Computing sign vector conditions for existence and uniqueness of equilibria of chemical reaction networks

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Chemical reaction network

Weighted directed graph $1 \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} 2$ rate constants $k_{12}, k_{21} > 0$

Stoichiometric complexes:

$$1A + 1B \rightleftarrows C$$

Kinetic complexes:

$$aA + bB \rightleftarrows C$$

MAK: $a = b = 1$

GMAK: $a, b \in \mathbb{R}$

$$\frac{d}{dt}\begin{pmatrix} x_A \\ x_B \\ x_C \end{pmatrix} = k_{12} x_A^a x_B^b \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix} + k_{21} x_C \begin{pmatrix} 1 \\ 1 \\ -1 \end{pmatrix}$$

Existence of (unique) equilibrium?

Stoichiometric subspace:

$$S = \operatorname{im} \begin{pmatrix} -1 & -1 & 1 \end{pmatrix}^\top$$

Kinetic-order subspace:

$$\widetilde{S} = \operatorname{im} \begin{pmatrix} -a & -b & 1 \end{pmatrix}^\top$$

MAK: $S = \widetilde{S}$

Deficiency zero theorem

Theorem (Feinberg, Horn, Jackson 1972)

For CRN with MAK, there is unique complex-balanced, asymptotically stable equilibrium in every stoichiometric class and for all rate constants iff $\delta = 0$ and network weakly reversible.

(Stoichiometric) deficiency:

$$\delta = m - l - \dim S,$$

m complexes, l connected components
Stoichiometric complexes:

$$\begin{tikzcd} A+B \arrow[r, shift left] & C \arrow[l, shift left] \arrow[d] & A \arrow[r, shift left] & E \arrow[l, shift left] \\ & D \arrow[ul] & & \end{tikzcd}$$

- Weakly reversible
- $m = 5, l = 2$
- $S = ?$

Stoichiometric and kinetic deficiency

$$
\begin{tikzcd}
A+B \arrow[r, shift left] & C \arrow[l, shift left] \arrow[d] & A \arrow[r, shift left] & E \arrow[l, shift left] \\
& D \arrow[ul] & &
\end{tikzcd}
\qquad
\begin{tikzcd}
aA+bB \arrow[r, shift left] & C \arrow[l, shift left] \arrow[d] & A \arrow[r, shift left] & E \arrow[l, shift left] \\
& cA+D \arrow[ul] & &
\end{tikzcd}
$$

$$
S = \operatorname{im} \begin{pmatrix} 1 & 1 & -1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 1 & 0 & 0 & 0 & -1 \end{pmatrix}^{\top}
\qquad
\widetilde{S} = \operatorname{im} \begin{pmatrix} a & b & -1 & 0 & 0 \\ c & 0 & -1 & 1 & 0 \\ 1 & 0 & 0 & 0 & -1 \end{pmatrix}^{\top}
$$

$$
\begin{aligned} \delta &= m - l - \dim S \\ &= 5 - 2 - 3 = 0 \end{aligned}
\qquad
\begin{aligned} \widetilde{\delta} &= m - l - \dim \widetilde{S} \\ &= 5 - 2 - 3 = 0 \end{aligned}
$$

- Perturb from MAK ($S = \widetilde{S}$)?

Müller, S. ; Hofbauer, J., and Regensburger, G.: *On the bijectivity of families of exponential/generalized polynomial maps*. In: SIAM Journal on Applied Algebra and Geometry 3 (2019), pp. 412–438.

Sign vectors

$$\operatorname{sign}\begin{pmatrix}-1\\0\\2\end{pmatrix} = \begin{pmatrix}-\\0\\+\end{pmatrix}$$

$x \in \mathbb{R}^n$: $\quad \operatorname{sign}(x) \in \{-,0,+\}^n$

$S \subseteq \mathbb{R}^n$: $\quad \operatorname{sign}(S) = \{\operatorname{sign}(x) \colon x \in S\} \subseteq \{-,0,+\}^n$

$$\left.\begin{array}{l} 0 < - \\ 0 < + \end{array}\right\} \quad \rightsquigarrow \quad \text{partial order on } \{-,0,+\}^n$$

Closure: $\quad \overline{\operatorname{sign}(S)} = \{\tau \in \{-,0,+\}^n \colon \tau \leq \rho \text{ for some } \rho \in \operatorname{sign}(S)\}$

$$\overline{\left\{\begin{pmatrix}+\\0\end{pmatrix}, \begin{pmatrix}-\\+\end{pmatrix}\right\}} = \left\{\begin{pmatrix}0\\0\end{pmatrix}, \begin{pmatrix}+\\0\end{pmatrix}, \begin{pmatrix}0\\+\end{pmatrix}, \begin{pmatrix}-\\0\end{pmatrix}, \begin{pmatrix}-\\+\end{pmatrix}\right\}$$

- Compute sign vectors?

