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Polyhedral methods for multistationarity

Alicia Dickenstein

Departamento de Matemática, FCEN,
Universidad de Buenos Aires,
and Instituto de Matemática Luis A. Santaló, UBA–CONICET

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Our goal

Describe open parameter regions in the space of constant rates + total amounts where multistationarity occurs.

- Almost all cells in a body have the same genetic information. Multistationarity in cellular networks can be viewed as a rationale for decision making and cell differentiation [Delbrück'49].
- The capacity of multistationarity of biochemical reaction networks for the production of proteins in a cell can produce different *epigenetic* differencies from cell to cell.

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A two–component system

Two-component signal transduction systems enable bacteria to sense, respond, and adapt to a wide range of environments, stressors, and growth conditions. It relies on phosphotransfer reactions.

$$HK_{00} \xrightarrow{k_1} HK_{p0} \xrightarrow{k_2} HK_{0p} \xrightarrow{k_3} HK_{pp}$$

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$$HK_{pp} + Htp \xrightarrow{k_5} HK_{p0} + Htp_p$$

$$Htp_p \xrightarrow{k_6} Htp,$$

$k = (k_1, \ldots, k_6)$ are positive rate constants.

The hybrid histidine kinase HK has two phosphorylable domains: the four possible states of HK are HK_{00}, HK_{P0}, HK_{0P}, HK_{PP}. Htp is the unphosphorylated response regulator protein, Htp_p the phosphorylated form.

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Call $x_1, \ldots, x_6$ the concentration of the species of the network:

$$\begin{aligned} X_1 &\xrightarrow{k_1} X_2 \xrightarrow{k_2} X_3 \xrightarrow{k_3} X_4 \\ X_3 + X_5 &\xrightarrow{k_4} X_1 + X_6 \\ X_4 + X_5 &\xrightarrow{k_5} X_2 + X_6 \\ X_6 &\xrightarrow{k_6} X_5 \end{aligned} \tag{1}$$

Under mass-action kinetics, we get the following dynamical system

$$\frac{dx_1}{dt} = -k_1x_1 + k_4x_3x_5, \qquad \frac{dx_2}{dt} = k_1x_1 - k_2x_2 + k_5x_4x_5,$$

$$\frac{dx_3}{dt} = k_2x_2 - k_3x_3 - k_4x_3x_5, \qquad \frac{dx_4}{dt} = k_3x_3 - k_5x_4x_5,$$

$$\frac{dx_5}{dt} = -k_4x_3x_5 - k_5x_4x_5 + k_6x_6, \qquad \frac{dx_6}{dt} = k_4x_3x_5 + k_5x_4x_5 - k_6x_6.$$

Linear dependencies give conservation relations

From $f_1 + f_2 + f_3 + f_4 = f_5 + f_6 = 0$, we get two conservation relations:

$$x_1 + x_2 + x_3 + x_4 = T_1,$$
$$x_5 + x_6 = T_2.$$

Thus, trajectories lie in a 4d-plane in 6d-space. Total amounts T_1, T_2 are determined by the initial conditions $x(0)$.

This system is multistationary for $k_3 > k_1$.

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Using polyhedral methods

Our problem is to determine values of $(k_1, \ldots, k_6, T_1, T_2)$ in $\mathbb{R}^8_{>0}$ for which the polynomial system

$$f_1(x) = \cdots = f_6(x) = \ell_1(x) - T_1 = \ell_2(x) - T_2 = 0,$$

has more than one positive solution $x \in \mathbb{R}^6_{>0}$.

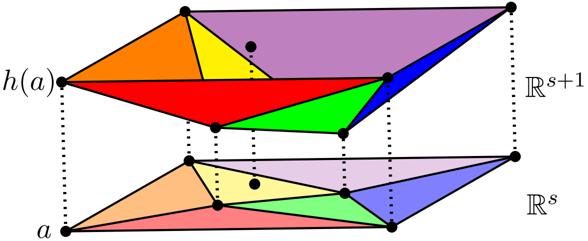
Theorem

Assume that $k_3 > k_1$. *Then,* $k_6\left(\frac{1}{k_2} + \frac{1}{k_3}\right) < k_6\left(\frac{1}{k_1} + \frac{1}{k_2}\right)$ *and for any choice of total concentration constants veriying the inequalities*

$$k_6\left(\frac{1}{k_2} + \frac{1}{k_3}\right) < \frac{T_1}{T_2} < k_6\left(\frac{1}{k_1} + \frac{1}{k_2}\right), \tag{2}$$

there exist positive constants N_1, N_2 *such that for any values of* β_4 *and* β_5 *satisfying* $\beta_4 > N_1$ *and* $\frac{\beta_5}{\beta_4} > N_2$*, the system has at least three positive steady states after modifying only the parameters* k_4, k_5 *via the rescaling* $\overline{k_4} = \beta_4\, k_4$, $\overline{k_5} = \beta_5\, k_5$.

