Computing reaction kinetic realizations of positive nonlinear systems using mixed integer programming

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Abstract: The reaction kinetic realizations of nonnegative polynomial systems are studied in this paper. It is briefly reviewed that a wide class of positive systems can be written in or simply transformed to kinetic form. Based on the structure of kinetic realizations, valuable information can be obtained about the dynamical properties of the investigated systems using the results of chemical reaction network theory (CRNT). Since the realizations of a given system can have many different structures, mixed integer linear programming is used to generate the ones with required properties (i.e. the minimal/maximal number of reactions or complexes).

Keywords: nonlinear systems, positive systems, chemical reaction networks, mixed integer optimization

1. INTRODUCTION

Positive (nonnegative) systems are characterized by the property that all state variables remain positive (nonnegative) if the trajectories start in the positive (nonnegative) orthant. Thus, positive systems play an important role in fields such as chemistry, economy, population dynamics or even in transportation modeling where the state variables of the models are often physically constrained to be nonnegative (Farina and Rinaldi, 2000).

Chemical Reaction Networks (CRNs) form a wide class of positive (or nonnegative) systems attracting significant attention not only among chemists but in numerous other fields such as physics, or even pure and applied mathematics where nonlinear dynamical systems are considered (Érdi and Tóth, 1989). Beside pure chemical reactions, CRNs are often used to model the dynamics of intracellular processes, metabolic or cell signalling pathways. The increasing interest towards reaction networks in the systems and control community is clearly shown by recent tutorial and survey papers (Sontag, 2001; Chellaboina et al., 2009).

One of the most important results in the analysis of CRNs was the definition of *deficiency* which is a nonnegative integer depending on the number of complexes and the properties of interconnections in the reaction graph (i.e. it is a purely structural property) (Feinberg, 1987). The *deficiency zero* property for a sufficiently reversible (more precisely: "weakly reversible") reaction network guarantees the global stability of the solutions of the system with a known Lyapunov function (Feinberg, 1987). In (Otero-Muras et al., 2008), an important link has been created between the structural properties of reaction networks and the possibility of *dissipative-Hamiltonian description* known from modern control theory.

It is known from the so-called "fundamental dogma of chemical kinetics" that reaction networks with different graph structures and even with different sets of complexes might generate identical dynamical system models (i.e. sets of differential equations). This means that CRNs with structurally very different reaction mechanisms can show exactly the same behaviour in the state space that is usually the space of chemical specie concentrations. However, many strong analysis results of chemical reaction network theory (CRNT) depend on the graph structure of the studied CRN. There is a clear need therefore to define and search for distinguished structures among the possible alternatives. The integration of logical expressions into mixed integer programming problems (Bemporad and Morari, 1999) has opened the possibility to formulate the computation of certain reaction structures with advantageous properties as optimization problems (Szederkényi, 2010b).

During the analysis of CRNs, the reaction structure is assumed to be given (at least partially) in vast majority of the cases. For the dynamic analysis of nonnegative polynomial systems, we will go in the opposite direction: the ODEs of the (not necessarily chemically originated) nonnegative system are given, and such kinetic reaction structures are searched for, that can be useful for determining important dynamical properties of the original system using the tools of CRNT.

2. BASIC NOTIONS

2.1 Positive (nonnegative) systems

The concepts and basic results in this subsection are mostly taken from (Chellaboina et al., 2009). A function

$f = [f_1 \ \dots \ f_n]^T : [0,\infty)^n \to \mathbb{R}^n$ is called *essentially nonnegative* if, for all $i = 1,\dots,n$, $f_i(x) \geq 0$ for all $x \in [0,\infty)^n$, whenever $x_i = 0$. In the linear case, when $f(x) = Ax$ the necessary and sufficient condition for essential nonnegativity is that the off-diagonal entries of A are nonnegative (such a matrix is often called a *Metzler-matrix*).

