Multistationarity and multistability in reaction networks

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Mathematical Modeling of Chemical Reaction Networks
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Monostationarity vs. multistationarity

- Monostationarity (unique positive steady state) underlies robust output.
- Multistationarity and multistability underlie flexible response and output switching.
- For instance, a bacterium *e.coli* can switch between digesting two forms of sugar based on environmental conditions.
- Which networks are capable of producing multistationarity?

Ruling out multistationarity

Theorem (B. Boros)

Every weakly reversible mass action system has a positive steady state in any positive compatibility class for any choice of rate constants.

Theorem (Feinberg)

Deficiency zero networks are not multistationary.

Suppose deficiency of a network G is zero.

- *If G is weakly reversible then for any choice of rate constants, there is a unique positive steady state in every positive compatibility class. Furthermore, each steady state is locally asymptotically stable.*
- *If G is not weakly reversible then there is no positive steady state for any choice of rate constants.*

Ruling out multistationarity

Theorem (Feinberg)

Consider a reaction network G with linkage classes G_1, G_2, …, G_l. Let δ denote the deficiency of G, and let δ_i denote the deficiency of G_i. Assume that:

1. *each linkage class G_i has only one terminal strong linkage class,*
2. $\delta_i \leq 1$ *for all* $i = 1, 2, \ldots, l$, *and*
3. $\sum_{i=1}^{l} \delta_i = \delta$.

Then G is not multistationary.

Ruling out multistationarity (other criteria)

- Injectivity and Jacobian conditions are helpful in ruling out multistationarity.
- Directed Species Reaction (DSR) graphs give related network conditions.

Reference: Badal Joshi, and Anne Shiu. A survey of methods for deciding whether a reaction network is multistationary. *"Chemical Dynamics"*, special issue of *Mathematical Modelling of Natural Phenomena*, Vol. 10, No. 5, (August 2015), pp. 47-67.

Open reaction networks

- Open networks exchange mass with the environment.
- Fully open networks have inflows and outflows for all species in the network.

Goal: Look for small fully open networks which are multistationary/multistable.

Small fully open networks

Example

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X$$

$$2X \xrightarrow{k_3} 3X$$

- Deficiency $\delta = 4 - 2 - 1 = 1 \implies$ Def. 0 does not apply!
- $\delta_1 = 0, \delta_2 = 0 \implies \delta \neq \delta_1 + \delta_2 \implies$ Def. 1 theorem does not apply!
- $\dot{x} = k_1 - k_2 x + k_3 x^2 = f(x)$ has Jacobian $f'(x) = -k_2 + 2k_3 x$ which has zero at $x = k_2/2k_3 > 0$. Since Jacobian changes sign, the network is NOT injective.

We escaped all three conditions $\implies$ multistationarity is possible.

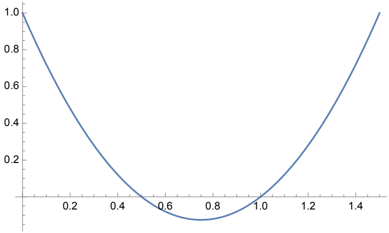
Small fully open networks

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X$$

$$2X \xrightarrow{k_3} 3X$$

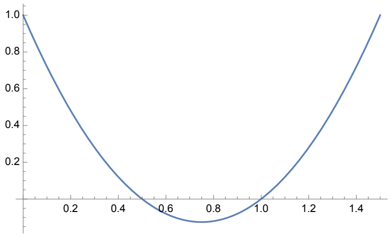
$$\dot{x} = k_1 - k_2 x + k_3 x^2$$

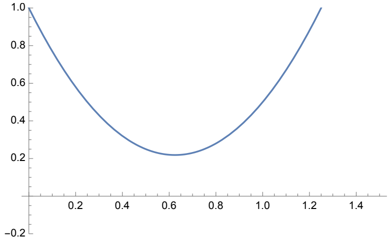
eg. $k_1 = 1, k_2 = 3, k_3 = 2 \implies \dot{x} = 1 - 3x + 2x^2$.



Steady states at $x_1 = 0.5$ and $x_2 = 1$.

$0 \rightleftarrows X, \quad 2X \to 3X$

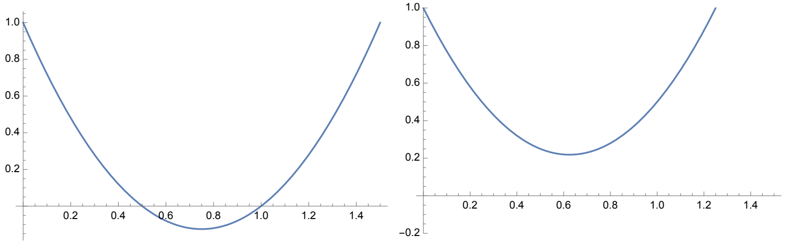




Steady states at $x_1 = 0.5$ and $x_2 = 1$.