There is a beautiful paper by Bihan, Santos and Spaenlehauer SIAGA'18 which uses regular subdivisions of the (convex hull of the) exponents to get a lower bound on the number of positive solutions, with combinatorial arguments to get new lower bounds in terms of the number s of variables and the difference between the cardinality of the support and s. This is on classical results on degenerations and was used in [Sturmfels'94] to study real roots of complete intersections.



Example

Consider $A = \{(0,0),(2,0),(0,1),$
$(2,1),(1,2),(1,3)\}$,

$$C = \begin{pmatrix} 1 & -2 & 1 & 1 & -1 & 0 \\ -2 & 1 & 0 & -1 & -1 & 1 \end{pmatrix}.$$

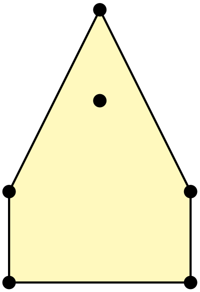
We get the polynomial system

$$\begin{array}{rcl} 1 - 2\,x^2 + y + x^2y - xy^2 & = & 0, \\ -2 + x^2 - x^2y - xy^2 + xy^3 & = & 0, \end{array},$$

which can be written as

$$C \begin{pmatrix} 1 & x^2 & y & x^2y & xy^2 & xy^3 \end{pmatrix}^t = 0.$$

$\mathrm{vol}_{\mathbb{Z}}(A) = 8 < 12 = 3 \cdot 4$



A definition

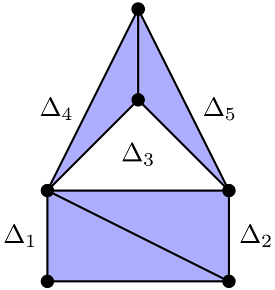
Let C be a $s \times n$ matrix with real entries. We say that an s-simplex $\Delta = \{a_{i_1}, \dots, a_{i_{s+1}}\}$ in A is positively decorated by C if the $s \times (s+1)$ submatrix C_Δ of C with columns indicated by $\{i_1, \dots, i_{s+1}\}$ satisfies the following:

All the coordinates of any non-zero vector in the kernel of the matrix C_Δ are non-zero and have the same sign.

Equivalently, all the values $(-1)^i \text{minor}(C_\Delta, i)$ are nonzero and have the same sign, where $\text{minor}(C_\Delta, i)$ is the determinant of the square matrix obtained by removing the i-th column.

Example

$$f_1 = 1 - 2\,x^2 + y + x^2y - xy^2,$$
$$f_2 = -2 + x^2 - x^2y - xy^2 + xy^3,$$



The simplex Δ_1 is positively decorated by C because the submatrix of C given by the columns of Δ_1

$$\begin{pmatrix} 1 & -2 & 1 \\ -2 & 1 & 0 \end{pmatrix}.$$

has maximal minors with alternating signs $(-1, 2, -3)$. Indeed, Δ_2, Δ_4 and Δ_5 are also positively decorated by C, but not Δ_3.

$\mathbf{f_1 = 0}$, $\mathbf{f_2 = 0}$ have 2 positive solutions but we can scale/ degenerate the coefficients to get a system with at least 4 positive roots.

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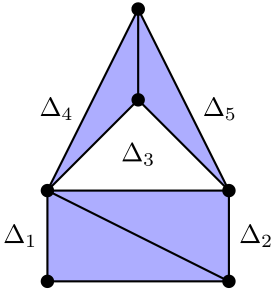

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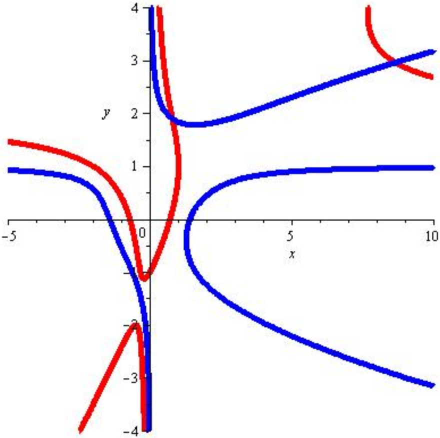
$\mathbf{f_1 = 0}$, $\mathbf{f_2 = 0}$, 2 POSITIVE SOLUTIONS



We can then scale/degenerate the coefficients to get a system with at least 4 positive roots.

