The multistationarity problem in dynamical systems with toric steady states

Alexandru Iosif
(Universidad Rey Juan Carlos de Madrid)

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Seminario del Área de Matemática Aplicada
Universidad Rey Juan Carlos

Problem 1
or describing the stationary points

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

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

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

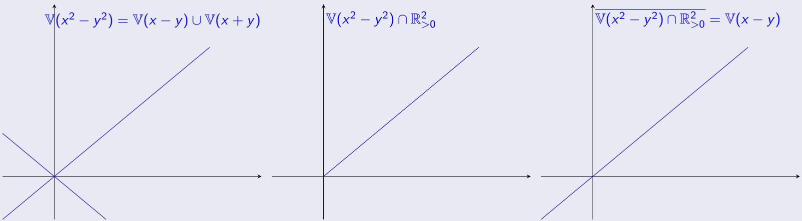
$$\langle P_1, \ldots, P_n \rangle \subset \mathbb{R}(k_1, \ldots, k_r)[x_1, \ldots, x_n].$$

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

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

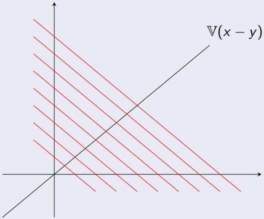
Solution to Problem 1"

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

$$\dot{x} = x - y$$
$$\dot{y} = -x + y$$

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* (2023). ArXiv:2212.14881

Example of Problem 1": Non-linear conservation law

Consider the folowing ODE system:

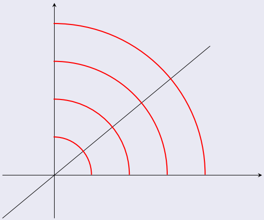
$$\begin{aligned} \dot{x} &= xy - y^2 \\ \dot{y} &= -x^2 + xy \end{aligned}$$

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
or the Multistationarity Problem

Problem 2

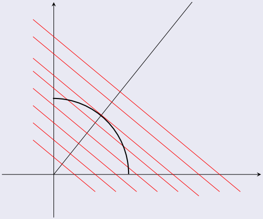
1. Classify all (or some) of the parameters $k_1, \ldots, k_r$ and the conservered quantities $c_1, \ldots, c_s$ with respecto to the existence of multiple steady states.
2. Often we are only interested in strictly positive solutions.

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.



Dynamical systems with (positive) toric steady states

Dynamical systems with (positive) toric steady states

Consider a polynomial ODE system

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

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 $k_1, \ldots, k_r$.

Definition (informal)

The dynamical system defined above has:

1. toric steady states if the ideal $I := \langle P_1, \ldots, P_n \rangle$ is binomial.
2. positive toric steady states if the variety $\overline{\mathbb{V}(I) \cap \mathbb{R}^n_{>0}}$ is binomial.

Example: Toric system

Dynamics:

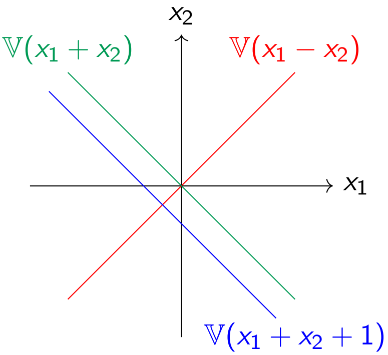
$$\dot{x}_1 = x_1^3 + x_1^2 x_2 - x_1 x_2^2 - x_2^3 + x_1^2 - x_2^2$$
$$= (x_1 - x_2)(x_1 + x_2)(x_1 + x_2 + 1)$$
$$\dot{x}_2 = -\dot{x}_1$$

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:

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

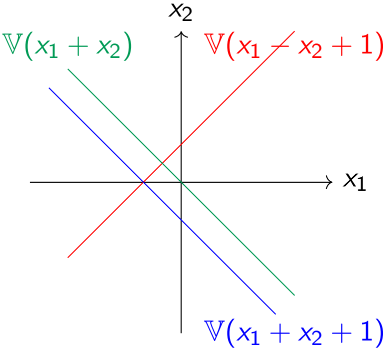
$\dot{x}_2 = -\dot{x}_1$

Positive steady states, V^+:

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

NONMonomial parameterization of V^+:

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



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.

