Structural analysis of kinetic systems with uncertain parameters

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Abstract

In this short paper the structural (i.e., reaction-graph-related) properties of kinetic systems with uncertain parameters are examined. It is briefly shown that certain structural analysis results developed earlier for non-uncertain kinetic systems can be generalized to the case when the monomial coefficients are represented as points of a convex polyhedron.

1. Introduction

Kinetic systems with polynomial non-linearities are typically used for the description of dynamical processes coming primarily from biochemistry [10]. However, their application domain is actually much wider than that, and extends to a large family of non-negative systems [1]. The simple factorization of kinetic models containing the Laplacian matrix of the reaction graph allows the development of efficient structure-computation methods in various optimization frameworks (see, e.g. [5, 6]).

Even if the monomials of a kinetic system are assumed to be known, the parameters (i.e. the monomial coefficients) are often uncertain in practice. For example, one may consider the situation when the kinetic polynomial ODE model is identified from noisy measurement data. In such a case, using the covariance matrix of the estimates, we can define a simple interval-based [7], or more generally, a polytopic uncertain model. The goal of this paper is to generalize and briefly illustrate some basic notions such as sparse and dense realizations (see [8]) and the corresponding computation model for uncertain kinetic systems.

2. Background

2.1. Kinetic systems

Non-negative polynomial systems are defined in the form:

$$\dot{x} = M \cdot \varphi(x) \tag{1}$$

where $x : \mathbb{R} \to \mathbb{R}^n$ is a non-negative valued function, $M \in \mathbb{R}^{n\times p}$ is a coefficient matrix and $\varphi : \overline{\mathbb{R}}^n_+ \to \overline{\mathbb{R}}^p_+$ is a monomial-type vector-mapping. The sign conditions of the elements of M ensuring the invariance of the non-negative orthant with respect to the dynamics (1) can be easily checked [2].

We consider kinetic systems as a special subset of non-negative dynamical systems, that are suitable for describing the dynamics of chemical reaction networks (CRNs). However, we treat kinetic models as a general nonlinear system class, and do not require that they are chemically realizable. Several thermodynamically relevant properties such as component mass conservation, detailed or complex balance can be ensured by adding further convex constraints to the computations (see, e.g. [4]).

In a **reaction network** reactions take place among complexes $C_1, \dots, C_m$, that are generated as formal linear combinations of species $X_1, \dots, X_n$. A reaction network can be characterized by two matrices. The **complex composition matrix** $Y \in \mathbb{N}^{n\times m}$ describes the structures of the complexes

$$C_j = \sum_{i=1}^{n} [Y]_{ij} \cdot X_i \quad i \in \{1, \dots, n\},\ j \in \{1, \dots, m\}$$

The presence of the reactions in the CRN are encoded trough the rate coefficients as the off diagonal elements of the **Kirchhoff matrix** $A_k \in \mathbb{R}^{m\times m}$, which is a Metzler

matrix with zero column-sums, i.e.

$$\sum_{i=1}^{m}[A_k]_{ij} = 0 \qquad \forall j \in \{1,\dots,m\} \tag{2}$$

$$[A_k]_{ij} \geq 0 \qquad i \neq j \tag{3}$$

According to this notation, there is a reaction $C_i \to C_j$ if and only if $[A_k]_{ji}$ is strictly positive. Since the kinetic model is uniquely determined by the complex composition matrix and the Kirchhoff matrix, we refer to a CRN by the corresponding matrix pair (Y, A_k).

If mass action kinetics is assumed, the equations governing the dynamics of the **concentrations of the species** in the CRN described by the function $x : \mathbb{R} \to \mathbb{R}^n_+$ can be written in the form of a polynomial system:

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

where $\psi : \overline{\mathbb{R}}^n_+ \to \overline{\mathbb{R}}^m_+$ is a monomial function with coordinate functions $\psi_j(x) = \prod_{i=1}^{n} x_i^{[Y]_{ij}},\ j \in \{1,\dots,m\}$.

A non-negative polynomial system (1) is called a **kinetic system** if there exists a reaction network (Y, A_k) so that the dynamics of the two models are equivalent, i.e.

$$M \cdot \varphi(x) = Y \cdot A_k \cdot \psi(x). \tag{5}$$

Reaction networks with different sets of complexes and reactions can be governed by the same dynamics [3, 10]. If Equation (5) is fulfilled, then the CRN (Y, A_k) is called a **dynamically equivalent realization** of the kinetic system (1).

We want to determine realizations on a fixed set of complexes, which defines the matrix Y and the monomial function ψ. The kinetic system (1) can be transformed so that the monomial function φ is equal to ψ (and $p = m$ holds), but the described dynamics remains the same. In this case Equation (5) can be written as:

$$M = Y \cdot A_k \tag{6}$$

A reaction network can also be represented by a weighted directed graph $G(V, E)$ called **Feinberg-Horn-Jackson graph** or reaction graph for brevity [10]. The vertices and edges represent the complexes and reactions, respectively. There is a directed edge from complex C_i to C_j if and only if $[A_k]_{ji}$ is positive, which is the weight of the edge.

