Sign Conditions for Injectivity of Generalized Polynomial Maps with Applications to Chemical Reaction Networks and Real Algebraic Geometry

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Solving Polynomial Equations workshop
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Outline of talk

- Steady states
- **Theorem**: sign conditions for \( \leq 1 \) positive real solution
- Connection to Descartes’ Rule of Signs
- *Four questions about steady states*
**Question 1: inward-pointing networks**

- **Theorem (Gopalkrishnan, Miller, AS 2014):**
  “Inward-pointing” networks like the one on the right (below) *always have* ≥ 1 *positive steady state.*
Question 1: inward-pointing networks

- **Theorem** (Gopalkrishnan, Miller, AS 2014): “Inward-pointing” networks like the one on the right (below) *always have* $\geq 1$ *positive steady state.*

- **Question:** What about networks like the one on the left?

- **Wild speculation:** The above pictures are Newton polytopes. Is there any connection to the Bernstein bound on the number of solutions in $(\mathbb{C}^*)^n$ arising from a mixed-volume computation?
**Question 2: Multisite Phosphorylation**

The $n$-site (sequential and distributive) phosphorylation network is:

\[
S_0 + E \xleftrightarrow{k_{off_0}} ES_0 \xrightarrow{k_{cat_0}} S_1 + E \xleftrightarrow{k_{off_1}} \cdots \xrightarrow{k_{cat_{n-1}}} S_{n-1} + E \xleftrightarrow{k_{off_{n-1}}} ES_{n-1} \rightarrow S_n + E
\]

\[
S_n + F \xleftrightarrow{l_{off_{n-1}}} FS_n \xrightarrow{l_{cat_{n-1}}} S_{n-1} + F \xleftrightarrow{l_{off_0}} \cdots \xrightarrow{l_{cat_0}} S_1 + F \xleftrightarrow{l_{off_0}} FS_1 \rightarrow S_0 + F
\]

The rates $k_{cat_0}, \ldots$ which yield multiple steady states are characterized by sign conditions, but what is the max #?

**Theorem** (Wang and Sontag 2008): The $n$-site phosphorylation system has $\leq 2n - 1$ steady states.

**Conjecture**: The $n$-site phosphorylation system has $\leq n + 1$ steady states for even $n$ and $\leq n$ for odd $n$.

The conjecture is true for $n = 1, 2$, and disproven by Flockerzi, Holstein, and Conradi for odd $n \geq 3$ and $n = 4$. What about even $n \geq 6$?
**Question 2: multisite phosphorylation**

The $n$-site (sequential and distributive) phosphorylation network is:

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\begin{align*}
S_0 + E &\xrightleftharpoons[k_{\text{off}_0}]{k_{\text{on}_0}} ES_0 \quad &S_1 + E &\xrightleftharpoons[k_{\text{off}_1}]{k_{\text{cat}_0}} \quad \cdots \quad S_{n-1} + E &\xrightleftharpoons[k_{\text{off}_{n-1}}]{k_{\text{on}_{n-1}}} ES_{n-1} \rightarrow S_n + E \\
S_n + F &\xrightleftharpoons[l_{\text{off}_{n-1}}]{l_{\text{on}_{n-1}}} FS_n \quad &S_{n-1} + F &\xrightleftharpoons[l_{\text{off}_0}]{l_{\text{cat}_0}} \quad \cdots \quad S_1 + F &\xrightleftharpoons[l_{\text{off}_1}]{l_{\text{cat}_n-1}} FS_1 \rightarrow S_0 + F
\end{align*}
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- **Theorem** (Wang and Sontag 2008): The $n$-site phosphorylation system has $\leq 2n - 1$ steady states.
**Question 2: Multisite Phosphorylation**

The \( n \)-site (sequential and distributive) phosphorylation network is:

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\begin{align*}
S_0 + E & \underset{k_{\text{off}0}}{\rightleftharpoons} ES_0 \underset{k_{\text{cat}0}}{\rightarrow} S_1 + E \quad \cdots \quad S_{n-1} + E & \underset{k_{\text{off}1}}{\rightleftharpoons} ES_{n-1} \rightarrow S_n + E \\
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- The rates \( k_{\text{cat}0}, \ldots \) which yield multiple steady states are characterized by sign conditions, but what is the max \#?

- **Theorem** (Wang and Sontag 2008): The \( n \)-site phosphorylation system has \( \leq 2n - 1 \) steady states.

- **Conjecture:** The \( n \)-site phosphorylation system has \( \leq n + 1 \) steady states for even \( n \) and \( \leq n \) for odd \( n \).

- Conjecture is true for \( n = 1, 2 \), and disproven by Flockerzi, Holstein, and Conradi for odd \( n \geq 3 \) and \( n = 4 \).

**What about even \( n \geq 6 \)?**
Can we do a direct analysis of the (multiple) steady states of this network (Fouchet and Regoes, Plos One 2008)?

Alternate approach: lifting steady states from small to large networks (next slide)
**Question 4: Lifting steady states**

- **Theorem** *(Joshi and AS 2013)*: Assume that $G$ and $N$ are networks with inflows/outflows, such that $N$ is obtained from $G$ by removing reactions and species. Then if $N$ admits multiple steady states, then $G$ does too.

**Question**: For which other pairs $(G, N)$ can we lift (multiple) steady states?
**Summary**

*Sign conditions for \( \leq 1 \) positive real solution* enable us to better understand steady states, but many open questions remain!
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Example:

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\begin{align*}
X_1 + X_2 & \leftrightarrow 0 \\
X_2 + X_3 & \leftrightarrow 0 \\
& \quad \vdots \\
X_{n-1} + X_n & \leftrightarrow 0 \\
2X_n & \leftrightarrow X_1
\end{align*}
\]

- If $n$ is even, no multiple steady states
  (by sign conditions in today’s talk)
- If $n$ is odd, network admits multiple steady states
  (by Schlosser and Feinberg 1993)
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- **Upcoming related talks:** Alicia Dickenstein (today at 4:35)
  and Frédéric Bihan (Wednesday at 11:35)
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- I am recruiting a postdoc.
Thank you.