Consider an autonomous nonlinear system

$$\dot{x} = f(x), \ x(0) = x_0 \tag{1}$$

where $f : \mathcal{X} \to \mathbb{R}^n$ is locally Lipschitz, $\mathcal{X}$ is an open subset of $\mathbb{R}^n$ and $x_0 \in \mathcal{X}$. Suppose that the nonnegative orthant $[0,\infty)^n = \mathbb{R}^n_+ \subset \mathcal{X}$. Then the nonnegative orthant is invariant for the dynamics (1) if and only if f is essentially nonnegative.

2.2 Nonlinear systems described by mass action kinetics

The overview in this subsection is largely based on (Szederkényi, 2010b). A CRN obeying the mass action law is a closed system under isothermal and isobaric conditions, where chemical species $\mathbf{X}_i$, $i = 1,...,n$ take part in r chemical reactions. The concentrations of the species denoted by x_i, $(i = 1,...,n)$ form the state vector, i.e. $x_i = [\mathbf{X}_i]$. The *elementary reaction steps* have the following form:

$$\sum_{i=1}^{n} \alpha_{ij}\mathbf{X}_i \to \sum_{i=1}^{n} \beta_{ij}\mathbf{X}_i, \quad j = 1,...,r \tag{2}$$

where α_{ij} is the so-called *stoichiometric coefficient* of component $\mathbf{X}_i$ in the jth reaction, and $\beta_{i\ell}$ is the stoichiometric coefficient of the product $\mathbf{X}_\ell$. The linear combinations of the species in eq. (2), namely $\sum_{i=1}^{n} \alpha_{ij}\mathbf{X}_i$ and $\sum_{i=1}^{n} \beta_{ij}\mathbf{X}_i$ for $j = 1,\dots,r$ are called the *complexes* and are denoted by $C_1, C_2, \dots, C_m$. Note that *the stoichiometric coefficients are always nonnegative integers in classical reaction kinetic systems.* The reaction rates of the individual reactions can be described as

$$\rho_j = k_j \prod_{i=1}^{n} [\mathbf{X}_i]^{\alpha_{ij}} = k_j \prod_{i=1}^{n} x_i^{\alpha_{ij}} \quad , \quad j = 1,...,r \tag{3}$$

where $k_j > 0$ is the *reaction rate constant* of the jth reaction.

If the reactions $C_i \to C_j$ and $C_j \to C_i$ take place at the same time in a reaction network for some i, j then this pair of reactions is called a reversible reaction (but it will be treated as two separate elementary reactions).

Similarly to (Feinberg, 1979), we can assign the following directed graph (see, e.g. (Bang-Jensen and Gutin, 2001)) to the reaction network (2) in a straightforward way. The directed graph $D = (V_d, E_d)$ of a reaction network consists of a finite nonempty set V_d of vertices and a finite set E_d of ordered pairs of distinct vertices called directed edges. The vertices correspond to the complexes, i.e. $V_d = \{C_1, C_2, \dots C_m\}$, while the directed edges represent the reactions, i.e. $(C_i, C_j) \in E_d$ if complex C_i is transformed to C_j in the reaction network. The reaction rate coefficients k_j for $j = 1,\dots,r$ in (3) are assigned as positive weights to the corresponding directed edges in the graph. Where it is more convenient, the notation k'_{ij} will be used for denoting the reaction rate coefficient corresponding to the reaction $C_i \to C_j$. A set of complexes $\{C_1, C_2, \dots, C_k\}$ is a *linkage class* of a reaction network if the complexes of the set are linked to each other in the reaction graph but not to any other complex (Feinberg, 1987).

