Dynamical systems with toric positive steady states (part of my PhD thesis which I will defend on May 3)

Alexandru Iosif
JRC-Aachen

(joint work with Carsten Conradi and Thomas Kahle)

SYMBIONT Project Meeting at INRIA Paris April 5 2019

Setting

- We look at mass-action networks.
- The dynamics of a mass-action network is given by ODEs

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

- There are also conservation laws $Zx = Zx(0)$.
- $Zx(0)$ is called a vector of total concentrations and it is denoted by c.

Problem

Decide whether there exist values of c such that

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

where $V^+ = \{(x, k) \in \mathbb{R}^{n+r}_{>0} | P(k, x) = 0\}$ is the positive steady state variety.

Setting

- In general this can be a hard problem.
- However, biological networks have special combinatorial properties.
- In 2017 Millán et al. introduced **MESSI Systems** (Modifications of type Enzyme-Substrate or Swap with Intermediates) and proved that many of them are **toric**, i.e. they have **binomial** steady state ideal.
- Binomials may also appear in tropical equilibrations.
- However a binomial steady state ideal imposes conditions on all the complex solutions of the system $P(k, x) = 0$.

Dynamical systems with toric positive steady states

Definition

Dynamical systems with toric positive steady states are mass-action networks whose positive steady state variety **admits a monomial parameterization**.

Definition

The positive steady state variety V^+ admits a monomial parameterization if there is a matrix $M \in \mathbb{Z}^{n \times d}$ of rank at most $n-1$ and a rational function $\gamma(k) : \mathcal{K}_\gamma^+ \to \mathbb{R}_{>0}$ such that

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

Monomial parameterizations of the positive steady states

Lemma

If V^+ admits a monomial parameterization, 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

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

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

Multistationarity in the space of total concentrations

Let $s = \operatorname{rank} Z$ and denote by $\mathbb{S}^{s-1} \subset \mathbb{R}^s$ the unit sphere. Let

$$\mathcal{C} = \{c \in \mathbb{R}^s_{>0} \mid \exists k \in \mathcal{K}^+_\gamma \text{ and } a \neq b \in \mathbb{R}^n_{>0} \\ \text{such that } (k,a),\ (k,b) \in V^+,\ \text{and } Za = Zb = c\}.$$

By the Tarski–Seidenberg Theorem, $\mathcal{C}$ is a semialgebraic set.

Theorem

If V^+ admits a monomial parameterization, then $\mathcal{C}$ is a cone with the origin removed, that is

$$\mathcal{C} = \left(\mathcal{C} \cap \mathbb{S}^{s-1}\right) \times \mathbb{R}_{>0}.$$

Example: the 2-site phosphorylation

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

$$A + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} AE_1 \xrightarrow{k_3} A_p + E_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} A_pE_1 \xrightarrow{k_6} A_{pp} + E_1$$

$$A_{pp} + E_2 \underset{k_8}{\overset{k_7}{\rightleftarrows}} A_{pp}E_2 \xrightarrow{k_9} A_p + E_2 \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} A_pE_2 \xrightarrow{k_{12}} A + E_2$$

Example: the 2-site phosphorylation

If all reactions are of mass-action form, we obtain the following ODEs:

$$\begin{aligned}
\dot{x}_1 &= P_1(x_1,\dots,x_9) = -k_1x_1x_2 + k_2x_3 + k_{12}x_9 \\
\dot{x}_2 &= P_2(x_1,\dots,x_9) = -k_1x_1x_2 + (k_2+k_3)x_3 - k_4x_2x_4 + (k_5+k_6)x_5 \\
\dot{x}_3 &= P_3(x_1,\dots,x_9) = k_1x_1x_2 - (k_2+k_3)x_3 \\
\dot{x}_4 &= P_4(x_1,\dots,x_9) = k_3x_3 - k_4x_2x_4 + k_5x_5 + k_9x_8 - k_{10}x_4x_7 + k_{11}x_9 \\
\dot{x}_5 &= P_5(x_1,\dots,x_9) = k_4x_2x_4 - (k_5+k_6)x_5 \\
\dot{x}_6 &= P_6(x_1,\dots,x_9) = k_6x_5 - k_7x_6x_7 + k_8x_8 \\
\dot{x}_7 &= P_7(x_1,\dots,x_9) = -k_7x_6x_7 + (k_8+k_9)x_8 - k_{10}x_4x_7 + (k_{11}+k_{12})x_9 \\
\dot{x}_8 &= P_8(x_1,\dots,x_9) = k_7x_6x_7 - (k_8+k_9)x_8 \\
\dot{x}_9 &= P_9(x_1,\dots,x_9) = k_{10}x_4x_7 - (k_{11}+k_{12})x_9.
\end{aligned}$$

Example: the 2-site phosphorylation

There are three independent linear relations among $P_1, \ldots, P_9$ and thus three linearly independent conservation laws:

$$\begin{aligned} x_2 + x_3 + x_5 &= c_1, \\ x_7 + x_8 + x_9 &= c_2, \\ x_1 + x_3 + x_4 + x_5 + x_6 + x_8 + x_9 &= c_3. \end{aligned}$$

