\left[z; \operatorname{dec}\Phi_2\right] \leqslant \int_{\mathcal{U}} \omega(s)ds. \tag{3.24}$$

Since (3.24) holds for any $z \in \operatorname{dec}\Phi_1$, it follows from (3.24) that (3.20) holds as well. □

Remark 3.13. Note that the function $\omega \in \mathbf{L}_+^1[a,b]$ (see (3.19)) provides a uniform with respect to measurable sets $\mathcal{U} \subset [a,b]$ estimate for the Hausdorff semideviation of the set Φ_1 from the set Φ_2.

Remark 3.14. The inequality (3.20) holds true even if the set $\operatorname{dec}\Phi_i$ is replaced with its closure $\overline{\operatorname{dec}}\,\Phi_i$, $i = 1,2$.

We say that a multivalued mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ is *integrally bounded on a set* $K \subset \mathbf{C}^n[a,b]$ if the image $\Phi(K)$ is integrally bounded.

Let $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$. We introduce an operator $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ by the formula

$$\widetilde{\Phi}(x) = \overline{\operatorname{dec}}\,\Phi(x). \tag{3.25}$$

Note that even if a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ is continuous, the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25) may be discontinuous. To illustrate this, let us consider an example.

Example 3.15. We define an integrable function $\varphi : [0,2] \times [0,1] \times [0,2] \to \mathbb{R}^1$ by

$$\varphi(x,r)(t) = \begin{cases} 1 & \text{if } t \in [x,x+r] \cap [0,2],\ r \neq 0, \\ 0 & \text{if } t \overline{\in} [x,x+r] \cap [0,2],\ r \neq 0, \\ 0 & \text{if } r = 0. \end{cases} \tag{3.26}$$

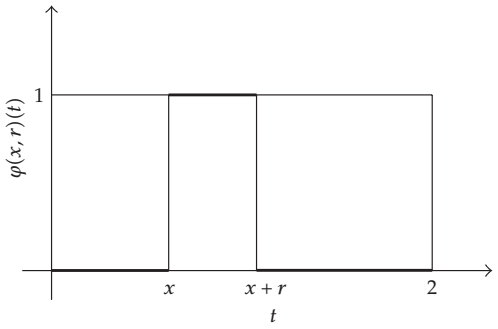

Figure 1

We also define a multivalued mapping $\Phi : [0,1] \to Q[L_1^1[0,2]]$ by the formula

$$\Phi(r) = \begin{cases} \bigcup\limits_{x\in[0,2]} \varphi(x,r) & \text{if } r \neq 0, \\ 0 & \text{if } r = 0. \end{cases} \tag{3.27}$$

Note that

$$h_{L_1^1[0,2]}\left[\Phi(r_1);\Phi(r_2)\right] = \left|r_1 - r_2\right| \tag{3.28}$$

for any $r_1, r_2 \in [0,1]$, but at the same time,

$$h_{L_1^1[0,2]}\left[\widetilde{\Phi}(0);\widetilde{\Phi}(r)\right] = 2 \tag{3.29}$$

for any $r \in (0,1]$.

Using Lemma 3.12, we obtain the following continuity conditions for the operator $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25).

Definition 3.16. Let $U \subset C^n[a,b]$. One says that a mapping $P : U \times U \to L_+^1[a,b]$ is symmetric on the set U if $P(x,y) = P(y,x)$ for any $x, y \in U$. One says that a mapping $P : U \times U \to L_+^1[a,b]$ is continuous in the second variable at a point (x,x) belonging to the diagonal of $U \times U$ if for any sequence $y_i \in U$ such that $y_i \to x$ as $i \to \infty$ it holds that $P(x,x) = \lim_{i\to\infty} P(x,y_i)$. One says that a mapping $P : U \times U \to L_+^1[a,b]$ is continuous in the second variable on the diagonal of $U \times U$ if P is continuous in the second variable at each point of this diagonal. Continuity in the fist variable is defined similarly.

Definition 3.17. Let $U \subset C^n[a,b]$. Suppose also that $P(x,x) = 0$ for any $x \in U$. One says that a mapping $P : U \times U \to L_+^1[a,b]$ has property $\mathcal{A}$ on the set U if it is continuous in the second variable on the diagonal of $U \times U$; it has property $\mathcal{B}$ on the set U if it is continuous in the first variable on the diagonal of $U \times U$; it has property $\mathcal{C}$ on the set U if it is continuous on the diagonal of $U \times U$ and symmetric on the set U.

Theorem 3.18. *Let $U \subset C^n[a,b]$. Suppose also that for a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ there exists a mapping $P : U \times U \to L_+^1[a,b]$ such that*

$$h^+_{L_1^n(\mathcal{U})}\left[\Phi(x),\Phi(y)\right] \leqslant \left\|P(x,y)\right\|_{L_1^1(\mathcal{U})} \tag{3.30}$$

for any $x, y \in U$ and any measurable set $\mathcal{U} \subset [a,b]$. Then for the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25)*, the inequality* (3.30)*, where $\Phi(\cdot) \equiv \widetilde{\Phi}(\cdot)$, is satisfied as well as for any $x, y \in U$ and any measurable set $\mathcal{U} \subset [a,b]$.*

Corollary 3.19. *If the mapping $P : U \times U \to L_+^1[a,b]$ in Theorem 3.18 has property $\mathcal{A}$ (resp., $\mathcal{B}$, $\mathcal{C}$) on the set $U \subset C^n[a,b]$, then the operator $\widetilde{\Phi} : C^n[a,b] \to \Pi[L_1^n[a,b]]$ given by* (3.25) *is Hausdorff lower semicontinuous (resp., Hausdorff upper semicontinuous, Hausdorff continuous) on the set $U \subset C^n[a,b]$.*

We say that the mapping $P : U \times U \to L_+^1[a,b]$ satisfying the inequality (3.30) for any measurable set $\mathcal{U} \subset [a,b]$ is a *majorant* mapping for $\Phi : C^n[a,b] \to Q[L_1^n[a,b]]$ on the set U.

Let a mapping $F_i : [a,b] \times \mathbb{R}^n \to \operatorname{comp}[\mathbb{R}^n]$, $i = 1,2$, be measurable as a composite function for every $x \in C^n[a,b]$. Let also F_i be integrally bounded for every bounded set $K \subset \mathbb{R}^n$. Consider a mapping $\mathcal{M} : C^n[a,b] \to Q[L_1^n[a,b]]$ given by

$$\mathcal{M}(x) = \mathcal{N}_1(x) \cup \mathcal{N}_2(x), \tag{3.31}$$

where the mapping $\mathcal{N}_i : C^n[a,b] \to \Pi[L_1^n[a,b]]$, $i = 1,2$, is the Nemytskii operator generated by the mapping $F_i : [a,b] \times \mathbb{R}^n \to \operatorname{comp}[\mathbb{R}^n]$, $i = 1,2$. For the operator $\mathcal{M} : C^n[a,b] \to Q[L_1^n[a,b]]$ given by (3.31), the majorant mapping $\widetilde{P} : C^n[a,b] \times C^n[a,b] \to L_+^1[a,b]$ can be defined as

$$\widetilde{P}(x,y)(t) = \max\left\{h^+\left[F_1(t,x(t));\ F_1(t,y(t))\right];\ h^+\left[F_2(t,x(t));F_2(t,y(t))\right]\right\}. \tag{3.32}$$

It follows from Theorem 3.18 that the operator $\widetilde{P}(\cdot,\cdot)$ given by (3.32) is also a majorant mapping for the mapping $\widetilde{\mathcal{M}} : C^n[a,b] \to \Pi[L_1^n[a,b]]$ given by (3.25), where $\Phi(\cdot) \equiv \mathcal{M}(\cdot)$. If the mapping $F_i : [a,b] \times \mathbb{R}^n \to \operatorname{comp}[\mathbb{R}^n]$, $i = 1,2$, is Hausdorff lower semicontinuous (resp., Hausdorff upper semicontinuous and Hausdorff continuous) in the second variable, then by Corollary 3.19, the mapping $\widetilde{\mathcal{M}} : C^n[a,b] \to \Pi[L_1^n[a,b]]$ given by (3.25) is Hausdorff lower semicontinuous (resp., Hausdorff upper semicontinuous and Hausdorff continuous).

Definition 3.20. One says that a multivalued mapping $\Phi : C^n[a,b] \to Q[L_1^n[a,b]]$ *has Property* $\mathcal{A}$ (resp., $\mathcal{B}$ and $\mathcal{C}$) if for this mapping there exists a majorant mapping $P : C^n[a,b] \times C^n[a,b] \to L_+^1[a,b]$ satisfying Property $\mathcal{A}$ (resp., $\mathcal{B}$ and $\mathcal{C}$).

4. Basic properties of generalized solutions of functional differential inclusions

Using decomposable hulls, we introduce in this section the concept of a generalized solution of a functional differential inclusion with a right-hand side which is not necessarily decomposable. Using, as mentioned in Section 3, basic topological properties of a mapping given by (3.25), we study the properties of a generalized solution of the initial value problem.

Consider the initial value problem for the functional differential inclusion

$$\dot{x} \in \Phi(x), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n), \tag{4.1}$$

where the mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ satisfies the following condition: for every bounded set $U \subset \mathbf{C}^n[a,b]$, the image $\Phi(U)$ is integrally bounded. Note that the right-hand side

of the inclusion (4.1) is not necessarily decomposable. Note also that $\dot{x}$ in (4.1) is not treated as a derivative at a point but as an element of $\mathbf{L}_1^n[a,b]$ (see [10, 23–25]). When we study such a problem, there may appear some difficulties described in the introduction. In this connection, we will introduce the concept of a generalized solution of the problem (4.1) and study the properties of this solution. Using the Nemytskii operator, which is decomposable, the initial value problem for a classical differential inclusion, that is, one without delay (see [10, 23–25]), can be reduced to (4.1).

Definition 4.1. An absolutely continuous function $x : [a,b] \to \mathbb{R}^n$ is called a generalized solution of the problem (4.1) if

$$\dot{x} \in \overline{\operatorname{dec}}\,\Phi(x), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n). \tag{4.2}$$

Note that from Lemma 3.7, it follows that if the set $\Phi(x)$ (see(4.1)) is decomposable, then a generalized solution of the problem (4.1) coincides with a classical solution.

Example 4.2. Consider an ordinary differential equation, $x \in [0,1]$,

$$\dot{x} = kx, \qquad x(0) = 1. \tag{4.3}$$

Its solution is the function $x = e^{kt}$.

We assume that the parameter k may take two values: 1 or 2. Then the trajectories of such a system are described by the differential inclusion

$$\dot{x} \in \Phi(t)x(t), \qquad x(0) = 1, \tag{4.4}$$

where $\Phi(t)$ is a multivalued function with the values from the set $\{1,2\}$. Note that $\overline{\operatorname{dec}}\,\Phi(t) = \Phi(t)$, that is, the set in the right-hand side of the inclusion is decomposable. In this case, a generalized solution of the inclusion coincides with a classical solution.

The latter differential inclusion describes the model that is controlled by the differential equation either with the parameter value $k = 1$ or with the parameter value $k = 2$. In this model, switchings from one law (equation) to another may take place any time.

In the limit case, all possible solutions fill entirely the set of all points between the graphs of the functions e^t and e^{2t}.

Example 4.3. Consider a simple pendulum. It consists of a mass m hanging from a string of length l and fixed at a pivot point P. When displaced to an initial angle and released, the pendulum will swing back and forth with periodic motion. The equation of motion for the pendulum is given by

$$\ddot{x} = -a \sin x, \tag{4.5}$$

where $x(t)$ is the angular displacement at the moment t, $a = g/l$, g is the acceleration of gravity, and l is the length of the string.

