Analyzing Multistationarity in Chemical Reaction Networks

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Outline

- Introduction: Mathematical chemistry; Mass-action kinetics
- Motivation, Previous results
- Problem statement
- Our approach & results

Mass Action Kinetics

Definitions

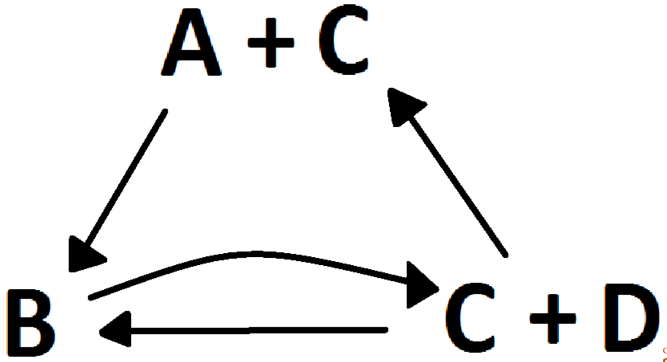
Any reaction network has a set of **Species**, $\mathcal{S}$, (chemicals or molecules) and a set of **Complexes**, $\mathcal{C}$, (compounds).
$\mathcal{S} = \{A, B, C, D\}$, and $\mathcal{C} = \{A + C, B, C + D\}$.

A + C

B **C + D**

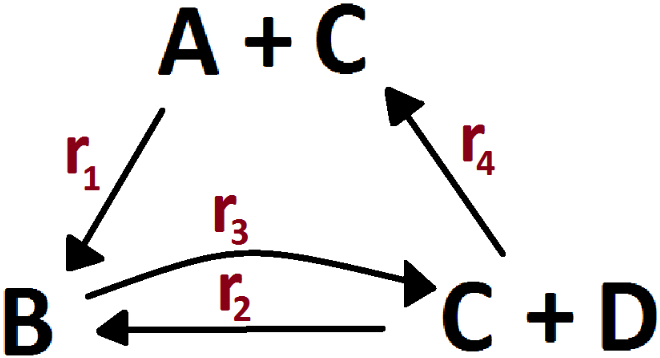
Definitions

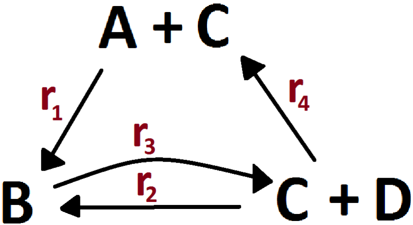
We also have **reactions**, $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$.
$\mathcal{R} = \{(A+C, B), (B, C+D), (C+D, B), (C+D, A+D)\}$



Definitions

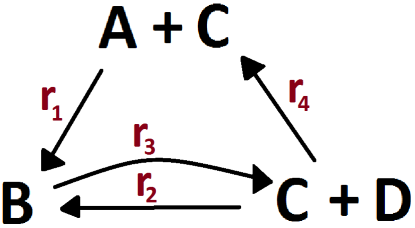
Each reaction has its own **Reaction rate**, denoted r_i.





Based on this reaction network, we can determine ODEs for each species:

$$\dot{A} = r_4 CD - r_1 AC$$
$$\dot{B} = r_1 AC + r_2 CD - r_3 B$$
$$\dot{C} = r_3 B - r_1 AC - r_2 CD$$
$$\dot{D} = r_3 B - r_4 CD - r_2 CD$$



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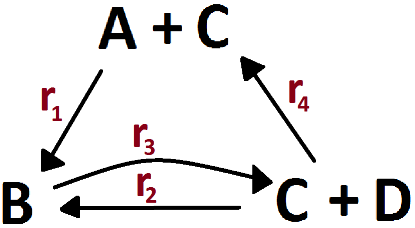
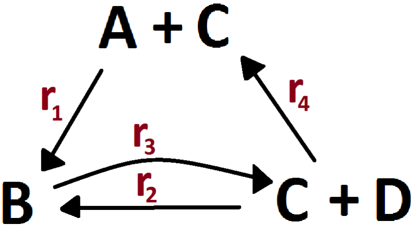
This system of ODEs guarantees that our system satisfies *the law of conservation of mass*.



