Identifiability of Mass Action Chemical Reaction Networks

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Introduction

A chemical reaction network, under the assumption of mass-action kinetics, gives rise to a dynamical system governing the concentrations of the different chemical species [1, 2, 3, 4, 5, 6, 7]. We are interested in studying the inverse problem, i.e., the identifiability of the reaction network and of its reaction rate constants, given the dynamics of chemical species concentrations.

In modern chemical and biochemical research, it has become very common to collect detailed information on time-dependent chemical concentration data for large networks of chemical reactions [? 8]. A great variety of computational methods have been developed for the identification of chemical reaction networks and their reaction rate constants from time-dependent measurements of chemical species concentrations.

On the other hand, *two different reaction networks might generate identical dynamical system models, making it impossible to discriminate between them, even if we are given experimental data of perfect accuracy and unlimited temporal resolution.* (Sometimes this limitation is referred to as the "fundamental dogma of chemical kinetics" [8, 9, 10].) We describe necessary and sufficient conditions for two reaction networks to give rise to the same dynamical system model.

Also, even if we know the reaction network that gives rise to the chemical dynamics under study, there might exist multiple sets of reaction rate constants that provide perfect fit for the data since they give rise to identical dynamical system models. We give a necessary and sufficient condition for the unique identifiability of the reaction rate constants of a chemical reaction network.

Acknowledgements. The authors are grateful for support from the United States National Science Foundation.

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Chemical reaction networks and mass-action kinetics

We use the standard terminology of Chemical Reaction Network Theory in the spirit of [3, 4, 6].

Notations

If I is a finite set, define:

- $\mathbb{R}_+^I = \left\{ \text{formal sums} \sum_{i \in I} \alpha_i i \text{ for all } \alpha_i \in \mathbb{R}_+ \right\}$

- *support* of $\alpha \in \mathbb{R}_+^I$: $supp(\alpha) = \{i \in I : \alpha_i \neq 0\}$.

- if $u = \sum_{i \in I} u_i i$ and $v = \sum_{i \in I} v_i i$ in $\mathbb{R}_+^I$, denote $u^v = \prod_{s \in \mathscr{S}} (u_s)^{v_s}$, setting $0^0 = 1$.

Chemical reaction network

Definition. A CRN is a triple $(\mathscr{S}, \mathscr{C}, \mathscr{R})$, where
$\mathscr{S}$ is the set of chemical *species*
$\mathscr{C} \subseteq \mathbb{R}_+^{\mathscr{S}}$ is the set of *complexes*
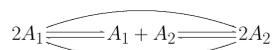$\mathscr{R} = \{y \to y'$, for some $y, y' \in \mathscr{C}\}$ is the set of *reactions*.
Moreover, the following are required. For any $y \in \mathscr{C}$:
(1) $y \to y \notin \mathscr{R}$
(2) there is $y' \in \mathscr{C}$ such that $y \to y'$ or $y' \to y$
and
(3) $\bigcup_{y \in \mathscr{C}} supp(y) = \mathscr{S}$.

Mass-action dynamics

Definition. A *mass-action system* is a chemical reaction network $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ and $k \in \mathbb{R}_+^{\mathscr{R}}$, where $k_{y \to y'}$ is the *reaction rate constant* of the reaction $y \to y' \in \mathscr{R}$. The corresponding ODE system is

$$\dot{c} = \sum_{y \to y' \in \mathscr{R}} k_{y \to y'} c^y (y' - y) =: r(\mathscr{R}, k)(c),$$

where $c \in \mathbb{R}^{\mathscr{S}}$ is the positive vector of species concentrations.

