Centrum voor Wiskunde en Informatica

REPORTRAPPORT

MAS

Modelling, Analysis and Simulation

Modelling, Analysis and Simulation

System theory of rational positive systems for cell reaction networks

J.H. van Schuppen

CWI is the National Research Institute for Mathematics and Computer Science. It is sponsored by the Netherlands Organization for Scientific Research (NWO).
CWI is a founding member of ERCIM, the European Research Consortium for Informatics and Mathematics.

CWI's research has a theme-oriented structure and is grouped into four clusters. Listed below are the names of the clusters and in parentheses their acronyms.

Probability, Networks and Algorithms (PNA)

Software Engineering (SEN)

Modelling, Analysis and Simulation (MAS)

Information Systems (INS)

System theory of rational positive systems for cell reaction networks

ABSTRACT

Biochemical reaction networks are in realistic cases best modeled as rational positive systems. Rational positive systems for biochemical cell reaction networks are defined as dynamic systems which are rational in the state but linear in the inputs. An academic example is provided. The positive orthant is positively or forward invariant for the differential equation of the system. Results are presented for the realizability of an input-output relation as a rational positive systems and for the form of state-space isomorphisms.

System Theory of Rational Positive Systems for Cell Reaction Networks

Jan H. van Schuppen

CWI, P.O. Box 94079, 1090 GB Amsterdam, The Netherlands
J.H.van.Schuppen@cwi.nl

Abstract. Biochemical reaction networks are in realistic cases best modeled as rational positive systems. Rational positive systems for biochemical cell reaction networks are defined as dynamic systems which are rational in the state but linear in the inputs. An academic example is provided. The positive orthant is positively or forward invariant for the differential equation of the system. Results are presented for the realizability of an input-output relation as a rational positive systems and for the form of state-space isomorphisms.

1 Introduction

The purpose of this paper is to present concepts, results, and problems of control and system theory for a subclass of the rational positive systems of which examples have been published as models of biochemical cell reaction networks.

The recent advances in knowledge for the genome of plants, animals, and humans now lead to increased interest in cell biology. Knowledge is needed on how a cell as a functional unit operates biochemically and how the reaction network is influenced by the genome via the enzymes. Metabolic networks, signal transduction networks, and genetic networks have been analyzed by biologists and mathematicians. In principle it is possible to model the complete biochemical reaction network of a cell though this program has so far been carried out only for small compartments of such networks.

Mathematical analysis for such reaction networks then leads to a system of ordinary differential equations or of partial differential equations. Often the ordinary differential equations are of polynomial or of rational form. The number of reactions in a cell can be as high as 15.000 (half the number of estimated genomes) and the number of chemical compounds as high as 20.000. A detailed mathematical analysis

of a mathematical model of the complete cell reaction network may therefore not be possible in the short run. Hence there is an interest to develop procedures to obtain from high-order mathematical models approximations in the form of low-order mathematical models. The formulation of approximate models requires understanding of the dynamics of the system, in particular of its algebraic and graph-theoretic structure and of its rate functions. It is the aim of the author to contribute to this research effort.

In this paper attention is restricted to mathematical models for biochemical cell reaction networks in the form of rational positive systems. These systems are called *positive* because the state vector represents masses or concentrations of chemical compounds and the external input vectors represent inputs into the network of externally available chemical compounds and of enzymes produced by the nucleus of the cell. The dynamics of the system is often modelled as a polynomial map but in this paper attention it is restricted to rational maps (each component equals a quotient of two polynomials). Such a dynamics arises in the model of Michealis-Menten kinetics due to a singular perturbation of a bilinear system. The mathematical model of glycolysis in the unicellular organism Trypanosoma brucei is phrazed almost entirely in terms of a rational positive system and this model is regarded as realistic, see [1, 12].

The subclass of rational positive systems considered in this paper is specific due to the conditions imposed by the modeling of biochemical cell reaction networks. It is precisely because of these physically determined conditions that the subclass merits further study. The properties of such systems differ to a minor extent from those of polynomial systems considered in, for example, [24]. The graph-theoretic and the algebraic structure of rational positive systems make the analysis interesting.

A summary of the main results follows. A brief formulation of the algebraic properties of positive real numbers and of rational positive functions is provided because of their major differences with respect to rational real functions (Section 2). A subclass of rational positive systems is defined (Section 3). An example is formulated and further references to models of biochemical cell reaction networks are mentioned (Section 4). The realization problem for rational positive systems is formulated and theorems on realization and on characterization of isomorphisms are stated (Section 5). The main contributions of the paper are:

- The mathematical framework of rational positive systems for biochemical reaction networks.
- The results on the realization problem for rational positive systems.

2 Rational positive functions

In this section notation for polynomials and rational functions is introduced and discussed.

Denote the set of the integers by $\mathbb{Z}$, the positive integers by $\mathbb{Z}_+$, and the natural numbers by $\mathbb{N} = \{0, 1, \ldots, \}$. For $n \in \mathbb{Z}_+$ denote the subsets $\mathbb{Z}_n = \{1, 2, \ldots, n\} \subset \mathbb{Z}$ and $\mathbb{N}_n = \{0, 1, 2, \ldots, n\} \subset \mathbb{N}$.

