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Computing zero deficiency realizations of kinetic systems

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ABSTRACT

In the literature, there exist strong results on the qualitative dynamical properties of chemical reaction networks (also called kinetic systems) governed by the mass action law and having zero deficiency. However, it is known that different network structures with different deficiencies may correspond to the same kinetic differential equations. In this paper, an optimization-based approach is presented for the computation of deficiency zero reaction network structures that are linearly conjugate to a given kinetic dynamics. Through establishing an equivalent condition for zero deficiency, the problem is traced back to the solution of an appropriately constructed mixed integer linear programming problem. Furthermore, it is shown that weakly reversible deficiency zero realizations can be determined in polynomial time using standard linear programming. Two examples are given for the illustration of the proposed methods.

1. Introduction

Nonnegative (or positive) dynamical systems, the state variables of which remain nonnegative for nonnegative initial conditions, have important significance in areas such as chemistry, biology, economics, and transportation where the described physical quantities changing in time and/or in space are naturally nonnegative [1,2]. An important subclass of nonnegative systems is the family of chemical reaction networks (CRNs, also called kinetic models) rooted in the dynamical description of the concentrations of interacting molecules. Actually, the application potential of kinetic models is much wider than pure chemistry, since nonnegative models from other fields such as disease dynamics, ecology, and transportation are often readily in (or can easily be transformed to) kinetic form [3,4]. Notable special cases of kinetic models are compartmental systems [2] and Lotka–Volterra systems [5]. Additionally, kinetic systems are the fundamental dynamic model building blocks in systems biology [6].

In (bio)chemical applications, the system parameters (typically the reaction rate coefficients) are uncertain, and often only their order of magnitude is known. Therefore, one of the main subjects of chemical reaction network theory (CRNT) is to give conditions on the qualitative behavior of kinetic models using mainly the stoichiometry and graph structure of reaction networks [7,8]. In [8,9], the authors introduce to the study of chemical reaction networks a parameter known as the deficiency, which is a nonnegative integer not depending on the rate coefficients. A classical result of CRNT with clear significance in nonlinear systems theory is the Deficiency Zero Theorem that establishes a robust stability property for deficiency zero reaction networks consisting of strongly connected reaction graph components with a known, parameter-independent logarithmic Lyapunov-function. A promising but technically challenging conjecture not requiring the zero deficiency but only the so-called complex-balanced property for the global stability of a kinetic system is the Global Attractor Conjecture that was proved in [10] for reaction networks having only one graph-component. Furthermore, the Boundedness Conjecture says that any weakly reversible reaction network with mass action kinetics has bounded trajectories (see, e.g. [11]). It is not surprising therefore that the useful properties of kinetic models have raised the interest of control scientists [12,13]. In [14], the deficiency zero theorem is revisited and generalized from a control-theoretical point of view by showing that a wide class of CRNs with a linear input structure can be easily stabilized asymptotically. It is shown in [15] that weakly reversible deficiency zero networks are input-to-state stable with respect to the time varying reaction

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rates as inputs. Moreover, it is possible to construct globally convergent observers for detectable deficiency zero models [16].

It has been known for a long time, however, that the reaction network representation of a kinetic dynamics is generally not unique, i.e. reaction networks with different structures and/or different set of chemical complexes may represent the same dynamics. This phenomenon is called macro-equivalence [7], confoundability [17] or dynamical equivalence [18], where the possible CRNs corresponding to the same dynamics are called realizations of a kinetic ODE model. The notion of linear conjugacy extends dynamical equivalence by allowing a positive diagonal linear transformation between the states of linearly conjugate realizations [19]. It is known, too, that important model properties such as deficiency, strong connectivity (also called weak reversibility), complex or detailed balance are realization dependent. Therefore, finding dynamically equivalent or linearly conjugate CRN structures with certain required properties can be an interesting and important problem for proving qualitative properties of the model. It was shown that several sub-problems of this class can be successfully solved in the framework of linear and mixed integer linear programming (see, e.g. [18,20]). In [21] an MILP-based procedure was proposed for finding weakly reversible linearly conjugate realizations of kinetic systems with minimal deficiency. The algorithm was based on the result that for weakly reversible realizations, maximizing the number of reaction graph components minimizes the deficiency. This method uses integer variables for the partitioning of complexes between linkage classes. However, it is known that MILP problems are generally NP-hard and therefore it is often computationally problematic to solve large problems containing integer variables. Moreover, for general non-weakly reversible CRN structures, the basic principle of [21] cannot be applied. Therefore, the approach of this paper is different, and our aim is to examine and use the special algebraic consequences of zero deficiency to give a general algorithm for computing such realizations of kinetic systems.

The structure of the paper is the following. In Section 2, the notations used for the representation of kinetic dynamics and linear conjugacy are introduced. Section 3 contains the main result that is an optimization based method for the computation of deficiency zero linearly conjugate kinetic realizations. In Section 4 two illustrative examples are shown, while Section 5 summarizes the contribution of the paper.