An example

$$2A_1 \rightleftharpoons A_1 + A_2 \rightleftharpoons 2A_2$$

$\mathscr{S} = \{A_1, A_2\}$
$\mathscr{C} = \{2A_1, A_1 + A_2, 2A_2\}$
$\mathscr{R} = \{2A_1 \rightleftharpoons A_1 + A_2, A_1 + A_2 \rightleftharpoons 2A_2, 2A_2 \rightleftharpoons 2A_1\}$

ODEs corresponding to our example

$$\begin{bmatrix} \dot{c}_1 \\ \dot{c}_2 \end{bmatrix} = k_{2A_1 \to A_1 + A_2} c^{2A_1} \begin{bmatrix} -1 \\ 1 \end{bmatrix} + k_{A_1 + A_2 \to 2A_1} c^{A_1 + A_2} \begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_{A_1 + A_2 \to 2A_2} c^{A_1 + A_2} \begin{bmatrix} -1 \\ 1 \end{bmatrix}$$
$$+ k_{2A_2 \to A_1 + A_2} c^{2A_2} \begin{bmatrix} 1 \\ -1 \end{bmatrix} + k_{A_1 \to 2A_2} c^{2A_1} \begin{bmatrix} -2 \\ 2 \end{bmatrix} + k_{2A_2 \to 2A_1} c^{2A_2} \begin{bmatrix} 2 \\ -2 \end{bmatrix}$$

$$= \begin{bmatrix} -k_{2A_1 \to A_1 + A_2} c_1^2 + k_{A_1 + A_2 \to 2A_1} c_1 c_2 - k_{A_1 + A_2 \to 2A_2} c_1 c_2 + k_{2A_2 \to A_1 + A_2} c_2^2 - 2k_{2A_1 \to 2A_2} c_1^2 + 2k_{2A_2 \to 2A_1} c_2^2 \\ k_{2A_1 \to A_1 + A_2} c_1^2 - k_{A_1 + A_2 \to 2A_1} c_1 c_2 + k_{A_1 + A_2 \to 2A_2} c_1 c_2 - k_{2A_2 \to A_1 + A_2} c_2^2 + 2k_{2A_1 \to 2A_2} c_1^2 - 2k_{2A_2 \to 2A_1} c_2^2 \end{bmatrix}.$$

Problem setup and results

Identifiability of rate constants given a reaction network and its mass-action dynamics

We are given a reaction network $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ and the differential equations that govern its dynamics. In general, it is not possible to identify the rate constants $k \in \mathbb{R}_+^{\mathscr{R}}$. For example the two different set of rates

$$
\begin{array}{ccc}
 & A_1 + A_2 & \\
 & 3 \uparrow & \\
 & A_0 & \xrightarrow{3} \\
2A_1 & \xrightarrow{3} & 2A_2
\end{array}
\qquad
\begin{array}{ccc}
 & A_1 + A_2 & \\
 & 1 \uparrow & \\
 & A_0 & \xrightarrow{4} \\
2A_1 & \xrightarrow{4} & 2A_2
\end{array}
$$

produce the same dynamics $\dot{c}_{A_0} = -9c_{A_0}, \; \dot{c}_{A_1} = \dot{c}_{A_2} = 9c_{A_0}.$

Definition. We say that a reaction network $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ has *uniquely identifiable rate constants* if $r(\mathscr{R}, k') \neq r(\mathscr{R}, k'')$ for any distinct rate constant vectors $k', \; k'' \in \mathbb{R}_+^{\mathscr{R}}$.

Then the following is true:

Theorem. *Under the mass-action kinetics assumption, a reaction network $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ has uniquely identifiable rate constants if and only if for each source complex $y_0 \in \mathscr{C}$, the reaction vectors $\{y' - y_0 : y_0 \to y' \in \mathscr{R}\}$ are linearly independent.*

Identifiability of the reaction network given the dynamics

Given the dynamics, i.e. the mass-action system of differential equations, it might be impossible to identify the reaction network uniquely. For instance, the following two networks give rise to the same system of ODEs, $[\dot{c}_{A_0}, \dot{c}_{A_1}, \dot{c}_{A_2}, \dot{c}_{A_3}] = [-1, 5/9, 2/9, 11/9]c_{A_0} =: K - A_0.$

$$
\begin{array}{ccc}
 & A_1 + A_2 & \\
 2/9 \uparrow & & \\
 & A_0 & \xrightarrow{11/18} \\
2A_1 & \xrightarrow{1/6} & 2A_3
\end{array}
\qquad
\begin{array}{ccc}
 & A_1 + A_3 & \\
 5/9 \uparrow & & \\
 & A_0 & \xrightarrow{1/3} \\
2A_2 & \xrightarrow{1/9} & 2A_3
\end{array}
$$

