Algebraic methods for the study of biochemical reaction networks

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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.

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

$$HK_{0p} + RR \xrightarrow{k_4} HK_{00} + RR_p$$

$$HK_{pp} + RR \xrightarrow{k_5} HK_{p0} + RR_p$$

$$RR_p \xrightarrow{k_6} RR,$$

$k = (k_1, \ldots, k_6)$ 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}. RR is the unphosphorylated response regulator protein, RR_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

$$\begin{aligned} \frac{dx_1}{dt} &= -k_1 x_1 + k_4 x_3 x_5, & \frac{dx_2}{dt} &= k_1 x_1 - k_2 x_2 + k_5 x_4 x_5, \\ \frac{dx_3}{dt} &= k_2 x_2 - k_3 x_3 - k_4 x_3 x_5, & \frac{dx_4}{dt} &= k_3 x_3 - k_5 x_4 x_5, \\ \frac{dx_5}{dt} &= -k_4 x_3 x_5 - k_5 x_4 x_5 + k_6 x_6, & \frac{dx_6}{dt} &= k_4 x_3 x_5 + k_5 x_4 x_5 - k_6 x_6. \end{aligned}$$

$$\frac{dx_1}{dt} = f_1(x) = -k_1x_1 + k_4x_3x_5, \qquad \frac{dx_2}{dt} = f_2(x) = k_1x_1 - k_2x_2 + k_5x_4x_5,$$
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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 $x(0)$.

$$\frac{dx_1}{dt} = f_1(x) = -k_1x_1 + k_4x_3x_5, \qquad \frac{dx_2}{dt} = f_2(x) = k_1x_1 - k_2x_2 + k_5x_4x_5,$$
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CRN with mass-action kinetics

- Starting data: a set of r reactions (labeled edges, e.g. $i \overset{\kappa_{ij}}{\to} j$, where $\kappa_{ij} \in \mathbb{R}_{>0}$ are the reaction rate constants) between m complexes (monomials e.g. $x^{y_i} = x_1^{y_{i1}} x_2^{y_{i2}} \cdots x_s^{y_{is}}$) composed of s species (variables $x_1, \ldots, x_s$).
- **Definition:** A *chemical reaction network* is a finite directed graph $G = (V, E, (\kappa_{ij})_{(i,j)\in E}, (y_i)_{i=1,\ldots,m})$ whose vertices are labeled by complexes and whose edges are labeled by parameters.

$$\begin{aligned} X_1 &\xrightarrow{k_1} X_2 \xrightarrow{k_2} X_3 \xrightarrow{k_3} X_4 \\ X_3 + X_5 &\xrightarrow{k_4} X_1 + X_6 \\ X_4 + X_5 &\xrightarrow{k_5} X_2 + X_6 \\ X_6 &\xrightarrow{k_6} X_5 \end{aligned} \tag{2}$$

6 reactions (arrows), 10 complexes (nodes), 6 species

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- View the concentrations $x_1, x_2, \dots, x_s$ as *functions of time*.
- *Mass-action kinetics* specified by the network G is the following autonomous system of ordinary differential equations:

$$\frac{dx}{dt} = \sum_{(i,j)\in E} \kappa_{i,j}\, x^{y_i}\, (y_j - y_i). \tag{3}$$

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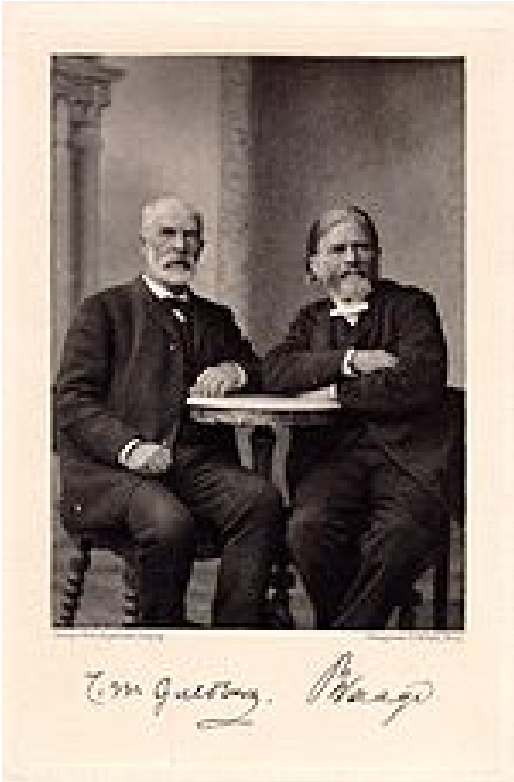
Law of Mass Action

Proposed by Cato Guldberg (1836–1902) (chemist) and Peter Waage (1833-1900) (mathematician).



Waage was a chemist and Guldberg was a mathematician. They were close friends and brothers in law. Waage's second wife was Guldberg's sister and they are Ragni Piene's great grandparents!
Published in Norwegian in 1862, in French in 1867, and in German around 1880, until it was recognized (in the meantime, it was rediscovered by van't Hoff.)

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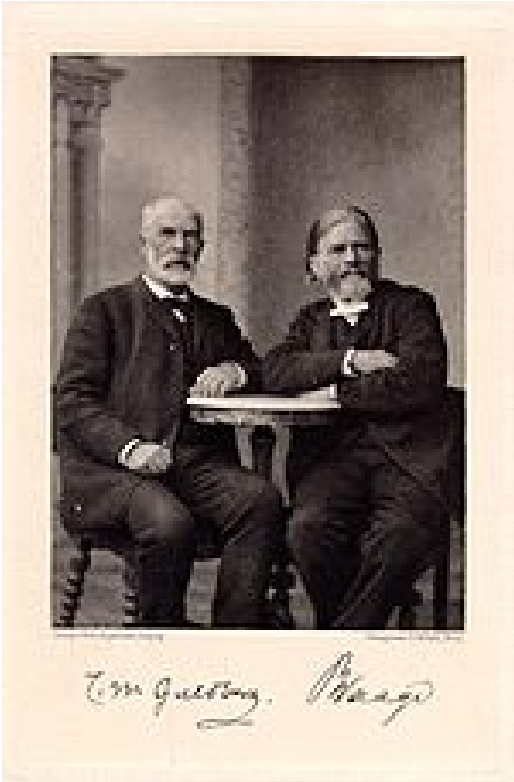