Example: the 2-site phosphorylation

One can show that the positive steady state variety V^+ admits a monomial parameterization of the form

$$x = \psi(k) \star \xi^A \text{ with } k \in \mathbb{R}^{12}_{>0} \text{ and } \xi \in \mathbb{R}^3_{>0} \text{ free, where}$$

$$\psi(k) = \Bigg(\frac{(k_2+k_3)k_4k_6(k_{11}+k_{12})k_{12}}{k_1k_3(k_5+k_6)k_9k_{10}}, \\ \frac{(k_5+k_6)k_9k_{10}}{k_4k_6(k_{11}+k_{12})}, \frac{k_{12}}{k_3}, \frac{k_{11}+k_{12}}{k_{10}}, \frac{k_9}{k_6}, \frac{k_8+k_9}{k_7}, 1, 1, 1 \Bigg)^T$$

and

$$A = \begin{pmatrix} 2 & -1 & 1 & 1 & 0 & 0 & 0 & 0 & 1 \\ -1 & 1 & 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ -1 & 1 & 0 & -1 & 0 & -1 & 1 & 0 & 0 \end{pmatrix}. \qquad (1)$$

Example: the 2-site phosphorylation

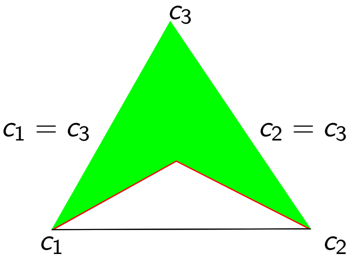
Theorem

In the space of total concentrations c_1, c_2, and c_3, if

$$\text{not } ((c_1 = c_3 \text{ and } c_2 \geq c_3) \text{ or } (c_2 = c_3 \text{ and } c_1 \geq c_3)),$$

then multistationarity is possible if and only if

$$c_2 < c_3 \text{ or } c_1 < c_3.$$



Example: the 2-site phosphorylation

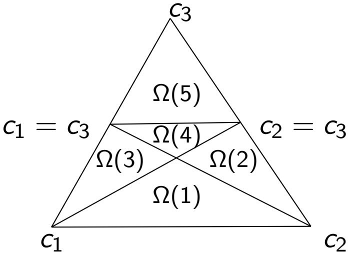
Theorem

In the space of total concentrations c_1, c_2, and c_3, if

$$\text{not } ((c_1 = c_3 \text{ and } c_2 \geq c_3) \text{ or } (c_2 = c_3 \text{ and } c_1 \geq c_3)),$$

then multistationarity is possible if and only if

$$c_2 < c_3 \text{ or } c_1 < c_3.$$



Certificates for monomial parameterizations

- The previous example has toric positive steady states because its steady state ideal is binomial!
- Find a class of **not necessarily binomial** systems **with positive toric** steady states.
- We don't have such a class, but we have a candidate.

The isolation property: doubling sets

- The right hand side of the ODE $\dot{x} = P(k, x)$ can be expressed as $S(k_1 m_1, \ldots, k_r m_r)^T$, where $S \in \mathbb{Z}^{n \times r}$ is the stoichiometric matrix.
- Let $E \in \mathbb{Z}_{\geq 0}^{r \times p}$ be a matrix whose columns are the rays of $\ker(S) \cap \mathbb{Z}_{\geq 0}^r$.
- 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:

$$\bullet \xleftarrow[k_i]{} \bullet \xrightarrow{k_j} \bullet$$

The isolation property: clusters

- 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 $\mathfrak{I}(k)$ 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 $\mathfrak{I}(k^*)$.

The isolation property: definition and main result

Definition

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

If $\mathcal{N}|_{k^*}$ has the isolation property, then $V^+|_{k^*}$ admits a monomial parameterization.

The strong isolation property

- Rate constants are usually measured quantities and hence parameters.
- By imposing more restrictions on the structure of the matrix E, one could get rid of the dependency on k in the previous theorem.
- This is the case for systems with the strong isolation property:

- Consider a family of mass-action networks $\mathcal{N}$ and denote by $\widetilde{\mathcal{N}}$ the elements of $\mathcal{N}$ with non-empty positive steady state variety.
- An element of $\widetilde{\mathcal{N}}$ has the strong isolation property if and only if all elements of $\widetilde{\mathcal{N}}$ have the strong isolation property.

- As the strong isolation property is a special case of the isolation property, the previous theorem applies to a full family of systems.

Example

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

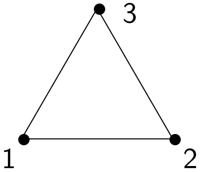
$$\dot{x} = -k_1 x^2 + (k_2 - k_3)xy, \quad \dot{y} = -\dot{x},$$

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

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

Example

- Let's compute the graph $\mathfrak{J}(k)$ 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 $E_1 \in \mathrm{span}(E_2, E_3)$, 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.

Further directions

- Find biologically interesting examples of non binomial mass-action networks with toric positive steady states.
- Given $\mathcal{N}$, is there an algorithm which decides whether exists $\mathcal{G}$ with the isolation property and the same dynamics or steady states as $\mathcal{N}$?
- Systems with the bridging property.

Merci pour votre attention!