There are several possibilities to represent the dynamic equations of mass action systems (see, e.g. Feinberg (1979)). The most advantageous form for our purposes is the one that is used e.g. in Lecture 4 of Feinberg (1979), i.e.

$$\dot{x} = Y \cdot A_k \cdot \psi(x) \tag{4}$$

where $x \in \mathbb{R}^n$ is the concentration vector of the species, $Y \in \mathbb{R}^{n\times m}$ stores the stoichiometric composition of the complexes, $A_k \in \mathbb{R}^{m\times m}$ contains the information corresponding to the weighted directed graph of the reaction network, and $\psi : \mathbb{R}^n \mapsto \mathbb{R}^m$ is a monomial-type vector mapping defined by

$$\psi_j(x) = \prod_{i=1}^{n} x_i^{y_{ij}}, \quad j = 1,\dots,m \tag{5}$$

where $y_{ij} = [Y]_{ij}$. The exact structure of Y and A_k is the following. The ith column of Y contains the composition of complex C_i, i.e. Y_{ji} is the stoichiometric coefficient of C_i corresponding to the specie $\mathbf{X}_j$. A_k is a column conservation matrix (i.e. the sum of the elements in each column is zero) defined as

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1}^{m} k'_{il}, & \text{if } i = j \\ k'_{ji}, & \text{if } i \neq j \end{cases} \tag{6}$$

In other words, the diagonal elements $[A_k]_{ii}$ contain the negative sum of the weights of the edges starting from the node C_i, while the off-diagonal elements $[A_k]_{ij}$, $i \neq j$ contain the weights of the directed edges (C_j, C_i) coming into C_i. Based on the above properties, it is appropriate to call A_k the *Kirchhoff matrix* of a reaction network.

To handle the exchange of materials between the environment and the reaction network, the so-called "zero-complex" can be introduced and used which is a special complex where all stoichiometric coefficients are zero i.e., it is represented by a zero vector in the Y matrix Feinberg (1979).

We can associate an n-dimensional vector with each reaction in the following way. For the reaction $C_i \to C_j$, the corresponding *reaction vector* denoted by h_k is given by

$$h_k = [Y]_{\cdot,j} - [Y]_{\cdot,i} \tag{7}$$

where $[Y]_{\cdot,i}$ denotes the ith column of Y. Similarly to reaction rate coefficients, whenever it is more practical, h'_{ij} denotes the reaction vector corresponding to the reaction $C_i \to C_j$.

The *rank* of a reaction network denoted by s is defined as the rank of the vector set $\{h_1, h_2 \dots, h_r\}$ where r is the number of reactions.

The deficiency d of a reaction network is defined as (Feinberg, 1979, 1987)

$$d = m - l - s \tag{8}$$

where m is the number of complexes in the network, l is the number of linkage classes and s is the rank of the reaction network.

A reaction network is called *reversible*, if each of its reactions is a reversible reaction. A reaction network is called

weakly reversible, if each complex in the reaction graph lies on at least one directed cycle (i.e. if complex C_j is reachable from complex C_i on a directed path in the reaction graph, then C_i is reachable from C_j on a directed path). An important point of the well-known *Deficiency Zero Theorem* (Feinberg, 1987) says that the ODEs of a weakly reversible deficiency zero CRN are globally stable with a known logarithmic Lyapunov function for all positive values of the reaction rate coefficients. Therefore (among other realization problems) it is of interest whether we can find a weakly reversible deficiency zero kinetic realization of a nonnegative polynomial system.

Using the notation $M = Y \cdot A_k$, eq. (4) can be written in the compact form

$$\dot{x} = M \cdot \psi(x) \tag{9}$$

The invariance of the nonnegative orthant for CRN dynamics is shown e.g. in (Chellaboina et al., 2009).

2.3 Mixed integer linear programming

A special subset of optimization problems is the class of Mixed Integer Linear Programs (MILPs) where the objective function and the constraints are linear functions of the decision variables. A mixed integer linear program with k variables (denoted by $w \in \mathbb{R}^k$) and p constraints can be written as (Nemhauser and Wolsey, 1988):

$$\begin{aligned} &\text{minimize } c^T w \\ &\text{subject to:} \\ &A_1 w = b_1 \\ &A_2 w \leq b_2 \\ &l_i \leq w_i \leq u_i \text{ for } i = 1, \ldots, k \\ &w_j \text{ is integer for } j \in I,\ I \subseteq \{1, \ldots, k\} \end{aligned} \tag{10}$$

where $c \in \mathbb{R}^k$, $A_1 \in \mathbb{R}^{p_1 \times k}$, $A_2 \in \mathbb{R}^{p_2 \times k}$, and $p_1 + p_2 = p$.