Denote the set of the real numbers by $\mathbb{R}$. The set of the *positive real numbers* is defined as $\mathbb{R}_+ = [0, \infty)$ and that of the *strictly positive real numbers* by $(0, \infty)$. This terminology is used in the literature and is preferred above the term of 'non-negative real numbers'. As an algebraic structure the set of the positive real numbers is a *semi-ring*, it has the operations of addition and multiplication with neutral elements 0 and 1 for respectively addition and multiplication but it does not have an inverse with respect to addition though it has one with respect to multiplication when attention is restricted to the subset $(0, \infty)$. Note that $\mathbb{R}_+$ is an *integral domain*, defined by the condition that for all $a, b \in \mathbb{R}_+$, $ab = 0$ implies that either $a = 0$ or $b = 0$.

Consider for $n \in \mathbb{Z}_+$ the set of n-tuples of positive real numbers as the *positive vector space* $(\mathbb{R}_+, \mathbb{R}_+^n)$ with the understanding that the first object of this tuple is only a semi-ring as defined above and that vector addition does not have an inverse.

A positive vector space can also be defined geometrically. A *cone* $V \subseteq \mathbb{R}_+^n$ is defined to be a subset such that (1) $V + V \subseteq V$: $\forall v_1, v_2 \in V$, $v_1 + v_2 \in V$; and (2) $\mathbb{R}_+ V \subseteq V$: $\forall v \in V$ and $\forall c \in \mathbb{R}_+$, $cv \in V$. If $S \subseteq \mathbb{R}_+^n$ is a subset then there exists a smallest cone containing this subset, this is called the *cone generated by* S, and the cone is denoted by $\mathrm{cone}(S)$. A cone $V \subseteq \mathbb{R}_+^n$ is said to be *polyhedral cone* if it is the intersection of a finite number of half spaces. This is equivalent with the statement that there exists a finite set of vectors $\{v_1, \ldots, v_m\} \subset \mathbb{R}_+^n$ such that $V = \mathrm{cone}(\{v_1, \ldots, v_m\})$. A finite set of vectors $\{v_1, \ldots, v_m\} \subset \mathbb{R}_+^n$ is said to be *positively dependent* if there exists $i \in \mathbb{Z}_n$ such that v_i is a positive linear combination of the other vectors, $v_i = \sum_{j \in \mathbb{Z}_n \setminus \{i\}} c_j v_j$ where for all $j \in \mathbb{Z}_n \setminus \{i\}, c_j \in \mathbb{R}_+$. It is called *positively independent* otherwise. A finite set of vectors $\{v_1, \ldots, v_m\} \subset \mathbb{R}_+^n$ is said to be a *frame* of a cone $V \subseteq \mathbb{R}_+^n$ if the cone is generated by the set and if the set is positively independent. Finally we can state the geometric interpretation. A subset $V \subseteq \mathbb{R}_+^n$ is a positive vector space if and only if it is a polyhedral cone. In this case the space admits a representation in terms of a frame. For the theory of cones and polyhedral cones, see [9, 19].

For $n \in \mathbb{Z}_+$ denote the set of positive matrices of size $n \times n$ as $\mathbb{R}_+^{n \times n}$. As an algebraic structure this set is a *dioid* because it has neither an inverse with respect to matrix addition nor with respect to matrix multiplication even if attention is restricted to nonsingular matrices (the inverse of a nonsingular positive matrix may have negative elements). However, it is commutative with respect to addition. Note that for all $n \in \mathbb{Z}_+$ with $n > 1$, $\mathbb{R}_+^{n \times n}$ is not an integral domain as the following example shows,

$$A = \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix} \in \mathbb{R}_+^{2 \times 2}, \quad A^2 = 0. \tag{1}$$

Notation and terminology for polynomial functions and rational functions in several variables follows. Fix $n \in \mathbb{Z}_+$, the dimension of the indeterminate, and denote the indeterminate by $x = (x_1, x_2, \ldots, x_n)$. Consider the multi index

$$k = \begin{pmatrix} k_1 & k_2 & \ldots & k_n \end{pmatrix}^T \in \mathbb{N}^n.$$

Note that the vector $k = 0 \in \mathbb{N}^n$ is admitted in the above definition. A *polynomial in n variables with positive coeffficients* is denoted by

$$p(x) = \sum_{k \in \mathbb{N}^n} c_p(k) \prod_{j=1}^{n} x_j^{k(j)} = \sum_{k \in \mathbb{N}^n} c_p(k) x^k, \ \ c_p(k) \in \mathbb{R}_+, \ \forall k \in \mathbb{N}^n,$$

$$p \in \mathbb{R}_+[x_1, \ldots, x_n], \ \text{abbreviated to } \mathbb{R}_+[x].$$

The understanding in the above definition is that there exist only a finite number of nonzero elements in the set $\{c_p(k) \in \mathbb{R}_+, k \in \mathbb{N}\}$. Abuse of notation will be made because $p \in \mathbb{R}_+[x]$ denotes both a polynomial as an algebraic object and the function $p : \mathbb{R}_+^n \to \mathbb{R}_+$.