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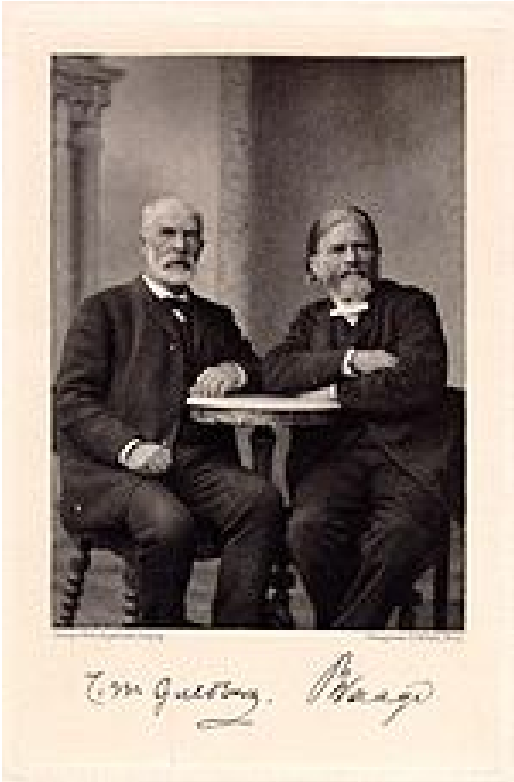

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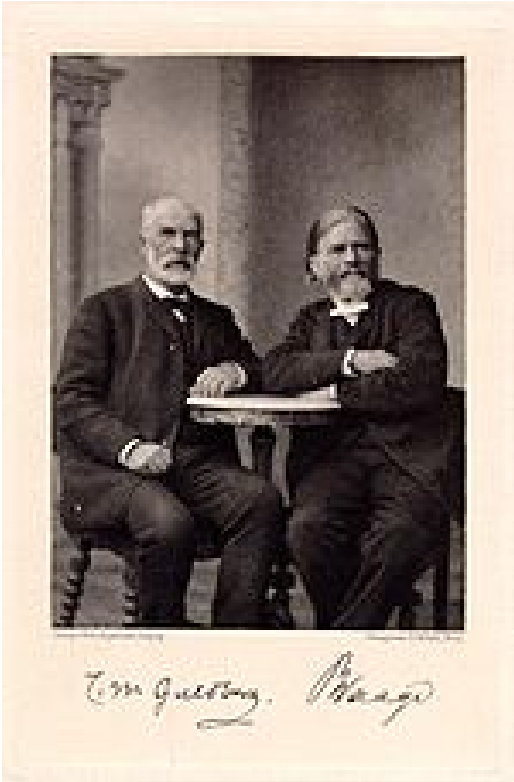

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Observations

$$\frac{dx}{dt} = \sum_{(i,j)\in E} \kappa_{i,j}\, x^{y_i}\, (y_j - y_i)$$

$$\frac{dx_k}{dt} = f_k(x),\ k = 1, \ldots, s, \qquad (4)$$

- $f_1, \ldots, f_s$ are polynomials in $\mathbb{R}[x_1, \ldots, x_s]$.
- Linear relations among the vectors $y_j - y_i$ give raise to linear conservation relations. Total amounts are determined by the initial conditions.
- By the form of the equations the (closed or open) positive orthant is forward invariant for the dynamics.
- In general, the rate constants $\kappa_{i,j}$ are unknown (difficult or impossible to be determined).

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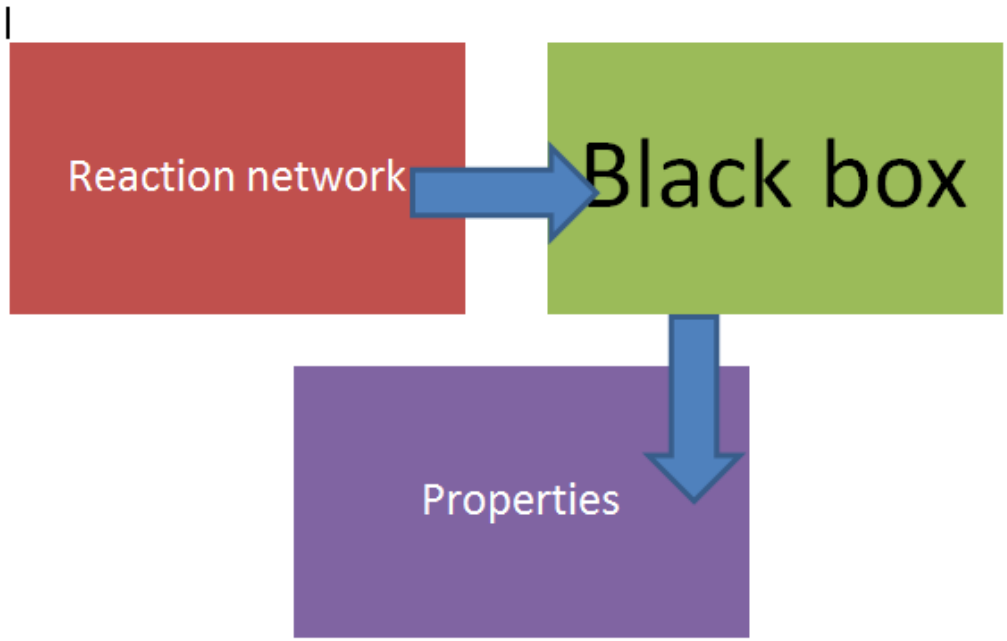
General goal

Analize mathematical models arising from biochemical reaction networks, formalize and make sense of biologist's intuitions, and make predictions from the structure of the network.



