Piecewise synergetic systems and applications in biochemical systems theory

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Abstract

We study piecewise synergetic systems originating from Biochemical Systems Theory. In the first part of the paper, the emphasis is put on practical calculations with such systems. We consider four examples: calculation of trajectories and steady states, solution of an optimization problem and a method of estimation of parameters (kinetic orders), all examples being biologically motivated. In the second part of the paper, we study convergence of solutions, in particularly, steady states, of a sequence of piecewise synergetic systems approximating an arbitrary compartment model. This convergence analysis is then applied to the optimization problem and the method of estimating sensitivities (kinetic orders) in a generic compartment model. In this paper we put forward arguments for the importance of the theoretical and numerical analysis of piecewise synergetic systems.

Keywords: Piecewise approximations, steady states, optimization, parameter estimation, uniform convergence.

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1 Introduction

The (local) sensitivity of a function $V = V(x_1, ..., x_{n+m}) > 0$ with respect to changes in the variable x_j at a point $P(x_1, ..., x_{n+m})$ is defined as

$$f_j(P) = \left(\frac{\partial V}{\partial x_j}\frac{x_j}{V}\right)_P. \tag{1}$$

Sensitivities play an important role in applications. For instance, they measure the local response of an enzyme, or any chemical reaction, to changes in its environment and are therefore called *kinetic orders* which are important characteristics of networks in Biochemical Systems Theory (BST). In Metabolic Control Analysis these quantities are known as *elasticities*.

If $f_j(P) = \text{const}$ $(j = 1, ..., n + m)$ in an open subset of $\mathbb{R}^{n+m}$, then V becomes a power function in this subset of the form $\alpha \prod_{j=1}^{n+m} x_j^{g_j}$ where $\alpha > 0$ and g_j are constants.

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However, for many typical nonlinear functions V arisen in applications, sensitivities may vary within Ω. Approximating sensitivities by piecewise constant functions, which is one of the ways to simplify modeling, yields a piecewise power function V.

In this paper we study differential equations with right-hand sides containing differences of piecewise power functions. Such systems are sometimes called piecewise synergetic systems (shortly, *p*iecewise S-systems). They constitute an important subclass of the so-called "compartment models" which are studied in Section 3.

The paper is divided in two main parts: Section 2 and Section 3. In the first part, we demonstrate why piecewise S-systems can be suitable for practical calculations. This part being of more applied character, contains four subsections. In the subsection 2.1 we offer a formal definition of a piecewise S-system and illustrate the dynamics of such systems by some examples. The subsection 2.2 explains how steady states of an arbitrary piecewise S-system can be calculated in a constructive way. In the next subsection 2.3 we solve a special optimization problem arisen in BST, while the last subsection 2.4 describes an iterative method of estimation of the sensitivities of a piecewise S-system.

Section 3 is more theoretical, and its aim is to interpret piecewise S-systems as approximations of general compartment models, i.e. systems of ordinary differential equations where the right-hand sides are the difference of two arbitrary positive functions. Convergence of approximations is treated in the subsection 3.1. Here we use the theory of differential inclusions to justify convergence of solutions, while convergence of steady states relies, in addition, upon the implicit function theorem. The subsection 3.2 deals with the biologically important optimization problem from Section 2 extended to general compartment models. The problem of estimation of sensitivities via approximation by piecewise S-systems is also briefly addressed in this subsection.

Finally, in the concluding section 4 we summarize our results and discuss some open problems.

2 Calculations with piecewise S-systems

2.1 Piecewise S-systems: definitions and examples

A general S-system, studied in BST, is defined as follows [14], [15], [24], [25]:

$$\dot{x_i} = \alpha_i \prod_{j=1}^{n+m} x_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} x_j^{h_{ij}}, \qquad i = 1, ..., n. \tag{2}$$

Here the index $i\,(i = 1, ..., n)$ refers to the n internal metabolites $x_i \geq 0$ which are dependent variables, while the higher indices $(n+1, ..., n+m)$ refer to the control (or independent) variables. The parameters $\alpha_i > 0$, $\beta_i > 0$, g_{ij}, and h_{ij} are constants. From the definition, it follows that the functions in (2) are power functions called *production* and *degradation* terms, respectively. Both have constant sensitivities, which are given by the exponents g_{ij}, h_{ij}, respectively. In BST, mathematical analysis based on S-systems is usually called *'Power-Law Formalism'* (see e.g. the above references and, in addition, [2], [18], [19], [20]).

With no control variables, the S-system (2) becomes

$$\dot{x_i} = \alpha_i \prod_{j=1}^{n} x_j^{g_{ij}} - \beta_i \prod_{j=1}^{n} x_j^{h_{ij}}, \qquad i = 1, ..., n. \tag{3}$$

S-systems are very advantageous in many biological and non-biological applications, as the systems' form considerably simplifies mathematical and numerical analysis. For instance, calculation of steady states for the S-systems is a linear problem (see [25] and the subsection 2.2).

However, in many biological models the sensitivities are not constant: several examples can be e.g. found in [11]. In such a case, mathematical analysis of biological systems may be quite difficult. On the other hand, there exists a well-elaborated tradition in theoretical biology to model real-life processes by means of step functions (see e.g. [7] and references therein). This assumption, which gives a piecewise continuous structure of the model, may considerably simplify the analysis of complex systems. Another

convention in mathematical biology says that any reasonable modeling paradigm should take into account biologically relevant characteristics. To sum up, piecewise approximations of sensitivities both preserves important biological structures and, as we will see below, makes mathematical analysis of complex systems more constructive.

In the case of piecewise constant sensitivities one gets the set Ω divided into finitely many subsets where the sensitivities become constants. This produces a family of S-systems, or in other words, *a piecewise S-system*. This is a new kind of generic representations of biochemical systems, which was suggested in ([17]), see also [3], which may be called 'Piecewise Power-Law Formalism' [10], [11].

Below we describe the notion of a piecewise S-system more precisely.

Let Ω be an open subset of the set $\mathbb{R}^{n+m}_+$ which contains vectors with positive components. Let $\{\Omega^k\}_{k=1}^N$ be a finite collection of open, non-empty subsets of Ω satisfying the property $\Omega^k \cap \Omega^l = \emptyset$ for every $k, l = 1, ..., N$, $k \neq l$ such that the closures $\bar{\Omega}^k$ of Ω^k cover Ω: $\bigcup\limits_{k=1}^{N} \bar{\Omega}^k \supset \Omega$. We will say in this case that $\{\Omega^k\}_{k=1}^N$ constitutes *an open partition of* Ω.

A piecewise S-system is now defined as follows:

$$\dot{x_i} = \alpha_i^k \prod_{j=1}^{n+m} x_j^{g_{ij}^k} - \beta_i^k \prod_{j=1}^{n+m} x_j^{h_{ij}^k} \qquad (x \in \Omega^k,\ k = 1, ..., N,\ i = 1, ..., n+m). \tag{4}$$

In the case of no control variables ($m = 0$) this system reads

$$\dot{x_i} = \alpha_i^k \prod_{j=1}^{n} x_j^{g_{ij}^k} - \beta_i^k \prod_{j=1}^{n} x_j^{h_{ij}^k} \qquad (x \in \Omega^k,\ k = 1, ..., N,\ i = 1, ..., n). \tag{5}$$

The systems with no control variables will be used in the parameter estimation algorithm, see the subsections 2.4 and 3.2.