Note that $\mathbb{R}_+[x]$ as an algebraic structure is a dioid, it has neither an inverse with respect to addition nor an inverse with respect to multiplication. The neutral element with respect to addition is the polynomial $p_0(x) = 0 \in \mathbb{R}_+$ and the neutral element with respect to multiplication is the polynomial $p_1(x) = 1 \in \mathbb{R}_+$. For a polynomial with the above representation define the *total degree* of $p = \sum_k c_p(k) x^k \in \mathbb{R}_+[x]$ as

$$\deg(p) = \max_{\{k \in \mathbb{N}^n \mid c_p(k) \neq 0\}} \sum_{i=1}^{n} k(i) \in \mathbb{N}.$$

Definition 1. *Consider the subset of positive polymials,*

$$\mathbb{R}_{+,1}[x] = \{p \in \mathbb{R}_+[x] \mid c_p(0) = 1\}.$$

The set of units, *the invertible elements, is* $\{1\}$.

An element $p \in \mathbb{R}_+[x]$ is said to be irreducible *if (1) p is not a unit, or, equivalently, $p \neq 1$; and if (2) $p = p_1 p_2$ with $p_1, p_2 \in \mathbb{R}_+[x]$ implies that either $p_1 = 1$ or $p_2 = 1$.*

The subset $\mathbb{R}_+[x]$ is an integral domain if $p \neq 0$ and $q \neq 0$ implies that $pq \neq 0$.

$\mathbb{R}_+[x]$ is an unique factorization domain if (1) for any $q \in \mathbb{R}_{+,1}[x]$ there exists a factorization of the form,

$$q(x) = \prod_{i=1}^{n} p_i(x), \ \forall i \in \mathbb{Z}_n, \ p_i \in \mathbb{R}_{+,1}[x] \ \text{irreducible;}$$

and if (2) the factorization is unique up to a reordering of the factors.

That $\mathbb{R}_{+,1}[x]$ is an integral domain follows directly from the definition of $\mathbb{R}_+[x]$. But $\mathbb{R}_{+,1}[x]$ is not an unique factorization domain as the following example establishes.

Example 1. Consider the following factorizations of the positive polynomial $p \in \mathbb{R}_+[x]$,

$$\begin{aligned} p(x) &= (x + 2b)(x + 3b)(x^2 - bx + 4b^2) \\ &= (x + 2b)(x^3 + 2bx^2 + b^2 x + 12b^3) \\ &= (x + 3b)(x^3 + bx^2 + 2b^2 x + 8b^3), \ \ b \in (0, \infty). \end{aligned}$$

The first factorization is a factorization over $\mathbb{R}$ but not a factorization over $\mathbb{R}_{+,1}$ because of the term $-bx$. Moreover, the quadratic polynomial is irreducible over $\mathbb{R}[x]$

because the discriminant is $D = b^2 - 16b^2 < 0$. The second and the third factorizations are both factorizations over $\mathbb{R}_+ [x]$ and, because of the first factorization, these factors are irreducible. Thus p has two different factorizations into irreducible factors.

Below use is made of an order on vectors in $\mathbb{N}^n$. See [15] for examples of such orders, of which one is the lexicographic order.

Definition 2. *Consider a finite set of positive polynomails $\{p_j \in \mathbb{R}_+ [x], j \in \mathbb{Z}_m\}$. Define the* common multiple *of this set as the positive polynomial $p \in \mathbb{R}_+ [x]$ such that for all $j \in \mathbb{Z}_m$ there exists a positive polynomial $q_j \in \mathbb{R}_+ [x]$ such that $p = q_j p_j$. Define the* least common multiple *of the finite set as the common multiple $p \in \mathbb{R}_+ [x]$ such that for any other common multiple $\bar{p} \in \mathbb{R}_+ [x]$, $\mathrm{order}(p) \leq \mathrm{order}(\bar{p})$. Denote then,*

$$p = \mathrm{lcm}(\{p_j \in \mathbb{R}_+ [x], j \in \mathbb{Z}_m\}, \mathbb{R}_+ [x], \mathrm{order}) = \mathrm{lcm}(\{p_j \in \mathbb{R}_+ [x], j \in \mathbb{Z}_m\}),$$

if the context is understood.

Notation

$$\mathbb{R}_{+,1} [x] = \{p \in \mathbb{R}_+ [x], \; c_p(0) = 1\},$$
$$\mathbb{R}_{+,0} = \{p \in \mathbb{R}_+ [x], \; c_p(0) = 0\}.$$

In this paper attention is restricted to a particular class of rational positive functions for which singularities cannot occur. For this purpose, define

$$\mathbb{R}_+ (x) = \left\{ \frac{p(x)}{q(x)} \mid p(x), q(x) \in \mathbb{R}_+ [x] \right\}, \; \mathbb{R}_+ (x) = \mathbb{R}_+ (x_1, \dots, x_n), \quad (2)$$

$$\mathbb{R}_{+,s} (x) = \left\{ \begin{array}{l} \frac{p(x)}{q(x)} \in \mathbb{R}_+ (x) \mid p(x) = \sum_{k \in \mathbb{N}} c_p(k) x^k, \; c_p(0) = 0, \\ q(x) = \sum_{k \in \mathbb{N}} c_q(k) x^k, \; c_q(0) = 1 \end{array} \right\}. \quad (3)$$

