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Efficient Computation of All Distinct Realization Structures of Kinetic Systems

Zoltan A. Tuza * **Bernadett Ács** ** **Gábor Szederkényi** **
Frank Allgöwer *

* *Institute for Systems Theory and Automatic Control, University of Stuttgart, Pfaffenwaldring 9, 70550 Stuttgart, Germany, Email: {zoltan.tuza, frank.allgower}@ist.uni-stuttgart.de*
** *Pázmány Péter Catholic University Faculty of Information Technology and Bionics, Práter u. 50/a, 1083 Budapest, Hungary, Email: {acs.bernadett, szederkenyi}@itk.ppke.hu*

Abstract: Structural non-uniqueness of (bio)chemical reaction networks realizing a given kinetic dynamics has been known for a long time, but it is often overlooked in practice. However, without appropriate prior information, this phenomenon seriously hinders the successful identification of biochemical models. Recently an algorithm with guaranteed polynomial time complexity between iterations has been developed to compute all distinct reaction graph structures corresponding to a given dynamics. This paper presents an improved version of this algorithm that is suitable to take the advantage of a multiprocessor environment. The computed structures are collected in a task queue, and two server processes coordinate the operation of the set of workers. The implementation is briefly described and the performance of the approach is illustrated on computational examples taken from the literature.

Keywords: Chemical reaction networks, Optimization, Parallel computation, Polynomial models

1. INTRODUCTION

Kinetic systems and their realizing reaction networks are popular tools for modeling (bio)chemical reactions in chemical and process engineering as well as in systems biology. This is mainly due to the useful relations between the structure of reaction networks and the properties of the differential equations describing the dynamics of the chemical reaction network. It is known, however, that the correspondence between the network structure and the dynamics is generally not one-to-one. This means that there might exist many different network structures (called realizations) translating to exactly the same set of differential equations, even if the set of complexes is fixed; see in Horn and Jackson (1972). It is also well-known that the inference of biochemical reaction networks is a challenging task due to the frequent lack of structural or practical identifiability, see more in Chis et al. (2011). Naturally, the possible structural non-uniqueness has a substantial impact on the identifiability of kinetic systems (see e.g. Craciun and Pantea (2008); Szederkényi et al. (2011)). Clearly, the different realizations share the same dynamical properties: e.g. a stability condition obtained using a certain reaction graph proves this property for the corresponding dynamical system itself. To exploit such properties several optimization based algorithms have been developed to determine realizations with preferred properties (cf. Szederkényi (2010b,a)).

In this paper we use two main notions to relate the kinetic dynamical system and the corresponding graph structures. The reaction networks yielding exactly the same kinetic differential equations are called *dynamically equivalent*. Johnston and Siegel (2011) introduced a positive linear diagonal transformation between the solutions (trajectories) of kinetic systems, in this case kinetic systems are called *linearly conjugate*. It is easy to see that dynamical equivalence is a special case of linear conjugacy (cf. Craciun and Pantea (2008), Johnston et al. (2012b)).

The computation of all structurally different graph structures is generally a combinatorial problem, but there are special properties we can exploit to significantly reduce the search space. First, there exist an upper and a lower bound for the possible number of reactions in a reaction network realizing a kinetic system. Szederkényi (2010a) reported a way to compute these bounds which are the so-called dense and sparse realizations, respectively. Second, it was proved that the dense realization is a unique super-structure for a given dynamics and contains all other possible realizations as proper sub-graphs (see e.g. Johnston et al. (2012a)).

Beyond the possibility of an exhaustive search, knowing all different realizations of a kinetic system enables us to study such properties of the whole solution set that we are not yet able to compute directly. An example for that is the enumeration of all structures with a given deficiency. Deficiency is a realization property but it may have immediate consequences on the stability and uniqueness of equilibria for kinetic systems as it was introduced in Feinberg (1987) and Feinberg (1988).

Tuza et al. (2013) reported the first solution to enumerate all sparse realizations of a kinetic system. Recently, Ács et al. (2016) developed the first provably correct algorithm with advantageous time complexity properties for computing all distinct reaction graph structures. Basically, this algorithm builds a hierarchical tree structure which contains all realizations as vertices of a tree. In the root we have the dense realization (the upper bound) and below that in each horizontal level we

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can find all the realizations with a smaller number of reactions, than one level above. Finally, at the bottom level we can find all realizations with the minimum number of reactions (i.e. the sparse realizations).

Based on the above, the aim of this paper is to present and evaluate an improved, computationally more efficient implementation of the method presented in Ács et al. (2016), and to illustrate the possible degree of structural non-uniqueness (and consequently, that of non-identifiability) using examples taken from the literature including models related to systems biology.

The paper is organized as follows: the next section briefly introduces the necessary mathematical background for the implementation. The third section presents the improved algorithm for computing all different graph structures and outlines the proof of correctness. Section 4 details the implementation. The computational results are presented in Section 5, while Section 6 concludes the paper.

2. REPRESENTATIONS OF KINETIC SYSTEMS

We consider reaction networks as a general system class representing a wide class of nonlinear dynamical systems with non-negative states (see e.g. in Chellaboina et al. (2009)). Throughout the paper we follow the notations of Ács et al. (2016).

