An Infinite Family of Networks with Multiple Non-Degenerate Equilibria

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Review

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

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Definition

The *stoichiometric matrix* Γ is the $|\mathcal{S}| \times |\mathcal{R}|$ matrix whose kth column is the reaction vector of the kth reaction $y_k \to y'_k$, *denoted* $(y'_k - y_k)$

What's a Steady State?

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

$$\frac{dx}{dt} = \Gamma \cdot \rho(x) \qquad (1)$$

Where $\rho(x) \in \mathbb{R}_{>0}^{|\mathcal{R}|}$ is the vector that encodes the reactants of the kth reaction in its kth coordinate.

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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 $\Gamma \cdot \rho(x^*) = 0$.

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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 $\mathbf{x}^*$.

The Network $\widetilde{K}_{m,n}$

Definition

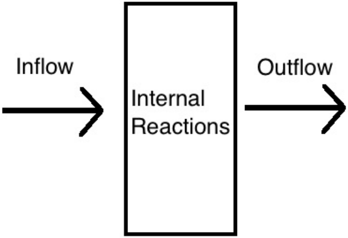
For positive integers $n \geq 2$, $m \geq 1$ we define the network $\widetilde{K}_{m,n}$ of order n and production factor m to be:

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

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.

$$\widetilde{K}_{m,n} = \begin{cases} X_1 + X_2 \to 0 \\ \quad\vdots \\ X_{n-1} + X_n \to 0 \\ X_1 \to mX_n \\ X_i \leftrightarrow 0 \quad \forall\, i \in \{1, 2, ..., n\} \end{cases}$$



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.

For any n, the system is given by,

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

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

Jacobian Matrix

$$
\begin{aligned}
df(\mathbf{x})_{(1,1)} &= -r_1x_2 - r_n - r_{n+1} \\
df(\mathbf{x})_{(1,2)} &= -r_1x_1 \\
\\
df(\mathbf{x})_{(i,i-1)} &= -r_{i-1}x_i \quad \forall\ i \in \{2, 3, ..., n-1\} \\
df(\mathbf{x})_{(i,i)} &= -r_{i-1}x_{i-1} - r_ix_{i+1} - r_{n+1} \\
df(\mathbf{x})_{(i,i+1)} &= -r_ix_i \\
\\
df(\mathbf{x})_{(n,1)} &= mr_n \\
df(\mathbf{x})_{(n,n-1)} &= -r_{n-1}x_n \\
df(\mathbf{x})_{(n,n)} &= -r_{n-1}x_{n-1} - r_{2n}
\end{aligned}
\tag{2}
$$

Jacobian Matrix

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

GOAL:

Find rates r_i and two steady state concentrations, $\mathbf{x}^*, \mathbf{x}^\#$, and show $Im(df(\mathbf{x})) = im(\Gamma)$.

Our Approach: Backtrack the Determinant Optimization Method

Theorem (Craicun & Feinberg, 2005)

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

The main conditions on internal and outflow reactions:

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

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

Stoichiometrix Matrix for $\widetilde{K}_{m,n}$

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

General solution: $\tilde{\eta}_{n-1} = (m+1)$, $\tilde{\eta}_j = 1$ for $j \neq n-1$ is a solution.

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General solution: $\tilde{\eta}_{n-1} = (m+1)$, $\tilde{\eta}_j = 1$ for $j \neq n-1$ is a solution.

Remark: Since the matrix Γ contains the identity, it is full rank. Thus we must show $\det(df(\mathbf{x})) \neq 0$ for S.S. solutions $\mathbf{x}$.

Overview: Finding S.S. Concentrations & Rates

- Extend $\tilde{\eta}$ to describe all internal and outflow reactions, $\eta^- \in \mathbb{R}^{2n}$.
- Let $\eta_i^- = \lambda \, \tilde{\eta}_i$ for all $i \in \{1, 2, .., k\}$.
- Otherwise, let $\eta_i^- = \epsilon$.
- When $n = 3$, $\eta^- = (\lambda, (m+1)\lambda, \lambda, \epsilon, \epsilon, \epsilon)$ for large λ, small ϵ.