If $p/q \in \mathbb{R}_{+,s} (x)$ then for all $x \in \mathbb{R}_+^n$, $q(x) \geq 1 > 0$ hence the quotient is well defined. Because $\mathbb{R}_+$ is an integral domain, addition and multiplication of elements of $\mathbb{R}_{+,s}$ is well defined and produces elements in $\mathbb{R}_{+,s}$,

$$\frac{p_1(x)}{q_1(x)} + \frac{p_2(x)}{q_2(x)} = \frac{p_1(x)q_2(x) + p_2(x)q_1(x)}{q_1(x)q_2(x)},$$

$$q_1(x)q_2(x) = \sum_{k \in \mathbb{N}} c_{q_1 q_2}(k) x^k, \; c_{q_1 q_2}(0) = c_{q_1}(0)c_{q_2}(0) = 1,$$

$$p_1(x)q_2(x) + p_2(x)q_1(x) = \sum_{k \in \mathbb{N}} c_{p_1 q_2 + p_1 q_2}(k) x^k,$$

$$c_{p_1 q_2 + p_2 q_2}(0) = c_{p_1}(0)c_{q_1}(0) + c_{p_2}(0)c_{q_2}(0) = 0.$$

In the remainder of the paper rational functions $p(x, x_{ex})/q(x, x_{ex})$ are considered for two sets of indeterminates $(x_1, \dots, x_n, x_{ex,1}, \dots, x_{ex,n_{ex}})$. In this case decompose the $k \in \mathbb{N}^{n+n_{ex}}$ vector as $k = (k_x, \; k_{x_{ex}})$ with $k_x \in \mathbb{N}^n$ and $k_{x_{ex}} \in \mathbb{N}^{n_{ex}}$. The following notation will be used,

$$p(x, x_{ex}) = \sum_{k \in \mathbb{N}^n} c_p(k) \prod_{j=1}^{n} x_j^{k_x(j)} \prod_{m=1}^{n_{ex}} x_{ex,m}^{k_{x_{ex}}(m)},$$

$$\deg_{x,ex}(p) = \max_{\{k \in \mathbb{N}^n \,|\, c_p(k) \neq 0\}} [\sum_{i=1}^{n} k_x(i) + \sum_{j=1}^{n_{ex}} k_{x_{ex}}(j)] \in \mathbb{N}.$$

Rational functions on a variety are treated in [6, Section 5.5] while rings of quotients are treated in [17, Chapter 10]. Algorithms for real algebraic geometry are provided in [3].

3 Rational positive systems

Rational positive systems arise as models in biochemical reaction networks as illustrated below. One way in which they arise is as singularly perturbed models of bilinear positive systems.

Definition 3. *A* rational positive systems for a cell reaction network *is defined as a dynamical system, as understood in system theory, defined by the differential equation*

$$\dot{x}(t) = N\mathrm{Diag}(r(x(t), x_{ex}))u(t) + Bv(t), \; x(t_0) = x_0, \tag{4}$$

or, per component $i \in \mathbb{Z}_n$,

$$\dot{x}_i(t) = \sum_{j=1}^{m} (N_{i,j}^+ - N_{i,j}^-) \left[\frac{p_j^+(x(t), x_{ex})}{q_j^+(x(t), x_{ex})} - \frac{p_j^-(x(t), x_{ex})}{q_j^-(x(t), x_{ex})} \right] u_j(t) + B_i v(t) \tag{5}$$

$$= f_i(x(t), x_{ex}, v(t), u(t)), \; x_i(t_0) = x_{i,0},$$

$$z(t) = H\mathrm{Diag}(r(x(t), x_{ex}))u(t), \tag{6}$$

with the definitions,

$$n, \, m \in \mathbb{Z}_+, \; n_v, \, n_{ex}, \, n_z \in \mathbb{N},$$

$$T = [t_0, \infty), \; \textit{the time index set,}$$

$$X = \mathbb{R}_+^n, \; \textit{the state set,}$$

$$X_{ex} = \mathbb{R}_+^{n_{ex}}, \; \textit{the set of external concentrations,}$$

$$V = \mathbb{R}_+^{n_v}, \; \textit{the set of the external input rate,}$$

$$U = \mathbb{R}_+^m, \; \textit{the input set of enzyme concentrations,}$$

$$N \quad \in \mathbb{Z}^{n \times m} \; \textit{called the} \; \text{stoichiometric matrix,}$$

$$\textit{with decomposition,} \; N = N^+ - N^-, \; N^+, N^- \in \mathbb{N}^{n \times m},$$

$$v : T \to V, \; \textit{the external input rate,}$$

$$u : T \to U, \; \textit{an input function,}$$

$$r : X \times X_{ex} \to \mathbb{R}^m, \; \forall j \in \mathbb{Z}_m,$$

$$r_j(x, x_{ex}) = \frac{p_j^+(x, x_{ex})}{q_j^+(x, x_{ex})} - \frac{p_j^-(x, x_{ex})}{q_j^-(x, x_{ex})}, \; (p^+/q^+), (p^-/q^-) \in \mathbb{R}_{+,s}(x, x_{ex}),$$

$$B = \begin{pmatrix} B_1 \\ \vdots \\ B_{n_v} \end{pmatrix} \in \mathbb{N}^{m \times n_v}, \ \forall i \in \mathbb{Z}_{n_v}, \ B_i \in \mathbb{N}^{1 \times n_v},$$

$$\mathrm{Diag}(r(x, x_{ex})) = \mathrm{Diag}((r_1(x, x_{ex})), \ldots, (r_m(x, x_{ex})) \in \mathbb{R}^{m \times m},$$

$$z : T \to \mathbb{R}^{n_z}, \ H \in \mathbb{N}^{n_z \times m},$$

where z represents the outflow rate of the system.