Stability of steady states!

$0 \rightleftarrows X, \quad 2X \to 3X$



Steady states at $x_1 = 0.5$ and $x_2 = 1$.

Stability of steady states!

- For some rate constants, there are no positive steady states.
- For some rate constants, there is one positive stable steady state and one positive unstable steady state.
- There is a degenerate case with a single unstable steady state.
- Network is <u>multistationary</u> but <u>NOT multistable</u>.

Small fully open networks

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X$$

$$3X \xrightarrow{k_3} 2X$$

$$\dot{x} = k_1 - k_2 x - k_3 x^3$$

Descartes' rule of signs

Consider a polynomial $p(x)$ in one variable x.

- Maximum number of possible positive zeros = number of sign changes.
- Maximum number of positive zeros − Actual number of positive zeros is an even number.

Exercise: Apply Descartes' rule of signs (ROS) to

$$p(x) = -3 + 4x + 7x^3 - x^8 + 2x^9 + 3x^{11} - 15x^{17}$$

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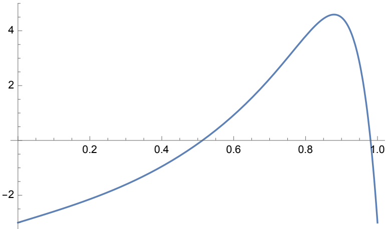
Exercise: Apply Descartes' rule of signs (ROS) to

$$p(x) = -3 + 4x + 7x^3 - x^8 + 2x^9 + 3x^{11} - 15x^{17}$$

Solution:

- Maximum number of positive zeros is 4.
- Actual number may be 4, 2 or 0.



Small fully open networks

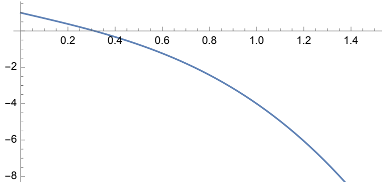
$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X$$

$$3X \xrightarrow{k_3} 2X$$

$$\dot{x} = k_1 - k_2 x - k_3 x^3$$

Apply Descartes' rule of signs:

- Maximum one positive steady state.
- Maximum number of steady states − Actual number of positive steady states is an even number.
- **Conclusion**: Exactly one positive steady state for all possible choices of rate constants.



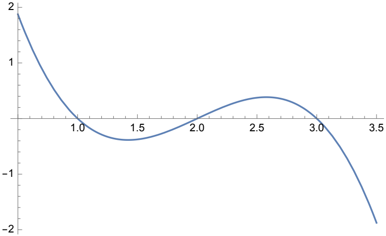
Small fully open networks

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X$$

$$2X \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3X$$

$$\dot{x} = k_1 - k_2 x + k_3 x^2 - k_4 x^3$$

eg. $k_1 = 6, k_2 = 11, k_3 = 6, k_4 = 1 \implies \dot{x} = 6 - 11x + 6x^2 - x^3.$



$$\dot{x} = 6 - 11x + 6x^2 - x^3 = (1 - x)(2 - x)(3 - x)$$

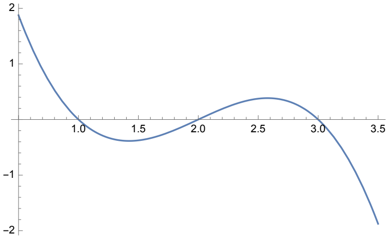
$0 \rightleftarrows X, \quad 2X \rightleftarrows 3X$

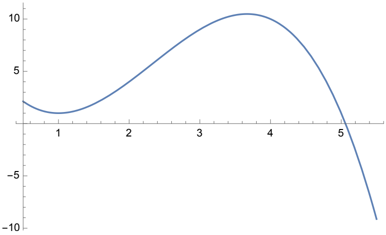
Descartes' rule of signs implies:

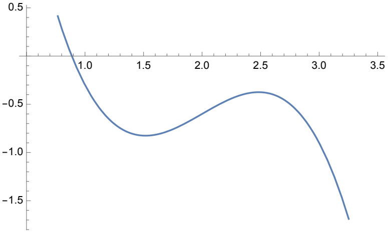
- Maximum three positive steady states.
- Number of steady states $\in \{1, 3\}$.
- (2 steady states are possible, but one is doubly degenerate. So counted with multiplicity there are 3 steady states).
- One stable steady state in all cases.
- When there are 3 steady states, 2 are stable and 1 is unstable.