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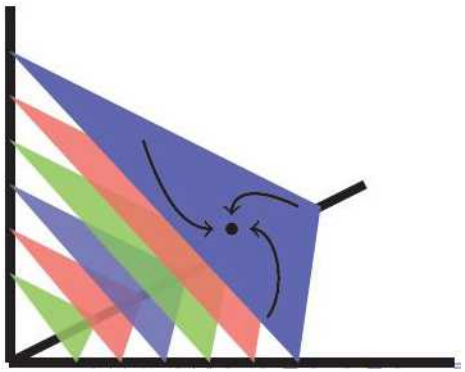
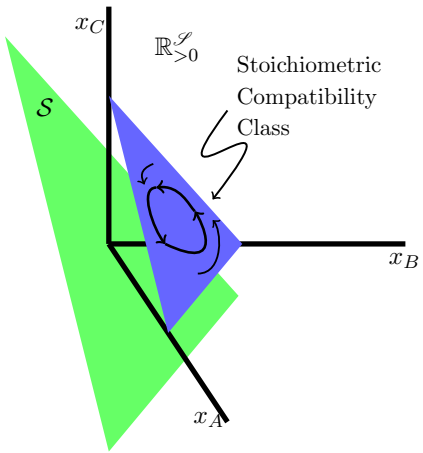
A chemical reaction system exhibits multiestationarity if it is possible to find more than one positive steady state in the same stoichiometric compatibility class = with the same total constants.





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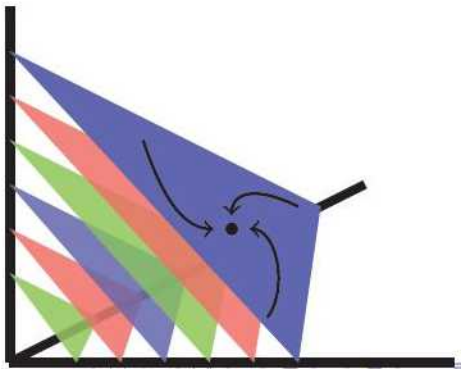
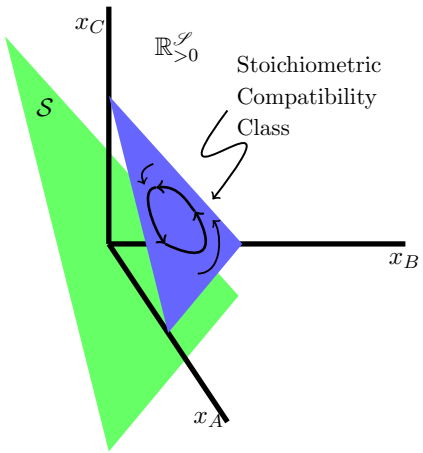
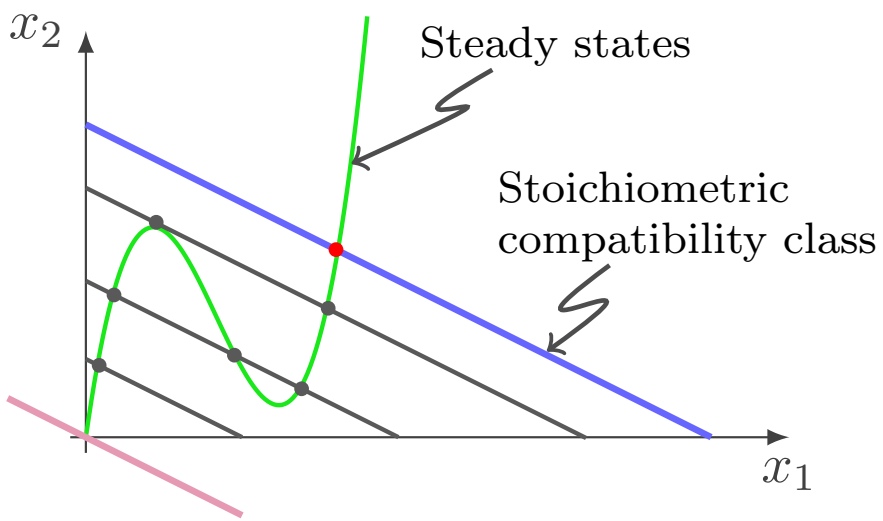




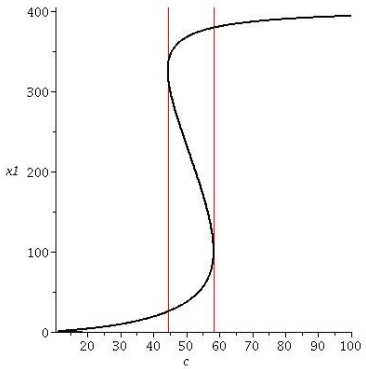
$$dx/dt = f(x)$$

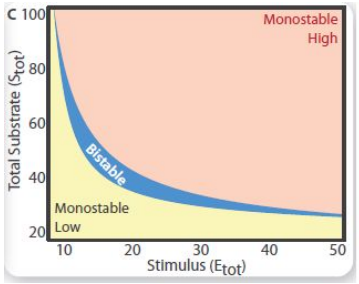
The green curve represents the steady states $f = 0$