The following conditions are assumed to hold:

1. *For all $j \in \mathbb{Z}_m$, (p_j^+, q_j^+) are assumed to be relatively prime polynomials and, similarly, (p_j^-, q_j^-) are assumed to be relatively prime polynomials.*
2. *For all $i \in \mathbb{Z}_n$, $j \in \mathbb{Z}_m$, $\forall x \in X$ and $\forall x_{ex} \in X_{ex}$,*

$$x_i = 0 \wedge N_{i,j}^+ - N_{i,j}^- > 0 \Rightarrow p_j^-(x, x_{ex}) = 0;$$
$$x_i = 0 \wedge N_{i,j}^+ - N_{i,j}^- < 0 \Rightarrow p_j^+(x, x_{ex}) = 0.$$

3. *For all $i \in \mathbb{Z}_{n_z}$ and $j \in \mathbb{Z}_m$, $\forall x \in X$ and $\forall x_{ex} \in X_{ex}$,*

$$H_{i,j} > 0 \ \Rightarrow \ p_j^-(x, x_{ex}) = 0.$$

4. *The components of r, thus $\{r_j(.), j \in \mathbb{Z}_m\}$, are linear independent functions.*
5. *For $T = [t_0, \infty)$, for any initial condition $x_0 \in \mathbb{R}^n$, any external concentration vector $x \in \mathbb{R}_+^{n_{ex}}$, and any continuous input functions $v : T \to \mathbb{R}_+^{n_v}$ and $u : T \to \mathbb{R}_+^m$ there exists a unique solution $x : T \to \mathbb{R}$ to the ordinary differential equation (4).*

The reader should clearly distinguish between the *external input rate* $v : T \to \mathbb{R}_+^{n_v}$ and the vector of *external concentrations* $x_{ex} \in \mathbb{R}_+^{n_{ex}}$. The external input rate represents a continuous flow of chemical compounds into the cell or part of the cell considered. An example of an external input rate is the flow of water molecules into the cell through the cell boundary. The external concentrations represent masses of concentrations or chemical compounds which are available in abundance and whose values do not change over time depending on the other state variables. Such an external concentration is assumed to be constant over time during the interval considered. In the example presented below, the external concentrations are present in the model while no external input rate is present.

Distinguish also the outflow rate z and the state x.

Comments on the conditions of Definition 3 follow. The first condition is to obtain a mathematically economical expression for the rate functions. If the condition is not met then it can be obtained by deleting common factors. The second condition is necessary and sufficient for the positive orthant $\mathbb{R}_+^n$ to be a positively invariant set of the system, see the next section. The third condition is to enforce that the outflow rate refers to an outflow only, there is no inflow into the systems. The fourth condition is to obtain a nonredundant set of reactions. If the condition is not met then the corresponding enzyme inputs can be combined so that a system with one reaction less is obtained. The last condition is needed for mathematical reasons.

For references on positive systems see [4, 8, 26].

4 Example

There follows an example of a rational positive system. For another example see [1]. The classical example is that of Michaelis-Menten kinetics which is obtained by singular perturbation of a bilinear rate function, see [10, 21].

Example 2. The following small example illustrates the transformation of a mathematical model of the biochemical processes of a cell to a dynamic system. The model is derived from the example described by J.M. Rohwer in [20, p. 32, 37]. See Figure 1. The inputs and state variables are, in terms of the notation used in that
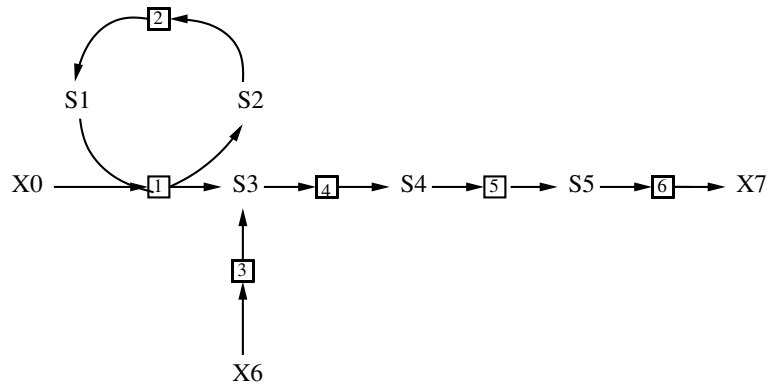

Fig. 1. The biochemical network of the example.

