Multistationarity and structure in enzymatic networks

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Workshop: S24 - Symbolic Computation: Theory, Algorithms and Applications

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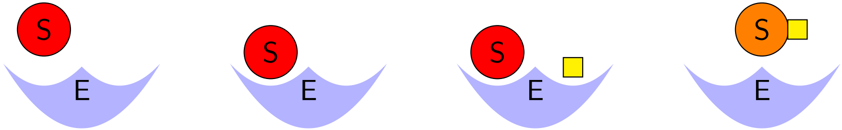
Summary

Enzymatic reactions

$$S_0 \xrightarrow{E} S_1$$



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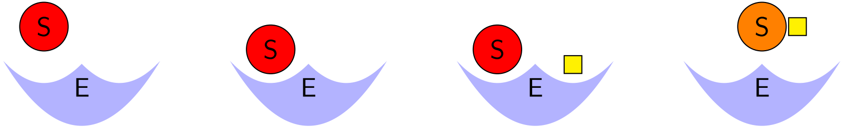
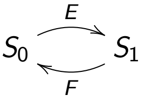




$$E + S_0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} ES_0 \xrightarrow{\kappa_3} E + S_1$$

$$F + S_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftarrows}} FS_1 \xrightarrow{\kappa_6} F + S_0$$

The system

Species:	S_0	S_1	E	F	ES_0	FS_1
Concentrations:	x_1	x_2	x_3	x_4	x_5	x_6

Under mass-action kynetics:

$$\dot{x}_1 = -\kappa_1 x_1 x_3 + \kappa_2 x_5 + \kappa_6 x_6 \qquad \dot{x}_4 = -\kappa_4 x_2 x_4 + (\kappa_5 + \kappa_6) x_6$$
$$\dot{x}_2 = -\kappa_4 x_2 x_4 + \kappa_5 x_6 + \kappa_3 x_5 \qquad \dot{x}_5 = \kappa_1 x_1 x_3 - (\kappa_2 + \kappa_3) x_5$$
$$\dot{x}_3 = -\kappa_1 x_1 x_3 + (\kappa_2 + \kappa_3) x_5 \qquad \dot{x}_6 = \kappa_4 x_2 x_4 - (\kappa_5 + \kappa_6) x_6$$

Conservation laws:

$$\begin{aligned} x_1 + x_2 + x_5 + x_6 &= c_S, \\ x_3 + x_5 &= c_E, \\ x_4 + x_6 &= c_F, \end{aligned} \qquad \leftrightsquigarrow \qquad W \cdot x = c$$

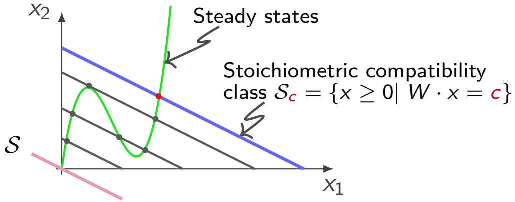
We call $\mathcal{S} = \{(x_1, \ldots, x_6) | \; W \cdot x = 0\}$ the *stoichiometric subspace.*

Multistationarity

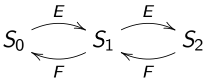
We consider the system with conservation laws:

$$\begin{cases} \dot{x}_i = f_{\kappa,i}(x_1, \ldots, x_s), \; i = 1, \ldots, s, \\ W \cdot x = c. \end{cases}$$

- Given reaction constants $\kappa > 0$, $x^* \in \mathbb{R}^s_{\geq 0}$ is a steady state if $f_\kappa(x^*) = 0$.
- If there exist reaction constants $\kappa > 0$ and conservation constants c, with **two or more** steady states such that $W \cdot x = c$, we say the systems exhibits multistationarity.



Intermediates



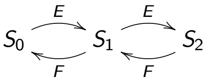
$$E + S_0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} ES_0 \xrightarrow{\kappa_3} E + S_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftarrows}} ES_1 \xrightarrow{\kappa_6} E + S_2$$

$$F + S_2 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftarrows}} FS_2 \xrightarrow{\kappa_9} F + S_1 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftarrows}} FS_1 \xrightarrow{\kappa_{12}} F + S_0$$

Question:

Which intermediate complexes are necessary to gain multistationarity?

