

Structural analysis of kinetic systems with uncertain parameters

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Kinetic systems

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

$$x : \mathbb{R} \rightarrow \mathbb{R}_+^n \quad M \in \mathbb{R}^{n \times p} \quad \varphi : \overline{\mathbb{R}}_+^n \rightarrow \overline{\mathbb{R}}_+^p$$

A polynomial system is kinetic $\iff$
there is a chemical reaction network (CRN) governed by the
same dynamics.

Chemical reaction networks

A CRN can be determined by

- ▶ a set of **species**: $\mathcal{S} = \{X_i \mid i = 1 \dots n\}$
- ▶ a set of **complexes**: $\mathcal{C} = \{C_j = \sum_{i=1}^n \alpha_{ji} X_i \mid \alpha_{ji} \in \mathbb{N}^+, j = 1 \dots m\}$
- ▶ a set of **reactions**: $\mathcal{R} \subseteq \{(C_i, C_j) \mid C_i, C_j \in \mathcal{C}\}$
- ▶ **reaction rate coefficients** $k_{ij} \in \mathbb{R}_+$

The properties are encoded by special matrices,

- ▶ **complex composition matrix** $Y \in \mathbb{N}^{n \times m}$, where $[Y]_{ij} = \alpha_{ji}$
- ▶ **Kirchhoff matrix** $A_k \in \mathbb{R}^{m \times m}$, where $[A_k]_{ij} = \begin{cases} k_{ji} & \text{if } i \neq j \\ -\sum_{l=1, l \neq i}^m k_{il} & \text{if } i = j \end{cases}$

Dynamical description

Assuming mass action kinetics

$$\dot{x} = Y \cdot A_k \cdot \psi^Y(x) \quad (2)$$

- ▶ $x : \mathbb{R} \rightarrow \mathbb{R}_+^n$ is the **concentrations of the species**
- ▶ $\psi^Y : \mathbb{R}^n \rightarrow \mathbb{R}^m$ is a monomial function, $\psi_j^Y(x) = \prod_{i=1}^n x_i^{[Y]_{ij}}$

The CRN referred to as the matrix pair (Y, A_k) is a **dynamically equivalent realization** of the kinetic system $\dot{x} = M \cdot \varphi(x)$ (1) if

$$M \cdot \varphi(x) = Y \cdot A_k \cdot \psi^Y(x) \quad (3)$$

After simplification, assuming a fixed set of complexes: $M = Y \cdot A_k$

Uncertain kinetic systems

The coefficient matrix M of the kinetic system $\dot{x} = M \cdot \varphi(x)$ is unknown.

- ▶ M is represented by the point $\widetilde{M} \in \mathbb{R}^{nm}$
- ▶ the possible points are in a convex polyhedron $\mathcal{M}$

$$\mathcal{M} = \{\widetilde{M} \in \mathbb{R}^{nm} \mid n_i \cdot \widetilde{M} \leq b_i, i \in \{1, \dots, p\}\} \quad (4)$$

The uncertain model – on a fixed set of complexes – is referred to as $[\mathcal{M}, Y]$.

The CRN (Y, A_k) is a **realization of the uncertain kinetic system** $[\mathcal{M}, Y]$ if

- ▶ there is a point $\widetilde{M} \in \mathcal{M}$ so that $M = Y \cdot A_k$ holds.
- ▶ this CRN is denoted as (M, A_k)

Computational model – LP

Variables: A_k (off-diagonal entries)
 M (or identically $\widetilde{M}$)

Constraints: $M = Y \cdot A_k$

$$\begin{aligned} \sum_{i=1}^m [A_k]_{ij} &= 0 & j = 1, \dots, m \\ [A_k]_{ij} &\geq 0 & i \neq j, \quad i, j = 1, \dots, m \\ \widetilde{M} \cdot n_i &\leq b_i & i = 1, \dots, p \end{aligned}$$

The **objective** can be defined according to the demands.

Graph representation

A CRN can be described by an edge weighted **directed graph** $G(V, E)$.

- ▶ the *vertices* correspond to the complexes, $V(G) = \mathcal{C}$
- ▶ the *directed edges* describe the reactions, $E(G) = \mathcal{R}$
- ▶ the *weights* are the reaction rate coefficients, $w((C_i, C_j)) = k_{ij}$
- ▶ no loops or multiple edges

Definition 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 $\widetilde{M} \in \mathcal{M}$.

Super-structure property

Definition 2

Let $\mathcal{G}$ be a set of directed graphs with labelled vertices. A directed graph is called the **super-structure** with respect to the set $\mathcal{G}$ if it contains every graph in the set as a subgraph, not considering the reaction rates, and it is minimal under inclusion.

The results depend on the super-structure property of the dense realizations.