One important example of partitions is described below.

Let Δ be an open polyhedral [4], [10] subset of the set $\mathbb{R}^{n+m}$ and $\{\Delta^k\}_{k=1}^N \subset \Delta$ be disjoint (open and polyhedral) sets given by

$$\Delta^k = \{y \in \Delta :\ d_{0j}^k + \sum_{i=1}^{n+m} d_{ij}^k y_i < 0\} \quad (k = 1, ..., N) \tag{6}$$

for some constants d_{ij}^k. Assume further that $\bigcup\limits_{k=1}^{N} \bar{\Delta}^k \supset \Delta$. If we now apply the exponential mapping $x = \exp(y)$, then the polyhedral partition $\{\Delta^k\}_{k=1}^N$ will be transformed into an open partition of the open set $\Omega = \exp(\Delta)$, given by the nonlinear surfaces

$$\Omega^k = \{x \in \Omega :\ d_{0j}^k + \sum_{i=1}^{n+m} d_{ij}^k \log x_i < 0\} \quad (k = 1, ..., N). \tag{7}$$

The dynamics of (4) inside each subset Ω^k is well-defined, while the trajectories' behavior close to the subsets' boundaries may become quite irregular due to the discontinuities of the right-hand sides in (4). Making use of the terminology introduced in [12], we say that a piece of the common boundary between two adjacent subsets is *a wall*. Then there essentially exist three types of walls: *transparent*, when trajectories cross the wall, *black*, when trajectories hit the wall from both sides, and *white*, when trajectories depart from the wall on both sides.

Below we provide an example illustrating different kinds of the dynamics of a piecewise S-system.

Example 1. Let

$$\begin{array}{ll} \dot{x}_1 = 1 - 4x_1 & \dot{x}_1 = 3 - 2x_1 \\ \dot{x}_2 = 0.5 - 2x_2, & \dot{x}_2 = 2 - x_2, \\ \text{if } x \in \Omega^1, & \text{if } x \in \Omega^2, \\ & \\ \dot{x}_1 = 0.5 - x_1 & \dot{x}_1 = 2 - x_1 \\ \dot{x}_2 = 1 - 2x_2, & \dot{x}_2 = 1 - 2x_2, \\ \text{if } x \in \Omega^3, & \text{if } x \in \Omega^4, \end{array} \tag{8}$$

$\Omega^1 = \{(x_1, x_2)|\ x_1 \in (0;1),\ x_2 \in (0;1)\}$, $\Omega^2 = \{(x_1, x_2)|\ x_1 \in (1;2),\ x_2 \in (0;1)\}$, $\Omega^3 = \{(x_1, x_2)|\ x_1 \in (1;2),\ x_2 \in (1;2)\}$, $\Omega^4 = \{(x_1, x_2)|\ x_1 \in (0;1),\ x_2 \in (1;2)\}$.

Some trajectories of the system are depicted in Fig. 1.

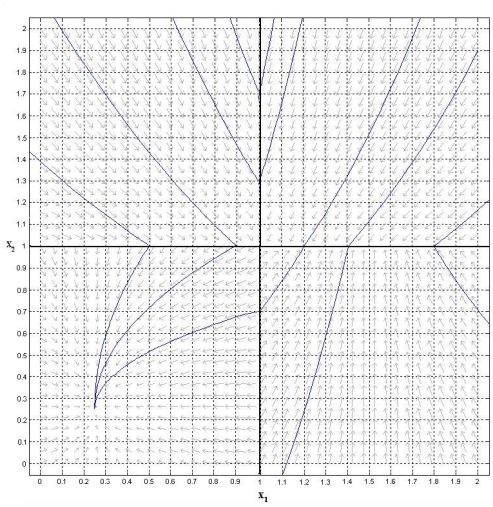

Figure 1: Trajectories of the piecewise S-system (8). The sub-domains are $\Omega^1 = \{(x_1, x_2)|\ x_1 \in (0;1),\ x_2 \in (0;1)\}$, $\Omega^2 = \{(x_1, x_2)|\ x_1 \in (1;2),\ x_2 \in (0;1)\}$, $\Omega^3 = \{(x_1, x_2)|\ x_1 \in (1;2),\ x_2 \in (1;2)\}$, $\Omega^4 = \{(x_1, x_2)|\ x_1 \in (0;1),\ x_2 \in (1;2)\}$; walls are $\Gamma^{1,2} = \{(x_1, x_2)|\ x_1 = 1,\ x_2 \in (0;1)\}$ (white), $\Gamma^{1,4} = \{(x_1, x_2)|\ x_1 \in (0;1),\ x_2 = 1\}$ (transparent), $\Gamma^{2,3} = \{(x_1, x_2)|\ x_1 \in (1;2),\ x_2 = 1\}$ and $\Gamma^{3,4} = \{(x_1, x_2)|\ x_1 = 1,\ x_2 \in (1;2)\}$ (black).

The solutions inside the boundaries are not a priori defined. However, if a piecewise system is meant to be an approximation to a regular, i.e. smooth, system, then this problem must be addressed (see [13], [22]). One way, which is considered in the subsection 3.1, is to convert a discontinuous system to a differential inclusion.

2.2 Steady states of piecewise S-systems

It is easy to calculate steady states of an S-system (see e.g. [25]). Indeed, the logarithmic transform of the steady state equations related to (2) yields the following linear system with respect to $y = \log x$:

$$\log \alpha_i + \sum_{j=1}^{n+m} g_{ij} y_j = \log \beta_i + \sum_{j=1}^{n+m} h_{ij} y_j, \qquad i = 1, ..., n, \tag{9}$$

or in the matrix form

$$Ay = By^0 + b, \tag{10}$$

where

$$A = (g_{ij} - h_{ij})_{1 \le i,j \le n} \quad B = (h_{ij} - g_{ij})_{1 \le i \le n,\ n+1 \le j \le n+m},$$
$$y = (y_1, ..., y_n), \quad y^0 = (y_{n+1}, ..., y_n), \quad b = (\log \beta_i - \log \alpha_i)_{1 \le i \le n}.$$

If the matrix A is invertible, then the system (10) has a unique solution $y^* = A^{-1}By^0 + A^{-1}b$ which depends on the vector y^0 of the control variables.

Going back to the original domain Ω one can perform a local stability analysis of the steady states $x^* = \exp(y^*)$ in an efficient way [25].

It is also easy to calculate steady states of a piecewise S-system.

Setting $x = (x_1, ..., x_n)$ we consider a partition $\{\Omega^k\}_{k=1}^N$ and the piecewise S-system (4) associated with this partition.