MESSI biological systems (Millán, Dickenstein; 2016)

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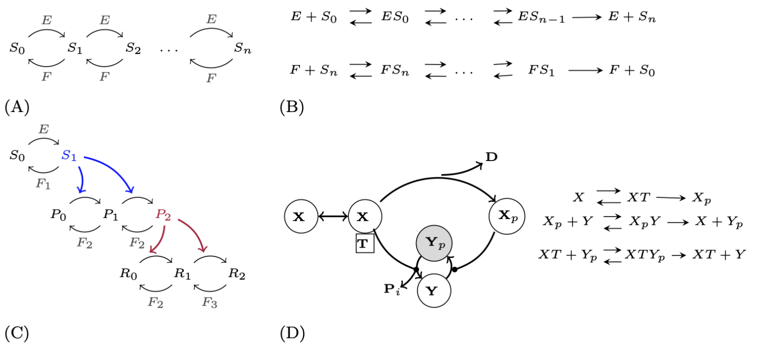


FIGURE 1. Examples of MESSI systems: Sequential n-site phosphorylation/dephosphorlation (A) distributive case [36, 51], (B) processive case [5, 31]; (C) Phosphorylation cascade; (D) Schematic diagram of an EnvZ-OmpR bacterial model [44].

(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 $\xi \in \mathbb{R}^{n-p}_{>0}$ 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 $g_1, \ldots, g_l \in \mathbb{R}[c]$, $\square \in \{>, \geq\}^l$, 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

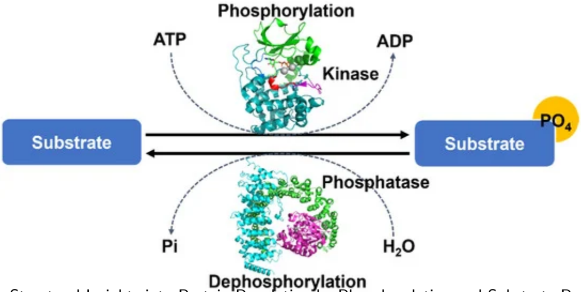
$$Z(a\xi^A - a) = 0 \text{ and } \mathcal{F}(g(Za) \,\square\, 0).$$

Example: the 2-site phosphorylation

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

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

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



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

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:

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

Example: the 2-site phosphorylation

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

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

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

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

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

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

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

$$[P] = \xi_3$$

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

$$[S_pP] = \xi_1$$

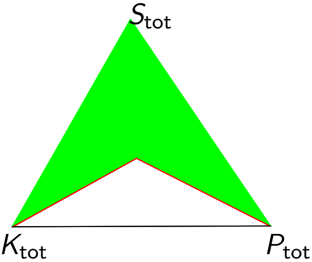
where $\xi_1,\ \xi_2,\ \xi_3 \in \mathbb{R}_{>0}$.

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

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



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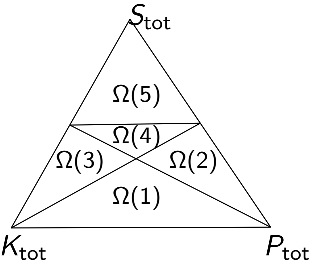


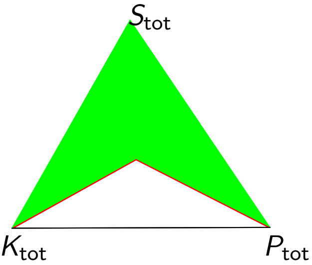
$$
\begin{aligned}
(\Omega(2),\delta_7):&\quad 0<\xi_3<\xi_1<1\ \wedge\ \xi_2>\tfrac{\xi_1^2}{\xi_3^2},\\
(\Omega(2),\delta_5):&\quad \xi_3>1\ \wedge\ 0<\xi_1<1\ \wedge\ \xi_2>\xi_3^2,\\
(\Omega(4),\delta_5):&\quad \xi_3>1\ \wedge\ 0<\xi_1<1\ \wedge\ \xi_2>\xi_3^2,\\
(\Omega(3),\delta_3):&\quad \xi_3^2<\xi_1<\xi_3<1\ \wedge \xi_2>1,\\
(\Omega(3),\delta_1):&\quad \xi_3>1\ \wedge\\
&\quad \left(\left(1<\xi_1<\xi_3^{2/3}\ \wedge\ \tfrac{\xi_1}{\xi_3}<\xi_2<\tfrac{\xi_1^{3/2}}{\xi_3}\right)\vee\left(\xi_3^{2/3}<\xi_1<\xi_3\ \wedge\ \tfrac{\xi_1}{\xi_3}<\xi_2<1\right)\right),\\
(\Omega(4),\delta_1):&\quad \xi_3>1\ \wedge\\
&\quad \left(\left(1<\xi_1<\xi_3^{2/3}\ \wedge\ \tfrac{\xi_1}{\xi_3}<\xi_2<\tfrac{\xi_1^{3/2}}{\xi_3}\right)\vee\left(\xi_3^{2/3}<\xi_1<\xi_3\ \wedge\ \tfrac{\xi_1}{\xi_3}<\xi_2<1\right)\right),\\
(\Omega(5),\delta_1):&\quad \xi_3>1\ \wedge\\
&\quad \left(\left(1<\xi_1<\xi_3^{1/2}\ \wedge\ \tfrac{\xi_1}{\xi_3}<\xi_2<\tfrac{\xi_1^2}{\xi_3}\right)\vee\left(\xi_3^{1/2}<\xi_1<\xi_3\ \wedge\ \tfrac{\xi_1}{\xi_3}<\xi_2<1\right)\right).
\end{aligned}
$$