The number of intersection points depends on the total constants

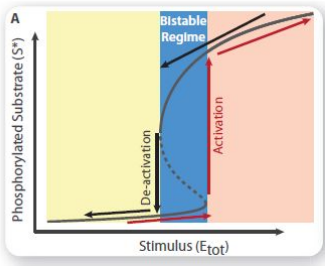


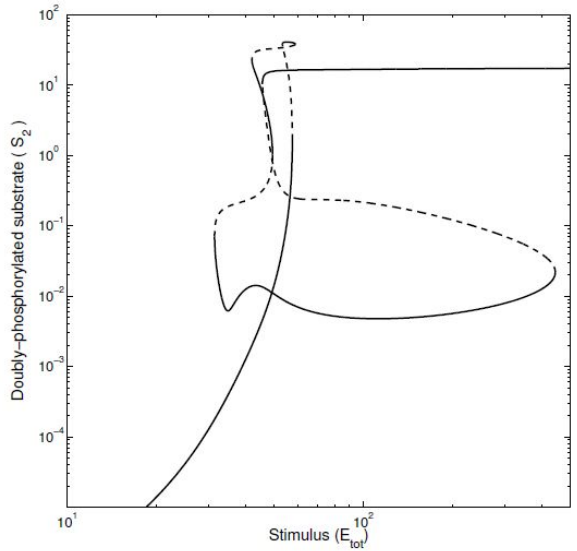
Usual multistationarity pictures



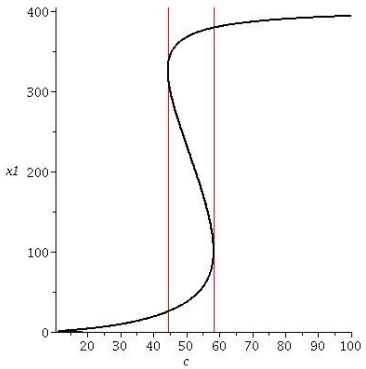


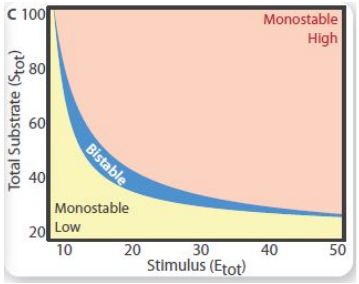
More complex:





Usual multistationarity pictures





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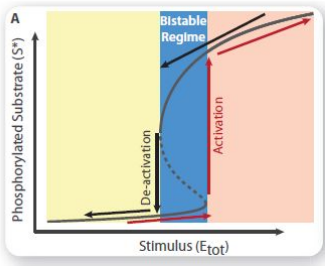

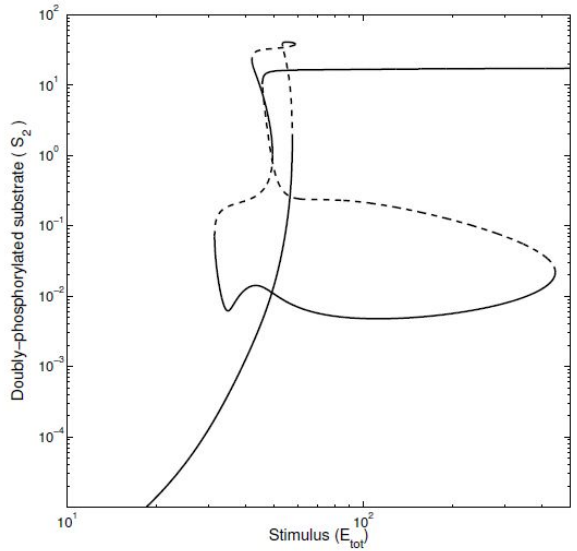

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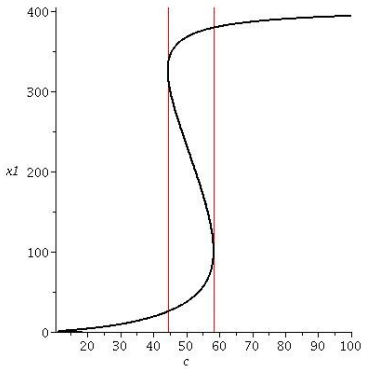

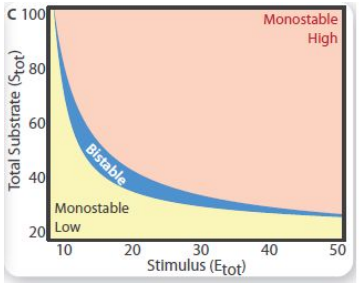

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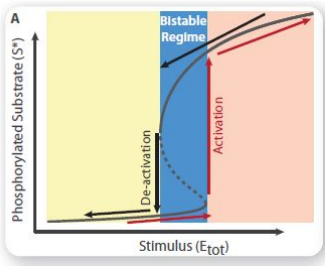

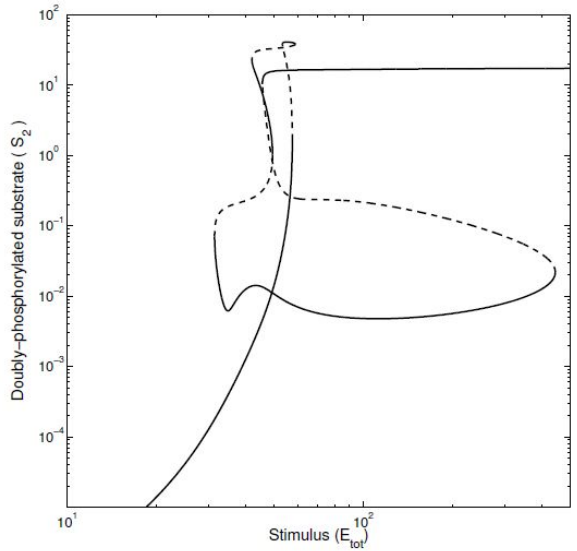

Why studying multistationarity?

- 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].
- [Ferrell '09]: Current state of systems biology is like planetary astronomy science before Kepler and Newton and cannot be studied without math and physics.
- Although all biological processes are complex and involve many variables, essential qualitative features of these processes can usually be understood in terms of a small number of crucial variables.
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Phosho-Dephosphorylation: "futile" cycle

$$S_0 + E \underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftarrows}} ES_0 \overset{k_{\text{cat}}}{\to} S_1 + E$$

$$S_1 + F \underset{\ell_{\text{off}}}{\overset{\ell_{\text{on}}}{\rightleftarrows}} FS_1 \overset{\ell_{\text{cat}}}{\to} S_0 + F$$

E and F *enzymes*, S_0 and S_1 *substrates*, S_0E and S_1F *intermediates*

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Two sequential phosphorylations

$$S_0 + E \underset{k_{\mathrm{off}_0}}{\overset{k_{\mathrm{on}_0}}{\rightleftarrows}} ES_0 \xrightarrow{k_{\mathrm{cat}_0}} S_1 + E \underset{k_{\mathrm{off}_1}}{\overset{k_{\mathrm{on}_1}}{\rightleftarrows}} ES_1 \xrightarrow{k_{\mathrm{cat}_1}} S_2 + E$$

$$S_2 + F \underset{l_{\mathrm{off}_1}}{\overset{l_{\mathrm{on}_1}}{\rightleftarrows}} FS_2 \xrightarrow{l_{\mathrm{cat}_1}} S_1 + F \underset{l_{\mathrm{off}_0}}{\overset{l_{\mathrm{on}_0}}{\rightleftarrows}} FS_1 \xrightarrow{l_{\mathrm{cat}_0}} S_0 + F$$

We number the species and their concentrations

x_1, x_2, x_3 = concentrations of S_0, S_1, S_2

y_1, y_2, y_3, y_4 = concentrations of the intermediate species

x_4 = concentration of the kinase E

x_5 = concentration of the phosphatase F.

