Multistationarity in chemical reaction networks

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Partial ordering on the set of multistationary CRNs

- Chemical reaction network: $(\mathcal{S}, \mathcal{C}, \mathcal{R})$
- Focus on the question of sufficient conditions for multistationarity.
- Can we define a sense in which a network $N_1 \subset_{contained} N_2$ such that the positive steady states of N_1 lift to the positive steady states of N_2?
- We will focus on each component:
  - Reactions
  - Species
  - Complexes

Reactions: Non-example

Steady states of N do not lift to steady states of G

$$N : A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B$$

$$G : A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B \qquad 0 \xrightarrow{k_A} A$$

- Clearly $N \subset_{subnetwork} G$.
- For network N, $A + B = c$, a constant and the steady state within each stoichiometric compatibility class "c" is given by $\left(\frac{k_2 c}{k_1 + k_2}, \frac{k_1 c}{k_1 + k_2}\right)$.
- G has no steady states.

Reactions: Non-example

$$N : A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B$$

$$G : A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B \qquad 0 \overset{k_A}{\rightarrow} A$$

- S_G: stoichiometric subspace of network G.
- m_G: maximum number of steady states that G admits within a stoichiometric compatibility class.
- $m_G \geq 2$: G admits MSS/ G is multistationary.
- We would "like that" if $N \subset_{subnetwork} G$, then $m_N \leq m_G$.
- Not true for previous example ($m_N = 1$, $m_G = 0$)
- Problem: $S_N = span\{(1, -1)\}$ and $S_G = span\{(1, 0), (1, -1)\}$ so that $S_N \subsetneq S_G$.

Reactions: subnetwork theorem

Theorem (BJ/Shiu)

Let N be a subnetwork of G such that $S_N = S_G$. Then, $m_G \geq m_N$.

Corollary

If G is obtained from N by making some of the irreversible reactions reversible, then $m_G \geq m_N$.

Reactions: sub-CFSTR theorem

- CFSTR: networks with all species in outflow.
- Let $r \in G \setminus N$ be a (true or nonflow) reaction. Two cases:

case 1. r does not involve any new species. $S_N = S_G$.

case 2. r involves new species. Augment N by adding flow reactions of the new species to get $\widetilde{N}$. $S_{\widetilde{N}} = S_G$.

Corollary

If N is a sub-CFSTR of G, then $m_G \geq m_N$.

Future work: How far can this theorem be stretched?

- $S_N = S_G$ too strong??
- What about the steady states themselves? Analytic results in parameter space??

Species: embedded network

- $N \subset_{embedded} G$ if N can be obtained from G by "removing reactions" or "removing species".
- Example of species removal:

$$A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B$$

$$2A \quad + B \quad \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3A$$

Species: embedded network

- $N \subset_{embedded} G$ if N can be obtained from G by "removing reactions" or "removing species".
- Example of species removal:

$$A \underset{k_2}{\overset{k_1}{\rightleftarrows}} \cancel{B}$$

$$2A \quad \cancel{+B} \quad \underset{k_4}{\overset{k_3}{\rightleftarrows}} 3A$$

Species: embedded network

- $\color{red}{N \subset_{embedded} G}$ if N can be obtained from G by "removing reactions" or "removing species".
- Example of species removal:

$$
\begin{aligned}
A &\underset{k_2}{\overset{k_1}{\rightleftarrows}} 0 \\
2A &\underset{k_4}{\overset{k_3}{\rightleftarrows}} 3A
\end{aligned}
$$

Non-example

$$G: \qquad 0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} A \qquad 3A \underset{k_4}{\overset{k_3}{\rightleftarrows}} 2A + B$$

- G has unique mass-action steady state $\left(\frac{k_1}{k_2}, \frac{k_1 k_3}{k_2 k_4}\right)$.

$$N \subset_{embedded} G: \qquad 0 \underset{k_2}{\overset{k_1}{\rightleftarrows}} A \qquad 3A \underset{k_4}{\overset{k_3}{\rightleftarrows}} 2A$$

- N does admit multiple positive mass-action steady states.
- $m_N > m_G$!!

Lifting steady states from embedded networks

Q. When does $N \subset_{embedded} G$ imply that $m_N \leq m_G$?

Definition

F_x is a flow-type subnetwork of G if (1) F_x only involves one species x and (2) $x = 1$ is an admissible nondegenerate steady state.

Examples of flow-type subnetworks:

1. $0 \leftrightarrows A$.
2. $0 \leftrightarrows 2A$.
3. $A \leftrightarrows 3A$.
4. $0 \leftrightarrows A \quad , \quad 2A \leftrightarrows 3A$.

Lifting steady states from embedded networks

Theorem (BJ/Shiu)

$N \subset_{embedded} G$ such that:

1. $S_N = \mathbb{R}^{|\mathcal{S}_N|}$
2. *If x is a species in $G \setminus N$, there exists $F_x \subset_{subnetwork} G$.*

$\implies m_N \leq m_G$.

