Deterministic reaction networks, part II
Parameter region of multistationarity

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PLAN FOR TODAY

I. Steady state equations

II. Decomposing the parameter space
   - Discriminants
   - Cylindrical Algrebraic Decomposition
   - Numerical methods

III. Parametrizations

IV. The critical polynomial
   - Verifying/Precluding multistationarity
   - Connectivity of the multistationarity region

V. Bounds on the number of positive steady states
   - Upper bounds
   - Lower bounds

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Notation and the running example

	running example
species $\{X_1, \ldots, X_n\}$	$\mathrm{X}_1, \quad \mathrm{X}_2$
reactions $\left\{ \sum_{i=1}^{n} a_{ij} X_i \xrightarrow{\kappa_i} \sum_{i=1}^{n} b_{ij} X_i \right\}_{j=1,\ldots,r}$	$\mathrm{X}_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{X}_2, \quad 2\mathrm{X}_1 + \mathrm{X}_2 \xrightarrow{\kappa_3} 3\mathrm{X}_1$

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The ODE system (1) is forward invariant on stoichiometric compatibility classes

$$\mathcal{P}_c = \{x \in \mathbb{R}^n_{\geq 0} \mid Wx = c\},$$

where $c \in \mathbb{R}^d, W \in \mathbb{R}^{d \times n}$ is a fullrank matrix such that $WN = 0$.

Running example

$$X_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_2 \qquad 2X_1 + X_2 \xrightarrow{\kappa_3} 3X_1$$

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

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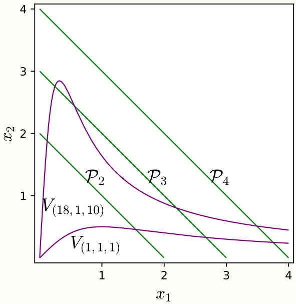
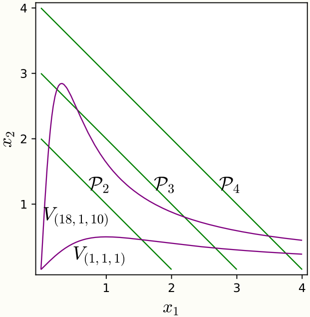


The parameter region of multistationarity

A parameter pair (κ, c) enables multistationarity, if the intersection of V_κ and $\mathcal{P}_c$ contains at least two positive points.



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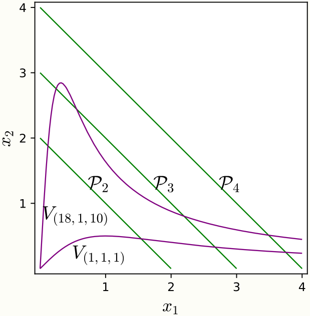
A parameter pair (κ, c) enables multistationarity, if the intersection of V_κ and $\mathcal{P}_c$ contains at least two positive points.

We call the set of all parameter pairs that enable multistationarity the parameter region of multistationarity.

$$\Omega := \left\{(\kappa, c) \in \mathbb{R}^r_{>0} \times \mathbb{R}^d \mid \#\left(V_\kappa \cap \mathcal{P}_c \cap \mathbb{R}^n_{>0}\right) \geq 2\right\}$$



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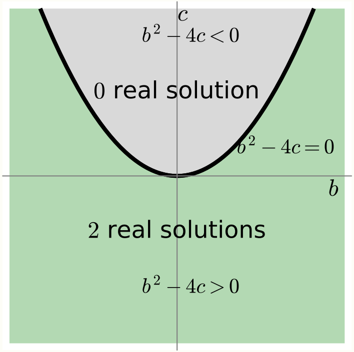

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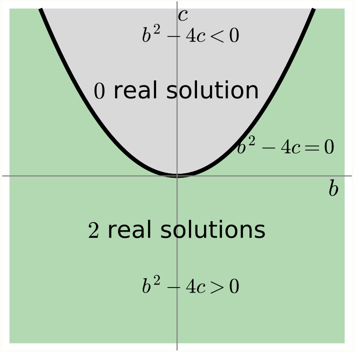

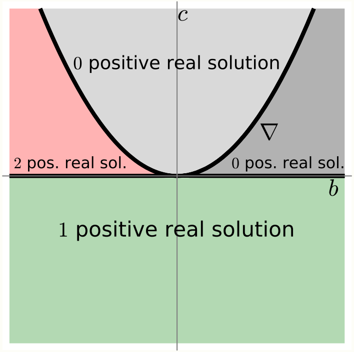

Cylindrical Algebraic Decomposition

There exists an algorithm that decomposes the parameter space into cells such that the number of positive real solutions is constant within each cell.

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$$\kappa_3 x_1^2 x_2 - \kappa_1 x_1 + \kappa_2 x_2 = 0, \qquad x_1 + x_2 = c$$

There is only one cell with at least two positive solutions. This cell is given by the inequalities

$$\kappa_2 > 0, \quad \kappa_3 > 0, \quad \kappa_1 > 8\kappa_2, \quad \xi_3 < c < \xi_4,$$

where ξ_3, ξ_4 denote the 3rd and 4th root of the polynomial

$$4c^4\kappa_2\kappa_3^2 - c^2\kappa_1^2\kappa_3 - 20c^2\kappa_1\kappa_2\kappa_3 + 8c^2\kappa_2^2\kappa_3 + 4\kappa_1^3 + 12\kappa_1^2\kappa_2 + 12\kappa_1\kappa_2^2 + 4\kappa_2^3.$$

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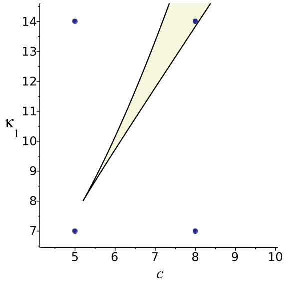

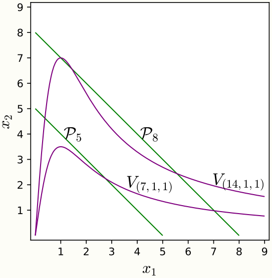

$$\kappa_2 = 1, \quad \kappa_3 = 1 \quad \kappa_1 > 8, \quad \xi_3 < c < \xi_4$$

Cylindrical Algebraic Decomposition

The CAD algorithm has double exponential complexity

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$$2^{2^1} = 4, \quad 2^{2^2} = 16, \quad 2^{2^3} = 256, \quad 2^{2^4} = 65536, \quad 2^{2^5} = 4294967296$$

Cylindrical Algrebraic Decomposition

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$2^{2^6} = 2^{64} \sim 1.84 \times 10^{19}$ is much larger than the number of sand grains on the beach...

Is the CAD algorithm useless?

Cylindrical Algrebraic Decomposition

Is the CAD algorithm useless? No!

