Faculty of Science

Positive solutions to polynomial systems and reaction networks

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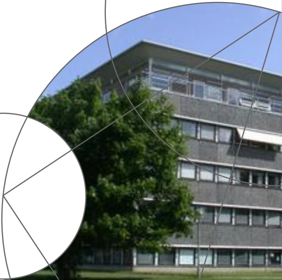


Plan

- Overview of the mathematical problem and origin.
- Dimension of steady states varieties (joint with Henriksson, Pascual-Escudero). Work in progress.
- Kac-Rice formulas for the parameter region of multistationarity (joint with Sadeghimanesh).

Overall goal: Study the positive solutions of polynomial systems as a function of the parameter values.

Systems of interest are of the form:

$$0 = -\kappa_1 x_1 + \kappa_2 x_2 x_3 - \kappa_3 x_1 x_4$$
$$0 = -\kappa_2 x_2 x_3 + \kappa_3 x_1 x_4 + \kappa_4 x_4$$

Variables: $x \in \mathbb{R}^4_{>0}$
Parameters: $\kappa \in \mathbb{R}^4_{>0}$
Solution set: $V_\kappa \subseteq \mathbb{R}^4_{>0}$

$$\begin{array}{rcl} \mathbb{R}^4_{>0} & \longrightarrow & \mathcal{P}(\mathbb{R}^4_{>0}) \\ (\kappa_1, \kappa_2, \kappa_3, \kappa_4) & \mapsto & V_\kappa \end{array}$$

or

$$0 = -\kappa_1 x_1 + \kappa_2 x_2 x_3 - \kappa_3 x_1 x_4$$
$$0 = -\kappa_2 x_2 x_3 + \kappa_3 x_1 x_4 + \kappa_4 x_4$$
$$c_1 = x_1 + x_2$$
$$c_2 = x_3 + x_4$$

Variables: $x \in \mathbb{R}^4_{>0}$
Parameters: $\kappa \in \mathbb{R}^4_{>0}, \quad c \in \mathbb{R}^2_{>0}$
Solution set: $C_{\kappa,c} \subseteq \mathbb{R}^4_{>0}$

$$\begin{array}{rcl} \mathbb{R}^4_{>0} \times \mathbb{R}^2_{>0} & \longrightarrow & \mathcal{P}(\mathbb{R}^4_{>0}) \\ (\kappa_1, \kappa_2, \kappa_3, \kappa_4, c_1, c_2) & \mapsto & C_{\kappa,c} \end{array}$$

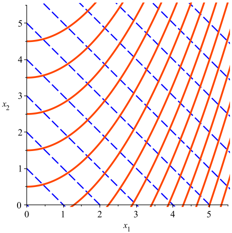
$$0 = -\kappa_1 x_1 + \kappa_2 x_2 x_3 - \kappa_3 x_1 x_4$$
$$0 = -\kappa_2 x_2 x_3 + \kappa_3 x_1 x_4 + \kappa_4 x_4$$
$$c_1 = x_1 + x_2$$
$$c_2 = x_3 + x_4$$

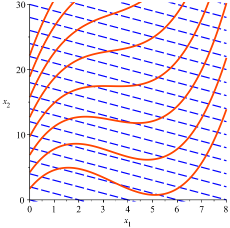
Variables: $x \in \mathbb{R}^4_{>0}$

Parameters: $\kappa \in \mathbb{R}^4_{>0}, \quad c \in \mathbb{R}^2_{>0}$

Solution set: $C_{\kappa,c} \subseteq \mathbb{R}^4_{>0}$

Geometrically:





(red, solid): Solution set of first part for different values of κ
(blue, dashed): linear subspaces for varying c.

Reaction networks

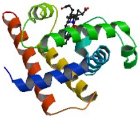
$$X_1 \longrightarrow X_2 \qquad 2X_2 \longrightarrow 2X_1 \qquad X_1 + X_2 \longrightarrow 2X_2$$

X_i can be "anything"

- Proteins and cell signaling

$$A + K \rightleftharpoons AK \longrightarrow A_p + K$$

$$\mathrm{HK_0} \to \mathrm{HK_p} \qquad \mathrm{HK_p}+\mathrm{RR} \to \mathrm{HK_0}+\mathrm{RR_p} \qquad \mathrm{RR_p} \to \mathrm{RR}$$



- People, like in SIR models, compartment models

$$S + I \longrightarrow 2I \qquad I \longrightarrow R$$

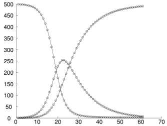


Figure 7.1. SIR model simulation.

- Animals, like in Lotka-Volterra models (rabbit and foxes)

$$0 \longrightarrow R \qquad R + F \longrightarrow 2F \qquad F \longrightarrow 0$$

- Chemical species, etc ...

Where the polynomial system comes from

- Reaction network:

$$X_1 \xrightarrow{\kappa_1} X_2 \qquad 2X_2 \xrightarrow{\kappa_2} 2X_1 \qquad X_1 + X_2 \xrightarrow{\kappa_3} 2X_2$$

- Dynamical system: (x_i = concentration of species X_i)

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -1 & 2 & -1 \\ 1 & -2 & 1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix},$$

Notation:

$$\begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix} = \kappa \circ x^B, \qquad B = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 2 & 1 \end{bmatrix}.$$

For arbitrary networks:

$$\dot{x} = N(\kappa \circ x^B), \qquad x \in \mathbb{R}^n_{\geq 0}, \quad B, N \in \mathbb{R}^{n \times m}, \quad \kappa \in \mathbb{R}^m_{>0}$$

N = stoichiometric matrix, $\kappa_j > 0$ reaction rate constant, $(\kappa \circ x^B)$ mass-action kinetics.

