Applications of Mathematics

Erich Bohl; Ivo Marek

Input-output systems in Biology and Chemistry and a class of mathematical models describing them

Applications of Mathematics, Vol. 50 (2005), No. 3, 219–245

Persistent URL: http://dml.cz/dmlcz/134604

INPUT-OUTPUT SYSTEMS IN BIOLOGY AND CHEMISTRY AND A CLASS OF MATHEMATICAL MODELS DESCRIBING THEM*

Erich Bohl, Konstanz, Ivo Marek, Praha

Abstract. Our aim is to show a class of mathematical models in application to some problems of cell biology. Typically, our models are described via classical chemical networks. This property is visualized by a conservation law. Mathematically, this conservation law guarantees most of the mathematical properties of the models such as global existence and uniqueness of solutions as well as positivity of the solutions for positive data. These properties are consequences of the fact that the infinitesimal generators forming the underlying dynamical systems are (nonlinear) negative M-operators.

Keywords: dynamical system, input-output system, chemical network, boundary layer

MSC 2000: 34A34, 47B65

1. Introduction

This paper tries to draw the attention to a special type of nonlinear ordinary dynamical systems describing a substantial class of biological and chemical situations in nature. It is built up of linear evolutions $\dot{\eta}_j(t) = A_j\eta_j(t)$, $j = 1, \ldots, L$, with negative of M-matrices A_j whose entries depend on the dynamical variables η_k, $k \neq j$, of the other subsystems involved. The nonlinear type is created via this dependence, i.e. the matrix of the complete system is blockwise diagonal: $A = \operatorname{diag}\{A_1, \ldots, A_L\}$. The theory of the subsystems is well developed. In particular, they all enjoy conservation laws. It is just these conservation laws that allow to interpret the models as classical circuits. This means that our models possess the property that the amount of various chemicals change during the time but the total amount of them remains

* This work was partially supported by the Grant Agency of the Czech Republic under contract No. 201/05/0453, the Information Society project No. 1ET400300415, and the grant of the Ministry of Education, Youth and Sports of the Czech Republic No. MSM 6840770010.

unchanged. Mathematically this fact is in a sense "visualized" through the form of the matrices of the systems: The off-diagonal elements are nonnegative and all the column sums of them equal zero. This knowledge can be used to develop a theory for the full system which is done in Section 4. It should be noted that our theory is slightly more general and allows to consider nonlinear systems whose matrices are not necessarily blockwise diagonal. Section 3 contains examples from biology and chemistry. Finally, in Section 5 we develop basic ideas for a definition of an overall speed of the action going on in the natural system observed.

2. Creating non-linearity on the basis of linear systems of canonical form

2.1. Linear systems of canonical form

We write $u \geqslant 0$ for $u = (u_1, \ldots, u_N) \in \mathbb{R}^N$ if $u_j \geqslant 0$, $j = 1, \ldots, N$ or equivalently, $u \in \mathbb{R}^N_+$. Similarly, $A \geqslant 0$ if $A = (a_{jk})$ and all the elements $a_{jk} \geqslant 0$, $1 \leqslant j, k \leqslant N$.

Let A be a real (N, N)-matrix where $N \in \mathbb{N}$. Consider the linear system

$$\dot{\eta}(t) = A\eta(t), \quad \eta(t) \in \mathbb{R}^N. \tag{2.1}$$

We say (2.1) is of *canonical form* if A satisfies[1]

$$A_{ij} \geqslant 0, \quad i \neq j, \tag{2.2}$$

$$A_{jj} = -\sum_{\substack{i=1 \\ i \neq j}}^{N} A_{ij}, \quad j = 1, \ldots, N. \tag{2.3}$$

Obviously, we have

$$\eta(t) = \exp\{tA\}\eta(0) \tag{2.4}$$

and hence the *conservation law*

$$\sum_{j=1}^{N} \eta_j(t) = \sum_{j=1}^{N} \eta_j(0) =: C_\eta \tag{2.5}$$

holds for any solution $\eta(t)$ of (2.1) whose matrix A satisfies conditions (2.2) and (2.3).

[1] In all our examples the elements of each infinitesimal generator defined via the matrix A satisfy conditions (2.2) and (2.3). Having this fact in mind we omit writing the diagonal elements and leave the appropriate diagonal space free.

2.2. Finitely many coupled canonical systems

We introduce non-linearity considering $L \in \mathbb{N}$ systems (2.1)

$$\dot{\eta}^{(k)}(t) = A^{(k)}\eta^{(k)}(t), \quad \eta^{(k)}(t) \in \mathbb{R}^{N_k}, \ N_k \in \mathbb{N}, \quad k = 1, \ldots, L, \tag{2.6}$$

where all (N_k, N_k)-matrices $A^{(k)}$ satisfy (2.2) and (2.3). Each of the L individual systems of (2.6) is linear in its unknown $\eta^{(k)}(t)$. The complete system (2.6), however, is non-linear since the entries of $A^{(k)}$ are functions of the components $\eta_j^{(\alpha)}(t)$, $\alpha \neq k$, which are *not* components of $\eta^{(k)}(t)$: $A^{(k)} = A^{(k)}(\gamma^{(k)})$ with $\gamma^{(k)} \in \mathbb{R}^{L_k}$, $k = 1, \ldots, L$, where $\gamma_j^{(k)} = \gamma_j^{(k)}(t)$ denotes a component of $\eta^{(\alpha)}(t)$ with $\alpha \neq k$. Introducing

$$M = \sum_{k=1}^{L} N_k$$

we have

$$1 \leqslant L_k \leqslant M - N_k$$

for the dimension L_k of $\gamma^{(k)}$, $k = 1, \ldots, L$. We combine the components

$$\eta_j^{(k)}(t), \quad j = 1, \ldots, N_k,$$

into a block-vector

$$\eta(t) := (\eta^{(1)}(t), \ldots, \eta^{(L)}(t)) \in \mathbb{R}^N, \tag{2.7}$$

and obtain the *non-linear dynamical system*

$$\dot{\eta}(t) = \operatorname{diag}(A^{(1)}, \ldots, A^{(L)})\eta(t) \tag{2.8}$$

whose solutions $\bar{\eta}(t)$ obviously satisfy the *conservation law*

$$\sum_{k=1}^{L} \sum_{j=1}^{N_k} \bar{\eta}_j^{(k)}(t) = \sum_{k=1}^{L} C_\eta^{(k)}, \quad t \geqslant 0.$$

We begin by describing six examples from Biology resulting in a chemical network. Application of the law of mass action yields the corresponding dynamical evolution in time of all the chemicals involved. This system of differential equations is always of the above form (2.6) with matrices of canonical form as described in Subsection 2.1. It seems that all chemical networks follow a dynamical evolution of the type described in Subsection 2.1 at least after some additions of dummy variables that do not change the basic dynamics of the other dynamical variables.

3. Examples

3.1. Michaelis-Menten kinetics

Our first system comes from Michaelis-Menten kinetics which follows the network

$$X + E_0 \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} E_0 + P. \tag{3.1}$$

We have $L = 2$,

$$\begin{cases} N_1 = 2\colon\ \eta^{(1)} = (e_0, e_1), & N_2 = 3\colon\ \eta^{(2)} = (x, e_1, p), \\ A^{(1)} = \begin{bmatrix} & \kappa_0 + k_{-0} \\ k_0 x & \end{bmatrix}, & A^{(2)} = \begin{bmatrix} & k_{-0} & 0 \\ k_0 e_0 & & 0 \\ 0 & \kappa_0 & \end{bmatrix}, \\ L_1 = 1\colon\ \gamma^{(1)} = (x), & L_2 = 1\colon\ \gamma^{(2)} = (e_0). \end{cases} \tag{3.2}$$

Here and in the sequel capital letters denote chemical species (E_0, E_1, X, P) and the respective small letters $(e_0(t), e_1(t), x(t), p(t))$ the corresponding concentrations at time $t \geqslant 0$. We leave a blank space for the diagonal elements since they are constructed as the negatives of the column sums according to (2.3) throughout. The network (3.1) describes a substrate X being transformed into a product P by means of an enzyme E_0 which has one binding side for X to form a complex E_1, the so called loaded form of the enzyme E_0.