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- When $n = 3$, $\eta^- = (\lambda, (m+1)\lambda, \lambda, \epsilon, \epsilon, \epsilon)$ for large λ, small ϵ.
- Define the augmented Jacobian,

$$
\mathrm{T}_\eta =
\begin{bmatrix}
\eta_1 + \eta_n + \eta_{n+1} & \eta_1 & 0 & \cdots & 0 \\
\eta_1 & \eta_1 + \eta_2 + \eta_{n+2} & \eta_2 & \cdots & 0 \\
0 & \eta_2 & \ddots & & \cdots 0 \\
\vdots & 0 & \ddots & & \ddots \\
0 & \vdots & \cdots & \eta_{n-2} + \eta_{n-1} + \eta_{2n-1} & \eta_{n-1} \\
-m\, \eta_3 & 0 & \cdots & \eta_{n-1} & \eta_{n-1} + \eta_{2n}
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$$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}.$$

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WE'RE SKIPPING THIS STEP: $\eta^0_{2n} = \frac{(m+1)(m\lambda^n+\lambda(m+1)\daleth_{n-2})}{(\lambda(m+2)+\epsilon)\daleth_{n-2}-\lambda^2\daleth_{n-3}} - \lambda(m+1)$, where

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

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

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

Overview: Finding S.S. 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.

Case $n = 3$

Here, we fix $n = 3$ and allow any integers $m \geq 2$.

$$T_\eta = \begin{pmatrix} \eta_1 + \eta_3 + \eta_4 & \eta_1 & 0 \\ \eta_1 & \eta_1 + \eta_2 + \eta_5 & \eta_2 \\ -m\ \eta_3 & \eta_2 & \eta_2 + \eta_6 \end{pmatrix}$$

Step 1: Find $\eta^- = (\lambda, (m+1)\lambda, \lambda, \epsilon, \epsilon, \epsilon)$

We let $\lambda = 1$ and $\epsilon = .1$. Then $\eta^- = (1, (m+1), 1, .1, .1, .1)$ satisfies the conditions of the hypothesis.

Case $n = 3$

$$T_{\eta^0} = \begin{pmatrix} 2.1 & 1 & 0 \\ 1 & 2.1 + m & m + 1 \\ -m & m + 1 & m + 1 + \eta_6^0 \end{pmatrix}$$

Step 2: Find $\eta^0 = (1, (m+1), 1, .1, .1, \eta_6^0)$

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Step 2: Find $\eta^0 = (1, (m+1), 1, .1, .1, \eta_6^0)$

We manipulate the determinant of $T_0 = 0$ to find a closed form for η_6

$$\eta_6^0 = \frac{3.1m^2 - .31m - 1.31}{2.1m + 3.41}$$

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Step 3: Find δ in the nullspace of T_{η^0}

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Step 3: Find δ in the nullspace of T_{η^0}

Using the first two rows of T_{η^0} and letting $\delta_1 = 1$ we get

$$\delta = \begin{pmatrix} 1 \\ -2.1 \\ \frac{2.1m+3.41}{m+1} \end{pmatrix}$$

The Reaction Rates

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

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

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

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and concentrations:

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

Note that only $\mathbf{x}_3^\#$, r_2 and r_6 depend on m.

The Determinant of Jacobians

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

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

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

Bounding the determinants

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

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

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

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

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Proven Bounds

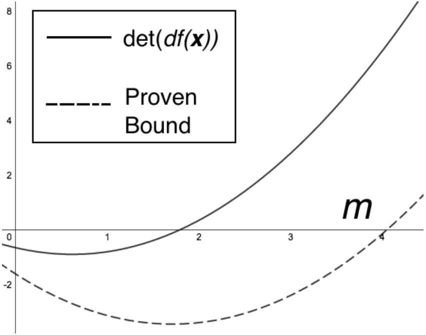
$$\det(df(\mathbf{x}^*)) > \;\; 0.6294m^2 - 2.156m - 1.61 \;\; \forall m \geq 2$$

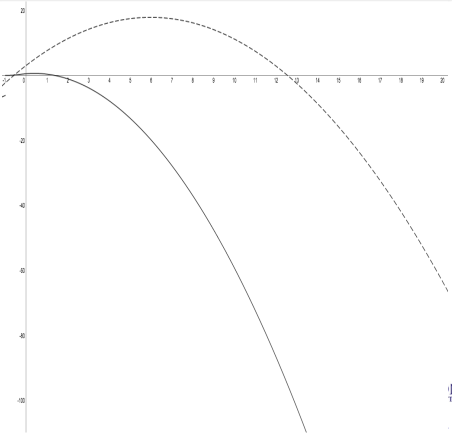
$$\det(df(\mathbf{x}^\#)) < -0.41295m^2 + 4.9437m + 3.06205. \;\; \forall m \geq 20$$

Bounding the determinants

Theorem

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





Degeneracy Examples

The method outlined by [C & F] Does not always create non-degenerate steady states! Varying values of ϵ (which still satisfy the hypothesis) can produce nondegenerate steady states for certain values of m.