Lifting steady states from embedded networks

Corollary

$N \subset_{embedded} G$ such that:

1. *N is a CFSTR.*
2. *G is a fully open CFSTR.*

$\implies m_N \leq m_G$.

Future work: How far can this theorem be pushed?? For instance, $m_G \geq m_N$ for the following network:

$G: \quad A \leftrightarrows B \qquad 2A + B \leftrightarrows 3A$

and N is obtained by removing species B.

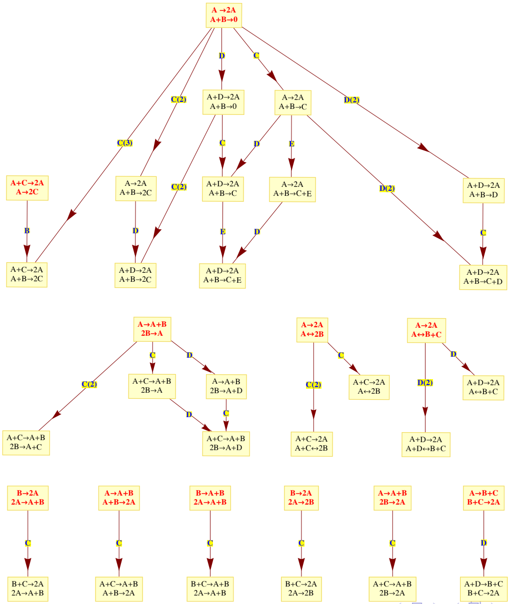
Atoms of multistationarity

Definition

G is an atom of multistationarity if:

1. $m_G \geq 2$.
2. There is no N such that $m_N \geq 2$ and $N \subset_{embedded} G$.

Two reaction bimolecular atoms of multistationarity



One reaction atoms

Theorem (BJ)

A one-reaction fully open network

$$X_i \rightleftarrows 0$$

$$a_1 X_1 + \ldots + a_n X_n \rightleftarrows b_1 X_1 + \ldots + b_n X_n, \quad (a_i, b_i \geq 0)$$

admits multiple steady states if and only if
$\sum_{b_i > a_i} a_i \geq 2$ *or* $\sum_{a_i > b_i} b_i \geq 2$

- A 1-rxn network is multistationary if and only if it is autocatalytic in some set of species which have at least two reactant molecules.

Examples of atoms:

CFSTR examples of atoms:

1. $0 \leftrightarrows A \quad , \quad mA \to nA, \quad (n > m \geq 2)$
2. $0 \leftrightarrows A, B \quad , \quad A + B \to mA + nB, \quad (m, n \geq 2)$
3. $0 \leftrightarrows A, B \quad , \quad A \to 2A \quad , \quad A + B \to 0.$
4. A 3-reaction atom (all species are in flow):

$$\begin{aligned} A + B &\to 0 \\ B + C &\to 0 \\ C &\to 2A \end{aligned}$$

Examples of atoms:

1. (all species are in flow):

$$\begin{aligned} A &\to 2C \\ C &\to B \\ 2B &\to 2A \end{aligned}$$

2. (all species are in flow):

$$\begin{aligned} A + B &\to 0 \\ A + C &\to 0 \\ B &\to C + D \\ D &\to C + E \end{aligned}$$

Q: Is there a characterization of atoms??

Enumeration of atoms?

Definition

A square network has n reactions and n species. The orientation of a square network $N: \quad X \to Y$ is defined to be

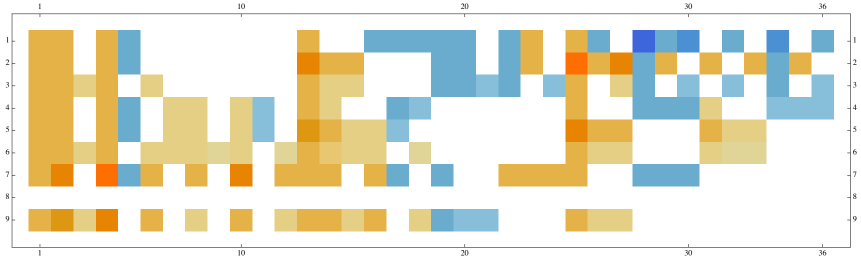
$$Or(N) = \det(X)\det(X - Y).$$

Theorem (Craciun/Feinberg, Joshi/Shiu)

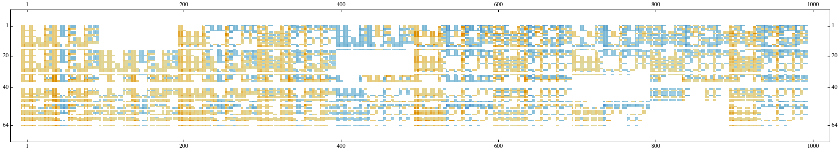
If $m_G \geq 2$, then there exists a square $N \subset_{embedded} G$ such that $Or(N) < 0$.

Q: Is there a characterization of square, negatively oriented networks? [Conjecture on partial ordering of square, negatively oriented nets]

Square, negatively oriented networks



Square, negatively oriented networks



Thank you!