A SageMath Package for Elementary and Sign Vectors with Applications to Chemical Reaction Networks

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VERSITÄT

Chemical reaction network (CRN)

Weighted directed graph

Rate constants $k_{12}, k_{21} > 0$

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

Stoichiometric complexes:

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

Kinetic complexes:

$$aA + bB \rightleftarrows C$$

MAK: $a = b = 1$

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

$$\frac{dx}{dt} = k_{12}\, x_1^a x_2^b \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix} + k_{21}\, x_3 \begin{pmatrix} 1 \\ 1 \\ -1 \end{pmatrix}$$

Exists (unique) positive complex-balanced equilibrium (CBE)?

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 (Horn, Jackson, Feinberg 1972)

For CRN with MAK, there is unique positive CBE in every stoichiometric class, and for all rate constants iff $\delta = 0$ and network weakly reversible.

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

- Weakly reversible ✓
- (Stoichiometric) deficiency:

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

  - m complexes
  - l connected components
  - $\dim S = ?$

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 ($S = \widetilde{S}$)? *Implementation?*

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.

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: G = DiGraph({1:[2], 2:[1, 3], 3:[1], 4:[5], 5:[4]})
sage: Y = matrix([[1, 1, 0, 0, 0], ...])
sage: Yt = matrix([[a, b, 0, 0, 0], ...])
sage: Y
[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]
sage: Yt
[a b 0 0 0]
[0 0 1 0 0]
[c 0 0 1 0]
[1 0 0 0 0]
[0 0 0 0 1]
```

```
sage: from sign_vector_conditions import *
sage: crn = GMAKSystem(G, Y, Yt)
sage: S = crn.stoichiometric_matrix
sage: St = crn.kinetic_order_matrix
sage: S
[-1 -1  1  0  0]
[ 0  0 -1  1  0]
[-1  0  0  0  1]
sage: St
[-a -b  1  0  0]
[ c  0 -1  1  0]
[-1  0  0  0  1]
sage: crn.are_deficiencies_zero()
True
sage: crn.is_weakly_reversible()
True
```

Other conditions for CBE (GMAK)? – Sign vectors

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 $0 < +$

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

- Closure: $\overline{\operatorname{sign} S} = \{\sigma \mid \sigma \leq \tau \text{ for some } \tau \in \operatorname{sign} S\}$

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

Compute sign vectors?

Computing sign vectors

- $S = \operatorname{im} \begin{pmatrix} -1 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ -1 & 0 & 0 & 0 & 1 \end{pmatrix}^\top$
- $\operatorname{sign} S = ?$
- $S = \ker W, \qquad W = \begin{pmatrix} 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 1 & 1 & 0 \end{pmatrix}$

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

- Cocircuits: Support-minimal elements (in $\operatorname{sign} S$)

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

minors → chirotopes → cocircuits ↔ sign vectors

Robust deficiency zero theorem

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

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

$$\operatorname{sign} S \subseteq \overline{\operatorname{sign} \widetilde{S}}.$$

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

```
sage: S                                  sage: St(a=2, b=1, c=1)
[-1 -1  1  0  0]                         [-2 -1  1  0  0]
[ 0  0 -1  1  0]                         [ 1  0 -1  1  0]
[-1  0  0  0  1]                         [-1  0  0  0  1]
sage: from sign_vectors.oriented_matroids import *
sage: covectors_from_matrix(S, kernel=False)
{(00000), (00+-0), (0-0+-), (+000-), (+-++-), (0--+-), ...}
sage: covectors_from_matrix(St(a=2, b=1, c=1), kernel=False)
{(00000), (+-++-), (0--+-), (+0+--), (+++--), (0-0+-), ...}
```

General a, b, c?

Closure condition

Proposition

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

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

(2) *For all* I: $\quad \det W_I \neq 0 \implies \det W_I \, \det \widetilde{W}_I > 0$ *(or "< 0")*.

```
sage: S
[-1 -1  1  0  0]
[ 0  0 -1  1  0]
[-1  0  0  0  1]
sage: W
[1 0 1 1 1]
[0 1 1 1 0]
```

```
sage: St
[-a -b  1  0  0]
[ c  0 -1  1  0]
[-1  0  0  0  1]
sage: Wt
[1  0  a a-c 1]
[0  1  b   b 0]
```

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: crn(a=2, b=1, c=1).has_robust_CBE()
True
sage: crn.has_robust_CBE()
[{a > 0, b > 0, a - c > 0}]
```

Other conditions?