Using (9) for each of the subsets we obtain

$$\log \alpha_i^k + \sum_{j=1}^{n+m} g_{ij}^k y_j = \log \beta_i^k + \sum_{j=1}^{n+m} h_{ij}^k y_j \ (y \in \Delta^k,\ k = 1, ..., N,\ i = 1, ..., n), \tag{11}$$

where $y = (y_1, ..., y_n)$. In the matrix form this system becomes

$$A^k y = B^k y^0 + b^k, \qquad y \in \Delta^k, \quad k = 1, ..., N, \tag{12}$$

where

$$A^k = (g_{ij}^k - h_{ij}^k)_{1 \le i,j \le n},\ B^k = (h_{ij}^k - g_{ij}^k)_{1 \le i \le n, n+1 \le j \le n+m},$$

$$y = (y_1, ..., y_n),\ y^0 = (y_{n+1}, ..., y_{n+m}),\ b^k = (\log \beta_i^k - \log \alpha_i^k)_{1 \le i \le n}.$$

Assuming all the matrices A^k to be invertible, we arrive at unique solutions

$$y^{k*} = (A^k)^{-1} B^k y^0 + (A^k)^{-1} b^k,$$

which depend on the vector Y_0 of the control variables. This also gives $x^{k*} = \exp(y^{k*})$ for each $k = 1, ..., N$.

The point x^{k*} for some $k = 1, ..., N$ is a steady state of the piecewise S-system (4) if and only if the following constraint is satisfied:

$$y^{k*} \in \Delta^k \ \text{ or, equivalently, } \ x^{k*} \in \Omega^k. \tag{13}$$

This may not be the case, in general.

Example 2. Let us consider the system

$$\begin{array}{l} \dot{x}_1 = x_1^2 - 2x_1^3, \\ \dot{x}_2 = 3x_1^2 x_2 - x_1 x_2^2, \\ \text{if } x \in \Omega^1,\ \Omega^1 = \{(x_1, x_2) |\ x_1 - x_2 < 0\}. \\ \text{and} \\ \dot{x}_1 = 2x_1 x_2^2 - x_1^2 x_2^4, \\ \dot{x}_2 = 4x_2 - 2x_2^2, \\ \text{if } x \in \Omega^2,\ \Omega^2 = \{(x_1, x_2) |\ x_2 - x_1 < 0\}; \end{array} \tag{14}$$

We denote $\Delta^1 = \{(y_1, y_2) |\ y_1 - y_2 < 0\}$ and $\Delta^2 = \{(y_1, y_2) |\ y_2 - y_1 < 0\}$. Using (9) we find that $y^{1*}(\log 0.5,\ \log 1.5) \in \Delta^1$, while $y^{2*}(\log 0.5,\ \log 2) \notin \Delta^2$. Thus, only x^{1*} is a steady state of the system (14).

As steady states may depend on external control parameters, the constraints may be violated when a steady state crosses the boundary between two sub-domains. A steady state may a) stay in a sub-domain; b) travel through the boundary; c) disappear.

Example 3. Let

$$\begin{array}{l} \dot{x}_1 = x_2 x_3 - 2x_3^2, \\ \dot{x}_2 = x_1 x_3^2 - x_1^2 x_3, \\ \text{if } x \in \Omega^1,\ \Omega^1 = \{(x_1, x_2, x_3) |\ x_1 - x_2 < 0,\ x_3 \in \mathbb{R}\}; \\ \text{and} \\ \dot{x}_1 = x_1^2 x_2 x_3 - x_2^2 x_3^2, \\ \dot{x}_2 = x_2 x_3 - x_1 x_3^2, \\ \text{if } x \in \Omega^2,\ \Omega^2 = \{(x_1, x_2, x_3) |\ x_2 - x_1 < 0,\ x_3 \in \mathbb{R}\}, \end{array} \tag{15}$$

where $x_3 \in \mathbb{R}$ is a control variable.

For $x_1 - x_2 < 0$ (resp. $x_1 - x_2 > 0$) the trajectories travel towards $x^{1*}(x_3, 2x_3, x_3)$ (resp. $x^{2*}(x_3^2, x_3^3, x_3)$). Thus, $x^{1*} \in \Omega^1$ and $x^{2*} \in \Omega^2$ for $0 < x_3 < 1$; $x^{1*} \in \Omega^1$ and $x^{2*} \in \Omega^1$ for $x_3 > 1$; $x^{1*} \in \Omega^1$, while $x^{2*} \in \Gamma$ for $x_3 = 1$, where $\Gamma = \{(x_1, x_2, x_3) \in \Omega |\ x_1 - x_2 = 0,\ x_3 \in \mathbb{R}_+ \setminus \{0\}\}$ is the wall between the sub-domains Ω^1 and Ω^2. It is easy to check that the steady state x^{1*} stays in the sub-domain Ω^1, while x^{2*} travels through the boundary and disappears when $x_3 = 1$.

2.3 Piecewise S-systems in optimization problems

The following system appears in BST if one applies *Law of Generalized Mass Action* (see e.g. [9]):

$$\dot{x}_i = \sum_{r=1}^{p} \mu_{ir} V_r(x_1, ..., x_{n+m}), \qquad i = 1, ..., n, \tag{16}$$

where the power functions $V_r(x_1, ..., x_{n+m})$ describe the rates of process r, while μ_{ir} is a stoichiometric factor that stands for the number of molecules of x_i produced, i.e. $\mu_{ir} = 1, 2, \ldots$ or $\mu_{ir} = -1, -2, \ldots$.

In [9] the following optimization problem, related to steady states of (16), was introduced and analyzed:

$$\begin{array}{c} U(V_r, \gamma_r, x_j) \to \min \\ \text{subject to} \quad \sum_{r=1}^{p} \mu_{ir} V_r(x_1, .., x_{n+m}) = 0, \qquad i = 1, ..., n, \\ V_r(x_1, x_2, ..., x_{n+m}) = \gamma_r \prod_{j=1}^{n+m} x_j^{f_{rj}}, \\ v_r, \gamma_r, x_j \in \mathbb{R}_+. \end{array} \tag{17}$$

Here $U : \mathbb{R}_+^p \times \mathbb{R}_+^p \times \mathbb{R}_+^n \to \mathbb{R}$ is the objective function which should be minimized under the above constraints describing the feasible set of the optimization problem.

The set of steady states in (16), which depends on the control variables $x_{n+1}, ..., x_{n+m}$ and which is the set where the objective function should be minimized, is in general non-convex, making the analysis complicated. A special optimization method to overcome this difficulty was suggested in [9]. The method utilizes and refines global optimization techniques described e.g. in [8]. In [21] this method was applied to specific models. Roughly, the idea of the method consists in finding the global minimum for convexifed optimization problems and subsequent iterative removing of unfeasible minima by imposing additional, integer-valued constraints.

Below we present the solution of this optimization problem for a piecewise S-system, where we, in addition, assume that the partition of Δ is polyhedral, i.e. is defined by (6). The general case will be analyzed in the next section.

