

Computing sparse and dense realizations of reaction kinetic systems

Gábor Szederkényi¹

Process Control Research Group, Systems and Control Laboratory
Computer and Automation Research Institute,
Hungarian Academy of Sciences
H-1518, P.O. Box 63, Budapest, Hungary
Tel: +36 1 279 6000
Fax: +36 1 466 7503
e-mail: szeder@sztaki.hu

Suggested running head: Sparse and dense realizations of reaction kinetic systems

The original publication is available at www.springerlink.com

DOI: [10.1007/s10910-009-9525-5](https://doi.org/10.1007/s10910-009-9525-5)

¹Process Control Research Group, Computer and Automation Research Institute, Hungarian Academy of Sciences, Budapest, Hungary, H-1518, P.O. Box 63

Abstract

A numerical procedure for finding the sparsest and densest realization of a given reaction network is proposed in this paper. The problem is formulated and solved in the framework of mixed integer linear programming (MILP) where the continuous optimization variables are the nonnegative reaction rate coefficients, and the corresponding integer variables ensure the finding of the realization with the minimal or maximal number of reactions. The mass-action kinetics is expressed in the form of linear constraints adjoining the optimization problem. More complex realization problems can also be solved using the proposed framework by modifying the objective function and/or the constraints appropriately.

Keywords: reaction kinetic systems, mass action kinetics, mixed integer linear programming

AMS classification: 80A30 chemical kinetics

1 Introduction

Reaction kinetic systems form a special class of positive systems with smooth nonlinearities where advantageous dynamic properties, such as global stability may be ensured thanks to the special structure of the system model. In the classical case, these systems are described by a set of ordinary differential equations (ODEs) with polynomial right-hand sides [36]. Beside the description of classical chemical reactions, reaction kinetic systems are the main building blocks of highly interconnected biochemical systems with complex behavior such as metabolic or cell signalling pathways [34].

One of the most significant results in the study of the dynamical properties of chemical reaction systems is described in [14, 15], where (among other important results) the global stability of so-called 'deficiency zero' reaction networks is proved with a given Lyapunov function. It is important to remark that the deficiency zero property is a structural feature of a certain class of reaction networks, therefore their stability does not depend on the system parameters. These concepts were revisited, extended and put into a control theoretic framework in [33]. Conditions for the local controllability and observability of chemical systems were given in [11] and [12], respectively. The relationship between the chemical network structure and the possibility of multiple equilibria is investigated in [5] from an algebraic and in [6, 8] from a graph-theoretic point of view. It was shown in [27] that reversible mass-action reaction networks with linearly independent reaction pairs possess a local dissipative-Hamiltonian structure in a neighborhood of any equilibrium point.

Several authors studied the possibilities of dimension reduction for large chemical networks. In [13], the characterization of nonnegative linear lumping schemes is given that preserves the kinetic

structure of the original system. The method of invariant manifold (MIM) is proposed in [18] and [19] for the reduced description of kinetic equations.

The so-called inverse problem of reaction kinetics (i.e. the characterization of those polynomial differential equations which are kinetic) was solved in [23]. It is known from the "fundamental dogma of chemical kinetics" that different reaction networks can produce the same kinetic differential equations [32]. Naturally, this property has an important impact on the identifiability of reaction rate constants [7].

Mixed integer optimization techniques have been widely and successfully used in the field of process analysis and synthesis [17], [29], [28]. Other application fields include Clar number calculation in chemistry [21, 31], vehicle routing, airline crew scheduling, production planning, etc. The techniques for transforming propositional logic into linear inequalities with integer and continuous variables have been worked out in e.g. [4], [28] and [35]. Based on this theoretical background, [30] presents a modelling framework for discrete optimization problems that relies on a logic representation in which mixed-integer logic is represented through disjunctions, and integer logic through propositions. Furthermore, [3] proposes a framework for modeling and controlling models of dynamical systems described by interacting physical laws, logical rules, and operating constraints.

The aim of this paper is to propose a numerical procedure for determining equivalent representations (i.e. reaction networks with possibly different structure and/or reaction rate coefficients from the original one but still leading to the same kinetic differential equations) called *realizations* of a given set of reaction kinetic differential equations with the minimal and maximal possible number of reactions. Chemical reactions are understood in a wide generalized sense in the paper (like, e.g. in [15] or [14]), because the constraints of (component) mass conservation are not taken into account.

The structure of the paper is the following. Section 2 contains the most important definitions and tools in the field of reaction networks and mixed integer linear programming used later in the paper. The main contribution can be found in section 3 where the realization problem is solved using the MILP framework. Illustrative examples showing the operation of the method are presented in section 4. Finally, section 5 contains the most important conclusions.