CYLINDRICAL ALGREBRAIC DECOMPOSITION

Is the CAD algorithm useless? No!

$$S + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} SE \xrightarrow{\kappa_3} S_p + E \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_pE \xrightarrow{\kappa_6} S_{pp} + E$$

$$S_{pp} + F \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_{pp}F \xrightarrow{\kappa_9} S_pF \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_p + F \qquad S_p + F \underset{\kappa_{13}}{\overset{\kappa_{12}}{\rightleftharpoons}} S_pF^* \xrightarrow{\kappa_{14}} SF \underset{\kappa_{16}}{\overset{\kappa_{15}}{\rightleftharpoons}} S + F$$

[Markevich, Hoek, Kholodenko, ’04]

Is the CAD algorithm useless? No!

$$\mathrm{S} + \mathrm{E} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{SE} \xrightarrow{\kappa_3} \mathrm{S_p} + \mathrm{E} \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} \mathrm{S_pE} \xrightarrow{\kappa_6} \mathrm{S_{pp}} + \mathrm{E}$$

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$x_1 = [\mathrm{S}]$, $x_2 = [\mathrm{S_p}]$, $x_3 = [\mathrm{S_{pp}}]$, $x_4 = [\mathrm{E}]$, $x_5 = [\mathrm{F}]$, $x_6 = [\mathrm{SE}]$, $x_7 = [\mathrm{S_pE}]$, $x_8 = [\mathrm{S_{pp}F}]$, $x_9 = [\mathrm{S_pF}]$, $x_{10} = [\mathrm{S_pF^*}]$, $x_{11} = [\mathrm{SF}]$.

[Markevich, Hoek, Kholodenko, ’04]

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$x_1 = [\mathrm{S}], x_2 = [\mathrm{S_p}], x_3 = [\mathrm{S_{pp}}], x_4 = [\mathrm{E}], x_5 = [\mathrm{F}], x_6 = [\mathrm{SE}], x_7 = [\mathrm{S_pE}], x_8 = [\mathrm{S_{pp}F}], x_9 = [\mathrm{S_pF}],$
$x_{10} = [\mathrm{S_pF^*}], x_{11} = [\mathrm{SF}].$

$$\dot{x}_1 = \kappa_2 x_6 + \kappa_{15} x_{11} - \kappa_1 x_1 x_4 - \kappa_{16} x_1 x_5 \qquad \dot{x}_3 = \kappa_6 x_7 + \kappa_8 x_8 - \kappa_7 x_3 x_5$$

$$\dot{x}_2 = \kappa_3 x_6 + \kappa_5 x_7 + \kappa_{10} x_9 + \kappa_{13} x_{10} - x_2 x_5 (\kappa_{11} + \kappa_{12}) - \kappa_4 x_2 x_4$$

$$\dot{x}_4 = x_6(\kappa_2 + \kappa_3) + x_7(\kappa_5 + \kappa_6) - \kappa_1 x_1 x_4 - \kappa_4 x_2 x_4$$

$$\dot{x}_5 = \kappa_8 x_8 + \kappa_{10} x_9 + \kappa_{13} x_{10} + \kappa_{15} x_{11} - x_2 x_5 (\kappa_{11} + \kappa_{12}) - \kappa_7 x_3 x_5 - \kappa_{16} x_1 x_5$$

$$\dot{x}_6 = \kappa_1 x_1 x_4 - x_6(\kappa_2 + \kappa_3), \qquad \dot{x}_7 = \kappa_4 x_2 x_4 - x_7(\kappa_5 + \kappa_6)$$

$$\dot{x}_8 = \kappa_7 x_3 x_5 - x_8(\kappa_8 + \kappa_9), \qquad \dot{x}_9 = \kappa_9 x_8 - \kappa_{10} x_9 + \kappa_{11} x_2 x_5$$

$$\dot{x}_{10} = \kappa_{12} x_2 x_5 - x_{10}(\kappa_{13} + \kappa_{14}), \qquad \dot{x}_{11} = \kappa_{14} x_{10} - \kappa_{15} x_{11} + \kappa_{16} x_1 x_5$$

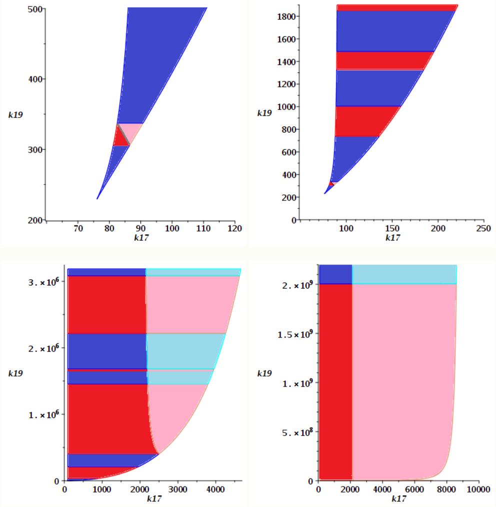
$$x_5 + x_8 + x_9 + x_{10} + x_{11} = \kappa_{17}, \quad x_4 + x_6 + x_7 = \kappa_{18}$$

$$x_1 + x_2 + x_3 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} = \kappa_{19}.$$

[Markevich, Hoek, Kholodenko, '04]

Cylindrical Algrebraic Decomposition

$\kappa_1 = 0.02$, $\kappa_2 = 1$, $\kappa_3 = 0.01$, $\kappa_4 = 0.032$, $\kappa_5 = 1$, $\kappa_6 = 15$, $\kappa_7 = 0.045$, $\kappa_8 = 1$, $\kappa_9 = 0.092$, $\kappa_{10} = 1$, $\kappa_{11} = 0.01$, $\kappa_{12} = 0.01$, $\kappa_{13} = 1$, $\kappa_{14} = 0.5$, $\kappa_{15} = 0.086$, $\kappa_{16} = 0.0011$, $\kappa_{18} = 50$



[Bradford, Davenport, England, Errami, Gerdt, Grigoriev, Hoyt, Košta, Radulescu, Sturm, Weber, ’20]

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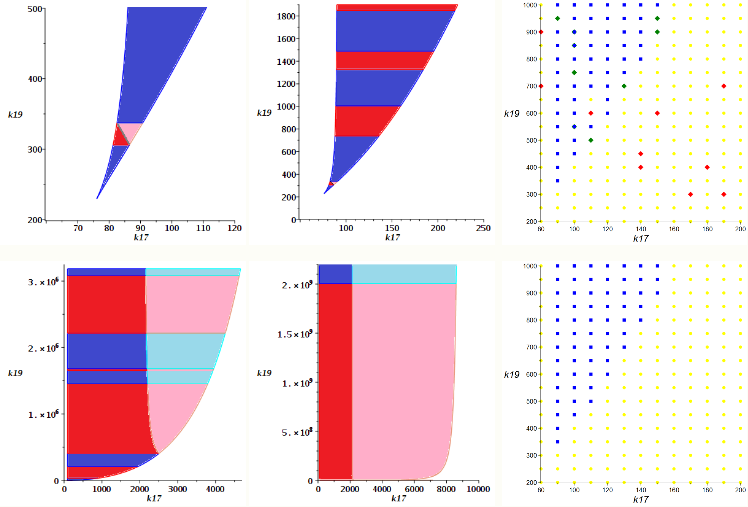

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NUMERICAL METHODS - MACHINE LEARNING

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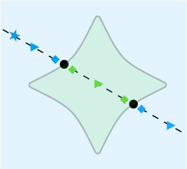

Visual representation of the sampling scheme where the star is a uniform random sample point, circles are points on the boundary, triangles are midpoints, and diamonds are near boundary points.