The differential equations and the conservation laws

$$\frac{dx_1}{dt} = -k_{on_0}x_1x_4 + k_{off_0}y_1 + l_{cat_0}y_4$$

$$\frac{dx_2}{dt} = -k_{on_1}x_2x_4 + k_{cat_0}y_1 + k_{off_1}y_2 - l_{on_0}x_2x_5 + l_{cat_1}y_3 + l_{off_0}y_4$$

$$\frac{dx_3}{dt} = k_{cat_1}y_2 - l_{on_1}x_3x_5 + l_{off_1}y_3$$

$$\frac{dy_1}{dt} = k_{on_0}x_1x_4 - (k_{off_0} + k_{cat_0})y_1$$

$$\frac{dy_2}{dt} = k_{on_1}x_2x_4 - (k_{off_1} + k_{cat_1})y_2$$

$$\frac{dx_4}{dt} = -k_{on_0}x_1x_4 - k_{on_1}x_2x_4 + (k_{off_0} + k_{cat_0})y_1 + (k_{off_1} + k_{cat_1})y_2$$

$$\frac{dx_5}{dt} = -l_{on_0}x_2x_5 - l_{on_1}x_3x_5 + (l_{off_1} + l_{cat_1})y_3 + (l_{off_0} + l_{cat_0})y_4$$

$$\frac{dy_3}{dt} = l_{on_1}x_3x_5 - (l_{off_1} + l_{cat_1})y_3$$

$$\frac{dy_4}{dt} = l_{on_0}x_2x_5 - (l_{off_0} + l_{cat_0})y_4$$

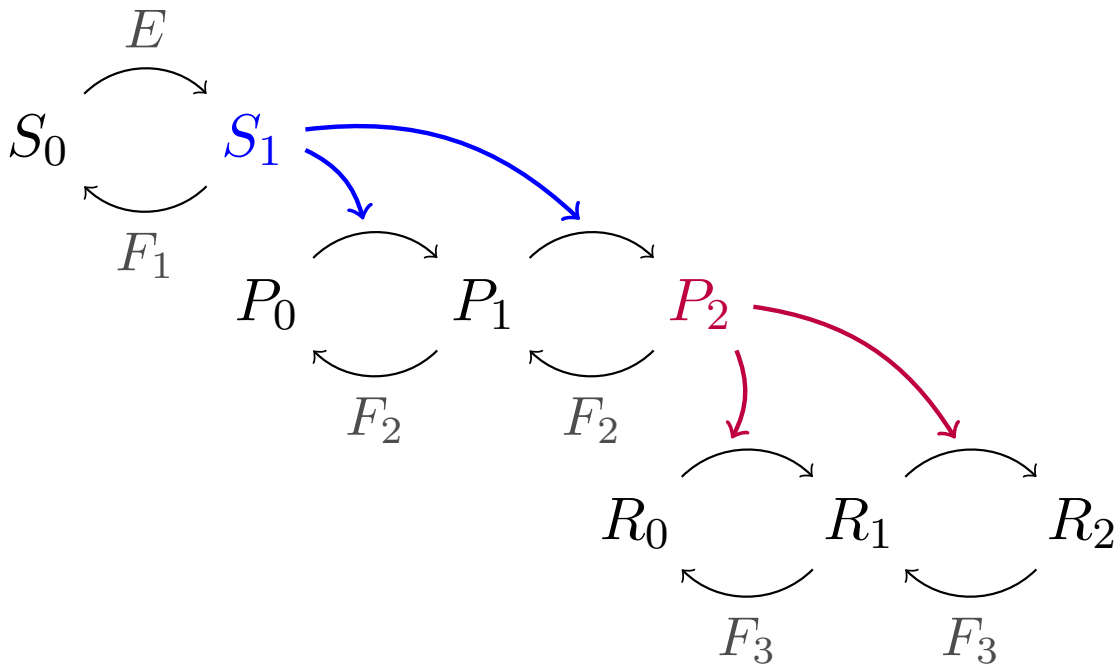
$$x_1 + x_2 + x_3 + y_1 + y_2 + y_3 + y_4 = S_{tot}$$