Where the polynomial system comes from

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -1 & 2 & -1 \\ 1 & -2 & 1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 \\ \kappa_2 x_2^2 \\ \kappa_3 x_1 x_2 \end{bmatrix},$$

Observe in the example:

$$\dot{x}_1 + \dot{x}_2 = 0, \qquad \text{so} \qquad x_1 + x_2 \text{ constant along trajectories.}$$

For arbitrary networks:

$$\dot{x} = N(\kappa \circ x^B), \qquad x \in \mathbb{R}^n_{\geq 0}, \quad B, N \in \mathbb{R}^{n \times m}, \quad \kappa \in \mathbb{R}^m_{>0},$$

any vector ω in the left-kernel of N satisfies

$$\omega \cdot \dot{x} = \omega^\top N(\kappa \circ x^B) = 0,$$

so

$$\omega \cdot x$$

is constant along trajectories.

Where the polynomial system comes from

- Reaction network:

$$X_1 \xrightarrow{\kappa_1} X_2 \qquad 2X_2 \xrightarrow{\kappa_2} 2X_1 \qquad X_1 + X_2 \xrightarrow{\kappa_3} 2X_2$$

- Dynamical system: (x_i = concentration of species X_i)

$$\dot{x} = N(\kappa \circ x^B), \qquad x \in \mathbb{R}^n_{\geq 0}, \quad B, N \in \mathbb{R}^{n \times m}, \quad \kappa \in \mathbb{R}^m_{>0}$$

N = stoichiometric matrix, $\kappa_j > 0$ reaction rate constant, $(\kappa \circ x^B)$ mass-action kinetics.

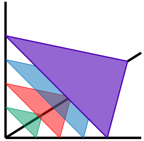
Positive steady states:

$$0 = N(\kappa \circ x^B), \qquad x \in \mathbb{R}^n_{\geq 0}, \quad B, N \in \mathbb{R}^{n \times m}, \quad \kappa \in \mathbb{R}^m_{>0}$$

- Stoichiometric compatibility classes: linear first integrals (= conservation laws)

$$Wx = c, \qquad x \in \mathbb{R}^n_{\geq 0}$$

W = matrix with rows a basis of the left kernel of N



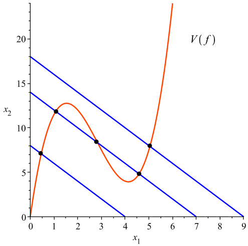
Steady states

The positive steady states of the ODE system (in each stoichiometric compatibility class) give rise to the sets

$$V_\kappa = \{x \in \mathbb{R}^n_{>0} \mid N(\kappa \circ x^B) = 0\},$$
$$C_{\kappa,c} = \{x \in \mathbb{R}^n_{>0} \mid N(\kappa \circ x^B) = 0, \quad W x = c\}.$$

In the example,

$$C_{\kappa,c} = \left\{ x \in \mathbb{R}^2_{>0} \;\middle|\; \begin{aligned} -\kappa_1 x_1 + 2\kappa_2 x_2^2 - \kappa_3 x_1 x_2 &= 0, \\ \kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_3 x_1 x_2 &= 0 \\ \kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_3 x_1 x_2 &= 0 \\ x_1 + x_2 &= c \end{aligned} \right\}.$$



Generically we "expect" the following to be true:

- each of the sets $C_{\kappa,c}$ is finite
- each of the sets V_κ has dimension $n - \text{rk}(N)$

The number of points in $C_{\kappa,c}$ might depend on the parameter values.

The mathematics of reaction networks

- Chemical reaction network theory (Feinberg, Horn, Jackson, 70ies).
  - Number of steady states and dynamics around steady states.
  - Relation between network structure and dynamical properties.
  - Celebrated result (deficiency zero): all networks in a certain class have a unique steady state, which is asymptotically stable (conjectured globally stable)

- Recently: Growing community of mathematicians with different background and focus on biochemical networks.
  - Provide (computational) strategies to determine network's dynamics.
  - Use theory from applied algebra, polyhedral geometry, dynamical systems, stochastic processes...

Some (algebraic) questions of interest

$$C_{\kappa,c} = \{x \in \mathbb{R}^n_{>0} |\ N v_\kappa(x) = 0, \quad Wx = c\}.$$

(Multistationarity) Is there a choice of κ and c such that

$$\# C_{\kappa,c} \geq 2 \quad ? \qquad\qquad \text{(essentially solved)}$$

(Parameter regions) For which choices of parameters $\# C_{\kappa,c} = M$? What properties has this region?

Some partial results. (See Telek's poster).

(Bistability and Oscillations) Is there a choice of κ and c such that $C_{\kappa,c}$ has two asymptotically stable positive steady states? A periodic solution?

The problem can be reduced to deciding whether a semi-algebraic system has a solution: the system is huge.

(Parametrizations) Is V_κ parametrizable?

It happens surprisingly often! (See Henriksson's poster for monomial parametrizations).

(Model reduction) Can we simplify the equations and preserve some properties of interest?