If all the variables can be real, then (10) is a simple linear programming problem that can be solved in polynomial time. However, if any of the variables is integer, then the problem becomes NP-hard. In spite of this, there exist a number of free (e.g. YALMIP or the GNU Linear Programming Kit) and commercial (such as CPLEX or TOMLAB) solvers that can efficiently handle many practical problems.

A propositional logic problem, where a statement denoted by S must be proved to be true given a set of compound statements containing so-called literals $S_1, \ldots, S_n$, can be solved by means of a linear integer program. For this, logical variables denoted by δ_i ($\delta_i \in \{0, 1\}$) must be associated with the literals S_i. Then the original compound statements can be translated to linear inequalities involving the logical variables δ_i (Raman and Grossmann, 1994; Bemporad and Morari, 1999). This theoretical background will be used in the following section to compute different kinetic realizations of polynomial systems in section 3.2.

3. REALIZATION OF NONLINEAR SYSTEMS IN REACTION KINETIC FORM

3.1 Kinetic realizability of positive (nonnegative) polynomial systems

An autonomous polynomial nonlinear system of the form (1) is called *kinetically realizable* or simply *kinetic*, if a mass action reaction mechanism given by eq. (4) can be associated to it that exactly realizes its dynamics, i.e. $f(x) = Y \cdot A_k \cdot \psi(x)$ where ψ contains the monomials, matrix Y has nonnegative integer elements and A_k is a valid Kirchhoff matrix (see section 2.2 for its properties). In such a case, the pair (Y, A_k) will be called a *realization* of the system (9) (note that Y contains all information about the composition of the monomials in ψ in the case of mass-action dynamics). As it is expected from linear algebra, the same polynomial system may have many parametrically and/or structurally different realizations, and this is particularly true for kinetic systems coming from application domains other than chemistry. The problem of kinetic realizability of polynomial vector fields was first examined and solved in (Hárs and Tóth, 1981) where the constructive proof contains a realization algorithm that produces the directed graph of a possible associated mass action mechanism. According to (Hárs and Tóth, 1981), the necessary and sufficient condition for kinetic realizability is that all coordinates functions of the right hand side of (1) must have the form

$$f_i(x) = -x_i g_i(x) + h_i(x),\ i = 1, \ldots, n \tag{11}$$

where g_i and h_i are polynomials with nonnegative coefficients.

The very short description of the realization algorithm presented in (Hárs and Tóth, 1981) is the following. Let us write the polynomial coordinate functions of the right hand side of a kinetic system (1) as

$$f_i(x) = \sum_{j=1}^{r_i} m_{ij} \prod_{k=1}^{n} x^{b_{jk}} \tag{12}$$

where r_i is the number of monomial terms in f_i. Let us denote the transpose of the ith standard basis vector in $\mathbb{R}^n$ as e_i and let $B_j = [b_{j1}\ \ldots\ b_{jn}]$.

Algorithm 1 by Hárs and Tóth (1981)
For each $i = 1, \ldots, n$ and for each $j = 1, \ldots, r_i$ do:
(1) $C_j = B_j + \text{sign}(m_{ij}) \cdot e_i$
(2) Add the following reaction to the graph of the realization

$$\sum_{k=1}^{n} b_{jk} \mathbf{X}_k \longrightarrow \sum_{k=1}^{n} c_{jk} \mathbf{X}_k$$

with reaction rate coefficient $|m_{ij}|$, where $C_j = [c_{j1}\ \ldots\ c_{jn}]$.

