Toric biochemical systems

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The distributive phosphorylation of a protein

$$S + K \underset{k_2}{\overset{k_1}{\rightleftarrows}} SK \xrightarrow{k_3} S_p + K \underset{k_5}{\overset{k_4}{\rightleftarrows}} S_pK \xrightarrow{k_6} S_{pp} + K$$

$$S_{pp} + P \underset{k_8}{\overset{k_7}{\rightleftarrows}} S_{pp}P \xrightarrow{k_9} S_p + P \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} S_pP \xrightarrow{k_{12}} S + P$$

Dynamics

Assumption

The dynamics of a class of such networks is encoded in their digraphs.

Mass-action hypothesis

It is often assumed that the speed of a reaction is proportional to the product of the concentrations of the reactants. (Polynomial Dynamics.)

Remark

From a statistical physics point of view the mass-action hypothesis is derived from the thermodynamic limit and the existence of fast particles with a simple enough geometry (a gas).

Not such a new theorem

Theorem (Savageau, Voit; 1987)

Consider the following dynamical system

$$\dot{x}_i = f_i(x_1, \dots, x_n), \quad x_i(0) = x_{i0}, \quad i \in [n], \tag{1}$$

where each f_i is a finite composition of elementary functions. Then there is a smooth change of variables such that system (1) can be expressed as

$$\dot{y}_i = \alpha_i \prod_{j=1}^{m} y_j^{a_{ij}} - \beta_i \prod_{j=1}^{m} y_j^{b_{ij}}, \quad y_i \geq 0, \quad y_i(0) = y_{i0}, \quad i \in [m], \tag{2}$$

where $\alpha_i, \beta_i \in \mathbb{R}_{\geq 0}$, $a_{ij}, b_{ij} \in \mathbb{R}$ and there are $m - n$ relations among y_i.

Multistationarity

- Often one does not try to solve these dynamical systems, but chooses a rather more modest objective: describe its steady states.
- Steady states contain information about long term dynamics and they can give clues about the existence of different *modi operandi*.
- In particular we are interested in the existence of multiple steady states (multistationarity).

Multistationarity

- The dynamics of a mass-action network is given as

$$\dot{x} = P(k,x) \in (\mathbb{R}[k_1,\ldots,k_m][x_1,\ldots,x_n])^n$$

- Often there are also linear conservation laws: $Zx = Zx(0) = c$.

Problem

Prove the existence of values of the parameters k and c such that

$$\#\left(V^+ \cap \{(x,k) \in \mathbb{R}^{n+m}_{>0} | Zx = c\}\right) \geq 2,$$

where $V^+ = \{(x,k) \in \mathbb{R}^{n+m}_{>0} | P(k,x) = 0\}$ is the **positive steady state variety**. If possible, classify the values of c (and maybe of k as well) with respect to multistationarity.

Toricity

Remark

While biochemical networks have many parameters, they tend to have nice algebraic and combinatorial properties. In particular many of them are **toric**.

There are many nonequivalent historically justified definitions of toric. Here:

Definition

V^+ is toric if there exist $M \in \mathbb{Z}^{n \times d}$ of rank at most $n-1$ and a rational function $\gamma(k) : \mathcal{K}_\gamma^+ \to \mathbb{R}_{>0}$ such that

$$(k, x) \in V^+ \Leftrightarrow x^M = \gamma(k).$$

Remark

This definition states that toric systems are described in terms of binomials.

Example: Toric system

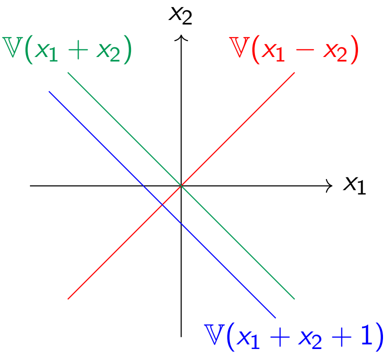
Dynamics:

$$\dot{x}_1 = x_1^3 + x_1^2 x_2 - x_1 x_2^2 - x_2^3 + x_1^2 - x_2^2$$
$$= (x_1 - x_2)(x_1 + x_2)(x_1 + x_2 + 1)$$
$$\dot{x}_2 = -\dot{x}_1$$