Today

- Expected dimension of the steady state variety
- Approximating the parameter region of multistationarity

Now: Expected dimension

Main problem

Data:

$N \in \mathbb{R}^{s\times r}$ full rank s,

$B \in \mathbb{R}^{n\times r}$,

$W \in \mathbb{R}^{d\times n}$, $d = n - s$.

Functions on $\mathbb{R}^n_{>0}$:

$$f_\kappa(x) = N(\kappa \circ x^B) \in \mathbb{R}^s,$$

$$F_{\kappa,c} = \big(N(\kappa \circ x^B), Wx - c\big) \in \mathbb{R}^n,$$

with $\kappa \in \mathbb{R}^r_{>0}$, $c \in W(\mathbb{R}^n_{>0})$.

$\mathbb{V}_{>0}(g)$: solutions of $g(x) = 0$ in $\mathbb{R}^n_{>0}$

Question (sloppy version). Is it true that for generic κ, c,

$$\dim(\mathbb{V}_{>0}(f_\kappa)) = d, \qquad \text{and} \qquad \dim(\mathbb{V}_{>0}(F_{\kappa,c})) = 0 \quad ?$$

(when the varieties are non-empty).

Why:

- Fundamental question of the objects under study
- Necessary to apply results from algebraic geometry
- Interest within CRNT

Examples: $\mathbb{V}_{>0}(f_\kappa)$ has generically the expected dimension, but "wrong" dimension for some κ.

- Linear example:

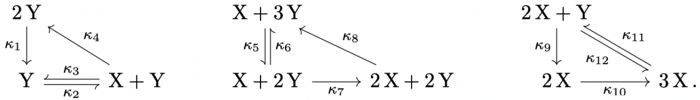
$$\kappa_1 x_1 - \kappa_2 x_2 + \kappa_3 = 0,$$
$$-\kappa_4 x_1 + \kappa_5 x_2 - \kappa_6 = 0, \qquad x \in \mathbb{R}^2, \quad \kappa \in \mathbb{R}^6_{>0}.$$

For almost all κ (det(coefficient matrix)$\neq 0$) there is one real solution. So either

$$\mathbb{V}_{>0}(f_\kappa) = \emptyset, \quad \text{or} \quad \dim(\mathbb{V}_{>0}(f_\kappa)) = 0.$$

Furthermore, $\mathbb{V}_{>0}(f_\kappa) \neq \emptyset$ in an open subset of parameters: $\frac{\kappa_3}{\kappa_6} < \frac{\kappa_2}{\kappa_5} < \frac{\kappa_1}{\kappa_4}$.

- With a reaction network:



With $\kappa_1 = \kappa_2 = \kappa_4 = \kappa_5 = \kappa_7 = \kappa_8 = \kappa_9 = \kappa_{10} = \kappa_{11} = 1$ and $\kappa_3 = \kappa_6 = \kappa_{12} = 4$:

$$\dim(\mathbb{V}_{>0}(f_\kappa)) = 1, \text{ while } d = 0.$$

Question formulated by the authors: Is there a weakly reversible network with infinitely many positive steady states for κ in an open subset of parameter space?

B. Boros, G. Craciun, and P. Y. Yu.
Weakly reversible mass-action systems with infinitely many positive steady states, 2020.

Examples: $\mathbb{V}_{>0}(f_\kappa)$ always the wrong dimension when non-empty, but empty for almost all κ.

- Linear example:

$$\kappa_1 x_1 - \kappa_2 x_2 + \kappa_3 = 0,$$
$$-\kappa_1 x_1 + \kappa_2 x_2 - \kappa_4 = 0, \qquad x \in \mathbb{R}^2, \quad \kappa \in \mathbb{R}^4_{>0}.$$

  It holds

$$\mathbb{V}_{>0}(f_\kappa) \neq \emptyset \quad \Leftrightarrow \quad \kappa_3 = \kappa_4.$$

  When $\mathbb{V}_{>0}(f_\kappa) \neq \emptyset$, it is a line, but $d = 0$, so the dimension is "wrong".

- With a reaction network:

$$X \xrightarrow{\kappa_1} Y, \qquad X \xrightarrow{\kappa_2} Z, \qquad Y + Z \xrightarrow{\kappa_3} X + Y + Z, \qquad Y + Z \xrightarrow{\kappa_4} 0.$$

  We have $d = 0$, so the "expected" dimension of $\mathbb{V}_{>0}(f_\kappa)$ is 0.

  BUT:

$$\mathbb{V}_{>0}(f_\kappa) \neq \emptyset \quad \Leftrightarrow \quad \kappa_1 = \kappa_2 \text{ and } \kappa_3 = 2\kappa_4,$$

  and in this case

$$\mathbb{V}_{>0}(f_\kappa) = \{\kappa_1 x - \kappa_4 y z = 0\},$$

  has dimension 2.

Examples: Real vs complex dimension

- Complex dimension: $\dim(\mathbb{V}_{\mathbb{C}}(f_\kappa)) \geq d$.
- Real dimension: the dimension can be smaller than d. Classical example:

$$f(x,y) = (x-1)^2 + (y-1)^2$$

$\mathbb{V}_{\mathbb{R}}(f) = \{(1,1)\}$ has dimension 0, while $\mathbb{V}_{\mathbb{C}}(f)$ has dimension 1.