2.2. Uncertain kinetic systems

If the parameters determining the model are not precisely known, the non-negative system describing the dynamics can be written using uncertain parameters.

We consider the matrix M decoding the coefficients of the monomials as a point $\widetilde{M}$ in the Euclidean space $\mathbb{R}^{nm}$. In the uncertain model we assume that all the possible points $\widetilde{M}$ are in a closed convex polyhedron $\mathcal{M}$, which is defined as the intersection of halfplanes determined by the facets of the polyhedron. The boundaries of the halfplanes are hyperplanes with normal vectors $n_1,\dots,n_p \in \mathbb{R}^{nm}$ and constants $b_1,\dots,b_p \in \mathbb{R}$. Applying these notations, the polyhedron $\mathcal{M}$ can be written as the set of solutions of a linear inequality system as follows.

$$\mathcal{M} = \{\widetilde{M} \in \mathbb{R}^{nm} \mid n_i \cdot \widetilde{M} \leq b_i, i \in \{1,\dots,p\}\} \tag{7}$$

In the case of the uncertain model, we examine realizations assuming a fixed set of complexes. Therefore, the parameters of the model are the matrix Y and the polyhedron $\mathcal{M}$, and a reaction network (Y, A_k) is called a realization of the uncertain kinetic system $[\mathcal{M}, Y]$ if there exists a coefficient matrix $M \in \mathbb{R}^{nm}$ so that the equation $M = Y \cdot A_k$ holds and the point $\widetilde{M}$ is in the polyhedron $\mathcal{M}$. This realization is referred to as (M, A_k).

2.3. Computational approach

A realization (M, A_k) of an uncertain kinetic system $[\mathcal{M}, Y]$ on a fixed set of complexes can be computed applying linear optimization.

In the optimization model the variables are all the entries of the matrix M and the off-diagonal entries of matrix A_k, while the additional required properties of a realization can be written as linear constraints. Dynamical equivalence is determined by Equation (6), the Kirchhoff property of matrix A_k is defined by Equations (2) and (3), and the the coefficients being in the possible set can be ensured by the inequalities in the definition (7) of the polyhedron $\mathcal{M}$. It is possible to define some additional linear constraints on the variables to characterize only special realizations of the model. Due to the linearity of the constraints, the set of possible realizations is a convex (constrained) polyhedron.

The objective function of the optimization model can be defined according to the properties of the realization in demand, as we will see in Section 3.

3. Realizations with special properties

Among the realizations of a kinetic system there are some with particular importance. A dynamically equivalent realization of a kinetic system with a fixed set of complexes having maximal or minimal number of reactions is called **dense** or **sparse realization**, respectively [8]. It is known that for any kinetic system there might be several different sparse realizations. However, the dense realization is structurally unique and defines a superstructure. The superstructure is the reaction graph of the dense realization that contains the reaction graphs of every realization of the kinetic

system as a subgraph. Such realizations can be introduced in the case of the uncertain model as well.

Definition 3.1. *A realization (M, A_k) of the uncertain kinetic system $[\mathcal{M}, Y]$ is called a dense (sparse) realization if there is a maximal (minimal) number of reactions taking place, considering all possible coefficient matrices $\widetilde{M} \in \mathcal{M}$.*

It can be proven that despite the different dynamical properties, the dense realization of the uncertain kinetic system has the superstructure property. The proof is based on the same idea as in the general case, see [9].

Proposition 3.2. *The dense realization of an uncertain kinetic system $[\mathcal{M}, Y]$ (considering a finite set of linear constraints on the parameters) determines a superstructure among all realizations of the (constrained) model.*

Proof. As we have seen, the set of possible realizations of the constrained uncertain kinetic system can be represented by a convex polyhedron $\mathcal{P}$. If the point $D \in \mathcal{P}$ represents a dense realization, then the superstructure property means that any coordinate of an arbitrary point in $\mathcal{P}$ can be positive only if the same coordinate in D is positive as well. Let us assume by contradiction that there is another realization $Q \in \mathcal{P}$ so that there is an index $j \in \{1, \dots nm\}$ for which $D_j = 0$ and $Q_j > 0$ hold. Because of the convexity of $\mathcal{P}$, the convex combination

$$R = c \cdot D + (1 - c) \cdot Q \qquad c \in (0, 1)$$

is also in the polyhedron, however R has more positive coordinates than the dense realization does, which is a contradiction. □

It follows that the structure of the dense realization is unique. If there were two different dense realizations, then the reaction graphs representing them would contain each other as subgraphs, consequently these graphs must be structurally identical.

If the parameters and constraints of the uncertain kinetic system allow, we might be able to prove the structural uniqueness of the uncertain model based on the following proposition.