Positive steady states, V^+:
$\frac{x_1}{x_2} = 1$, $x_1, x_2 > 0$

Monomial parameterization of V^+:

$$\text{im}\begin{pmatrix} \mathbb{R}_{>0} & \to & \mathbb{R}^2_{>0} \\ t & \mapsto & (t, t) \end{pmatrix}$$



Example: Non toric system

Dynamics:

$\dot{x}_1 = x_1^3 + x_1^2 x_2 - x_1 x_2^2 - x_2^3 + 2x_1^2 + 2x_1 x_2 + x_1 + x_2 =$
$(x_1 - x_2 + 1)(x_1 + x_2)(x_1 + x_2 + 1)$

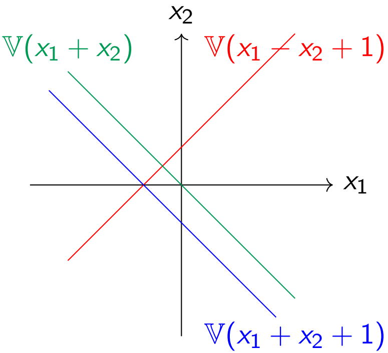
$\dot{x}_2 = -\dot{x}_1$

Positive steady states, V^+:

$x_1 = x_2 - 1$, $x_1, x_2 > 0$

NONMonomial parameterization of V^+:

$$\text{im}\begin{pmatrix} \mathbb{R}_{>0} & \to & \mathbb{R}^2_{>0} \\ t & \mapsto & (t-1, t) \end{pmatrix}$$



MESSI biological systems (Millán, Dickenstein; 2016)

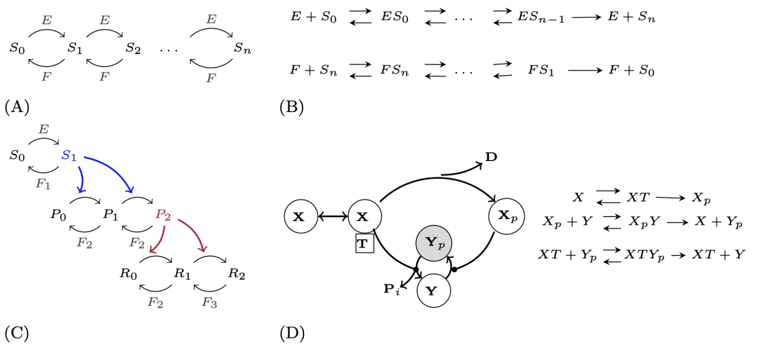


FIGURE 1. Examples of MESSI systems: Sequential n-site phosphorylation/dephosphorlation (A) distributive case [36, 51], (B) processive case [5, 31]; (C) Phosphorylation cascade; (D) Schematic diagram of an EnvZ-OmpR bacterial model [44].

(Taken from Millán and Dickenstein, 2016.)

Experiment (Grigoriev, I., Rahkooy, Sturm, Weber; 2019)

For 129 models with fixed parameters, chosen from the database BioModels, the following classification arises:

Over $\mathbb{C}$

- For 22 of them, V^* is the coset of a multiplicative group.
- For 52 of them, $V^* = \emptyset$ and $\langle P \rangle$ has a binomial/monomial Gröbner basis.
- For 25 of them computations did not finish after 6 hours.

Over $\mathbb{R}$

- For 20 of them, V^* is the coset of a multiplicative group.
- For 53 of them, $V^* = \emptyset$.
- For 35 of them computations did not finish after 6 hours.

Here $V^* = \{x \in (\mathbb{K}^*)^n | P = 0\}$ and $\mathbb{K}^*$ is the multiplicative group of $\mathbb{K}$.

Dimension of the multistationarity problem

If n and r denote the number of variables and parameters, respectively, then detecting multistationarity can be a $2n + r$ dimensional problem.

Lemma (Conradi, I., Kahle; 2018)

In the toric case detecting multistationarity is an $n + q$ dimensional problem, where $q < n$ denotes the dimension of the corresponding torus.

Theorem (Conradi, I., Kahle; 2018)

In the toric case multistationarity is a scale invariant in the space of linear conserved quantities.

Corollary

In the toric case detecting multistationarity is an $n + q - 1$ dimensional problem. Moreover, restricting the values of the linear conserved quantities does not increase the dimension of this problem.