Computing sign vectors

$$S = \operatorname{im} \begin{pmatrix} 1 & 1 & -1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 1 & 0 & 0 & 0 & -1 \end{pmatrix}^{\top}$$

$$\operatorname{sign}(S) = ?$$

$$S = \ker(W),\ W = \begin{pmatrix} 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 1 & 1 & 0 \end{pmatrix}$$

I	$\det(W_I)$	chirotope
$\{1,2\}$	1	$+$
$\{1,3\}$	1	$+$
$\{1,4\}$	1	$+$
$\{1,5\}$	0	0
$\{2,3\}$	-1	$-$
$\{2,4\}$	-1	$-$
$\vdots$	$\vdots$	$\vdots$

Support minimal elements (cocircuits) in $\operatorname{sign}(S)$

$$\begin{pmatrix} 0 \\ 0 \\ + \\ - \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ + \\ - \\ 0 \\ + \end{pmatrix}, \begin{pmatrix} 0 \\ + \\ 0 \\ - \\ + \end{pmatrix}, \begin{pmatrix} + \\ 0 \\ 0 \\ 0 \\ - \end{pmatrix}, \begin{pmatrix} + \\ + \\ 0 \\ - \\ 0 \end{pmatrix}, \begin{pmatrix} + \\ + \\ - \\ 0 \\ 0 \end{pmatrix}, \ldots \in \operatorname{sign}(S)$$

- Chirotopes determine all cocircuits
- Cocircuits determine all sign vectors
- Implementation
- Package for SageMath

Robust deficiency zero theorem

Theorem (robust $\delta = \widetilde{\delta} = 0$ theorem)

For CRN with GMAK, there is unique complex-balanced equilibrium in every stoichiometric class, for all rate constants, and all small perturbations of kinetic orders iff $\delta = \widetilde{\delta} = 0$, *network weakly reversible, and* $\mathrm{sign}(S) \subseteq \overline{\mathrm{sign}(\widetilde{S})}$

$$A + B \rightleftarrows C \qquad\qquad aA + bB \rightleftarrows C$$

$$S = \mathrm{im}\begin{pmatrix}-1 & -1 & 1\end{pmatrix}^{\top} \qquad\qquad \widetilde{S} = \mathrm{im}\begin{pmatrix}-a & -b & 1\end{pmatrix}^{\top}$$

$$\mathrm{sign}(S) = \left\{ \begin{pmatrix}0\\0\\0\end{pmatrix}, \begin{pmatrix}+\\+\\-\end{pmatrix}, \begin{pmatrix}-\\-\\+\end{pmatrix} \right\}$$

- $\mathrm{sign}(\widetilde{S})$? a, b?

Closure condition

Proposition

$S = \ker(W), \widetilde{S} = \ker(\widetilde{W})$. *The following are equivalent:*

(1) $\operatorname{sign}(S) \subseteq \overline{\operatorname{sign}(\widetilde{S})}$

(2) (a) *For all* I, $\det(W_I) \neq 0 \Rightarrow \det(W_I)\det(\widetilde{W}_I) > 0$; *or*

(b) *For all* I, $\det(W_I) \neq 0 \Rightarrow \det(W_I)\det(\widetilde{W}_I) < 0$.

$I \subseteq \{1, \ldots, n\}$ *with* $|I| = d$

$$\begin{tikzcd} A + B \arrow[r, shift left] & C \arrow[l, shift left] \arrow[d] & A \arrow[r, shift left] & E \arrow[l, shift left] \\ & D \arrow[ul] & & \end{tikzcd} \qquad \begin{tikzcd} aA + bB \arrow[r, shift left] & C \arrow[l, shift left] \arrow[d] & A \arrow[r, shift left] & E \arrow[l, shift left] \\ & cA + D \arrow[ul] & & \end{tikzcd}$$

$$W = \begin{pmatrix} 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 1 & 1 & 0 \end{pmatrix} \qquad \widetilde{W} = \begin{pmatrix} 1 & 0 & a & a-c & 1 \\ 0 & 1 & b & b & 0 \end{pmatrix}$$

- Unique equilibrium? – Find conditions on a, b, c.