Proposition 1

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

Proof of Proposition 1

Proof.

The possible solutions of the LP model are in a convex polyhedron

$$\mathcal{P} \subset \mathbb{R}^{m^2 - m + mn}$$

Let the point $Q \in \mathcal{P}$ represent a dense realization

it has the maximum number of positive coordinates.

Let us assume that there is an other point $R \in \mathcal{P}$ for which

$\exists i \in \{1, \dots, m^2 - m + mn\}$ so that $Q_i = 0$ but $R_i > 0$

Consider an interior point S of the interval $(Q, R) \subset \mathcal{P}$

$$(Q, R) = \{S \in \mathbb{R}^{m^2 - m + mn} \mid S = c \cdot Q + (1 - c) \cdot R, c \in (0, 1)\}$$

$$\forall j \in \{1, \dots, m^2 - m + mn\} \quad [Q_j > 0 \text{ or } R_j > 0] \implies S_j > 0$$

There are more positive coordinates in S than in the dense realization

$\implies$ a contradiction.



Structural uniqueness

Proposition 2

The dense and sparse realizations of the (constrained) uncertain kinetic system has the same number of reactions

$\iff$ *all realizations of the model are structurally identical.*

Proof.

- ▶ If in the dense and sparse realizations there is the same number of reactions $\implies$ all realizations have the same number of reactions.
- ▶ The structure of the dense realization is unique $\implies$ all realizations must be structurally identical to the dense realization.



Algorithm for determining a dense realization

There are several solutions:

- ▶ apply integer variables $\rightarrow$ MILP
- ▶ work only under special restrictions

The idea of our polynomial-time method:

- ▶ Compute realizations to every reaction where it is present
- ▶ Define a convex combination of the representing points (with nonzero coefficients)
- ▶ If a reaction can be present in a realization $\Rightarrow$ the realization represented by the convex combination contains it as well

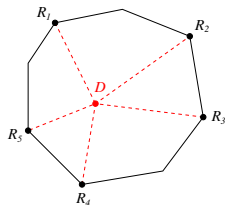


Figure: Dense realization as the convex combination

Procedure applied during the algorithm

FindPositive($\mathcal{M}, Y, L, H$) returns

- ▶ a realization of the uncertain model $[\mathcal{M}, Y]$ represented by the point $Q \in \mathcal{P}$
 - ▶ fulfils a finite set L of linear inequalities
 - ▶ objective function: $\sum_{j \in H} q_j$ is maximal
- ▶ set B of indices – $k \in B$ if and only if $Q_k > 0$
- ▶ If there is no realization fulfilling the constraints, then $Q = \mathbf{0}$ and $B = \emptyset$ is returned.

Algorithm 1

```
1: procedure COMPUTE_DENSE( $\mathcal{M}, Y, L$ )
2:    $H := \{1, 2, \dots, mn + m^2 - m\}$ 
3:    $B := H$ 
4:    $Result := \mathbf{0} \in \mathbb{R}^{m^2 - m + n}$ 
5:    $loops := 0$ 
6:   while  $B \neq \emptyset$  do
7:      $(Q, B) := \text{FindPositive}(\mathcal{M}, Y, L, H)$ 
8:      $Result := Result + Q$ 
9:      $H := H \setminus B$ 
10:     $loops := loops + 1$ 
11:  end while
12:   $Result := Result / loops$ 
13:  if  $Result = \mathbf{0}$  then
14:    There is no such realization.
15:  else
16:     $Result$  is a dense realization.
17:  end if
18: end procedure
```

Uncertain model example

The uncertain model is generated from the kinetic system $\dot{x} = M \cdot \psi$

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

with a fixed set of complexes given by the matrix

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

The complex polyhedron representing the possible solutions:

$$\mathcal{M} = \{M_{ij} - \delta \leq \widetilde{M}_{ij} \leq M_{ij} + \delta \mid M_{ij} \neq 0\}$$

Realizations of the uncertain model

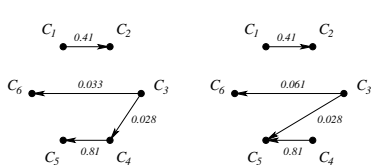


Figure: Sparse, $\delta = 0.01$

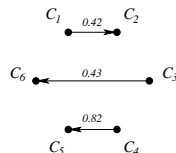


Figure: Sparse, $\delta = 0.02$

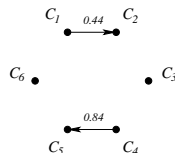


Figure: Sparse, $\delta = 0.04$

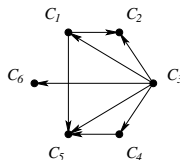


Figure: Dense, $0 \leq \delta \leq 0.04$

Thank you for your attention!