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

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



Sufficient conditions for toricity

Proposition (Corollary to 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 $\overline{\mathbb{V}_{\mathbb{R}}(I) \cap \mathbb{R}^n_{>0}}$.

One posible answer (not discussed in this talk):

Theorem (Conradi, I., Kahle; 2019)

Isolation property $\implies$ $\overline{\mathbb{V}_{\mathbb{R}}(I) \cap \mathbb{R}^n_{>0}}$ is toric.

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¡Muchas Gracias!

Vă Mulțumesc!

Using the Tarski-Seidenberg Algorithm to compute the discriminant of a linear section of a positive toric variety

The statement of the problem

What we have: a system of equations

- m positive parameters $k_1, k_2, \ldots, c_1, c_2, \ldots$.
- n variables $x_1, \ldots, x_n$.
- A family of binomial systems [a]: $B_i(\mathbf{k}, \mathbf{x}) = 0$, $i \in [n-s]$.
- A family of linear systems: $L_j(\mathbf{c}, \mathbf{x}) = 0$, $j \in [s]$.

[a] Actually they only need be positive toric

What we want: a discriminant variety

- A semialgebraic variety $\Delta \subseteq \mathbb{R}^m_{\geq 0}$ which separates the space of parameters in conected components corresponding to equal number of positive solutions of the system $\{B_i(\mathbf{k}, \mathbf{x}) = 0, L_j(\mathbf{c}, \mathbf{x}) = 0 \mid i \in [n-s], j \in [s]\}$.

- Since $B_i(\mathbf{k},\mathbf{x}) = 0$, $i \in [n-s]$, are binomials, we have that:

$$\mathbb{V}\left(B(\mathbf{k},\mathbf{x})\right) \cap \mathbb{R}^n_{>0} = \mathrm{im}\left(\begin{array}{ccc} \phi : \mathbb{R}^d_{>0} & \to & \mathbb{R}^n_{>0} \\ \xi & \mapsto & \psi(\mathbf{k}) \star \xi^A \end{array} \right)$$

  where $\star$ is the coordinate-wise product, ξ^A is vector of monomials and $d < n$.

- For each $j \in [d]$, consider the ideal:

$$I_j := \langle L(\mathbf{c}, \phi(\mathbf{k})\xi^A)\rangle \cap \mathbb{Q}(\mathbf{k})[\xi_j]$$

- **Condition:** exists p_j a generator of I_j

Tarski and Seidenberg come into action

Let s_j be the Sturm sequence of p_j and compute the product $\Delta_S(p_j)$ of numerators and denominators of the principal coefficients and nonzero constant terms of each element of s_j.

Definition

The Sturm discrimiant of the system $\{B(\mathbf{k},\mathbf{x}) = 0, L(\mathbf{c},\mathbf{x}) = 0\}$ is

$$\Delta_S(I) := \prod_{j=1}^{n} \Delta_S(p_j).$$

Theorem (Corollary to Tarski-Seidenberg [1930,1948])

The Sturm discriminant separates the space of parameters in regions with equal number of positive roots.

Macaulay2

sturmdiscriminants / **SturmDiscriminants.m2**

```
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    Version => "0.1",
    Date => "October 2018",
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        PackageImports => {"Elimination"},
    DebuggingMode => false
)

export {
     -- 'Official' functions
     "SturmDiscriminant",
     "SturmSequence"
```

Maple

maplesturmdiscriminants / SturmDisciminants.mpl

```
#####
with(PolynomialIdeals):
with(Groebner):
with(Student[MultivariateCalculus]):
with(Student[LinearAlgebra]):
with(combinat):

#####
SturmDiscriminants := module()
description "Sturm Discriminants";
#Author: Alexandru Iosif
option package;


#####
export SturmSequence, SturmDiscriminant, MonomialExponent, areAlgebraicallyIndependent, GenericPolynomial;

```

The discriminant of the dual site phosphorylation

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

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

I believe that this is the first time someone succeds in computing the discriminant of this syatem:
https://bitbucket.org/alexandru-iosif/maplesturmdiscriminants/src/master/Discriminant2sites.txt