Parametric uniqueness of deficiency zero reaction networks

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Abstract

In this paper it is shown that deficiency zero mass action reaction networks containing one terminal linkage class are parametrically and therefore structurally unique with a fixed complex set. Clearly, weakly reversible deficiency zero networks with one linkage class belong to this class. However, it is shown through an illustrative example that deficiency zero networks with several linkage classes can have multiple dynamically equivalent realizations, even if the individual linkage classes are weakly reversible.

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1 Introduction

According to the well-known "fundamental dogma of chemical kinetics" different reaction networks can produce the same kinetic differential equations [9]. This means, that dynamically equivalent representations called *realizations* - i.e. reaction networks with possibly different structure and/or reaction rate coefficients from the original one - may exist that still lead to the same kinetic differential equations. This fact has a great importance from the viewpoint of analyzing the properties of a reaction kinetic system given by its kinetic differential equations, because some of the most important structural properties, such as (weak) reversibility or deficiency are realization-dependent, i.e. they may change depending of the particular realization.

Reaction kinetic systems form a special sub-class of positive systems with smooth, polynomial nonlinearities in the ordinary differential equation (ODE) description implied by the mass action law [13]. Beside the description of classical chemical reactions, chemical reaction networks (CRNs) are the main building blocks of highly interconnected biochemical networks with complex behavior such as metabolic or cell signalling pathways [12].

Because of the significance of structural properties [4, 1, 2], it is of great practical and theoretical interest to find realizations of a given reaction kinetic system with desired properties. The first step to this is to solve the so-called inverse problem of reaction kinetics (i.e. the characterization of those polynomial differential equations which are kinetic), that was published in [7]. Recently, optimization-based computational algorithms have been presented for the construction of CRN structures with preferred properties such as reversibility or minimal/maximal number of reactions and complexes in [10] and [11].

The aim of this paper is to analyze the relations between the structural properties and realization uniqueness of reaction networks. Chemical reactions are understood in a wide generalized sense in the paper (like, e.g. in [4] or [3]), because the constraints of (component) mass conservation are not taken into account.

2 Description and relevant properties of chemical reaction networks

2.1 Dynamics and structure of reaction networks obeying the mass action law

Let us suppose $\mathbf{X}_i,\ i = 1, ..., n$ chemical species taking part in r chemical reactions. The concentrations $x_i,\ i = 1, ..., n$ form the state vector the elements of which are non-negative by nature. The *elementary reaction steps* taking place between the chemical species are in the following form [6]:

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

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. (1), namely $\sum_{i=1}^{n} \alpha_{ij}\mathbf{X}_i$ and $\sum_{i=1}^{m} \beta_{ij}\mathbf{X}_i$ for $j = 1, \ldots, r$ are called the *complexes* and are denoted by $C_1, C_2, \ldots, C_m$. The stoichiometric coefficients are always non-negative integers.

We say that the reaction network (1) obeys the *mass action law (MAL)*, if the reaction rate of the above reactions can be described as

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

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 jth reaction, that is always positive.

We use the following dynamical description to describe the time-evolution of specie concentrations [3, 4]:

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

where $Y \in \mathbb{R}^{n\times m}$ 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

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

where $y_{ij} = [Y]_{ij}$. The explanation of the structures 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

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

Based on the above, we will call a quadratic matrix a *Kirchhoff matrix*, if it is a column conservation matrix with non-positive diagonal and non-negative off-diagonal entries. Using Y and A_k, it is possible to assign a weighted directed graph (often called 'Feinberg-Horn-Jackson graph') to a reaction network, where the vertices correspond to complexes, reactions are represented by directed edges between complexes, and the weights corresponding to directed edges are the appropriate reaction rate coefficients [4, 13]. We note that the Laplacian matrix of a weighted directed graph is often defined as $-A_k^T$.

A set of complexes $\{C_1, C_2, \ldots, C_k\}$ 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 [4] (i.e. the individual linkage classes form the connected components of the directed graph of the reaction network). Two different complexes are said to be *strongly linked* if there exists a directed path from one complex to the other, and a directed path from the second complex back to the first. Moreover, each complex is defined to be strongly linked to itself. A *strong linkage class* is a set of complexes with the following properties: each pair of complexes in the set is strongly linked, and no complex in the set is strongly linked to a complex that is not in the set. A *terminal strong linkage class* is a strong linkage class that contains no complex that reacts to a complex in a different strong linkage class (i.e. there is no "exit" from a terminal strong linkage class through a directed edge).