Roughly speaking, condition (11) means that kinetic systems cannot contain negative cross-effects. From this, it is easy to see that all nonnegative linear systems are kinetic, since a linear system characterized by a Metzler matrix where only the diagonal elements can have negative coefficients is obviously in the form of (11). Moreover, classical Lotka-Volterra systems (that are known to be nonnegative) with the equations

$$\dot{x}_i = x_i(b_i + \sum_{j=1}^{n} a_{ij} x_j), \quad i = 1, \ldots, n \tag{13}$$

with $a_{ij}, b_i \in \mathbb{R}$ are always kinetic according to the condition (11). However, there are many essentially nonnegative polynomial systems that are not directly kinetic, since

some of the monomials in f_i that do not contain x_i have negative coefficients. Such an example is shown in the following equations

$$\begin{aligned} \dot{x}_1 &= -x_1x_2 + x_2^2 - 4x_2 + 4 \\ \dot{x}_2 &= x_2^2 + x_1^2 - 2x_1 + 2 \end{aligned} \tag{14}$$

To circumvent this problem, one possible way is to embed (14) into the LV class shown in (13), that can be done algorithmically (Hernández-Bermejo and Fairén, 1995). However, this solution usually results in the significant dimension increase of the state space (i.e. in the increase of species in the corresponding kinetic realization). If the equations and the possible initial conditions guarantee that all state variables remain strictly positive throughout the solutions, then a more advantageous method is a simple state-dependent time-rescaling (see, e.g Szederkényi et al. (2005)) of the equations in the following way

$$dt = \prod_{i=1}^{n} x_i dt' \tag{15}$$

Applying (15), the equations of the original system (14) are written as

$$\begin{aligned} x_1' &= -x_1^2x_2^2 + x_1x_2^3 - 4x_1x_2^2 + 4x_1x_2 \\ x_2' &= x_1x_2^3 + x_1^3x_2 - 2x_1^2x_2 + 2x_1x_2 \end{aligned} \tag{16}$$

where $x_i' = \frac{dx_i}{dt'}$. It is easy to see that eq. (16) is kinetic. The reaction network obtained by using **Algorithm 1** can be seen in Fig. 1 where the reaction rate coefficients are written close to the arrows representing reactions. It is important to emphasize that as a result of the time-rescaling, the number of state variables (species) and that of the monomials (complexes) remain the same as in the original system. Moreover, such a time-rescaling preserves the important qualitative properties of the system and the solutions, since t' is a strictly monotonously increasing continuous and invertible function of t.

As we can see later in section 4, **Algorithm 1** usually produces a redundant reaction structure with more reactions and/or complexes than the minimal number needed for the kinetic representation of the studied polynomial system. Therefore, mixed integer linear programming will be applied as a useful tool to select required structures from the possible reaction graphs.

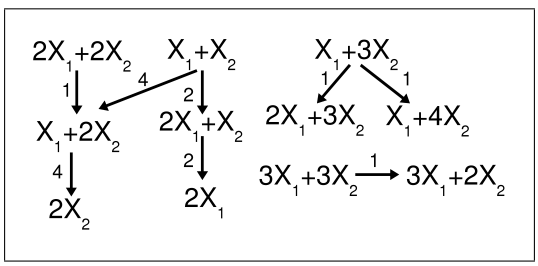

Fig. 1. Reaction network realizing eq. (16)

3.2 Computing realizations of kinetic systems with given properties using mixed integer programming

This subsection summarizes the basic principles for determining certain realizations of kinetic systems using MILP, the details can be found in (Szederkényi, 2010b).

Problem setup, known and unknown data The starting point is that a kinetic polynomial system of the form (9) is given with its parameters. This means that M is known, the stoichiometrix matrix Y is also known from the monomials of ψ, and we would like to determine the Kirchhoff matrix $A_k \in \mathbb{R}^{m\times m}$ that fulfils given requirements.