3.2. The transport $B =$ **pyruvat** $\to D =$ **lactat**

Here the network is

$$\begin{cases} A + E_0 \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} E_1, \\ B + E_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_2 \overset{\kappa}{\rightharpoonup} E_0 + D, \\ B + E_0 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E_3. \end{cases} \tag{3.3}$$

We have $L = 3$ and

$$\begin{cases} N_1 = 4\colon\ \eta^{(1)} = (e_0, e_1, e_2, e_3), \\ A^{(1)} = \begin{bmatrix} & k_{-0} & \kappa & k_{-2} \\ k_0 a & & k_{-1} & 0 \\ 0 & k_1 b & & 0 \\ k_2 b & 0 & 0 & \end{bmatrix}, \\ L_1 = 2\colon\ \gamma^{(1)} = (a, b), \end{cases} \tag{3.4}$$

$$
\begin{cases}
N_2 = 4\colon\ \eta^{(2)} = (b, e_2, e_3, d), \\
A^{(2)} = \begin{bmatrix} & k_{-1} & k_{-2} & 0 \\ k_1 e_1 & & 0 & 0 \\ k_2 e_0 & 0 & & 0 \\ 0 & \kappa & 0 & \end{bmatrix}, \\
L_2 = 2\colon\ \gamma^{(2)} = (e_0, e_1),
\end{cases} \tag{3.5}
$$

$$
\begin{cases}
N_3 = 4\colon\ \eta^{(3)} = (a, e_1, e_2, d), \\
A^{(3)} = \begin{bmatrix} & k_{-0} & 0 & 0 \\ k_0 e_0 & & k_{-1} & 0 \\ 0 & k_1 b & & 0 \\ 0 & 0 & \kappa & \end{bmatrix}, \\
L_3 = 2\colon\ \gamma^{(3)} = (e_0, b).
\end{cases} \tag{3.6}
$$

The action (3.3) describes the transformation of pyruvat B into lactat D using an intermediate E_1 which is produced in the first line of the network. The basic step in the second line of (3.3) is in the spirit of Michaelis-Menten kinetics (3.1), however, inhibited by E_0 as pointed out in the last line of (3.3).

The subsequent sections deal with transport phenomena: A substrate X is offered to a cell and tries to find its way into the interior of the latter. To this end the substrate must overcome the outer membrane to reach the periplasm where it is called X_p. Its next step is to penetrate through the inner membrane to finally reach the cytoplasm where we denote X by X_i. If X_a is the name for X in the outside region of the cell the complete action may be described as

$$
X_a \to X_i. \tag{3.7}
$$

We must understand the dynamics of the process if we want to interprete up-take experiments where X_i is measured at consecutive times $t_1 < t_2 < \ldots < t_N$.

The transport system is a so called ABC-transporter supported by binding protein Z in the periplasm and membrane components R attached to the inner membrane. The passage

$$
X_a \to X_p \tag{3.8}
$$

through the outer membrane is supposed to work on the basis of diffusion. We begin in Subsection 3.3 with the often occurring case [7] where the outer membrane is no obstacle to the passage (3.8) so that simply $X_a = X_p$. This describes the core of the action. Here and in the sequel E_j denote intermediates occurring in the course of the action.

3.3. Binding protein dependent ABC-transporter

The corresponding network reads

$$\begin{cases} X_p + Z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_1, \\ E_1 + R \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E_2 \overset{\kappa_1}{\rightarrow} R + Z + X_i, \\ R + Z \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E_3. \end{cases} \tag{3.9}$$

Here $L = 3$ and

$$\begin{cases} N_1 = 4\colon\ \eta^{(1)} = (z, e_1, e_2, e_3), & N_2 = 3\colon\ \eta^{(2)} = (r, e_2, e_3), \\ A^{(1)} = \begin{bmatrix} & k_{-1} & \kappa_1 & k_{-3} \\ k_1 x_p & & k_{-2} & 0 \\ 0 & k_2 r & & 0 \\ k_3 r & 0 & 0 & \end{bmatrix}, & A^{(2)} = \begin{bmatrix} & k_{-2} + \kappa_1 & k_{-3} \\ k_2 e_1 & & 0 \\ k_3 z & 0 & \end{bmatrix}, \\ L_1 = 2\colon\ \gamma^{(2)} = (x_p, r), & L_2 = 2\colon\ \gamma^{(2)} = (z, e_1), \end{cases} \tag{3.10}$$

$$N_3 = 4\colon\ \eta^{(3)} = (x_p, e_1, e_2, x_i),$$
$$A^{(3)} = \begin{bmatrix} & k_{-1} & 0 & 0 \\ k_1 z & & k_{-2} & 0 \\ 0 & k_2 r & & 0 \\ 0 & 0 & \kappa_1 & \end{bmatrix},$$
$$L_3 = 2\colon\ \gamma^{(3)} = (z, r).$$

3.4. ABC-transporter and outer membrane

The network reads [34]

$$\begin{cases} X_a \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} X_p, \\ X_p + Z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_1, \\ E_1 + R \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E_2 \overset{\kappa_1}{\rightarrow} R + Z + X_i, \\ R + Z \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E_3. \end{cases} \tag{3.11}$$

Note the diffusive character of the passage through the outer membrane in the first line. The dynamical equations: $L = 3$ and

$$
\begin{cases}
N_1 = 4\colon\ \eta^{(1)} = (z, e_1, e_2, e_3), & N_2 = 3\colon\ \eta^{(2)} = (r, e_2, e_3), \\
A^{(1)} = \begin{bmatrix} & k_{-1} & \kappa_1 & k_{-3} \\ k_1 x_p & & k_{-2} & 0 \\ 0 & k_2 r & & 0 \\ k_3 r & 0 & 0 & \end{bmatrix}, & A^{(2)} = \begin{bmatrix} & k_{-2} + \kappa_1 & k_{-3} \\ k_2 e_1 & & 0 \\ k_3 z & 0 & \end{bmatrix}, \\
L_1 = 2\colon\ \gamma^{(1)} = (x_p, r), & L_2 = 2\colon\ \gamma^{(2)} = (z, e_1),
\end{cases} \tag{3.12}
$$

$$
N = 5\colon\ \eta^{(3)} = (x_a, x_p, e_1, e_2, x_i),
$$

$$
A^{(3)} = \begin{bmatrix} & k_{-0} & 0 & 0 & 0 \\ k_0 & & k_{-1} & 0 & 0 \\ 0 & k_1 z & & k_{-2} & 0 \\ 0 & 0 & k_2 r & & 0 \\ 0 & 0 & 0 & \kappa_1 & \end{bmatrix},
$$

$$
L_3 = 2\colon\ \gamma^{(3)} = (z, r).
$$

3.5. *ABC*-transporter: Regulation by phosphorus

This example deals with the regulation of our transporter by phosphorus P. We begin with our standard network

$$
\begin{cases}
X_a \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} X_p, \\
X_p + Z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_1, \quad E_1 + R \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E_2 \overset{\kappa_1}{\rightharpoonup} R + Z + X_i, \\
Z + R \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E_3
\end{cases} \tag{3.13}
$$

and add the influence of P

$$
R + P \underset{k_{-11}}{\overset{k_{11}}{\rightleftharpoons}} U \tag{3.14}
$$

on the membrane components R followed by

$$
\begin{cases}
E_1 + U \underset{k_{-12}}{\overset{k_{12}}{\rightleftharpoons}} E_{12} \overset{\kappa_{12}}{\rightharpoonup} R + Z + X_i, \\
Z + U \underset{k_{-13}}{\overset{k_{13}}{\rightleftharpoons}} E_{13}
\end{cases} \tag{3.15}
$$

inhibiting the actual transport of x_i.

