Duality in mass-action networks: A step closer to a new case of the Global Attractor Conjecture?

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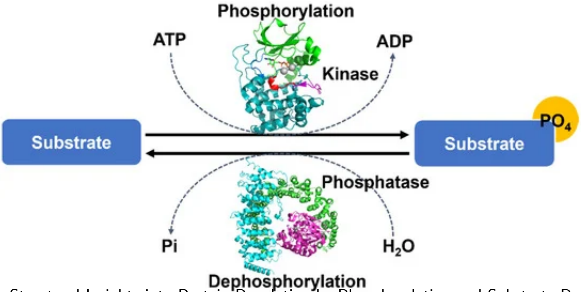
Motivation: the 2-site phosphorylation

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

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

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



[Source: Seok, S.-H. Structural Insights into Protein Regulation by Phosphorylation and Substrate Recognition of Protein Kinases/Phosphatases. Life 2021, 11, 957]

Consider a polynomial ODE system

$$\begin{cases} \dot{x}_1 &= P_1(k_1, \ldots, k_r; x_1, \ldots, x_n), \\ \vdots & \\ \dot{x}_n &= P_n(k_1, \ldots, k_r; x_1, \ldots, x_n), \end{cases}$$

where $k_1, \ldots, k_r \in \mathbb{R}_{>0}$ are parameters, $x_1 \geq 0$, …, $x_n \geq 0$, and

$$P_1, \ldots, P_n \in \mathbb{R}(k_1, \ldots, k_r)[x_1, \ldots, x_n]$$

are polynomials in $x_1, \ldots, x_n$ and rational functions in $k_1, \ldots, k_r$.

Example

$$\begin{cases} \dot{x} &= \quad k_1 x^2 - \frac{k_2}{k_3} y \\ \dot{y} &= -k_1 xy + \frac{k_2}{k_3} y^7 \end{cases}$$

Problem 1

Find the **steady state variety**, that is, solve the polynomial system $\dot{x}_1 = \ldots = \dot{x}_n = 0$ for complex/real $x_1, \ldots, x_n$.

Problem 1'

Find the largest $\mathcal{K} \subset \mathbb{R}^r_{>0}$ such that, whenever $(k_1, \ldots, k_r) \in \mathcal{K}$, the polynomial system $\dot{x}_1 = \ldots = \dot{x}_n = 0$ has non-negative solutions $x_1, \ldots, x_n$.

Problem 1"

Add to Problem 1/1' restrictions derived from conservation laws of the Polynomial ODE system.

Solution to Problem 1

Compute a (comprehensive) Gröbner basis for the ideal

$$\langle P_1, \ldots, P_n \rangle \subset \mathbb{R}(k_1, \ldots, k_r)[x_1, \ldots, x_n].$$

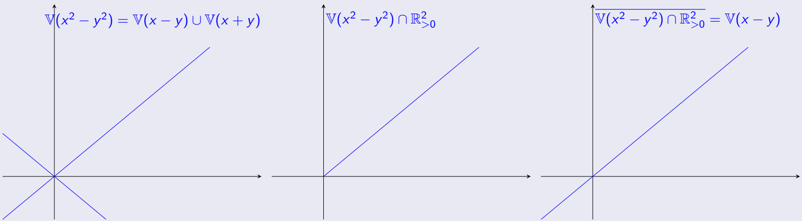
Then restrict solutions to $\mathbb{R}^n_{>0}$.

Example of Problem 1

$$\begin{aligned} \dot{x} &= x^2 - y^2 \\ \dot{y} &= -x^2 + y^2 \end{aligned}$$

Note: $I := \langle x^2 - y^2, -x^2 + y^2 \rangle = \langle x^2 - y^2 \rangle$

Then a Gröbner basis of I is $\{x^2 - y^2\}$.