If the amplitude of angular displacement is small enough that the small angle approximation holds true, then the equation of motion reduces to the equation of simple harmonic motion

$$\ddot{x} = -ax. \tag{4.6}$$

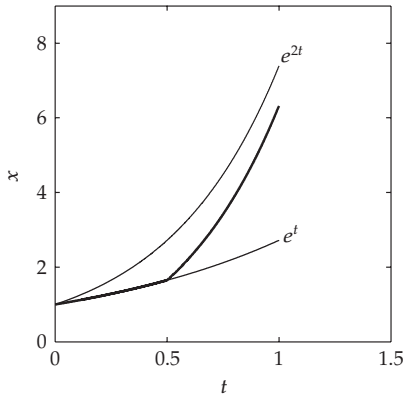

Figure 2: The solution of the differential inclusion that corresponds to switching from $k = 1$ (control law 1) to $k = 2$ (control law 2) at the moment $t = 1/2$.

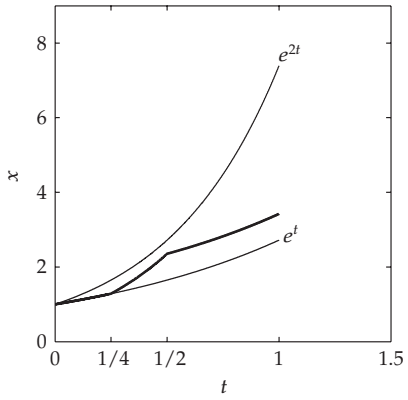

Figure 3: The solution of the differential inclusion that corresponds to two switchings: from $k = 1$ to $k = 2$ at the moment $t = 1/4$ and from $k = 2$ to $k = 1$ at the moment $t = 1/2$.

Let us now assume that the length of the string l may change, that is, it may take an value from a finite set $\{l_1, \ldots, l_m\}$. In this case, the equation of simple harmonic motion transforms to the differential inclusion with a multivalued mapping

$$\ddot{x} \in \Phi(x), \tag{4.7}$$

where $\Phi(x) = \bigcup_{i=1}^{m} -(g/l_i)x$.

We assume that switching from one length (equation) to another may take place any time. Then the generalized solutions of the inclusion treat all available trajectories (states) corresponding to all switchings.

Definition 4.4. An operator $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ is called a Volterra-Tikhonov (or simply a Volterra) operator (see [26]) if the equality $x = y$ on $[a,\tau]$, $\tau \in (a,b]$, implies $(\Phi(x))|_\tau = (\Phi(y))|_\tau$, where $(\Phi(z))|_\tau$ is the set of all functions from $\Phi(z)$ restricted to $[a,\tau]$.

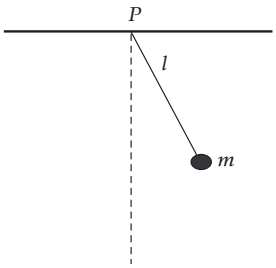

Figure 4

In what follows, we assume that the operator $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ (the right-hand side of the inclusion (4.1)) is a Volterra operator. This implies that the operator $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ given by (3.25) is also a Volterra operator.

Let $\tau \in (a,b]$. Let us determine the continuous mapping $V_\tau : \mathbf{C}^n[a,\tau] \to \mathbf{C}^n[a,b]$ by

$$(V_\tau x) = \begin{cases} x(t) & \text{if } t \in [a,\tau], \\ x(\tau) & \text{if } t \in (\tau,b]. \end{cases} \tag{4.8}$$

Definition 4.5. One says that an absolutely continuous function $x : [a,\tau] \to \mathbb{R}^n$ is a generalized solution of the problem (4.1) on the interval $[a,\tau]$, $\tau \in (a,b]$, if x satisfies $\dot{x} \in (\overline{\operatorname{dec}}\, \Phi(V_\tau(x)))|_\tau$ and $x(a) = x_0$, where the continuous mapping $V_\tau : \mathbf{C}^n[a,\tau] \to \mathbf{C}^n[a,b]$ is given by (4.8).

A function $x : [a,c) \to \mathbb{R}^n$, which is absolutely continuous on any interval $[a,\tau] \subset [a,c)$, $c \in (a,b]$, is called a generalized solution of the problem (4.1) on the interval $[a,c)$ if for each $\tau \in (a,c)$ the restriction of x to $[a,\tau]$ is a generalized solution of the problem (4.1) on the interval $[a,\tau]$.

A generalized solution $x : [a,c) \to \mathbb{R}^n$ of the problem (4.1) on the interval $[a,c)$ is said to be nonextendable if there is no generalized solution y of the problem (4.1) 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 $t \in [a,c)$.

In Theorems 4.6–4.12 below, we assume that the mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property $\mathcal{A}$. Due to Corollary 3.19, the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25) is lower semicontinuous. Due to [27, 28], the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ admits a continuous selection. Therefore, the following propositions on local solutions of the problem (4.1) are straightforward.

Theorem 4.6. *There exists $\tau \in (a,b]$ such that a generalized solution of the problem* (4.1) *is defined on the interval $[a,\tau]$.*

Theorem 4.7. *A generalized solution $x : [a,c) \to \mathbb{R}^n$ of the problem* (4.1) *admits a continuation if and only if $\overline{\lim}_{t\to c-0}|x(t)| < \infty$.*

Theorem 4.8. *If y is a generalized solution of the problem* (4.1) *on the interval $[a,\tau]$, $\tau \in (a,b)$, then there exists a nonextendable solution x of the problem* (4.1) *defined on the interval $[a,c)$ ($c \in (\tau,b]$), or on the entire interval $[a,b]$, such that $x(t) = y(t)$ for each $t \in [a,\tau]$.*

Let $H(x_0,\tau)$ be the set of all generalized solutions of the problem (4.1) on the interval $[a,\tau]$ ($\tau \in (a,b]$).

We say that generalized solutions of the problem (4.1) *admit a uniform a priori estimate* if there exists a number $r > 0$ such that for every $\tau \in (a, b]$, there is no generalized solution $y \in H(x_0, \tau)$ satisfying $\|y\|_{\mathbf{C}^n[a,\tau]} > r$.

Theorems 4.6–4.8 yield the following result.

Theorem 4.9. *Let the generalized solutions of the problem* (4.1) *admit a uniform a priori estimate. Then* $H(x_0, \tau) \neq \varnothing$ *for any* $\tau \in (a, b]$ *and there exists a number* $r > 0$ *such that* $\|y\|_{\mathbf{C}^n[a,\tau]} \leqslant r$ *for any* $\tau \in (a, b]$, $y \in H(x_0, \tau)$.

Definition 4.10. One says that a mapping $\Phi : \mathbf{C}^n[a, b] \to Q[\mathbf{L}_1^n[a, b]]$ has Property Γ_1 if there exists an isotonic continuous operator $\Gamma_1 : \mathbf{C}_+^1[a, b] \to \mathbf{L}_+^1[a, b]$ satisfying the following conditions:

(i) for any function $x \in \mathbf{C}^n[a, b]$ and any measurable set $\mathcal{U} \subset [a, b]$, one has

$$\left\|\Phi(x)\right\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \left\|\Gamma_1(Zx)\right\|_{\mathbf{L}_1^1(\mathcal{U})}, \tag{4.9}$$

where the continuous mapping $Z : \mathbf{C}^n[a, b] \to \mathbf{C}_+^1[a, b]$ is given by

$$(Zx)(t) = \left|x(t)\right|; \tag{4.10}$$

(ii) the local solutions of the problem

$$\dot{y} = \Gamma_1(y), \qquad y(a) = \left|x_0\right| \tag{4.11}$$

admit a uniform a priori estimate.

Lemma 4.11. *Suppose that a multivalued mapping* $\Phi : \mathbf{C}^n[a, b] \to Q[\mathbf{L}_1^n[a, b]]$ *has Property* Γ_1. *Then so does the mapping* $\widetilde{\Phi} : \mathbf{C}^n[a, b] \to \Pi[\mathbf{L}_1^n[a, b]]$ *given by* (3.25).

Proof. It suffices to show that

$$\left\|\operatorname{dec}\Phi(x)\right\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \left\|\Gamma_1(Zx)\right\|_{\mathbf{L}_1^1(\mathcal{U})} \tag{4.12}$$

for any function $x \in \mathbf{C}^n[a, b]$ and any measurable set $\mathcal{U} \subset [a, b]$. Indeed, let a function $y \in \operatorname{dec}\Phi(x)$ be as in (3.1). By (4.9),

$$\int_{\mathcal{U}_i \cap \mathcal{U}} \left|x_i(s)\right| ds \leqslant \left\|\Gamma_1(Zx)\right\|_{\mathbf{L}_1^1(\mathcal{U}_i \cap \mathcal{U})} \tag{4.13}$$

for each $i = 1, 2, \ldots, m$. Hence, we have that for the function $y \in \operatorname{dec}\Phi(x)$, the estimate

$$\int_{\mathcal{U}} \left|y(s)\right| ds \leqslant \left\|\Gamma_1(Zx)\right\|_{\mathbf{L}_1^1(\mathcal{U})} \tag{4.14}$$

is satisfied as well. This gives the inequality (4.12). The proof is complete. □

Let a continuous operator $\Theta : \mathbf{D}^n[a, b] \to \mathbf{C}_+^1[a, b]$ be given by

$$(\Theta z)(t) = \left|z(a)\right| + \int_a^t \left|\dot{z}(s)\right| ds. \tag{4.15}$$

Theorem 4.12. *Suppose that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property Γ_1. Then the set $H(x_0,\tau)$ is nonempty for any $\tau \in (a,b]$ and there exists a number $r > 0$ such that $\|y\|_{\mathbf{C}^n[a,\tau]} \leqslant r$ for any $y \in H(x_0,\tau)$, $\tau \in (a,b]$.*

Proof. Indeed, let $x \in H(x_0,\tau)$ ($\tau \in (a,b]$). From Lemma 4.11, it follows that for any $t \in [a,\tau]$,

$$(\Theta x)(t) \leqslant |x_0| + \int_a^t (\Gamma_1(Zx))(s)ds \leqslant |x_0| + \int_a^t (\Gamma_1(\Theta x))(s)ds, \tag{4.16}$$

where the function Θx is given by (4.15). Due to the theorem on integral inequalities for an isotonic operator (see [29]), this implies that we actually have $\Theta x \leqslant \xi_0$, where ξ_0 is the upper solution of the problem (4.11). Thus, there is no $x \in H(x_0,\tau)$ satisfying the inequality $\|x\|_{\mathbf{C}^n[a,\tau]} > \|\xi_0\|_{\mathbf{C}^1[a,b]}$. From this, it follows that the set of all local generalized solutions of the problem (4.1) admits a uniform a priori estimate. Applying Theorem 4.9 completes the proof. □

Let a linear continuous operator $\Lambda : \mathbf{L}_1^n[a,b] \to \mathbf{C}^n[a,b]$ be given by

$$(\Lambda z)(t) = \int_a^t z(s)ds, \quad t \in [a,b]. \tag{4.17}$$

We say that $\Lambda : \mathbf{L}_1^n[a,b] \to \mathbf{C}^n[a,b]$ is the *operator of integration.*

Theorem 4.13. *Let the set of all local generalized solutions of the problem* (4.1) *admit a uniform a priori estimate. Suppose also that $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property $\mathcal{C}$. Then for any function $v \in \mathbf{L}_1^n[a,b]$ and any $\varepsilon > 0$, there exists a generalized solution $x \in \mathbf{D}^n[a,b]$ of the problem* (4.1) *such that*

$$\left\|\dot{x} - v\right\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \rho_{\mathbf{L}_1^n(\mathcal{U})}\left[v, \overline{\operatorname{dec}}\,\Phi(x)\right] + \varepsilon\mu(\mathcal{U}) \tag{4.18}$$

for any measurable set $\mathcal{U} \subset [a,b]$.