The optimization problem we study in this subsection is formulated as follows:

$$\begin{array}{c} \mathcal{U}(x) \to \min \\ \text{subject to} \quad \log \alpha_i^k + \sum_{j=1}^{n+m} g_{ij}^k \log x_j = \log \beta_i^k + \sum_{j=1}^{n+m} h_{ij}^k \log x_j \ \ (i = 1, ..., n) \\ \text{when} \quad x \in \Omega^s, k = 1, ..., N, \\ x = (x_1, , .., x_{n+m}), \end{array} \tag{18}$$

where $\mathcal{U} : \mathbb{R}_+^{n+m} \to \mathbb{R}$ is the objective function.

Using the logarithmic transformation $y_j = \log x_j$ we get from (18) the following piecewise linear optimization problem:

$$\begin{array}{c} U(y_1, ..., y_{m+n}) \to \min \\ \text{subject to} \\ \log \alpha_i^k + \sum_{j=1}^{n+m} g_{ij}^k y_j = \log \beta_i^k + \sum_{j=1}^{n+m} h_{ij}^k y_j \ \ (y \in \Delta^k, k = 1, ..., N, i = 1, ..., n) \\ \text{and} \quad a_{j0}^s + \sum_{k=1}^{n} a_{jk}^s y_k \le 0, \end{array} \tag{19}$$

or in the matrix form

$$\begin{array}{c} U(Y,Y_0)\to \min \\ \text{subject to} \quad A^kY=B^kY_0+b^k \ \text{ and } \ (Y,Y_0)\in\Delta^k, k=1,...,N, \\ Y=(y_1,,..,y_n), \quad Y_0=(y_{n+1},,..,y_{n+m}), \end{array} \tag{20}$$

where $U(y_1,...,y_n)=\mathcal{U}(\exp(y_1),\exp(y_{n+m}))$, and the matrices A^k, B^k and the vectors b^k are defined in (12).

We see that the optimization problem (18) becomes piecewise linear in Δ.

If the matrices A^k are invertible (which simply means the uniqueness of a steady state for each value of the control variables), then the linear system can be resolved with respect to $y_1,...,y_n$. Inserting this expression into the objective function removes the number of variables and the constraints, and the optimization problem becomes

$$\begin{array}{c} U((A^k)^{-1}B^kY_0+(A^k)^{-1}b^k,Y_0)\to \min \\ \text{subject to} \quad Y=((A^k)^{-1}B^kY_0+(A^k)^{-1}b^k,Y_0)\in\Delta^k, k=1,...,N, \\ Y_0=(y_{n+1},,..,y_{n+m}). \end{array} \tag{21}$$

Thus, this optimization problem is convex within each polyhedral (i.e. also convex) subset Δ^k, and the steady states can be easily calculated using the formulas from the subsection 3.2. The global minima can be then obtained by comparing the local minima within each subset, so that the calculations become straightforward and no additional convexification technique is needed.

As we will show in the next section, this algorithm is generic, i.e. can be applied - through approximations by piecewise S-systems - to an arbitrary compartment model (see Section 3).

2.4 Parameter estimation by the alternating regression method

In this subsection we consider a practically important problem of estimating sensitivities (kinetic orders) of the piecewise S-system (5). One of the methods, which is called Alternating Regression (AR) and which works particularly well for S-systems (2), was introduced in [1]. In this paper we apply this method to piecewise S-systems (5) with no control parameters.

The advantage of AR is its linear character at each step, i.e. it is solely based on the linear regression. Another nice feature is that the algorithm works separately for each number i ("decoupling"). On the other hand, convergence of the AR iterations is a complicated issue and it is beyond the scope of the present paper. For some problems arising when justifying the convergence in the case of plain S-systems see e.g. [1] and [23].

We assume that each metabolite x_i was observed at times $t_1,t_2,...,t_M$ giving a set of values $\{x_i(t_1),x_i(t_2),...,x_i(t_M)\}$, $i=1,...,n$. We also assume that we can measure or compute the slopes $\delta x_i(t_l)=\dot{x}_i(t_l)$, $l=1,...,M$, $i=1,...,n$.

Given these time series, we want to estimate the sensitivities of the system (5).

The partition $\{\Omega^k\}_{k=1}^N$ of Ω induces the partition $\{t_1^k,t_2^k,...,t_{M^k}^k\}_{k=1}^N$ of the time series $t_1,t_2,...,t_M$.

Let

$$X^k=\begin{pmatrix} 1 & \log x_1(t_1^k) & \dots & \log x_n(t_1^k) \\ 1 & \log x_1(t_2^k) & \dots & \log x_n(t_2^k) \\ \vdots & \vdots & \ddots & \vdots \\ 1 & \log x_1(t_l^k) & \dots & \log x_n(t_l^k) \\ \vdots & \vdots & \ddots & \vdots \\ 1 & \log x_1(t_{M^k}^k) & \dots & \log x_n(t_{M^k}^k) \end{pmatrix}.$$

We compute the matrices

$$C^k=((X^k)^TX^k)^{-1}(X^k)^T, \ k=1,...,N. \tag{22}$$

The iteration procedure is described below.

Step 1. Assume that the parameters $\{\beta_i^k,h_{i1}^k,...,h_{in}^k, \ i=1,...,n\}_{k=1}^N$ of the degradation term are available. Compute the parameters $\{\alpha_i^k,g_{i1}^k,...,g_{in}^k, \ i=1,...,n\}_{k=1}^N$ of the production term.

To do that, we rewrite system (5) as

$$\alpha_i^k \prod_{j=1}^{n} x_j^{g_{ij}^k}(t_l^k) = \beta_i^k \prod_{j=1}^{n} x_j^{h_{ij}^k}(t_l^k) + \delta x_i(t_l^k), \qquad l = 1, ..., M^k,$$

and perform the logarithmic transformation

$$\log \alpha_i^k + \sum_{j=1}^{n} g_{ij}^k \log x_j(t_l^k) = \log\big(\beta_i^k \prod_{j=1}^{n} x_j^{h_{ij}^k}(t_l^k) + \delta x_i(t_l^k)\big), \qquad l = 1, ..., M^k.$$

Substituting the values for the parameters $\beta_i^k, h_{i1}^k, ..., h_{in}^k$ and $\delta x_i(t_l^k)$, $l = 1, ..., M^k$, $i = 1, ..., n$ we compute the M^k-dimensional vector $D_i^k = \log\big(\beta_i^k \prod_{j=1}^{n} x_j^{h_{ij}^k}(t_l^k) + \delta x_i(t_l^k)\big)^T$ and estimate the regression coefficients of the linear regression by

$$G_i^k = C^k \cdot D_i^k,$$

where C^k is given by (22), $G_i^k = \big(\log \alpha_i^k, g_{i1}^k, ..., g_{in}^k\big)^T$, $i = 1, ..., n$, $k = 1, ..., N$. Thus, we obtain the set $\{\alpha_i^k, g_{i1}^k, ..., g_{in}^k,\ i = 1, ..., n\}_{k=1}^N$.