For the reaction $C_i \to C_j$, the corresponding *reaction vector* v_{ij} is defined as

$$v_{ij} = [Y]_{\cdot,j} - [Y]_{\cdot,i} \tag{6}$$

where $[Y]_{\cdot,i}$ denotes the ith column of Y. The *rank* of a reaction network denoted by s is defined as the rank of the vector set $H = \{v_{ij} \mid C_i \to C_j \text{ exists}\}$. We use the classical definition for the deficiency δ of a reaction network [4]:

$$\delta = m - l - s \tag{7}$$

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

2.2 Dynamically equivalent reaction networks

It is known that reaction networks with different structures and/or parametrizations can give rise to the same kinetic differential equations [9, 10, 11]. Therefore, we will call two reaction networks given by the matrix pairs $(Y^{(1)}, A_k^{(1)})$ and $(Y^{(2)}, A_k^{(2)})$ *dynamically equivalent*, if

$$Y^{(1)}A_k^{(1)}\psi^{(1)}(x) = Y^{(2)}A_k^{(2)}\psi^{(2)}(x) = f(x), \tag{8}$$

where for $i = 1, 2$, $Y^{(i)} \in \mathbb{R}^{n\times m_i}$ have nonnegative integer entries, $A_k^{(i)}$ are valid Kirchhoff matrices, and

$$\psi_j^{(i)}(x) = \prod_{k=1}^{m_i} x_k^{[Y^{(i)}]_{kj}}, \quad j = 1, \dots, m. \tag{9}$$

In this case, $(Y^{(i)}A_k^{(i)})$ for $i = 1, 2$ are called *realization*s of a kinetic vector field f. It is also appropriate to call $(Y^{(1)}, A_k^{(1)})$ a *realization* of $(Y^{(2)}, A_k^{(2)})$ and vica versa.

3 Realizations of deficiency zero CRNs with one terminal strong linkage class are unique

In this section, we will prove that CRNs with one terminal strong linkage class cannot have multiple different realizations, if the set of complexes is fixed. For this, we will use the following standard notations. The dimension of a vector space V is denoted by $\dim(V)$. For an arbitrary matrix M, its rank, image and kernel is denoted by $\operatorname{rank}(M)$, $\operatorname{Im} M$, and $\operatorname{Ker} M$, respectively. Furthermore, let us denote the ith column of a matrix M with $[M]_{.,i}$.

Additionally, the following relations known from linear algebra and CRN theory will be used. (For **R1**-**R4**, the reader is referred to e.g. [8], while **R5**, **R6** can be found in [3] and [5], respectively)

R1 For any two matrices A, B for which AB exists $\operatorname{rank}(AB) \leq \min(\operatorname{rank}(A), \operatorname{rank}(B))$.

R2 (Rank-nullity theorem) For any $k \times l$ matrix M, $\dim(\operatorname{Im} M) + \dim(\operatorname{Ker} M) = l$.

R3 For any matrices A, B such that the product BA exists

$$\dim(\operatorname{Im} A \cap \operatorname{Ker} B) = \dim(\operatorname{Im} A) - \dim(\operatorname{Im}(BA)) = \dim(\operatorname{Ker}(BA)) - \dim(\operatorname{Ker} A) \tag{10}$$

R4 The maximal rank of a set $V = \{v^{(1)}, \ldots, v^{(k)}\}$ of n-dimensional vectors for which $\sum_{i=1}^{n} v_i^{(j)} = 0$, for $j = 1, \ldots, k$ and $k >= n$, is $n-1$. To see this, let us form the following matrix from the vectors $v^{(1)}, \ldots, v^{(k)}$

$$M = [v^{(1)}\ v^{(2)}\ \ldots\ v^{(k)}] \tag{11}$$

The maximal row rank of M is clearly $n-1$, since the zero vector can be constructed as a nontrivial linear combination (i.e. a simple addition) of the rows of V. The row and column ranks of any matrix are always equal, therefore the maximal number of linearly independent vectors in V is $n-1$.

R5 If a CRN with the Kirchhoff matrix $A_k \in \mathbb{R}^{m \times m}$ has one terminal strong linkage class, then $\dim(\text{Im } A_k) = m-1$.

R6 If each linkage class of a CRN given by (Y, A_k) contains precisely one terminal strong linkage class, then the deficiency δ of the network is $\delta = \dim(\text{Im } A_k \cap \text{Ker } Y)$.

Taking into consideration the preliminary facts **R1-R6**, we can now state our main theorem.

Theorem 3.1. *Any deficiency zero CRN given by (Y, A_k) with one terminal strong linkage class is parametrically and therefore structurally unique, if the set of complexes is fixed, i.e. there is no Kirchhoff matrix A'_k different from A_k such that $Y \cdot A_k = Y \cdot A'_k$.*

Proof. (Indirect) Let us assume that there exists a Kirchhoff matrix $A'_k \neq A_k$ such that $YA_k = YA'_k$. Then $Y(A_k - A'_k) = 0$. Let $\hat{A}_k = A_k - A'_k$. It is clear that $\hat{A}_k$ is also a column conservation matrix (not necessarily Kirchhoff), and that the columns of $\hat{A}_k$ belong to the kernel of Y, i.e. $[\hat{A}_k]_{.,i} \in \text{Ker } Y$ for $i = 1, \ldots, m$. From this it follows that $\dim(\text{Ker } Y) \geq 1$ since $\hat{A}_k$ is nonzero.