The characteristics of the mass-action dynamics can be expressed in the form of the following equality and inequality constraints:

$$Y \cdot A_k = M \tag{17}$$

$$\sum_{i=1}^{m} [A_k]_{ij} = 0, \quad j = 1, \ldots, m \tag{18}$$

$$[A_k]_{ij} \geq 0, \quad i, j = 1, \ldots, m, \quad i \neq j \tag{19}$$

$$[A_k]_{ii} \leq 0, \quad i = 1, \ldots, m \tag{20}$$

where the decision variables are the elements of A_k. Clearly, constraints (18)-(20) express that we are searching for a valid Kirchhoff connection matrix. To make the forthcoming optimization problems computationally tractable, appropriate upper and lower bounds are introduced for the elements of A_k as

$$0 \leq [A_k]_{ij} \leq l_{ij}, \quad i, j = 1, \ldots, m, \quad i \neq j \tag{21}$$

$$l_{ii} \leq [A_k]_{ii} \leq 0, \quad i = 1, \ldots, m. \tag{22}$$

Determining realizations with the minimal/maximal number of reactions. In this problem set, we are searching for such A_k that contains the minimal/maximal number of nonzero off-diagonal elements. For this, we introduce logical variables denoted by δ and construct the following compound statements

$$\delta_{ij} = 1 \leftrightarrow [A_k]_{ij} > \epsilon, \quad i, j = 1, \ldots, m, \quad i \neq j \tag{23}$$

where the symbol "$\leftrightarrow$" represents "if and only if", and $0 < \epsilon \ll 1$ (i.e. elements of A_k below ϵ are treated as zero). Taking into consideration (21), statement (23) can be translated to the following linear inequalities (see, e.g. Bemporad and Morari (1999))

$$0 \leq [A_k]_{ij} - \epsilon\delta_{ij}, \quad i, j = 1, \ldots, m, \; i \neq j \tag{24}$$

$$0 \leq -[A_k]_{ij} + l_{ij}\delta_{ij}, \quad i, j = 1, \ldots, m, \; i \neq j \tag{25}$$

Now we are able to compute the realization containing the minimal/maximal number of reactions by minimizing/maximizing the objective function

$$C_1(\delta) = \sum_{\substack{i,j=1 \\ i \neq j}}^{m} \delta_{ij} \tag{26}$$

Computing realizations with the minimal/maximal number of complexes. To minimize/maximize the number of non-isolated complexes in the reaction graph, instead of (23), the following statement can be introduced

$$\delta_i = 1 \leftrightarrow \sum_{j_1=1}^{m} A_k(i, j_1) + \sum_{j_2=1}^{m} A_k(j_2, i) > \epsilon, \quad i = 1, \ldots, m \tag{27}$$

that can also be translated into appropriate linear equalities. The objective function to be minimized/maximized is now

$$C_2(\delta) = \sum_{i=1}^{m} \delta_i \tag{28}$$

Some immediate consequences. Let us call the realization with the minimal and maximal number of reactions the *sparse* and *dense* realization of a given kinetic system, respectively. Then the following facts can be proved for a fixed parameter set of the realized ODE (Szederkényi, 2010a):

(1) The unweighted graph of any realization must be a subgraph of the unweighted graph of the dense realization.
(2) The graph structure of the dense realization is unique.
(3) Based on the dense realization, it can be immediately decided whether there exists a fully or weakly reversible realization containing the same complexes as the dense realization.

4. EXAMPLES

The first example in this section illustrates the finding of a weakly reversible deficiency zero realization and thus proving global stability. The goal of the second example is to show the algorithmic determination of a reaction structure that was proved to be minimal previously, and in parallel, the possible effect of parameter change on the structure of the sparse realization.

4.1 System stability investigation through reaction kinetic description

The following polynomial system is given:

$$\begin{aligned}\dot{x}_1 &= x_3^2 - x_1x_2 + x_3x_4 - 2x_1x_2^2x_3\\ \dot{x}_2 &= x_3^2 - x_1x_2 + 2x_3x_4 - 4x_1x_2^2x_3\\ \dot{x}_3 &= -2x_3^2 + x_1x_2 - x_1x_2^2x_3 + 2x_4^3\\ \dot{x}_4 &= x_1x_2 - x_3x_4 + 4x_1x_2^2x_3 - 3x_4^3\end{aligned} \tag{29}$$