reference:

$$n = 5, \; n_{ex} = 2, \; n_z = 1, \; m = 6,$$
$$x_1 = s_1, \; \ldots, \; x_5 = s_5, \; u_1 = e_1, \; \ldots, \; u_6 = e_6, \; x_{ex,1} = X0, \; x_{ex,2} = X6,$$
$$z = X7.$$

The stoichiometric matrix and the rate functions are:

$$N = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix},$$

$$r_1(x, x_{ex}) = \frac{10 x_{ex,1} x_1}{1 + x_{ex,1} x_1 + x_2 x_3} - \frac{x_2 x_3}{1 + x_{ex,1} x_1 + x_2 x_3}$$

$$= \frac{p_1^+(x, x_{ex})}{q_1^+(x, x_{ex})} - \frac{p_1^-(x, x_{ex})}{q_1^-(x, x_{ex})},$$

$$r_2 = \frac{10 x_2}{1 + x_1 + x_2} - \frac{x_1}{1 + x_1 + x_2},$$

$$r_3 = \frac{5 x_{ex,2}}{1 + x_3 + x_{ex,2}} - \frac{x_3}{1 + x_3 + x_{ex,2}},$$

$$r_4 = \frac{10 x_3}{1 + x_3 + x_4} - \frac{x_4}{1 + x_3 + x_4},$$

$$r_5 = \frac{10 x_4}{1 + x_4 + x_5} - \frac{x_5}{1 + x_4 + x_5}, \quad r_6 = \frac{10 x_5}{1 + x_5},$$

$$H = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \in \mathbb{Z}^{1 \times m}.$$

The resulting dynamic system then has the form

$$\dot{x}(t) = N \, \mathrm{Diag}(r(x(t), x_{ex})) u(t), \; x(t_0) = x_0,$$
$$z(t) = H \mathrm{Diag}(r(x(t), x_{ex})) u(t).$$

Note that for each $i \in \mathbb{Z}_6 = \{1, 2, 3, 4, 5, 6\}$, in the function $r_i : \mathbb{R}_+^n \times \mathbb{R}_+^{n_{ex}} \to \mathbb{R}$ each of the terms in the difference is a rational function in the indeterminates $(x_1, \ldots, x_n, x_{ex,1}, \ldots, x_{ex,n_{ex}})$ of which the numerator and the denominator degrees are equal. Note that for $i = 1$,

$$x_1 = 0 \wedge N_{11} = -1 \Rightarrow p_1^+(x, x_{ex}) = 0;$$
$$x_1 = 0 \wedge N_{12} = +1 \Rightarrow p_2^-(x, n_{ex}) = 0; \text{etc. for } i = 2, \ldots, 5.$$

Biochemical reaction networks are used to represent metabolic networks but also signal transduction network (with as purpose to communication signals), and genetic networks (with as purpose to control the operation of a cell from the nucleus).

Other references on dynamic systems for biochemical cell reaction networks are [7, 11]. For models on polynomial systems see [24]. General references on nonlinear systems as considered in control and system theory include [13, 14, 18, 23]. Rational systems without the positivity condition have been treated in [2, 27].

5 Realization of rational positive systems

The realization problem of system theory aims at studying dynamic systems as relations between input and output functions. The conditions for the existence and

uniqueness of a realization reappear as conditions for the existence of control laws or of observers for such systems. The results of the realization problem are also relevant for identifiability and for system reduction.

Problem 1. *Realization problem for positive rational systems of biochemical reaction networks.* Consider a relation between a positive input function and a positive output function, both sufficiently differentiable,

$$u : T \to \mathbb{R}_+^m, v : T \to \mathbb{R}_+^{n_v}, \; y : T \to \mathbb{R}_+^p,$$
$$0 = f(u(t), u^{(1)}(t), \dots, u^{(r)}(t), v(t), v^{(1)}(t), \dots, v^{(q)}(t),$$
$$y(t), y^{(1)}(t), \dots, y^{(s)}(t)),$$

or a set of such functions. Does there exist a rational positive system and a set of initial conditions $X_0 \subseteq X$, such that, if the positive input u and the external input rate are applied to the system, then the output of the system equals the considered output,

$$\dot{x}(t) = N\mathrm{Diag}(r(x(t)))u(t) + Bv(t), \; x(t_0) = x_0,$$
$$y(t) = Cx(t).$$

If so, classify all such systems.

At the time this paper is written, a few results for Problem 1 have been formulated. The approach is to develop realization theory according to the lines of the references [22, 25]. See also the references on realization theory for semirings, [5, 16]. In this paper attention is restricted to two aspect of the realization problem.

First consider the existence of realizations. The existence of discrete-time and continuous-time polynomial systems has been treated by E.D. Sontag, see the references quoted above. It is known how to formulate realizability conditions for rational systems in terms of polynomial maps. However, the positivity makes this transformation more delicate and the algorithms are quite different.