Happens with reaction networks

$$2X \xrightarrow{\kappa_1} 3X, \qquad X \underset{\kappa_3}{\overset{\kappa_2}{\rightleftarrows}} 0, \qquad 2Y \xrightarrow{\kappa_4} X + 2Y, \qquad X + Y \xrightarrow{\kappa_5} Y$$

We have $d = 1$. With $\kappa_1 = \kappa_2 = \kappa_5 = 2, \kappa_3 = \kappa_4 = 1$,

$$f_\kappa(x,y) = (x-1)^2 + (y-x)^2, \qquad \text{so } \dim(\mathbb{V}_{\mathbb{R}}(f_\kappa)) = 0 < d.$$

Always

$$\dim(\mathbb{V}_{\mathbb{R}}(f_\kappa)) \leq \dim(\mathbb{V}_{\mathbb{C}}(f_\kappa)).$$

Both dimensions agree if $\mathbb{V}_{\mathbb{C}}(f_\kappa)$ contains a non-singular real point.

Can we have $\dim(\mathbb{V}_{\mathbb{R}}(f_\kappa)) < \dim(\mathbb{V}_{\mathbb{C}}(f_\kappa))$ generically in κ?

Examples: Other types of parametric systems

In all the examples above: the dimension is wrong only in a proper Zariski closed set of parameters.

Parametric systems can have the wrong dimension in an open set of parameters:

$$\kappa_1 x_1 - \kappa_2 x_2 = 0,$$
$$(\kappa_1 x_1 - \kappa_2 x_2)(\kappa_1 x_1 + \kappa_2 x_2) = \kappa_1^2 x_1^2 - \kappa_2^2 x_2^2 = 0, \qquad x \in \mathbb{R}^2, \quad \kappa \in \mathbb{R}^2_{>0}.$$

The generic complex dimension is 1, and we would expect it to be 0 (as the equations are linearly independent).

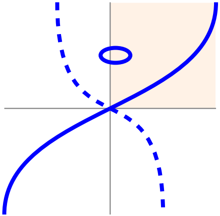
Can the complex dimension be wrong for an open set of parameters,
for the type of systems we consider?

The variety of interest

- Viewing $\mathbb{V}_{>0}(f_\kappa)$ in the affine complex space:

  Let $Y_1, \dots, Y_\ell$ be the irreducible components of $\mathbb{V}_\mathbb{C}(f_\kappa)$ that intersect $\mathbb{R}^n_{>0}$. Define:

  $$\mathbb{V}^\mathbb{C}_{>0}(f_\kappa) = Y_1 \cup \cdots \cup Y_\ell$$



- This set is not necessarily the Zariski closure of $V_{>0}(f_\kappa)$!!

  We have though

  $$\overline{\mathbb{V}_{>0}(f_\kappa)} \subseteq \mathbb{V}^\mathbb{C}_{>0}(f_\kappa),$$

  and equality holds if all irreducible components $Y_1, \dots, Y_\ell$ have a non-singular positive real point.

All definitions analogous for $F_{\kappa,c}$.

Formalizing the question

Data:

$$N \in \mathbb{R}^{s\times r} \text{ full rank } s,$$
$$B \in \mathbb{R}^{n\times r},$$
$$W \in \mathbb{R}^{d\times n},\ d = n - s.$$

Functions on $\mathbb{R}^n_{>0}$:

$$f_\kappa(x) = N(\kappa \circ x^B) \in \mathbb{R}^s,$$
$$F_{\kappa,c} = \big(N(\kappa \circ x^B), Wx - c\big) \in \mathbb{R}^n,$$

with $\kappa \in \mathbb{R}^r_{>0}$, $c \in W(\mathbb{R}^n_{>0})$.

Consider the semi-algebraic sets of parameters where the varieties are non-empty:

$$\mathcal{D} = \big\{\kappa \in \mathbb{R}^r_{>0} : \mathbb{V}_{>0}(f_\kappa) \neq \emptyset\big\}$$
$$\mathcal{F} = \big\{(\kappa, c) \in \mathbb{R}^r_{>0} \times \mathbb{R}^d : \mathbb{V}_{>0}(F_{\kappa,c}) \neq \emptyset\big\}.$$

Question. Under what conditions is it true that for generic κ, c (outside a proper Zariski closed set of $\mathcal{D}$, resp $\mathcal{F}$),

$$\dim(\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)) = d, \qquad \text{and} \qquad \dim(\mathbb{V}^{\mathbb{C}}_{>0}(F_{\kappa,c})) = 0 \quad ?$$

Under what conditions the above holds over the real numbers?

Generic dimension

$N \in \mathbb{R}^{s\times r}$ of full rank s, $B \in \mathbb{Z}^{n\times r}_{\geq 0}$, $W \in \mathbb{R}^{d\times n}$ of full rank $d = n - s$, $\kappa \in \mathbb{R}^r_{>0}$, $c \in W(\mathbb{R}^n_{>0})$.

$$f_\kappa(x) = N(\kappa \circ x^B) \in \mathbb{R}^s, \qquad \mathcal{D} = \big\{\kappa \in \mathbb{R}^r_{>0} \colon \mathbb{V}_{>0}(f_\kappa) \neq \emptyset\big\},$$

$$F_{\kappa,c} = \big(N(\kappa \circ x^B), Wx - c\big) \in \mathbb{R}^n, \qquad \mathcal{F} = \big\{(\kappa, c) \in \mathbb{R}^r_{>0} \times \mathbb{R}^d \colon \mathbb{V}_{>0}(F_{\kappa,c}) \neq \emptyset\big\}.$$

Theorem 1. [Feliu, Henriksson, Pascual-Escudero]

- If $\mathcal{D} \subseteq \mathbb{R}^r_{>0}$ has nonempty Euclidean interior in $\mathbb{R}^r_{>0}$, then there exists a nonempty Zariski open subset $\mathcal{U} \subseteq \mathcal{D}$ such that

$$\dim(\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)) = d, \quad \text{for all } \kappa \in \mathcal{U}.$$

- If the Euclidean interior of $\mathcal{D} \subseteq \mathbb{R}^r_{>0}$ is empty, then

$$\dim(\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)) > d, \quad \text{for all } \kappa \in \mathcal{D}.$$

- Analogous for $F_{\kappa,c}$ by considering $\mathcal{F}$.