Degenerating with one parameter t

If we take $h \in \mathbb{R}^6$ inducing this subdivision, there exists $t_0 \in \mathbb{R}_{>0}$ such that for all $0 < t < t_0$, the number of (nondegenerate) solutions of the following deformed system is at least 4:

$$\begin{aligned} t^{h_1} - t^{h_2} 2x^2 + t^{h_3} y + t^{h_4} x^2 y - t^{h_5} xy^2 &= 0, \\ -t^{h_1} 2 + t^{h_2} x^2 - t^{h_4} x^2 y - t^{h_5} xy^2 + t^{h_6} xy^3 &= 0, \end{aligned}$$

E.g. $h_1 = 1$, $h_2 = 0$, $h_3 = 0$, $h_4 = 0$, $h_5 = 1$, $h_6 = 3$, $t = 1/12$.

The command `firstoct`

- We can check e.g using a symbolic command (like `firstoct` in Singular) or numerically, that there are 4 positive roots. In general, though, the number of positively decorated simplices in a regular subdivision is smaller than the number of positive roots.

```
> LIB "signcond.lib";
> ring r= 0, (x,y), dp;
> ideal i = 1/12-2*x^2+y+x^2*y-(1/12)*x*y^2,
-2*(1/12)+x^2-x^2*y-1/12)*x*y^2+(1/12)^3*x*y^3;
> ideal j = std(i);
> firstoct(j);
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```

- The symbolic procedure [Pedersen-Roy-Szipgrglas '91] is based on the computation of signatures of traces going back to Hermite and it doesn' t work for families (too many branchings).

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Obtaining a region of multistationarity

[Bihan, D., Giaroli, J. Algebra' 20]

Let $A = \{a_1, \ldots, a_n\}$ in $\mathbb{R}^s$ and $C = (c_{i,j}) \in \mathbb{R}^{s \times n}$. Assume there are p n-simplices $\Delta_1, \ldots, \Delta_p$ contained in A, that are part of a regular subdivision of A and positively decorated by C.

Let $\mathcal{C}_{\Delta_1,\ldots,\Delta_p}$ be the cone of all height vectors $h \in \mathbb{R}^n$ that induce a regular subdivision of A containing $\Delta_1, \ldots, \Delta_p$:

$$\mathcal{C}_{\Delta_1,\ldots,\Delta_p} = \{h \in \mathbb{R}^n : \langle m_r, h \rangle > 0,\ r = 1, \ldots, \ell\}. \tag{3}$$

Then, $\forall \varepsilon \in (0,1)^\ell$ there exists $t_0(\varepsilon) > 0$ s.t $\forall \gamma$ in the open set $\mathbf{U}$

$$\mathbf{U} = \cup_{\varepsilon \in (0,1)^\ell} \{\gamma \in \mathbb{R}^n_{>0} \,;\, \gamma^{m_r} < t_0(\varepsilon)^{\varepsilon_r},\ r = 1 \ldots, \ell\},$$

the system

$$\sum_{j=1}^{n} c_{ij}\, \gamma_j\, x^{a_j} = 0, \quad i = 1, \ldots, s, \tag{4}$$

has at least p nondegenerate positive solutions.

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Difficulties we need to overcome

- Even if deciding if simplices are part of a same regular subdivision is algorithmic, how to do this when the dimension or the number of monomials is big (or when they are not upper bounded)?

One way out: If two simplices share a facet, then this is always the case! But this restricts our lower bound to 2... in fact, to 3 if there are no relevant boundary steady states We were able to find more for sequential phosphorylations with n-sites [Giaroli-Rischter-P. Millám-D. '19]