Standard Representation

We can re-express the ODEs in a linear system of a **Stoichiometric Matrix**, Γ, and a **Reaction vector**, ρ.

$$\begin{aligned} \dot{A} &= r_4 CD - r_1 AC \\ \dot{B} &= r_1 AC + r_2 CD - r_3 B \\ \dot{C} &= r_3 B - r_1 AC - r_2 CD \\ \dot{D} &= r_3 B - r_4 CD - r_2 CD \end{aligned} = \begin{pmatrix} -1 & 0 & 0 & 1 \\ 1 & 1 & -1 & 0 \\ -1 & -1 & 1 & 0 \\ 0 & -1 & 1 & -1 \end{pmatrix} \cdot \begin{pmatrix} r_1 AC \\ r_2 CD \\ r_3 B \\ r_4 CD \end{pmatrix} = \Gamma \cdot \rho$$



Standard Representation

This is called the **Mass-Action Kinetics System**

$$\dot{\bar{x}} = \begin{pmatrix} -1 & 0 & 0 & 1 \\ 1 & 1 & -1 & 0 \\ -1 & -1 & 1 & 0 \\ 0 & -1 & 1 & -1 \end{pmatrix} \cdot \begin{pmatrix} r_1 AC \\ r_2 CD \\ r_3 B \\ r_4 CD \end{pmatrix} = \Gamma \cdot \rho(\bar{r}, \bar{x})$$

where $\overline{x}$ is the vector of species **concentrations**, and $\overline{r}$ is the vector of *reaction rates*

Definitions

- A **steady state** (or **equilibria**) of a chemical reaction network (CRN) with reaction rates $\bar{r}$, is a set of species concentrations $\bar{x}$ such that

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- A CRN is **multistationary** if, for a *fixed* set of reaction rates $\bar{r}$, there exist distinct non-trivial steady states $\bar{x}_1$ and $\bar{x}_2$ such that

$$\Gamma \cdot \rho(\bar{r}, \bar{x}_1) = \Gamma \cdot \rho(\bar{r}, \bar{x}_2) = \bar{0}$$

Multistationarity is of interest to both scientists and mathematicians.

Theorem (Joshi and Shiu)

If N is an embedded subnetwork of G, under certain hypotheses then if N admits m positive non-degenerate steady states (for some fixed choice of reaction rates), then G also admits m positive, non-degenerate steady states (for some fixed choice of reaction rates).*

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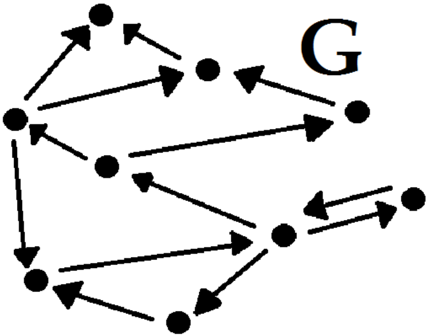

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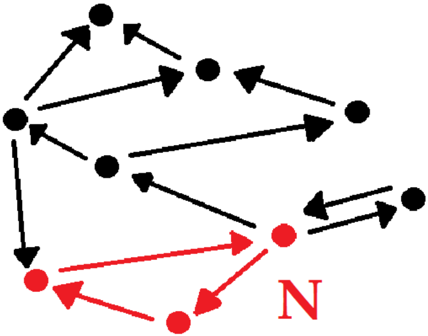

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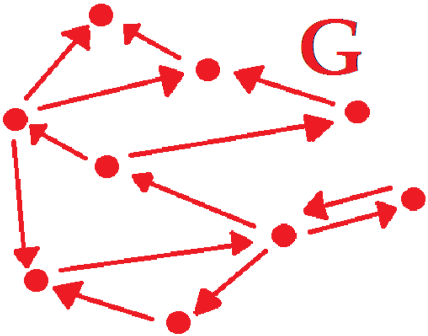

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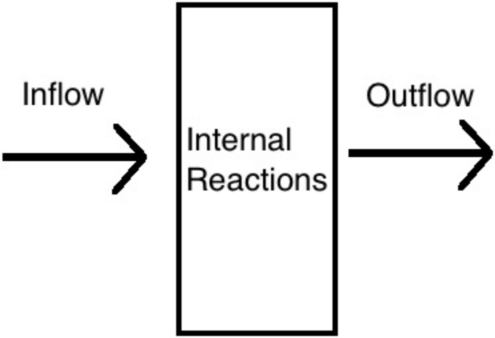
- This allows us to determine information of a complicated system from a simpler system...
- ... As long as we know a lot about these smaller *embedded networks*.
- This motivates creating a **catalog** of multistationary networks with **positive non-degenerate** steady states.
- Our work was on a particular infinite familiy of CRNs...

* The hypothesis we will consider is when "N is a CFSTR embedded in the fully open network G"



For $m, n \in \mathbb{N}$, we define the reaction networks

$$\widetilde{K}_{m,n} = \begin{cases} X_1 + X_2 \to 0 \\ \quad\vdots \\ X_{n-1} + X_n \to 0 \\ X_1 \to mX_n \\ X_i \leftarrow 0 \quad \text{(Inflow)} \\ X_i \to 0 \quad \text{(Outflow)}. \end{cases}$$

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$\widetilde{K}_{m,n}$ was known to be multistationary for odd n and $m \geq 2$. However, **non-degeneracy** is required for this family to be added to the catalog. Existence of multiple **non-degenerate** steady states for $\widetilde{K}_{m,n}$ was conjectured to be true (If true, $\widetilde{K}_{m,n}$ would be the first infinite family of reaction networks proven to exhibit multiple nondegenerate equilibria).