Conclusion: We cannot have the wrong (complex) dimension generically in $\mathcal{D}$, as long as $\mathbb{V}_{>0}(f_\kappa) \neq \emptyset$ for "enough" κ's.

Idea of the proof

- Consider the enlarged variety

$$\mathcal{E} := \{(\kappa, x) \in \mathbb{R}^r_{>0} \times \mathbb{R}^n_{>0} \colon N(\kappa \circ x^B) = 0\}.$$

  It admits a parametrization obtained by isolating $s = \mathrm{rk}(N)$ of the parameters κ. Its closure $\overline{\mathcal{E}} \subseteq \mathbb{C}^{r+n}$ is an irreducible variety of dimension $r + d$.

- The projection

$$\pi \colon \overline{\mathcal{E}} \longrightarrow \mathbb{C}^r \qquad (\kappa, x) \longmapsto \kappa$$

  is a morphism of irreducible varieties, which is dominant.

- A version of the Theorem of the dimension of fibers gives that for κ in a nonempty open Zariski set $\widetilde{\mathcal{U}}$, either

$$\dim(\pi^{-1}(\kappa)) = \dim(\overline{\mathcal{E}}) - \dim(\mathbb{C}^r) = r + d - r = d,$$

  or $\pi^{-1}(\kappa)$ empty.

- Finally, use $\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa) \subseteq \pi^{-1}(\kappa)$ to conclude that $\dim(\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)) = d$ for $\kappa \in \widetilde{\mathcal{U}} \cap \mathcal{D} \neq \emptyset$.

(Analogous for $F_{\kappa,c}$.)

Non-degeneracy

How do we check that $\mathcal{D}$ and $\mathcal{F}$ contain open sets of parameters?

A solution x^* to a system $g(x) = 0$, with $g = (g_1, \dots, g_s) \in \mathbb{R}[x_1, \dots, x_n]$, $s \leq n$, is said to be non-degenerate, if

$$\operatorname{rk} J_g(x^*) = s.$$

Fact: A non-degenerate point x^* is non-singular in $\mathbb{V}(g)$.

So if $\dim(\mathbb{V}_{\mathbb{C}}(g)) = d$ and $\mathbb{V}_{\mathbb{R}}(g)$ has a non-degenerate point, we have also $\dim(\mathbb{V}_{\mathbb{R}}(g)) = d$.

Implicit Function Theorem:

- If $f_\kappa(x) = 0$ has a non-degenerate solution for some κ, then $\mathcal{D}$ contains an open set of parameters κ.
- Idem for $F_{\kappa,c}(x)$.

Theorem on non-degeneracy

The converse is true!

Theorem 2. [Feliu, Henriksson, Pascual-Escudero] (Analogous for $F_{\kappa,c}(x)$.)

$f_\kappa(x) = 0$ has a non-degenerate solution for some κ

$\iff$ $\mathcal{D}$ has nonempty Euclidean interior

$\iff$ $\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)$ is equidimensional of dimension d generically for $\kappa \in \mathcal{D}$

$\iff$ $\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)$ is equidimensional of dimension d for some $\kappa \in \mathcal{D}$

$\iff$ $\dim(\mathbb{V}^{\mathbb{R}}_{>0}(f_\kappa)) = d$ generically for $\kappa \in \mathcal{D}$

This system had solutions for all κ_1, κ_2, so $\mathcal{D}$ contains an open set, but all solutions are degenerate

$$\begin{aligned} \kappa_1 x_1 - \kappa_2 x_2 &= 0, \\ \kappa_1^2 x_1^2 - \kappa_2^2 x_2^2 &= 0, \qquad x \in \mathbb{R}^2, \quad \kappa \in \mathbb{R}^2_{>0}. \end{aligned}$$

Many families of networks are known to have non-degenerate steady states: injective networks, weakly reversible networks.

Checking non-degeneracy is easy!

- There is a bijection of sets

$$\begin{array}{rcl}\{(\kappa,x)\in\mathbb{R}^r_{>0}\times\mathbb{R}^n_{>0}\colon N(\kappa\circ x^B)=0\} & \longleftrightarrow & \big(\ker(N)\cap\mathbb{R}^r_{>0}\big)\times\mathbb{R}^n_{>0}\\ (\kappa,x) & \mapsto & (\kappa\circ x^B,\frac{1}{x})\end{array}$$

that induces a bijection between the sets of matrices

$$\{J_{f_\kappa}(x)\colon \kappa\in\mathbb{R}^r_{>0}, x\in\mathbb{V}_{>0}(f_\kappa)\} \ \leftrightarrow\ \{N\,\mathrm{diag}(\omega)B^\top\,\mathrm{diag}(h)\colon \omega\in\ker(N)\cap\mathbb{R}^r_{>0}, h\in\mathbb{R}^n_{>0}\}$$

- This gives:

$f_\kappa(x)=0$ has a non-degenerate solution x^* for some κ^* $\Leftrightarrow$ $\mathrm{rk}(N\,\mathrm{diag}(\omega)B^\top)=s$ for some $\omega\in\ker(N)\cap\mathbb{R}^r_{>0}$.