Intermediates



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- We prove this system (and many other *frequent* systems) *without* any intermediates is (are) monostationary. By visually inspecting associated digraphs.

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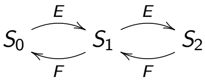

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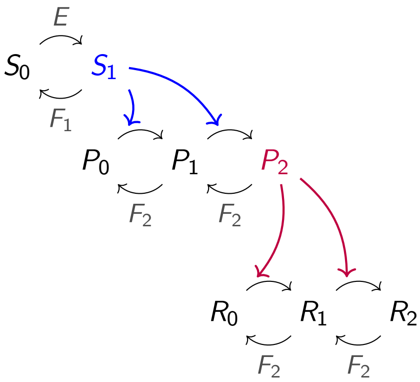
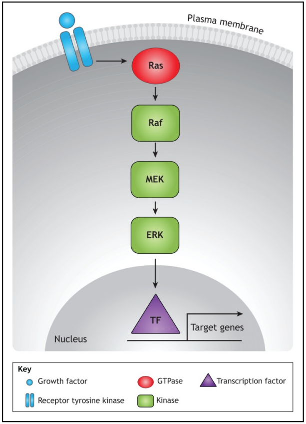
Question:

Which intermediate complexes are necessary to gain multistationarity?

- We prove this system (and many other *frequent* systems) *without* any intermediates is (are) monostationary. By visually inspecting associated digraphs.
- These are *MESSI* systems [PM-Dickenstein '18]: *Modifications of type Enzyme-Substrate or Swap with Intermediates*. In these systems there is a *partition* of the set of species and only *certain* reactions can occur.

Example: Three-layer cascade





The extracellular signal-regulated kinase (ERK) pathway leads to activation of the effector molecule ERK, which controls downstream responses by phosphorylating a variety of substrates, including transcription factors. (*Outstanding questions in developmental ERK signaling*, A. L. Patel, S. Y. Shvartsman, Development (2018), 145(14): dev143818.)

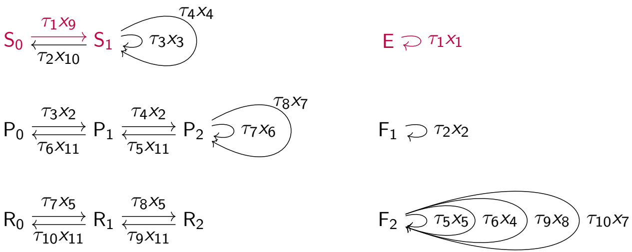
Monostationary MESSI (Dickenstein-Giaroli-PM-Rischter '21):

Let G be MESSI and [hypotheses: see example]. Then, the system is *monostationary*.

Three-layer cascade without intermediates: G without intermediates ✓

$$S_0 + E \xrightarrow{\tau_1} S_1 + E, \quad S_1 + F_1 \xrightarrow{\tau_2} S_0 + F_1$$
$$P_0 + S_1 \xrightarrow{\tau_3} P_1 + S_1 \xrightarrow{\tau_4} P_2 + S_1, \quad P_2 + F_2 \xrightarrow{\tau_5} P_1 + F_2 \xrightarrow{\tau_6} P_0 + F_2$$
$$R_0 + P_2 \xrightarrow{\tau_7} R_1 + P_2 \xrightarrow{\tau_8} R_2 + P_2, \quad R_2 + F_2 \xrightarrow{\tau_9} R_1 + F_2 \xrightarrow{\tau_{10}} R_0 + F_2.$$

MG_2 without parallel edges between $\neq$ nodes ✓:



G_2° connected by ! simple paths ✓:

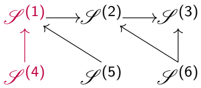
$$S_0 \underset{\tau_2 x_{10}}{\overset{\tau_1 x_9}{\rightleftarrows}} S_1$$

$$P_0 \underset{\tau_6 x_{11}}{\overset{\tau_3 x_2}{\rightleftarrows}} P_1 \underset{\tau_5 x_{11}}{\overset{\tau_4 x_2}{\rightleftarrows}} P_2$$

$$R_0 \underset{\tau_{10} x_{11}}{\overset{\tau_7 x_5}{\rightleftarrows}} R_1 \underset{\tau_9 x_{11}}{\overset{\tau_8 x_5}{\rightleftarrows}} R_2$$

(† the underlying undirected graph is a forest ✓)

G_E without directed cycles ✓:



with
$\mathscr{S}^{(1)} = \{S_0, S_1\}$
$\mathscr{S}^{(2)} = \{P_0, P_1, P_2\}$
$\mathscr{S}^{(3)} = \{R_0, R_1, R_2\}$
$\mathscr{S}^{(4)} = \{E\}$, $\mathscr{S}^{(5)} = \{F_1\}$, $\mathscr{S}^{(6)} = \{F_2\}$.