Definition. Let $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a chemical reaction network. Define the following family of functions:

$$Dyn(\mathscr{R}) = \left\{ r(\mathscr{R}, k) : k \in \mathbb{R}_+^{\mathscr{R}} \right\}.$$

Definition. Two chemical reaction networks $(\mathscr{S}, \mathscr{C}', \mathscr{R}')$ and $(\mathscr{S}, \mathscr{C}'', \mathscr{R}'')$ are called *confoundable* if $Dyn(\mathscr{R}') \cap Dyn(\mathscr{R}'') \neq \emptyset.$

Definition. For a reaction network $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ and $y_0 \in \mathscr{C}$ we denote by

$$Cone_{\mathscr{R}}(y_0) = \left\{ \sum_{y_0 \to y' \in \mathscr{R}} \alpha_{y_0 \to y'} (y' - y_0) : \alpha_{y_0 \to y'} > 0 \text{ for all } y_0 \to y' \in \mathscr{R} \right\},$$

the open convex cone generated by the set of reaction vectors $\{y' - y_0 : y_0 \to y' \in \mathscr{R}\}.$

Theorem. *Under the mass-action kinetics assumption, two chemical reaction networks $(\mathscr{S}, \mathscr{C}', \mathscr{R}')$ and $(\mathscr{S}, \mathscr{C}'', \mathscr{R}'')$ are confoundable if and only if they have the same source complexes and $Cone_{\mathscr{R}'}(y) \cap Cone_{\mathscr{R}''}(y)$ is nonempty for every source complex y.*

Revisiting our example

Denote $K = [0, 5/9, 2/9, 11/9]$ in the vector space generated by A_0, A_1, A_2 and A_3.. Then both networks are dynamically equivalent to the formal reaction $A_0 \to K$:

$$K - A_0 = \begin{bmatrix} -1 & -1 & -1 \\ 1 & 2 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 2 \end{bmatrix} \begin{bmatrix} 2/9 \\ 1/6 \\ 11/8 \end{bmatrix} = \begin{bmatrix} -1 & -1 & -1 \\ 1 & 0 & 0 \\ 0 & 2 & 0 \\ 1 & 0 & 2 \end{bmatrix} \begin{bmatrix} 5/9 \\ 1/9 \\ 1/3 \end{bmatrix}.$$

$K - A_0$ lies in the positive cones generated by the two sets of reaction vectors.

Cone configuration corresponding to the example
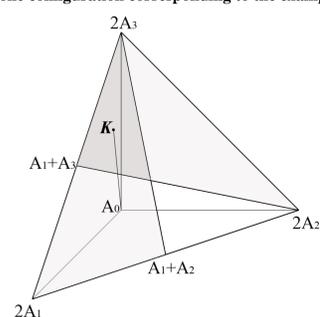
Applications

Modeling unimolecular and bimolecular reaction networks

We are given the dynamics of a chemical reaction network with species $A_1, \ldots, A_n$. We don't know what the reactions are but we know that all complexes are of the form A_i, $2A_i$ or $A_i + A_j$.

It is natural to try to construct a corresponding reaction network model that takes into account all the possible reactions, even if for some reactions the rate constants will turn out very small or zero. Since multiple reaction networks might produce the same dynamics, we look for a model that has a minimal number of reactions. This reduces the number of parameters (i.e., reaction rate constants) involved.