$$x_4 + y_1 + y_2 = E_{tot}$$

$$x_5 + y_3 + y_4 = F_{tot}.$$

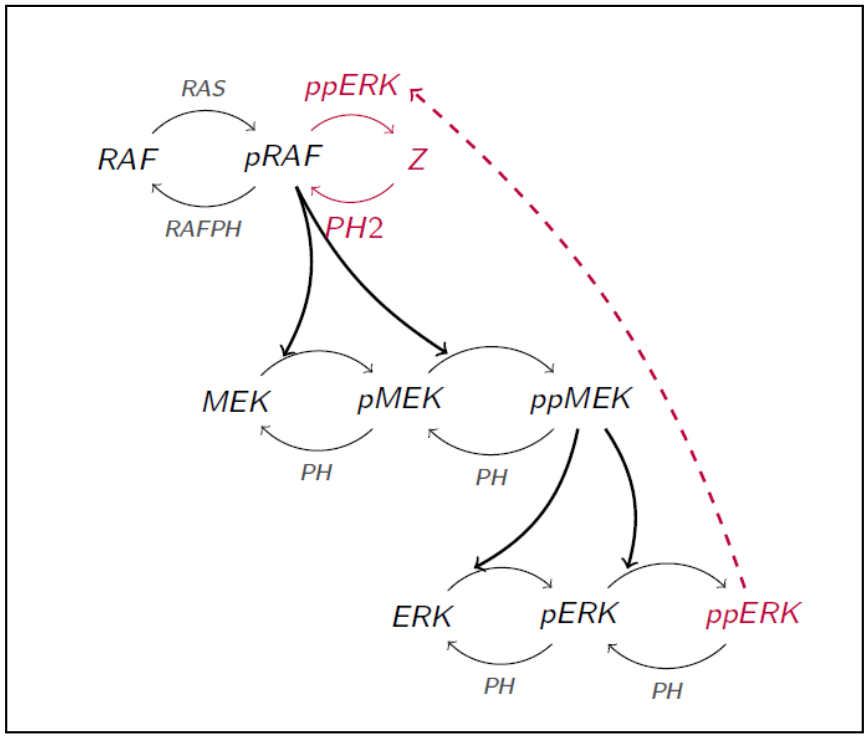
Other important examples of networks

Phosphorylation cascades



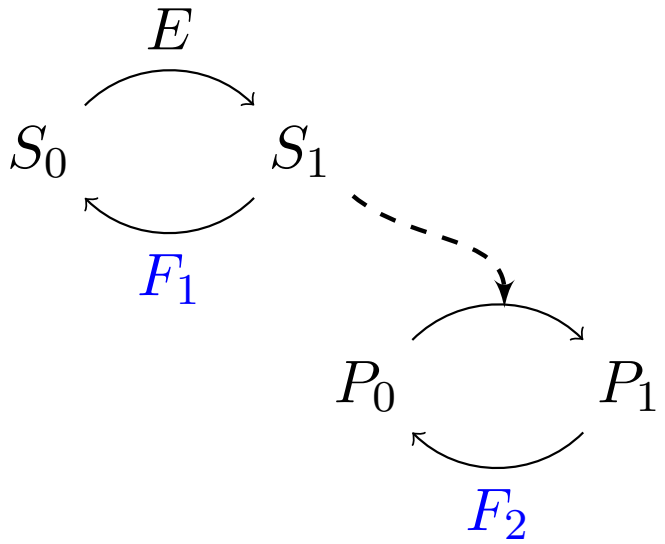
Other important examples of networks

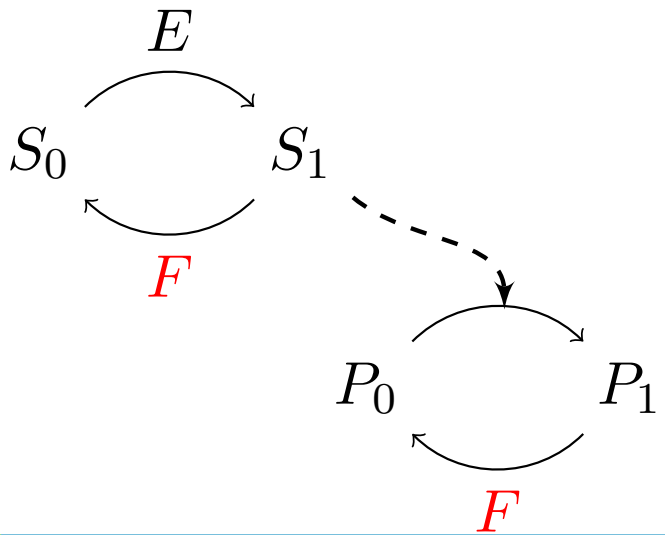
Phosphorylation cascades with retroactivity