It can be seen that (29) is essentially nonnegative and kinetic. After running **Algorithm 1**, we obtain a network with 19 complexes and 16 reactions that is visible in Fig. 2, where the numbering of complexes (in rectangles) is the following:

$$\begin{aligned}&1 : 2\mathbf{X}_3,\ 2 : \mathbf{X}_3 + \mathbf{X}_4,\ 3 : \mathbf{X}_1 + 2\mathbf{X}_3,\ 4 : \mathbf{X}_2 + 2\mathbf{X}_3,\\ &5 : \mathbf{X}_3,\ 6 : \mathbf{X}_1 + \mathbf{X}_3 + \mathbf{X}_4,\ 7 : \mathbf{X}_2 + \mathbf{X}_3 + \mathbf{X}_4,\\ &8 : \mathbf{X}_1 + \mathbf{X}_2,\ 9 : \mathbf{X}_1 + 2\mathbf{X}_2 + \mathbf{X}_3,\ 10 : \mathbf{X}_1,\ 11 : \mathbf{X}_2,\\ &12 : \mathbf{X}_1 + \mathbf{X}_2 + \mathbf{X}_4,\ 13 : \mathbf{X}_1 + \mathbf{X}_2 + \mathbf{X}_3,\ 14 : 2\mathbf{X}_2 + \mathbf{X}_3,\\ &15 : \mathbf{X}_1 + 2\mathbf{X}_2,\ 16 : \mathbf{X}_1 + 2\mathbf{X}_2 + \mathbf{X}_3 + \mathbf{X}_4,\\ &17 : 3\mathbf{X}_4,\ 18 : \mathbf{X}_3 + 3\mathbf{X}_4,\ 19 : 2\mathbf{X}_4\end{aligned} \tag{30}$$

It is remarked that the CRN in Fig. 2 is not the dense realization (since that contains even more reactions). The sparse realization of the system shown in Fig. 2 is much simpler as it is visible in Fig. 3. It is easy to see from the figure that the sparse realization is weakly reversible. Furthermore, it can be checked that the deficiency of the sparse realization is 0 (in sharp contrast with the deficiency of 12 of the original netwok in Fig. 2). Therefore, the autonomous system (29) has well-characterizable equilibrium points in the positive orthant that are globally stable with a known entropy-like Lyapunov function (Feinberg, 1987).

4.2 Realizations of a dynamical system with possible bistability

Now we would like to examine the kinetic realizations of the following dynamical system

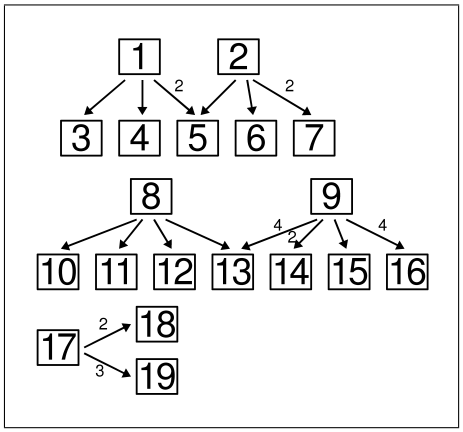

Fig. 2. Reaction network realizing eq. (29) obtained using **Algorithm 1**. Only those reaction rate coefficients are indicated that are different from 1.

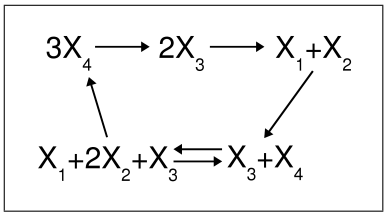

Fig. 3. Sparse realization of the CRN shown in fig. 2. All reaction rate coefficients are 1.

$$\begin{aligned}\dot{x}_1 &= p_1x_2 - p_2x_1^2 - p_3x_1x_2 - p_4x_1\\ \dot{x}_2 &= p_5x_1^2 - p_6x_2,\end{aligned} \tag{31}$$

where the parameters $p_1, \ldots, p_6$ are all positive real numbers. Fig. 4 shows the graph of the realization that is given by **Algorithm 1**.

