An Infinite Family of Networks with Multiple Non-Degenerate Equilibria

Bryan Félix[1] & Zev Woodstock[2]

[1]University of Texas at Austin
[2]James Madison University

MathFest, 2015

What are Chemical Reaction Networks?

Definition

A chemical reaction network $G = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ consists of three finite sets:

1. a set of species $\mathcal{S}$,
2. a set $\mathcal{C}$ of complexes, and
3. a set $\mathcal{R} \subseteq \mathcal{C} \times \mathcal{C}$ of reactions

Example

Let $\mathcal{S} = \{A, B\}$, $\mathcal{C} = \{0, A, B, A + B\}$ and $\mathcal{R} = \{(A + B, 0), (A, B)\}$ then, the network associated is:

$$A + B \to 0$$
$$A \to B$$

The Reaction Kinetics System

Definition

The *stoichiometric matrix* Γ is the $|\mathcal{S}| \times |\mathcal{R}|$ matrix whose k^{th} column is the vector $y_j - y_i$ of the k^{th} reaction $y_i \to y_j$.

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Definition

The *reactant vector* $\rho(x) \in \mathbb{R}^{|\mathcal{R}|}$ is the vector whose k^{th} entry represents the k^{th} reactant complex:

$$\alpha_1 X_1 + \alpha_2 X_2 + \cdots + \alpha_{|\mathcal{S}|} X_{|\mathcal{S}|}$$

as the product:

$$r_k X_1^{\alpha_1} X_2^{\alpha_2} \cdots X_{|\mathcal{S}|}^{\alpha_{|\mathcal{S}|}}$$

where $r_k \in \mathbb{R}^+$ is the reaction rate of the k^{th} reaction.

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The **reaction kinetics system** defined by a reaction network G is given by the following system of ODEs:

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Definition

A **steady state** of a reaction kinetics system $\frac{dx}{dt} = \Gamma \cdot \rho(x)$ is a non-negative concentration vector $x^* \in \mathbb{R}_{\geq 0}^{|\mathcal{S}|}$ for which $\Gamma \cdot \rho(x^*) = 0$.

Definition

A steady state $x^* \in \mathbb{R}_{>0}^{|\mathcal{S}|}$ is **nondegenerate** if $im(df(\mathbf{x}^*)) = im(\Gamma)$, where $df(\mathbf{x}^*)$ denotes the Jacobian of the reaction kinetics system at $\mathbf{x}^*$.

A Good Candidate: The Network $\widetilde{K}_{m,n}$

For positive integers $n \geq 2$, $m \geq 1$ we define the network $\widetilde{K}_{m,n}$ of order n and production factor m to be:

$$X_1 + X_2 \to 0$$
$$\vdots$$
$$X_{n-1} + X_n \to 0$$
$$X_1 \to mX_n$$
$$X_i \to 0$$
$$0 \to X_i$$

Theorem (Shiu & Joshi, 2015)

For positive integers $n \geq 2$ and $m \geq 2$, the fully open extension $\widetilde{K}_{m,n}$ is multistationary if n is odd.

Some Properties of $\widetilde{K}_{m,n}$

For any n, the system is given by,

$$\text{Reactions} \quad \begin{cases} X_1 + X_2 \overset{r_1}{\to} 0 & X_1 \overset{r_{n+1}}{\to} 0 & 0 \overset{r_{2n+1}}{\to} X_1 \\ X_2 + X_3 \overset{r_2}{\to} 0 & X_2 \overset{r_{n+2}}{\to} 0 & 0 \overset{r_{2n+2}}{\to} X_2 \\ \vdots & \vdots & \vdots \\ X_{n-1} + X_n \overset{r_{n-1}}{\to} 0 & X_{n-1} \overset{r_{2n-1}}{\to} 0 & 0 \overset{r_{3n-1}}{\to} X_{n-1} \\ X_1 \overset{r_3}{\to} mX_3 & X_n \overset{r_{2n}}{\to} 0 & 0 \overset{r_{3n}}{\to} X_n \end{cases}$$