If $\Phi : \mathbf{C}^n[a,b] \to \Omega(Q[\mathbf{L}_1^n[a,b]])$, then the theorem is also valid for $\varepsilon = 0$.

Proof. Let $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ have Property $\mathcal{C}$. Then by Corollary 3.19, the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25) is continuous. Therefore (see [30–32]), given a number $\varepsilon > 0$ and a function $v \in \mathbf{L}_1^n[a,b]$, there exists a continuous mapping $\varphi : \mathbf{C}^n[a,b] \to \mathbf{L}_1^n[a,b]$ satisfying $\varphi(y) \in \widetilde{\Phi}(y)$ and

$$\left\|\varphi(y) - v\right\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \rho_{\mathbf{L}_1^n(\mathcal{U})}\left[v, \overline{\operatorname{dec}}\,\Phi(y)\right] + \varepsilon\mu(\mathcal{U}) \tag{4.19}$$

for any $y \in \mathbf{C}^n[a,b]$ and any measurable set $\mathcal{U} \subset [a,b]$. It follows from Theorem 4.9 that $H(x_0,\tau) \neq \varnothing$ for any $\tau \in (a,b]$, and that there exists a number $r > 0$ such that $\|y\|_{\mathbf{C}^n[a,\tau]} \leqslant r$ for each $\tau \in (a,b]$, $y \in H(x_0,\tau)$. Now, we show that there exists $x \in H(x_0,b)$ satisfying (4.18). Consider the problem

$$\dot{x} \in \overline{\operatorname{dec}}\,\Phi(W_r(x)), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n), \tag{4.20}$$

where the continuous mapping $W_r : \mathbf{C}^n[a,b] \to \mathbf{C}^n[a,b]$ is given by

$$(W_r x)(t) = \begin{cases} x(t) & \text{if } |x(t)| \leqslant r+2, \\ \dfrac{r+2}{|x(t)|}x(t) & \text{if } |x(t)| > r+2. \end{cases} \tag{4.21}$$

We denote by $H(W)$ the set of all solutions of the problem (4.20). Let us show that $H(W) = H(x_0, b)$. It follows from the definition of the mapping $W_r : \mathbf{C}^n[a,b] \to \mathbf{C}^n[a,b]$ (see (4.21)) that $H(x_0,b) \subset H(W)$. Let us prove that $H(W) \subset H(x_0,b)$. Assume the converse. Then there exists $y \in H(W)$ such that $\|y\|_{\mathbf{C}^n[a,b]} > r+2$. Since $y(a) = x_0$, we have $|y(a)| < r+2$. This implies that there exists a number $\tau \in (a,b]$ such that $\|y|_\tau\|_{\mathbf{C}^n[a,\tau]} = r+1$ ($y|_\tau$ is the restriction of the function y to $[a,\tau]$). By (4.21), we have $y|_\tau \in H(x_0,\tau)$. This contradicts to the definition of the number r. Hence, $H(x_0,b) = H(W)$. Consider a continuous operator $\Psi : \mathbf{C}^n[a,b] \to \mathbf{C}^n[a,b]$ given by

$$\Psi(x) = x_0 + \Lambda\varphi\big(W_r(x)\big), \tag{4.22}$$

where the operator $\Lambda : \mathbf{L}_1^n[a,b] \to \mathbf{C}^n[a,b]$ is the operator of integration defined by (4.17), and $\varphi : \mathbf{C}^n[a,b] \to \mathbf{L}_1^n[a,b]$ is a continuous selection of the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25). The function φ ia also assumed to satisfy (4.19). Since the operator $W_r : \mathbf{C}^n[a,b] \to \mathbf{C}^n[a,b]$ is bounded, we obtain that the image $\Psi(\mathbf{C}^n[a,b])$ is a relatively compact subset of $\mathbf{C}^n[a,b]$. Hence, the set $U = \overline{\mathrm{co}}\,\Psi(\mathbf{C}^n[a,b])$ is a convex compact set. Since the operator $\Psi : \mathbf{C}^n[a,b] \to \mathbf{C}^n[a,b]$ given by (4.22) takes the set U into itself, we have, by Schauder theorem, that the mapping $\Psi(\cdot)$ has a fixed point. This fixed point x is the solution of the problem (4.20). It follows from the above equality $H(W) = H(x_0,b)$ that this solution $x \in H(W)$ is a generalized solution of the problem (4.1). Since $\dot{x} = \varphi(x)$, we see that (4.19) implies (4.18).

Let us prove the second statement of the theorem. Let $\Phi : \mathbf{C}^n[a,b] \to \Omega(Q[\mathbf{L}_1^n[a,b]])$. Suppose also that Φ has Property C. Then by Lemma 3.9, $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$. Hence for each $i = 1,2,\ldots$, there exists a generalized solution $x_i \in \mathbf{D}^n[a,b]$ of the problem (4.1) such that for any measurable set $\mathcal{U} \subset [a,b]$, the inequality (4.18) is valid for $\dot{x} = \dot{x}_i$ and $\varepsilon = 1/i$. Since the set $H(x_0,b)$ is bounded, we see that the sequence $\{\dot{x}_i\}$ is weakly compact in $\mathbf{L}_1^n[a,b]$. Without loss of generality, it can be assumed that $\dot{x}_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ and $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$. Let us show that x is a generalized solution of the problem (4.1). In other words, we have to prove that $\dot{x} \in \overline{\mathrm{dec}}\,\Phi(x)$. Assume that the functions $y_i \in \overline{\mathrm{dec}}\,\Phi(x)$, $i = 1,2,\ldots$, satisfy

$$\big\|y_i - \dot{x}_i\big\|_{\mathbf{L}_1^n[a,b]} = \rho_{\mathbf{L}_1^n[a,b]}\big[\dot{x}_i; \overline{\mathrm{dec}}\,\Phi(x)\big] \tag{4.23}$$

(as $\overline{\mathrm{dec}}\,\Phi(x) \in \Pi[\mathbf{L}_1^n[a,b]]$, these functions do exist). It follows from (4.23) that

$$\big\|y_i - \dot{x}_i\big\|_{\mathbf{L}_1^n[a,b]} \leqslant h_{\mathbf{L}_1^n[a,b]}\big[\overline{\mathrm{dec}}\,\Phi(x_i);\ \overline{\mathrm{dec}}\,\Phi(x)\big]. \tag{4.24}$$

Since the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$ given by (3.25) is continuous, we obtain, by (4.24), that $y_i - \dot{x}_i \to 0$ in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. Since $\dot{x}_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$, we have that $y_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. Therefore, the convexity of the set $\overline{\mathrm{dec}}\,\Phi(x)$ implies that $\dot{x} \in \overline{\mathrm{dec}}\,\Phi(x)$ (see [21]). Thus, x is a generalized solution of the problem (4.1).

Further, let us show that (4.19) holds for the solution x and for $\varepsilon = 0$. Since $\dot{x}_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$, we have, by [21], that for each $m = 1,2,\dots$, there exist numbers $i(m)$, $\lambda_j^m \geqslant 0$, $j = 1,2,\dots,i(m)$, satisfying the following conditions: $\sum_{j=1}^{i(m)} \lambda_j^m = 1$; the sequence $\{\beta_m = \sum_{j=1}^{i(m)} \lambda_j^m \dot{x}_{j+m}\}$ tends to $\dot{x}$ in $\mathbf{L}_1^n[a,b]$. Since

$$\left\|\dot{x} - v\right\|_{\mathbf{L}_1^n[a,b]} \leqslant \left\|\dot{x} - \beta_m\right\|_{\mathbf{L}_1^n[a,b]} + \sum_{j=1}^{i(m)} \lambda_j^m \left\|\dot{x}_{j+m} - v\right\|_{\mathbf{L}_1^n[a,b]} \tag{4.25}$$

for each $m = 1,2,\dots$, it follows, due to the choice of the sequence $\{\dot{x}_i\}$, that

$$\left\|\dot{x} - v\right\|_{\mathbf{L}_1^n[a,b]} \leqslant \left\|\dot{x} - \beta_m\right\|_{\mathbf{L}_1^n[a,b]} + \sum_{j=1}^{i(m)} \lambda_j^m \rho_{\mathbf{L}_1^n[a,b]}\left[v; \overline{\operatorname{dec}}\,\Phi(x_{j+m})\right] + (b-a)\sum_{j=1}^{i(m)} \lambda_j^m \frac{1}{j+m} \tag{4.26}$$

for each $m = 1,2,\dots$.

Since

$$\lim_{i\to\infty} \rho_{\mathbf{L}_1^n[a,b]}\left[v; \overline{\operatorname{dec}}\,\Phi(x_i)\right] = \rho_{\mathbf{L}_1^n[a,b]}\left[v; \overline{\operatorname{dec}}\,\Phi(x)\right], \tag{4.27}$$

it follows that letting $m \to \infty$ in the previous inequality, we obtain

$$\left\|\dot{x} - v\right\|_{\mathbf{L}_1^n[a,b]} = \rho_{\mathbf{L}_1^n[a,b]}\left[v; \overline{\operatorname{dec}}\,\Phi(x)\right]. \tag{4.28}$$

Finally, note that by the decomposability of the set $\overline{\operatorname{dec}}\,\Phi(x)$, this equality holds for any measurable set $\mathcal{U} \subset [a,b]$. This completes the proof. □

Theorems 4.12 and 4.13 yield the following result.

Corollary 4.14. *Suppose that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Properties Γ_1 and $\mathcal{C}$. Then for any function $v \in \mathbf{L}_1^n[a,b]$ and any $\varepsilon > 0$, there exists a generalized solution $x \in \mathbf{D}^n[a,b]$ of the problem* (4.1) *such that* (4.18) *holds for any measurable set $\mathcal{U} \subset [a,b]$.*

If $\Phi : \mathbf{C}^n[a,b] \to \Omega(Q[\mathbf{L}_1^n[a,b]])$, then the corollary is also valid for $\varepsilon = 0$.

Remark 4.15. Consider the convex compact set $U = \overline{\operatorname{co}}\,\widetilde{\Psi}(\mathbf{C}^n[a,b]) \subset \mathbf{C}^n[a,b]$, where the mapping $\widetilde{\Psi} : \mathbf{C}^n[a,b] \to 2^{\mathbf{C}^n[a,b]}$ is given by

$$\widetilde{\Psi}(x) = x_0 + \Lambda\widetilde{\Phi}\big(W_r(x)\big). \tag{4.29}$$

Here, the operators $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ and $W_r : \mathbf{C}^n[a,b] \to \mathbf{C}^n[a,b]$ are determined by (3.25) and (4.21), respectively. If a number $r > 0$ is such that $\|y\|_{\mathbf{C}^n[a,\tau]} \leqslant r$ for any $\tau \in (a,b]$, $y \in H(x_0,\tau)$, then due to the the coincidence of the sets $H(W)$ and $H(x_0,b)$ (see the proof of Theorem 4.13), $H(x_0,b) \subset U$.

Definition 4.16. Given $\varepsilon \geq 0$, $p \geq 0$, $u \in \mathbf{L}_+^1[a,b]$, one says that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property $\Gamma_2^{u,\varepsilon,p}$ if there exists an isotonic and continuous Volterra operator $\Gamma_2 : \mathbf{C}_+^1[a,b] \to \mathbf{L}_+^1[a,b]$ satisfying the following conditions:

(i) $\Gamma_2(0) = 0$;
(ii) for any functions $x, y \in \mathbf{C}^n[a,b]$ and any measurable set $\mathcal{U} \subset [a,b]$, one has

$$h_{\mathbf{L}_1^n(\mathcal{U})}\big[\Phi(x);\Phi(y)\big] \leqslant \big\|\Gamma_2\big(Z(x-y)\big)\big\|_{\mathbf{L}_1^1(\mathcal{U})}, \tag{4.30}$$

where the continuous mapping $Z : \mathbf{C}^n[a,b] \to \mathbf{C}_+^1[a,b]$ is determined by (4.10);
(iii) the set of all local solutions of the problem

$$\dot{y} = u + \varepsilon + \Gamma_2(y), \qquad y(a) = p, \tag{4.31}$$

admits a uniform a priori estimate.