2 Basic notions

2.1 Mass action reaction networks

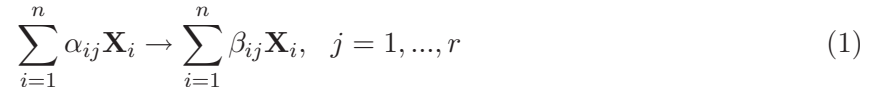
The original physical picture underlying the reaction kinetic system class is a closed system under isothermal and isobaric conditions, where chemical species \mathbf{X}_i , $i = 1, \dots, n$ take part in r chemical

reactions. The system is perfectly stirred, i.e. concentrated parameter in the simplest case. The concentrations x_i , $i = 1, \dots, n$ form the state vector the elements of which are non-negative by nature. For the sake of simplicity, physico-chemical properties of the system are assumed to be constant.

The origin of mass action law lies in the *molecular collision picture* of chemical reactions. Here the reaction occurs when either two reactant molecules collide, or a reactant molecule collides with an inactive (e.g. solvent) molecule. Clearly, the probability of having a reaction is proportional to the probability of collisions, that is proportional to the concentration of the reactant(s).

2.1.1 Chemical reactions obeying the mass action law

A straightforward generalization of the above molecular collision picture is when we allow to have multi-molecule collisions to obtain *elementary reaction steps* in the following form [20]:



where α_{ij} is the so-called *stoichiometric coefficient* of component \mathbf{X}_i in the j th reaction, i.e. the number of colliding \mathbf{X}_i molecules, and β_{ij} is the stoichiometric coefficient of the product \mathbf{X}_i . The linear combinations of the species in eq. (1), 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 non-negative integers in classical reaction kinetic systems*.

According to the extended molecular picture, the reaction rate of the above reactions can be described as

$$\rho_j = k_j \prod_{i=1}^n [\mathbf{X}_i]^{\alpha_{ij}} = k_j \prod_{i=1}^n x_i^{\alpha_{ij}}, \quad j = 1, \dots, r \quad (2)$$

where $[\mathbf{X}_i] = x_i$ is the concentration of the component \mathbf{X}_i , and $k_j > 0$ is the *reaction rate constant* of the j th reaction, that is always positive.

If the reactions $C_i \rightarrow C_j$ and $C_j \rightarrow C_i$ 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).

2.2 Graph representation of mass-action systems

Similarly to [14], we can assign the following directed graph (see, e.g. [2]) to the reaction network (1) 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 rates k_j for $j = 1, \dots, r$ in (2) are assigned as positive weights to the corresponding directed edges in the graph. A *walk* in the reaction graph is an alternating sequence $W = C_1 E_1 C_2 E_2 \dots C_{k-1} E_{k-1} C_k E_k$ where $C_i \in V_d$, $E_i \in E_d$ for $i = 1, \dots, k$. W is a *directed path* if all the vertices in it are distinct. P is called a *directed cycle* if the vertices C_1, C_2, \dots, C_{k-1} are distinct, $k \geq 3$ and $C_1 = C_k$. 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 [15].

2.3 Differential equations of mass-action systems

There are several possibilities to represent the dynamic equations of mass action systems (see, e.g. [14], [19], or [7]). The most advantageous form for our purposes is the one that is used e.g. in Lecture 4 of [14], i.e.

$$\dot{x} = Y \cdot A_k \cdot \psi(x) \quad (3)$$

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

$$\psi_j(x) = \prod_{i=1}^n x_i^{y_{ij}}, \quad j = 1, \dots, m \quad (4)$$

where $y_{ij} = [Y]_{ij}$. The exact structure of Y and A_k is the following. The i th 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

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1}^m k_{il}, & \text{if } i = j \\ k_{ji}, & \text{if } i \neq j \end{cases} \quad (5)$$

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 with the all stoichiometric coefficients zero i.e., it is represented by a zero vector in the Y matrix (for the details, see, e.g. [14] or [5]).

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

$$e_k = [Y]_{\cdot,j} - [Y]_{\cdot,i} \quad (6)$$

where $[Y]_{\cdot,i}$ denotes the i th column of Y . Any convention can be used for the numbering of the reaction vectors (e.g. the indices i and j in (6) can be treated as digits in a decimal system). The *rank* of a reaction network denoted by s is defined as the rank of the vector set $\{e_1, e_2, \dots, e_r\}$ where r is the number of reactions. The deficiency δ of a reaction network is defined as [14, 15]

$$\delta = m - l - s \quad (7)$$

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. The deficiency is a very useful tool for studying the dynamical properties of reaction networks and for establishing parameter-independent global stability conditions [15, 16].

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).