The part of the transport in (3.15) is considered to be much less active then the transport step in the third line of (3.13). Here $L = 3$ and

$$N_1 = 6\colon\ \eta^{(1)} := (z, e_1, e_2, e_3, e_{12}, e_{13}),$$

$$A^{(1)} = \begin{bmatrix} & k_{-1} & \kappa_1 & k_{-3} & \kappa_{12} & k_{-13} \\ k_1 x_p & & k_{-2} & 0 & k_{-12} & 0 \\ 0 & k_2 r & & 0 & 0 & 0 \\ k_3 r & 0 & 0 & & 0 & 0 \\ 0 & k_{12} u & 0 & 0 & & 0 \\ k_{13} u & 0 & 0 & 0 & 0 & \end{bmatrix},$$

$$L_1 = 3\colon\ \gamma^{(1)} = (x_p, r, u),$$

$$N_2 = 6\colon\ \eta^{(2)} := (r, e_2, e_3, e_{12}, e_{13}, u),$$

$$A^{(2)} = \begin{bmatrix} & k_{-2} + \kappa_1 & k_{-3} & k_{12} & 0 & k_{-11} \\ k_2 e_1 & & 0 & 0 & 0 & 0 \\ k_3 z & 0 & & 0 & 0 & 0 \\ 0 & 0 & 0 & & 0 & k_{12} e_1 \\ 0 & 0 & 0 & 0 & & k_{13} z \\ k_{11} p & 0 & 0 & k_{-12} & k_{-13} & \end{bmatrix},$$

$$L_2 = 3\colon\ \gamma^{(3)} = (z, e_1, p),$$

$$N_3 = 6\colon\ \eta^{(3)} := (x_a, x_p, e_1, e_2, e_{12}, x_i),$$

$$A^{(3)} = \begin{bmatrix} & k_{-0} & 0 & 0 & 0 & 0 \\ k_0 & & k_{-1} & 0 & 0 & 0 \\ 0 & k_1 z & & k_{-2} & k_{-12} & 0 \\ 0 & 0 & k_2 r & & 0 & 0 \\ 0 & 0 & k_{12} u & 0 & & 0 \\ 0 & 0 & 0 & \kappa_1 & \kappa_{12} & \end{bmatrix},$$

$$L_3 = 3\colon\ \gamma^{(3)} = (z, r, u).$$

3.6. Transport of trehalose

Finally, the combined transport of trehalose D and glucosis G where G only enters the inner part of the cell where it is called G_i. This is a model considered in the PhD. Thesis of I. Hendekovic [17].

The answer of the input G_a, D_a is G_i alone:

$$D_a, G_a \to G_i. \tag{3.16}$$

Let us turn to the details of the network: First, diffusion through the outer membrane

$$D_a \underset{k_{-0}}{\overset{k_0}{\rightleftharpoons}} D_p, \quad G_p \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} G_a. \tag{3.17}$$

Next, the transformation of D_p into G_p

$$D_p + T \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_1 \overset{\kappa_1}{\to} 2G_p + T \tag{3.18}$$

using trehalose T. Furthermore, the formation of an inactive complex E_i via

$$G_p + T \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} E_i. \tag{3.19}$$

Finally, the transfer of G_i

$$G_p + A \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E_2 \overset{\kappa_2}{\to} G_i + A \tag{3.20}$$

into the inner part of the cell. The concentration of T and A is denoted by τ, a, respectively. The dynamical system shows $L = 3$,

$$\begin{cases} N_1 = 8, \\ \eta^{(1)} = (d_a^*, d_p^*, e_1^*, g_p, e_2, g_i, g_a, e_i) = (2d_a, 2d_p, 2e_1, g_p, e_2, g_i, g_a, e_i), \\ A^{(1)} = \begin{bmatrix} & k_{-0} & 0 & 0 & 0 & 0 & 0 & 0 \\ k_0 & & k_{-1} & 0 & 0 & 0 & 0 & 0 \\ 0 & k_1\tau & & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \kappa_1 & & k_{-2} & 0 & k_{-3} & k_{-4} \\ 0 & 0 & 0 & k_2 a & & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \kappa_2 & & 0 & 0 \\ 0 & 0 & 0 & k_3 & 0 & 0 & & 0 \\ 0 & 0 & 0 & k_4\tau & 0 & 0 & 0 & \end{bmatrix}, \\ L_1 = 2\text{: } \gamma^{(2)} = (\tau, a), \end{cases} \tag{3.21}$$

$$\begin{cases} N_2 = 3\text{: } \eta^{(2)} = (\tau, e_1, e_i), & N_3 = 2\text{: } \eta^{(3)} = (a, e_2), \\ A^{(2)} = \begin{bmatrix} & k_{-1} + \kappa_1 & k_{-4} \\ k_1 d_p & & 0 \\ k_4 g_p & 0 & \end{bmatrix}, & A^{(3)} = \begin{bmatrix} & k_{-2} + \kappa_2 \\ k_2 g_p & \end{bmatrix}, \\ L_2 = 2\text{: } \gamma^{(2)} = (d_p, g_p), & L_3 = 1\text{: } \gamma^{(3)} = (g_p). \end{cases} \tag{3.22}$$

4. Theoretical results

Mathematical models considered in this contribution have been developed in a series of papers [4], [5], [6], [9], [10], [11]. The development culminated in two publications [12], [13] where the principle of total concentration conservation law was recognized as decisive for the existence of positive solutions and stationary states. The models investigated in the papers mentioned above are applied in the present study. It is shown that all hypotheses used in [12], [13] are satisfied in all examples of Section 3 and an appropriate theory is established.

4.1. Mathematical structures of the model

Consider the system (2.6) with (2.2), (2.3) and (2.4) for the matrices $A^{(k)}(\gamma^{(k)})$, $k = 1, \dots, L$. In what follows we need finer structure for the entries of $A^{(k)}$, which is suggested by our examples. First, we assume the representation

$$A^{(k)}(\gamma^{(k)}) = B^{(k)} + G^{(k)}(\gamma^{(k)}), \quad k = 1, \dots, L, \tag{4.1}$$

with (N_k, N_k)-matrices $B^{(k)}$, $G^{(k)}(\gamma^{(k)})$. Next we note that in the examples the entries of $G^{(k)}(\gamma^{(k)})$ are polynomials in the components of $\gamma^{(k)}$. For example, take the ABC-transport in Subsection 3.4. Then

$$B^{(1)} = \begin{bmatrix} & k_{-1} & \kappa_1 & k_{-3} \\ 0 & & k_{-2} & 0 \\ 0 & 0 & & 0 \\ 0 & 0 & 0 & \end{bmatrix}, \quad G^{(1)}(\gamma^{(1)}) = \begin{bmatrix} & 0 & 0 & 0 \\ k_1 x_p & & 0 & 0 \\ 0 & k_2 r & & 0 \\ k_3 r & 0 & 0 & \end{bmatrix}, \tag{4.2}$$

$$B^{(2)} = \begin{bmatrix} & k_2 + \kappa_1 & k_{-3} \\ 0 & & 0 \\ 0 & 0 & \end{bmatrix}, \quad G^{(2)}(\gamma^{(2)}) = \begin{bmatrix} & 0 & 0 \\ k_2 e_1 & & 0 \\ k_3 z & 0 & \end{bmatrix}$$

and similarly for $B^{(3)}$ and $G^{(3)}(\gamma^{(3)})$. Here all entries of $G^{(k)}(\gamma^{(k)})$ are polynomials of degree 0 or 1. However, for our theory we can manage with more general conditions.

4.2. Basic hypotheses

Assume N is a positive integer. We denote by $\mathcal{C}([0, +\infty), \mathbb{R}^N)$ the space of all vector-valued continuous functions on the interval $[0, +\infty)$ with the standard maximum norm. The symbol $\mathcal{C}_+([0, +\infty), \mathbb{R}^N)$ denotes the subset of $\mathcal{C}([0, +\infty), \mathbb{R}^N)$ consisting of all nonnegative vector-valued functions on $[0, +\infty)$.

Generally, let $\mathcal{E}$ be a Banach space over the reals and $\mathcal{E}'$ its norm-dual. We write $[u, y']$ instead of $y'(u)$, $u \in \mathcal{E}$, $y' \in \mathcal{E}'$. In case $\mathcal{E} = \mathbb{R}^N$ the symbol $[\cdot, \cdot]$ may coincide with the standard inner product on $\mathbb{R}^N$. This notation cannot lead to any misunderstanding.

Let G be a continuous mapping of the space $\mathcal{C}_+([0,+\infty),\mathbb{R}^N)$ into the space of $N\times N$ M-matrices. Let us denote the space of $N\times N$ matrices with real entries by $\mathbf{B}(\mathbb{R}^N)$.