2.1 Algebraic characterization

A reaction network can be characterized by three sets:

(1) a set of **species**: $\mathcal{S} = \{X_i \mid i \in \{1, \dots, n\}\}$
(2) a set of **complexes**: $\mathcal{C} = \{C_j \mid j \in \{1, \dots, m\}\}$, where
$$C_j = \sum_{i=1}^{n} \alpha_{ji} X_i \qquad j \in \{1, \dots, m\}$$
$$\alpha_{ji} \in \mathbb{N}_0 \qquad j \in \{1, \dots, m\},\ i \in \{1, \dots, n\},$$
(3) and a set of **reactions**: $\mathcal{R} \subseteq \{(C_i, C_j) \mid C_i, C_j \in \mathcal{C}\}$ Each ordered pair (C_i, C_j) has a reaction rate coefficient $k_{ij} \in \mathbb{R}_+^n$ so that the corresponding reaction $C_i \to C_j$ takes place if and only if $k_{ij} > 0$.

The structure of the reaction network can be characterized by special matrices: the complex composition matrix $Y \in \mathbb{N}_0^{n \times m}$ describes the complexes as follows

$$[Y]_{ij} = \alpha_{ji} \qquad i \in \{1, \dots, n\},\ j \in \{1, \dots, m\},$$

and the set of reactions is encoded by the Kirchhoff matrix $A_k \in \mathbb{R}^{m \times m}$ as

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

2.2 Dynamical description

If mass action kinetics is assumed and the concentrations of the species depending on time are represented by the function $x : \mathbb{R} \to \mathbb{R}_+^n$, the time evolution of the model can be characterized by a polynomial dynamical system:

$$\dot{x} = Y \cdot A_k \cdot \psi(x) \tag{1}$$

where $\psi : \mathbb{R}_+^n \to \mathbb{R}_+^m$ is a monomial-type vector-mapping defined by

$$\psi_j(x) = \prod_{i=1}^{n} x_i^{Y_{ij}}, \quad j = 1, \dots, m. \tag{2}$$

It is visible from (1) and (2) that the ODEs of a reaction network can be characterized by the matrix pair Y and A_k.

Obviously, (1) can be written as a polynomial system of the form

$$\dot{x} = M \cdot \varphi(x) \tag{3}$$

where $x : \mathbb{R} \to \mathbb{R}_+^n$ is a function, $M \in \mathbb{R}^{n \times p}$ a coefficient matrix and $\varphi : \mathbb{R}_+^n \to \mathbb{R}_+^p$ a monomial function. The polynomial system (3) is called a **kinetic system** if there exists a reaction network governed by the same dynamics, i.e. the following equation is fulfilled:

$$M \cdot \varphi(x) = Y \cdot A_k \cdot \psi(x), \ \ \forall x. \tag{4}$$

In this case the reaction network represented by the matrices Y and A_k is called a **dynamically equivalent realization** of the kinetic system (3). We remark that the monomial functions φ and ψ are generally not identical, since the set of complexes determining the monomials is not fixed. However, the set of complexes can be suitably complemented; we can assume without the loss of generality that $\varphi = \psi$ holds (see e.g. Ács et al. (2016) for details).

The notion of dynamical equivalence can be generalized to the case when the state vector is subject to a positive linear diagonal state transformation, performed by a positive definite diagonal matrix $T \in \mathbb{R}^{n \times n}$ as follows: $\bar{x} = T^{-1} \cdot x$. According to the definition in Johnston et al. (2012a): a reaction network defined by matrices Y and A_k' is called a **linearly conjugate** realization of the kinetic system (3) if the following equations hold:

$$Y \cdot A_k = T^{-1} \cdot M \tag{5}$$

$$A_k' = A_k \cdot \Phi_T, \tag{6}$$

where $\Phi_T \in \mathbb{R}^{m \times m}$ is a positive definite diagonal matrix so that $[\Phi_T]_{ii} = \psi_i(T \cdot \mathbf{1})$ for $i \in \{1, \dots, n\}$, and $\mathbf{1} \in \mathbb{R}^n$ is a vector with all coordinates equal to 1.

2.3 Graph representation

The above notions give reaction networks a natural representation as weighted directed graphs $G(V, E)$ called **Feinberg-Horn-Jackson graphs**, or simply **reaction graphs** as follows:

- vertices: $V(G) = \mathcal{C}$
- edges: $E(G) = \mathcal{R}$
- edge weights: $w(C_i, C_j) = k_{ij}$

It can be seen that the reaction graph is encoded by the matrix A_k, but since we want to determine only the structures of the realizations from now on we consider reaction graphs as unweighted directed graphs.

2.4 Distinguished reaction graph structures

The **dense realization** of a kinetic system—where the maximum number of reactions take place—has a special property that guarantees the applicability of the algorithm presented in this paper. Ács et al. (2015) proves that among linearly conjugate realizations fulfilling a finite set of linear constraints on the parameters there is a realization determining a super-structure. This super-structure is the unweighted reaction graph of the dense realization which contains the reaction graph structures of all possible linearly conjugate realizations of the model with linear constraints as subgraphs.

The **sparse realizations** of a kinetic system are such realizations where the minimum number of reactions take place. In