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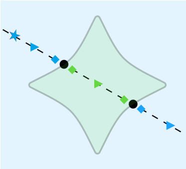

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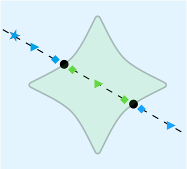

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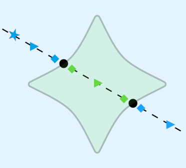

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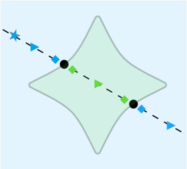

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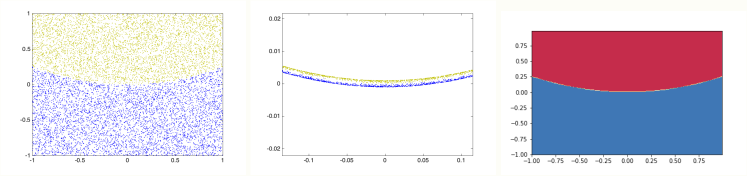

(a) (b) (c)

(a) Uniform random sampled data, (b) near boundary data, and (c) decision boundary from neural network trained on data from (b) for $f(x; b, c) = x^2 + bx + c$. The blue region has 2 real solutions while the gold and red regions have 0 real solutions.

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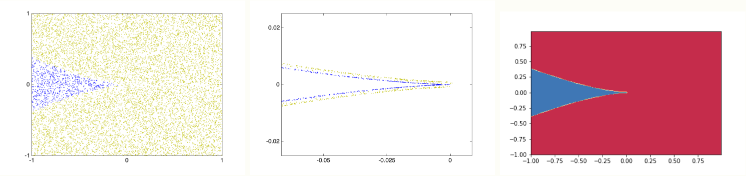

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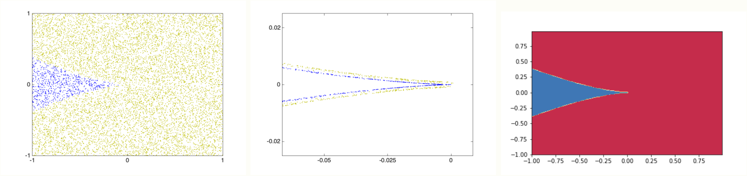

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[Harrington, Mehta, Byrne, Hauenstein, Decomposing the parameter space of biological networks via a numerical discriminant approach, '20]

NUMERICAL METHODS - KAC-RICE FORMULAS

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$$X_1 \xrightarrow{\kappa_1} X_2 \xrightarrow{\kappa_2} X_3 \xrightarrow{\kappa_3} X_4 \qquad X_3 + X_5 \xrightarrow{\kappa_4} X_1 + X_6$$

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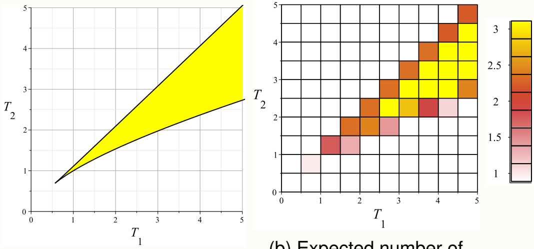

(a) CAD decomposition

(b) Expected number of solutions

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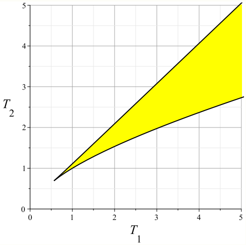

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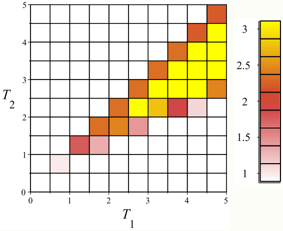

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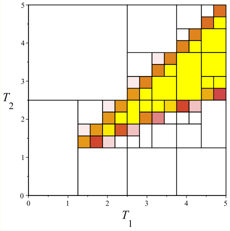

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Parametrizations - Running example

$$V_\kappa = \{x \in \mathbb{R}^2_{>0} \mid -\kappa_1 x_1 + \kappa_2 x_2 + \kappa_3 x_1^2 x_2 = 0,\ \kappa_1 x_1 - \kappa_2 x_2 - \kappa_3 x_1^2 x_2 = 0\}$$

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Positive roots if this univariate polynomial correspond one-to-one to positive steady states.

Parametrization of the steady state variety

There are several relevant reaction networks whose steady state variety admits a parametrization

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- [Detecting and precluding toricity in reaction network theory, Henriksson, Feliu '24+]

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Critical function

- Let $M_\kappa(x)$ be the matrix obtained from the Jacobian $J_f(x,\kappa)$ of $f_\kappa(x) := Nv_\kappa(x)$ by replacing some (specific) rows by the rows of W.

"KEY THEOREM"

Theorem [Conradi, Feliu, Mincheva, Wiuf, '19]

Let $c \in \mathbb{R}^d$ such that $\mathcal{P}_c \cap \mathbb{R}^n_{>0} \neq \emptyset$ and let $s = (N)$.

Furthermore, assume that

(I) The reaction network is dissipative.

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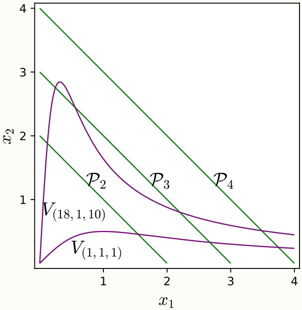
(B) If $(-1)^s \det(M_\kappa(x)) > 0$ for all $x \in V_\kappa \cap \mathcal{P}_c \cap \mathbb{R}^n_{>0}$, then the parameter pair (κ, c) does not enable multistationarity i.e. $(\kappa, c) \notin \Omega$.

Running example

$$X_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_2 \qquad 2X_1 + X_2 \xrightarrow{\kappa_3} 3X_1$$

$$(-1)^s \det(M_\kappa(x)) = \kappa_3 x_1^2 - 2\kappa_3 x_1 x_2 + \kappa_1 + \kappa_2$$



RUNNING EXAMPLE

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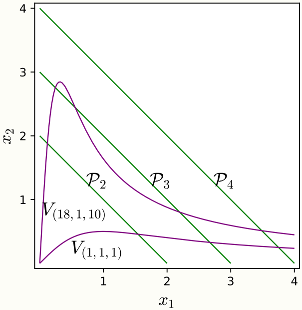

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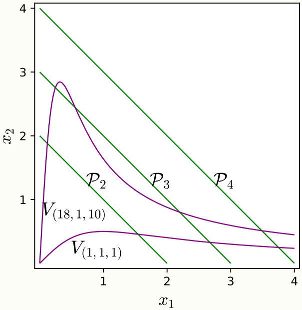
since $Wx^* = 3$, $\big((18,1,10),3\big) \in \Omega$ by the key theorem



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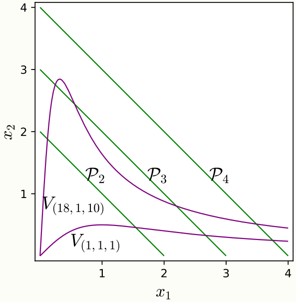

