Generalized mass action systems and positive solutions of polynomial systems

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C}$$

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Chemical reaction network theory (CRNT)

Chemical reaction networks with mass-action kinetics (MAK)
give rise to polynomial ODE systems with positive parameters

CRNT:

Uniqueness and existence of positive steady states
– independent of parameters (rate constants)
– depending only on network properties

Corresponding polynomial systems with positive parameters:

Uniqueness and existence of positive real solutions
– independent of parameters

generalized mass-action kinetics
depending on the relation between coefficients and exponents

Mass-action kinetics (MAK)

Reaction:

$$1\,\mathrm{A} + 1\,\mathrm{B} \to \mathrm{C}$$

A, B ... reactant *species*
C ... product species

MAK reaction rate:

$$v = k\,c_A^1\,c_B^1$$

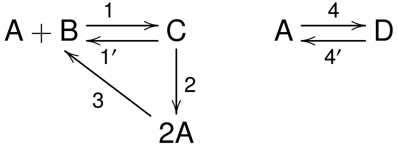
$k > 0$ ... *rate constant*
$c_\mathrm{A} = c_\mathrm{A}(t) \geq 0$ ... concentration of A

Contribution to network dynamics:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} c_\mathrm{A} \\ c_\mathrm{B} \\ c_\mathrm{C} \\ \vdots \end{pmatrix} = k\,c_\mathrm{A} c_\mathrm{B} \begin{pmatrix} -1 \\ -1 \\ 1 \\ 0 \end{pmatrix} + \cdots$$

Chemical reaction networks

Example:



A+B, C, 2A, A, D . . . *complexes*

Dynamics for rate constants $k = (k_1, k_{1'}, k_2, k_3, k_4, k_{4'})$:

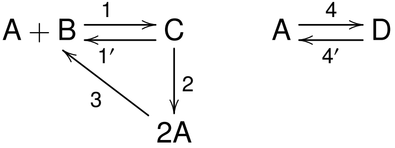
$$\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} c_A \\ c_B \\ c_C \\ c_D \end{pmatrix} = \begin{pmatrix} -1 & 2 & -1 & -1 \\ -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} k_1 c_A c_B - k_{1'} c_C \\ k_2 c_C \\ k_3 c_A^2 \\ k_4 c_A - k_{4'} c_D \end{pmatrix} = N\, v_k(c)$$

N . . . *stoichiometric matrix*

v_k . . . net reaction rates

Deficiency

Example:



$$N = \begin{pmatrix} -1 & 2 & -1 & -1 \\ -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

Definition

A network is *weakly reversible* if each connected component is strongly connected. Its *deficiency* is given by

$$\delta = m - \ell - s.$$

m . . . number of complexes
ℓ . . . number of connected components
s . . . dimension of stoichiometric subspace $S = \mathrm{im}(N)$

$$\delta = 5 - 2 - 3 = 0$$

Deficiency zero theorem

Dynamics:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = N\, v_k(c)$$

$\Rightarrow \quad c(t) \in (c(0) + S) \quad$ with $S = \mathrm{im}(N)$

$(c(0) + S)_{\geq 0}$ ... stoichiometric compatibility class

Theorem

A reaction network with zero deficiency has a unique asymptotically stable positive steady state in each stoichiometric compatibility class for all positive rate constants if and only if it is weakly reversible.

(Horn-Jackson '72, Horn '72, Feinberg '72)

Deficiency zero theorem

Example:

$$N\,v_k(c) = \begin{pmatrix} -1 & 2 & -1 & -1 \\ -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} k_1\,c_A c_B - k_{1'}\,c_C \\ k_2 c_C \\ k_3 c_A^2 \\ k_4 c_A - k_{4'} c_D \end{pmatrix} = 0$$

Deficiency zero theorem ⇒ unique positive steady state $Nv_k(c) = 0$ in each stoichiometric compatibility class for all rate constants

Polynomial equations with parameters:

$$\{c > 0 \,|\, N\,v_k(c) = 0\} \cap (c' + S)_{\geq 0}$$

contains exactly one element for all $c' > 0$ and all $k > 0$

Graph Laplacian

Minimal example:

$$\mathrm{A} + \mathrm{B} \underset{1'}{\overset{1}{\rightleftarrows}} \mathrm{C}$$

Dynamics:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix} \left(k_1 \, c_{\mathrm{A}} c_{\mathrm{B}} - k_1' \, c_{\mathrm{C}} \right) = N \, v_k(c)$$

Decomposition:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} -k_1 & k_{1'} \\ k_1 & -k_{1'} \end{pmatrix} \begin{pmatrix} c_{\mathrm{A}} c_{\mathrm{B}} \\ c_{\mathrm{C}} \end{pmatrix} = Y \, A_k \, \Psi(c)$$

(Horn-Jackson '72)

A_k ... weighted graph Laplacian

Complex balancing equilibria

Decomposition:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = Y\, A_k\, \psi(c)$$

Complex balancing equilibria:

$$Z_k = \{c > 0 \,|\, A_k\, \psi(c) = 0\}$$

Deficiency:

$$\delta = \dim(\ker(Y) \cap \mathrm{im}(A_k))$$

Parametrization of complex balancing equilibria:

Proposition

$$c^* \in Z_k \neq \emptyset \quad \Rightarrow \quad Z_k = \left\{c^* \circ \mathrm{e}^v = (c_1^*\, \mathrm{e}_1^v, \ldots, c_n^*\, \mathrm{e}_n^v) \,|\, v \in S^\perp\right\}$$

(Horn-Jackson '72)

Monomial param.: $\quad Z_k = \left\{c^* \circ x^W = (c_1 x^{w^1}, \ldots, c_n x^{w^n}) \,|\, x \in \mathbb{R}^d_>\right\}$

with $W = (w^1, \ldots, w^n) \in \mathbb{R}^{d \times n}$ of rank d s.t. $S = \ker(W)$

Birch's theorem

$$S = \ker(W) \quad \text{with} \quad W = (w^1, \ldots, w^n) \in \mathbb{R}^{d \times n}$$

Existence/uniqueness of complex balancing equilibria in each stoichiometric compatibility class, that is, exactly one element in

$$\left\{c^* \circ x^W \,|\, x \in \mathbb{R}^d_>\right\} \cap (c' + \ker(W))$$

for all $c^* > 0$ and $c' > 0$ ⇔ surjectivity/injectivity of

$$f_{c^*} : \mathbb{R}^d_> \to C^\circ \subseteq \mathbb{R}^d, \quad x \mapsto \sum_{k=1}^n c^*_k \, x^{w^k} w^k$$

for all $c^* > 0$, with the polyhedral cone

$$C = \left\{\sum_{k=1}^n c_k \, w^k \in \mathbb{R}^d \,|\, c \in \mathbb{R}^n_\geq\right\}.$$

Theorem

The map f_{c^*} is a bijection (real analytic isomorphism) for all $c^* > 0$.

(Birch '63, Horn-Jackson '72, Fulton '93)

Martin W. Birch

M. W. Birch, Maximum likelihood in three-way contingency tables, *J. Roy. Statist. Soc. Ser. B* **25** (1963), 220–233.

Statistical Laboratory, University of Cambridge, 1961

Source `http://www.statslab.cam.ac.uk/Dept/Photos/pic61.html`

Martin W. Birch (1939–69)

Birch's theorem

Minimal example:

$$S = \text{im}(-1, -1, 1)^T = \ker(W)$$

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

Birch's theorem ⇒ There exists a unique solution $x \in \mathbb{R}^3_>$ for

$$c_1^* \, x_1 \begin{pmatrix} 1 \\ 0 \end{pmatrix} + c_2^* \, x_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} + c_3^* \, x_1 x_2 \begin{pmatrix} 1 \\ 1 \end{pmatrix} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

for all right-hand sides $y \in \mathbb{R}^2_>$ and for all parameters $c^* \in \mathbb{R}^3_>$.

All mass action systems arising from

$$\mathsf{A} + \mathsf{B} \underset{1'}{\overset{1}{\rightleftarrows}} \mathsf{C}$$

have a unique positive steady state.

Generalized mass action kinetics

Mass action rate law is valid
for elementary reactions in homogeneous and dilute solutions.

Intracellular environments are highly structured;
more general reaction rates needed for applications in cell biology.

Generalized mass action systems

Minimal example:

$$\begin{array}{ccc} \mathrm{A} + \mathrm{B} & \overset{1}{\underset{1'}{\rightleftarrows}} & \mathrm{C} \\ \vdots & & \vdots \\ \alpha\mathrm{A} + \beta\mathrm{B} & & \gamma\mathrm{C} \end{array}$$

$\alpha, \beta, \gamma > 0$ ... kinetic orders
$\alpha\mathrm{A} + \beta\mathrm{B}, \gamma\mathrm{C}$ ... kinetic complexes

Reaction rates:

$$v_1 = k_1 c_\mathrm{A}^\alpha c_\mathrm{B}^\beta \quad \text{and} \quad v_{1'} = k_{1'} c_\mathrm{C}^\gamma$$

Dynamics, decomposition:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} -k_1 & k_{1'} \\ k_1 & -k_{1'} \end{pmatrix} \begin{pmatrix} c_\mathrm{A}^\alpha c_\mathrm{B}^\beta \\ c_\mathrm{C}^\gamma \end{pmatrix} = Y\, A_k\, \tilde{\psi}(c)$$

Generalized mass action systems

$$\begin{array}{ccc} \mathsf{A} + \mathsf{B} & \underset{1'}{\overset{1}{\rightleftarrows}} & \mathsf{C} \\ \vdots & & \vdots \\ \alpha\mathsf{A} + \beta\mathsf{B} & & \gamma\mathsf{C} \end{array}$$

Stoichiometric subspace:

$$N = \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix}, \quad S = \mathrm{im}(N)$$

Kinetic-order subspace:

$$\tilde{N} = \begin{pmatrix} -\alpha \\ -\beta \\ \gamma \end{pmatrix}, \quad \tilde{S} = \mathrm{im}(\tilde{N})$$

