Reaction networks with (generalized) mass-action kinetics: Sign vector conditions for the existence of a unique general equilibrium

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Chemical reaction network (CRN)

- Weighted directed graph
- Rate constants $k_{12}, k_{21} > 0$

$$1 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} 2$$

- Stoichiometric complexes: $1A + 1B \rightleftharpoons C$
- Kinetic complexes: $aA + bB \rightleftharpoons C$

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

- MAK: $a = b = 1$
- GMAK: $a, b \in \mathbb{R}$

- Stoichiometric subspace:

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

- Kinetic-order subspace:

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

- MAK: $S = \widetilde{S}$

Implementation (SageMath)

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

```
sage: from sign_vector_conditions import *
sage: species("A,B,C,D,E");
sage: var("a,b,c");  # parameters
sage: rn = ReactionNetwork()
sage: rn.add_complexes([(1,A+B,a*A+b*B),(2,C),...,(5,E)])
sage: rn.add_reactions([(1,2),(2,1),(2,3),(3,1),(4,5),...])
sage: rn.stoichiometric_matrix
[-1  1  0  1 -1  1]
[-1  1  0  1  0  0]
[ 1 -1 -1  0  0  0]
[ 0  0  1 -1  0  0]
[ 0  0  0  0  1 -1]
```

$\rightarrow N$

```
sage: rn.kinetic_order_matrix
[-a   a   c  a-c -1   1]
[-b   b   0   b   0   0]
[ 1  -1  -1   0   0   0]
[ 0   0   1  -1   0   0]
[ 0   0   0   0   1  -1]
```

$\rightarrow \widetilde{N}$

Positive equilibria

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

$$\frac{dx}{dt} = N(k \circ x^{\widetilde{Y}_s}) = \begin{pmatrix} -1 & 1 & 0 & 1 & -1 & 1 \\ -1 & 1 & 0 & 1 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix} \begin{pmatrix} k_{12}\ x_A^a x_B^b \\ k_{21}\ x_C \\ k_{23}\ x_C \\ k_{31}\ x_A^c x_D \\ k_{45}\ x_A \\ k_{54}\ x_E \end{pmatrix}$$

$$= \underbrace{\begin{pmatrix} 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}}_{Y} \underbrace{\begin{pmatrix} -k_{12} & k_{21} & k_{31} & 0 & 0 \\ k_{12} & -k_{21}+k_{31} & 0 & 0 & 0 \\ 0 & k_{23} & -k_{31} & 0 & 0 \\ 0 & 0 & 0 & -k_{45} & k_{54} \\ 0 & 0 & 0 & k_{45} & -k_{54} \end{pmatrix}}_{\text{Graph Laplacian } L_k} \underbrace{\begin{pmatrix} x_A^a x_B^b \\ x_C \\ x_A^c x_D \\ x_A \\ x_E \end{pmatrix}}_{x^{\widetilde{Y}}} = Y L_k x^{\widetilde{Y}}$$

- Positive equilibria:

$$\{x \in \mathbb{R}^n_> : N(k \circ x^{\widetilde{Y}_s}) = 0\}$$

- Positive complex-balanced equilibria (CBE):

$$\{x \in \mathbb{R}^n_> : L_k x^{\widetilde{Y}} = 0\}$$

Sign vector conditions for CBE

- Unique existence
- Uniqueness
- Robustness

S. Müller, G. Regensburger, A:
A SageMath package for elementary and sign vectors with applications to chemical reaction networks. In: Mathematical software - ICMS (2024)
https://arxiv.org/abs/2407.12660

S. Müller, J. Hofbauer, and G. Regensburger:
On the bijectivity of families of exponential/generalized polynomial maps. In: SIAM Journal on Applied Algebra and Geometry 3 (2019)
https://doi.org/10.1137/18M1178153