Other important examples of networks

Different phosphatases vs same phosphatase in a cascade





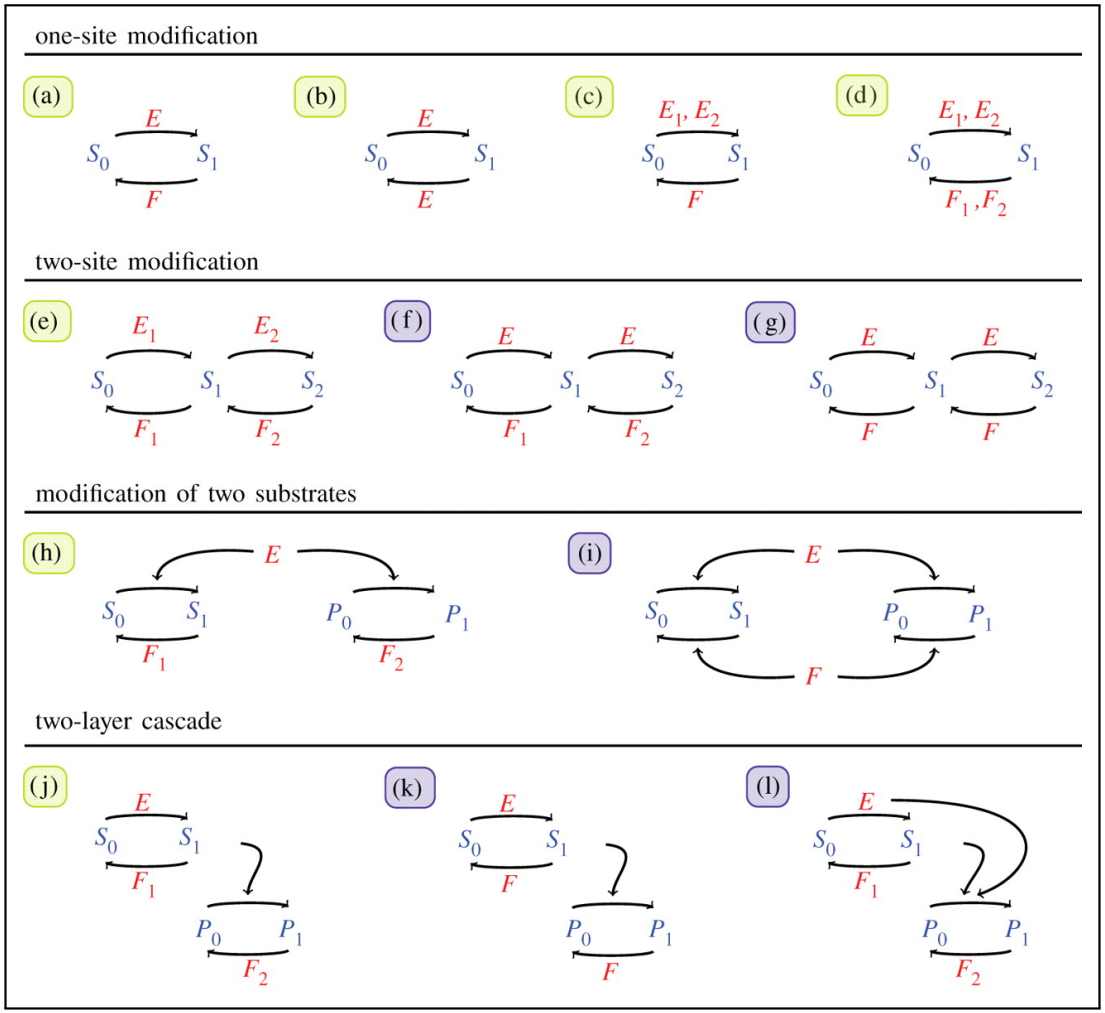
Example: Processive phosphorilations

$$S_0 + K \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_0K \underset{k_4}{\overset{k_3}{\rightleftharpoons}} S_1K \underset{k_6}{\overset{k_5}{\rightleftharpoons}} \dots \underset{k_{2n}}{\overset{k_{2n-1}}{\rightleftharpoons}} S_{n-1}K \xrightarrow{k_{2n+1}} S_n + K$$

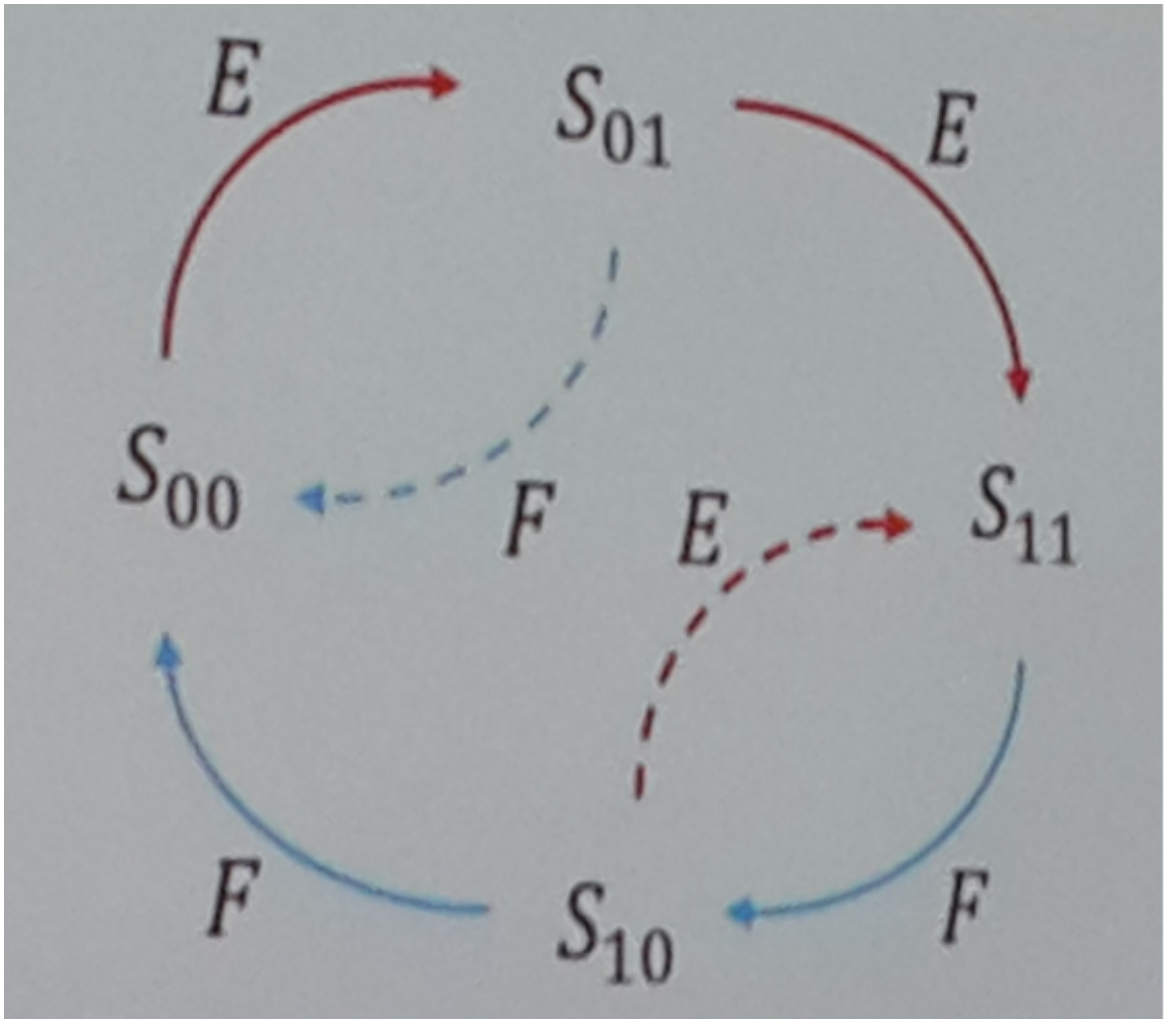
$$S_n + F \underset{\ell_{2n}}{\overset{\ell_{2n+1}}{\rightleftharpoons}} S_nF \underset{\ell_{2n-2}}{\overset{\ell_{2n-1}}{\rightleftharpoons}} \dots \underset{\ell_4}{\overset{\ell_5}{\rightleftharpoons}} S_2F \underset{\ell_2}{\overset{\ell_3}{\rightleftharpoons}} S_1F \xrightarrow{\ell_1} S_0 + F$$

C. Conradi and A. Shiu. *A global convergence result for processive multisite phosphorylation systems, 2015.*

Small motifs ([Alon'07, Feliu-Wiuf'12])