Step 2. Assume that the production term parameters $\{\alpha_i^k, g_{i1}^k, ..., g_{in}^k,\ i = 1, ..., n\}_{k=1}^N$ are available. Compute the parameters $\{\beta_i^k, h_{i1}^k, ..., h_{in}^k,\ i = 1, ..., n\}_{k=1}^N$ of the degradation term.

We rewrite system (5) as

$$\beta_i^k \prod_{j=1}^{n} x_j^{h_{ij}^k}(t_l^k) = \alpha_i^k \prod_{j=1}^{n} x_j^{g_{ij}^k}(t_l^k) - \delta x_i(t_l^k), \qquad l = 1, ..., M^k,$$

and perform again the logarithmic transformation

$$\log \beta_i^k + \sum_{j=1}^{n} h_{ij}^k \log x_j(t_l^k) = \log(\alpha_i^k \prod_{j=1}^{n} x_j^{g_{ij}^k}(t_l^k) - \delta x_i(t_l^k)), \qquad l = 1, ..., M^k.$$

Using the values for the parameters $\alpha_i^k, g_{i1}^k, ..., g_{in}^k$ and $\delta x_i(t_l^k)$, $l = 1, ..., M^k$, $i = 1, ..., n$ we compute the M^k-dimensional vector $P_i^k = \log\big(\alpha_i^k \prod_{j=1}^{n} x_j^{g_{ij}^k}(t_l^k) - \delta x_i(t_l^k)\big)^T$ and find the regression coefficients of the linear regression from

$$H_i^k = C^k \cdot P_i^k,$$

where C^k is given by (22), $H_i^k = \big(\log \beta_i^k, h_{i1}^k, ..., h_{in}^k\big)^T$, $i = 1, ..., n$, $k = 1, ..., N$. By this, we obtain the set $\{\beta_i^k, h_{i1}^k, ..., h_{in}^k,\ i = 1, ..., n\}_{k=1}^N$.

The algorithm starts with an initial guess on the sensitivities of the degradation term. One can use the same set $\{\beta_i^{(0)}, h_{i1}^{(0)}, ..., h_{in}^{(0)}\}_{i=1}^n$ for the entire domain Ω or, alternatively, if there is any information on the model's structure, different sets of initial sensitivities can be chosen for the subsets Ω^k, $k = 1, ..., N$. Steps 1 and 2 are then repeated successively in every Ω^k, $k = 1, ..., N$, until a solution is found or some termination criterion is satisfied. Thus, we obtain the sequences of values $\{\alpha_i^{k(\nu)}, \beta_i^{k(\nu)}, g_{i1}^{k(\nu)}, ..., g_{in}^{k(\nu)}, h_{i1}^{k(\nu)}, ..., h_{in}^{k(\nu)},\ i = 1, ..., n\}_{k=1}^N$, $\nu = 0, 1, 2, ...$, which upon convergence give us the unknown sensitivities of the piecewise S-system (5).

In the subsection 3.2, we combine this procedure with approximation by piecewise S-systems, thus making Alternating Regression generic.

3 Piecewise S-systems as approximations of general compartment models

A *compartment model* has the following form:

$$\dot{x}_i = V_i^+(x_1, ..., x_{n+m}) - V_i^-(x_1, ..., x_{n+m}), \qquad i = 1, ..., n, \tag{23}$$

where the influx/efflux function $V^{\pm}$ accounts for the rate of a production and degradation of the quantity x_i, respectively, and x_j $(j = n+1, ..., n+m)$ represent control parameters.

For instance, in a general metabolic network used in BST one has n internal metabolites $x_i \geq 0$ $(i = 1, ..., n)$, while the other variables represent external metabolites (see e.g. [14], [15], [16], [24], [25]).

In this section we regard piecewise S-systems as approximations of the nonlinear system (23). The aim is to answer the question which is often ignored in applied analysis: Why should a sufficiently good approximation mimic the properties of the approximated model? We study the calculation algorithms for piecewise S-systems from the first part of the paper and show that, under some assumptions, the targets of these algorithms in the limit indeed coincide with the respective targets of the approximated system. This justifies a generic method of analysis of compartment models, which combines universality of approximations by piecewise S-systems with the algorithmic simplicity of calculations with these systems.

Below we always assume that Ω is an open subset of $\mathbb{R}^{n+m}_+$ such that its closure $\bar{\Omega}$ is a compact subset of $\mathbb{R}^{n+m}_+ \setminus \{\bar{0}\}$. We also let $\{\Omega^k_N\}_{k=1}^N$ be an open partition of Ω for any natural N, so that $\bigcup\limits_{k=1}^{N} \bar{\Omega}_k = \bar{\Omega}$, $\Omega_k \cap \Omega_l = \emptyset$ if $k \neq l$. Finally, we put $\delta_N = \max\limits_{1 \leq k \leq N} \mathrm{diam}(\Omega^k_N)$.

3.1 Convergence of solutions of piecewise S-systems

Let $v^{k+}_{iN}(x) = \alpha^k_{iN} \prod\limits_{j=1}^{n+m} x_j^{g^k_{ijN}}$, and $v^{k-}_{iN}(x) = \beta^k_{iN} \prod\limits_{j=1}^{n+m} x_j^{h^k_{ijN}}$, $k = 1, ..., N$. We also put $V^+_{iN} = v^{k+}_{iN}$ and $V^-_{iN} = v^{k-}_{iN}$ for $x \in \Omega^k_N$.

The approximating S-systems become

$$\dot{x}_i = V^+_{iN}(x_1, ..., x_{n+m}) - V^-_{iN}(x_1, ..., x_{n+m}), \qquad x \in \Omega,\ i = 1, ..., n+m. \tag{24}$$

The sensitivities (1) of the jth variable of ith influx and the ith efflux of the systems (23) and (24) at a point $P \in \Omega$ will be denoted as $f^+_{ij}(P)$, $f^-_{ij}(P)$ and $f^+_{ijN}(P)$, $f^-_{ijN}(P)$, respectively. The results will be formulated in terms of the sensitivities of the two systems.

The first theorem of this subsection ensures uniform convergence of the right-hand sides.

Theorem 1 *Let the functions $V^{\pm}_i(x)$ $(x \in \bar{\Omega})$ $i = 1, ..., n+m$ be of the C^1-type (i.e. differentiable in Ω with the continuous in $\bar{\Omega}$ partial derivatives). Let the sequence of partitions $\{\Omega^k_N\}_{k=1}^N$ of Ω have the property $\delta_N \to 0$ $(N \to \infty)$. Assume that for any $i = 1, ..., n+m$ and $k = 1, ..., N$ there exist points $r^{k+}_{iN}, q^{k+}_{iN}, r^{k-}_{iN}, q^{k-}_{iN} \in \Omega^k_N$ such that the following is satisfied*

$$\begin{array}{ll} V^+_i(r^{k+}_{iN}) = v^+_{iN}(r^{k+}_{iN}), & V^-_i(r^{k-}_{iN}) = v^-_{iN}(r^{k-}_{iN}), \\ f^+_{ij}(q^{k+}_{iN}) = f^+_{ijN}(q^{k+}_{iN}); & f^-_{ij}(q^{k-}_{iN}) = f^-_{ijN}(q^{k-}_{iN}) \end{array} \tag{25}$$

for all $N \in \mathbb{N}$, $i = 1, ..., n$, $j = 1, ...n+m$. Then for any $\varepsilon > 0$ there exists a number N_0 such that

$$\sup_{x \in \Omega_{iN},\ i=1,...,N} |V^{\pm}_{iN}(x) - V^{\pm}_i(x)| < \varepsilon$$

for all $N \geq N_0$.