$$\text{ODE's} \begin{cases} \dot{x}_1 & = -r_1 x_1 x_2 - r_n x_1 - r_{n+1} x_1 + r_{2n+1} \\ \dot{x}_i & = -r_{i-1} x_{i-1} x_i - r_i x_i x_{i+1} - r_{n+i} x_i + r_{2n+i}, \text{ for } 2 \leq i \leq n-1 \\ \dot{x}_n & = -r_{n-1} x_{n-1} x_n + m r_n x_1 - r_{2n} x_n + r_{3n} \end{cases}$$

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

$$df(\mathbf{x})_{(1,1)} = -r_1 x_2 - r_n - r_{n+1}$$
$$df(\mathbf{x})_{(1,2)} = -r_1 x_1$$

$$df(\mathbf{x})_{(i,i-1)} = -r_{i-1} x_i \quad \forall\ i \in \{2, 3, ..., n-1\}$$
$$df(\mathbf{x})_{(i,i)} = -r_{i-1} x_{i-1} - r_i x_{i+1} - r_{n+1}$$
$$df(\mathbf{x})_{(i,i+1)} = -r_i x_i$$

$$df(\mathbf{x})_{(n,1)} = m r_n$$
$$df(\mathbf{x})_{(n,n-1)} = -r_{n-1} x_n$$
$$df(\mathbf{x})_{(n,n)} = -r_{n-1} x_{n-1} - r_{2n}$$

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

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

Goal

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But,

$$\Gamma = \left[\begin{array}{cccccc|c|c} -1 & 0 & 0 & \dots & 0 & -1 & & \\ -1 & -1 & 0 & \dots & 0 & 0 & & \\ 0 & -1 & -1 & \dots & \vdots & \vdots & -I^n & I^n \\ 0 & 0 & -1 & \ddots & \vdots & \vdots & & \\ \vdots & \vdots & \vdots & \ddots & -1 & 0 & & \\ 0 & 0 & 0 & \dots & -1 & m & & \end{array}\right]$$

Hence, $Im(\Gamma) = \mathbb{R}^n$

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Hence, $Im(\Gamma) = \mathbb{R}^n$

NEW GOAL:

Find rates r_i and two steady state concentrations, $\mathbf{x}^*, \mathbf{x}^{\#}$, and show $\det(df(\mathbf{x})) \neq 0$.

The problem

Conjecture (Shiu & Joshi, 2015)

For positive integers $n \geq 2$ and $m \geq 2$, if n is odd, then $\widetilde{K}_{m,n}$ admits multiple positive **non-degenerate** steady states.

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Approach

Backtrack the **Determinant Optimization Method** by Craicun & Feinberg, 2005

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If two conditions hold for a chemical reaction system, then it has the capacity for at least two steady state equilibria.

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The main conditions on internal and outflow reactions:

$$(I) \qquad \det(y_1, y_2, ..., y_n) \cdot \det((y_1 - y_1'), (y_2 - y_2'), ..., (y_n - y_n')) < 0$$

$$(II) \qquad \sum_{i=1}^{k} \tilde{\eta}_i (y_i - y_i') \in \mathbb{R}_+^{\mathcal{S}} \text{ for positive numbers } \tilde{\eta}_1, ..., \tilde{\eta}_k.$$

Remark: The network $\widetilde{K}_{m,n}$ satisfies **both** conditions.