Solution to Problem 1'

Quantifier elimination for

$$\exists x_1, \dots x_n \in \mathbb{R} \text{ such that}$$
$$P_1 = 0, \dots, P_n = 0,\ k_1 > 0, \dots, k_r > 0,\ x_1 \geq 0, \dots, x_n \geq 0.$$

Example of Problem 1'

$$\begin{aligned} \dot{x} &= \ \ ax^2 + bx + c \\ \dot{y} &= -ax^2 - bx - c \end{aligned}$$

Then the quantified statement

$$\begin{aligned} &\exists x, y \in \mathbb{R} \text{ such that :} \\ &ax^2 + bx + c = 0 \wedge -ax^2 - bx - c = 0 \\ &\wedge a > 0 \wedge b > 0 \wedge c > 0 \\ &\wedge x \geq 0 \wedge y \geq 0 \end{aligned}$$

is equivalent to quantifier free statement

$$a > 0 \wedge b > 0 \wedge c > 0 \wedge b^2 - 4ac \geq 0 \wedge ac \leq 0$$

which is equivalent to the easier quantifier free formula

$$a, b, c \in \emptyset.$$

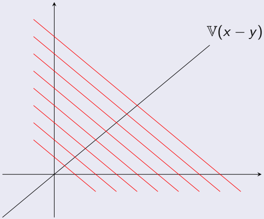
Solution to Problem 1"

1.* Every conservation law $\phi(\mathbf{k}, \mathbf{x}) = c$ of the previous ODE system derives from a syzygy $\mathbf{g}$ of the vector $(P_1, \ldots, P_n)$, where $\nabla \times g = 0$ and $\nabla \phi = \mathbf{g}$.
2. For linear conservation laws just use linear algebra.

Example of Problem 1": Linear conservation law

$$\begin{aligned} \dot{x} &= x - y \\ \dot{y} &= -x + y \end{aligned}$$

A Gröbner basis of I is $\{x - y\}$.
Conservation Law: $\dot{x} + \dot{y} = 0 \implies x + y = c$.



*Desoeuvres, Iosif, Lüders, Radulescu, Rahkooy, Seiß, Sturm. *A Computational Approach to Complete Exact and Approximate Conservation Laws of Chemical Reaction Networks* (2024). SIADS

Example of Problem 1": Non-linear conservation law

Consider the folowing ODE system:

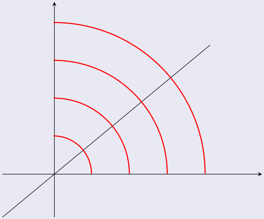
$$\begin{aligned} \dot{x} &= xy - y^2 \\ \dot{y} &= -x^2 + xy \end{aligned}$$

We have the relation $2x\dot{x} + 2y\dot{y} = 0$, obtained from the syzygy $2x(xy - y^2) + 2y(-x^2 + xy) = 0$. Since $\partial_y 2x = \partial_x 2y$, there is a ϕ such that $\nabla(x, y) = \phi$:

$$\phi = x^2 + y^2.$$

Hence we get the conservation law

$$x^2 + y^2 = \text{constant}.$$



Problem 2

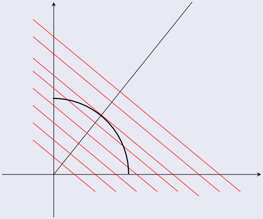
1. Classify all (or some) of the parameters $k_1, \ldots, k_r$ and the conservered quantities $c_1, \ldots, c_s$ with respecto to the existence of multiple steady states.
2. Often we are only interested in strictly positive solutions.

Example of Problem 2

Consider the following ODE system

$$\begin{aligned} \dot{x} &= (x^2 + y^2 - 2)(x - y) \\ \dot{y} &= -\dot{x} \end{aligned}$$

It has the conservation law $x + y = c$. If $c < 2$ there are three steady states. If $c \geq 2$ there is only one steady state.