Definition (Non-degneracy)

A steady state $\bar{x}$ is **non-degenerate** if $Im(\Gamma) = Im(\text{Jacobian of } \widetilde{K}_{m,n} \text{ at } \bar{x})$

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Stoichiometric matrix for $\widetilde{K}_{m,n}$ is given by

$$-\Gamma_{1,..,2n} = \left(\begin{array}{ccccc|c} 1 & 0 & 0 & \cdots & 1 & \\ 1 & 1 & 0 & \cdots & 0 & \\ 0 & 1 & 1 & \cdots & 0 & I_{n\times n} \\ 0 & 0 & \ddots & \ddots & 0 & \\ 0 & 0 & \cdots & 1 & -m & \end{array}\right)$$

so it's full rank!

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Problem Re-statement

Find a set of rates $\bar{r}$ and distinct nontrivial steady states $\bar{x}_1$, $\bar{x}_2$ of $\widetilde{K}_{m,n}$ such that (for $i = 1, 2$)

- Steady states: $\Gamma \cdot \rho(\bar{r}, \bar{x}_i) = 0$
- Nondegeneracy: $\det(J|_{\bar{r},\bar{x}_i}) \neq 0$

Jacobian of $\widetilde{K}_{m,n}$

$J|_{\bar{r},\bar{x}} =$

$$\begin{bmatrix} -r_1x_2 - r_n - r_{n+1} & -r_1x_1 & 0 & \dots & 0 & 0 \\ -r_1x_2 & -r_1x_1 - r_2x_3 - r_{n+2} & -r_2x_2 & \dots & \vdots & \vdots \\ 0 & -r_2x_3 & -r_2x_2 - r_3x_4 - r_{n+3} & \ddots & 0 & 0 \\ 0 & 0 & -r_3x_4 & \ddots & -r_{n-2}x_{n-2} & 0 \\ \vdots & \vdots & \vdots & \ddots & -r_{n-2}x_{n-2} - r_{n-1}x_n - r_{2n-1} & -r_{n-1}x_{n-1} \\ mr_n & 0 & 0 & \dots & -r_{n-1}x_n & -r_{n-1}x_{n-1} - r_{2n} \end{bmatrix}$$

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where r_i are ordered $X_i + X_{i+1} \xrightarrow{r_i} 0, X_1 \xrightarrow{r_n} mX_n$, $X_i \xrightarrow{r_{n+i}} 0$, $0 \xrightarrow{r_{2n+i}} X_i$

ODE's $\begin{cases} \dot{x}_1 &= -r_1x_1x_2 - r_nx_1 - r_{n+1}x_1 + r_{2n+1} \\ \dot{x}_i &= -r_{i-1}x_{i-1}x_i - r_ix_ix_{i+1} - r_{n+i}x_i + r_{2n+i}, \text{ for } 2 \leq i \leq n-1 \\ \dot{x}_n &= -r_{n-1}x_{n-1}x_n + mr_nx_1 - r_{2n}x_n + r_{3n} \end{cases}$

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MULTIPLE EQUILIBRIA IN COMPLEX CHEMICAL REACTION NETWORKS: I. THE INJECTIVITY PROPERTY*

GHEORGHE CRACIUN† AND MARTIN FEINBERG‡

Abstract. The capacity for multiple equilibria in an isothermal homogeneous continuous flow stirred tank reactor is determined by the reaction network. Examples show that there is a very delicate relationship between reaction network structure and the possibility of multiple equilibria. We suggest a new method for discriminating between networks that have the capacity for multiple equilibria and those that do not. Our method can be implemented using standard computer algebra software and gives answers for many reaction networks for which previous methods give no information.

Key words. equilibrium points, chemical reaction networks, chemical reactors, mass-action kinetics

AMS subject classifications. 80A30, 37C25, 65H10

Find the steady states

Hand-wavy Approach

- Their proofs are constructive up to one use of the IVT.

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- Reverse-engineer Craicun and Feinberg's proofs to construct explicit rates and two distinct steady states that guarantee multistationarity for $\widetilde{K}_{m,n}$, and cross your fingers for non-degeneracy.
- We re-package their theorems into an algorithm for explicitly finding rates and steady states for any reaction network satisfying their hypothesis. (so no one would have to unwind their paper again)

How to show non-degeneracy

Once we had the process for creating reaction rates and steady states, we used the following approach:

- Find steady states and reaction rates for $\widetilde{K}_{m,n}$, but leave m to be a general variable ≥ 2.