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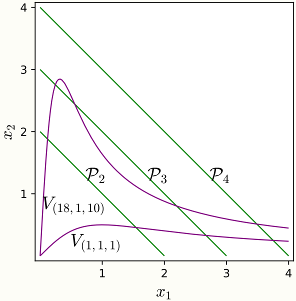

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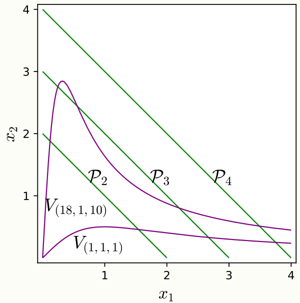
no contradiction, since $(1,2) \notin V_{(1,1,1)}$



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Evaluating $\det(M_\kappa(x))$ at $(x_1, x_2) = (x_1, \frac{\kappa_1 x_1}{\kappa_3 x_1^2 + \kappa_2})$, we get

$$\frac{\kappa_3^2 x_1^4 + (2\kappa_2\kappa_3 - \kappa_1\kappa_3)x_1^2 + \kappa_1\kappa_2 + \kappa_2^2}{\kappa_3 x_1^2 + \kappa_2}, \tag{2}$$

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which takes negative values if and only if

$$0 < (-2\kappa_2\kappa_3 + \kappa_1\kappa_3)^2 - 4\kappa_3^2(\kappa_1\kappa_2 + \kappa_2^2) = (\kappa_1 - 8\kappa_2)\kappa_1\kappa_3^2.$$

Running example

Evaluating $\det(M_\kappa(x))$ at $(x_1, x_2) = (x_1, \frac{\kappa_1 x_1}{\kappa_3 x_1^2 + \kappa_2})$, we get

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This is the same region as we computed using Cylindrical Algebraic Decomposition!

PLAN FOR TODAY

I. Steady state equations ✔
II. Decomposing the parameter space ✔
   - Discriminants ✔
   - Cylindrical Algrebraic Decomposition ✔
   - Numerical methods ✔
III. Parametrizations ✔
IV. The critical polynomial
   - Verifying/Precluding multistationarity ✔
   - Connectivity of the multistationarity region
V. Bounds on the number of positive steady states
   - Upper bounds
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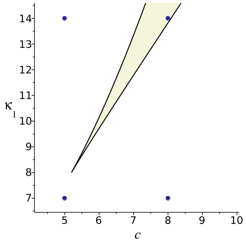
Is the parameter region of multistationarity connected?



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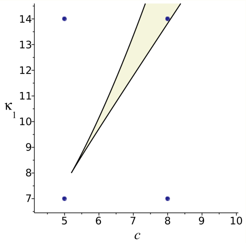

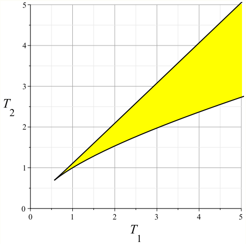

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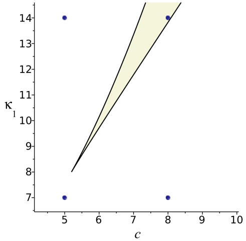

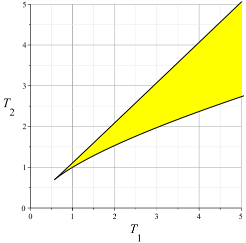

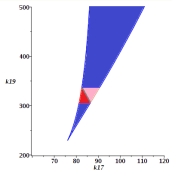

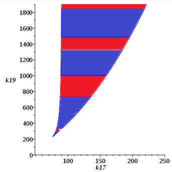

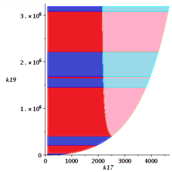

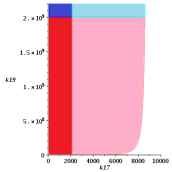

Criterion for connectivity

Theorem [Feliu, T., '23]

For a dissipative reaction network without relevant boundary steady states, there exists a polynomial

$$q\colon \mathbb{R}^n_{>0} \times \mathbb{R}^\ell_{>0} \to \mathbb{R}$$

such that if $q^{-1}(\mathbb{R}_{<0})$ is connected and its closure equals $q^{-1}(\mathbb{R}_{\leq 0})$, then the parameter region of multistationarity is connected.

RUNNING EXAMPLE

$$X_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X_2 \qquad 2X_1 + X_2 \xrightarrow{\kappa_3} 3X_1$$

$$q(h, \lambda) = h_1\lambda_2 - h_1\lambda_1 + h_2\lambda_1 + h_2\lambda_2$$

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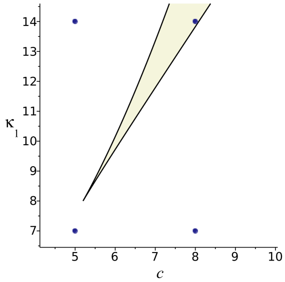
One can check that $q^{-1}(\mathbb{R}_{<0})$ is path connected and its closure equals $q^{-1}(\mathbb{R}_{\leq 0})$. So we can conclude that the parameter region of multistationarity is connected.



2-SITE PHOSPHORYLATION SYSTEM

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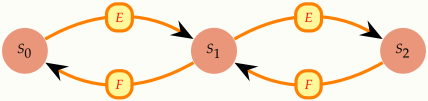
Example: 2-site phosphorylation system



$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

$$S_2 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} FS_2 \xrightarrow{\kappa_{12}} S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F$$

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- Is $q^{-1}(\mathbb{R}_{<0})$ connected?

$q(h,\lambda) = -\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_6h_7 - \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_6h_7 -$
$\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_6h_7 - \lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_6h_7 -$
$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_1h_2h_3h_6h_7 - \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_3h_6h_7 -$
$\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_3h_6h_7 - \lambda_2^3\lambda_3\lambda_5^2h_0h_1h_2h_3h_6h_7 - \lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_1h_2h_3h_6h_7 -$
$\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_3h_6h_7 - \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_3h_6h_7 - \lambda_2^3\lambda_4\lambda_5^2h_0h_1h_2h_3h_6h_7 -$
$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_1h_2h_3h_6h_7 - \lambda_0\lambda_2^2\lambda_5^3h_0h_1h_2h_3h_6h_7 - \lambda_1\lambda_2^2\lambda_5^3h_0h_1h_2h_3h_6h_7 -$
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$\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_1h_2h_4h_6h_7 - \lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_1h_2h_4h_6h_7 -$
$\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_4h_6h_7 - \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_4h_6h_7 - \lambda_2^3\lambda_3\lambda_5^2h_0h_1h_2h_4h_6h_7$

$$-\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_1h_2h_4h_6h_7 - \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_4h_6h_7 - \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_4h_6h_7 - \lambda_2^3\lambda_4\lambda_5^2h_0h_1h_2h_4h_6h_7 -$$
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$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_2h_3h_4h_6h_7 - \lambda_0\lambda_2^2\lambda_5^3h_0h_2h_3h_4h_6h_7 - \lambda_1\lambda_2^2\lambda_5^3h_0h_2h_3h_4h_6h_7 - \lambda_2^3\lambda_5^3h_0h_2h_3h_4h_6h_7 -$$
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$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_7 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_7 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_7 + \lambda_2^3\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_7 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_7 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_7 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_7$$