Given $y \in \mathbf{D}^n[a,b]$ and $\varkappa \in \mathbf{L}_+^1[a,b]$, the following estimate will be used in the sequel:

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}\big[\dot{y};\Phi(y)\big] \leqslant \int_{\mathcal{U}} \varkappa(s)ds \tag{4.32}$$

for each measurable set $\mathcal{U} \subset [a,b]$.

Theorem 4.17. *Let functions $y \in \mathbf{D}^n[a,b]$ and $\varkappa \in \mathbf{L}_+^1[a,b]$ satisfy the inequality* (4.32) *for each measurable set $\mathcal{U} \subset [a,b]$. Suppose that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property $\Gamma_2^{\varkappa,\varepsilon,p}$, where $\varepsilon \geqslant 0$, $p = |x_0 - y(a)|$, and x_0 is the initial condition of the problem* (4.1). *Then for any generalized solution of the problem* (4.1) *satisfying*

$$\big\|\dot{x} - \dot{y}\big\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \rho_{\mathbf{L}_1^n(\mathcal{U})}\big[\dot{y};\overline{\operatorname{dec}}\,\Phi(x)\big] + \varepsilon\mu(\mathcal{U}) \tag{4.33}$$

for any measurable set $\mathcal{U} \subset [a,b]$, the following conditions are satisfied:

(1)

$$\Theta(x-y)(t) \leqslant \xi(\varkappa,\varepsilon,p)(t) \tag{4.34}$$

for each $t \in [a,b]$, where the function $\xi(\varkappa,\varepsilon,p) \in \mathbf{D}^1[a,b]$ is the upper solution of the problem (4.31) *for $u = \varkappa$ and $p = |x_0 - y(a)|$, and the mapping $\Theta : \mathbf{D}^n[a,b] \to \mathbf{C}_+^1[a,b]$ is given by* (4.15)*;*
(2)

$$\big|\dot{x}(t) - \dot{y}(t)\big| \leqslant \varkappa(t) + \varepsilon + \big(\Gamma_2\big(\xi(\varkappa,\varepsilon,p)\big)\big)(t) \tag{4.35}$$

for almost all $t \in [a,b]$.

Proof. First, note that since the mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property $\Gamma_2^{\varkappa,\varepsilon,p}$, it follows from Theorem 3.18 that so does the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ determined by (3.25). Further, the inequality (4.33) yields that

$$\big\|\dot{x} - \dot{y}\big\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \rho_{\mathbf{L}_1^n(\mathcal{U})}\big[\dot{y};\overline{\operatorname{dec}}\,\Phi(y)\big] + h_{\mathbf{L}_1^n(\mathcal{U})}\big[\overline{\operatorname{dec}}\,\Phi(y);\overline{\operatorname{dec}}\,\Phi(x)\big] + \varepsilon\mu(\mathcal{U}) \tag{4.36}$$

for any measurable set $\mathcal{U} \subset [a,b]$.

Remark 4.15 and relations (4.36), (4.32), and (4.30) imply that for any measurable set $\mathcal{U} \subset [a,b]$, we obtain the inequality

$$\|\dot{x} - \dot{y}\|_{\mathbf{L}_1^n(\mathcal{U})} \leqslant \int_{\mathcal{U}} \big(\varkappa(s) + \varepsilon + \Gamma_2\big(Z(x-y)\big)(s)\big)ds, \tag{4.37}$$

where the mapping $Z : \mathbf{C}^n[a,b] \to \mathbf{C}_+^1[a,b]$ is given by (4.10). It follows from this inequality that

$$\big|\dot{x}(t) - \dot{y}(t)\big| \leqslant \varkappa(t) + \varepsilon + \Gamma_2\big(Z(x-y)\big)(t) \tag{4.38}$$

for almost all $t \in [a,b]$. Since $Z(x-y)(t) \leqslant \Theta(x-y)(t)$ for all $t \in [a,b]$ (see (4.10), (4.15)) and the operator $\Gamma_2 : \mathbf{C}_+^1[a,b] \to \mathbf{L}_+^1[a,b]]$ (see (4.38)) is isotonic, we have that

$$\big|\dot{x}(t) - \dot{y}(t)\big| = \dot{\Theta}(x-y)(t) \leqslant \varkappa(t) + \varepsilon + \Gamma_2\big(\Theta(x-y)\big)(t) \tag{4.39}$$

for almost all $t \in [a,b]$. Therefore, (4.39) and the theorem on differential inequalities with an isotonic operator (see [29]) imply (4.34) for any $t \in [a,b]$. The inequality (4.35) follows from (4.34) and (4.39). The proof is complete. □

Theorems 4.13 and 4.17 yield the following result.

Theorem 4.18. *Let functions $y \in \mathbf{D}^n[a,b]$ and $\varkappa \in \mathbf{L}_+^1[a,b]$ satisfy* (4.32) *for each measurable set $\mathcal{U} \subset [a,b]$. Suppose that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property $\Gamma_2^{\varkappa,\varepsilon,p}$, where $\varepsilon \geq 0$, $p = |x_0 - y(a)|$, x_0 is the initial condition in the problem* (4.1). *Let the set of all local generalized solutions of the problem* (4.1) *admit a uniform a priori estimate. Then for $\varepsilon > 0$, there exists a generalized solution $x \in \mathbf{D}^n[a,b]$ of the problem* (4.1) *which satisfies* (4.34) *and* (4.35) *for all $t \in [a,b]$ and for almost all $t \in [a,b]$, respectively.*

If $\Phi : \mathbf{C}^n[a,b] \to \Omega(Q[\mathbf{L}_1^n[a,b]])$, then the theorem is also valid for $\varepsilon = 0$.

Corollary 4.19. *Let functions $y \in \mathbf{D}^n[a,b]$ and $\varkappa \in \mathbf{L}_+^1[a,b]$ satisfy* (4.32) *for each measurable set $\mathcal{U} \subset [a,b]$. Suppose that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has properties Γ_1 and $\Gamma_2^{\varkappa,\varepsilon,p}$, where $\varepsilon \geq 0$, $p = |x_0 - y(a)|$, x_0 is the initial condition in the problem* (4.1). *Then for $\varepsilon > 0$, there exists a generalized solution $x \in \mathbf{D}^n[a,b]$ of the problem* (4.1) *which satisfies* (4.34) *and* (4.35) *for all $t \in [a,b]$ and for almost all $t \in [a,b]$, respectively.*

If $\Phi : \mathbf{C}^n[a,b] \to \Omega(Q[\mathbf{L}_1^n[a,b]])$, then the corollary is also valid for $\varepsilon = 0$.

Remark 4.20. It follows from the proof of Theorem 4.17 that Theorems 4.17, 4.18, and Corollary 4.19 are also valid if the functions $y \in \mathbf{D}^n[a,b]$ and $\varkappa \in \mathbf{L}_+^1[a,b]$ satisfy

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}\big[\dot{y}; \overline{\operatorname{dec}}\,\Phi(y)\big] \leqslant \int_{\mathcal{U}} \varkappa(s)ds \tag{4.40}$$

for each measurable set $\mathcal{U} \subset [a,b]$.

Definition 4.21. An absolutely continuous function $x \in \mathbf{D}^n[a,b]$ is called a generalized quasisolution of the problem (4.1) if there exists a sequence of functions $x_i \in \mathbf{D}^n[a,b]$, $i = 1,2,\ldots$, such that the following conditions hold:

(i) $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$;
(ii) $\dot{x}_i \in \overline{\operatorname{dec}}\,\Phi(x)$ and $x_i(a) = x_0$ for each $i = 1,2,\ldots$.

Note that by Lemma 3.7, if the set $\Phi(x)$ mentioned in Definition 4.21 is decomposable, then a generalized quasisolution coincides with a quasisolution defined in [9, 33], where $\Phi(\cdot)$ is the Nemytskii operator. Note also that this definition of a generalized quasisolution differs from the definition of a quasitrajectory given in [9, 33, 34] due to the condition $\dot{x}_i \in \overline{\operatorname{dec}}\,\Phi(x)$. Using Definition 4.21, we can obtain more general results on the properties of quasisolutions (see Remark 4.23). Moreover, this definition is more suitable for applications.

Let $\mathscr{M}(x_0)$ be the set of all generalized quasisolutions of the problem (4.1).

We define a mapping $\widetilde{\Phi}_{\mathrm{co}} : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$ by the formula

$$\widetilde{\Phi}_{\mathrm{co}}(x) = \overline{\mathrm{co}}\big(\overline{\operatorname{dec}}\,\Phi(x)\big). \tag{4.41}$$

We call $\widetilde{\Phi}_{\mathrm{co}} : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$ the *convex decomposable hull.*

Consider the problem (4.1) with the convex decomposable hull $\widetilde{\Phi}_{\mathrm{co}} : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$ given by (4.41) leading to

$$\dot{x} \in \widetilde{\Phi}_{\mathrm{co}}(x), \qquad x(a) = x_0 \quad \big(x_0 \in \mathbb{R}^n\big). \tag{4.42}$$

Let $H_{\mathrm{co}}(x_0,\tau)$ be the set of all solutions of the problem (4.42) on the interval $[a,\tau]$ $(\tau \in (a,b])$.

Theorem 4.22. $\mathscr{M}(x_0) = H_{\mathrm{co}}(x_0,b)$.

Proof. First, we will show that $H_{\mathrm{co}}(x_0,b) \subset \mathscr{M}(x_0)$. Let $x \in H_{\mathrm{co}}(x_0,b)$. By [35], for $\dot{x} \in \mathbf{L}_1^n[a,b]$, there exists a sequence $y_i \in \overline{\operatorname{dec}}\,\Phi(x)$, $i = 1,2,\ldots$, such that $y_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. This implies that $x_i = x_0 + \Lambda y_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$, where $\Lambda : \mathbf{L}_1^n[a,b] \to \mathbf{C}^n[a,b]$ is the operator of integration (see (4.17)). Hence, $H_{\mathrm{co}}(x_0,b) \subset \mathscr{M}(x_0)$.

Let us now prove that $\mathscr{M}(x_0) \subset H_{\mathrm{co}}(x_0,b)$. Let $x \in \mathscr{M}(x_0)$. Then there exists a sequence $x_i \in \mathbf{D}^n[a,b]$, $i = 1,2,\ldots$, satisfying the following conditions: (1) $\dot{x}_i \in \overline{\operatorname{dec}}\,\Phi(x)$ (see (4.41)) and $x_i(a) = x_0$ for each $i = 1,2,\ldots$; (2) $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$. Since the sequence $\dot{x}_i$, $i = 1,2,\ldots$, is weakly compact, we can assume without loss of generality that $\dot{x}_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. Since $\dot{x}_i \in \widetilde{\Phi}_{\mathrm{co}}(x)$ (see (4.41)), it follows that $\dot{x} \in \widetilde{\Phi}_{\mathrm{co}}(x)$ (see [21]). Hence $x \in H_{\mathrm{co}}(x_0,b)$ and therefore $\mathscr{M}(x_0) \subset H_{\mathrm{co}}(x_0,b)$. □

Remark 4.23. Theorem 4.22 may still remain valid even if the mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ is discontinuous and its image $\Phi(\mathcal{B})$ is not integrally bounded for every bounded set $\mathcal{B} \subset \mathbf{C}^n[a,b]$. The proof of Theorem 4.22 is only based on the fact that every value of this mapping is integrally bounded, rather than on the assumption that Φ is a Volterra operator.