Using the notation

$$M = Y \cdot A_k, \quad (8)$$

equation (3) can be written in the compact form

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

Example 2.1. Consider the reaction network the graph of which is shown in Fig. 1 with the parameters:

$$k_1 = 1, k_2 = 1.1, k_3 = 1, k_4 = 1, k_5 = 1.1, k_6 = 0.1, k_7 = 3, k_8 = 1$$

Let us number the complexes as

$$C_1 = \mathbf{X}_1 + \mathbf{X}_2, C_2 = \mathbf{X}_1 + 2\mathbf{X}_2, C_3 = 2\mathbf{X}_2, C_4 = 2\mathbf{X}_1 + 3\mathbf{X}_2$$

Then the matrices of the description (3) are the following:

$$Y = \begin{bmatrix} 1 & 1 & 0 & 2 \\ 1 & 2 & 2 & 3 \end{bmatrix} \quad (10)$$

$$A_k = \begin{bmatrix} -2 & 1.1 & 0 & 0 \\ 1 & -2.3 & 3 & 1 \\ 1 & 0.1 & -3 & 1 \\ 0 & 1.1 & 0 & -2 \end{bmatrix} \quad (11)$$

$$M = YA_k = \begin{bmatrix} -1 & 1 & 3 & -3 \\ 2 & 0 & 0 & -2 \end{bmatrix} \quad (12)$$

2.4 Mixed integer linear programming (MILP) and propositional calculus

A mixed integer linear program is the maximization or minimization of a linear function subject to linear constraints. A mixed integer linear program with k variables (denoted by $y \in \mathbb{R}^k$) and p constraints can be written as [26]:

$$\begin{aligned} & \text{minimize } c^T y \\ & \text{subject to:} \\ & A_1 y = b_1 \\ & A_2 y \leq b_2 \\ & l_i \leq y_i \leq u_i \text{ for } i = 1, \dots, k \\ & y_j \text{ is integer for } j \in I, I \subseteq \{1, \dots, k\} \end{aligned} \quad (13)$$

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 (13) 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 [24] or the GNU Linear Programming Kit [25]) and commercial (such as CPLEX or TOMLAB [22]) solvers that can efficiently handle many practical problems.

As it has been mentioned in the Introduction, literals in propositional calculus can be transformed into linear inequalities. The notations of the following summary are mostly from [3]. A statement, such as $x \leq 0$ that can have a truth value of "T" (true) or "F" false is called a *literal* and will be denoted by S_i . In Boolean algebra, literals can be combined into *compound statements* using the following *connectives*: " \wedge " (and), " \vee " (or), " \sim " (not), " \rightarrow " (implies), " \leftrightarrow " (if and only if), " \oplus " (exclusive or). The truth table for the previously listed connectives is given in Table 1.

A propositional logic problem, where a statement S_1 must be proved to be true given a set of compound statements containing literals S_1, \dots, 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 . A list of equivalent compound statements and linear equalities or inequalities taken from [35] is shown in Table 2. In our case, the δ_i logical variables will be used for indicating whether the corresponding computed reaction rate coefficients are different from zero or not.

3 Computing dense and sparse realizations of reaction networks

Consider the polynomial system (9). We will call the matrix M in (9) *admissible*, if the polynomial differential equations describe a mass-action reaction network. Conditions for this were first given in [23] but not through the properties of M . The matrix pair (Y, A_k) is called a *realization* of an admissible matrix M if $Y \cdot A_k = M$, the elements of Y are non-negative integers, and A_k is a column conservation matrix with non-positive diagonal and non-negative off-diagonal elements. This way, we can define the alternative realizations of a reaction network, since M is computable from the structure and parameters of a given reaction system.

The starting point for the forthcoming calculations is that a reaction network is given with its reaction graph or equivalently with its realization (Y, A_k) and we want to compute its sparsest or densest realization denoted by (Y^s, A_k^s) and (Y^d, A_k^d) , respectively. Furthermore, we make the restriction that the complexes in the newly found realizations form a subset of the original complexes, i.e. $\text{col}(Y^s) \subseteq \text{col}(Y)$ and $\text{col}(Y^d) \subseteq \text{col}(Y)$. In principle, the alternative realizations may contain such complexes that do not appear in the original reaction network, but we won't elaborate on this case. It is assumed that a maximal possible set of complexes for the reaction network is given in advance. We remark, that obviously, the sparsest or densest realization may not be unique (parametrically and/or structurally), but here our goal is to find one possible solution.