Proof.

We check the uniform convergence for a fixed scalar function $V = V^{\pm}_i$. We denote the associated sequence of approximations by V_N, so that $V_N = v^k_N$ on Ω^k_N.

Let $\Delta \subset \mathbb{R}^{n+m}$ be the image of Ω under the logarithmic transformation $y = \log x$ and $\{\Delta^k_N\}_{k=1}^N$ be the induced open partition of Δ. Thus, $\Delta^k_N \cap \Delta^l_N = \emptyset$ for every $k \neq l$, $k, l = 1, ..., N$ and $\bigcup\limits_{k=1}^{N} \bar{\Delta}^k_N = \bar{\Delta}$.

We set also $\Psi(y) = \log V(x)$, $\Psi_N(y) = \log V_N(x)$ and $\psi^k_N(y) = \log v^k_N(x)$, $y = \log x$, $\alpha^k_N = v^k_N(1, ..., 1)$, $c^k_N = \log \alpha^k_N$.

The logarithmic images of the points from (25), corresponding to the chosen function $V = V_i^{\pm}$, will be denoted by R_N^k and Q_N^k, respectively. According to the assumptions of the theorem we may write $\Psi(R_N^k) = \psi_N^k(R_N^k)$ for the respective points and $f_{jN}^k \equiv f_j(q_N^k) = f_{jN}(q_N^k)$ for the respective kinetics orders $f(P)$ and $f_N(P)$ of the functions V and V_N.

By construction we obtain $\psi_N^k(y) = c_N^k + \sum\limits_{j=1}^{n} f_{jN}^k y_j$, where $c_N^k = \log \alpha_N^k$, which therefore becomes a piecewise linear approximation of the function $\Psi(y)$ on $\bar{\Delta}$.

For $y \in \Delta_N^k$ we have $\psi_N^k(y) = \nabla\psi_N^k(Q_N^k)(y - R_N^k) + \Psi(R_N^k)$, where $R_N^k, Q_N^k \in \Delta_N^k$. The mean value theorem yields also $\Psi(y) - \Psi(R_N^k) = \nabla\Psi(R_0)(y - R_N^k)$, where $R_0(y) \in \Delta_N^k$ may depend on y. Thus,

$$|\Psi_N(y) - \Psi(y)| = |\nabla\psi_N^k(Q_N^k) - \nabla\Psi(R_0)| \cdot |y - R_N^k|.$$

As the function $\nabla\Psi$ is continuous on $\bar{\Delta}$, it is also uniformly continuous there. This and the fact that the maximum of the diameters of the sub-domains δ_N^k tend to 0 as N tends to ∞ (because $\delta_N \to 0$ as $N \to \infty$) yield that for sufficiently large N $|\Psi_N^k(y) - \Psi(y)| < \varepsilon$ on Δ_N^k for any $k = 1, .., N$, which together with the continuity of the exponential transformation proves the theorem. $\square$

Our next aim is to study convergence of solutions, in particular, steady states. We first have to define solutions of the approximating piecewise S-systems.

Following [10], we use the theory of differential inclusions to define continuous, everywhere defined approximating solutions. The price we have to pay is non-uniqueness of these solutions outside the partition sets Ω.

Assume that a point $x \in \Omega$ is contained in the closures of the subsets $\Omega_N^{k_l}$, where l runs over some set L, but not in the closures of the subsets Ω_N^k ($k \neq k_l,\ l \in L$). Let $f_N(x, l)$ be the right-hand side of the piecewise S-system (24) for $x \in \Omega_N^{k_l}$ ($l \in L$) and define $F_N(x)$ to be the least convex set containing all vectors $f_N(x, l)$ ($l \in L$), i.e. $F_N(x) = \mathrm{co}\{f_N(x, l) \mid l \in L\}$. Consider the following differential inclusion:

$$\dot{x}_i \in F_{iN}(x_1, ..., x_{n+m}), \qquad i = 1, ..., n. \tag{26}$$

A solution of (26) on an interval $[a, b]$ is an absolutely continuous function $x(t)$ which satisfies (26) almost everywhere on $[a, b]$. According to [5], the initial value problem $x(a) = x_0 \in \Omega$ for (26) has a local solution continuously depending on the control variables (i.e. parameters). However, this solution is, in general, not unique. If $x(t)$, $t \in I$, I is an open sub-interval of $[a, b]$, belongs to some Ω_N^k, then by definition $x(t)$ is a conventional solution of the kth S-system in (24). In the black walls (attracting discontinuity sets) the solution is now well-defined.

In particular, constant solutions of (26) are by definition steady states of (24). This uncovers, for instance, 'hidden' steady states of these S-systems, which in the limit may converge to a proper steady state of the original system (23).

The $n \times n$-matrix $J(P)$ in the theorem below contains the differences $f_{ij}^+(P) - f_{ij}^-(P)$ as its entries, where $f_{ij}^{\pm}(P) = \left(\frac{\partial V_i^{\pm}}{\partial x_j}\frac{x_j}{V_i^{\pm}}\right)_P$, $1 \leq i, j \leq n$ are the kinetic orders of the functions $V_i^{\pm}$, respectively. We call a steady state x^* of the system (23) nondegenerate if $\det J(x^*) \neq 0$.

Theorem 2 *Let all the assumptions of Theorem 1 be fulfilled and $x_N \in \Omega$, $x_N \to x_0 \in \Omega$ as $N \to \infty$. Then any sequence of parametrized solutions $x_{jN}(t, x_{n+1}, ..., x_{n+m})$ ($t \in [a, b]$, $j = 1, ...n$) to the inclusions (26) satisfying $x_{jN}(a, x_{n+1}, ..., x_{n+m}) = x_{jN}$ ($j = 1, ...n$) contains a subsequence which uniformly on $[a, b]$ converges to the parametrized solution $x_j(t, x_{n+1}, ..., x_{n+m})$ ($t \in [a, b]$, $j = 1, ...n$) of (23) satisfying $x_j(a, x_{n+1}, ..., x_{n+m}) = x_{j0}$ ($j = 1, ...n$). In particular, any convergent sequence of steady states x_N^* to (26) converges to a steady state x^*.*

Conversely, if a steady state x^* of the system (23) is nondegenerate and the partition is chosen in such a way that for any natural N the point x^* belongs to some Ω_N^k, then there exists a sequence x_N^* of steady states of the system (24), which converges to x^* as $N \to \infty$.