Proposition 3.3. *The dense and sparse realizations of the (constrained) uncertain kinetic system has the same number of reactions if and only if all realizations of the model are structurally identical.*

Proof. According to the definitions, if in the dense and sparse realizations there is the same number of reactions, then in all realizations there must be the same number of reactions. Since the structure of the dense realization is unique, there cannot be two realizations with the maximal number of reactions and with different structures, therefore all realizations must be structurally identical to the dense realization. The converse statement is trivial. □

The dense realization of the (constrained) uncertain kinetic system can be determined by a recursive algorithm, based on the same idea as the method in [9]. The basic principle of the computation is the following. For every reaction, a realization is assigned that contains that reaction, if possible. A realization usually contains several reactions, therefore, generally there is no need to perform a separate optimization step for each reaction. The convex combination of the computed realizations is also a realization, where all reactions are present that are in the computed realizations. Consequently it represents a dense realization. The computation can be performed in polynomial time since it requires at most $m(n + m - 1)$ LP optimization steps and some minor computation.

In the algorithm the realizations are determined using the following procedure:

FindPositive$(\mathcal{M}, Y, L, H)$ returns a point $Q \in \mathcal{P}$ that represents a realization of the uncertain model $[\mathcal{M}, Y]$, fulfils a finite set L of linear inequalities, and considering a set H of indices the value of the objective function $\sum_{j \in H} q_j$ is maximal. The procedure also returns the set B of indices where $k \in B$ if and only if $Q_k > 0$. If there is no such realization then the pair $(\mathbf{0}, \emptyset)$ is returned.
Based on the above, the algorithm for determining the dense superstructure of uncertain models is as follows.

Algorithm 1

procedure COMPUTE_DENSE($\mathcal{M}, Y, L$)
  $H := \{1, 2, \dots, mn + m^2 - m\}$
  $B := H$
  $Result := \mathbf{0} \in \mathbb{R}^{m^2 - m + n}$
  $loops := 0$
  while $B \neq \emptyset$ **do**
    $(Q, B) :=$ FindPositive$(\mathcal{M}, Y, L, H)$
    $Result := Result + Q$
    $H := H \setminus B$
    $loops := loops + 1$
  end while
  $Result := Result/loops$
  if $Result = \mathbf{0}$ **then**
    There is no such realization.
  else
    $Result$ is a dense realization.
  end if
end procedure

4. Example

In this section the realizations of a Lotka-Volterra type uncertain kinetic system are examined. For simplicity we define the uncertain parameters so that each of them must be within a predefined distance to the nominal parameter. The nominal model is defined by the matrices

$$M = \begin{bmatrix} 0.4 & 0 & -0.018 & 0 & 0 & 0 \\ 0 & 0 & 0.023 & -0.8 & 0 & 0 \end{bmatrix}$$

$$Y = \begin{bmatrix} 1 & 2 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 & 2 \end{bmatrix}$$

We assume that the nonzero entries in M are uncertain, and thus the elements $\widetilde{M} \in \mathcal{M}$ are given by:

$$\begin{cases} M_{ij} - \delta \leq \widetilde{M}_{ij} \leq M_{ij} + \delta \text{ for } i,j \text{ s.t. } M_{ij} \neq 0 \\ \widetilde{M}_{ij} = 0 \text{ for } i,j \text{ s.t. } M_{ij} = 0, \end{cases}$$

where δ is a positive real number. It is easy to see that the polyhedron $\mathcal{M}$ is a 4- dimensional cube. In the case of $\delta = 0.01$, there are two structurally different sparse realizations. By increasing δ to 0.04 the sparse realization becomes unique, but there are less reactions in it.

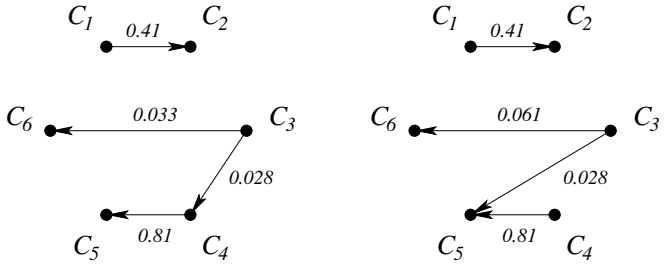

Figure 1: Different sparse realizations in case of $\delta = 0.01$

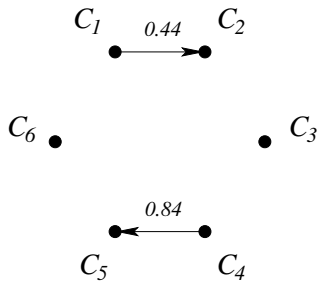

Figure 2: Sparse realization for $\delta = 0.04$

It is generally expected that in the dense realization the number of reactions increases with the extension of uncertainty intervals. However, in the case of the present example, we find that it remains structurally the same for the values 0.01 and 0.04 of δ.

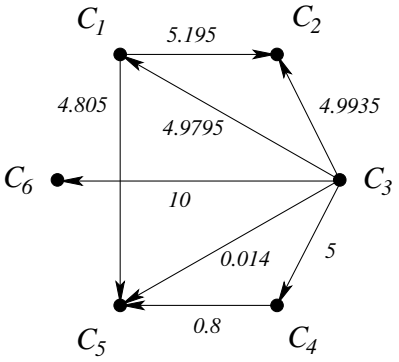

Figure 3: The reaction graph of the dense realization

It can be seen in Figs. 1, 2 and 3 that all the depicted reaction graphs are indeed subgraphs of the graph corresponding to the dense realization.

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