$$+\lambda_2^3\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_7+\lambda_0\lambda_1\lambda_2\lambda_5^3h_2h_3h_4h_5h_6h_7+\lambda_0\lambda_2^2\lambda_5^3h_2h_3h_4h_5h_6h_7+\lambda_1\lambda_2^2\lambda_5^3h_2h_3h_4h_5h_6h_7+$$

$$\lambda_2^3\lambda_5^3h_2h_3h_4h_5h_6h_7+\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_5h_8+$$

$$\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_3h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_3h_5h_8+$$

$$\lambda_2^3\lambda_3\lambda_5^2h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_3h_5h_8+\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_3h_5h_8+$$

$$\lambda_2^3\lambda_4\lambda_5^2h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_1h_2h_3h_5h_8+\lambda_0\lambda_2^2\lambda_5^3h_0h_1h_2h_3h_5h_8+\lambda_1\lambda_2^2\lambda_5^3h_0h_1h_2h_3h_5h_8+\lambda_2^3\lambda_5^3h_0h_1h_2h_3h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_2h_4h_5h_8+\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_1h_2h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_1h_2h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_2h_4h_5h_8+\lambda_2^3\lambda_3\lambda_5^2h_0h_1h_2h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_1h_2h_4h_5h_8+\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_4h_5h_8+\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_2h_4h_5h_8+\lambda_2^3\lambda_4\lambda_5^2h_0h_1h_2h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_1h_2h_4h_5h_8+\lambda_0\lambda_2^2\lambda_5^3h_0h_1h_2h_4h_5h_8+\lambda_1\lambda_2^2\lambda_5^3h_0h_1h_2h_4h_5h_8+\lambda_2^3\lambda_5^3h_0h_1h_2h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_1h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_1h_3h_4h_5h_8+\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_1h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_1h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_1h_3h_4h_5h_8+\lambda_2^3\lambda_3\lambda_5^2h_0h_1h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_1h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_1h_3h_4h_5h_8+\lambda_2^3\lambda_4\lambda_5^2h_0h_1h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_1h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_5^3h_0h_1h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_5^3h_0h_1h_3h_4h_5h_8+\lambda_2^3\lambda_5^3h_0h_1h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_2h_3h_4h_5h_8+\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_2h_3h_4h_5h_8+\lambda_2^3\lambda_3\lambda_5^2h_0h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_2h_3h_4h_5h_8+\lambda_2^3\lambda_4\lambda_5^2h_0h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_5^3h_0h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_5^3h_0h_2h_3h_4h_5h_8+\lambda_2^3\lambda_5^3h_0h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_1h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_1h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_1h_2h_3h_4h_5h_8+\lambda_2^3\lambda_3\lambda_4\lambda_5h_1h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_1h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_1h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_1h_2h_3h_4h_5h_8+\lambda_2^3\lambda_3\lambda_5^2h_1h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_1h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_1h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_1h_2h_3h_4h_5h_8+\lambda_2^3\lambda_4\lambda_5^2h_1h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_1h_2h_3h_4h_5h_8+\lambda_0\lambda_2^2\lambda_5^3h_1h_2h_3h_4h_5h_8+\lambda_1\lambda_2^2\lambda_5^3h_1h_2h_3h_4h_5h_8+\lambda_2^3\lambda_5^3h_1h_2h_3h_4h_5h_8+$$

$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_2h_4h_5h_6h_8+\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_2h_4h_5h_6h_8+\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_2h_4h_5h_6h_8+\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_2h_4h_5h_6h_8$$

$$+\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_2h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_2h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_2h_4h_5h_6h_8 + \lambda_2^3\lambda_3\lambda_5^2h_0h_2h_4h_5h_6h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_2h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_2h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_2h_4h_5h_6h_8 + \lambda_2^3\lambda_4\lambda_5^2h_0h_2h_4h_5h_6h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_2h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_5^3h_0h_2h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_5^3h_0h_2h_4h_5h_6h_8 + \lambda_2^3\lambda_5^3h_0h_2h_4h_5h_6h_8 +$$
$$2\,\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_3h_4h_5h_6h_8 + 2\,\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_3h_4h_5h_6h_8 +$$
$$2\,\lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_3h_4h_5h_6h_8 + 2\,\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_3h_4h_5h_6h_8 +$$
$$2\,\lambda_2^3\lambda_3\lambda_5^2h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_3h_4h_5h_6h_8 + 2\,\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_3h_4h_5h_6h_8 +$$
$$2\,\lambda_2^3\lambda_4\lambda_5^2h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_2^2\lambda_5^3h_0h_3h_4h_5h_6h_8 + 2\,\lambda_1\lambda_2^2\lambda_5^3h_0h_3h_4h_5h_6h_8 +$$
$$2\,\lambda_2^3\lambda_5^3h_0h_3h_4h_5h_6h_8 + \lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_6h_8 +$$
$$\lambda_2^3\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_8 +$$
$$\lambda_2^3\lambda_3\lambda_5^2h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_8 +$$
$$\lambda_2^3\lambda_4\lambda_5^2h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_1\lambda_2\lambda_5^3h_2h_3h_4h_5h_6h_8 + \lambda_0\lambda_2^2\lambda_5^3h_2h_3h_4h_5h_6h_8 + \lambda_1\lambda_2^2\lambda_5^3h_2h_3h_4h_5h_6h_8 +$$
$$\lambda_2^3\lambda_5^3h_2h_3h_4h_5h_6h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_1h_2h_3h_5h_7h_8 + 2\,\lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_1h_2h_3h_5h_7h_8 +$$
$$2\,\lambda_2^3\lambda_3\lambda_4\lambda_5h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_2^2\lambda_3\lambda_5^2h_1h_2h_3h_5h_7h_8 + 2\,\lambda_1\lambda_2^2\lambda_3\lambda_5^2h_1h_2h_3h_5h_7h_8 +$$
$$2\,\lambda_2^3\lambda_3\lambda_5^2h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_2^2\lambda_4\lambda_5^2h_1h_2h_3h_5h_7h_8 + 2\,\lambda_1\lambda_2^2\lambda_4\lambda_5^2h_1h_2h_3h_5h_7h_8 +$$
$$2\,\lambda_2^3\lambda_4\lambda_5^2h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_1\lambda_2\lambda_5^3h_1h_2h_3h_5h_7h_8 + 2\,\lambda_0\lambda_2^2\lambda_5^3h_1h_2h_3h_5h_7h_8 + 2\,\lambda_1\lambda_2^2\lambda_5^3h_1h_2h_3h_5h_7h_8 +$$
$$2\,\lambda_2^3\lambda_5^3h_1h_2h_3h_5h_7h_8 + \lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_1h_2h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_1h_2h_4h_5h_7h_8 +$$
$$\lambda_2^3\lambda_3\lambda_4\lambda_5h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_1h_2h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_1h_2h_4h_5h_7h_8 +$$
$$\lambda_2^3\lambda_3\lambda_5^2h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_1h_2h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_1h_2h_4h_5h_7h_8 +$$
$$\lambda_2^3\lambda_4\lambda_5^2h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_1\lambda_2\lambda_5^3h_1h_2h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_5^3h_1h_2h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_5^3h_1h_2h_4h_5h_7h_8 + \lambda_2^3\lambda_5^3h_1h_2h_4h_5h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_7h_8 + \lambda_2^3\lambda_3\lambda_4\lambda_5h_2h_3h_4h_5h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_2h_3h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_5h_7h_8 + \lambda_2^3\lambda_3\lambda_5^2h_2h_3h_4h_5h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_2h_3h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_5h_7h_8 + \lambda_2^3\lambda_4\lambda_5^2h_2h_3h_4h_5h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_2h_3h_4h_5h_7h_8 + \lambda_0\lambda_2^2\lambda_5^3h_2h_3h_4h_5h_7h_8 + \lambda_1\lambda_2^2\lambda_5^3h_2h_3h_4h_5h_7h_8 + \lambda_2^3\lambda_5^3h_2h_3h_4h_5h_7h_8 -$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_2h_3h_6h_7h_8 - \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_2h_3h_6h_7h_8 - \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_2h_3h_6h_7h_8 - \lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_2h_3h_6h_7h_8 -$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_2h_3h_6h_7h_8 - \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_2h_3h_6h_7h_8 - \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_2h_3h_6h_7h_8 - \lambda_2^3\lambda_3\lambda_5^2h_0h_2h_3h_6h_7h_8$$