Define the **augmented Jacobian**,

$$T_\eta =$$

$$\begin{bmatrix} \eta_1+\eta_n+\eta_{n+1} & \eta_1 & 0 & \cdots & 0 \\ \eta_1 & \eta_1+\eta_2+\eta_{n+2} & \eta_2 & \cdots & 0 \\ 0 & \eta_2 & \ddots & & \cdots 0 \\ \vdots & 0 & \ddots & & \ddots \\ 0 & \vdots & \cdots & \eta_{n-2}+\eta_{n-1}+\eta_{2n-1} & \eta_{n-1} \\ -m\ \eta_3 & 0 & \cdots & \eta_{n-1} & \eta_{n-1}+\eta_{2_n} \end{bmatrix}.$$

We define, for large λ and small ϵ, η_i to be:

$$\begin{cases} \lambda & \text{for } 1 \le i \le n-2 \text{ and } i = n \\ (m+1)\lambda & \text{for } i = n-1 \\ \epsilon & \text{for } n+1 \le i \le 2n \end{cases}$$

Delta Vector

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We use this to find $\delta \in \mathbb{R}^{|\mathcal{S}|}_{\neq 0}$ such that $T_{\eta^0} \cdot \delta = 0$.
Letting $\eta^0 = \eta^-$ for all entries excluding η^0_{2n}, we see

$$T_{\eta^0} = \begin{bmatrix} 2\lambda+\epsilon & \lambda & 0 & \cdots & 0 \\ \lambda & 2\lambda+\epsilon & \lambda & \cdots & 0 \\ 0 & \lambda & 2\lambda+\epsilon & \lambda \quad \cdots & 0 \\ \vdots & 0 & \ddots & \ddots & \ddots \\ 0 & \vdots & \cdots & \lambda+\lambda(m+1)+\epsilon & \lambda(m+1) \\ -m\lambda & 0 & \cdots & \lambda(m+1) & \lambda(m+1)+\eta^0_{2n} \end{bmatrix}.$$

The general solution of η_{2n}^0

$$\eta_{2n}^0 = \frac{(m+1)(m\lambda^n + \lambda(m+1)\daleth_{n-2})}{(\lambda(m+2)+\epsilon)\daleth_{n-2} - \lambda^2\daleth_{n-3}} - \lambda(m+1)$$

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where

$$\daleth_i = \frac{1}{2^{i+1}(\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}}} \cdot (-\epsilon + 2\lambda(\epsilon + 2\lambda - (\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}})^i + (\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}}(\epsilon+2\lambda-(\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}})^i + \epsilon + 2\lambda((\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}} + \epsilon + 2\lambda)^i + (\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}}((\epsilon)^{\frac{1}{2}}(\epsilon+4\lambda)^{\frac{1}{2}} + \epsilon + 2\lambda)^i)$$

Delta Recurrence

Next, we find $\delta \in \mathbb{R}^{|\mathcal{S}|}_{\neq 0}$ such that $T_{\eta^0} \cdot \delta = 0$. Note that the nullspace of T_{η^0} is non trivial, since $\det(T_{\eta^0}) = 0$. We let

$$\begin{aligned}
\delta_0 &= 0 \qquad \text{(For convenience)} \\
\delta_1 &= \delta_1 \\
\delta_k &= \frac{-(2\lambda + \epsilon)}{\lambda}\delta_{k-1} - \delta_{k-2} \text{ for } 2 \leq k \leq n-1 \\
\delta_n &= \frac{-(\lambda(m+2) + \epsilon)}{\lambda(m+1)}\delta_{n-1} - \frac{1}{m+1}\delta_{n-2}
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The recurrence is given by

$$\delta_k = \delta_1 \lambda \cdot \frac{(\sqrt{4\lambda\epsilon + \epsilon^2} - (2\lambda + \epsilon))^k - (-\sqrt{4\lambda\epsilon + \epsilon^2} - (2\lambda + \epsilon))^k}{2^k \lambda^k \sqrt{4\lambda\epsilon + \epsilon^2}}$$

Concentrations & Rates

- Now we use $\delta \in NS(T_{\eta^0})$, to define all rates

$$r_i = \frac{\langle y_i, \delta \rangle}{e^{\langle y_i, \delta \rangle} - 1} \eta_i^0$$

and concentrations

$$\mathbf{x}^* = (1, 1, ..., 1)$$

$$\mathbf{x}^{\#} = (e^{\delta_1}, e^{\delta_2}, ..., e^{\delta_n}),$$

which are proven to be **TWO** distinct steady states.

