Atoms of multistationarity in reaction networks

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Dynamics in Networks with Special Properties
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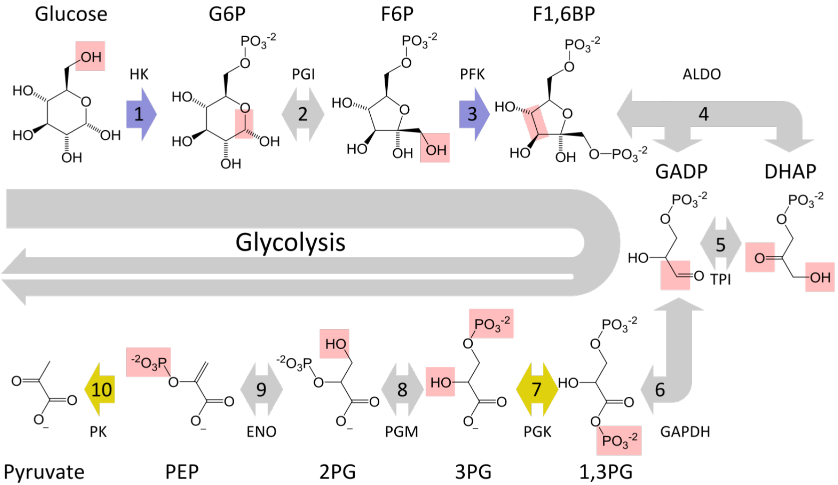
Glucose
G6P
F6P
F1,6BP
HK
1
PGI
2
PFK
3
ALDO
4
GADP
DHAP
5
TPI
Glycolysis
6
GAPDH
7
PGK
8
PGM
9
ENO
10
PK
Pyruvate
PEP
2PG
3PG
1,3PG

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)

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

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

Reference: K. Gatermann, M. Eiswirth, A. Sensse, Toric ideals and graph theory to analyze Hopf bifurcations in mass action systems. **Journal of Symbolic Computation** Vo1. 40, (2005), pp. 1361–1382.

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Reaction Network + Mass-action kinetics yields

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

Q. Does the phosphofructokinase reaction network admit multiple steady states?

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

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\end{aligned}$$

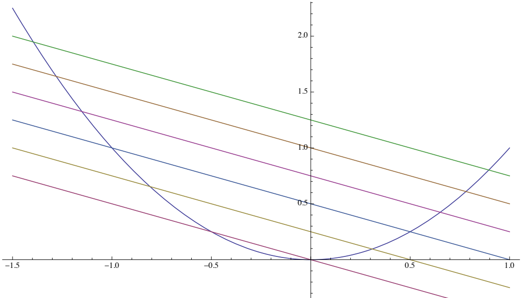
Q. Does the phosphofructokinase reaction network $\boxed{\textit{admit}}$ multiple steady states?

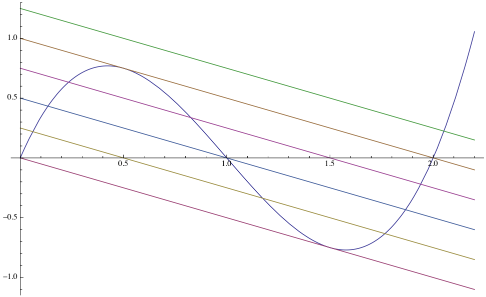
$$Y \rightleftarrows 2X$$

Stoichiometric subspace:
span $\{(2,-1),(-2,1)\} = \{(x,y) | x + 2y = 0\}$

$$\dot{x} = 2k_1 y - 2k_2 x^2 = 0$$
$$\dot{y} = -k_1 y + k_2 x^2 = 0$$

$$y = \frac{k_2}{k_1} x^2 \quad , \quad x + 2y = c$$





- $\mathrm{cap}_{\mathrm{pos}}(G) = 2$, $\mathrm{cap}_{\mathrm{nondeg}}(G) = 2$ and $\mathrm{cap}_{\mathrm{exp-stab}}(G) = 1$
- $\mathrm{cap}_{\mathrm{pos}}(G) = 2 \implies G$ is multistationary.
- $\mathrm{cap}_{\mathrm{nondeg}}(G) = 2 \implies G$ is nondegenerately multistationary.
- $\mathrm{cap}_{\mathrm{exp-stab}}(G) = 1 \implies G$ is not multistable.

Q. Does a given reaction network admit multiple positive steady states?

Strategy: Examine “pieces” of network.

Example (It's complicated!)