$$-\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_2h_3h_6h_7h_8 - \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_2h_3h_6h_7h_8 - \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_2h_3h_6h_7h_8 - \lambda_2^3\lambda_4\lambda_5^2h_0h_2h_3h_6h_7h_8 -$$
$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_2h_3h_6h_7h_8 - \lambda_0\lambda_2^2\lambda_5^3h_0h_2h_3h_6h_7h_8 - \lambda_1\lambda_2^2\lambda_5^3h_0h_2h_3h_6h_7h_8 - \lambda_2^3\lambda_5^3h_0h_2h_3h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_0h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_0h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_3\lambda_4\lambda_5h_0h_3h_4h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_0h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_0h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_0h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_3\lambda_5^2h_0h_3h_4h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_0h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_0h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_0h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_4\lambda_5^2h_0h_3h_4h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_0h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_5^3h_0h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_5^3h_0h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_5^3h_0h_3h_4h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_2h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_3\lambda_4\lambda_5h_2h_3h_4h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_5^2h_2h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_5^2h_2h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_3\lambda_5^2h_2h_3h_4h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_2h_3h_4h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_4h_6h_7h_8 + \lambda_2^3\lambda_4\lambda_5^2h_2h_3h_4h_6h_7h_8 +$$
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$$\lambda_0\lambda_1\lambda_2\lambda_4\lambda_5^2h_2h_3h_5h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_5h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_4\lambda_5^2h_2h_3h_5h_6h_7h_8 + \lambda_2^3\lambda_4\lambda_5^2h_2h_3h_5h_6h_7h_8 +$$
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$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_2h_4h_5h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_5^3h_2h_4h_5h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_5^3h_2h_4h_5h_6h_7h_8 + \lambda_2^3\lambda_5^3h_2h_4h_5h_6h_7h_8 +$$
$$\lambda_0\lambda_1\lambda_2\lambda_3\lambda_4\lambda_5h_3h_4h_5h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_3\lambda_4\lambda_5h_3h_4h_5h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_3\lambda_4\lambda_5h_3h_4h_5h_6h_7h_8 + \lambda_2^3\lambda_3\lambda_4\lambda_5h_3h_4h_5h_6h_7h_8 +$$
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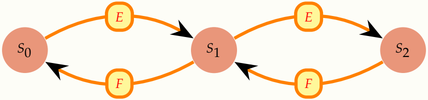
$$\lambda_0\lambda_1\lambda_2\lambda_5^3h_3h_4h_5h_6h_7h_8 + \lambda_0\lambda_2^2\lambda_5^3h_3h_4h_5h_6h_7h_8 + \lambda_1\lambda_2^2\lambda_5^3h_3h_4h_5h_6h_7h_8 + \lambda_2^3\lambda_5^3h_3h_4h_5h_6h_7h_8$$

2-SITE PHOSPHORYLATION SYSTEM

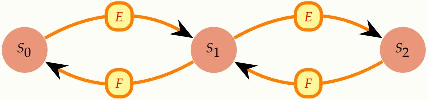


$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

$$S_2 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} FS_2 \xrightarrow{\kappa_{12}} S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} FS_1 \xrightarrow{\kappa_6} S_0 + F$$

- number of variables of $q = 15$
- number of monomials of $q = 400$

2-SITE PHOSPHORYLATION SYSTEM



$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} ES_0 \xrightarrow{\kappa_3} S_1 + E \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} ES_1 \xrightarrow{\kappa_9} S_2 + E$$

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- number of variables of $q = 15$
- number of monomials of $q = 400$
- Is $q^{-1}(\mathbb{R}_{<0})$ connected?

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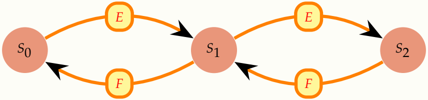
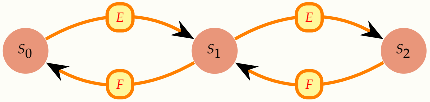


$$\mathrm{S_0 + E} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{ES_0} \xrightarrow{\kappa_3} \mathrm{S_1 + E} \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} \mathrm{ES_1} \xrightarrow{\kappa_9} \mathrm{S_2 + E}$$

$$\mathrm{S_2 + F} \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} \mathrm{FS_2} \xrightarrow{\kappa_{12}} \mathrm{S_1 + F} \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} \mathrm{FS_1} \xrightarrow{\kappa_6} \mathrm{S_0 + F}$$

- number of variables of $q = 15$
- number of monomials of $q = 400$
- Is $q^{-1}(\mathbb{R}_{<0})$ connected?
- Yes, its signed support has a separating hyperplane [Feliu,T.,'22]

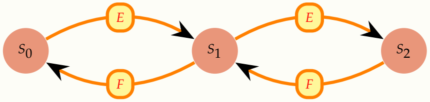
NETWORKS WITH CONNECTED MULTISTATIONARITY REGION



	n	r	ℓ	$\#\sigma_+(q)$	$\#\sigma_-(q)$	t. comp. q	t. find sep. hyp.
HHK	6	6	2	17	2	0.03 s	0.01 s
2-site	9	12	6	288	112	0.99 s	0.28 s
3-site	12	18	9	2560	1536	1 m 24 s	4.4 s
4-site	15	24	12	??	??	∞	??
2 site F_i	10	12	6	304	48	1.84 s	0.4 s
2 substr.	12	15	8	5088	224	35.68 s	10.36 s
ERK	12	18	9	15040	3432	4 m 4 s	49 s

[Feliu,T., '23]