Monomial parameterizations of the positive steady states

Lemma (Conradi, I., Kahle; 2018)

If V^+ is toric, then there are $A \in \mathbb{Q}^{(n-p)\times n}$ of rank $n-p$ with $AM = 0$, a function $\psi : \mathcal{K}_\gamma^+ \to \mathbb{R}^n$, and an exponent $\eta \in \mathbb{Z}_{>0}$, such that ψ^η is a rational function and the following are equivalent:

a) $(k, x) \in V^+$,

b) $k \in \mathcal{K}_\gamma^+$ and there exist $\xi \in \mathbb{R}_{>0}^{n-p}$ such that $x = \psi(k) \star \xi^A$, where $\star$ denotes the coordinate-wise product.

Definition

The matrix A from the previous lemma is called the **exponent matrix** of the monomial parameterization.

Multistationarity in the space of total concentrations

Theorem (Conradi, I., Kahle; 2018)

Assume V^+ is toric with exponent matrix $A \in \mathbb{Q}^{(n-p)\times n}$, let $g_1, \dots, g_l \in \mathbb{R}[c]$, $\square \in \{>, \geq\}^l$, and $\mathcal{F}(g(c) \square 0)$ be any logical combination of the inequalities $g(c) \square 0$. Then there are $k \in \mathcal{K}_\gamma^+$ such that there is multistationarity in the region defined by $\mathcal{F}(g(c) \square 0)$ if and only if there are $a \in \mathbb{R}^n_{>0}$ and $\xi \in \mathbb{R}^{(n-p)}_{>0} \setminus \{\mathbf{1}\}$ such that

$$Z(a\xi^A - a) = 0 \text{ and } \mathcal{F}(g(Za) \square 0).$$

Example: the 2-site phosphorylation

The following network is the sequential distributive 2-site phosphorylation:

$$S + K \underset{k_2}{\overset{k_1}{\rightleftarrows}} SK \xrightarrow{k_3} S_p + K \underset{k_5}{\overset{k_4}{\rightleftarrows}} S_pK \xrightarrow{k_6} S_{pp} + K$$

$$S_{pp} + P \underset{k_8}{\overset{k_7}{\rightleftarrows}} S_{pp}P \xrightarrow{k_9} S_p + P \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} S_pP \xrightarrow{k_{12}} S + P$$

Example: the 2-site phosphorylation

Dynamics:

$$
\begin{aligned}
[\dot{S}] &= -k_1[S][K] + k_2[SK] + k_{12}[S_pP] \\
[\dot{K}] &= -k_1[S][K] + (k_2 + k_3)[SK] - k_4[K][S_p] + (k_5 + k_6)[S_pK] \\
[\dot{SK}] &= k_1[S][K] - (k_2 + k_3)[SK] \\
[\dot{S_p}] &= k_3[SK] - k_4[K][S_p] + k_5[S_pK] + k_9[S_{pp}P] - k_{10}[S_p][P] + k_{11}[S_pP] \\
[\dot{S_pK}] &= k_4[K][S_p] - (k_5 + k_6)[S_pK] \\
[\dot{S_{pp}}] &= k_6[S_pK] - k_7[S_{pp}][P] + k_8[S_{pp}P] \\
[\dot{P}] &= -k_7[S_{pp}][P] + (k_8 + k_9)[S_{pp}P] - k_{10}[S_p][P] + (k_{11} + k_{12})[S_pP] \\
[\dot{S_{pp}P}] &= k_7[S_{pp}][P] - (k_8 + k_9)[S_{pp}P] \\
[\dot{S_pP}] &= k_{10}[S_p][P] - (k_{11} + k_{12})[S_pP].
\end{aligned}
$$

Example: the 2-site phosphorylation

Conservation laws:

$$
\begin{aligned}
[K] + [SK] + [S_p K] &= K_{\text{tot}}, \\
[S_{pp} P] + [S_p P] + [P] &= P_{\text{tot}}, \\
[S] + [S_p] + [S_{pp}] + [SK] + [S_p K] + [S_{pp} P] + [S_p P] &= S_{\text{tot}}.
\end{aligned}
$$