Introductory example (phosphorylation of a protein)

[“Stoichiometric” point of view]
Consider the following directed graph:

$$x_1 x_2 \underset{k_2}{\overset{k_1}{\rightleftarrows}} x_3 \xrightarrow{k_3} x_1 x_4$$

It represents a dynamical system:

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

More explicitely:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix} = \left[\begin{pmatrix} 0 & 1 & 1 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix} - \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 0 \end{pmatrix} \right] \begin{pmatrix} k_1 & 0 & 0 \\ 0 & k_2 & 0 \\ 0 & 0 & k_3 \end{pmatrix} \begin{pmatrix} x_1 x_2 \\ x_3 \\ x_3 \end{pmatrix}$$

Introductory example (phosphorylation of a protein)

[“Laplacian” point of view]

Consider the following directed graph:

$$x_1 x_2 \underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}} x_3 \xrightarrow{k_{23}} x_1 x_4$$

It represents a dynamical system:

$$\dot{x} = \left(x^Y\right)^T A_k Y$$

More explicitely:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix}^T = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix}^T \begin{pmatrix} -k_{12} & k_{12} & 0 \\ k_{21} & -k_{21} - k_{23} & k_{23} \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 \end{pmatrix}$$

The general object of study

"Stoichiometric" Definition

A mass-action network is a quadruple (k, x, Y_e, Y_p), where $k := (k_1, \ldots, k_r)$ are real positive parameters, $x := (x_1, \ldots, x_n)$ are real positive variables, and $Y_e, Y_p \in \mathbb{Z}_{\geq 0}^{r \times n}$. Such mass-action network can always be represented as a directed graph whose i^{th} arrow is

$$\prod_{j=1}^{n} x_j^{Y_{e,ji}} \xrightarrow{k_i} \prod_{j=1}^{n} x_j^{Y_{p,ji}},$$

and it defines the following dynamical system:

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

where x^{Y_e} is a column vector whose i^{th} coordinate is $\prod_{j=1}^{n} x_j^{Y_{e,ji}}$.

The general object of study

"Laplacian" Definition

A mass-action network is a triple (k, x, Y), where $k := \{k_{ij} | i, j \in [m], i \neq j\}$ are real positive parameters, $x := (x_1, \ldots, x_n)$ are real positive variables, and $Y \in \mathbb{Z}_{\geq 0}^{m \times n}$. Such mass-action network can always be represented as a directed graph whose arrows are

$$\prod_{l=1}^{n} x_l^{Y_{il}} \xrightarrow{k_{ij}} \prod_{l=1}^{n} x_l^{Y_{jl}},$$

and it defines the following dynamical system:

$$\dot{x} = \left(x^Y\right)^T A_k Y$$

where x^Y is a column vector whose i^{th} coordinate is $\prod_{j=1}^{n} x_j^{Y_{ji}}$ and A_k is the negative of the Laplacian of the corresponding directed graph.

Toricity in mass-action networks

There are basically two different (but related) notions of toricity:

1. **Toric dynamical systems**: It refers to mass-action networks with the property that, for any complex, the amount produced of that complex at steady state is equal to the amount consumed by reactions. *Equivalently, they are systems for which the equation* $\left(x^Y\right)^T A_k = 0$ *admits a solution* $x^* \in \mathbb{R}^n_{>0}$ *(a Birch point).*
2. **Networks with toric steady states**: They are systems whose steady state variety is a toric variety. They can further be classified into
   1. **Networks with binomial steady state ideal**.
   2. **Systems with the isolation property**.
   3. **Networks with positive toric steady states** (the weakest).

Toric Dynamical Systems $\subset$ Binomial Ideal $\subset$ Positive toric steady states.

Conjecture* : $\quad$ **II**

Isolation Property $\subset$ Positive toric steady states.

*This conjecture was informally proposed to me by Carsten Conradi and Thomas Kahle during my PhD (2016-2019). Now I might have a proof of it.