2. Kinetic systems and their realizations

The basic notions and tools related to reaction kinetic systems and their realizations are briefly summarized in this section with an emphasis on their effect on the structural stability. The following mathematical notations will be used in the paper. $\mathbb{R}^n_+$ and $\bar{\mathbb{R}}^n_+$ denote the positive and nonnegative orthant of the n-dimensional Euclidean space $\mathbb{R}^n$, respectively, and $\mathbf{0}$ denotes the zero vector. Similarly, $\mathbf{1}$ denotes a column vector, all entries of which are 1. For an n-dimensional column vector v, $\mathrm{diag}(v)$ is the $n \times n$ diagonal matrix with $v_1, \ldots, v_n$ in its diagonal. For an arbitrary matrix M, $\mathrm{im}(M)$, $\ker(M)$ and $\mathrm{col}(M)$ denote the image, kernel and the set of columns of M, respectively. The element in the ith row and jth column of a matrix M is denoted by $M_{i,j}$ or $[M]_{i,j}$ whenever the latter is more convenient. $V^\perp$ and $\dim(V)$ denote the orthogonal complement and dimension of the vector space V, respectively, while the sum of vector spaces V_1 and V_2 is defined as $V_1 + V_2 = \{v_1 + v_2 \mid v_1 \in V_1, v_2 \in V_2\}$. The set of natural numbers (including zero) is denoted by $\mathbb{N}_0$. Two matrices $M_1, M_2 \in \mathbb{R}^{n\times m}$ are called *structurally equal* if the positions of the zero and non-zero elements are the same in M_1 and M_2, i.e. $[M_1]_{i,j} \neq 0$ if and only if $[M_2]_{i,j} \neq 0$. Additionally, we will use the following notations known from propositional calculus: '$\Longrightarrow$' and '$\Longleftrightarrow$' denote the 'implies' and 'if and only if' relations between logical expressions having the 'true' or 'false' value.

2.1. The algebraic structure of kinetic systems

The general form of dynamic models studied in this paper is the following

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

where $x \in \mathbb{R}^n$ is the state vector, $Y \in \mathbb{N}_0^{n\times m}$, $A_k \in \mathbb{R}^{m\times m}$ is a special Metzler-matrix defined as:

$$[A_k]_{i,j} = \begin{cases} -\sum_{h=1, h\neq i}^{m} k_{hi} & \text{if} \quad i = j \\ k_{ji} \geq 0 & \text{if} \quad i \neq j. \end{cases} \tag{2}$$

It is clear from (2) that A_k is a matrix with non-positive diagonal and non-negative off-diagonal elements and zero column sums. Therefore, A_k is often called the *Kirchhoff-matrix* of the system in the theory of kinetic systems. The monomial vector function $\psi : \mathbb{R}^n \to \mathbb{R}^m$ is defined as

$$\psi_j(x) = \prod_{i=1}^{n} x_i^{Y_{i,j}}, \quad j = 1, \ldots, m. \tag{3}$$

It is easy to show that (1) defines a nonnegative system, i.e. the nonnegative orthant is invariant for its dynamics (see, e.g. [13]). With the notation $M = Y \cdot A_k$, the model (1) can be written as

$$\dot{x} = M \cdot \psi(x). \tag{4}$$

A polynomial dynamical system with state vector $x \in \mathbb{R}^n$ is called *to have the kinetic property* (or simply *kinetic*) if there exist $Y \in \mathbb{N}_0^{n\times m}$ and an $m \times m$ Kirchhoff matrix A_k such that the ODEs of the system can be written in the form of Eq. (1), where ψ is given by (3). The following necessary and sufficient condition for a general polynomial system to be kinetic was given in [22]. Consider a polynomial system written as

$$\dot{x} = \tilde{M} \cdot \tilde{\psi}(x) \tag{5}$$

where $\tilde{M} \in \mathbb{R}^{n\times\tilde{m}}$ and $\tilde{\psi}_j(x) = \prod_{i=1}^{n} x_i^{B_{i,j}}$, $i = 1, \ldots, \tilde{m}$ with $B \in \mathbb{N}_0^{n\times\tilde{m}}$. Then, (5) can be written into the form (1), i.e. there exist appropriate matrices Y and A_k such that

$$\tilde{M} \cdot \tilde{\psi}(x) = Y \cdot A_k \cdot \psi(x), \quad \forall x \in \bar{\mathbb{R}}^n_+ \tag{6}$$

if and only if the following condition is fulfilled for $\tilde{M}$ and B:

$$\text{if } \tilde{M}_{i,j} < 0, \text{ then } B_{i,j} > 0, \quad \text{for } i = 1, \ldots, n, \quad j = 1, \ldots, \tilde{m}. \tag{7}$$

Condition (7) expresses the fact that kinetic systems cannot contain negative cross-effects [3]. In [22], in the framework of a constructive proof, a simple procedure was described to generate a possible Y, A_k pair (called the *canonical mechanism*) such that (6) holds. It has to be noted however, that Y and A_k fulfilling (6) for given $\tilde{M}$ and $\tilde{\psi}$ are generally non-unique.

The chemically originated notions of kinetic systems are the following. The *species* of the system are denoted by $X_1, \ldots, X_n$, and the concentrations of the species are the state variables of (1), i.e. $x_i \geq 0$ for $i = 1, \ldots, n$. The structure of kinetic systems is given in terms of its *complexes* C_j, $j = 1, \ldots, m$ that are formally the nonnegative integer linear combinations of the species, i.e. $C_j = \sum_{i=1}^{n} [Y]_{i,j} X_i$ for $j = 1, \ldots, m$, and therefore Y is also called the *complex composition matrix*.

The chemical reactions $C_i \to C_j$ where $i \neq j$, with the *reaction rate coefficient* $k_{ij} > 0$, represent the transformation of the complexes into each other with the so-called mass action law type *reaction rate* r_{ij} given by

$$r_{ij}(x) = k_{ij}\psi_i(x) = k_{ij} \prod_{\ell=1}^{n} x_\ell^{Y_{\ell,i}}, \tag{8}$$

where $k_{ij} = [A_k]_{j,i}$ as it is written in (2). If $[A_k]_{j,i} = 0$ for any $i \neq j$, it means that the reaction $C_i \to C_j$ is not present in the system.