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

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

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

$$\begin{array}{rcl} & N_1 \cup N_2 : & \\ A \to B & , & 3A + B \to 4A \\ A + B \to 0 & , & 3A \to 4A + B \end{array}$$

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

Q. When do network components inform about the full network?

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)

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

Let S_G represent the stoichiometric subspace of G.

Theorem (J and Shiu, '12)

1. *If N is a subnetwork of G such that $S_N = S_G$ then* $\mathrm{cap}_{\mathrm{nondeg}}(G) \geq \mathrm{cap}_{\mathrm{nondeg}}(N)$ *and* $\mathrm{cap}_{\mathrm{exp-stab}}(G) \geq \mathrm{cap}_{\mathrm{exp-stab}}(N)$ *(independent of kinetics).*
2. *Suppose N is obtained from G by removing some species and:*

   (a) *S_N is full-dimensional, and*

   (b) *G contains both inflow and outflow reactions for any species that is in G but not in N.*

   Then $\mathrm{cap}_{\mathrm{nondeg}}(G) \geq \mathrm{cap}_{\mathrm{nondeg}}(N)$ *and* $\mathrm{cap}_{\mathrm{exp-stab}}(G) \geq \mathrm{cap}_{\mathrm{exp-stab}}(N)$.

Theorem (J and Shiu, '12)

If N is a fully open embedded network of a fully open network G, then $\mathrm{cap}_{\mathrm{nondeg}}(G) \geq \mathrm{cap}_{\mathrm{nondeg}}(N)$ *and* $\mathrm{cap}_{\mathrm{exp-stab}}(G) \geq \mathrm{cap}_{\mathrm{exp-stab}}(N)$.

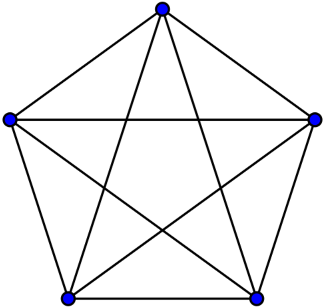
Example (Fully Open Network G and Embedded (Fully Open) Network N)

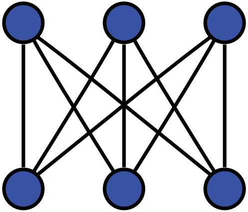
$$
\begin{aligned}
0 &\rightleftarrows A, B, C, D, E \\
A + C &\rightleftarrows 2A \\
C + D &\rightleftarrows A + B \\
A + C + E &\rightleftarrows 2D + B
\end{aligned}
$$

We know that the following network is nondegenerately multistationary:

$$
\begin{aligned}
0 &\rightleftarrows A, B \\
A &\rightarrow 2A \\
0 &\leftarrow A + B
\end{aligned}
$$

Kuratowski's Theorem: Every nonplanar graph contains $K_{3,3}$ or K_5 as a graph minor.



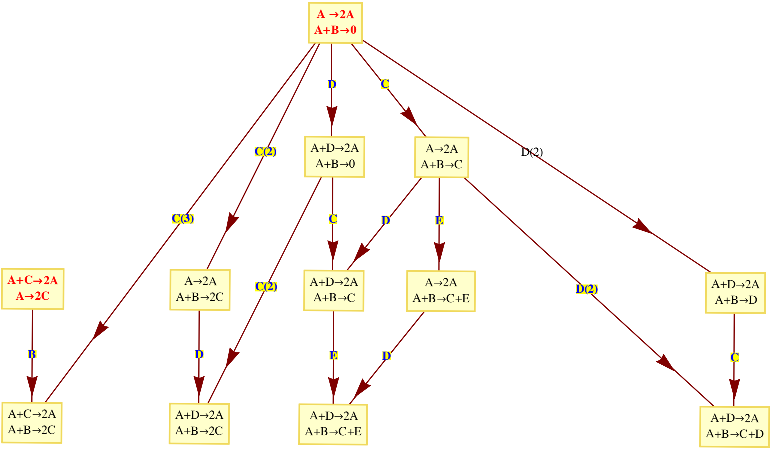


These are "atoms of nonplanarity"

Nondegenerately multistationary fully open networks that are embedding-minimal are atoms of multistationarity.

Towards a catalog of atoms of multistationarity.

Nondegenerately multistationary fully open networks that are embedding-minimal are atoms of multistationarity.