Proof. According to [5], the set $\{x_{jN}(t, x_{n+1}, ..., x_{n+m}) \mid N \in \mathbb{N}\}$ is compact in the topology of the uniform convergence on $[a, b]$, so that the sequence contains a uniformly convergence subsequence that approaches the

solution of the limit system (23) satisfying the required initial condition. If the solution of the limit system is unique, then possibly different approximations will give the same limit solution, so that non-uniqueness of the Filippov solutions would not be a big problem. We notice also that uniqueness of the approximating solutions holds automatically inside any Ω_N^k.

To prove the second statement, let us, first of all, observe that the nondegeneracy assumption of Theorem 2 implies invertibility of the matrices A^k defined in (12). Thus, we can apply the implicit function theorem for systems (24) which are sufficiently close to the given one. This ensures the existence and uniqueness of approximating steady states inside any Ω_N^k. $\square$

Remark 1. Theorem 2 remains valid if we replace the assumptions of Theorem 1 with its conclusion. The latter is, for instance, satisfied if the C^1-convergence of the approximating right-hand sides is known (see also Theorem 4 for a detailed description of this alternative assumption).

3.2 Convergence in the optimization problem and the alternating regression

Consider the following nonlinear optimal control problem for the system (23) which generalizes the problem (17):

$$\begin{gathered} \mathcal{U}(x) \to \min \\ \text{subject to} \quad V_i^+(x_1,...,x_{n+m}) - V_i^-(x_1,...,x_{n+m}) = 0, \qquad i = 1,...,n, \\ x_j \in \mathbb{R}_+. \end{gathered} \tag{27}$$

Here $\mathcal{U} : \mathbb{R}_+^{n+m} \to \mathbb{R}$ is a given objective function.

The approximating problems will be defined as in (20) for the sequence of the partitions Δ_N:

$$\begin{gathered} U(Y, Y_0) \to \min \\ \text{subject to} \quad A_N^k Y = B_N^k Y_0 + b_N^k \ \text{ and } \ (Y, Y_0) \in \Delta_N^k, k = 1,...,N, \\ Y = (y_1,...,y_n), \quad Y_0 = (y_{n+1},...,y_{n+m}). \end{gathered} \tag{28}$$

Clearly, the exponential transformation of the feasibility set for this problem gives the set of steady states for the piecewise S-system (24).

Recall that a steady state x^* for (23) is said to be nondegenerate if $\det J(x^*) \neq 0$, where $J(P)$ is defined right before the theorem 2.

Theorem 3 *Let all the assumptions of the theorem 1 be fulfilled, the objective function $\mathcal{U}$ be continuous in $\bar{\Omega}$ and the affine optimization problems (28) have the solutions $y_N^* \in \bigcup_{j=1}^{N} \Delta_N^k$ for any $N \in \mathbb{N}$.*

If, in addition, all steady states for (23) are nondegenerate and the partitions Ω_N are chosen in such a way that for any $N \in \mathbb{N}$ these steady states belong to some Ω_N^k, then any converging subsequence of the compact sequence $x_N^* = \exp(y_N^*)$ has a limit x^* which is a solution of the optimization problem (27).

Conversely, if x^* is a unique solution to the problem (27), this solution is nondegenerate, and the partition Ω_N is chosen in such a way that for any $N \in \mathbb{N}$ the point x^* belongs to some Ω_N^k, then there exists a sequence y_N^* of the solutions of the approximating problems (28), for which the sequence $x_N^* = \exp(y_N^*)$ converges to x^* as $N \to \infty$.

Proof. Using the theorem 1 we observe that the sequence $x_N^* = \exp(y_N^*)$ from the first part of the theorem indeed is always compact and its limit is a steady state for the system (23). If all steady states for this system are nondegenerate, then for any of it, say $\tilde{x}^*$, there exists a sequence of steady states $\tilde{x}_N^*$ of the approximating piecewise S-systems that converges to $\tilde{x}^*$. Therefore,

$$\mathcal{U}(x^*) = \lim_{N\to\infty} \mathcal{U}(x_N^*) \leq \lim_{N\to\infty} \mathcal{U}(\tilde{x}_N^*) = \mathcal{U}(\tilde{x}_*),$$

which proves that x^* is the solution to the problem (27).

On the other hand, assume that x^* is a unique solution to the problem (27) and it is nondegenerate. Assume further that $\tilde{x}_N^*$ is a sequence of steady states of the approximating piecewise S-systems (24) that

converges to x^*. If now $y_N^* \in \bigcup_{j=1}^{N} \Delta_N^k$ are solutions to the approximating problems (28) and $x_N^* = \exp(y_N^*)$, then we have

$$\mathcal{U}(x^*) = \lim_{k\to\infty} \mathcal{U}(\tilde{x}_{N_k}^*) \geq \lim_{k\to\infty} \mathcal{U}(x_{N_k}^*) = \mathcal{U}(\tilde{x}_*),$$

where x_{N_k} is a convergent subsequence of the compact sequence x_N, which tends to $\tilde{x}_*$. By uniqueness of x^*, we therefore get $x^* = \tilde{x}^*$, and the theorem is proved. $\square$

Now we revisit the parameter estimation method studied in the subsection 2.4, applying it to the generic compartment model (23). As it is put in the review paper [2], 'the estimation problem is almost always complicated and continues to be the bottleneck of biomathematical modeling'. As S-systems are better studied in this respect than many other systems, the idea to represent a complicated nonlinear biomathematical model as a piecewise S-system may be fruitful.

Below we demonstrate how this algorithm indeed can be adapted for (23), at least under the assumption that $m = 0$, i.e. that the control variables are absent. Then the system becomes

$$\dot{x}_i = V_i^+(x_1, ..., x_n) - V_i^-(x_1, ..., x_n), \qquad i = 1, ..., n \tag{29}$$

where $x = (x_1, ..., x_n)^T$, $V_i^+, V_i^- : \mathbb{R}_+^n \to \mathbb{R}_+ \setminus \{0\}$.

The aim is to estimate the sensitivities of the influx end efflux functions $V_i^{\pm}$. The following result follows directly from the previous convergence theorems:

Theorem 4 *Let the functions $V_i^{\pm}$ $(i = 1, ..., n)$ be C^1 in Ω, C in $\bar{\Omega}$ and $V_i^{\pm}(x_1, ..., x_n) \geq \mu > 0$ for all $(x_1, ..., x_n) \in \Omega$. Assume that the sequence of open partitions $\{\Omega_N^k\}_{k=1}^N$ of Ω have the property $\delta_N \to 0$ $(N \to \infty)$. Assume further that for any $\varepsilon > 0$ there exists a number N_0 such that*

$$\sup_{x\in\Omega_{iN},\ i=1,...,N} \left(|V_{iN}^{\pm}(x) - V_i^{\pm}(x)| + \sum_{j=1}^{n} \left| \frac{\partial V_{iN}^{\pm}(x)}{\partial x_j} - \frac{\partial V_i^{\pm}(x)}{\partial x_j} \right| \right) < \varepsilon$$

for all $N \geq N_0$. Finally, we suppose that the AR method from the subsection 2.4 converges for all sufficiently large natural N and at least one initial guess on sensitivities. Then for all $x \in \bigcup_{i=1}^{\infty} \Omega_i$ and any $\varepsilon > 0$ there is a natural number K and an initial guess on sensitivities such that after finitely many iterations the AR method gives an ε-approximation to all sensitivities of the influx and efflux functions $V_i^{\pm}$ of System (29) at the point x. $\square$

4 Summary and discussions

In this paper we studied some properties of piecewise S-systems. The aim was two-fold: 1) to show efficiency and simplicity of practical calculations with such systems and 2) to justify the method of approximation of general compartment models by piecewise S-systems. All approximations used in this paper are designed in terms of sensitivities (kinetic orders), which is crucial for many applications in Biochemical Systems Theory and other fields.