Easy! Take a random point after finding generators of the polyhedral cone $\ker(N)\cap\mathbb{R}^r_{>0}$

Example

Reaction network:

$$3X \xrightarrow{\kappa_1} X + 2Y, \quad X + 2Y \xrightarrow{\kappa_2} 3Y, \quad 3Y \xrightarrow{\kappa_3} 2X + Y, \quad 2X + Y \xrightarrow{\kappa_4} 3X$$

gives rise to

$$N = \begin{bmatrix} -2 & -1 & 2 & 1 \\ 2 & 1 & -2 & -1 \end{bmatrix}, \quad s = 1, \quad B = \begin{bmatrix} 3 & 1 & 0 & 2 \\ 0 & 2 & 3 & 1 \end{bmatrix},$$

$$\ker(N) \cap \mathbb{R}^r_{>0} = \{\lambda_1(1,0,0,2) + \lambda_2(1,0,1,0) + \lambda_3(0,1,0,1) + \lambda_4(0,2,1,0) \colon \lambda_i > 0\}.$$

By letting N' be obtained by removing the second row of N, and considering $\omega \in \ker(N) \cap \mathbb{R}^4_{>0}$:

$$N' \operatorname{diag}(\omega) B^\top = \begin{bmatrix} -2\lambda_1 - 6\lambda_2 + \lambda_3 - 2\lambda_4 & 2\lambda_1 + 6\lambda_2 - \lambda_3 + 2\lambda_4 \end{bmatrix}$$

We have

$$\operatorname{rk}(N' \operatorname{diag}(\omega) B^\top) = 1 \quad \Leftrightarrow \quad 2\lambda_1 + 6\lambda_2 - \lambda_3 + 2\lambda_4 \neq 0.$$

Conclusion: There exist non-degenerate steady states, and hence,

- $\overline{\mathcal{D}} = \mathbb{C}^r$, and $\mathcal{D}$ contains an open Euclidean set.
- For almost all $\kappa \in \mathcal{D}$,

$$\dim(\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)) = 1.$$

Example

Recall from before:

$$X \xrightarrow{\kappa_1} Y, \quad X \xrightarrow{\kappa_2} Z, \quad Y+Z \xrightarrow{\kappa_3} X+Y+Z, \quad Y+Z \xrightarrow{\kappa_4} 0.$$

We had $d=0$, but

$$\mathbb{V}_{>0}(f_\kappa) \neq \emptyset \quad \Leftrightarrow \quad \kappa_1 = \kappa_2 \text{ and } \kappa_3 = 2\kappa_4,$$

and in this case

$$\mathbb{V}_{>0}(f_\kappa) = \{\kappa_1 x - \kappa_4 yz = 0\},$$

has dimension 2.

Let's find non-degenerate steady states:

$$\ker(N) \cap \mathbb{R}^r_{>0} = \{\lambda(1,1,2,1) \colon \lambda > 0\},$$

so

$$N \operatorname{diag}(\omega) B^\top = \begin{bmatrix} -2\lambda & 2\lambda & 2\lambda \\ \lambda & -\lambda & -\lambda \\ \lambda & -\lambda & -\lambda \end{bmatrix}$$

We have

$$\det(N \operatorname{diag}(\omega) B^\top) = 0, \qquad \text{for all } \lambda,$$

so all steady states are degenerate.

This means that for almost all κ, the steady states variety is empty (as we knew), and it has the wrong dimension.

Wrapping up

- Under what conditions is it true that for generic κ, c (outside a proper Zariski closed subset of $\mathcal{D}$, resp. $\mathcal{F}$),

$$\dim(\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)) = d, \qquad \text{and} \qquad \dim(\mathbb{V}^{\mathbb{C}}_{>0}(F_{\kappa,c})) = 0 \quad ?$$

  When $f_\kappa(x) = 0$, resp. $F_{\kappa,c}(x) = 0$, have a non-degenerate solution. If the systems have the right dimension for one parameter choice, then this holds generically.

- Can $\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)$ have the wrong dimension for an (Euclidean) open subset of parameters in $\mathbb{C}^r$?

  No.

- Is there a weakly reversible network with infinitely many positive steady states for κ in an open subset of parameter space? (Boros, Craciun, Yu)

  No. Weakly reversible networks cannot have the wrong dimension for almost all κ, as there are non-degenerate steady states. Furthermore it is known that $\mathcal{D} = \mathbb{R}^r_{>0}$.

What we still would like to show

Do these results extend to the dimension over $\mathbb{R}$? YES.

But we cannot conclude that

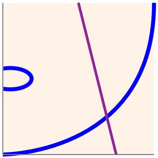
$$\mathbb{V}^{\mathbb{R}}_{>0}(f_\kappa)$$

is generically equidimensional of dimension d.