- We get polynomials with non-generic coefficients, which are rational functions of the original rate constants κ and need to assert that we can rescale κ. We heavily use the results about the structure of (s-toric) MESSI systems.

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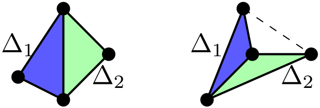

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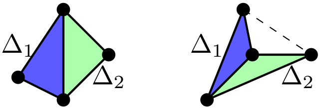

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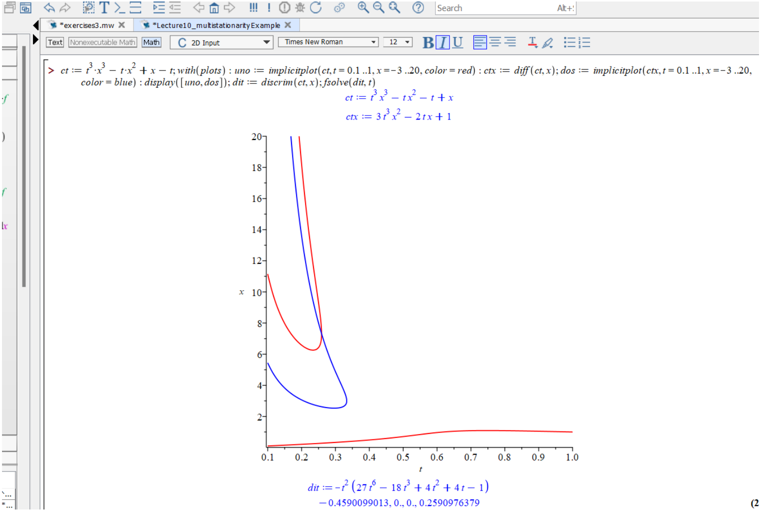
The case $n = 1$ goes back to Newton

Explanation on the blackboard!

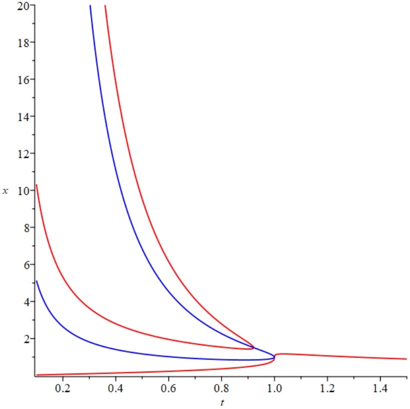


The case $n = 1$ goes back to Newton

$ct3 := t^3 \cdot x^3 - 3 \cdot t \cdot x^2 + 3 \cdot x - t$; with(plots) : uno3 := implicitplot(ct3, t = 0.1 ..1.5, x = −3 ..20, color = red) : ctx3 := diff(ct3, x); dos3 := implicitplot(ctx3, t = 0.1 ..1.5, x = −3 ..20, color = blue) : display([uno3, dos3]); dit3 := discrim(ct3, x); fsolve(dit3, t)

$$ct3 := t^3 x^3 - 3 t x^2 - t + 3 x$$

$$ctx3 := 3 t^3 x^2 - 6 t x + 3$$



$$dit3 := -27 t^2 \left(t^6 - 6 t^3 + 4 t^2 + 4 t - 3\right)$$

$$-0.8187057148, 0., 0., 0.9223015953, 1., 1. \qquad (28)$$

Proof for the two component system

- From $f_2 = f_3 = f_4 = f_5 = 0$ we get:

$$x_1 = \frac{k_4k_5x_4x_5^2}{k_1k_3},\ x_2 = \frac{k_4k_5x_4x_5^2}{k_2k_3} + \frac{k_5x_4x_5}{k_2},\ x_3 = \frac{k_5x_4x_5}{k_3},\ x_6 = \frac{k_4k_5x_4x_5^2}{k_3k_6}$$

- We get the equations:

$$\frac{k_4k_5x_4x_5^2}{k_1k_3} + \frac{k_4k_5x_4x_5^2}{k_2k_3} + \frac{k_5x_4x_5}{k_2} + \frac{k_5x_4x_5}{k_3} + x_4 - T_1 = 0,$$

$$x_5 + \frac{k_4k_5x_4x_5^2}{k_3k_6} + \frac{k_5x_4x_5}{k_6} - T_2 = 0.$$

- We can write this system as

$$C \begin{pmatrix} x_4 & x_5 & x_4x_5 & x_4x_5^2 & 1 \end{pmatrix}^t = 0,$$

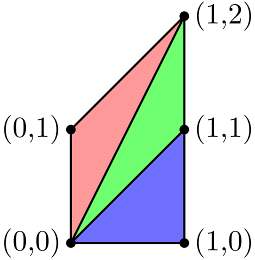
$$C = \begin{pmatrix} 1 & 0 & C_{13} & C_{14} & -T_1 \\ 0 & 1 & C_{23} & C_{24} & -T_2 \end{pmatrix},$$

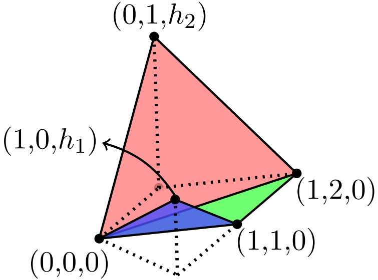
and $C_{13} = k_5\left(\frac{1}{k_2} + \frac{1}{k_3}\right)$, $C_{14} = \frac{k_4k_5}{k_3}\left(\frac{1}{k_1} + \frac{1}{k_2}\right)$, $C_{23} = \frac{k_5}{k_6}$, $C_{24} = \frac{k_4k_5}{k_3k_6}$.

If we order the variables (x_4, x_5), the support of this system is:

$$\mathcal{A} = \{(1,0),(0,1),(1,1),(1,2),(0,0)\}.$$

We depict the 2-simplices $\Delta_1 = \{(1,0),(1,1),(0,0)\}$, $\Delta_2 = \{(1,1),(1,2),(0,0)\}$ and $\Delta_3 = \{(0,1),(1,2),(0,0)\}$, which form a regular triangulation of $\mathcal{A}$, associated for instance with any height function $h : \mathcal{A} \to \mathbb{R}$ satisfying $h(1,0) = h_1, h(0,1) = h_2$, $h(1,1) = 0$, $h(1,2) = 0$, and $h(0,0) = 0$, with $h_1, h_2 > 0$.





- Δ_1 is pos. decorated by C if and only if

$$T_1\, k_2\, k_3 - T_2\, k_2\, k_6 - T_2\, k_3\, k_6 > 0,$$

and Δ_3 is pos. decorated by C if and only if