We are going to consider a family of matrices of the form

$$\{B+G(u(t))\},\quad t\in[0,+\infty).$$

Our investigation will be based on the following hypotheses (i)–(iv).

(i) Matrix $-B$ and each of the matrices $-G(u)$, $u\in\mathbb{R}^N_+$, are M-matrices, i.e.

$$B=-cI+C,\quad C\geqslant 0,\quad c=r(C),$$

and

$$G(u)=-r(H(u)I+H(u),\quad H(u)\geqslant 0,$$

where $r(A)$ denotes the spectral radius of A.

(ii) There exists a componentwise strictly positive vector $\hat{x}'$ such that[2]

$$B^T\hat{x}'=0,\quad [G(u)]^T\hat{x}'=0,\quad \forall\, u\in\mathbb{R}^N_+. \tag{4.3}$$

Property (ii) is called the *total concentration conservation law.*

(iii) The map $G\colon\ \mathbb{R}^N_+\to\mathbf{B}(\mathbb{R}^N)$ is such that there exist positive reals p and c independent of $u\in\mathbb{R}^N_+$ such that for every $u\in\mathbb{R}^N_+$,

$$\|G(u)\|_{\mathbb{R}^N}\leqslant c\|u\|^p_{\mathbb{R}^N}.$$

(iv) For any positive real a there exists a positive constant L_a such that

$$\|G(u)u-G(v)v\|_{\mathbf{B}(\mathbb{R}^N)}\leqslant L_a\|u-v\|_{\mathbb{R}^N}$$

holds for any $u,v\in\mathbb{R}^N_+$ and that $\|u\|\leqslant a$, $\|v\|\leqslant a$.

All pairs $B^{(i)}$, $G^{(i)}(\gamma^{(i)})$ and the block-diagonal matrices in (2.8) of our examples qualify under the assumptions made sofar. Indeed, the entries of $G^{(i)}(u)$ in the examples are polynomials, so that (iii) and (iv) hold. Furthermore,

$$\hat{x}'=(1,1,\ldots,1)$$

for all $B^{(i)}$ and $G^{(i)}(u)$ so that (4.3) follows from the construction (2.7) and (2.8).

Some basic properties of the mathematical model presented in the previous sections are shown to be consequences of the analysis carried out in this section.

[2] The superscript T denotes the transpose.

P r o b l e m (P). Under the hypotheses (i)–(iv), determine all solutions to the Cauchy problem

$$\frac{\mathrm{d}u}{\mathrm{d}t}(t) = Bu(t) + G(u(t))u(t), \quad u(0) = u_0 \in \mathbb{R}^N_+, \ t > 0. \tag{4.4}$$

This means, determine all solutions to the problem

$$u(t) = \mathcal{T}(t; B)u_0 + \int_0^t \mathcal{T}(t-s; B)G(u(s))u(s)\,\mathrm{d}s, \quad t > 0, \ u_0 \in \mathbb{R}^N_+, \tag{4.5}$$

where

$$\mathcal{T}(t; B) = \exp\{Bt\}, \quad t > 0.$$

Proposition 4.1. *Let $\|\cdot\|$ be any norm on $\mathbb{R}^N$ and $U \in \mathbb{R}^N$.*
There exists a positive real κ independent of U (dependent on $\|\cdot\|$) such that

$$\| |U| \| \leqslant \kappa[|U|, \hat{x}'] \tag{4.6}$$

where $\hat{x}'$ comes from the total concentration conservation property (4.3) *and $|U(t)|$ is defined by the formula*

$$|U| = U_+ + U_-, \tag{4.7}$$

U_+, U_- denoting the positive and negative parts of U, respectively.

P r o o f. It is easy to see that the expression

$$\nu(U) = [|U|, \hat{x}']$$

defines a norm on $\mathbb{R}^N$ (actually, ν is the weighted 1-norm). The validity of the statement is then a consequence of the fact that all norms on $\mathbb{R}^N$ are equivalent.

4.3. Global existence, uniqueness and positivity

Problem (P) can be considered as a special case of a more general problem formulated in terms of abstract spaces and operators operating on them and studied in [13]. Here we want to show that the theory developed in [13] possesses broad field of applications and may thus serve as a confirmation of its usefulness in mathematical modelling of problems of Chemistry and Biology.

Since our model is formed via ordinary differential equations, our theory is based on the properties of the exponential of B and its suitable perturbations $G(u)$.

The main goal of this section is a theory covering existence, uniqueness and asymptotic behavior of solutions to Problem (P). While the arguments for proving local

existence of solutions and uniqueness are standard, some less standard arguments are needed for analyzing the asymptotic behavior of solutions and for proving existence of stationary states. In this context we point out the importance of the total concentration conservation law. This law offers a basis for global existence as well as existence of stationary states. In other words, it expresses in a form of a principle the deep influence of the order structure and the Frobenius theory of matrices whose elements are nonnegative reals.

Proposition 4.2. *The following statements* $B1^0$–$B4^0$ *hold true:*

B1^0 *The semigroup of operators* $\{\exp\{Bt\};\ t \geqslant 0\}$ *satisfies the total concentration conservation law, i.e.*

$$\exp\{B^T t\}\hat{x}' = \hat{x}' \quad \forall\, t > 0.$$

B2^0 *Each matrix of the semigroup of operators* $\{\exp\{Bt\}\}$ *is such that* $\exp\{Bt\}u_0 \in \mathbb{R}^N_+$ *whenever* $u_0 \in \mathbb{R}^N_+$, *i.e. all the matrices* $\exp\{B^T t\}$, $t > 0$, *are nonnegative.*

B3^0 *The spectrum* $\sigma(B)$ *contains the eigenvalue* 0 *and to this eigenvalue there corresponds a projection* P_B *represented by a nonnegative matrix.*

B4^0 *There are positive real numbers* α, γ *and* τ *independent of* $t \in [0, +\infty)$ *such that*

$$\|(I - P_B)\mathcal{T}(t; B)\|_{\mathbf{B}(\mathbb{R}^N)} \leqslant \gamma \mathrm{e}^{-\alpha t}, \quad t > \tau. \tag{4.8}$$

P r o o f. B1^0 Obviously we have

$$\mathcal{T}(t; B)^T \hat{x}' = \sum_{k=0}^{\infty} \frac{t^k}{k!} (B^T)^k \hat{x}' = \hat{x}'.$$

B2^0 Let $u \in \mathbb{R}^N_+$. Then, since $B = C - cI, C \geqslant 0$, all components of the vector

$$\mathcal{T}(t; B)u = \exp\{-ct\} \sum_{k=0}^{\infty} \frac{t^k}{k!} C^k u$$

are nonnegative.

Statements B3^0 and B4^0 are consequences of the fact that the matrix $-B$ is a singular M-matrix [3].

Proposition 4.3. *Assume U is a nonnegative solution to Problem* (P). *This solution possesses the following properties:*

G1^0 *Formula*

$$[U(t), \hat{x}'] = [U(0), \hat{x}'], \quad U(0) = u_0,$$

holds for all t in the domain of existence of $U(t)$.

G2^0 *There exists a constant c independent of t in the domain of existence of the solution $\mathcal{D}(U)$ such that the relation*

$$\|U(t)\| \leqslant c \tag{4.9}$$

holds for all $t \in \mathcal{D}(U)$.

G3^0 *For every $u_0 \in \mathbb{R}^N_+$ there exists an interval $J = [0, \sigma]$, $\sigma = \sigma(u_0) \geqslant 0$ and a nonnegative solution U to Problem* (P) *in J.*

G4^0 *Any solution of Problem* (P) *nonnegative in $[0, \sigma]$ can be continued for all $t \in [0, +\infty)$.*

P r o o f. *G*1^0 It is easy to see that

$$[|U(t)|, \hat{x}'] = [U(t), \hat{x}'] = [u_0, \hat{x}']. \tag{4.10}$$

To prove *G*2^0 we apply Proposition 4.1, (4.10) and derive

$$\|U(t)\| \leqslant \kappa[|U(t)|, \hat{x}'] \leqslant \kappa[u_0, \hat{x}'] = c.$$

*G*3^0 The existence of a local solution is guaranteed by the moderate magnitude of the nonlinear term in (4.4) for small t's i.e., by condition (iii). Uniqueness of solutions is guaranteed by the Lipschitz condition (iv). Positivity of $U(t)$ is a consequence of the existence of tight approximate solutions to solutions of Problem (P) the existence of which is shown in Section 4.4, and of nonnegativity of exponentials of matrices with nonnegative off-diagonal elements.