Sign vectors

- Sign vector:
  Element in $\{-, 0, +\}^n$

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

- $S \subseteq \mathbb{R}^n$:

$$\operatorname{sign} S = \{\operatorname{sign} x \mid x \in S\} \subseteq \{-, 0, +\}^n$$

- Partial order on $\{-, 0, +\}^n$ with $0 < -$ and $0 < +$

$$\begin{pmatrix}0\\0\end{pmatrix} < \begin{pmatrix}0\\+\end{pmatrix} < \begin{pmatrix}-\\+\end{pmatrix}$$

- Nonnegative sign vectors:

$$(\operatorname{sign} S)_\oplus = \{\operatorname{sign} x \mid x \in S \text{ and } x \geq 0\} = \operatorname{sign} S \cap \{0, +\}^n$$

Exactly one CBE

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

Deficiency: $\#\text{vert} - \#\text{comp} - \dim S$

- $S = \operatorname{im} N \quad \rightarrow \delta = 5 - 2 - 3 = 0$
- $\widetilde{S} = \operatorname{im} \widetilde{N} \quad \rightarrow \widetilde{\delta} = 5 - 2 - 3 = 0$

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

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

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

(2) $\forall \widetilde{\tau} \in (\operatorname{sign} \widetilde{S}^{\perp})_{\oplus}$: $\exists \tau \in (\operatorname{sign} S^{\perp})_{\oplus}$ *with* $\tau \leq \widetilde{\tau}$; *and*

(3) $(S, \widetilde{S})$ *is nondegenerate.* $\rightarrow$ *Recursive algorithm*

```
sage: rn(a=2, b=1, c=1).has_exactly_one_cbe()
True
```

Computing sign vectors

- $\mathcal{N} = \begin{pmatrix} 1 & 0 \\ 2 & 1 \\ 0 & 2 \\ 0 & 3 \end{pmatrix}$
- $\operatorname{sign} \operatorname{im} \mathcal{N} = ?$

I	$\det \mathcal{N}_{\mathrm{I}}$	chirotope
$\{1,2\}$	1	$+$
$\{1,3\}$	2	$+$
$\{1,4\}$	3	$+$
$\{2,3\}$	4	$+$
$\{2,4\}$	6	$+$
$\{3,4\}$	0	0

- Cocircuits: Support-minimal elements

$$\begin{pmatrix} 0 \\ - \\ - \\ - \end{pmatrix}, \begin{pmatrix} + \\ 0 \\ - \\ - \end{pmatrix}, \begin{pmatrix} + \\ + \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ + \\ + \\ + \end{pmatrix}, \begin{pmatrix} - \\ 0 \\ + \\ + \end{pmatrix}, \begin{pmatrix} - \\ - \\ 0 \\ 0 \end{pmatrix} \in \operatorname{sign} \operatorname{im} \mathcal{N}$$

max. minors $\longrightarrow$ chirotopes $\longrightarrow$ cocircuits $\longrightarrow$ sign vectors

Uniqueness & Multistationarity

Theorem

For CRN with GMAK, there is at most one positive CBE in every stoichiometric class and for all rate constants iff

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

Corollary

Equivalent are:

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

(2) *Either* $\det \mathcal{N}_I \det \widetilde{\mathcal{N}}_I \geq 0$ *for all* I, *or* $\det \mathcal{N}_I \det \widetilde{\mathcal{N}}_I \leq 0$ *for all* I.

```
sage: rn.has_at_most_one_CBE()
[{a >= 0, b >= 0, a - c >= 0}]
```

Corollary

Weakly reversible CRN with GMAK has multiple CBE iff

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

$a < 0$ or $b < 0$ or $a < c$

General equilibria

$$\frac{dx}{dt} = N(k \circ x^{\widetilde{Y}_s}) = 0 \longrightarrow A(c \circ x^B) = 0?$$

- Unique existence for all parameters c?
- A, $B \rightarrow \mathcal{A}$, $\mathcal{B}$ (add row of 1s)
- Subspaces $T = \ker \mathcal{A}$, $D = \ker \mathcal{B}$