3.1 Representation of mass action kinetics as linear equality constraints

For the computations, let us represent the Kirchhoff matrix of a reaction network containing m complexes as

$$A_k = \begin{bmatrix} -a_{11} & a_{12} & \dots & a_{1m} \\ a_{21} & -a_{22} & \dots & a_{2m} \\ \vdots & & & \vdots \\ a_{m1} & a_{m2} & \dots & -a_{mm} \end{bmatrix} \quad (14)$$

Keeping in mind the properties of A_k , the negative sign in (14) for the diagonal elements a_{ii} for $i = 1, \dots, m$ will allow us to set a uniform nonnegativity (or identically tractable lower and upper bound) constraint for all a_{ij} in the later computations.

Let us denote the i th row and i th column of a matrix W by $[W]_{i,\cdot}$ and $[W]_{\cdot,i}$, respectively. Using (14), the individual linear equations of the matrix equation (8) can be written as

$$-y_{11}a_{11} + y_{12}a_{21} + \dots + y_{1m}a_{m1} = [M]_{11} \quad (15)$$

$$\vdots$$

$$-y_{n1}a_{11} + y_{n2}a_{21} + \dots + y_{nm}a_{m1} = [M]_{n1} \quad (16)$$

$$y_{11}a_{12} - y_{12}a_{22} + \dots + y_{1m}a_{m2} = [M]_{12} \quad (17)$$

$$\vdots$$

$$y_{n1}a_{12} - y_{n2}a_{22} + \dots + y_{nm}a_{m2} = [M]_{n2} \quad (18)$$

$$\vdots$$

$$y_{11}a_{1m} + y_{12}a_{2m} + \dots - y_{1m}a_{mm} = [M]_{1m} \quad (19)$$

$$\vdots$$

$$y_{n1}a_{1m} + y_{n2}a_{2m} + \dots - y_{nm}a_{mm} = [M]_{nm} \quad (20)$$

The property that A_k is a column conservation matrix can also be expressed in the form of linear

equations:

$$-a_{11} + a_{21} + a_{31} + a_{41} = 0 \quad (21)$$

$$a_{12} - a_{22} + a_{32} + a_{42} = 0 \quad (22)$$

$$\vdots$$

$$a_{1m} + a_{2m} + \dots - a_{mm} = 0 \quad (23)$$

Equations (15)-(23) can be written in the following more compact form:

$$\begin{bmatrix} \bar{Y}^1 & 0 & 0 & \dots & 0 \\ 0 & \bar{Y}^2 & 0 & \dots & 0 \\ \vdots & & & & \\ 0 & 0 & 0 & \dots & \bar{Y}^m \end{bmatrix} \begin{bmatrix} [A_k]_{\cdot,1} \\ [A_k]_{\cdot,2} \\ \vdots \\ [A_k]_{\cdot,m} \end{bmatrix} = \begin{bmatrix} [\bar{M}]_{\cdot,1} \\ [\bar{M}]_{\cdot,2} \\ \vdots \\ [\bar{M}]_{\cdot,m} \end{bmatrix} \quad (24)$$

where the zeros denote zero matrix blocks of size $(n+1) \times m$ and

$$\bar{Y}^i = \begin{bmatrix} [Y]_{\cdot,1} & [Y]_{\cdot,2} & \dots & [Y]_{\cdot,i-1} & -[Y]_{\cdot,i} & [Y]_{\cdot,i+1} & \dots & [Y]_{\cdot,m} \\ 1 & 1 & \dots & 1 & -1 & 1 & \dots & 1 \end{bmatrix} \in \mathbb{R}^{(n+1) \times m}, \quad (25)$$

$$\bar{M} = \begin{bmatrix} M \\ 0 & \dots & 0 \end{bmatrix} \in \mathbb{R}^{(n+1) \times m} \quad (26)$$

3.2 Constructing the optimization problem

It is visible from (24) that the optimization variable will contain the reaction rate coefficients, i.e. the elements of A_k as the matrix Y is known and fixed by the problem statement. For the sake of simplicity, let us use the notation

$$z = \begin{bmatrix} z^{(1)} \\ z^{(2)} \\ \vdots \\ z^{(m)} \end{bmatrix} = \begin{bmatrix} [A_k]_{\cdot,1} \\ [A_k]_{\cdot,2} \\ \vdots \\ [A_k]_{\cdot,m} \end{bmatrix} \quad (27)$$

where obviously, $z^{(i)} \in \mathbb{R}^m$, $i = 1, \dots, m$.