A positive toric system

Dynamics:

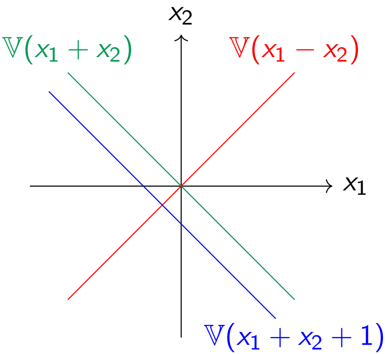
$$\dot{x}_1 = x_1^3 + x_1^2 x_2 - x_1 x_2^2 - x_2^3 + x_1^2 - x_2^2$$
$$= (x_1 - x_2)(x_1 + x_2)(x_1 + x_2 + 1)$$
$$\dot{x}_2 = -\dot{x}_1$$

Positive steady states, V^+:

$\frac{x_1}{x_2} = 1$, $x_1, x_2 > 0$

Monomial parameterization of V^+:

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



A positive non toric system

Dynamics:

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

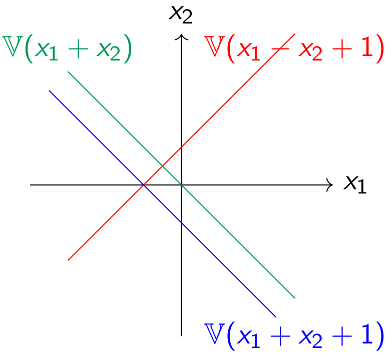
$\dot{x}_2 = -\dot{x}_1$

Positive steady states, V^+:

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

NONMonomial parameterization of V^+:

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



Example 2.1.1. Let $s = 2$, $n = 3$, and let G be the complete bidirected graph on three nodes labeled by c_1^2, c_1c_2, and c_2^2. Here the mass-action kinetics system (1.3) equals

$$\frac{d}{dt}\left(c_1,\, c_2\right) \quad = \quad \left(c_1^2 \quad c_1c_2 \quad c_2^2\right) \cdot A_\kappa \cdot \begin{pmatrix} 2 & 0 \\ 1 & 1 \\ 0 & 2 \end{pmatrix}, \tag{2.1}$$

where A_κ is the following matrix:

$$\begin{pmatrix} -\kappa_{12} - \kappa_{13} & \kappa_{12} & \kappa_{13} \\ \kappa_{21} & -\kappa_{21} - \kappa_{23} & \kappa_{23} \\ \kappa_{31} & \kappa_{32} & -\kappa_{31} - \kappa_{32} \end{pmatrix}.$$

This is a toric dynamical system if and only if the following algebraic identity holds:

$$(\kappa_{21}\kappa_{31} + \kappa_{32}\kappa_{21} + \kappa_{23}\kappa_{31})(\kappa_{13}\kappa_{23} + \kappa_{21}\kappa_{13} + \kappa_{12}\kappa_{23}) \;=\; (\kappa_{12}\kappa_{32} + \kappa_{13}\kappa_{32} + \kappa_{31}\kappa_{12})^2. \tag{2.2}$$

The equation (2.2) appears in [Hor73b, Equation (3.12)] where it is derived from the necessary and sufficient conditions for complex-balancing in mass-action kinetics given by [Hor72]. Our results in Section 2.2 provide a refinement of these conditions.

[Source: Anne Shiu's Thesis]

Theorem (Corollary to Eisenbud, Sturmfels; 1996)

If I is a binomial ideal, then, for generic $\mathbf{k}$, $\mathbb{V}(I)$ is a finite union of cosets of the same multiplicative group.

Why binomials? (Mathematical answer)

1. Binomials are special but trinomials are not: every ecuation systems can be expressed as a systems of trinomials (by introducing new variables).
2. Yet, look at the following theorem.

Theorem (Savageau, Voit; 1987)

Consider the following dynamical system

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

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

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

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.

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 $\mathbb{K}$.

Two algebro-combinatorial objects

1. Siphons: subsets of the variables having the potential of being absent in a steady state. They are related to the cone $\ker(A_p - A_e)^T \cap \mathbb{R}^n_{\geq 0}$.
2. (Pre)clusters[†]: partition of the arrow set collecting relations between the coordinates of the cone $\ker(A_p - A_e) \cap \mathbb{R}^r_{\geq 0}$.

Conjecture:

Siphons and clusters are related through some duality relation.

Evidence for the conjecture

The set of *(pre)clusters* is dual[a] to the set of *maximal invariant polyhedral supports* (MIPS).