Closure condition – Maximal minors

Show: For all I, $\det(W_I) \neq 0 \Rightarrow \det(W_I)\det(\widetilde{W}_I) > 0$.

$$W = \begin{pmatrix} 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 1 & 1 & 0 \end{pmatrix}$$

$$\widetilde{W} = \begin{pmatrix} 1 & 0 & a & a-c & 1 \\ 0 & 1 & b & b & 0 \end{pmatrix}$$

I	$\det(W_I)$	$\det(\widetilde{W}_I)$	
$\{1,2\}$	1	1	✓
$\{1,3\}$	1	b	$b > 0$
$\{1,5\}$	0	0	✓
$\{2,3\}$	-1	$-a$	$a > 0$
$\{2,4\}$	-1	$c-a$	$c < a$
$\{3,4\}$	0	bc	✓
$\vdots$	$\vdots$	$\vdots$	

```
sage: W  = matrix([[1, 0, 1, 1, 1],
....:              [0, 1, 1, 1, 0]])
sage: var('a, b, c')
sage: Wt = matrix([[1, 0, a, a - c, 1],
....:              [0, 1, b,     b, 0]])
sage: from sign_vector_conditions import *
sage: condition_closure_minors(W, Wt)
{a > 0, a - c > 0, b > 0}
```

Uniqueness

Theorem

For CRN with GMAK, there is at most one complex-balanced equilibrium in every stoichiometric class and for all rate constants iff

$$\operatorname{sign}(S) \cap \operatorname{sign}(\widetilde{S}^{\perp}) = \{0\}.$$

$$S = \operatorname{im} \begin{pmatrix} -1 & -1 & 1 \end{pmatrix}^{\top} \qquad \widetilde{S} = \operatorname{im} \begin{pmatrix} -a & -b & 1 \end{pmatrix}^{\top}$$

```
sage: S = matrix([[-1, -1, 1]])
sage: var('a, b');
sage: St = matrix([[-a, -b, 1]])
sage: from sign_vectors.oriented_matroids import *
sage: covectors_from_matrix(S, kernel=False)
{(000), (--+), (++-)}
sage: assume(a > 0, b > 0)
sage: covectors_from_matrix(St, kernel=True)
{(000), (+-+), (---), (-+0), (-+-), (+0+), (-++),
   (-0-), (+++), (+--), (0++), (0--), (+-0)}
```

- What about general $a, b \in \mathbb{R}$?

Uniqueness – Maximal minors

Corollary

Let $S = \ker(W)$, $\widetilde{S} = \ker(\widetilde{W})$. *The following are equivalent:*

(1) $\operatorname{sign}(S) \cap \operatorname{sign}(\widetilde{S}^{\perp}) = \{0\}$

(2) *Exactly one of the following holds:*

- (a) *For all* $I \subseteq \{1, \ldots, n\}$ *with* $|I| = d$, $\det(W_I)\det(\widetilde{W}_I) \geq 0$.
- (b) *For all* $I \subseteq \{1, \ldots, n\}$ *with* $|I| = d$, $\det(W_I)\det(\widetilde{W}_I) \leq 0$.

$$S = \operatorname{im}\begin{pmatrix}-1 & -1 & 1\end{pmatrix}^\top \qquad \widetilde{S} = \operatorname{im}\begin{pmatrix}-a & -b & 1\end{pmatrix}^\top$$

$$W = \begin{pmatrix}1 & 0 & 1\\ 0 & 1 & 1\end{pmatrix} \qquad \widetilde{W} = \begin{pmatrix}1 & 0 & a\\ 0 & 1 & b\end{pmatrix}$$

I	$\det(W_I)$	$\det(\widetilde{W}_I)$	
$\{1,2\}$	1	1	✓
$\{1,3\}$	1	b	$b \geq 0$
$\{2,3\}$	-1	$-a$	$a \geq 0$

Multistationarity

Corollary

Weakly reversible generalized mass-action system has capacity for multiple complex-balanced equilibria iff

$$\operatorname{sign}(S) \cap \operatorname{sign}(\widetilde{S}^{\perp}) \neq \{0\}.$$

$$A + B \rightleftharpoons C \qquad\qquad aA + bB \rightleftharpoons C$$

I	$\det(W_I)$	$\det(\widetilde{W}_I)$
$\{1,2\}$	1	1
$\{1,3\}$	1	b
$\{2,3\}$	-1	$-a$

$\rightsquigarrow$ $a < 0$ or $b < 0$

Exactly one equilibrium

Theorem ($\delta = \widetilde{\delta} = 0$ theorem)

For a CRN with GMAK, there is a unique complex-balanced equilibrium in every stoichiometric class and for all rate constants iff $\delta = \widetilde{\delta} = 0$*, network weakly reversible and*

(1) $\mathrm{sign}(S) \cap \mathrm{sign}(\widetilde{S}^{\perp}) = \{0\}$;

(2) *for every non-zero* $\widetilde{\tau} \in \mathrm{sign}(\widetilde{S}^{\perp})_{\oplus}$*, there is non-zero* $\tau \in \mathrm{sign}(S^{\perp})_{\oplus}$ *such that* $\tau \leq \widetilde{\tau}$*; and*

(3) $(S, \widetilde{S})$ *is non-degenerate.*

- Recursive algorithm
- Implementation

Outlook

- SageMath packages
  - Sign vectors, oriented matroids, elementary vectors
    `https://github.com/MarcusAichmayr/sign_vectors`
  - Sign vector conditions for chemical reaction networks
    (not yet public)