Definition 4.24. One says that a compact convex set $U \subset \mathbf{C}^n[a,b]$ has Property $\mathfrak{D}$ if $\mathscr{M}(x_0) \subset U$, and for any $x \in \mathscr{M}(x_0)$, there exists a sequence of absolutely continuous functions $x_i : [a,b] \to \mathbb{R}^n$, $i = 1,2,\ldots$, such that

(i) $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$;
(ii) $x_i \in U$, $\dot{x}_i \in \overline{\operatorname{dec}}\,\Phi(x)$ and $x_i(a) = x_0$ for each $i = 1,2,\ldots$.

Lemma 4.25. *Suppose that the set of all local solutions of the problem* (4.41) *admits a uniform a priori estimate. Then, there exists a set* $U \subset \mathbf{C}^n[a,b]$ *satisfying Property* $\mathfrak{D}$.

Proof. It follows from Theorem 4.22 and Remark 4.15 that the set $U = \overline{\mathrm{co}}\widetilde{\Psi}(\mathbf{C}^n[a,b])$ has Property $\mathfrak{D}$. Here, the mapping $\widetilde{\Psi} : \mathbf{C}^n[a,b] \to 2^{\mathbf{C}^n[a,b]}$ is determined by (4.29), where $\widetilde{\Phi}(\cdot) \equiv \widetilde{\Phi}_{\mathrm{co}}(\cdot)$. □

Lemma 4.26. *Let sets* $\Phi_i \in \Pi[\mathbf{L}_1^n[a,b]]$, $i = 1,2$, *satisfy* $\Phi_i = S(F_i(\cdot))$, $i = 1,2$, *where* $F_i : [a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ *are measurable mappings. Then for any measurable set* $\mathcal{U} \subset [a,b]$, *one has*

$$h_{\mathbf{L}_1^n(\mathcal{U})}\big[\Phi_1;\Phi_2\big] \leqslant \int_{\mathcal{U}} h\big[F_1(t);F_2(t)\big]\,dt \leqslant 2h_{\mathbf{L}_1^n(\mathcal{U})}\big[\Phi_1;\Phi_2\big]. \tag{4.43}$$

Proof. Let $\mathcal{U} \subset [a,b]$ be a measurable set. Put

$$\widetilde{\mathcal{U}} = \big\{t \in \mathcal{U} : h^+\big[F_1(t);F_2(t)\big] \geq h^+\big[F_2(t);F_1(t)\big]\big\}. \tag{4.44}$$

The set $\widetilde{\mathcal{U}} \subset \mathcal{U}$ is measurable. Since

$$\int_{\mathcal{U}} h\big[F_1(t);F_2(t)\big]\,dt = \int_{\widetilde{\mathcal{U}}} h^+\big[F_1(t);F_2(t)\big]\,dt + \int_{\mathcal{U}\setminus\widetilde{\mathcal{U}}} h^+\big[F_2(t);F_1(t)\big]\,dt, \tag{4.45}$$

we have

$$\int_{\mathcal{U}} h\big[F_1(t);F_2(t)\big]\,dt = h^+_{\mathbf{L}_1^n(\widetilde{\mathcal{U}})}\big[\Phi_1;\Phi_2\big] + h^+_{\mathbf{L}_1^n(\mathcal{U}\setminus\widetilde{\mathcal{U}})}\big[\Phi_2;\Phi_1\big]. \tag{4.46}$$

This implies (4.43), and the proof is completed. □

Let $F : [a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ be a measurable mapping. Let a mapping $\mathrm{co}\,F : [a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ be defined by

$$(\mathrm{co}\,F)(t) = \mathrm{co}\,\big(F(t)\big). \tag{4.47}$$

Corollary 4.27. *Let sets* $\Phi_i \in \Pi[\mathbf{L}_1^n[a,b]]$, $i = 1,2$, *satisfy* $\Phi_i = S(F_i(\cdot))$, $i = 1,2$, *where* $F_i : [a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ *are measurable mappings. Then for any measurable set* $\mathcal{U} \subset [a,b]$, *one has*

$$h_{\mathbf{L}_1^n(\mathcal{U})}\big[\overline{\mathrm{co}}(\Phi_1);\overline{\mathrm{co}}(\Phi_2)\big] \leqslant 2h_{\mathbf{L}_1^n(\mathcal{U})}\big[\Phi_1;\Phi_2\big]. \tag{4.48}$$

Proof. By [35], we have that $\overline{\mathrm{co}}(\Phi_i) = S(\mathrm{co}F_i(\cdot))$, $i = 1,2$. Therefore,

$$h_{\mathbf{L}_1^n(\mathcal{U})}\big[\overline{\mathrm{co}}(\Phi_1);\overline{\mathrm{co}}(\Phi_2)\big] \leqslant \int_{\mathcal{U}} h\big[(\mathrm{co}F_1)(t);(\mathrm{co}F_2)(t)\big]\,dt \tag{4.49}$$

for any measurable set $\mathcal{U} \subset [a,b]$. Since, for any measurable set $\mathcal{U} \subset [a,b]$,

$$\int_{\mathcal{U}} h\big[(\mathrm{co}F_1)(t);(\mathrm{co}F_2)(t)\big]\,dt \leqslant \int_{\mathcal{U}} h\big[(F_1)(t);(F_2)(t)\big]\,dt, \tag{4.50}$$

we obtain, due to (4.43), the inequality (4.48). □

Definition 4.28. One says that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property Γ_3 if Property $\Gamma_2^{0,0,0}$ is satisfied and the following conditions hold:

(i) $\Gamma_2(0) = 0$;
(ii) on every interval $[a,\tau]$ ($\tau \in (a,b]$), there exists a unique zero solution of the problem (4.31), where $u = 0$, $\varepsilon = 0$, $p = 0$.

Theorem 4.29. *Suppose that the set of all local generalized solutions of the problem* (4.1) *admits a uniform a priory estimate. Suppose also that a mapping* $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ *satisfies Property* Γ_3. *Then,* $H(x_0,b) \neq \varnothing$ *and*

$$\overline{H(x_0,b)} = H_{\mathrm{co}}(x_0,b), \tag{4.51}$$

where $\overline{H(x_0,b)}$ *is the closure of the set* $H(x_0,b)$ *in* $\mathbf{C}^n[a,b]$.

Proof. Let us first prove that the set $H_{\mathrm{co}}(x_0)$ is closed in $\mathbf{C}^n[a,b]$. Indeed, suppose that a sequence $x_i \in H_{\mathrm{co}}(x_0)$, $i = 1,2,\dots$, tends to x in $\mathbf{C}^n[a,b]$ as $i \to \infty$. Since the sequence $\{\dot{x}_i\}$ is integrally bounded, it follows that $x_i \in \mathbf{D}^n[a,b]$ and $\dot{x}_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. For each $i = 1,2,\dots$, let the function $z_i \in \widetilde{\Phi}_{\mathrm{co}}(x)$ satisfy

$$\left\|\dot{x}_i - z_i\right\|_{\mathbf{L}_1^n[a,b]} = \rho_{\mathbf{L}_1^n[a,b]}\left[\dot{x}_i; \widetilde{\Phi}_{\mathrm{co}}(x)\right], \tag{4.52}$$

where $\widetilde{\Phi}_{\mathrm{co}} : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$ is the convex decomposable hull given by (4.41). Since the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25) is Hausdorff continuous, it follows from (4.48) that so is the mapping $\widetilde{\Phi}_{\mathrm{co}}(x) : \mathbf{C}^n[a,b] \to \Omega(\Pi[\mathbf{L}_1^n[a,b]])$. Therefore, (4.52) implies that $\dot{x}_i - z_i \to 0$ in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. Hence, $z_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. Since the set $\widetilde{\Phi}_{\mathrm{co}}(x)$ is convex, we have (see [21]) that $\dot{x} \in \widetilde{\Phi}_{\mathrm{co}}(x)$. Therefore, the set $H_{\mathrm{co}}(x_0)$ is closed in $\mathbf{C}^n[a,b]$.

Now, let us prove the equality (4.51). The closedness of the set $H_{\mathrm{co}}(x_0)$ yields that $\overline{H(x_0,b)} \subset H_{\mathrm{co}}(x_0)$. Further, let us show that $H_{\mathrm{co}}(x_0) \subset \overline{H(x_0,b)}$. Suppose $x \in H_{\mathrm{co}}(x_0)$. Then from Theorem 4.22, it follows that there exists a sequence $y_i \in \mathbf{D}^n[a,b]$, $i = 1,2,\dots$, such that $y_i \in \widetilde{\Phi}(x)$, $y_i(a) = x_0$, $i = 1,2,\dots$ (x_0 is the initial condition in the problem (4.1)) and $y_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$. Since the mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}_1^n[a,b]]$ has Property Γ_3, we see that, due to (4.30),

$$\rho_{\mathbf{L}_1^n(\mathcal{U})}\left[\dot{y}_i; \Phi(y_i)\right] \leqslant h_{\mathbf{L}_1^n(\mathcal{U})}\left[\Phi(x); \Phi(y_i)\right] \leqslant \int_{\mathcal{U}} \left(\Gamma_2(Z(x - y_i))\right)(s)ds \tag{4.53}$$

for each $i = 1,2,\dots$ and any measurable set $\mathcal{U} \subset [a,b]$. Here, the operator $Z : \mathbf{C}^n[a,b] \to \mathbf{C}_+^1[a,b]$ is given by (4.10). Since the mapping $\Gamma_2 : \mathbf{C}_+^1[a,b] \to \mathbf{L}_+^1[a,b]$ is continuous and $\Gamma_2(0) = 0$, we have that $\varkappa_i = \Gamma_2(Z(x - y_i)) \to 0$ in $\mathbf{L}_1^1[a,b]$ as $i \to \infty$. Since the problem (4.31) with $u = 0$, $\varepsilon = 0$, and $p = 0$ only has the zero solution on each interval $[a,\tau]$ ($\tau \in (a,b]$), we see that the set of all local solutions of the problem (4.31) with $u = \varkappa_i$, $\varepsilon = 1/i$, and $p = 0$ admits a uniform a priori estimate starting from some $i = 1,2,\dots$ (see [36]). Renumerating, we may assume without loss of generality that this holds true for all $i = 1,2,\dots$. This implies (see [29]) that for each $i = 1,2,\dots$, there exists the upper solution $\xi(\varkappa_i, 1/i, 0)$ of the problem (4.31) with $u = \varkappa_i$, $\varepsilon = 1/i$, and $p = 0$. Hence, it follows from Theorem 4.18 that for each $i = 1,2,\dots$, there exists

a generalized solution $x_i \in \mathbf{D}^n[a,b]$ of the problem (4.1) satisfying $\Theta(x_i - y_i) \leqslant \xi(\varkappa_i, 1/i, 0)$, where the continuous operator $\Theta : \mathbf{D}^n[a,b] \to \mathbf{C}^1_+[a,b]$ is given by (4.15). Since $\xi(\varkappa_i, 1/i, 0) \to 0$ in $\mathbf{C}^1[a,b]$ as $i \to \infty$, we have that $\Theta(x_i - y_i) \to 0$ as $i \to \infty$. Since $y_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$, we see that $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$. Therefore, $x \in \overline{H(x_0,b)}$ and consequently $H_{\mathrm{co}}(x_0) \subset \overline{H(x_0,b)}$. This yields (4.51). The proof is complete. □

Corollary 4.30. *Suppose that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}^n_1[a,b]]$ has Properties Γ_1 and Γ_3. Then $H(x_0,b) \neq \varnothing$ and the equality* (4.51) *is satisfied.*

Remark 4.31. If the solution set of a differential inclusion with nonconvex multivalued mapping is dense in the solution set of the convexified inclusion, then such a property is called the density principle. The density principle is a fundamental property in the theory of differential inclusions (see [13]). Many papers (e.g., [3, 4, 6, 10–12, 23–25, 29–32, 37–39]) deal with the justification of the density principle. Theorem 4.29 and Corollary 4.30 justify the density principle for the generalized solutions of the problem (4.1).