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- Bound the function (above or below) by a polynomial in m (for both steady states).
- Numerically verify the leftover values of m.

$n = 3$ case

At the end of the day, we had these rates

$$r_1 = \frac{-1.1}{e^{-1.1}-1} \approx 1.65 \qquad r_2 = \frac{1.31}{e^{\frac{1.31}{m+1}} - 1} \qquad r_3 = \frac{1}{e-1} \approx .58$$

$$r_4 = \frac{.1}{e-1} \approx .06 \qquad r_5 = \frac{-.21}{e^{-2.1}-1} \approx .24 \qquad r_6 = \frac{m - 1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1}$$

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and two steady-state concentrations:

$$\begin{aligned} \bar{\mathbf{x}}_1 &= (1, 1, 1) \\ \bar{\mathbf{x}}_2 &= (e, e^{-2.1}, e^{\frac{2.1m+3.41}{m+1}}) \end{aligned}$$

Note that only $(\bar{\mathbf{x}}_2)_3, r_2$ and r_6 depend on m.

$n = 3$ case

Based on these inequalities we proved, with some help from Dr. Dean Baskin,

$$0.14m > r_6 = \frac{m - 1.31}{e^{\frac{2.1m+3.41}{m+1}} - 1} > 0.13m - 0.5$$

$$m + 1 > r_2 = \frac{1.31}{e^{\frac{1.31}{m+1}} - 1} \geq m \qquad \forall\ m \geq 2$$

$$e^{\frac{2.1y+3.41}{y+1}} > (\bar{x}_2)_3 = e^{\frac{2.1m+3.41}{m+1}} > e^{2.1} \qquad \forall\ m \geq y$$

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Proven Bounds

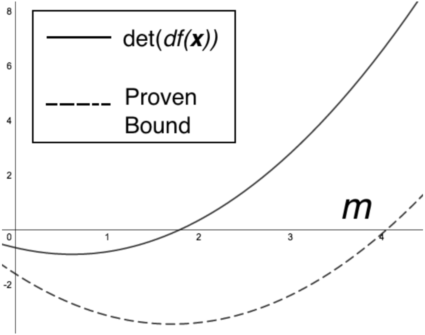
$$\det(J|_{\bar{r},\bar{x}_1}) > \ 0.6294m^2 - 2.156m - 1.61 \ \ \forall m \geq 2$$

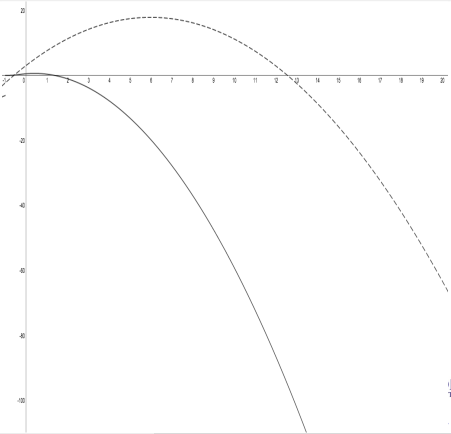
$$\det(J|_{\bar{r},\bar{x}_2}) < -0.41295m^2 + 4.9437m + 3.06205 \ \ \forall m \geq 20$$

$n = 3$ case

Theorem (BF & ZW)

The chemical reaction system $\widetilde{K}_{m,3}$ has multiple positive non-degenerate steady states for $m \geq 2$.





The leftovers

Existence of multiple non-degenerate equilibria for $\widetilde{K}_{m,n}$ is still conjectured to be true.

- We verified "by hand" existence of non-degenerate equilibria for small values: odd $5 \leq n \leq 11$ and all $2 \leq m \leq 5$.

The leftovers

Existence of multiple non-degenerate equilibria for $\widetilde{K}_{m,n}$ is still conjectured to be true.

- We verified "by hand" existence of non-degenerate equilibria for small values: odd $5 \leq n \leq 11$ and all $2 \leq m \leq 5$.
- I believe we have enough to prove the conjecture *for sufficiently large* m, odd n.
- We can prove bounds on all of the x_i andr_i that depend on m (in fact, very few actually depend on it)
- Ultimately it comes down to finding a non-recursive formula for $\det(J|_{\bar{r},\bar{x}})$.

Thank you!

References:

- *Analyzing Multistationarity in Chemical Reaction Networks with the Determinant Optimization Method*, B. Félix, A. Shiu, and Z. Woodstock **Applied Mathematics and Computation** 287– 288:60–73, 2016.
- *Multiple Equilibria in Complex Chemical Reaction Networks: I. The Injectivity Property*, G. Craciun and M. Feinberg. **SIAM Journal of Applied Math**