Example $n = 3$

Using the formulas in previous slides, we compute our rates:

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

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

and concentrations:

$$\begin{aligned} \mathbf{x}^* &= (1, 1, 1) \\ \mathbf{x}^\# &= \left(e, e^{-2.1}, e^{\frac{2.1m+3.41}{m+1}}\right) \end{aligned}$$

Note that only $\mathbf{x}_\mathbf{3}^\#$, r_2 and r_6 depend on m.

The Determinant of Jacobians

By substitution we obtain the determinant of the Jacobian for the system:

$$\det(df(\mathbf{x}^*)) = r_2 r_1 r_3 m - (r_2 + r_6)(r_1 r_3 + r_1 r_4 + r_1 r_5 + r_3 r_5 + r_4 r_5) - r_2 \; r_6 (r_1 + r_3 + r_4)$$

$$\det(df(\mathbf{x}^{\#})) = r_2 x_2((r_1 x_2 + r_3 + r_4)(r_2 \; x_3) + r_1 x_1 m r_3) - (r_2 x_2 + r_6)(r_1 x_2 + r_3 + r_4)(r_1 x_1 + r_2 \; x_3 + r_5) + (r_2 x_2 + r_6)(r_1 x_1 r_1 x_2)$$

Bounding the determinants

Based on the following inequalities,

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

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

$$e^{\frac{2.1y+3.41}{y+1}} > x_3 = e^{\frac{2.1m+3.41}{m+1}} > e^{2.1} \qquad \forall \ \ m \ \geq \ y$$

we can bound the determinants of our Jacobians,

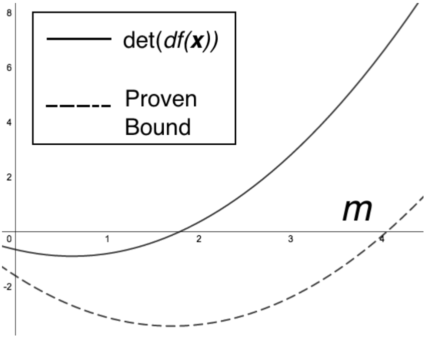
Proven Bounds

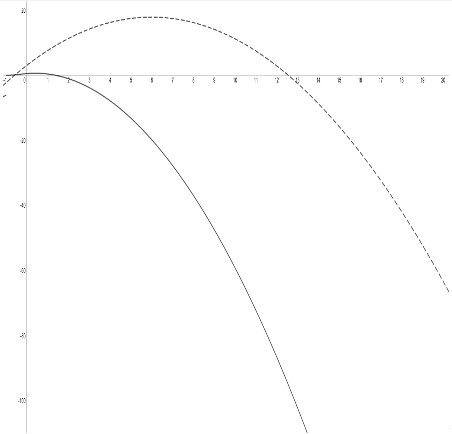
$$\det(df(\mathbf{x}^*)) > \ 0.6294m^2 - 2.156m - 1.61 \ \ \forall m \geq 2$$

$$\det(df(\mathbf{x}^\#)) < -0.41295m^2 + 4.9437m + 3.06205. \ \ \forall m \geq 20$$

Theorem

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





Conclusion

1. We have patrially solved the conjecture for $n = 3$ and any m.
2. We have also solved the conjecture for $n \leq 11$ and small m by using our approach. We have showed that the Determinant Optimization Method can create **degenerate** steady sates

Some future directions:

1. A more interesting problem is to solve the conjecture for fixed m, in particular, $m = 2$.
2. Find an alternate method to get closed forms for the steady states of a chemical reaction network.
3. Find different criteria to characterize steady states as non degenerate.

Acknowledgements

Dr. Anne Shiu
Texas A & M University
NSF

Acknowledgements

Dr. Anne Shiu
Texas A & M University
NSF
Many Thanks to:
$\mathbb{Z}$ev Woodstock & $\mathbb{C}$aitlin Lienkaemper