5. Generalized approximate solutions of the functional differential equation

Approximate solutions are of great importance in the study of differential equations and inclusions (see [4, 40–43]). They are used in the theorems on existence (e.g., Euler curves) as well as in the study of the dependence of a solution on initial conditions and the right-hand side of the equation. In [40, 41], the definition of an approximate solution of a differential equation with piecewise continuous right-hand side was given, using so-called internal and external perturbations. This definition not only deals with small changes of the right-hand side within its domain of continuity, but also with the small changes in the boundaries of these domains. A more general definition of an approximate solution, which can be used not only for the study of functional differential equations with discontinuous right-hand sides but also for differential inclusions with upper semicontinuous convex right-hand sides, was given in [4]. In this paper, the following important property was justified for such an inclusion: the limit of approximate solutions is again a solution of functional differential inclusion. In the present paper, we introduce various definitions of generalized approximate solutions of a functional differential inclusion. The main difference of our definitions from the one given in [4] is that the values of a multivalued mapping are not convexified. Due to this, the topological properties of the sets of generalized approximate solutions are studied and the density principle is proven.

Since a generalized solution of the problem (4.1) is determined by the closed decomposable hull of a set, it is natural to raise the following question: how robust is the set of the generalized solutions of (4.1) with respect to small perturbations of $\overline{\mathrm{dec}}\,\Phi(x)$? It follows from Remark 3.10 that constructing $\overline{\mathrm{dec}}\,\Phi(x)$ for each fixed $x \in \mathbf{C}^n[a,b]$ is equivalent to finding a measurable, integrally bounded mapping $\Delta_x : [a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ satisfying

$$\overline{\mathrm{dec}}\,\Phi(x) = S\big(\Delta_x(\cdot)\big). \tag{5.1}$$

The mapping $\Delta_x : [a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ is, in the sequel, written as $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ and called a mapping *generating* the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}^n_1[a,b]]$ given by (3.25).

Denote by $K([a,b] \times [0,\infty))$ the set of all continuous functions $\eta : [a,b] \times [0,\infty) \to [0,\infty)$ satisfying the following conditions:

(1) for each $\delta \geqslant 0$, $\eta(\cdot,\delta) \in \mathbf{L}_1^1[a,b]$;
(2) for each $\delta \geqslant 0$, there exists a function $\beta_\delta(\cdot) \in \mathbf{L}_1^1[a,b]$ such that $\eta(t,\tau) \leqslant \beta_\delta(t)$ for almost all $t \in [a,b]$ and all $\tau \in [0,\delta]$;
(3) $\lim_{\delta\to 0+0}\eta(t,\delta) = \eta(t,0) = 0$ for almost all $t \in [a,b]$.

Since the mappings $\Delta(\cdot,\cdot)$ and $\Phi(\cdot)$ are related by the equality (5.1), we have that the robustness of the set of the generalized solutions of (4.1) with respect to small perturbations of $\overline{\mathrm{dec}}\,\Phi(x)$ can be studied via the robustness properties of Δ. Assume that the perturbation $\Delta_\eta(t,x,\delta)$ (e.g., an error in measurements of $\Delta(t,x)$) is given by

$$\Delta_\eta(t,x,\delta) = \big(\Delta(t,x)\big)^{\eta(t,\delta)}, \tag{5.2}$$

where $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$ (here, $(\Delta(t,x))^{\eta(t,\delta)}$ is an η-neighborhood of the set $\Delta(t,x)$, see Preliminaries).

Note that (5.2) yields

$$h\big[\Delta(t,x);\Delta_\eta(t,x,\delta)\big] = \eta(t,\delta) \tag{5.3}$$

for all $(t,x) \in [a,b]\times\mathbf{C}^n[a,b]$. Thus, (5.3) implies that

$$\lim_{\delta\to+0} h\big[\Delta(t,x);\Delta_\eta(t,x,\delta)\big] = 0 \tag{5.4}$$

for each function $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$, almost all $t \in [a,b]$, and all $x \in \mathbf{C}^n[a,b]$. Therefore, all mappings $\Delta_\eta : [a,b]\times\mathbf{C}^n[a,b]\times[0,\infty) \to \mathrm{comp}\,[\mathbb{R}^n]$ defined by (5.2) and depending on $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$ are close (in the sense of (5.4)) to the mapping $\Delta : [a,b]\times\mathbf{C}^n[a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$. The mapping $\Delta_\eta : [a,b]\times\mathbf{C}^n[a,b]\times[0,\infty) \to \mathrm{comp}\,[\mathbb{R}^n]$ is called the *approximating operator*.

We define a mapping $\widetilde{\Phi}_\eta : \mathbf{C}^n[a,b]\times[0,\infty) \to \Pi[\mathbf{L}_1^n[a,b]]$ by the formula

$$\widetilde{\Phi}_\eta(x,\delta) = S\big(\Delta_\eta(\cdot,x,\delta)\big), \tag{5.5}$$

where the operator $\Delta_\eta : [a,b]\times\mathbf{C}^n[a,b]\times[0,\infty) \to \mathrm{comp}\,[\mathbb{R}^n]$ is given by (5.2). The equalities (5.3) and (5.5) imply that

$$h_{\mathbf{L}_1^n[a,b]}\big[\widetilde{\Phi}_\eta(x,\delta);\widetilde{\Phi}(x)\big] = \int_a^b \eta(t,\delta)\,dt \tag{5.6}$$

for any $x \in \mathbf{C}^n[a,b]$.

It follows from (5.6) and the Lebesgue theorem that

$$\lim_{\delta\to 0+0} h_{\mathbf{L}_1^n[a,b]}\big[\widetilde{\Phi}_\eta(x,\delta);\widetilde{\Phi}(x)\big] = 0. \tag{5.7}$$

Thus, all mappings $\widetilde{\Phi}_\eta : \mathbf{C}^n[a,b]\times[0,\infty) \to \Pi[\mathbf{L}_1^n[a,b]]$ defined by (5.2) and (5.5) and depending on $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$ are close (in the sense of (5.7)) to the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25).

Lemma 5.1 (see [6]). *Let X be a normed space and let $U \subset X$ be a convex set. Then*

$$h_X\left[B_X[x_1, r_1] \cap U; B_X[x_2, r_2] \cap U\right] \leqslant \left\|x_1 - x_2\right\|_X + \left|r_2 - r_1\right| \tag{5.8}$$

for all $x_1, x_2 \in U$ and all $r_1, r_2 > 0$.

Denote by $P(\mathbf{C}^n[a,b] \times [0,\infty))$ the set of all continuous functions $\omega : \mathbf{C}^n[a,b] \times [0,\infty) \to [0,\infty)$ such that $\omega(x,0) = 0$ for any $x \in \mathbf{C}^n[a,b]$ and $\omega(x,\delta) > 0$ for any $(x,\delta) \in \mathbf{C}^n[a,b] \times (0,\infty)$.

Let $U \subset \mathbf{C}^n[a,b]$ be a closed convex set and let $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$. We define a multivalued mapping $M_U(\omega) : U \times [0,\infty) \to \Omega(U)$ by

$$M_U(\omega)(x,\delta) = \overline{B_{\mathbf{C}^n[a,b]}\left[x, \omega(x,\delta)\right]} \cap U. \tag{5.9}$$

The inequality (5.8) yields the following result.

Lemma 5.2. *Let $U \subset \mathbf{C}^n[a,b]$ be a closed convex set and let $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$. Then, a multivalued mapping $M_U(\omega) : U \times [0,\infty) \to \Omega(U)$ given by* (5.9) *is Hausdorff continuous.*

We define a mapping $\varphi_U(\omega) : [a,b] \times U \times [0,\infty) \to [0,\infty)$ by the formula

$$\varphi_U(\omega)(t,x,\delta) = \sup_{y \in M_U(\omega)(x,\delta)} h\left[\Delta(t,x); \Delta(t,y)\right], \tag{5.10}$$

where the mapping $M_U(\omega) : U \times [0,\infty) \to \Omega(U)$ is given by (5.9) and the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$ generates the mapping $\widetilde{\Phi}$ given by (3.25).

It is natural to address the value of the function $\varphi_U(\omega)(\cdot,\cdot,\cdot)$ at the point $(t,x,\delta) \in [a,b] \times U \times [0,\infty)$ as the *modulus of continuity of the mapping* $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$ at the point (t,x) with respect to the variable $x \in U$. We call the function $\omega(\cdot,\cdot)$ the *radius of continuity*, while the function $\varphi_U(\cdot,\cdot,\cdot)$ itself is called the *modulus of continuity of the mapping* $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$ *with respect to the radius of continuity* $\omega(\cdot,\cdot)$.

Definition 5.3. One says that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}^n[a,b]]$ has Property $\widetilde{C}$ if the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$ generating the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25) is Hausdorff continuous in the second variable for almost all $t \in [a,b]$.

Lemma 5.4. *Suppose that for a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}^n[a,b]]$, there exists an isotonic continuous operator $\Gamma : \mathbf{C}_+^1[a,b] \to \mathbf{L}_+^1[a,b]$ satisfying the following conditions:*

(i) $\Gamma(0) = 0$;

(ii) *the inequality* (4.30), *where $\Gamma_2 \equiv \Gamma$, is satisfied for any $x, y \in \mathbf{C}^n[a,b]$ and any measurable set $\mathcal{U} \subset [a,b]$.*

Then the mapping $\Phi(\cdot)$ has Property $\widetilde{\mathcal{C}}$.

Proof. Let $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$. Let us show that

$$\lim_{i \to \infty} h\left[\Delta(t,x_i); \Delta(t,x)\right] = 0 \tag{5.11}$$

for almost all $t \in [a,b]$.

For each $i = 1, 2, \ldots$, put $y_i = \sup_{j \geqslant i} \|x_j - x\|_{\mathbf{C}^n[a,b]}$. Due to Theorem 3.18, (4.43), and the isotonity of the operator $\Gamma : \mathbf{C}^1_+[a,b] \to \mathbf{L}^1_+[a,b]$, for each $i = 1, 2, \ldots$ and almost all $t \in [a,b]$, we have

$$h\big[\Delta(t,x_i);\Delta(t,x)\big] \leqslant 2\Gamma\big(Z(x_i - x)\big)(t) \leqslant 2\Gamma(y_i)(t). \tag{5.12}$$

Since the sequence $\Gamma(y_i)$, $i = 1, 2, \ldots$, decreases, we obtain, due to the continuity of the mapping $\Gamma(\cdot)$ and the equality $\Gamma(0) = 0$, the equality (5.11). This completes the proof. □

Lemma 5.5. *Let U be a nonempty, convex, compact set in the space $\mathbf{C}^n[a,b]$ and let $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$. Suppose also that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}^n_1[a,b]]$ has Property $\widetilde{C}$. Then the mapping $\varphi_U(\omega) : [a,b] \times U \times [0,\infty)$ given by* (5.10) *has the following properties:*

(i) *$\varphi_U(\omega)(\cdot,x,\delta)$ is measurable for any $(x,\delta) \in U \times [0,\infty)$;*
(ii) *$\varphi_U(t,\cdot,\cdot)$ is continuous on $U \times [0,\infty)$ for almost all $t \in [a,b]$;*
(iii) *for any $x \in U$ and for almost all $t \in [a,b]$,*

$$\lim_{z \to x, \delta \to 0+0} \varphi_U(\omega)(t,x,\delta) = 0; \tag{5.13}$$

(iv) *there exists an integrable function $p_U : [a,b] \to [0,\infty)$ such that $\varphi_U(\omega)(t,x,\delta) \leqslant p_U(t)$ for almost all $t \in [a,b]$, any $x \in U$, and all $\delta \in [0,\infty)$.*

Definition 5.6. Let $U \subset \mathbf{C}^n[a,b]$. One says that the function $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$ provides on U a uniform with respect to the radius of continuity $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$ estimate from above for the modulus of continuity of the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$; if for any $\varepsilon > 0$ there exists $\delta(\varepsilon) > 0$ such that for almost all $t \in [a,b]$, all $x \in U$, and $\delta \in (0, \delta(\varepsilon)]$, one has

$$\varphi_U(\omega)(t,x,\delta) \leqslant \eta(t,\varepsilon), \tag{5.14}$$

where $\varphi_U : [a,b] \times U \times [0,\infty) \to [0,\infty)$ is given by (5.10).