When we seek the sparsest realization of the original reaction network (A_k, Y) then we are searching for the sparsest solution of (24), i.e. the one containing the maximal number of zeros (or

the minimal number of zeros, if the densest realization is to be computed). For this, let us associate logical variables $\delta_j^{(i)}$ with the continuous variables $z_j^{(i)}$ for $i, j = 1, \dots, m$. Then the optimization variable previously denoted by y is

$$y = \begin{bmatrix} z \\ \delta \end{bmatrix}. \quad (28)$$

Following from the problem statement and construction, the lower bound for the continuous variables is zero. For the solvability of the MILP problem, also an upper bound is introduced for z , i.e.

$$0 \leq z_i \leq u_i, \quad u_i > 0, \quad i = 1, \dots, m^2 \quad (29)$$

To minimize (or maximize) the number of nonzeros in the continuous solution part z , the following compound statement have to be translated to linear inequalities

$$\delta_i = 1 \leftrightarrow z_i > 0, \quad i = 1, \dots, m^2 \quad (30)$$

To be able to numerically distinguish between practically zero and nonzero solutions, (30) is modified to

$$\delta_i = 1 \leftrightarrow z_i > \epsilon, \quad i = 1, \dots, m^2 \quad (31)$$

where $0 < \epsilon \ll 1$ (i.e. solutions below ϵ are treated as zero). Taking into consideration (29), the linear inequalities corresponding to (31) are

$$0 \leq z_i - \epsilon \delta_i, \quad i = 1, \dots, m^2 \quad (32)$$

$$0 \leq -z_i + u_i \delta_i, \quad i = 1, \dots, m^2 \quad (33)$$

Now, the MILP problem for finding the sparsest realization can be constructed as

$$\text{minimize } \sum_{m^2+1}^{2m^2} y_i \tag{34}$$

subject to:

$$\begin{bmatrix} \bar{Y}^1 & 0 & 0 & \dots & 0 \\ 0 & \bar{Y}^2 & 0 & \dots & 0 \\ \vdots & & & & \\ 0 & 0 & 0 & \dots & \bar{Y}^m \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_{m^2} \end{bmatrix} = \begin{bmatrix} [\bar{M}]_{\cdot,1} \\ [\bar{M}]_{\cdot,2} \\ \vdots \\ [\bar{M}]_{\cdot,m} \end{bmatrix} \tag{35}$$

$$0 \leq y_i \leq u_i \text{ for } i = 1, \dots, m^2 \tag{36}$$

$$0 \leq y_i - \epsilon y_{i+m^2}, \quad i = 1, \dots, m^2 \tag{37}$$

$$0 \leq -y_i + u_i y_{i+m^2}, \quad i = 1, \dots, m^2 \tag{38}$$

$$y_j \text{ is integer for } j = m^2 + 1, \dots, 2m^2 \tag{39}$$

In the case when the densest realization is searched for, the optimization task (34) is simply changed to

$$\text{minimize } \left(- \sum_{m^2+1}^{2m^2} y_i \right) \tag{40}$$

Remark 1. By setting the lower and upper bounds for y_i differently from what is given in (36), the presence or omission of certain reactions can be forced during the optimization.

Remark 2. The block-diagonal structure of the coefficient matrix in (35) and the independence of the inequalities (36)-(38) allow us to partition the optimization variable y to m partitions and thus to solve the m resulting MILP subproblems parallelly which is a significant advantage from a computational point of view [1].

Remark 3. The block-diagonal structure mentioned in the previous remark makes it possible to combine different objective functions for different source complexes (since column i of A_k contains the rate coefficients corresponding to the reactions starting from complex C_i). E.g., the number of reactions starting from certain complexes can be minimized while it can be maximized for other complexes.

Remark 4. We note that the sparsest solution of certain sets of underdetermined linear equations can be obtained in polynomial time using linear programming (LP) [10, 9]. However, the applicability conditions of this LP solution are not fulfilled for many reaction networks.

4 Examples

The following examples were computed using the MILP solver of the YALMIP toolbox [24] under the MATLAB[®] computational environment.

Example 4.1. Consider again the simple reaction network of Example 2.1. Using the method described in section 3, the densest and sparsest realizations are shown in Figs 2 and 3, respectively. The Kirchoff-matrix of the sparsest realization is

$$A_k^s = \begin{bmatrix} -2 & 1 & 0 & 0 \\ 1 & -2 & 3 & 1 \\ 1 & 0 & -3 & 1 \\ 0 & 1 & 0 & -2 \end{bmatrix}, \quad (41)$$

while the densest realization is characterized by

$$A_k^d = \begin{bmatrix} -1.7 & 1.1 & 0.966 & 0.3 \\ 0.1 & -2.3 & 0.1 & 0.1 \\ 1.3 & 0.1 & -2.033 & 1.3 \\ 0.3 & 1.1 & 0.966 & -1.7 \end{bmatrix}, \quad (42)$$

Furthermore $Y^s = Y^d = Y$. It is easy to check that $Y^s \cdot A_k^s = Y^d \cdot A_k^d = M$. The deficiency of all three networks is 1, since $m = 4$, $l = 1$ and $s = 2$ in every case. Furthermore, each realization has the weak reversibility property.