Complex balancing equilibria:

$$c^* \in \tilde{Z}_k = \left\{ c > 0 \,|\, A_k \, \tilde{\psi}(c) = 0 \right\} \quad \Rightarrow \quad \tilde{Z}_k = \{ c^* \circ \mathrm{e}^v \mid v \in \tilde{S}^\perp \}$$

Deficiency zero/Birch's theorem?

$$S = \ker(W) \quad \text{and} \quad \tilde{S} = \ker(\tilde{W})$$
$$\text{with} \quad W = (w^1, \ldots, w^n) \quad \text{and} \quad \tilde{W} = (\tilde{w}^1, \ldots, \tilde{w}^n)$$

Existence/uniqueness of complex balancing equilibria in each stoichiometric compatibility class, that is, exactly one element in

$$\{c^* \circ \mathrm{e}^v \mid v \in \tilde{S}^\perp\} \cap (c' + S)$$

for all $c^* > 0$ and $c' > 0$ $\Leftrightarrow$ surjectivity/injectivity of the generalized polynomial map

$$f_{c^*} : \mathbb{R}^d_> \to C^\circ \subseteq \mathbb{R}^d, \quad x \mapsto \sum_{k=1}^n c^*_k \, x^{\tilde{w}^k} \, w^k \tag{gpm}$$

for all $c^* > 0$.

Deficiency zero theorem: $S = \tilde{S}$

Birch' theorem: $\tilde{W} = W$

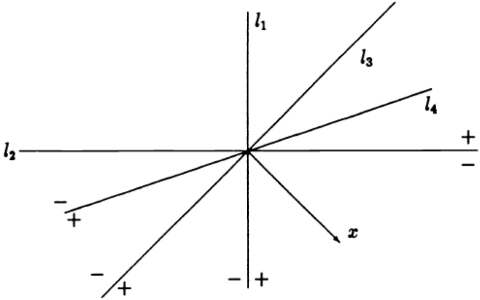
How much can we perturb the exponents/subspace/cone?

Sign vectors

For $x \in \mathbb{R}^n$, obtain the *sign vector* $\sigma(x) \in \{-, 0, +\}^n$ by applying the sign function componentwise:

$$\sigma\begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix} = \begin{pmatrix} + \\ 0 \\ - \end{pmatrix}$$

Point configurations, hyperplane arrangements, face lattices of cones
Theory of *oriented matroids*



Source: Bachem-Kern ’92

Generalized Birch's theorem

Theorem

If $\sigma(\tilde{S}) = \sigma(S)$ *and* $(+, \ldots, +)^T \in \sigma(S^\perp)$,
then the generalized polynomial map f_{c^*}*, defined in Eqn.* (gpm),
is a real analytic isomorphism for all $c^* > 0$.

CRNT:

Theorem

If a reaction network with zero deficiency is weakly reversible and conservative, then there exists a unique positive steady state in each stoichiometric compatibility class, for all positive rate constants and all kinetic complexes with $\sigma(\tilde{S}) = \sigma(S)$.

Generalized Birch's theorem

Minimal example:

$$S = \operatorname{im}(-1,-1,1)^T \quad \text{and} \quad \tilde{S} = \operatorname{im}(-\alpha,-\beta,\gamma)^T \text{ with } \alpha,\beta,\gamma > 0$$

$$\sigma(S) = \left\{ \begin{pmatrix} - \\ - \\ + \end{pmatrix}, \begin{pmatrix} + \\ + \\ - \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \right\} = \sigma(\tilde{S}) \quad \text{and} \quad \begin{pmatrix} 1 \\ 1 \\ 2 \end{pmatrix} \in S^\perp$$

$$W = \begin{pmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \end{pmatrix} \quad \text{and} \quad \tilde{W} = \begin{pmatrix} \gamma & 0 & \alpha \\ 0 & \gamma & \beta \end{pmatrix}$$

Theorem $\Rightarrow$ There exists a unique solution $x \in \mathbb{R}^3_>$ for

$$c_1^* \, x_1^\gamma \begin{pmatrix} 1 \\ 0 \end{pmatrix} + c_2^* \, x_2^\gamma \begin{pmatrix} 0 \\ 1 \end{pmatrix} + c_3^* \, x_1^\alpha x_2^\beta \begin{pmatrix} 1 \\ 1 \end{pmatrix} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix}$$

for all $y \in \mathbb{R}^2_>$, all parameters $c^* \in \mathbb{R}^3_>$, and all exponents $\alpha,\beta,\gamma > 0$.

All generalized mass action systems arising from the minimal example have a unique positive steady state.

Outlook

- Stability of complex balancing equilibria
- Injectivity and multiple general steady states
- Generalized mass action systems
  and (dynamically) equivalent mass action systems
- Algorithms for sign vector (software for oriented matroids)
- Examples from cell biology

Thanks!

References

with S. Müller,
Generalized mass action systems: complex balancing equilibria and sign vectors of the stoichiometric and kinetic-order subspaces, *SIAM Journal on Applied Mathematics* **72** (2012), 1926–1947.

with S. Müller, E. Feliu, C. Conradi, A. Shiu, A. Dickenstein,
Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry, 2013, 25 pp. Submitted. `arXiv:1311.5493 [math.AG]`