It is enough to show that there exists a nonempty open Zariski subset of $\mathcal{D}$ where ALL irreducible components of $\mathbb{V}^{\mathbb{C}}_{>0}(f_\kappa)$ have a non-singular point in $\mathbb{R}^n_{>0}$.

Theorem 3. [Feliu, Henriksson, Pascual-Escudero] (Analogous for $F_{\kappa,c}$.)

If $f_\kappa(x) = 0$ has a non-degenerate solution x^* for some κ^*, then there exists a nonempty Zariski open subset $\mathcal{U} \subseteq \mathcal{D}$ such that for all $\kappa \in \mathcal{U}$, any $x \in \mathbb{V}_{>0}(f_\kappa)$ with $Wx = Wx^*$ is non-degenerate.



Ideas to prove the claim:

(1) Projectivize Theorem 3.

(2) Vary W.

Approximating the parameter region of multistationarity

- Grid description of the parameter region of multistationarity
- Given a box in parameter space, is there a point where $\#C_{\kappa,c} \geq 2$?
- Given two points in the parameter region of multistationarity, which one is more "robust"?

Feliu, Sadeghimanesh (2022) *Kac-Rice formulas and the number of solutions of parametrized systems of polynomial equations*, Mathematics of Computation

Parameter region of multistationarity?

The answer is often complex...

$$\mathrm{HK}_{00} \xrightarrow{\kappa_1} \mathrm{HK}_{\mathrm{p}0} \xrightarrow{\kappa_2} \mathrm{HK}_{0\mathrm{p}} \xrightarrow{\kappa_3} \mathrm{HK}_{\mathrm{pp}}$$
$$\mathrm{HK}_{0\mathrm{p}} + \mathrm{RR} \xrightarrow{\kappa_4} \mathrm{HK}_{00} + \mathrm{RR}_{\mathrm{p}}$$
$$\mathrm{HK}_{\mathrm{pp}} + \mathrm{RR} \xrightarrow{\kappa_5} \mathrm{HK}_{\mathrm{p}0} + \mathrm{RR}_{\mathrm{p}}$$
$$\mathrm{RR}_{\mathrm{p}} \xrightarrow{\kappa_6} \mathrm{RR}$$

The network has three positive steady states if and only if

$$a_2 > 0 \qquad 9a_0a_3 + a_1a_2 < 0$$
$$27a_0^2a_3^2 + 18a_0a_1a_2a_3 - 4a_0a_2^3 + 4a_1^3a_3 - a_1^2a_2^2 < 0 \qquad -6a_0a_2 + 2a_1^2 > 0,$$

where

$$\begin{aligned} a_0 &= (\kappa_1 + \kappa_2)\kappa_4\kappa_5\kappa_6 > 0 \\ a_1 &= (\kappa_1(c_1\kappa_2\kappa_4 + \kappa_2\kappa_6 + \kappa_3\kappa_6) - c_2(\kappa_1 + \kappa_2)\kappa_4\kappa_6)\kappa_5 \\ a_2 &= (\kappa_1\kappa_2\kappa_3(c_1\kappa_5 + \kappa_6) - c_2\kappa_1(\kappa_2 + \kappa_3)\kappa_5\kappa_6) \\ a_3 &= -c_2\kappa_1\kappa_2\kappa_3\kappa_6 < 0. \end{aligned}$$

Kothamanchu, Feliu, Cardelli, Soyer (2015)

Theorem. (A Kac-Rice formula). [Feliu, Sadeghimanesh] $A = A_1 \times \cdots \times A_n \subseteq \mathbb{R}^n$ a box. $f_\kappa : A \to \mathbb{R}^n$ a polynomial map whose coefficients are in $\mathbb{R}[\kappa]$, $\kappa = (\kappa_1, \dots, \kappa_m)$ with $m \geq n$. κ_i follows a uniform distribution on an interval B_i and density ρ_i.

Define $\widetilde{B} = B_{n+1} \times \cdots \times B_m$ and let $\bar{\kappa} = (\kappa_{n+1}, \dots, \kappa_m)$. Assume

$$f_{\kappa,i}(x) = h_i(\bar{\kappa}, x)\kappa_i + q_i(\bar{\kappa}, x), \qquad i = 1, \dots, n.$$

For $(\bar{\kappa}, x) \in \widetilde{B} \times A$ define

$$g_{\bar{\kappa},i}(x) := \frac{-q_i(\bar{\kappa}, x)}{h_i(\bar{\kappa}, x)}, \quad i = 1, \dots, n, \quad \bar{\rho}(\bar{\kappa}, x) := \left(\prod_{i=1}^{n} \rho_i(g_{\bar{\kappa},i}(x))\right) \left(\prod_{i=n+1}^{m} \rho_i(\kappa_i)\right).$$

If (...), then

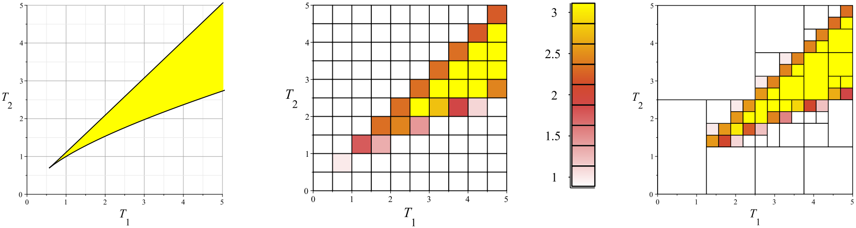
$$\mathbb{E}(\#(f_\kappa^{-1}(0) \cap A)) = \int_A \int_{\widetilde{B}} \left| \det\left(J_{g_{\bar{\kappa}}}(x)\right) \right| \bar{\rho}(\bar{\kappa}, x)\, d\kappa_{n+1} \dots d\kappa_m\, dx.$$

- The conditions of the theorem always hold for reaction networks
- We have computed the Kac-Rice integral using Monte-Carlo integration and parallellization.