(Joint work with Shiu) Up to symmetry, the CFSTR atoms of multistationarity that have only two non-flow reactions (irreversible or reversible) and complexes that are at most bimolecular:

1. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A \to 2A,\ A + B \to 0\}$
2. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A \to 2A,\ A \leftrightarrows 2B\}$
3. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ 0 \leftrightarrows C,\ A \to 2A,\ A \leftrightarrows B + C\}$
4. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A \to A + B,\ 2B \to A\}$
5. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A \to A + B,\ 2B \to 2A\}$
6. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A \to A + B \to 2A\}$
7. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A \to A + B,\ 2B \to A + B\}$
8. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ B \to 2A \to A + B\}$
9. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ B \to 2A \to 2B\}$
10. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ 0 \leftrightarrows C,\ A \to B + C \to 2A\}$
11. $\{0 \leftrightarrows A,\ 0 \leftrightarrows B,\ A + B \to 2A,\ A \to 2B\}$

Theorem (J '13)

Let $a_1, a_2, \ldots, a_n, b_1, b_2, \ldots, b_n \geq 0$. 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

$$\max\left\{ \sum_{i:b_i>a_i} a_i \ , \ \sum_{i:a_i>b_i} b_i \right\} > 1$$

[1]

[1] Formulated at MBI summer program

Two families of atoms containing one non-flow reaction

1.

$$
\begin{aligned}
0 &\leftrightarrow A \\
mA &\rightarrow nA \qquad n > m > 1
\end{aligned}
$$

2.

$$
\begin{aligned}
0 &\leftrightarrow A \\
0 &\leftrightarrow B \\
A + B &\rightarrow mA + nB \qquad n > 1\ ,\ \ m > 1
\end{aligned}
$$

Two families of atoms containing one non-flow reaction

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$$0 \leftrightarrow A$$
$$mA \rightarrow nA \qquad n > m > 1$$

2.

$$0 \leftrightarrow A$$
$$0 \leftrightarrow B$$
$$A + B \rightarrow mA + nB \qquad n > 1\ ,\ m > 1$$

- Infinitely many atoms!
- No one-reaction at-most-bimolecular atoms.

Q. Are there finitely many or infinitely many at-most-bimolecular atoms?

Sequestration Network

$$
\begin{aligned}
X_1 &\to mX_n \\
X_1 + X_2 &\to 0 \\
&\vdots \\
X_{n-1} + X_n &\to 0
\end{aligned}
$$

(where $n \geq 2$, $m \geq 1$)

Theorem (J & Shiu '15)

- *The fully open extension $\widetilde{K}_{m,n}$ of the sequestration network $K_{m,n}$ is multistationary if and only if $m > 1$ and $n > 1$ is odd.*
- *No fully open network that is an embedded network of $\widetilde{K}_{m,n}$ (besides $\widetilde{K}_{m,n}$ itself) is multistationary.*

- $\widetilde{K}_{m,n}$ for $m > 1$ and odd n is a candidate for being fully open atom of multistationarity.
- Future work: Nondegeneracy [2] of steady states.

[2] $K_{2,3}$ is nondegenerate and therefore an atom of multistationarity (Bryan Félix, Anne Shiu, Zev Woodstock (2015))

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Reaction Network + Mass-action kinetics yields

$$\begin{aligned}
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\end{aligned}$$

Q. Does the phosphofructokinase reaction network admit multiple steady states?

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

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

$$\cancel{\xrightarrow{k_8}}\; 0$$

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

Step 3. Remove species

Delete species Y:

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

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

Step 4.

Resulting network is the *smallest* atom of multistationarity

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

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

$$0 = \dot{x} = k_3 - k_2 x + k_1 x^2$$

for $k_2^2 > 4k_1 k_3$ has two positive steady states:

$$x^{\pm} = k_2 \pm \sqrt{k_2^2 - 4k_1 k_3}$$

Lifting steady states to the full system

For $\epsilon > 0$, there exist k_4 and k_5 sufficiently large, and k_8 sufficiently small such that the fixed points of the full system are within an ϵ-ball of

$$(X^*, Y^*, Z^*) = \left(\frac{1}{2k_1}(k_2 + \sqrt{k_2^2 - 4k_1k_3}), \quad 1, \quad \frac{k_7}{2k_1k_6}(k_2 + \sqrt{k_2^2 - 4k_1k_3}) \right)$$

$$(X^{**}, Y^{**}, Z^{**}) = \left(\frac{1}{2k_1}(k_2 - \sqrt{k_2^2 - 4k_1k_3}), \quad 1, \quad \frac{k_7}{2k_1k_6}(k_2 - \sqrt{k_2^2 - 4k_1k_3}) \right)$$

Summary

- Network embedding provides a tool for lifting nondegenerate multistationarity from smaller embedded networks.
- Need a catalog of atoms of multistationarity. Moving in that direction.

Thank you!