Linearly binomial MESSI networks and extensions (Dickenstein-Giaroli-PM-Rischter '21):

If moreover †, then G and any canonical extension G_C of G are *linearly binomial networks*.

Linearly binomial systems

Idea:

They are such that the polynomial system of equations $f_\kappa(x) = 0$ is equivalent, via linear operations, to a binomial system.

Formally: If there exist binomials $\bar{h}_{j_1}, \bar{h}_{j_2}, \ldots, \bar{h}_{j_{s-d}}$ and a matrix $M(\kappa)$ defined $\forall \kappa > 0$, such that $\det M(\kappa) > 0$, and

$$(\bar{h}_{j_1}, \bar{h}_{j_2}, \ldots, \bar{h}_{j_{s-d}})^\top \quad := \quad M(\kappa)\ (f_{j_1}, f_{j_2}, \ldots, f_{j_{s-d}})^\top\ ,$$

we can consider the *augmented system* $h_{c,a}$:

$$h_{c,a}(x)_i = \begin{cases} \bar{h}_{j_t} = x^{\gamma_t} - a_t \cdot x^{\delta_t} & \text{if } i \ = \ j_t \in \{j_1, j_2, \ldots, j_{s-d}\}, \\ (Wx - c)_t & \text{otherwise.} \end{cases}$$

Which intermediates are necessary for multistationarity?

- This question was addressed in [Sadeghimanesh-Feliu '19], where they coined the expression *circuits of multistationarity* to name the *minimal* sets of intermediate complexes with which the system has the capacity for multistationarity.

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- For linearly binomial networks we implemented in Maple their criterion by means of an equivalent formulation with a critical function [Dickenstein-PM-Shiu-Tang '19] (based on degree theory; see [Conradi-Feliu-Mincheva-Wiuf '17]) to obtain the minimal subsets of intermediates that guarantee multistationarity.

In [Dickenstein-PM-Shiu-Tang '19]:

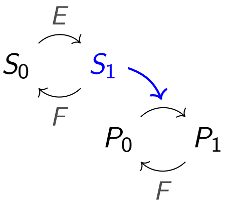
$$C(x) \;:=\; (\det \mathrm{Jac}(h))\,\big|_{a=\frac{x^\gamma}{x^\delta}} \underset{\substack{\text{linearly}\\ \text{binomial}\\ \text{system}}}{=} \frac{x^\alpha}{x^\beta} \cdot B(x)\ ,$$

with $B(x)$ a homogeneous polynomial *only on the* x *variables* of degree $s - \dim(\mathcal{S})$, and all its monomials have exponents in $\{0,1\}^s$.

Then, if G conservative $+$ no relevant boundary steady states:

- **Multistationarity:** if and only if $B(x)$ has a coefficient with sign $(-1)^{\dim(\mathcal{S})+1}$.
- Every $x^* \in \mathbb{R}^s_{>0}$ with $\mathrm{sign}(B(x^*)) = (-1)^{\dim(\mathcal{S})+1}$ gives a witness to multistationarity (technical).