Example: the 2-site phosphorylation

The positive steady state variety V^+ admits a monomial parameterization:

$$[S] = \frac{(k_2+k_3)k_4k_6(k_{11}+k_{12})k_{12}}{k_1k_3(k_5+k_6)k_9k_{10}}\frac{\xi_1^2}{\xi_2\xi_3}$$

$$[K] = \frac{(k_5+k_6)k_9k_{10}}{k_4k_6(k_{11}+k_{12})}\frac{\xi_2\xi_3}{\xi_1}$$

$$[SK] = \frac{k_{12}}{k_3}\xi_1$$

$$[S_p] = \frac{k_{11}+k_{12}}{k_{10}}\frac{\xi_1}{\xi_3}$$

$$[S_pK] = \frac{k_9}{k_6}\xi_2$$

$$[S_{pp}] = \frac{k_8+k_9}{k_7}\frac{\xi_2}{\xi_3}$$

$$[P] = \xi_3$$

$$[S_{pp}P] = \xi_2$$

$$[S_pP] = \xi_1$$

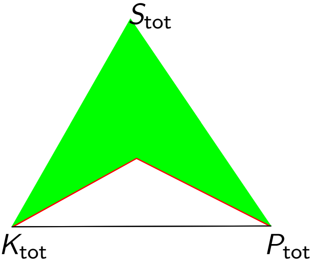
where $\xi_1,\ \xi_2,\ \xi_3 \in \mathbb{R}_{>0}$.

Example: the 2-site phosphorylation

Theorem (Bihan, Dickenstein, Giaroli; Conradi, I., Kahle; 2018)

Generically, in the space of linear conserved quantities K_{tot}, P_{tot}, and S_{tot}, multistationarity is possible if and only if

$$P_{\text{tot}} < S_{\text{tot}} \text{ or } K_{\text{tot}} < S_{\text{tot}}.$$



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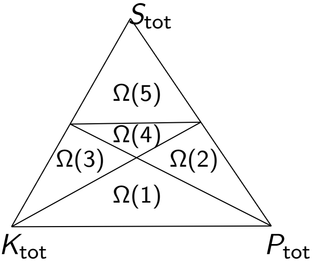
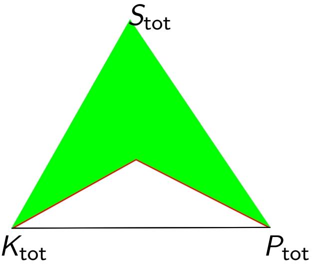


What about the n-site phosphorylation?

Theorem (Bihan, Dickenstein, Giaroli; 2018)

In the space of linear conserved quantities K_{tot}, P_{tot}, and S_{tot}, multistationarity is possible if

$$P_{tot} < S_{tot} \text{ or } K_{tot} < S_{tot}.$$



Sufficient conditions for toricity

Proposition (Eisenbud, Sturmfels; 1994)

Let $I \subseteq \mathbb{R}[x_1, \ldots, x_n]$ be a binomial ideal. Then the variety $\overline{\mathbb{V}_{\mathbb{R}}(I) \cap \mathbb{R}^n_{>0}}$ is empty or toric.

Corollary

If $\{\dot{x}_i = P_i | i \in [n]\}$ has binomial ideal $\langle P_1, \ldots, P_n \rangle \subseteq \mathbb{R}[x_1, \ldots, x_n]$ and at least a positive steady state, then V^+ is toric

Problem

Find other certificates for the toricty of mass-action networks.

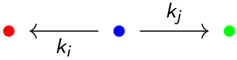
The isolation property

- The dynamics of a mass-action network:

$$\dot{x} = (Y_p - Y_e)\text{diag}(k)x^{Y_e},$$

where $Y_e,\ Y_p \in \mathbb{Z}^{n\times r}_{\geq 0}$.

- $(Y_p - Y_e)\text{diag}(k)x^{Y_e} = 0$ if and only if $\text{diag}(k)x^{Y_e} \in \ker(Y_p - Y_e) \cap \mathbb{R}^{n\times r}_{\geq 0}$.
- Let $E \in \mathbb{Z}^{r\times p}$ such that $\ker(Y_p - Y_e) \cap \mathbb{Z}^{r}_{\geq 0} = \text{cone}(E)$.
- Let D denote the set of all pairs $\{i, j\}$, $i < j$, such that k_i and k_j index two reactions with the same source:



The isolation property

- We slightly change the point of view: we consider a family of mass-action networks with fixed rate constants: $\mathcal{N} = (\mathcal{N}|_{k^*})_{k^* \in \mathbb{R}^r_{>0}}$.
- Consider the family of graphs $\mathfrak{J}(k)$ with vertex set $[r]$ and edge set

$$\{\{i,j\} | \frac{E_i \nu}{E_i \lambda} = \frac{E_j \nu}{E_j \lambda} \ \forall \nu, \lambda \in \Lambda_D(k)\}, \text{ where}$$

E_i denotes the i^{th} row of E and

$$\Lambda_D(k) = \{\lambda \in \mathbb{R}^p_{\geq 0} | E\lambda > 0 \text{ and } (E_i k_j - E_j k_i)\lambda = 0 \ \forall \{i,j\} \in D\}.$$

Definition

A **cluster** of $\mathcal{N}|_{k^*}$ is any connected component of $\mathfrak{J}(k^*)$.

The isolation property

Definition (Local version of a definition by Conradi and Flockerzi; 2011)

A mass-action network $\mathcal{N}|_{k^*}$ has the **isolation property** if $V^+|_{k^*} \neq \emptyset$ and any two rows of E indexed by different clusters have disjoint supports.

Theorem (Conradi, I., Kahle; 2019)

If $\mathcal{N}|_{k^*}$ has the isolation property, then it is toric.

The strong isolation property

Definition

Denote by C the set of minimal internal cycles of $\mathcal{N}$. A **precluster** is a connected component of the graph with vertices $[r]$ and edges $D \cup C$

Definition

A mass-action network has the **strong isolation property** if $V^+ \neq \emptyset$ and any two rows of E indexed by different **preclusters** have disjoint supports.

Fact

Preclusters are subsets of clusters.

Corollary

If $\mathcal{N}$ has the strong isolation property, then $\mathcal{N}|_{k^*}$ is toric for all $k^* \in \mathbb{R}^r_{>0}$ such that $V^+|_{k^*} \neq \emptyset$.

Example

$$2X \underset{k_2}{\overset{k_1}{\rightleftarrows}} X + Y \xrightarrow{k_3} 2Y$$

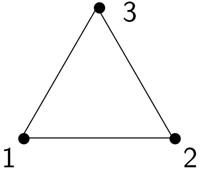
$$\dot{x} = -k_1 x^2 + (k_2 - k_3)xy, \quad \dot{y} = -\dot{x},$$

$$Y_p - Y_e = \begin{pmatrix} -1 & 1 & -1 \\ 1 & -1 & 1 \end{pmatrix}, \; E = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \end{pmatrix}, \text{ and } D = \{\{2,3\}\}$$

$$\begin{aligned} \Lambda_D(k) &= \{\lambda \in \mathbb{R}^2_{\geq 0} \; | E\lambda > 0 \text{ and } (E_2 k_3 - E_3 k_2)\lambda = 0\} = \\ &= \{\lambda \in \mathbb{R}^2_{>0} \; | \qquad (E_2 k_3 - E_3 k_2)\lambda = 0\} = \\ &= \{\lambda \in \mathbb{R}^2_{>0} \; | \qquad (\lambda_1 + \lambda_2)k_3 - \lambda_2 k_2 = 0\} = \\ &= \begin{cases} \emptyset & \text{if } k_2 \leq k_3, \\ \{(\alpha, \frac{k_3}{k_2 - k_3}\alpha) | \alpha \in \mathbb{R}_{>0}\} & \text{otherwise .} \end{cases} \end{aligned}$$

Example

- When $k_2 > k_3$ $\mathfrak{J}(k)$ has edge set $\{\{i,j\} | \frac{E_i \nu}{E_i \lambda} = \frac{E_j \nu}{E_j \lambda} \ \forall \nu, \lambda \in \Lambda_D(k)\}$.
- As $2,3$ is a doubling set, $\{2,3\}$ is an edge of $\mathfrak{J}(k)$.
- As $E_1 \in \text{span}(E_2, E_3)$, also $\{1,2\}$ and $\{1,3\}$ are edges of $\mathfrak{J}(k)$.



- Clearly, rows of E indexed by different clusters have disjoint supports.
- Hence, as for $k_2 > k_3$ the positive steady state variety is non-empty, for $k_2 > k_3$ this network has the isolation property.

A few further directions

- Chambers versus multistationarity.
- Isolation property and mass-action representations.
- Duality between linear conserved quantities and internal cycles.
- Tropical equilibration branches as toric approximations.
- Partial toricity.

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Merci pour votre attention !