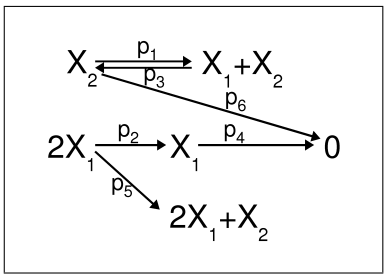

Fig. 4. Realization of eq. (31) given by **Algorithm 1**

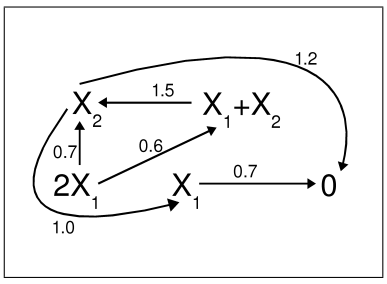

Fig. 5. A computed sparse realization of eq. (31)

The following randomly chosen parameter values were used for the forthcoming computations: $p_1 = 1$, $p_2 = 2$, $p_3 = 1.5$, $p_4 = 0.7$, $p_5 = 1.3$, $p_6 = 2.2$. The realization

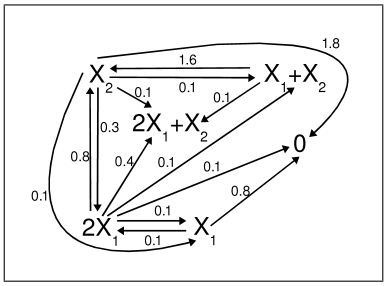

Fig. 6. Dense realization of eq. (31)

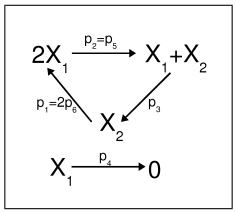

Fig. 7. The "smallest" chemical reaction network with bistability

obtained by first minimizing the number of complexes and then minimizing the number of reactions is shown in Fig. 5. It contains 6 reactions similarly to the initial network, but the number of necessary complexes is only 5 instead of the previous 6. This clearly shows that the structure of sparse realizations is not unique. From the dense realization of the system shown in Fig. 6 we can see that the complexes $2\mathbf{X}_1 + \mathbf{X}_2$ and the zero complex ($\mathbf{0}$) cannot be source complexes in any realization (i.e. no directed edge can start from them in the reaction graph). Furthermore, the unweighted graph of Fig. 5 is indeed a subgraph of the unweighted graph of the dense realization. An interesting structural change can be observed if we modify two parameter values as follows: $p_6 = \frac{1}{2}p_1, p_5 = p_2$. A sparse realization for this case is shown in Fig. 7. With the above parameter change, we could generate the chemical reaction network with possible bistability that is proved to be minimal in (Wilhelm, 2009), where minimal means (in decreasing order of priority): minimal number of reactions, minimal number of complexes, minimal number of terms in the ODEs. (Note that the particular network shown in (Wilhelm, 2009) is mass balanced and therefore does not use the zero complex but this is just a technical question of initial assumptions and the two networks can be transformed to each other algorithmically)

5. CONCLUSIONS

The kinetic realizations of nonnegative autonomous polynomial systems have been studied in this paper. The main underlying motivation is to examine dynamical properties (stability, possibility of multiplicities, etc.) using the related results of chemical reaction network theory (CRNT). For this, realizations with given properties are particularly helpful that are computed using mixed integer linear programming. The realization with the minimal number of complexes and/or reactions (i.e. the sparse realization) is useful in finding a low deficiency network structure for which the stability results of CRNT can be successfully applied. On the other hand, the structure of the dense realization is unique (with a fixed parameter set), and it shows the maximal set of possible reactions between the complexes. These results hopefully contribute to the exploitation of the potential of CRNT in the framework of nonlinear systems and control theory.

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