[a] We will make precise the duality in the next slides

[†] Clusters were introduced in 2011 by Conradi and Flockerzi. In this talk we use the term in a slightly more general sense.

The state of art in a ("non-commutative") diagram

$$
\begin{array}{ccc}
\ker(A_p - A_e) & \xleftrightarrow{\text{dual}} & \ker\left((A_p - A_e)^T\right) \\
\downarrow & & \downarrow \\
\text{Clustering graph} & & \text{Chamber decomposition} \\
\wr\| & & \wr\| \\
 & & \text{Decorations of invariant polyhedra} \\
 & & \downarrow \\
\{P \mid P \text{ is a precluster}\} & \xleftrightarrow{\text{dual}} & \{M \mid M \text{ is a MIPS}\} \\
\downarrow \text{Refine} & & \downarrow \text{"Refine"} \\
\{C \mid C \text{ is a cluster}\} & \xleftrightarrow{\text{¿duality relation?}} & \{S \mid S \text{ is a siphon}\}
\end{array}
$$

The dual network

Definition (Stoichiometric version)

The dual of the network (k, x, Y_e, Y_p) is the network (x, k, Y_e^T, Y_p^T).

Definition (Laplacian version)

The dual of the network (k, x, Y) is ...[a].

[a] While we do not have yet a good duality definition in this formalism, finding one is quite desirable, for all the work of Craciun et al. on the Global Atractor Conjecture is done in this formalism.

Why should we care?

The following appear in Anne Shiu's Thesis:

1. "Relevant siphons determine which faces of an invariant polyhedron contain steady states [...] only faces that arise from siphons can admit ω-limit points".
2. "To prove the conjecture it is sufficient to verify that no positive trajectory approaches such a steady state".

Theorem (Craciun, Dickenstein, Shiu, Sturmfels; 2007)

Consider a conservative toric dynamical system whose invariant polyehdra are two-dimensional. Then the Birch point is a global attractor of its invariant polyhedron.

Why should we care?

Global atractor conjecture (Horn, 1972)

For toric dynamical systems, the Birch point is a global attractor of its invariant polyhedron.

A more modest question

Is it possible to use duality to prove the conjecture in codimension 2?

Why should we care?

Definition

$\Sigma = \{x_i | i \in I \subseteq [n]\}$ is a *maximal invariant polyhedral supports* (MIPS) if all combinatorial types of decorated invariant abstract polyhedra are invariant under $x_i \mapsto x_j \; \forall \; x_i, x_j \in \Sigma$ (related to $\ker(A_p - A_e)^T \cap \mathbb{R}^n_{\geq 0}$).

Definition (extension of Conradi-Flockerzi)

Consider the graph G over $[r]$ wich has an edge $\{i, j\}$ whenever the i^{th} and the j^{th} arrow have the same source and let $n_1, \ldots, n_r$ denote the rows of a matrix with columns the rays $\ker(A_p - A_e) \cap \mathbb{Z}^r_{\geq 0}$. If to the graph G we add the edges $\{i, s\}$ and $\{j, s\}$ whenever n_s is in the span of $\{n_i, n_j\}$ for each edge $\{i, j\}$ of G, we obtain the preclustering graph. A precluster is a connected component of the preclustering graph.

Why should we care?

Theorem (I.)

For conservative mass-action networks that do not have two species with exactly the same rates the set of preclusters is dual to the set of MIPS.

Idea of the proof:

For conservative systems the duality between the conservation and the stoichiometric space can be interpreted in terms of a duality between the corresponding nonnegative cones. As there is a one to one correspondence between the extreme rays of the stoichiometric cone and the minimal cycles of the mass-action network, one can conclude that conserved quantities are dual to minimal cycles.

Why should we care?

Theorem (Corollary to some of Anne Shiu's results)

Siphons are subsets of maximal symmetric chamber supports.

"Proof":

Just read Chapter 3 of Anne Shiu's Thesis, compare to our defintion of maximal symmetric champer supports (which already appers implicitely there), and you will see that this result is obvious.

Bibliography

Vă mulțumesc!
Eskerrik asko!
¡Muchas gracias!

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