*G*4^0 Assume U is a nonnegative solution of Problem (P) for $t \in [0, \tau]$, $0 \leqslant \tau \leqslant \sigma$. Any continuation of U is a solution to

$$u(t) = \mathcal{T}(t; B)u(\tau) + \int_\tau^t \mathcal{T}(t - s; B)G(u(s))u(s)\,\mathrm{d}s. \tag{4.11}$$

Let $\mathcal{E} = \mathcal{C}([\tau, \tau + \Delta\tau])$ with the $\|\cdot\|_{\mathbb{R}^N}$-maximum norm

$$\|u\|_{\mathcal{E}} = \mathrm{Max}\{\|u(s)\|_{\mathbb{R}^N} :\ s \in [\tau, \tau + \Delta\tau]\} \tag{4.12}$$

and $\mathcal{S}\colon\ \mathcal{E} \to \mathcal{E}$, where

$$[\mathcal{S}(u)](t) = \int_\tau^{\tau + \Delta\tau} \mathcal{T}(t - s; B)G(u(s))u(s)\,\mathrm{d}s, \quad t \in [\tau, \Delta\tau].$$

It is known that the iteration process

$$u^{k+1}(t) - \mathcal{T}(t-s;B)u(\tau) = \int_\tau^t \mathcal{T}(t-s;B)G(u^k(s))u^k(s)\,\mathrm{d}s$$

is norm-convergent if the map $\mathcal{S}$ is Lipschitzian with the Lipschitz constant smaller than 1. In order to show these properties of the map $\mathcal{S}$ we make use of hypotheses (ii) and (iv) from Subsection 4.2 and derive the estimate

$$\begin{cases} \|\mathcal{S}(u) - \mathcal{S}(v)\|_{\mathcal{E}} = \operatorname{Max}\{\|\mathcal{S}(u)(s) - \mathcal{S}(v)(s)\|_{\mathbb{R}^N} :\ s \in [\tau, \tau + \Delta\tau]\} \\ \quad \leqslant \Delta\tau L_\kappa \operatorname{Max}\{\|u(s) - v(s)\|_{\mathbb{R}^N} :\ s \in [\tau, \tau + \Delta]\} = \mathcal{L}\|u - v\|_{\mathcal{E}}. \end{cases} \tag{4.13}$$

Obviously, choosing $\Delta\tau$ appropriately, the constant $\mathcal{L}$ becomes smaller than 1. Thus, we obtain a prolonged solution from the interval $[0, \tau]$ to the interval $[0, \tau + \Delta\tau]$. Let $0 < t < +\infty$ be arbitrary. Since the estimate (4.13) is uniform with respect to τ and $\Delta\tau$, the above prolongation procedure of a solution can be continued till its domain of definition becomes $[0, +\infty)$. The proof is complete. □

Proposition 4.4. *Given an initial vector $u_0 \in \mathbb{R}^N_+$, then any solution U to Problem* (P) *satisfies $U(t) \in \mathbb{R}^N_+$ for all $t > 0$.*

P r o o f. To be able to exploit the nonnegativity of $H(u(t))$ for $u(t) \in \mathbb{R}^N_+$ let us rewrite the original Cauchy problem in the form

$$\dot{u}(t) = Bu(t) - r(H(u(t))u(t)) + H(u(t))u(t), \quad u(0) = u_0,$$

and introduce $w(t)$ by setting

$$u(t) = \exp\{-\varrho t\}w(t), \tag{4.14}$$

where the constant c comes from (4.9) and ϱ satisfying $0 < c \leqslant \varrho \in \mathbb{R}^1$ is taken sufficiently large. Since we know already that any nonnegative solution to Problem (P) is uniformly bounded, we can set

$$\varrho = \varrho(u_0) = \sup\{r(H(u(t)))\colon\ t \in [0, \sigma],\ \sigma \geqslant 0\}.$$

After making substitution (4.14) we see that the original Cauchy problem takes the form

$$\dot{w}(t) = Bw(t) + \varrho w(t) - r(H(\exp\{-\varrho t\}w(t)))w(t) + H(\exp\{-\varrho t\}w(t)))w(t),$$

$w(0) = u_0$.

Applying the Picard-Lindelöf successive approximations with the starting vector $w_0 = u_0$ we have

$$w_{k+1}(t) = \mathcal{T}(t;B)u_0 + \int_0^t \mathcal{T}(t-s;B)\{\varrho - r(H(\exp\{-\varrho s\}w_k(s)))\}w_k(s)\,\mathrm{d}s + \int_0^t \mathcal{T}(t-s;B)H(\exp\{-\varrho s\}w_k(s))w_k(s)\,\mathrm{d}s$$

and conclude that since all the elements of the iteration sequence $\{w_k(t)\}$ are in $\mathbb{R}^N_+$, also its limit $w(t)$ belongs to $\mathbb{R}^N_+$ for all t's for which the iteration process is convergent. This happens to be the case for $0 < t < \delta$, $\delta > 0$. It follows that $w(t)$ being in $\mathbb{R}^N_+$ implies that $u(t) \in \mathbb{R}^N_+$.

This procedure can be applied starting at any $t_0 > 0$ instead of 0 assuming that $u(t) \in \mathbb{R}^N_+$ for $0 < t \leqslant t_0$. This completes the proof. □

4.4. Asymptotic behavior

This subsection is devoted to the description of the asymptotic behavior of the solutions to Problem (P). The properties discovered are then applied in Section 5.

We want to show that positive solutions to Problem (P) get stationary. To this purpose we first define a suitable approximation to the exact solution to Problem (P) and estimate its decay for large times. Then, we use a splitting of the generator of the dynamical system (4.4) into a sum of a linear infinitesimal generator and its perturbation in order to overcome some technical difficulties in the analysis of the behavior of solutions for large times. In doing so the equivalent formulation of Problem (P) as an integral equation of convolution type (4.5) appears to be very useful.

Assume n is a positive integer such that $0 < T = n\tau$, $\tau \in \mathbb{R}^1$. Define

$$\begin{cases} u_\tau(t) = \exp\{t[B + G(u_0)]\}u_0, \quad 0 \leqslant t \leqslant \tau, \\ u_\tau(t) = \exp\{t[B + G(u_\tau(\tau))]\}u_\tau(\tau), \quad \tau \leqslant t \leqslant 2\tau, \\ \qquad \dots \\ u_\tau(t) = \exp\{t[B + G(u_\tau((k-1)\tau))]\}u_\tau((k-1)\tau), \quad (k-1)\tau \leqslant t \leqslant k\tau, \\ \qquad \dots \\ u_\tau(t) = \exp\{t[B + G(u_\tau((n-1)\tau))]\}u_\tau((n-1)\tau), \quad (n-1)\tau \leqslant t \leqslant n\tau, \\ u_\tau(t) = u_\tau(n\tau), \quad n\tau \leqslant t < +\infty. \end{cases} \tag{4.15}$$

By $P_{B+G(u)}$ we denote the Perron eigenprojection of the matrix $B + G(u)$. We set

$$w(t) = u_\tau(t) - P_{B+G(u_\tau(t))}u_\tau(t), \tag{4.16}$$

where u_τ is defined via formulas (4.15).

Assume $\varepsilon > 0$ is chosen arbitrary. Since

$$w(t) = (I - P_{B+G(u_\tau(t))})w(t)$$

the fact that $B + G(u_\tau(t))$ is a negative of an M-matrix implies that the nonzero eigenvalues of the exponential $\exp\{t[B + G(u_\tau(t))]\}$ are generally complex values having the form $\exp\{\mu + \mathrm{i}\nu\}$ with $\mu < 0$ and thus

$$\|w(T)\| < \varepsilon \tag{4.17}$$

for T sufficiently large. Consequently,

$$\lim_{T\to\infty} w(T) = 0. \tag{4.18}$$

Moreover, the decay in the zero-convergence is exponential and thus,

$$\int_0^\infty \|w(t)\| \,\mathrm{d}t < +\infty.$$

R e m a r k 4.1. The vector-function u_τ is just a theoretical tool to estimating some parts of the true solution U such as $w(T)$ and is not proposed for use in practical computations.