Networks with connected multistationarity region



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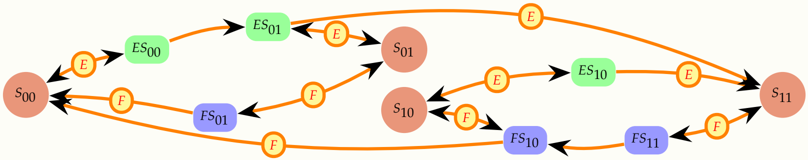
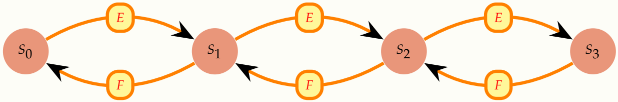
[Feliu,T., '23]



NETWORKS WITH CONNECTED MULTISTATIONARITY REGION



	n	r	ℓ	$\#\sigma_+(q)$	$\#\sigma_-(q)$	t. comp. q	t. find sep. hyp.
HHK	6	6	2	17	2	0.03 s	0.01 s
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4-site	15	24	12	??	??	∞	??
2 site F_i	10	12	6	304	48	1.84 s	0.4 s
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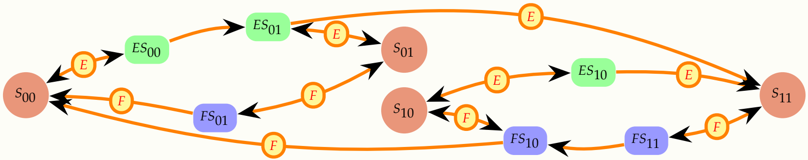
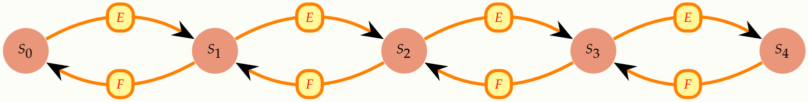
[Feliu,T., '23]





	n	r	ℓ	$\#\sigma_+(q)$	$\#\sigma_-(q)$	t. comp. q	t. find sep. hyp.
HHK	6	6	2	17	2	0.03 s	0.01 s
2-site	9	12	6	288	112	0.99 s	0.28 s
3-site	12	18	9	2560	1536	1 m 24 s	4.4 s
4-site	15	24	12	??	??	∞	??
2 site F_i	10	12	6	304	48	1.84 s	0.4 s
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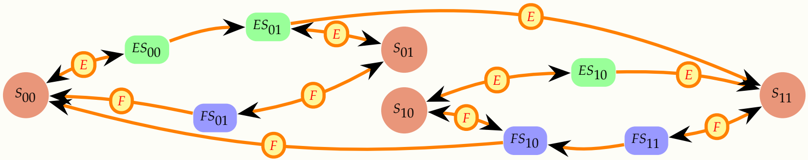
ERK	12	18	9	15040	3432	4 m 4 s	49 s

[Feliu,T., '23]



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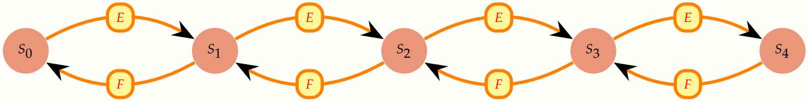

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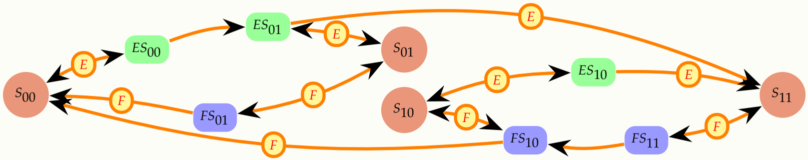
HHK	6	6	2	17	2	0.03 s	0.01 s
2-site	9	12	6	288	112	0.99 s	0.28 s
3-site	12	18	9	2560	1536	1 m 24 s	4.4 s
4-site	15	24	12	75	54	0.53 s	does not exist
2 site F_i	10	12	6	304	48	1.84 s	0.4 s
2 substr.	12	15	8	5088	224	35.68 s	10.36 s
ERK	12	18	9	15040	3432	4 m 4 s	49 s

[Feliu,T., ’23], [T., ’24], [Kaihnsa, T., ’24+]



Allosteric reciprocal enzyme regulation

[Reciprocal enzyme regulation as a source of bistability in covalent modification cycles, Straub, Conradi, '13]

$$S + KL \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} SKL \xrightarrow{\kappa_3} S_p + KL \quad S_p + P \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_pP \xrightarrow{\kappa_6} S + P$$

$$K + L \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} KL \quad P + L \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} PL$$

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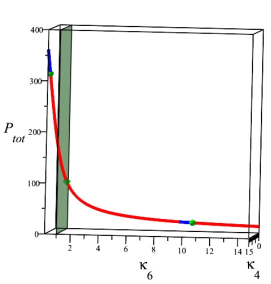

Using the Key Theorem, one can show that $\{(\kappa, c) \mid \kappa_3 = \kappa_6\} \cap \Omega = \emptyset$

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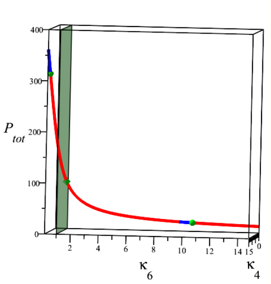
$$\mathrm{S} + \mathrm{KL} \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{SKL} \xrightarrow{\kappa_3} \mathrm{S_p} + \mathrm{KL} \qquad \mathrm{S_p} + \mathrm{P} \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} \mathrm{S_pP} \xrightarrow{\kappa_6} \mathrm{S} + \mathrm{P}$$

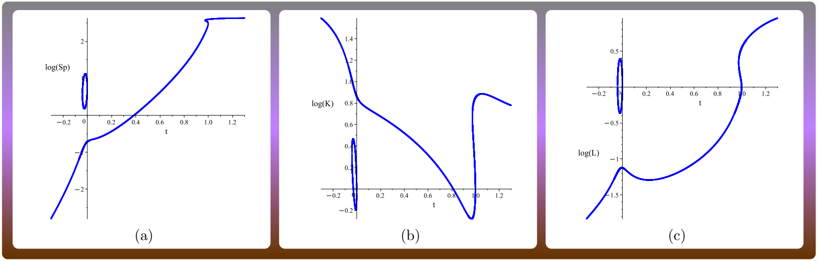
$$\mathrm{K} + \mathrm{L} \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} \mathrm{KL} \qquad \mathrm{P} + \mathrm{L} \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} \mathrm{PL}$$

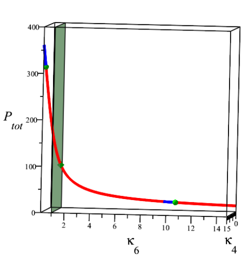


Using the Key Theorem, one can show that $\{(\kappa, c) \mid \kappa_3 = \kappa_6\} \cap \Omega = \emptyset$

$\{(\kappa, c) \mid \kappa_3 < \kappa_6\} \cap \Omega = \emptyset, \qquad \{(\kappa, c) \mid \kappa_3 > \kappa_6\} \cap \Omega = \emptyset$

Allosteric reciprocal enzyme regulation





Plan for today

I. Steady state equations ✔
II. Decomposing the parameter space ✔
- Discriminants ✔
- Cylindrical Algrebraic Decomposition ✔
- Numerical methods ✔