Theorem 1. *Consider the functions,*

$$T = \mathbb{R}_+, \; u : T \to U = \mathbb{R}_+^m, \tag{7}$$
$$y : T \to Y = \mathbb{R}_+^p, \; y \text{ continuously differentiable,}$$
$$0 = H(y(t), \dot{y}(t), u(t)), \; \forall t \in T, \; H : \mathbb{R}^p \times \mathbb{R}^p \times \mathbb{R}^m \to \mathbb{R}^{n_H}. \tag{8}$$

There exists a rational positive system for a cell reaction network as defined in Definition 3 in the form of,

$$\dot{x}(t) = N\mathrm{Diag}(x(t))u(t), \; x(t_0) = x_0,$$
$$y(t) = x(t),$$

such that the relation between the enzyme concentration u and the output function $y = x$ equals the function H if and only if the relation H can be transformed to

$$q(y(t))\dot{y}_i(t) = \sum_{j=1}^{m} N_{i,j} k_j(y(t))[p_j^+(y(t)) - p_j^-(y(t))]u_j(t), \;\; \forall i \in \mathbb{Z}_p, \qquad (9)$$

$$for \; q \in \mathbb{R}_{+,1}[x], \; k_j \in \mathbb{R}_{+,1}[y], \; p_j^+, p_j^- \in \mathbb{R}_{+,0}, \; \forall i \in \mathbb{Z}_n, \; j \in \mathbb{Z}_m,$$

$$q = \mathrm{lcm}(\{k_j \in \mathbb{R}_+[x], j \in \mathbb{Z}_m\}).$$

Problem 2. *State space isomorphism problem.* Consider the class of rational positive systems,

$$\dot{x}(t) = N\mathrm{Diag}(r(x(t))u(t) + Bv(t), \; x(t_0) = x_0. \qquad (10)$$

Which class of functions $s : \mathbb{R}_+^n \to \mathbb{R}_+^n$, state-space transformations, leave the class of systems invariant? Thus, if $\bar{x}(t) = s(x(t))$ is then the differential equation of $\bar{x}$ identical to that of x?

The usefulness of Problem 2 is that it may assist in formulating the most intrinsic definition of rational positive systems.

Theorem 2. *Consider a rational positive system with output equal to the state vector,*

$$\dot{x}_i(t) = \sum_{j=1}^{m}(N_{i,j}^+ - N_{i,j}^-)\left[\frac{p_j^+(x(t))}{q_j^+(x(t))} - \frac{p_j^-(x(t))}{q_j^-(x(t))}\right]u_j(t),$$

$$x_i(t_0) = x_{i,0}, \; \forall i \in \mathbb{Z}_n.$$

Consider the function $s : \mathbb{R}_+^n \to \mathbb{R}_+^n$. Assume that (1) s is a rational function in the class $\mathbb{R}_{+,s}(x)$; (2) that s is invertible and $s^{-1} : \mathbb{R}_+^n \to \mathbb{R}_+^n$ is also an element of $\mathbb{R}_{+,s}(x)$. Define the new state variable $\bar{x}(t) = s(x(t))$.

(a) Then the differential equation for $\bar{x}$ is also a rational positive system in the class of Definition 3 with representation identical to that of x,

$$\dot{\bar{x}}_i(t) = \sum_{j=1}^{m}(N_{i,j}^+ - N_{i,j}^-)\left[\frac{p_j^+(\bar{x}(t))}{q_j^+(\bar{x}(t))} - \frac{p_j^-(\bar{x}(t))}{q_j^-(\bar{x}(t))}\right]u_j(t), \; \bar{x}_i(t_0) = \bar{x}_{i,0}.$$

if and only if for all $x \in \mathbb{R}_+^n$, $\forall i \in \mathbb{Z}_n$, and $\forall j \in \mathbb{Z}_m$,

$$s'(x)Nr(x) = Nr(x), \;\; \forall x \in X, \qquad (11)$$

$$s'(x)_{ik} = \partial s_i(x)/\partial x_k, \;\; \forall i, k \in \mathbb{Z}_n, \; \forall x \in X, \qquad (12)$$

$$hence \; s'(x)_{ik} \in \mathbb{R}_{+,s}(x).$$

(b) If the graph matrix associated with the system has no cycles then the equation

$$s'(x)N = N,$$

implies that $s'(x) = I$.

(c) If in addition to the assumptions stated above, $s(x) = Mx$ for a monomial matrix $M \in \mathbb{R}_+^{n \times n}$ then the equation (11) implies that $s(x) = x$.

Example 3. Consider Example 2. Consider the equation

$$s'(x)N = N,$$

for $s : X \to X$ satisfying the assumptions of Theorem 2. From the definition of the matrix N one obtains that,

$$s'(x) = \begin{pmatrix} s'_{11}(x) & s'_{11}(x) - 1 & 0 & 0 & 0 \\ s'_{22}(x) - 1 & s'_{22}(x) & 0 & 0 & 0 \\ s'_{31}(x) & s'_{31}(x) & 1 & 0 & 0 \\ s'_{41}(x) & s'_{41}(x) & 0 & 1 & 0 \\ s'_{51}(x) & s'_{51}(x) & 0 & 0 & 1 \end{pmatrix}.$$

There exist functions s satisfying the condition of the above theorem. Consider,

$$f : \mathbb{R}_+ \to \mathbb{R}_+, \quad a, b \in (0, \infty),$$

$$\bar{x} = f(x) = \frac{ax}{1 + bx}, \quad x = f^{-1}(\bar{x}) = \frac{\bar{x}/a}{1 + b/a\bar{x}}.$$

By considering a function $s : \mathbb{R}_+^n \to \mathbb{R}_+^n$ of which each component corresponds to the function f but for different values of the parametres, one obtains a function s satisfying the conditions of the theorem. It is an open problem to classify all functions s satisfying this condition.