Conclusion: Network is multistable.

$$0 \rightleftarrows X, \quad 2X \rightleftarrows 3X$$







2 species, 1 non-flow reaction

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X, \qquad 0 \underset{k_4}{\overset{k_3}{\rightleftarrows}} Y$$

$$X + Y \underset{k_6}{\overset{k_5}{\rightleftarrows}} 2X + 2Y$$

$$\dot{x} = k_1 - k_2 x + k_5 xy - k_6 x^2 y^2$$
$$\dot{y} = k_3 - k_4 y + k_5 xy - k_6 x^2 y^2$$

- Note $k_1 - k_2 x^* = k_3 - k_4 y^*$.
- Solve above for y^* and plug into $0 = k_1 - k_2 x^* + k_5 x^* y^* - k_6 {x^*}^2 {y^*}^2$
- Get equation in x^* and solve.
- Calculate y^*.

3 species, 1 non-flow reaction

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X, \qquad 0 \underset{k_4}{\overset{k_3}{\rightleftarrows}} Y, \qquad 0 \underset{k_6}{\overset{k_5}{\rightleftarrows}} Z$$

$$aX + bY + cZ \underset{k_8}{\overset{k_7}{\rightleftarrows}} dX + eY + fZ$$

$$\begin{aligned}
\dot{x} &= k_1 - k_2 x + k_7 x^a y^b z^c - k_8 x^d y^e z^f \\
\dot{y} &= k_3 - k_4 y + k_7 x^a y^b z^c - k_8 x^d y^e z^f \\
\dot{z} &= k_5 - k_6 z + k_7 x^a y^b z^c - k_8 x^d y^e z^f
\end{aligned}$$

Gets harder with more species!

Single irreversible non-flow reaction

Theorem (Joshi)

Let n be a positive integer. Let $a_1, a_2, \ldots, a_n, b_1, b_2, \ldots, b_n$ be nonnegative integers.
The (general) fully open network with one irreversible non-flow reaction and n species:

$$0 \leftrightarrows X_1 \qquad 0 \leftrightarrows X_2 \quad \cdots \quad 0 \leftrightarrows X_n$$
$$a_1 X_1 + \cdots + a_n X_n \to b_1 X_1 + \cdots + b_n X_n$$

is multistationary if and only if $\sum_{i: b_i > a_i} a_i > 1$.

Single reversible non-flow reaction

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Let n be a positive integer. Let $a_1, a_2, \ldots, a_n, b_1, b_2, \ldots, b_n$ be nonnegative integers. The (general) fully open network with one reversible non-flow reaction and n species:

$$0 \leftrightarrows X_1 \qquad 0 \leftrightarrows X_2 \quad \cdots \quad 0 \leftrightarrows X_n$$
$$a_1X_1 + \ldots a_nX_n \leftrightarrows b_1X_1 + \ldots b_nX_n$$

is multistationary if and only if $\sum_{i:b_i>a_i} a_i > 1$ or $\sum_{i:a_i>b_i} b_i > 1$.

Exercises

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X, \qquad 0 \underset{k_4}{\overset{k_3}{\rightleftarrows}} Y, \qquad 0 \underset{k_6}{\overset{k_5}{\rightleftarrows}} Z$$

$$aX + bY + cZ \xrightarrow{k_7} dX + eY + fZ \tag{1}$$

Exercise 1: Find values of a, b, c, d, e, f such that the reaction network (1) is multistationary.

Exercise 2: Find values of a, b, c, d, e, f such that the reaction network (1) is not multistationary.

Exercise 3: Is the following reaction network multistationary?

$$0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} X, \qquad 0 \underset{k_4}{\overset{k_3}{\rightleftarrows}} Y$$

$$X + Y \underset{k_6}{\overset{k_5}{\rightleftarrows}} 2X + 2Y$$

Inheritance of multistationarity

Example

$$\boxed{N_1 : \quad A \to B \quad , \quad 3A + B \to 4A}$$

$$\boxed{N_2 : \quad A + B \to 0 \quad , \quad 3A \to 4A + B}$$

Both N_1 and N_2 admit multiple steady states within their respective stoichiometric compatibility classes. But

$$N_1 \cup N_2 :$$

$$\begin{aligned} A \to B \quad &, \quad 3A + B \to 4A \\ A + B \to 0 \quad &, \quad 3A \to 4A + B \end{aligned}$$

$N_1 \cup N_2$ does not admit multiple steady states.