A simple continuity argument shows that u_τ is a useful approximation to the true solution to Problem (P). As a result of the above observations we obtain

Proposition 4.5. *Choose $\varepsilon > 0$ arbitrary. Then for any real $0 < T < +\infty$ there is a positive real number $\tau = \tau(\varepsilon)$ such that the relation*

$$\|U(t) - u_\tau(t)\| < \varepsilon$$

holds for all t for which $0 \leqslant t \leqslant T$.

A similar analysis to that as presented above for the solution projected into the complement of the Perron eigenspace of $B + G(U)$ can be done in the same manner for the complement of the Perron eigenspace of $G(U)$. Actually, we have

Proposition 4.6. *Assume u_τ is an approximate solution to a unique nonnegative solution of Problem* (P) *in $[0, +\infty)$ as defined in* (4.15). *Then*

$$\lim_{s\to\infty} (I - P_{G(u_\tau(s))})u_\tau(s) = 0$$

and the speed of convergence is exponential.

Corollary 4.1. *Let U be a unique nonnegative solution of Problem* (P) *in* $[0, +\infty)$. *Then*

$$\lim_{s\to\infty}(I - P_{G(U(s))})U(s) = 0 \tag{4.19}$$

and the speed of convergence in (4.19) *is exponential.*

Having in mind Proposition 4.6 and its Corollary that the decay in the zero-convergence of $\|(I - P_{G(U(s))})U(s)\|$ is exponential we can apply the above observations to prove

Theorem 4.1. *Let $U = U(t)$ denote a unique nonnegative solution to Problem* (P). *Then*

$$\lim_{t\to\infty} U(t) = U(\infty)$$

exists and $U(\infty)$ is a solution of the equation

$$[B + G(U(\infty))]U(\infty) = 0. \tag{4.20}$$

P r o o f. Using the representation of the solution U

$$\begin{aligned} U(t) = {} & \exp\{Bt\}u_0 + (I - P_B)\int_0^t \exp\{(t-s)B\}G(U(s))U(s)\,\mathrm{d}s \\ & + P_B\int_0^t G(U(s))U(s)\,\mathrm{d}s \end{aligned}$$

and letting $t \to +\infty$ we want to deduce the relation

$$\begin{aligned} \lim_{t\to\infty} U(t) = {} & \lim_{t\to\infty} P_B u_0 + \lim_{t\to\infty}\int_0^t (I - P_B)\exp\{(t-s)B\}G(U(s))U(s)\,\mathrm{d}s \\ & + \lim_{t\to\infty}\int_0^t P_B G(U(s))U(s)\,\mathrm{d}s. \end{aligned}$$

The existence of

$$\lim_{t\to\infty}\int_0^t (I - P_B)\exp\{(t-s)B\}G(U(s))U(s)\,\mathrm{d}s$$

follows from B4^0 of Proposition 4.2 and from the uniform boundedness of $G(U(s)$ and $U(s)$.

The existence of

$$\lim_{t\to\infty}\int_0^t P_B G(U(s))U(s)\,\mathrm{d}s$$

is based on the uniform boundedness of $G(U(s))$ and $U(s)$ as in the previous case and on Corollary 4.1.

We conclude that

$$U(\infty) = \lim_{t\to\infty} U(t) = P_B u_0 + \int_0^\infty (I - P_B) \exp\{(t-s)B\} G(U(s))U(s)\,\mathrm{d}s + \int_0^\infty P_B G(U(s))U(s)\,\mathrm{d}s.$$

Relation (4.20) is then obtained as a consequence of the fact that

$$\lim_{s\to\infty} \frac{\mathrm{d}}{\mathrm{d}t} U(s) = 0.$$

The proof is complete. □

4.5. Markovian properties of the models

An interesting though rather elementary property of the models describing our biological/chemical networks consists in the fact that the models are governed by hidden Markov chains. A statement explaining the situation in more detail is

Proposition 4.7. *Assume $\hat{x}' = e = (1,\dots,1)^T \in \mathbb{R}^N$. Assume U is a unique solution of Problem* (P) *and $U(\infty) = \lim_{t\to\infty} U(t)$.*

Then each of the matrices

$$\begin{cases} \exp\{Bt\} & \text{with } B = C - r(C)I, \\ \exp\{G(U(t))t\} & \text{with } G(U(t)) = H(U(t)) - r(H(U(t))I, \\ \exp\{[B + G(U(t))]t\} & \end{cases}$$

is column stochastic for $t \in [0, +\infty)$.

The theory developed in this paper thus possesses a stochastic interpretation though in no way associated with randomness. This fact can be in an efficient way exploited in practical computations [22].

5.1. Towards a definition of speed

The theoretical results obtained in Section 4 allow a singular perturbation argument in order to arrive at an analytical expression which defines the global speed of the action symbolized by a chemical network.

One way of understanding such a network is in terms of an *input-output-system*: there is an input of chemicals and an output of chemicals the concentrations of which at time $t \geqslant 0$ are denoted by $\eta_{\text{in}}(t)$, $\eta_{\text{out}}(t)$, respectively. The action of the network is understood to be the response η_{out} to a trigger η_{in}. All the other chemicals occurring in the network act to bring about this transition.

This view calls for a description in the form

$$\dot{\eta}_{\text{out}}(t) = F(\eta_{\text{in}}(t)), \quad t \geqslant 0 \tag{5.1}$$

along with a conservation law

$$\eta_{\text{in}}(t) + \eta_{\text{out}}(t) = \eta_{\text{in}}(0) + \eta_{\text{out}}(0) =: C, \quad t \geqslant 0. \tag{5.2}$$

Formula (5.1) means that the rate of change of the input is a function of the output alone and (5.2) requires that the sum of input and output concentrations be conserved at all times. The other chemicals in the network just define the machinery sending η_{in} to η_{out}. The input-output focus of the network concentrates on what is being offered to the machinery η_{in} and what comes out of it η_{out}. The rest just defines the *machinery*.

Typical examples are *enzyme actions* of any kind (as an example see (3.1) in Section 3.1): the enzyme E converts the substrate X into Product P:

$$\eta_{\text{in}} = \text{concentration of substrate} \longrightarrow \text{concentration of product} = \eta_{\text{out}}. \tag{5.3}$$

Another group of examples are *membrane actions* (for example (3.9) in Section 3.3 or (3.11) in Section 3.4): a machinery which allows a cell to let substrate X sitting at the outside of the cell to find its way through the periplasm into the cythoplasm where it is called X_i:

$$\eta_{\text{in}} = \text{concentration of X} \longrightarrow \text{concentration of } X_i = \eta_{\text{out}}. \tag{5.4}$$

A typical experiment with an input-output set-up prescribes $\eta_{\text{in}}(0) > 0$ and observes the output-data

$$t_j, \quad \eta_{\text{out}}(t_j), \quad j = 1, \ldots, N. \tag{5.5}$$

The objective of this experiment in the case of an enzyme-action is to learn something about the *efficiency* of the action. Efficiency is measured by the speed of the action: instantaneous response corresponds to high speed and high efficiency. We come to the concept of *speed* for a chemical network in the next Subsection 5.2. In the case of membrane-actions the speed yields information on the affinity of the cell to the substrate. In our paper [14] we used uptake experiments to understand the underlying chemical reaction network. As a result, *speed* is an important concept in Biology.