Example



We analyzed

$$C(x) = \frac{x_3 x_{10}}{x_4 x_8} B(x),$$

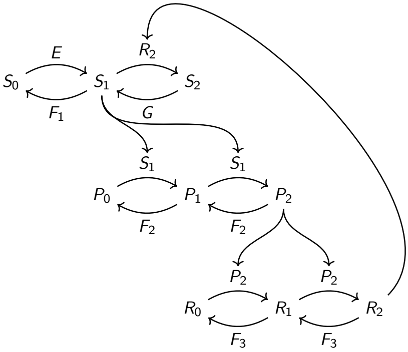
with $B(x) = x_1x_{10}x_2x_5 + x_1x_{10}x_2x_6 + x_1x_{10}x_2x_7 + x_1x_{10}x_2x_8 + x_1x_{10}x_5x_9 + x_1x_{10}x_6x_9 + x_1x_{10}x_7x_9 + x_1x_{10}x_8x_9 \underline{- x_1x_2x_5x_8} + x_1x_2x_7x_8 \underline{- x_1x_5x_8x_9} + x_1x_7x_8x_9 + x_{10}x_2x_5x_9 + x_{10}x_2x_6x_9 + x_{10}x_2x_7x_9 + x_{10}x_2x_8x_9 + x_{10}x_3x_5x_9 + x_{10}x_3x_6x_9 + x_{10}x_3x_7x_9 + x_{10}x_3x_8x_9 + x_{10}x_4x_5x_9 + x_{10}x_4x_6x_9 + x_{10}x_4x_7x_9 + x_{10}x_4x_8x_9 + x_{10}x_5x_6x_9 \underline{- x_2x_5x_8x_9} + x_2x_7x_8x_9 + x_3x_4x_5x_9 + x_3x_4x_6x_9 + x_3x_4x_7x_9 + x_3x_4x_8x_9 + x_3x_7x_8x_9 + x_4x_5x_6x_9 \underline{- x_4x_5x_8x_9 - x_4x_6x_7x_9} + x_4x_7x_8x_9$.

Sets of intermediate complexes: $\{x_2, x_8\}$, $\underline{\{x_8\}}$, $\{x_4, x_8\}$, $\underline{\{x_4, x_6\}}$.

Determine the *circuits of multistationarity*

We also computed

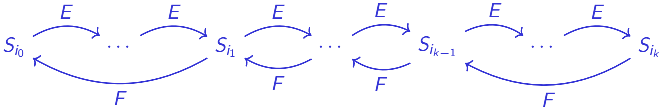
- We computed the circuits of multistationarity for the 3-layer cascade and for the following version with retroactivity.
- Note that the number of variables is greater than 20 and the number of parameters is greater than 35.



Signaling cascade with feedback loop

The sequential but not distributive phosphorylation/dephosphorylation cycle (Dickenstein, Giaroli, PM, Rischter '21):

G_I with $I = \{i_0 = 0 < i_1 < \cdots < i_k = n\}$:

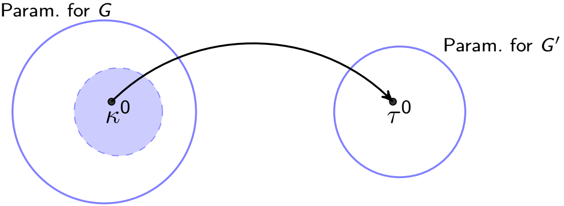


The canonical circuits of multistationarity of G_I are

$$\{S_0+E\}, \{S_1+E\}, \ldots, \{S_{i_{k-1}-1}+E\}, \{S_{i_2}+F\}, \{S_{i_3}+F\}, \ldots \{S_{i_k}+F\}.$$

That means that every complex but $S_{i_{k-1}}+E, S_{i_{k-1}+1}+E, \ldots, S_n+E, S_{i_0}+F$ and $S_{i_1}+F$ is a canonical circuit of multistationarity and these are the only ones.

Regions for lifting of multistationarity (Dickenstein-Giaroli-PM-Rischter '21, based on Feliu-Wiuf '13):



Consider $\mathcal{F}_{\tau_0} = \{\kappa > 0 \,:\, \tau(\kappa) = \tau^0\}$ and the sets $\mathcal{W}_\varepsilon = \{\kappa > 0 \,:\, \mu_{i,y}(\kappa) < \varepsilon \; \forall y \in \mathscr{C}_{G'},\, i = 1, \ldots, p\}$ for $\varepsilon > 0$. Then,

1. $\mathcal{F}_{\tau_0,\varepsilon} := \mathcal{F}_{\tau_0} \cap \mathcal{W}_\varepsilon$ is a nonempty open set $\forall \varepsilon > 0$.
2. If G' has m nondegenerate positive steady states in $\mathcal{S}_{c'}$, there exists $\varepsilon_0 > 0$ s.t. $\forall \kappa \in \mathcal{F}_{\tau_0,\varepsilon}$, with $0 < \varepsilon < \varepsilon_0$, there are at least m nondegenerate positive steady states of G in $\mathcal{S}_c$. (And more technical details.)

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Thanks for you attention!

(And for organizing this session, and for the invitation!)