Feliu, Sadeghimanesh (2022)

Approximating the parameter region

These figures are for the hybrid two-component system, fixing κ and having $c_1, c_2 = T_1, T_2$ free, only for illustration.



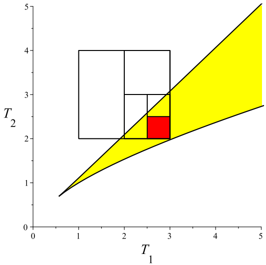
(a) (b) (c)

(a) CAD. Three solutions in the yellow region.
(b-c) Using boxes and Kac-Rice formula

Feliu, Sadeghimanesh (2022)

Finding a box of multistationarity

Step	Sub-box B	$\hat{r}(B)$	Chosen sub-box
0	$[1,3] \times [2,4]$	$\simeq 1.29$	✓
1	$[1,2] \times [2,4]$	$\simeq 1.00$	
	$[2,3] \times [2,4]$	$\simeq 1.58$	✓
2	$[2,3] \times [2,3]$	$\simeq 2.16$	✓
	$[2,3] \times [3,4]$	$\simeq 1.00$	
3	$[2,2.5] \times [2,3]$	$\simeq 1.68$	
	$[2.5,3] \times [2,3]$	$\simeq 2.65$	✓
4	$[2.5,3] \times [2,2.5]$	$\simeq 3.00$	✓
	$[2.5,3] \times [2.5,3]$	$\simeq 2.30$	



- $\hat{r}(B)$ is the (approximated) value of the Kac-Rice integral in the box B.
- The final sub-box is colored in red and is entirely inside the multistationary region (colored in yellow).
- The sub-boxes with $\hat{r} = 1$ are outside the yellow region, and the sub-boxes with $1 < \hat{r} < 3$, have intersection with both the white and yellow regions.

Feliu, Sadeghimanesh (2022)

Dual phosphorylation

$$A + K \rightleftharpoons AK \longrightarrow A_p + K \rightleftharpoons A_pK \longrightarrow A_{pp} + K$$

$$A_{pp} + F \rightleftharpoons A_{pp}F \longrightarrow A_p + F \rightleftharpoons A_pF \longrightarrow A + F$$

The system has 15 parameters, and can be reduced to 3 variables.

Consider the box

$$B = (0.5, 1.5) \times (509.5, 510.5) \times (1.5, 2.5) \times (1.5, 2.5) \times (0.5, 1.5) \times (0.5, 1.5) \\ \times (1.5, 2.5) \times (0.5, 1.5) \times (0.5, 1.5) \times (1.5, 2.5) \times (0.5, 1.5) \times (0.5, 1.5) \times (110, 150) \\ \times (20, 30) \times (15, 25).$$

We obtain $\hat{r}(B) = 1.45$ with standard error $\hat{e} = 0.015$, in ~ 7.6 hours (~ 30 minutes with 32 parallel workers). The box intersects the region of multistationarity.

With 32 workers, after 16 hours, we obtain the following box inside the region of multistationarity:

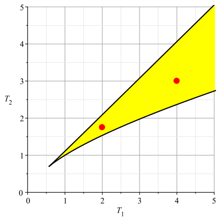
$$(1.125, 1.25) \times (510.0, 510.25) \times (1.5, 1.75) \times (2.25, 2.5) \times (0.5, 0.75) \times (0.5, 0.75) \times (2.25, 2.5) \\ \times (0.5, 0.75) \times (0.75, 1.0) \times (2.0, 2.25) \times (0.75, 1.0) \times (1.25, 1.5) \times (117.5, 120.0) \\ \times (25.0, 27.5) \times (15.0, 20.0),$$

($\hat{r} = 2.94$, $\hat{e} = 0.017$, with 10^{12} sampled points).

Feliu, Sadeghimanesh (2022)

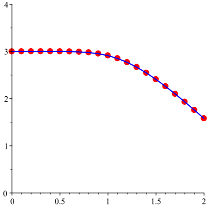
Work in progress

Given two points in the multistationarity region, which one is furthest from the boundary of the region?

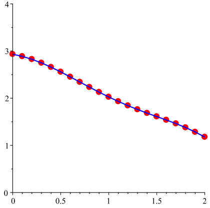


Idea:

- Compute the Kac-Rice integral with truncated normal distributions on the parameters centered on the original parameters and increasing variance.
- The value of the integral will decrease when the variance is large enough to include points outside the multistationarity region. The latest this happens, the furthest the point is from the boundary



$(T_1, T_2) = (4, 3)$



$(T_1, T_2) = (2, 1.75)$

y-axis $= \mathbb{E}(\#(f^{-1}(0) \cap \mathbb{R}_{>0}))$.

x-axis: $2 + \log_{10} \sigma^2$.

Support of the distribution:

$[T_1 - 1.75, T_1 + 1.75] \times [T_2 - 1.75, T_2 + 1.75]$.

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PhD and postdoc positions available in my group

Thank you for your attention