III. Parametrizations ✔
IV. The critical polynomial ✔
- Verifying/Precluding multistationarity ✔
- Connectivity of the multistationarity region ✔

V. Bounds on the number of positive steady states
- Upper bounds
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Vertically parametrized polynomial equation systems

$$\begin{pmatrix} 3\kappa_1 & \kappa_2 & -\kappa_3 & \kappa_4 & -\kappa_5 \\ 5\kappa_1 & \kappa_2 & -2\kappa_3 & \kappa_4 & -\kappa_5 \end{pmatrix} \begin{pmatrix} 1 \\ x^2 \\ y^2 \\ x^2y^2 \\ xy \end{pmatrix}$$

Vertically parametrized polynomial equation systems

$$\begin{pmatrix} 3\kappa_1 & \kappa_2 & -\kappa_3 & \kappa_4 & -\kappa_5 \\ 5\kappa_1 & \kappa_2 & -2\kappa_3 & \kappa_4 & -\kappa_5 \end{pmatrix} \begin{pmatrix} 1 \\ x^2 \\ y^2 \\ x^2y^2 \\ xy \end{pmatrix}$$

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Vertically parametrized polynomial equation systems

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Bézout bound: in $\mathbb{C}^2$ the system has at most

$$\deg(f_1) \cdot \deg(f_2) = 4 \cdot 4 = 16 \text{ solutions}$$

VERTICALLY PARAMETRIZED POLYNOMIAL EQUATION SYSTEMS

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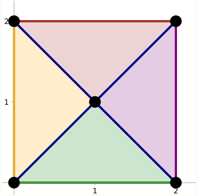
BKK bound: the system has at most
$\mathrm{MV}(\mathrm{Conv}(A), \mathrm{Conv}(A)) = \mathrm{vol}(\mathrm{Conv}(A)) = 8$ solutions in $(\mathbb{C}^*)^2$.



BKK BOUND

The BKK bound has been applied to reaction networks in

- [The steady-state degree and mixed volume of a chemical reaction network, Gross, Hill, '20]

  The n-site phosphorylation network has mixed volume

$$\frac{(n+1)(n+4)}{2} - 1 \qquad .$$

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- [Mixed volumes of networks with binomial steady-states, Coons, Curiel, Gross, '24]

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For generic $\kappa \in \mathbb{C}^5$, the system has
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$4 < 8 = \mathrm{MV}(\mathrm{Conv}(A), \mathrm{Conv}(A)) = \mathrm{vol}(\mathrm{Conv}(A))$ solutions in $(\mathbb{C}^*)^2$.

It is given by a tropical intersection number [Helminck, Ren '22], [Helminck, Henriksson, Ren '24].

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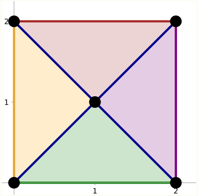
Lower bounds: positively decorated simplices

Let $A \in \mathbb{Z}^{n\times r}$, $N \in \mathbb{R}^{n\times r}$ with $\operatorname{rk} A = \operatorname{rk} N = n \le r$, let $h \in \mathbb{Q}$, $t^h := (t^{h_1}, \ldots, t^{h_r})$ and let Γ_h be a subdivision of the columns of A induced by h.



$h = (0, 0, 0, 0, -1)$

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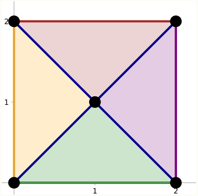
Theorem [Bihan, Santos, Spaenlehauer, '18]

There exists $\varepsilon \in \mathbb{R}_{>0}$ such that for all $t \in (0, \varepsilon)$ the number of positive real solutions of

$$N \operatorname{diag}(t^h) x^A = 0$$

is at least the number of positively decorated n-simplices in Γ_h.



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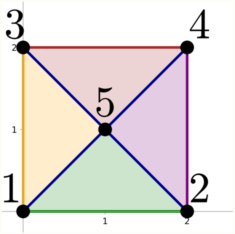
Positively decorated simplices

$$N = \begin{pmatrix} -1 & -1 & 1 & 0 & 0 \\ -2 & 0 & 0 & -1 & 1 \end{pmatrix}, \quad A = \begin{pmatrix} 0 & 2 & 0 & 2 & 1 \\ 0 & 0 & 2 & 2 & 1 \end{pmatrix}$$



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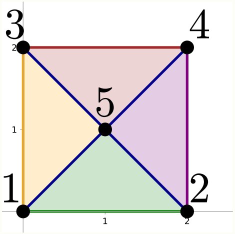
$$N_{\{1,2,5\}} = \begin{pmatrix} -1 & -1 & 0 \\ -2 & 0 & 0 \end{pmatrix}$$



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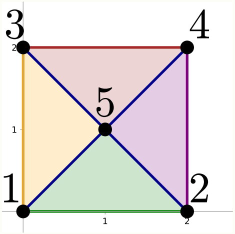

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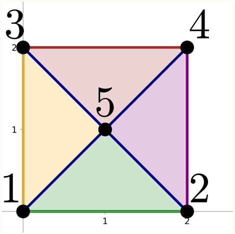

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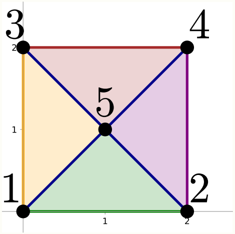

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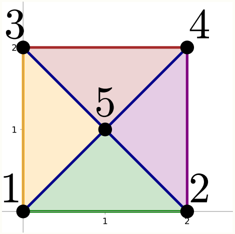
$\implies$ number of positive solutions of $N\,\mathrm{diag}(t^h)x^A = 0$ is at least 1 for $t \in (0, \varepsilon)$



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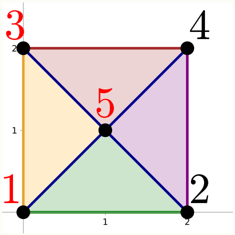
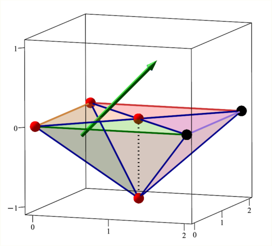
POSITIVE TROPICALIZATION

Proposition [Rose, T., ’24+]

Assume $h \in \mathbb{Q}^r$. Then there is an injective map

$$\Big\{\text{positively decorated } n\text{-simplex in } \Gamma_h\Big\} \to \operatorname{Trop}^+\big(\ker N_{t^h} \cap \operatorname{im} \varphi_A\big)$$





Positive tropicalization

Proposition [Rose, T., '24+]

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For $t > 0$ small enough, the number of positive real solutions of

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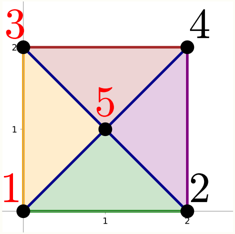

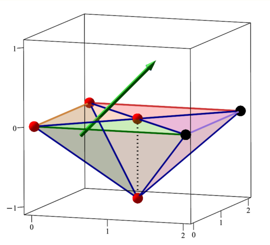

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Thank you for your attention!