Let $U \subset \mathbf{C}^n[a,b]$ and $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$. One defines a function $\lambda_U(\omega) : [a,b] \times [0,\infty) \to [0,\infty)$ by

$$\lambda_U(\omega)(t,\delta) = \sup_{x \in U} \varphi_U(\omega)(t,x,\delta). \tag{5.15}$$

Lemma 5.1 yields the following result.

Corollary 5.7. *Let U be a nonempty, convex, compact set in the space $\mathbf{C}^n[a,b]$ and let $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$. Suppose also that a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}^n_1[a,b]]$ has Property $\widetilde{C}$. Then the mapping $\lambda_U(\omega) : [a,b] \times [0,\infty) \to [0,\infty)$ given by* (5.15) *belongs to the set $K([a,b] \times [0,\infty))$ and provides a uniform (in the sense of Definition 5.6) estimate from above for the modulus of continuity of the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$.*

Remark 5.8. Corollary 5.7 yields that if U is a nonempty, convex, compact set in the space $\mathbf{C}^n[a,b]$ and a mapping $\Phi : \mathbf{C}^n[a,b] \to Q[\mathbf{L}^n_1[a,b]]$ has Property $\widetilde{C}$, then for a given $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$, there exists at least one function $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$ that provides a uniform (in the sense of Definition 5.6) estimate from above for the modulus of continuity of the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$.

Let $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$. For each $\delta \in [0,\infty)$, consider the initial value problem

$$\dot{x} \in \tilde{\Phi}_\eta(x,\delta), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n), \tag{5.16}$$

where the mapping $\tilde{\Phi}_\eta : \mathbf{C}^n[a,b] \times [0,\infty) \to \Pi[\mathbf{L}_1^n[a,b]]$ is given by (5.1) and (5.5).

Since the operator $\tilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25) is a Volterra operator, we see that the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$ has the following property: if $x = y$ on $[a,\tau]$ $(\tau \in (a,b])$, then $\Delta(t,x) = \Delta(t,y)$ for almost all $t \in [a,\tau]$. This property, (5.1), and (5.4) imply that the operator $\tilde{\Phi}_\eta : \mathbf{C}^n[a,b] \times [0,\infty) \to \Pi[\mathbf{L}_1^n[a,b]]$ is a Volterra operator for each $\delta \in [0,\infty)$.

Any solution of the problem (5.16) with a given $\delta > 0$ is said to be a generalized δ-solution (a generalized approximate solution with external perturbations) of the problem (4.1). We denote by $H_{\eta(\delta)}(U)$ the set of all generalized δ-solutions of (4.1) belonging to $U \subset \mathbf{C}^n[a,b]$.

Theorem 5.9. *Suppose that a set $U \subset \mathbf{C}^n[a,b]$ has Property $\mathfrak{D}$. Then for any function $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$ that provides a uniform (in the sense of Definition 5.6) estimate from above for the modulus of continuity of the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$, one has*

$$H_{\mathrm{co}}(x_0,b) = \bigcap_{\delta>0} \overline{H_{\eta(\delta)}(U)}, \tag{5.17}$$

where $\overline{H_{\eta(\delta)}(U)}$ is the closure of $H_{\eta(\delta)}(U)$ in $\mathbf{C}^n[a,b]$.

Proof. First, let us prove that

$$H_{\mathrm{co}}(x_0,b) \subset \bigcap_{\delta>0} \overline{H_{\eta(\delta)}(U)}. \tag{5.18}$$

Let $x \in H_{\mathrm{co}}(x_0,b)$. Let us show that x is a limit point of the set $H_{\eta(\delta)}(U)$ for any $\delta > 0$. By Theorem 4.22, x is a generalized quasisolution of the problem (4.1). Moreover, $x \in U$. Since the set U has Property $\mathfrak{D}$, we see that there exists a sequence of absolutely continuous functions $x_i : [a,b] \to \mathbb{R}^n$, $i = 1,2,\ldots$, such that the following conditions hold: $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$; $x_i \in U$, $\dot{x}_i \in \overline{\operatorname{dec}}\,\Phi(x)$, and $x_i(a) = x_0$ for each $i = 1,2,\ldots$. Suppose that $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$ provides a uniform (in the sense of Definition 5.6) estimate from above for the modulus of continuity of the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \operatorname{comp}[\mathbb{R}^n]$. Then there exists i_1 such that $\|x - x_i\|_{\mathbf{C}^n[a,b]} < \omega(x,\delta)$ for each $i \geqslant i_1$. This implies that $x_i \in \overline{B_{\mathbf{C}^n[a,b]}[x,\omega(x,\delta)]}$ for each $i \geqslant i_1$. Therefore, $x_i \in M_U(\omega)(x,\delta)$ for each $i \geqslant i_1$. By Definition 5.6, there exists a number $i_2 \geqslant i_1$ such that

$$\varphi_U(\omega)\left(t,x,\|x - x_i\|_{\mathbf{C}^n[a,b]}\right) \leqslant \eta(t,\delta) \tag{5.19}$$

for any $i \geqslant i_2$ and almost all $t \in [a,b]$.

The inequality (5.19) yields that

$$\rho\left[\dot{x}_i(t); \Delta(t,x_i)\right] \leqslant h\left[\Delta(t,x); \Delta(t,x_i)\right] \leqslant \varphi_U(\omega)\left(t,x,\|x - x_i\|_{\mathbf{C}^n[a,b]}\right) \leqslant \eta(t,\delta) \tag{5.20}$$

for each $i \geqslant i_2$ and almost all $t \in [a,b]$. By (5.20), $x_i \in H_{\eta(\delta)}(U)$ for each $i \geqslant i_2$. This implies that x is a limit point of the set $H_{\eta(\delta)}(U)$. Therefore, $x \in \overline{H_{\eta(\delta)}(U)}$, and consequently (5.18), is satisfied.

Let us prove the opposite inclusion

$$\bigcap_{\delta>0}\overline{H_{\eta(\delta)}(U)} \subset H_{\mathrm{co}}(x_0,b). \tag{5.21}$$

Let $x \in \bigcap_{\delta>0}\overline{H_{\eta(\delta)}(U)}$. This implies that for each $i = 1,2,\dots$, there exists $x_i \in H_{\eta(1/i)}(U)$ satisfying $\|x - x_i\|_{C^n[a,b]} < 1/i$. Suppose that functions $z_i \in \overline{\mathrm{dec}}\,\Phi(x)$ satisfy

$$\left|\dot{x}_i(t) - z_i(t)\right| = \rho\left[\dot{x}_i(t); \Delta(t,x)\right] \tag{5.22}$$

for each $i = 1,2,\dots$ and almost all $t \in [a,b]$. Let us show that

$$\lim_{i\to\infty}\left\|\dot{x}_i - z_i\right\|_{\mathbf{L}_1^n[a,b]} = 0. \tag{5.23}$$

Since $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$, by the Lebesgue theorem, we have that

$$\lim_{i\to\infty}\int_a^b \eta\left(t,\frac{1}{i}\right)dt = 0. \tag{5.24}$$

By (5.22), the estimates

$$\left|\dot{x}_i(t) - z_i(t)\right| \leqslant h\left[\Delta(t,x_i)^{\eta(t,1/i)}; \Delta(t,x)\right] \leqslant \eta\left(t,\frac{1}{i}\right) + h\left[\Delta(t,x); \Delta(t,x_i)\right] \tag{5.25}$$

are satisfied for each $i = 1,2,\dots$ and almost all $t \in [a,b]$. Therefore,

$$\int_a^b \left|\dot{x}_i(t) - z_i(t)\right|dt \leqslant \int_a^b \eta\left(t,\frac{1}{i}\right)dt + 2h_{\mathbf{L}_1^n[a,b]}\left[\overline{\mathrm{dec}}\,\Phi(x); \overline{\mathrm{dec}}\,\Phi(x_i)\right] \tag{5.26}$$

for each $i = 1,2,\dots$. By (5.24) and due to the continuity of the mapping $\tilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25), we have (5.23).

Since $\dot{x}_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$, we have that $z_i \to \dot{x}$ weakly in $\mathbf{L}_1^n[a,b]$ as $i \to \infty$. Therefore, by [21], $\dot{x} \in \tilde{\Phi}_{\mathrm{co}}(x)$ and hence $x \in H(x_0,b)$. Thus, (5.21) is valid. Hence, (5.17) holds and the proof is complete. □

Theorem 5.10. *Suppose that a set $U \subset \mathbf{C}^n[a,b]$ has Property $\mathfrak{D}$. Then,*

$$\overline{H(x_0,b)} = \bigcap_{\delta>0}\overline{H_{\eta(\delta)}(U)} \tag{5.27}$$

for any $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$ if and only if the equality (4.51) *is satisfied.*

Proof. Let us prove the *sufficiency.* Assume that (4.51) holds. Let us show that the equality (5.27) is satisfied for any function $\eta(\cdot,\cdot) \in K([a,b]\times[0,\infty))$. By the definition of the problem (5.16), the inclusion

$$H(x_0,b) \subset H_{\eta(\delta)}(U) \tag{5.28}$$

is satisfied for any $\delta > 0$. Therefore, for any $\delta > 0$, we have the inclusion

$$\overline{H(x_0, b)} \subset \overline{H_{\eta(\delta)}(U)} \tag{5.29}$$

and consequently the inclusion

$$\overline{H(x_0, b)} \subset \bigcap_{\delta>0} \overline{H_{\eta(\delta)}(U)} \tag{5.30}$$

holds. Now, let us check that the opposite relation

$$\bigcap_{\delta>0} \overline{H_{\eta(\delta)}(U)} \subset \overline{H(x_0, b)}, \tag{5.31}$$

which is, by (4.51), equivalent to the inclusion

$$\bigcap_{\delta>0} \overline{H_{\eta(\delta)}(U)} \subset H_{\mathrm{co}}(x_0, b), \tag{5.32}$$

holds as well. The latter relation can be proven similarly to Theorem 5.9.

The *necessity* follows readily from Theorem 5.9. The proof is complete. □

Remark 5.11. Note that the equality (5.27) describes the robustness property of the set $H(x_0, b)$ with respect to external perturbations $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$. These external perturbations (e.g., $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$) characterize an error in measurements of the values of the mapping $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25).

On the other hand, each generalized solution $x : [a,b] \to \mathbb{R}^n$ of the problem (4.1) may also be measured with a certain error. This error may be described by a function belonging to the set $P(\mathbf{C}^n[a,b] \times [0,\infty))$ and it may be characterized by so-called internal perturbations, which are defined below. Let us show further that internal perturbations influence essentially the properties of generalized solutions of the problem (4.1).