Theorem

There is unique positive equilibrium if

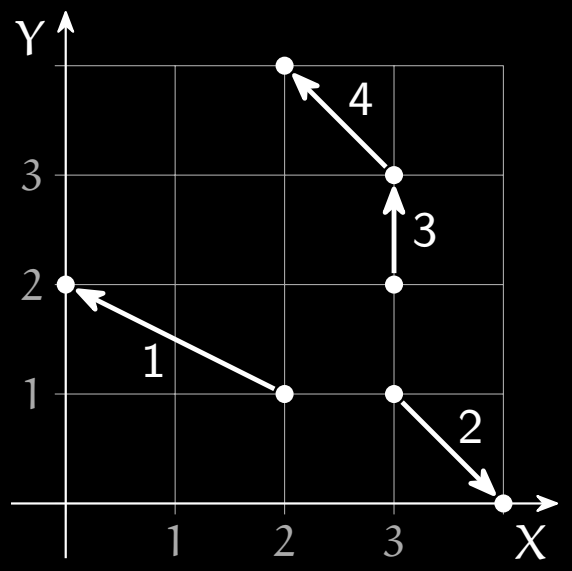
(1) $\operatorname{sign} T \cap \operatorname{sign} D^{\perp} = \{0\}$; *and*

(2) $\mu\big((\operatorname{sign} \ker A)_{\oplus} \setminus \{0\}\big) \cap \operatorname{sign} D^{\perp} = \{0\}$.

- $\mu(+) = 0$, $\mu(0) = +$

Abhishek Deshpande and Stefan Müller. *Existence of a unique solution to parametrized systems of generalized polynomial equations*. (2024)
https://arxiv.org/abs/2409.11288

General equilibria – Example (MAK)



$$2X + Y \xrightarrow{1} 2Y \qquad 3X + Y \xrightarrow{2} 4X$$

$$3X + 2Y \xrightarrow{3} 3X + 3Y \xrightarrow{4} 2X + 4Y$$

$$A = \begin{pmatrix} -2 & 1 & 0 & -1 \\ 1 & -1 & 1 & 1 \end{pmatrix} \qquad B = \begin{pmatrix} 2 & 3 & 3 & 3 \\ 1 & 1 & 2 & 3 \end{pmatrix}$$

$$\mathcal{A} = \begin{pmatrix} -2 & 1 & 0 & -1 \\ 1 & -1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{pmatrix}, \quad \mathcal{B} = \begin{pmatrix} 2 & 3 & 3 & 3 \\ 1 & 1 & 2 & 3 \\ 1 & 1 & 1 & 1 \end{pmatrix}$$

$$c_1 \begin{pmatrix} -2 \\ 1 \end{pmatrix} x^2 y + c_2 \begin{pmatrix} 1 \\ -1 \end{pmatrix} x^3 y + c_3 \begin{pmatrix} 0 \\ 1 \end{pmatrix} x^3 y^2 + c_4 \begin{pmatrix} -1 \\ 1 \end{pmatrix} x^3 y^3 = 0$$

```
sage: species("X,Y")
sage: rn = ReactionNetwork()
sage: rn.add_complexes([(1,2*X+Y),(2,2*Y),(3,3*X+Y),...])
sage: rn.add_reactions([(1,2),(3,4),(5,6),(6,7)])
sage: rn.has_exactly_one_equilibrium()
True
sage: rn.remove_reaction(6,7)  # reaction 4
sage: rn.has_exactly_one_equilibrium()
True
```

Summary & Outlook

- Conditions for CBE
  - Unique existence
  - Uniqueness
  - Multistationarity
  - Robustness
- Unique existence of general equilibria
  - Sufficient sign vector conditions
  - Equivalent conditions – Algorithm? Implementation?
- Package (SageMath)
  - Documentation
  - Examples
  - https://github.com/MarcusAichmayr/sign_vector_conditions