Inheritance of multistationarity

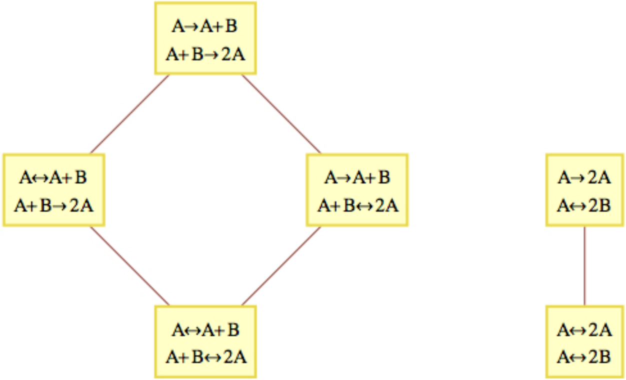
Theorem

Let N and G be reaction networks that are related in at least one of the following ways:

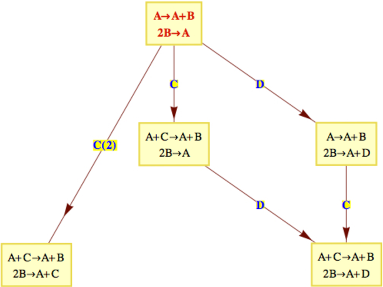
1. *N is a subnetwork of G which has the same stoichiometric subspace as G (Joshi, Shiu),*
2. *N is weakly reversible and G is fully open extension of N (Craciun, Feinberg),*
3. *Fully open N is embedded in fully open G (Joshi, Shiu),*
4. *N is an induced network of G obtained by removing one or more intermediates (Feliu, Wiuf).*

Then, if N admits m positive nondegenerate steady states (for some choice of rate constants), then G admits at least m positive nondegenerate steady states (for some choice of rate constants). Also, if N admits q positive, stable steady states, then G admits at least q positive, stable steady states.

Inheritance of multistationarity



Inheritance of multistationarity



Example (Fully Open Network G)

$$
\begin{aligned}
0 &\rightleftarrows A, B, C, D, E \\
A + C &\rightleftarrows 2A \\
C + D &\rightleftarrows A + B \\
A + C + E &\rightleftarrows 2D + B
\end{aligned}
$$

Example (Fully Open Network G and Embedded (Fully Open) Network N)

$$0 \rightleftarrows A, B, C, D, E$$

$$A + C \rightleftarrows 2A$$

$$C + D \rightleftarrows A + B$$

$$A + C + E \rightleftarrows 2D + B$$

Example (Fully Open Network G and Embedded (Fully Open) Network N)

$$0 \rightleftarrows A, B, C, D, E$$
$$A + C \rightleftarrows 2A$$
$$C + D \rightleftarrows A + B$$
$$A + C + E \rightleftarrows 2D + B$$

We know that the following network is nondegenerately multistationary:

$$0 \rightleftarrows A, B$$
$$A \to 2A$$
$$0 \leftarrow A + B$$

Phosphofructokinase reaction network (part of glycolysis)

X: Fructose-1,6-biphosphate, Y: Fructose-6-phosphate
Z: Intermediate species (alternate form of Fructose-1,6-biphosphate)

$$2X + Y \underset{k_8}{\overset{k_1}{\rightleftarrows}} 3X$$

$$Y \underset{k_5}{\overset{k_4}{\rightleftarrows}} 0 \underset{k_2}{\overset{k_3}{\rightleftarrows}} X \underset{k_6}{\overset{k_7}{\rightleftarrows}} Z$$

Reaction Network + Mass-action kinetics yields

$$\begin{aligned}
\dot{x} &= k_1 x^2 y - k_8 x^3 + k_3 - (k_2 + k_7)x + k_6 z \\
\dot{y} &= -k_1 x^2 y + k_8 x^3 - k_4 y + k_5 \\
\dot{z} &= k_7 x - k_6 z
\end{aligned}$$

Is the phosphofructokinase reaction network multistationary?

Step 1. Remove reaction

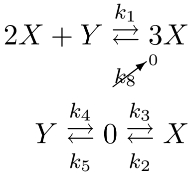
System with and without Z are steady-state equivalent (up to projection):

$$2X + Y \underset{k_8}{\overset{k_1}{\rightleftarrows}} 3X$$

$$Y \underset{k_5}{\overset{k_4}{\rightleftarrows}} 0 \underset{k_2}{\overset{k_3}{\rightleftarrows}} X \quad \cancel{\underset{k_6}{\overset{k_7}{\rightleftarrows}} Z}$$

Resulting network is fully open.

Step 2. Remove reaction



Step 3. Remove species

Delete species Y:

$$2X \quad \cancel{+Y} \xrightarrow{k_1} 3X$$

$$\cancel{Y \underset{k_5}{\overset{k_4}{\rightleftarrows}}} \quad 0 \underset{k_2}{\overset{k_3}{\rightleftarrows}} X$$

Atom of multistationarity

Resulting network is multistationary!
Saw earlier it has 2 positive steady states.

$$2X \xrightarrow{k_1} 3X$$

$$0 \underset{k_2}{\overset{k_3}{\rightleftarrows}} X$$

Conclusion: Glycolysis is multistationary.

Thank you!