Here is an example. Let us take Michaelis-Menten kinetics of Subsection 3.1: Put

$$\eta_{\text{in}}(t) := x(t), \quad \eta_{\text{out}}(t) := p(t), \tag{5.6}$$

observe that both variables show up in $\eta^{(2)}$ alone (see (3.2)) and that

$$\dot{\eta}_{\text{out}}(t) = \kappa_0 e_1(t), \tag{5.7}$$

which is not quite the form as required by (5.1). We rather have to express $e_1(t)$ in terms of $\eta_{\text{in}}(t)$:

$$e_1(t) = G(\eta_{\text{in}}(t)). \tag{5.8}$$

This is achieved if we replace

$$\dot{\eta}^{(1)}(t) = A^{(1)}(\eta_{\text{in}}(t))\eta^{(1)}(t), \tag{5.9}$$

($A^{(1)}$ from (3.2)) by

$$\begin{gathered} 0 = A^{(1)}(\eta_{\text{in}}(t))\eta^{(1)}(t), \\ \eta_1^{(1)}(t) + \eta_2^{(1)}(t) = \eta_1^{(1)}(0) + \eta_2^{(1)}(0) =: E_0 \end{gathered} \tag{5.10}$$

yielding

$$\begin{gathered} -k_0\eta_{\text{in}}(t)\eta_1^{(1)}(t) + (\kappa_0 + k_{-0})\eta_2^{(1)}(t) = 0, \\ \eta_1^{(1)}(t) + \eta_2^{(1)}(t) = E_0 \end{gathered}$$

or

$$\begin{aligned} e_0(t) = \eta_1^{(1)}(t) &= E_0 \cdot \frac{\kappa_0 + k_{-0}}{\kappa_0 + k_{-0} + k_0\eta_{\text{in}}(t)}, \\ e_1(t) = \eta_2^{(1)}(t) &= E_0 \cdot \frac{k_0\eta_{\text{in}}(t)}{\kappa_0 + k_{-0} + k_0\eta_{\text{in}}(t)}. \end{aligned} \tag{5.11}$$

Using

$$\overline{K}_0 := \frac{k_0}{\kappa_0 + k_{-0}}$$

we arrive at

$$e_1(t) = E_0 \cdot \frac{\overline{K}_0 \eta_{\text{in}}(t)}{1 + \overline{K}_0 \eta_{\text{in}}(t)}, \tag{5.12}$$

the desired representation (5.8) of $e_1(t)$ in terms of $\eta_{\text{in}}(t)$ alone. Now (5.7) turns into

$$\dot{\eta}_{\text{out}}(t) = \kappa_0 \cdot E_0 \cdot \frac{\overline{K}_0 \eta_{\text{in}}(t)}{1 + \overline{K}_0 \eta_{\text{in}}(t)}, \quad t \geqslant 0, \tag{5.13}$$

which is equation (5.1) with

$$F(\eta) = \kappa_0 \cdot E_0 \cdot \frac{\overline{K}_0 \eta}{1 + \overline{K}_0 \eta}$$

in this case.

Note that (5.10) is the steady-state condition for (5.9)! Hence, (5.9) becomes stationary at any time $t \geqslant 0$ instantaneously adjusting $\eta^{(1)}(t)$ to the current level of $\eta_{\text{in}}(t)$ so that the result is still time dependent. But this is exactly the *pseudo-steady-state solution* of

$$\begin{aligned} \dot{\eta}^{(1)}(t) &= A^{(1)}(\eta_{\text{in}}(t))\eta^{(1)}(t), \\ \dot{\eta}^{(2)}(t) &= A^{(2)}(\eta_1^{(1)}(t))\eta^{(2)}(t), \\ \eta^{(1)} &= (e_0, e_1), \\ \eta^{(2)} &= (\eta_{\text{in}}, e_1, \eta_{\text{out}}) \end{aligned} \tag{5.14}$$

with $A^{(1)}$, $A^{(2)}$ from (3.2): it is the standard steady-state of the $\eta^{(1)}$-system which depends on t due to the dependence on $\eta_{\text{in}}(t)$ and is therefore only *pseudo*-steady! The same solution we obtain if we introduce a *fast timescale*

$$s = \mu t, \quad \mu \gg 1 \tag{5.15}$$

and replace (5.14) by

$$\begin{aligned} \dot{\eta}^{(1)}(s) &= A^{(1)}(\eta_{\text{in}}(t))\eta^{(1)}(s), \\ \dot{\eta}_{\text{in}}(t) &= -k_0 e_0(s)\eta_{\text{in}}(t) + k_{-0} e_1(s), \\ \dot{\eta}_{\text{out}}(t) &= \kappa_0 e_1(s). \end{aligned} \tag{5.16}$$

Here $\dot{\eta}^{(1)}(s)$ is the derivative with respect to the fast time s of (5.15) and $\dot{\eta}_{\text{in}}(t)$ denotes the corresponding derivative with respect to the slow time t. By singular perturbation theory [36] the solution

$$\eta^{(1)}(\mu t) = (e_0(\mu t), e_1(\mu t)),\ \eta_{\text{in}}(t),\ \eta_{\text{out}}(t) \tag{5.17}$$

converges pointwise to the pseudo-steady-state solution described above as $\mu \to +\infty$. Therefore we can replace the solutions of (5.16) by (5.11) and

$$\begin{aligned} \dot{\eta}_{\text{in}}(t) &= E_0\eta_{\text{in}}(t) \cdot \frac{-k_0(\kappa_0 + k_{-0}) + k_{-0}k_0}{\kappa_0 + k_{-0} + k_0\eta_{\text{in}}(t)}, \\ \dot{\eta}_{\text{out}}(t) &= E_0\eta_{\text{in}}(t) \cdot \frac{\kappa_0 k_0}{\kappa_0 + k_{-0} + k_0\eta_{\text{in}}(t)} = -\dot{\eta}_{\text{in}}(t) \end{aligned} \tag{5.18}$$

for μ sufficiently large. Obviously, (5.18) yields

$$\dot{\eta}_{\text{in}}(t) + \dot{\eta}_{\text{out}}(t) = 0 \quad \text{for } t \geqslant 0,$$

thus establishing the conservation law (5.2). Hence, the pseudo-steady-state solution reduces the network to the input-output description (5.1), (5.2). The theory in Section 4 is necessary to prove the convergence of (5.17) as $\mu \to +\infty$ (for Theorem of Vasileva-Tichonov see [36]).

It is important to note that (5.16) describes the experiment and the pseudo-steady-state solution serves as a good approximation to the true solution of (5.16). The advantage of the pseudo-steady-state description is that it allows the interpretation of an input-output-system with closed expressions for the equations of the slow variables. It needs experimental care to really guarantee that the data follow the solution of (5.16).

It is obvious how to reduce the general system (2.6) to (5.1), (5.2): define η_{in}, η_{out} and assume that the dynamical equations for η_{in} and η_{out} occur in the system for $k = L$ in (2.6) alone. Put all components $\eta_j^{(k)}$ except of η_{in}, η_{out} on the fast time scale $s = \mu t$ and let η_{in} and η_{out} evolve on the slow scale t. Finally, construct the pseudo-steady-state solution whose only dynamical equations are of the form (5.1), (5.2).

5.2. Singular perturbation and speed expression

The theory in Section 4 allows the transition to the pseudo-steady-state solution producing the description (5.1), (5.2). But (5.1) says that an input of

$$x = \eta_{\text{in}}(t) \quad \text{at a fixed time } t$$

yields an output of speed

$$\dot{\eta}_{\text{out}}(t) = F(\eta_{\text{in}}(t)) = F(x).$$

We define this derivative to be the speed v of the output in response to the input x:

$$v = F(x), \tag{5.19}$$

which is an equation associating with any input the speed of the underlying chemical network. In particular, we have arrived at (5.13) for the network (3.1), which tells us that

$$v = \kappa_0 E_0 \cdot \frac{\overline{K}_0 x}{1 + \overline{K}_0 x}$$

results, the well known Michaelis-Menten expression widely used in literature of Biology and Chemistry.

The definition of the speed via (5.19) based on the pseudo-steady state procedure of Section 5.1 introduced in the 1913 paper [26] has been generalized to other networks set up to understand different phenomena in up-take mechanisms of cells [7], [8], [14], [15], [25], [35]. The speed of up-take of the substrate is influenced by changes of the chemical network which can be experimentally arranged. The measurements must follow a particular speed expression which can be checked numerically. This is done for different situations in [7], [14], [25], [35] governed by various networks all satisfying the conditions of this paper. For example [14] develops a speed expression for the network in Subsection 3.4 proving that the reaction in the last line of (3.11) needs to be there, which was at that time unclear. The difference in the speed expression of the network (3.11) with and without the last line was compared to actual data with the result that the shorter network could not be the correct answer.