6 Concluding remarks

The paper presents the class of rational positive systems as mathematical models of biochemical cell reaction networks. Results are presented for: the realization problem of rational positive systems.

Further research is required for: (1) the decomposition of the system in traps, internal sources, and irreducible subsystems; (2) the calculation and the computation of steady states and of steady outflow rates; (3) the realization problem for rational positive systems including factorization of positive polynomials; and (4) control of rational positive systems.

Acknowledgements

References

1. B.M. Bakker. *Control and regulation of glycolis in Trypanosoma brucei*. PhD thesis, Vrije Universiteit, Amsterdam, 1998.
2. Z. Bartosiewicz. Rational systems and observation fields. *Systems & Control Lett.*, 9:379–386, 1987.
3. S. Basu, R. Pollack, and M.-F. Roy. *Algorithms in real algebraic geometry*. Number 10 in Algorithms and Computation in Mathematics. Springer, Berlin, 2003.
4. A. Berman, M. Neumann, and R.J. Stern. *Nonnegative matrices in dynamic systems*. John Wiley & Sons, New York, 1989.
5. J. Berstel and C. Reutenauer. *Rational series and their languages*. EATCS Monographs on Theoretical Computer Science. Springer-Verlag, 1984.
6. D.A. Cox, J.B. Little, and D. O'Shea. *Ideals, varieties, algorithms: An introduction to computational algebraic geometry and commutative algebra*. Undergraduate Texts in Mathematics. Springer, Berlin, 1992.
7. C. Fall, E. Marland, J. Wagner, and J. Tyson. *Computational cell biology*. Number 20 in Interdisciplinary Mathematics. Springer, New York, 2002.
8. L. Farina and S. Rinaldi. *Positive linear systems: Theory and applications*. Pure and Applied Mathematics. John Wiley & Sons, New York, 2000.
9. M. Gerstenhaber. Theory of convex polyhedral cones. In Tj.C. Koopmans, editor, *Activity analysis of production and allocation*, pages 298–316. Wiley & Sons, New York, 1951.
10. F.G. Heineken, H.M. Tsuchiya, and R. Aris. On the mathematical status of the pseudo-steady state hypothesis of biochemical kinetics. *Math. Biosciences*, 1:95–113, 1967.
11. R. Heinrich and S. Schuster. *The regulation of cellular systems*. Chapman and Hall, New York, 1996.
12. Sandre Helfert, Antonio M. Estévez, Barbara Bakker, Paul Michels, and Christine Clayton. Roles of triosephosphate isomerase and aerobic metabolism in trypanosoma brucei. *Biochem. J.*, 357:117–125, 2001.
13. A. Isidori. *Nonlinear control systems (3rd. ed.)*. Springer, Berlin, 1995.
14. A. Isidori. *Nonlinear control systems II*. Communications and Control Engineering Series. Springer-Verlag, London, 1999.
15. M. Kreuzer and L. Robbiano. *Computational commutative algebra 1*. Springer, Berlin, 2000.
16. W. Kuich and A. Salomaa. *Semirings, automata, languages*. EATCS Monographs on Theoretical Computer Science. Springer-Verlag, 1986.
17. T.-Y. Lam. *Lectures on modules and rings*. Number 189 in Graduate Texts in Mathematics. Springer, Berlin, 1999.
18. H. Nijmeijer and A.J. van der Schaft. *Nonlinear dynamical control systems*. Springer-Verlag, Berlin, 1990.
19. R.T. Rockafellar. *Convex analysis*. Princeton University Press, Princeton, 1970.
20. J.M. Rohwer. *Interaction of functional units in metabolism*. PhD thesis, Vrije Universiteit, Amsterdam, 1997.
21. L.A. Segel and M. Slemrod. The quasi-steady-state assumption: A case study in perturbation. *SIAM Rev.*, 31:446–477, 1989.
22. E.D. Sontag. Realization theory of discrete-time nonlinear systems: I. The bounded case. *IEEE Trans. Circuits & Systems*, 26:342–356, 1979.
23. E.D. Sontag. *Mathematical control theory: Deterministic finite dimensional systems (2nd. Ed.)*. Number 6 in Graduate Text in Applied Mathematics. Springer, New York, 1998.

24. E.D. Sontag. Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction. *IEEE Trans. Automatic Control*, 46:1028–1047, 2001.
25. E.D. Sontag and Y. Rouchaleau. On discrete-time polynomial systems. *Nonlinear analysis*, 1:55–64, 1976.
26. J.M. van den Hof. *System theory and system identification of compartmental systems*. PhD thesis, University of Groningen, Groningen, 1996.
27. Yuan Wang and Eduardo D. Sontag. Algebraic differential equations and rational control systems. *SIAM J. Control & Opt.*, 30:1126–1149, 1992.