$$T_1\, k_1\, k_2 - T_2\, k_1\, k_6 - T_2\, k_2\, k_6 < 0.$$

- If both conditions hold, then Δ_2 is also positively decorated by C if and only if $k_1 < k_3$. So, the three simplices are positively decorated by C under the validity of condition in our statement.

- Assume both inequalities hold. Then, there exists $t_0 \in \mathbb{R}_{>0}$ such that for all $0 < t < t_0$,

$$\begin{aligned} t^{h_1} x_4 + C_{13}\, x_4 x_5 + C_{14}\, x_4 x_5^2 - T_1 &= 0, \\ t^{h_2} x_5 + C_{23}\, x_4 x_5 + C_{24}\, x_4 x_5^2 - T_2 &= 0, \end{aligned}$$

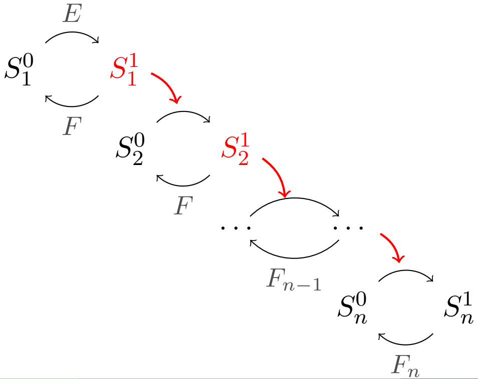
has at least three positive nondegenerate solutions.

- Then, we need to find a scaling in terms of the coefficients of this system and finally prove that this can achieved by properly scaling the original coefficients (k, T). We use the MESSI structure for this.

Cascade with n tiers

How many variables?

There are $s \leq n-1$ phosphatases with any pattern of repetition (or not), but the first two are equal. The number of variables is of the order of 4n and the number of conservation relations is of the order of 2n, so both dimension and codimension of the steady state variety tend to ∞ with n.



Cascade with n tiers

Multistationarity parameters for any value of n

$$
\begin{aligned}
\alpha_1 =& \frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}} F_{tot} - S_{1,tot} \\
\alpha_2 =& (\frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} + 1) F_{tot} - S_{1,tot} \\
\alpha_3 =& \frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} \frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}} F_{tot} + (\frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} + 1 - \frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}}) E_{tot} - \frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} S_{1,tot} \\
\alpha_4 =& (\frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} + 1)(\frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}} + 1) F_{tot} + (\frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}} - \frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} - 1) S_{2,tot} - (\frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}} + 1) S_{1,tot}
\end{aligned}
$$

Assume one of the following sets of inequalities occurs:

$$
\frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} + 1 > \frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}}, \; \alpha_1, \alpha_4 < 0, \alpha_2, \alpha_3 > 0,
$$

$$
\frac{\ell_{\mathrm{cat}_1}}{k_{\mathrm{cat}_1}} + 1 < \frac{\ell_{\mathrm{cat}_2}}{k_{\mathrm{cat}_2}}, \; \alpha_1, \alpha_4 > 0, \alpha_2, \alpha_3 < 0.
$$

Then, we are able to find (for any n) conditions on some of the remaining rate constants for which multistationarity occurs.

Comments

- The number of conserved quantities is increased at each tier.