Summarizing, there is a demand for a general theory of particular non-linear dynamical systems satisfying the conditions in this paper. The definition of η_{in} and η_{out} is dictated by the biological and experimental situation: it must be easy to prescribe $\eta_{\text{in}}(0)$ and to measure $\eta_{\text{out}}(t)$ for as many values of t as possible. We conclude with a table of reasonable choices in our examples (see Tab. 1).

network	η_{in}	η_{out}
(3.3)	b	d
(3.9)	$x_a = x_p$	x_i
(3.11), (3.13)	x_a	x_i
(3.16)–(3.20)	d_a or g_a	g_i

Table 1. Choice of η_{in} and η_{out}.

6. Concluding remarks

In the conclusion we may assess the models studied. They have turned out to be very useful not only as a mean for explanation of some mechanisms governing the situations we can meet in real biology but also as a tool for making strategies how to organize practical experiments in order to detect some phenomena in biological research. In our case, inspired by the Michaelis-Kenten kinetics, this is in particular the two-speed situation whose appearance has been discovered in all cases examined in this study also due to our mathematical models.

Acknowledgements. The author express their sincere thanks to the anonymous referees for their comments and suggestions and the linguistic supervisor for his help.

References

[1] *B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts, and J. D. Watson*: Molecular Biology of the Cell. Garland Publishing, New York-London, 1989.
[2] *A. Berman, M. Neumann, R. J. Stern*: Nonnegative Matrices in Dynamic Systems. J. Wiley, New York, 1989.
[3] *A. Berman, R. J. Plemmons*: Nonnegative Matrices in the Mathematical Sciences. Academic Press, New York-San Francisco-London, 1979.
[4] *E. Bohl*: A boundary layer phenomenon for linear systems with a rank deficient matrix. Z. Angew. Math. Mech. *7/8* (1991), 223–231.
[5] *E. Bohl*: Constructing amplification via chemical circuits. In: Biomedical Modeling Simulation (J. Eisarfeld, D. S. Leonis, M. Witken, eds.). Elsevier Science Publ., Amsterdam, 1992, pp. 331–334.
[6] *E. Bohl*: Structural amplification in chemical networks. In: Complexity, Chaos and Biological Evolution (E. Mosekilde, L. Mosekilde, eds.). Plenum Press, New York, 1991, pp. 119–128.
[7] *E. Bohl, W. Boos*: Quantitative analysis of binding protein-mediated ABC transport systems. J. Theor. Biology *186* (1997), 65–74.
[8] *E. Bohl, W. Boos*: Binding protein-dependent transporters: An answer of mathematics to biology. J. Comput. Appl. Math. *63* (1995), 11–25.
[9] *E. Bohl, P. Lancaster*: Perturbation of spectral inverses applied to a boundary layer phenomenon arising in chemical networks. Linear Algebra Appl. *180* (1993), 35–59.
[10] *E. Bohl, I. Marek*: A model of amplification. J. Comput. Appl. Math. *63* (1995), 27–47.
[11] *E. Bohl, I. Marek*: A nonlinear model involving M-operators. An amplification effect measured in the cascade of vision. J. Comput. Appl. Math. *60* (1995), 13–28.
[12] *E. Bohl, I. Marek*: A stability theorem for a class of linear evolution systems. Integral Equations Oper. Theory *34* (1999), 251–269.
[13] *E. Bohl, I. Marek*: Existence and uniqueness results for nonlinear cooperative systems. Oper. Theory, Adv. Appl. *130* (2002), 153–170.
[14] *E. Bohl, H. A. Shuman, W. Boos*: A mathematical treatment of the kinetics of binding protein-dependent transport systems reveals that both loaded and the unloaded binding proteins iteract with the membrane components. Theoret. Biol. *172* (1995), 83–94.
[15] *W. Boos, J. M. Lucht*: Periplasmic binding-protein-dependent ABC transporters. In: Escherichia coli and Salmonella typhimurium. Cellular and Molecular Biology (F. C. Neidhardt, R. Curtiss, J. L. Ingraham, E. C. C. Lin, K. B. Low, B. Magasanik,

W. S. Reznikoff, M. Riley, M. Schaechter, H. E. Umbarger, eds.). American Society of Microbiology, Washington, DC, 1996, pp. 1175–1209.

[16] *A. Cornish-Bowden*: Fundamentals of Enzyme Kinetics. Portland Press, London, 1995.

[17] *I. Hendekovic*: Konstanz University PhD. Thesis, to be completed in 2005.

[18] *E. Hille, R. S. Phillips*: Functional Analysis and Semi-groups. Amer. Math. Soc. Coll. Publ. Vol. XXXI, third printing of Revised Edition, Providence, 1974.

[19] *J. Keener, J. Sneyd*: Mathematical Physiology. Springer-Verlag, New York, 1998.

[20] *M. G. Krein, M. A. Rutman*: Linear operators leaving invariant a cone in a Banach space. Uspekhi mat. nauk III (1948), 3–95 (Russian); AMS Translations *26* (1950).

[21] *J. R. Manson, W. Boos, P. J. Bassfort, B. A. Rasmussen*: Dependence of maltose and chemotaxis on the amount of maltose-binding protein. J. Biol. Chem. *260* (1985), 9727–9733.

[22] *I. Marek*: Schwarz-like methods for approximate solving cooperative systems. Kybernetika *40* (2004), 611–624.

[23] *I. Marek, D. Szyld*: Pseudoirreducible and pseudoprimitive operators. Linear Algebra Appl. *154–156* (1991), 779–791.

[24] *I. Marek, K. Žitný*: Analytic Theory of Matrices for Applied Sciences, Vol. 1. Teubner Texte zur Mathematik, Band 60. Leipzig, 1983.

[25] *G. Merino, W. Boos, H. A. Shuman, E. Bohl*: The inhibition of maltose transport by unliganded form of the maltose-binding protein of Escherichia coli: Experimental findings and mathematical treatment. J. Theor. Biology *177* (1995), 171–179.

[26] *L. Michaelis, M. L. Menten*: Die Kinetic der Invertierung. Biochem. Z. *49* (1913), 333–369.

[27] *J. Monod, J. Wyman, J. P. Changeux*: On the nature of allosteric transitions. A plausible model. J. Mol. Biol. *12* (1965), 88–118.

[28] *I. Sawashima*: On spectral properties of some positive operators. Natur. Sci. Rep. Ochanomizu Univ. *15* (1964), 53–64.

[29] *H. H. Schaefer*: Banach Lattices and Positive Operators. Springer-Verlag, Berlin-Heidelberg-New York, 1974.

[30] *H. H. Schaefer*: Topological Vector Spaces. Springer Verlag, New York-Heidelberg-Berlin, 1971.

[31] *H. Schneider, M. Vidysagar*: Cross-positive matrices. SIAM J. Numer. Anal. *7* (1970), 508–519.

[32] *S. Szmelcman, M. Schwartz, T. J. Silhavy, W. Boos*: Maltose transport in Escherichia coli K12. A comparison of transport kinetics in wild and λ-resistant mutants with the dissociation constant of the maltose-binding protein as measured by fluorescence quenching. Eur. J. Biochem. *65* (1976), 13–19.

[33] *A. E. Taylor, D. C. Lay*: Introduction to Functional Analysis, second edition. J. Wiley, New York, 1980.

[34] *C. Tralau*: Das Upg-Transportsystem in Escherichia coli: Mathematische Modellierung und experimentelle Befunde. Berichte aus der Biologie. Shaker Verlag, Aachen, 2003, Dissertation der Universität Konstanz.

[35] *C. Tralau, G. Greller, M. Pajatsch, W. Boos, E. Bohl*: Mathematical treatment of transport data of bacterial transport systems to estimate limitation in diffusion through the outer membrane. J. Theor. Biol. *207* (2000), 1–14.

[36] *A. B. Vasil'eva*: Asymptotic behaviour of solutions to certain problems involving nonlinear differential equations containing a small parameter multiplying the highest derivatives. Russ. Math. Surv. *18* (1963), 13–84.

Authors' addresses: *E. Bohl*, Universität Konstanz, 784 34 Konstanz, Bundesrepublik Deutschland, e-mail: `bohl@ehrnum10.mathe.uni-konstanz.de`; *Ivo Marek*, School of Civil Engineering, Czech Institute of Technology, Thákurova 7, CZ-166 29 Prague 6, Czech Republic, e-mail: `marek@ms.mff.cuni.cz`.