Example 4.2. In this example, the starting point is the reaction network described in [7] as Fig. 6 in section 6. The network is replotted in Fig. 4. For the sake of simplicity, let us choose all the reaction rate coefficients to be 1 in the network. The Y and A_k matrices of the original reaction system are

$$Y = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 2 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 & 2 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 2 & 1 & 0 & 0 & 0 & 1 \end{bmatrix}, \quad (43)$$

$$A_k = \begin{bmatrix} -4 & 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -7 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad (44)$$

The first column of zeros in Y denotes the zero complex.

Here, only the sparsest realization is computed. The structure and parameters of the sparsest realization are shown in Fig. 5. The Kirchhoff matrix of the network is

$$A_k^s = \begin{bmatrix} -3 & 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -7 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad (45)$$

The coefficient matrix of the differential equations is given by

$$M = Y A_k = Y A_k^s = \begin{bmatrix} 1 & 0 & 0 & 0 & -7 & 1 & 0 & 1 & 0 & 1 \\ 1 & -1 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & -2 \\ 1 & 0 & -1 & 0 & 4 & 0 & 0 & -2 & 0 & 0 \\ 1 & 0 & 0 & -1 & 4 & -2 & 0 & 0 & 0 & 0 \end{bmatrix} \quad (46)$$

It is visible that the sparse realization contains 12 reactions. Two complexes from the original 11, namely $\mathbf{X}_1 + \mathbf{X}_3$ and $\mathbf{X}_1 + \mathbf{X}_2$ can be left out of the network since the corresponding columns and rows in A_k^s contain zeroes. It is easy to compute that the deficiencies of the original structure in Fig. 4 and that of the sparsest realization in Fig. 5 are $\delta_1 = 6$ ($m_1 = 11, l_1 = 1, s_1 = 4$) and $\delta_2 = 4$ ($m_2 = 9, l_2 = 1, s_2 = 4$), respectively. It is interesting to compare that the equivalent simplified realization on the right hand side of Fig. 6. in [7] contains 8 complexes, but 14 reactions and has a deficiency of 3. This shows the expectable fact that the minimization of the number of reactions does not necessarily result in a realization that has the lowest deficiency. However, the sparsest realization has the minimal number of parameters (i.e. reaction rate coefficients).

Example 4.3. Fig. 6 shows a simple reaction network with two linkage classes. Let the reaction rate coefficients be 1 for each reaction again. The deficiency of the network is 4 ($m = 8, l = 2, s = 2$). The Y and A_k matrices of the network are

$$Y = \begin{bmatrix} 1 & 0 & 1 & 3 & 2 & 1 & 0 & 1 \\ 0 & 1 & 1 & 1 & 1 & 2 & 3 & 3 \end{bmatrix} \quad (47)$$

$$A_k = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \end{bmatrix} \quad (48)$$

Both the sparsest and densest realization have been computed for this network. Fig. 7 shows the sparsest realization containing only 6 complexes and 4 reactions with the Kirchoff matrix

$$A_k^s = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1.33 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1.33 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -2.5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1.5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \end{bmatrix} \quad (49)$$

The deficiency of the sparse realization is 2 ($m = 6, l = 2, s = 2$).

The computed dense realization is depicted in Fig. 8. It is visible that in contrast to the previous two cases, the densest realization consists of only one linkage class. Since most elements of A_k are 0.1 (see eq. 50), only those reaction rates are indicated in the figure that are different from this value. In this case, the number of complexes is 8, the number of reactions is 29 and the Kirchhoff matrix is given by

$$A_k^d = \begin{bmatrix} -1 & 0.5 & 0.5 & 0 & 0.1 & 0.1 & 0 & 0 \\ 1 & -2 & 0.2 & 0 & 0.1 & 0.1 & 0 & 0 \\ 0 & 0.1 & -1.2 & 0 & 0.1 & 0.1 & 0 & 0 \\ 0 & 1 & 0.1 & 0 & 0.1 & 0.1 & 0 & 0 \\ 0 & 0.1 & 0.1 & 0 & -3 & 0.1 & 0 & 0 \\ 0 & 0.1 & 0.1 & 0 & 0.1 & -1.1 & 0 & 0 \\ 0 & 0.1 & 0.1 & 0 & 1.1 & 0.2 & 0 & 0 \\ 0 & 0.1 & 0.1 & 0 & 1.4 & 0.4 & 0 & 0 \end{bmatrix} \quad (50)$$

The deficiency of the dense realization is 5 ($m = 8, l = 1, s = 2$). It is again straightforward to check that

$$M = YA_k = YA_k^s = YA_k^d = \begin{bmatrix} -1 & 4 & 0 & 0 & -4 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 5 & 0 & 0 & 0 \end{bmatrix} \quad (51)$$

5 Conclusions

An optimization-based method has been proposed in this paper for the computation of sparse and dense realizations of reaction networks obeying the mass-action law. Starting from an appropriate form (3) of the kinetic equations, the mass-action kinetics can be expressed as linear constraints with a block-diagonal structure. The computation of the densest and sparsest realizations is traced back to a MILP problem where the optimization variables are the reaction rate coefficients and the corresponding integer auxiliary variables.