- Proof has several steps: we first parametrize the steady state variety using results about MESSI systems, we get a system which is sparse but the new constants are (explicit) rational functions on the given rate constants (not generic and many times, too many of them positive), we then identify two simplices that share a facet for any value of n, we use the previous theorem to describe an open set in this new set of constants, and then we lift the conditions to the original constants.

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Multistationarity for sequential phosphorylations

Wang and Sontag (2008) showed that for certain choices of parameters, the system can have $2[\frac{n}{2}] + 1 = n$ for n odd, $n + 1$ for n even stoichiometrically compatible positive steady states.

Feliu, Rendall and Wiuf (2019) showed that "half" of them can be stable for certain parameters. Evidence had been given by Thomson and Gunawardena (2009).

Conradi, Feliu, Mincheva and Wiuf (2017) gave conditions on the reaction rate constants to guarantee or preclude multistationarity (≥ 3) based on degree theory.

Conradi and Mincheva (2014) gave a sufficient multistationarity condition on the reaction rate constants for $n = 2$. Total amounts are given in a precise implicit form, so as many witnesses as wished can be constructed.

We give open parameter regions in the space of all parameters with $2[\frac{n}{2}] + 1$ sc pss, while assuming in the modeling that roughly only $\frac{1}{4}$ of the intermediates occur, but only one suffices!

We also describe how to implement these tools to search for multistationarity regions in a computer algebra system and present some computer aided results for $n \leq 5$.

The method is systematic and can be applied to other networks.

We don't expect that any reduction/degeneration method could get the conjectured upper bound $2n - 1$.

A sample computational results

$n = 4$

Assume $S_{tot} > E_{tot} + F_{tot}$. If the rate constants and total concentrations are in one of the regions described below

1. $\frac{k_{\text{cat}_2}}{\ell_{\text{cat}_2}} < \frac{F_{tot}}{E_{tot}} < \min\left\{\frac{k_{\text{cat}_1}}{\ell_{\text{cat}_1}}, \frac{k_{\text{cat}_3}}{\ell_{\text{cat}_3}}\right\}$,
2. $\frac{k_{\text{cat}_0}}{\ell_{\text{cat}_0}} < \frac{F_{tot}}{E_{tot}} < \min\left\{\frac{k_{\text{cat}_1}}{\ell_{\text{cat}_1}}, \frac{k_{\text{cat}_3}}{\ell_{\text{cat}_3}}\right\}$,
3. $\max\left\{\frac{k_{\text{cat}_0}}{\ell_{\text{cat}_0}}, \frac{k_{\text{cat}_2}}{\ell_{\text{cat}_2}}\right\} < \frac{F_{tot}}{E_{tot}} < \frac{k_{\text{cat}_3}}{\ell_{\text{cat}_3}}$,
4. $\max\left\{\frac{k_{\text{cat}_0}}{\ell_{\text{cat}_0}}, \frac{k_{\text{cat}_2}}{\ell_{\text{cat}_2}}\right\} < \frac{F_{tot}}{E_{tot}} < \frac{k_{\text{cat}_1}}{\ell_{\text{cat}_1}}$,

then after rescaling of the k_{on}'s and ℓ_{on}'s the distributive sequential 4-site phosphorylation system has at least 5 steady states.