We define a mapping $\Delta_{\mathrm{ext}} : [a,b] \times \mathbf{C}^n[a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ by

$$\Delta_{\mathrm{ext}}(t,x) = \overline{\mathrm{ext}}(\mathrm{co}\,\Delta(t,x)), \tag{5.33}$$

where $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ is the mapping generating the operator $\widetilde{\Phi} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by (3.25); see the definition of $\overline{\mathrm{ext}}(\mathrm{co}\,\Delta(t,x))$ in Section 2. Let us remark that the mapping $\Delta_{\mathrm{ext}}(\cdot,x)$ is measurable (see [25]) and integrally bounded for each $x \in \mathbf{C}^n[a,b]$.

Consider the operator $\widetilde{\Phi}_{\mathrm{ext}} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ given by

$$\widetilde{\Phi}_{\mathrm{ext}}(x) = S(\Delta_{\mathrm{ext}}(\cdot,x)), \tag{5.34}$$

where the mapping $\Delta_{\mathrm{ext}} : [a,b] \times \mathbf{C}^n[a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ is given by (5.33).

Remark 5.12. Note that for each $x \in \mathbf{C}^n[a,b]$, the set $\widetilde{\Phi}_{\mathrm{ext}}(x)$ has the following property

$$\overline{\mathrm{co}}(\widetilde{\Phi}_{\mathrm{ext}}(x)) = \overline{\mathrm{co}}(\overline{\mathrm{dec}}\,\Phi(x)). \tag{5.35}$$

Also, $\widetilde{\Phi}_{\mathrm{ext}}(x)$ is the minimal set among all nonempty closed in $\mathbf{L}_1^n[a,b]$ decomposable subsets of $\overline{\mathrm{dec}}\,\Phi(x)$ satisfying (5.35).

Consider the problem

$$\dot{x} \in \widetilde{\Phi}_{\mathrm{ext}}(x), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n). \tag{5.36}$$

We call any solution (resp., quasisolution) of (5.36) a *generalized extreme* (in the sense of the definition in Section 2) *solution* (resp., *generalized extreme quasisolution*) of the problem (4.1).

Let $\mathscr{H}_{\mathrm{ext}}(x_0)$ be the set of all generalized extreme quasisolutions of the problem (4.1). Theorem 4.22, Remark 4.23, and equality (5.35) imply the following result.

Corollary 5.13. $\mathscr{H}_{\mathrm{ext}}(x_0) = H_{\mathrm{co}}(x_0, b)$.

Let $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$, $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$. Let also U be a convex closed set in $\mathbf{C}^n[a,b]$. We define mappings $\widetilde{\Phi}_{\eta,\omega} : U \times [0,\infty) \to \mathrm{comp}\,[\mathbf{L}_1^n[a,b]^*]$, $\Delta_{\mathrm{ext},\eta} : [a,b] \times \mathbf{C}^n[a,b] \times [0,\infty) \to \mathrm{comp}\,[\mathbb{R}^n]$, $\widetilde{\Phi}_{\mathrm{ext},\eta} : \mathbf{C}^n[a,b] \times [0,\infty) \to \Pi[\mathbf{L}_1^n[a,b]]$, $\widetilde{\Phi}_{\mathrm{ext},\eta,\omega} : \mathbf{C}^n[a,b] \times [0,\infty) \to \mathrm{comp}\,[\mathbf{L}_1^n[a,b]^*]$ by the formulas

$$\begin{aligned}
\widetilde{\Phi}_{\eta,\omega}(x,\delta) &= \widetilde{\Phi}_{\eta}\big(\big(M_U(\omega)(x,\delta)\big),\delta\big),\\
\big(\Delta_{\mathrm{ext},\eta}\big)(t,x,\delta) &= \big(\Delta_{\mathrm{ext}}(t,x)\big)^{\eta(t,\delta)},\\
\big(\widetilde{\Phi}_{\mathrm{ext},\eta}\big)(x,\delta) &= S\big(\Delta_{\mathrm{ext},\eta}(\cdot,x,\delta)\big),\\
\widetilde{\Phi}_{\mathrm{ext},\eta,\omega}(x,\delta) &= \widetilde{\Phi}_{\mathrm{ext},\eta}\big(\big(M_U(\omega)(x,\delta)\big),\delta\big),
\end{aligned} \tag{5.37}$$

where the mappings $\widetilde{\Phi}_{\eta} : \mathbf{C}^n[a,b] \times [0,\infty) \to \Pi[\mathbf{L}_1^n[a,b]]$, $M_U(\omega) : U \times [0,\infty) \to \Omega(U)$, $\Delta_{\mathrm{ext}} : [a,b] \times \mathbf{C}^n[a,b] \times [0,\infty) \to \mathrm{comp}\,[\mathbb{R}^n]$ are given by the equalities (5.5), (5.9), and (5.33), respectively.

For each $\delta > 0$, consider the following problems on $U \subset \mathbf{C}^n[a,b]$:

$$\dot{x} \in \widetilde{\Phi}_{\eta,\omega}(x,\delta), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n), \tag{5.38}$$

$$\dot{x} \in \widetilde{\Phi}_{\mathrm{ext},\eta,\omega}(x,\delta), \qquad x(a) = x_0 \quad (x_0 \in \mathbb{R}^n), \tag{5.39}$$

where the mappings $\widetilde{\Phi}_{\eta,\omega} : U \times [0,\infty) \to \mathrm{comp}[\mathbf{L}_1^n[a,b]^*]$, $\widetilde{\Phi}_{\mathrm{ext},\eta,\omega} : U \times [0,\infty) \to \mathrm{comp}[\mathbf{L}_1^n[a,b]^*]$ are given by (5.37).

We call any solution of the problem (5.38) with a fixed $\delta > 0$ a *generalized δ-solution* of the problem (4.1), or a *generalized approximate solution* of (4.1) with external and internal perturbations. For each $\delta > 0$, we denote by $H_{\eta(\delta),\omega(\delta)}(U)$ ($H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)$) the set of all solutions of the problem (5.38) ((5.39)) on $U \subset \mathbf{C}^n[a,b]$. Since $\widetilde{\Phi}_{\mathrm{ext},\eta,\omega}(x,\delta) \subset \widetilde{\Phi}_{\eta,\omega}(x,\delta)$ for any $\delta > 0$ and any $x \in U$, we see that $H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U) \subset H_{\eta(\delta),\omega(\delta)}(U)$ for any $\delta > 0$.

Theorem 5.14. *Let the set $U \subset \mathbf{C}^n[a,b]$ have Property $\mathfrak{D}$. Then for any $\eta(\cdot,\cdot) \in K([a,b] \times [0,\infty))$, $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$, one has*

$$H_{\mathrm{co}}(x_0,b) = \bigcap_{\delta>0} \overline{H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)} = \bigcap_{\delta>0} \overline{H_{\eta(\delta),\omega(\delta)}(U)}, \tag{5.40}$$

where $\overline{H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)}$ and $\overline{H_{\eta(\delta),\omega(\delta)}(U)}$ are the closures of the sets $H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)$ and $H_{\eta(\delta),\omega(\delta)}(U)$, respectively, in the space $\mathbf{C}^n[a,b]$.

Proof. First of all, let us check that

$$H_{\mathrm{co}}(x_0,b) \subset \bigcap_{\delta>0} \overline{H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)}. \tag{5.41}$$

Let $x \in H(x_0,b)$. We show that x is a limit point of the set $H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)$ for any $\delta > 0$. By Corollary 5.13, x is a generalized extreme quasisolution of the problem (4.1). Since the set U has Property $\mathfrak{D}$, we see that $x \in U$ and there exists a sequence of absolutely continuous functions $x_i : [a,b] \to \mathbb{R}^n$, $i = 1,2,\ldots$, with the following properties: $x_i \to x$ in $\mathbf{C}^n[a,b]$ as $i \to \infty$; $x_i \in U$, $\dot{x}_i \in \widetilde{\Phi}_{\mathrm{ext}}(x)$, and $x_i(a) = x_0$ for each $i = 1,2,\ldots$. Here, the operator $\widetilde{\Phi}_{\mathrm{ext}} : \mathbf{C}^n[a,b] \to \Pi[\mathbf{L}_1^n[a,b]]$ is given by (5.33) and (5.34).

Let us prove also that there exists a number i_0 such that for each $i \geqslant i_0$,

$$x_i \in H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U). \tag{5.42}$$

Since $\omega(\cdot,\cdot) \in P(\mathbf{C}^n[a,b] \times [0,\infty))$, we see that there exists a number i_0 such that for each $i \geqslant i_0$, $x \in B_{\mathbf{C}^n[a,b]}[x_i;\omega(x_i,\delta)]$. This implies that for each $i \geqslant i_0$, we have that $x \in M_U(x_i,\delta)$ (see (5.9)). Therefore, for each $i \geqslant i_0$, the inclusion $\widetilde{\Phi}_{\mathrm{ext}}(x) \subset \widetilde{\Phi}_{\mathrm{ext},\eta,\omega}(x_i,\delta)$ holds. Hence, for each $i \geqslant i_0$, we have (5.42). This means that x is a limit point of the set $H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)$. Therefore, $x \in \overline{H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)}$ and (5.41) is satisfied.

The relation

$$\bigcap_{\delta>0} \overline{H_{\mathrm{ext},\eta(\delta),\omega(\delta)}(U)} \subset H_{\mathrm{co}}(x_0,b) \tag{5.43}$$

can be proven similarly to (5.21) (see the proof of Theorem 5.9). The second equality of (5.40) can be proven in the same way. This completes the proof of the theorem. □

Remark 5.15. Theorem 5.14 says that no measurement accuracy of the values of the mapping $\Delta : [a,b] \times \mathbf{C}^n[a,b] \to \mathrm{comp}\,[\mathbb{R}^n]$ could guarantee the "reconstruction" of the set $\overline{H(x_0,b)}$ by means of $\overline{H_{\eta(\delta),\omega(\delta)}(U)}$. That is only possible if the density principle holds for the generalized solutions.

6. Conclusion

The main results of the paper can be summarized as follows. For the decomposable hull of a mapping, we have obtained the conditions for the property of the Hausdorff lower semicontinuity (resp., upper semicontinuity and continuity). We considered a functional differential inclusion with a Volterra multivalued mapping which is not necessarily decomposable. The concept of a generalized solution of the initial value problem for such an inclusion was introduced and its properties were studied. Conditions for the local existence and continuation of a generalized solution to the initial value problem were obtained. We have offered some estimates, which characterize the closeness of generalized solutions and a given absolutely continuous function. These estimates were derived from the conditions for the existence of a generalized solution satisfying the inequality (4.18) (see Theorem 4.13 and Corollary 4.14).

The concept of a generalized quasisolution of the initial value problem was introduced. We proved that the set of all generalized quasisolutions of the initial value problem coincides

with the solution set of the functional differential inclusion with the convex decomposable hull of the right-hand side. Using this fact as well as the estimates characterizing the closeness of generalized solutions and a given absolutely continuous function, we obtained the density principle for the generalized solutions.

Asymptotic properties of the set of generalized approximate solutions (generalized δ-solutions) were studied. It was proven that the limit of the closures of the sets of generalized approximate solutions coincides with the closure of the set of the generalized solutions if and only if the density principle holds for the generalized solutions.

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List of changes (made after submission)

1) Paper II, Section 1.Introduction. There was a misprint at the end of the fifth paragraph. "ction" was corrected to "function".

2) Paper II, Section 3.2. There was a misprint in the last line of Proof of Theorem 3. (y_S, x_R^0) was corrected to (y_S^0, x_R^0).

2) Paper II, Appendix. Sections Appendix and References interchanged their order. Now Appendix is located after References. Section References was also missing its title.