The proposed method can be used e.g. for finding the "most identifiable" parametrization of a complex reaction network (i.e. the one that has the minimal number of rate coefficients as parameters to be estimated). In the author's opinion, the presented examples raise interesting problems worth further studying, especially about which important properties of reaction networks can be determined directly from their differential equations.

6 Acknowledgements

This research was partially supported by the grant no. OTKA K67625. The author is a grantee of the Bolyai János Research Scholarship of the Hungarian Academy of Sciences. The author thanks Prof. Katalin Hangos and Tamás Péni at the Systems and Control Laboratory of the Computer and Automation Research Institute for their helpful comments.

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Tables

S_1	S_2	$\sim S_1$	$S_1 \vee S_2$	$S_1 \wedge S_2$	$S_1 \rightarrow S_2$	$S_1 \leftrightarrow S_2$	$S_1 \oplus S_2$
T	T	F	T	T	T	T	F
T	F	F	T	F	F	F	T
F	T	T	T	F	T	F	T
F	F	T	F	F	T	T	F

Table 1: Truth table

compound statement	equivalent linear equality/inequality
$S_1 \vee S_2$	$\delta_1 + \delta_2 \geq 1$
$S_1 \wedge S_2$	$\delta_1 = 1, \delta_2 = 1$
$\sim S_1$	$\delta_1 = 0$
$S_1 \rightarrow S_2$	$\delta_1 - \delta_2 \leq 0$
$S_1 \leftrightarrow S_2$	$\delta_1 - \delta_2 = 0$
$S_1 \oplus S_2$	$\delta_1 + \delta_2 = 1$

Table 2: Equivalent compound statements and linear equalities/inequalities

Figures

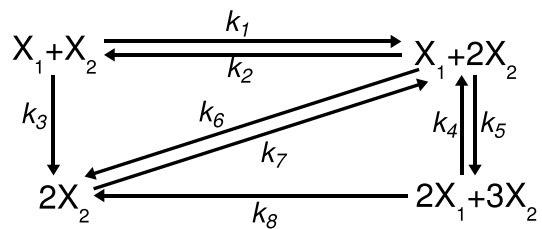


Figure 1: Simple reaction network of Example 2.1

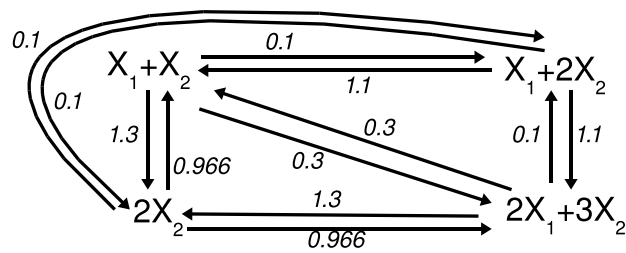


Figure 2: Densest realization of the reaction network of Example 2.1

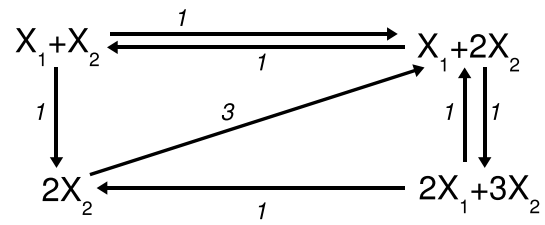


Figure 3: Sparsest realization of the reaction network of Example 2.1

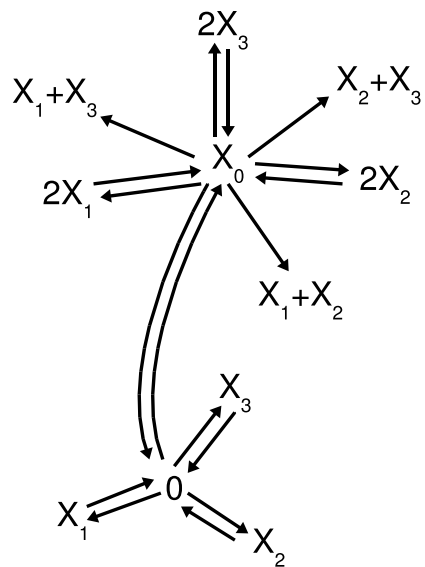


Figure 4: Reaction network of Example 4.2. All the rate coefficients are set to 1.