We consider the dynamically equivalent reduced network obtained by keeping only the reactions that generate each source cone $Cone_{\mathscr{R}}(y_0)$. Doing so

we reduce the number of parameters of the model from $O(n^4)$ to $O(n^3)$.
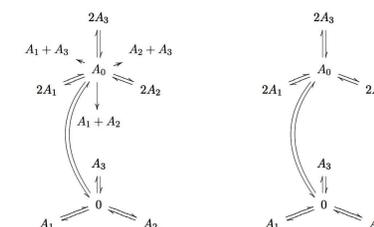
Remark. For the configuration (c) the choice of the minimal set of reactions is not unique, *and no matter which minimal set of reactions is chosen, the rate constants are not uniquely determined.* In other words:

No dynamically equivalent subnetwork has uniquely identifiable rate constants in this case. This fact must be taken into account whenever we try to design a numerical procedure to estimate the rate constants from experimental data.

Reduced networks for the three types of sources

Modelling unimolecular and bimolecular reaction networks

If two reaction networks $\mathscr{R}', \mathscr{R}''$ have the property that $Dyn(\mathscr{R}') \subseteq Dyn(\mathscr{R}'')$ then dynamical properties of $\mathscr{R}'$ can be inferred from looking at the (possibly simpler) network $\mathscr{R}''$. Such properties are therefore *transferred* from $\mathscr{R}''$ to $\mathscr{R}'$.
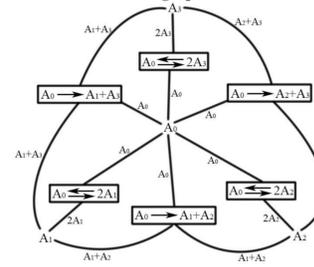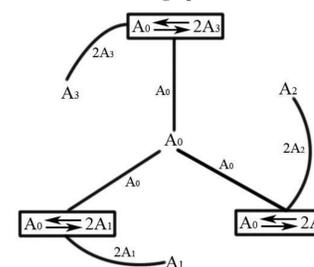For the following dynamically equivalent reaction networks

the large $\mathscr{R}'$ cannot have multiple equilibria for any value of its rate constants, because the reduced $\mathscr{R}''$ has this property, from the SR graph theorem.

SR graph terminology

The *nodes* consist of species and reactions (each reaction or pair of reversible reactions appear in a single node). The *edges* connect species nodes and reaction nodes as follows: if a species appears in a reaction, then there is an edge joining the corresponding species and reaction nodes; m that edge is *labeled* with the complex in which the species appears.

A *c-pair* (complex pair) is a pair of edges that meet at a reaction node and have the same label. A cycle is odd (*o-cycle*) or even (*e-cycle*) wihr respect to the number of its c-pairs. In particular, cycles with no c-pairs are e-cycles. The *stoichiometric coefficient* of an edge is the coefficient of the adjacent species in the complex label of the edge. Cycles for which alternately multiplying and dividing the stoichiometric coefficients along its edges gives the result 1 are called *s-cycles*. We say that two cycles *split a c-pair* if there is a c-pair that lies in the union of the sets of edges of the two cycles, but not in their intersection.

Theorem. *Let $\mathscr{R}$ be a reaction network such that all the cycles of its SR graph are o-cycles or s-cycles, and no two e-cycles split a c-pair. Then the mass-action dynamical system associated to $\mathscr{R}$ cannot have multiple positive equilibria, for any value of the rate constant vector k.*
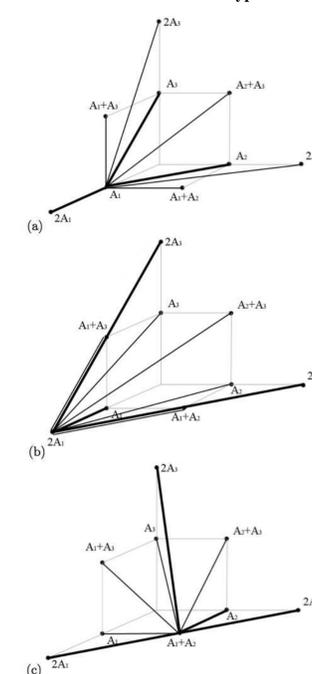
The SR graph of $\mathscr{R}'$

The SR graph of $\mathscr{R}''$