The following results can be highlighted:

1. Proof of convergence of properly defined solutions and steady states of piecewise S-systems approximating compartment model systems.

2. Justification of a novel method of estimation of sensitivities in a general compartment model, which is based on alternating regression and piecewise power-law approximations.

3. An alternative, essentially linear, approach to an optimal control problem arisen in Biochemical Systems Theory, which is based on approximation by piecewise S-systems.

To our opinion, theoretical and applied analysis of piecewise S-systems should be continued. For instance, one may address the following open problems:

1. Is it possible to describe solutions and steady states of piecewise S-systems in their discontinuity sets using the singular perturbation analysis, rather than differential inclusions. This approach, which is more constructive and usually gives uniqueness of solutions, is suggested in the paper [13] for the case of genetic models and shown to work for some other nonlinear systems in the paper [22].

2. To what extent is it possible to relax the assumption of Theorem 1 requiring that the diameters of the partition subsets (i.e. the mesh of the partition) tend to zero? The problem is of interest in connection with the linear regression algorithm which is based on automated partitioning and which was introduced in [4], adapted for BST in [10] and studied mathematically in [11]. As the mesh of the partitions in this algorithm may not necessarily approach zero (this depends heavily on the shape of the functions in the right-hand side), our results do not cover this case.

3. What conditions would ensure the possibility to study asymptotic properties of the general compartment model (23) via its approximations by piecewise S-systems?

4. What modifications are required in the algorithm described in the subsection 2.4 if the matrices $C^k = (X^k)^T(X^k)$ become singular or almost singular? This effect, known as multicollinearity, might cause serious numerical problems and should be definitely treated properly, for instance, by applying the partial least-squares regression. A careful analysis of this situation was, however, beyond the scope of the present paper.

References

[1] Chou IC, Martens H, Voit EO (2006), Parameter estimation in biochemical systems models with alternating regression, Theor. Biol. Med. Model. 3.

[2] Chou IC, Voit EO (2009) Recent developments in parameter estimation and structure identification of biochemical and genomic systems. Math. Biosci. 219(2):57-83.

[3] Coelho PMBM, Salvador A, Savageau MA (2010), Relating mutant genotype to phenotype via quantitative behavior of the NADPH redox cycle in human Erythrocytes. PloS ONE 5(9), e13031:1-13.

[4] Ferrari-Trecate G, and Muselli M (2002), A New Learning Method for Piecewise Linear Regression. Lect Notes Comput Sci 2415:444-449.

[5] Filippov AF (1998), Differential Equations With Discontinuous Right-Hand Sides, Kluwer, Dordrecht.

[6] Gutenkunst RN, Waterfall JJ, Casey FP, Brown KS, Myers CR, Sethna JP (2007), Universally sloppy parameter sensitivities in systems biology models. BMC Syst. Biol. 3:18711878.

[7] de Jong H (2002), Modeling and simulation of genetic regulatory systems: a literature review, J. Comput. Biol. 9:67-104.

[8] Floudas CA (2000), Deterministic global optimization: Theory. Methods and Applications. Dordrecht, The Nether-lands: Kluwer, Academic Publishers.

[9] Guillen-Gosalbez G, Sorribas A (2009), Identifying quantitative operation principles in metabolic pathways: a systematic method for searching feasible enzyme activity patterns leading to cellular adaptive responses. BMC Bioinformatics 10, 386.

[10] Machina A, Ponosov A, Voit EO (2010), Automated piecewise power-law modeling of biological systems. J Biotechnol, 149(3):154-165.

[11] Ponosov A, Machina A, Tafintseva V (2016), Convergence properties of piecewise power approximations. Appl. Math. 7:1440-1445.

[12] Plahte E, Mestl T, Omholt SW (1998), A methodological basis for description and analysis of systems with complex switch-like interactions, J. Math. Biol. 36:321-348.

[13] Plahte E, Kjøglum S (2005), Analysis and generic properties of GRNs with graded response functions, Physica D, 201(1-2):150-176.

[14] Savageau MA (1969), Biochemical systems analysis. I. Some mathematical properties of the rate law for the component enzymatic reactions, J Theor Biol, 25(3):365-9.

[15] Savageau MA (1969), Biochemical systems analysis. II. The steady-state solutions for an n-pool system using a power-law approximation. J Theor Biol. 25(3):370-9.

[16] Savageau MA (1970), Biochemical systems analysis. III. Dynamic solutions using a power-law approximation. J Theor Biol. 26(2):215-26.

[17] Savageau MA (2002), Alternative designs for a genetic switch: analysis of switching times using the piecewise power-law representation. Math. Biosci. 180:237-53.

[18] Sorribas A, Savageau MA (1989), A comparison of variant theories of intact biochemical systems. I. Enzyme-enzyme interactions and biochemical systems theory. Math. Biosci. 94:161-193.

[19] Sorribas A, Savageau MA (1989), A comparison of variant theories of intact biochemical systems. II. Flux-oriented and metabolic control theories. Math. Biosci. 94:195-238.

[20] Sorribas A, Savageau MA (1989), Strategies for representing metabolic pathways within biochemical systems theory: reversible pathways. Math. Biosci. 94:239-269.

[21] Sorribas A, Pozo C, Vilaprinyo E, Guillen-Gosalbez G, Jimenez L, Alves R (2010), Optimization and evolution in metabolic pathways: global optimization techniques in Generalized Mass Action models, J. Biotechnol. 149(3):141–153.

[22] Tafinsteva V, Machina A, Ponosov A (2013), Polynomial representations of piecewise-linear differential equations arising from gene regulatory networks. Nonlin An: Real World Appl. 14(3):1732-1754.

[23] Tafintseva V, Tøndel K, Ponosov A, Martens H (2014), Structure of sloppiness in a nonlinear model. Chemometrics. 28:645-655.

[24] Voit EO et al. (1991), Canonical Nonlinear Modeling. S-System Approach to Understanding Complexity, Van Nostrand Reinhold, NY.

[25] Voit EO (2000), Computational analysis of biochemical systems: a practical guide for biochemists and molecular biologists, Cambridge University Press, New York.