From **R5** we know that $\dim(\text{Im } A_k) = m-1$. From **R3** and **R6** it follows that $\dim(\text{Im } A_k) = \dim(\text{Im}(YA_k))$, i.e. $\dim(\text{Im}(YA_k)) = m-1$. Using **R1** we get that $\dim(\text{Im } Y) \geq m-1$ that implies $\dim(\text{Ker } Y) \leq 1$. From the two estimations on the dimension of Ker Y we obtain that $\dim(\text{Ker } Y) = 1$, and (by using **R2**) that $\dim(\text{Im } Y) = m-1$.

Since $\hat{A}_k$ is a column conservation matrix, for any $v \in \text{Ker } Y$ it is true that $\sum_{i=1}^{m} v_i = 0$. Then, according to **R4**, Ker $Y \subset$ Im A_k, and therefore $\dim(\text{Im } A_k \cap \text{Ker } Y)$ cannot be zero, which is a contradiction. □

The following points are important to remark.

1. Deficiency zero weakly reversible networks with one linkage class form an important subset of the CRNs for which Theorem 3.1 is valid.

2. If for a given set of complexes Y, a CRN has two different dynamically equivalent realizations characterized by A_k and A'_k, then it has infinitely many, because e.g. $A'_k = \frac{A_k + A'_k}{2}$ also defines a valid realization with Y.

3. To obtain other possible realizations, A_k can be modified such that any vector constructed as a linear combination of the basis of Ker Y and satisfying that the sum of its elements is zero (i.e. the column conservation property) can be added to any column of A_k as long as the off diagonal and diagonal entries in the resulting A'_k matrix remain non-negative and non-positive, respectively (see Example 3.1).

4. Theorem 3.1 is naturally valid for CRNs composed of multiple linkage classes each of which has precisely one terminal linkage class, if the sets of species belonging to the individual linkage classes are mutually disjoint. In this case, the linkage classes can be treated as separate independent CRNs. However, if there are common species between the linkage classes, then zero deficiency and even (weak) reversibility of the linkage classes are not sufficient for the uniqueness of the realization, as Example 3.1 will show.

Example 3.1. In this example we will show that deficiency 0 does not guarantee the uniqueness of the realization in the case of multiple linkage classes. Consider the reaction network the graph of which is shown in Fig. 1. Let us number the complexes as

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

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

$$Y = \begin{bmatrix} 1 & 2 & 0 & 3 \\ 0 & 1 & 2 & 1 \end{bmatrix},\ A_k = \begin{bmatrix} -1 & 2 & 0 & 0 \\ 1 & -2 & 0 & 0 \\ 0 & 0 & -3 & 2 \\ 0 & 0 & 3 & -2 \end{bmatrix} \tag{12}$$

$$M = YA_k = \begin{bmatrix} 1 & -2 & 9 & -6 \\ 1 & -2 & -3 & 2 \end{bmatrix} \tag{13}$$

$$\text{Ker } Y = \text{span}\left\{ \begin{bmatrix} 4 \\ -2 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} -1 \\ -1 \\ 0 \\ 1 \end{bmatrix} \right\}, \tag{14}$$

A vector v with zero sum can easily be constructed from the above basis of Ker Y as

$$v = \begin{bmatrix} 4 \\ -2 \\ 0 \\ 1 \end{bmatrix} + 3 \begin{bmatrix} -1 \\ -1 \\ 0 \\ 1 \end{bmatrix} = \begin{bmatrix} 1 \\ -5 \\ 1 \\ 3 \end{bmatrix} \tag{15}$$

If we add v to the second column of A_k, we obtain a Kirchhoff matrix that defines another realization of the initial CRN:

$$A'_k = \begin{bmatrix} -1 & 3 & 0 & 0 \\ 1 & -7 & 0 & 0 \\ 0 & 1 & -3 & 2 \\ 0 & 3 & 3 & -2 \end{bmatrix} \tag{16}$$

It can be checked that $M = YA_k = YA'_k$. It is noticable from Fig. 2 that the deficiency of the second realization with A'_k is 1, because it contains only one linkage class.

4 Conclusions

It has been shown that the realizations of deficiency zero reaction networks with one strong terminal linkage class are unique if the set of chemical complexes is fixed. The result is therefore valid for weakly reversible deficiency zero networks with one linkage class. The given easily verifiable structural condition can be useful during the modeling and structure or parameter estimation of dynamic processes described by chemical reaction networks. It has also been shown through an example that the deficiency zero property in itself is not enough for realization uniqueness.

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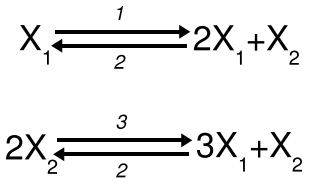

Figure 1: Simple reaction network of Example 3.1

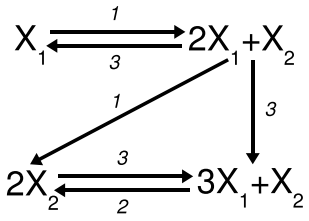

Figure 2: Dynamically equivalent one linkage class realization of the CRN of Example 3.1

Figure captions

- Fig. 1: Simple reaction network of Example 3.1
- Fig. 2: One linkage class realization of the CRN of Example 3.1