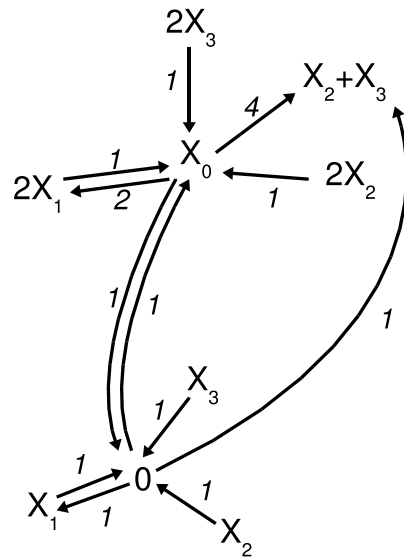


Figure 5: Sparsest realization of the reaction network of Example 4.2

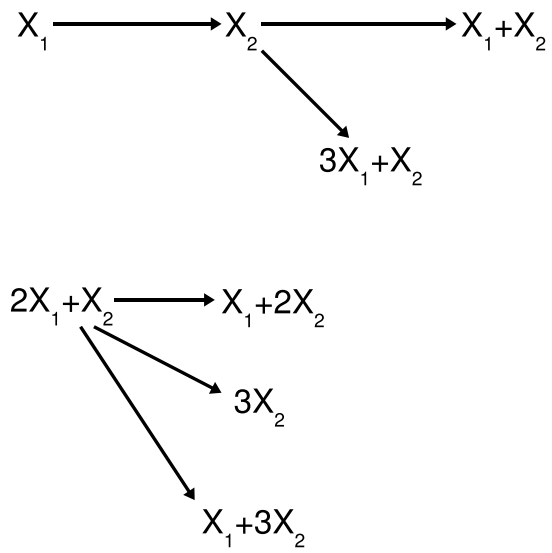


Figure 6: Reaction network of Example 4.3. All the rate coefficients are chosen to be 1.

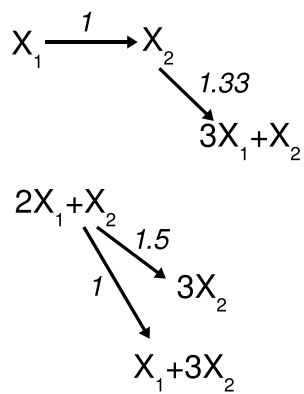


Figure 7: Sparsest realization of the reaction network of Example 4.3

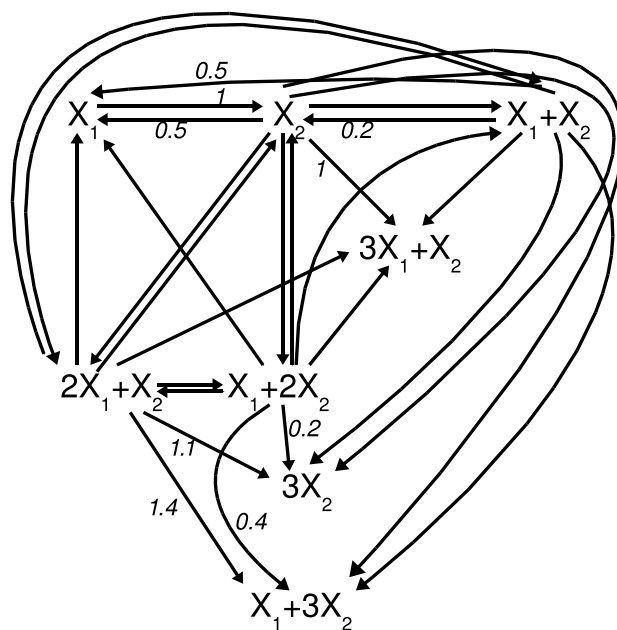


Figure 8: Densest realization of the reaction network of Example 4.3. Only those reaction rate coefficients are indicated that are different from 0.1.

Table and figure captions

- Table 1: Truth table
- Table 2: Equivalent compound statements and linear equalities/inequalities
- Fig. 1: Simple reaction network of Example 2.1
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- Fig. 5: Sparsest realization of the reaction network of Example 4.2
- Fig. 6: Reaction network of Example 4.3. All the rate coefficients are chosen to be 1.
- Fig. 7: Sparsest realization of the reaction network of Example 4.3
- Fig. 8: Densest realization of the reaction network of Example 4.3. Only those reaction rate coefficients are indicated that are different from 0.1.