Uniqueness and multistationarity

Theorem

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

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

$S = \ker W, \qquad \widetilde{S} = \ker \widetilde{W}$

Corollary

The following are equivalent:

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

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

```
sage: crn.has_at_most_1_CBE()
[{a >= 0, b >= 0, a - c >= 0}]
```

Multistationarity?

Corollary

Weakly reversible CRN with GMAK has capacity for multiple CBE iff

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

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

Exactly one equilibrium

Nonnegative sign vectors: $\mathsf{T}_\oplus = \mathsf{T} \cap \{0,+\}^n$

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) *for every nonzero $\widetilde{\tau} \in (\operatorname{sign} \widetilde{S}^\perp)_\oplus$, there is nonzero $\tau \in (\operatorname{sign} S^\perp)_\oplus$ with $\tau \leq \widetilde{\tau}$; and*

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

Nondegenerate? – Recursive algorithm, implementation

Exactly one equilibrium – Degenerate

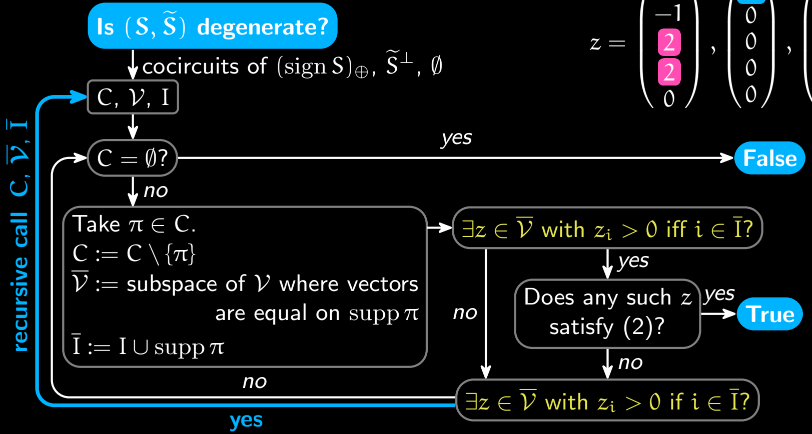
$(S, \widetilde{S})$ **degenerate** if cocircuits $C \subseteq (\operatorname{sign} S)_\oplus$ and $z \in \widetilde{S}^\perp$ exist with

(1) (a) for all $\pi \in C$, $z_i = z_j > 0$ for all $i, j \in \operatorname{supp} \pi$,

(b) for all $i \notin \bigcup_{\pi \in C} \operatorname{supp} \pi$, $z_i \leq 0$; and

(2) $\operatorname{supp} \tau \not\subseteq \operatorname{supp} z$ for all cocircuits $\tau \in (\operatorname{sign} S^\perp)_\oplus$.

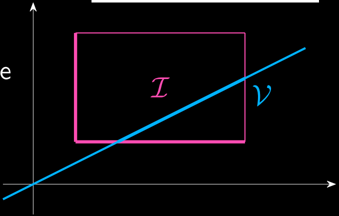
$$z = \begin{pmatrix} \boxed{1} \\ -1 \\ \boxed{2} \\ \boxed{2} \\ 0 \end{pmatrix}, \quad \overbrace{\begin{pmatrix} \boxed{+} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ \boxed{+} \\ \boxed{+} \\ 0 \end{pmatrix}}^{\in C}$$



Summary and outlook

- Conditions for CBE – Sign vectors
    - Robustness ✓
    - Uniqueness ✓
    - Multistationarity ✓
    - Existence ✓

- Intersection of subspace and intervals
    - Based on theorems of the alternative
        - Minty's Lemma
    - Extended Abstract (Proceedings)
    - Upcoming preprint (CASC '24)



- Packages (SageMath)
    - Documentation
    - Examples
    - Sign vector conditions for CRNs:
      https://github.com/MarcusAichmayr/sign_vector_conditions
    - Sign vectors, oriented matroids, elementary vectors, existence:
      https://github.com/MarcusAichmayr/elementary_vectors