Shvartsman's enzymatic network



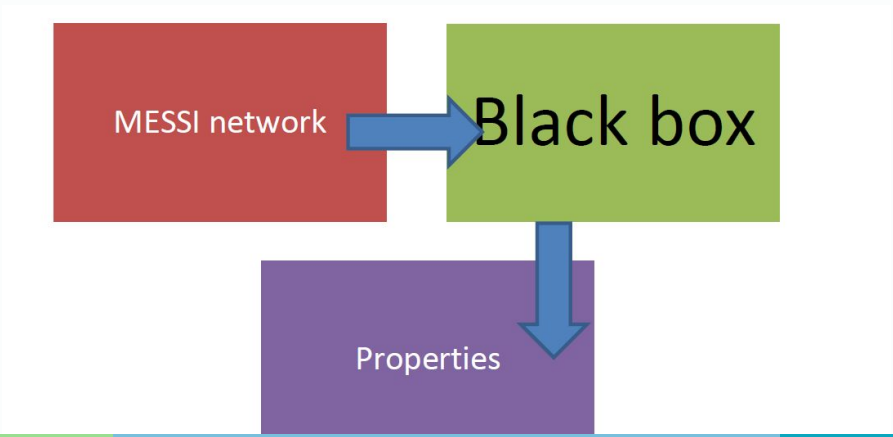
A common structure (arXiv:1612.08763)

MESSI systems

We identified with Mercedes Pérez Millán a **common structure** in many popular biological networks that describe Modifications of type Enzyme-Substrate or Swap with Intermediates, which allows us to prove general results valid in all these networks. MESSI systems include **all** the previous ones.

Less general, but stil quite general goal

Analyze MESSI systems, prove results and give algorithms based on structure of the network to predict conservation relations, persistence and the capacity for multistationarity.



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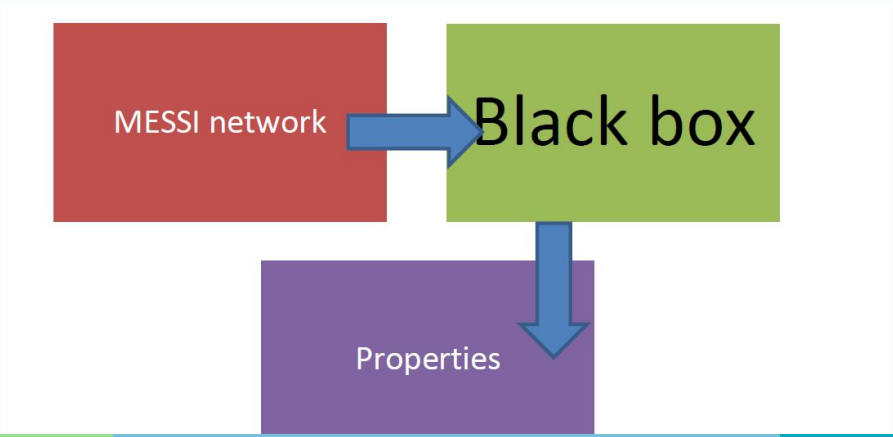

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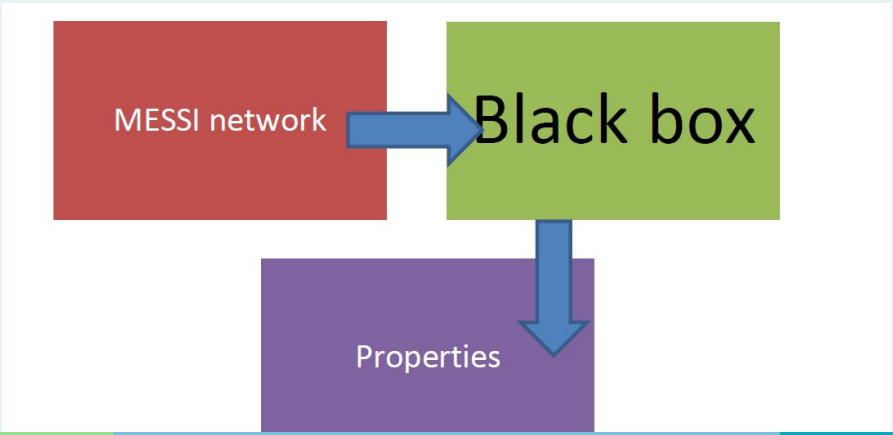

Definition of a MESSI system

A MESSI network is a chemical reaction network satisfying the following properties. When endowed with mass-action kinetics, we have a MESSI system.

- There exists a **partition** of the set $\mathcal{S}$ of species:

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  Examples: All the examples we mentioned . . . plus many other common biochemical models.

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Examples: All the examples we mentioned . . . plus many other common biochemical models.

Definition of a MESSI system

$$\mathcal{S} = \underbrace{\mathcal{S}^{(0)}}_{\text{intermediates}} \bigsqcup \underbrace{\mathcal{S}^{(1)} \bigsqcup \mathcal{S}^{(2)} \bigsqcup \cdots \bigsqcup \mathcal{S}^{(M)}}_{\text{non-intermediates or core}}.$$

- Reactions satisfy:
  - For any intermediate X_k, there exist core complexes $X_i + X_j$ and $X_\ell + X_m$ such that $X_i + X_j \to_\circ X_k$ and $X_k \to_\circ X_\ell + X_m$.
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Feliu and Wiuf 2013, Thomson and Gunawardena 2009, Gnacadja 2011.

Enzymes and swaps

- In a reaction $X_i + X_\ell \to X_j + X_\ell$, we say that X_ℓ acts as an enzyme.
- A reaction $X_i + X_\ell \to X_j + X_m$, with i, ℓ, j, m distinct, is called a swap.
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Conserved quantities: Theorem 1 [D.-P. M.]

A MESSI system has one (independent) linear conservation relation associated to each of the subsets $S^{(\alpha)}, 1 \leq \alpha \leq M$, in the partition of the species set corresponding to non-intermediate species:

$$\sum_{\mathbf{X_i} \in \mathcal{S}^{(\alpha)}} x_i + \sum_{\mathbf{X_k} \in \mathrm{Int}_\alpha} x_k = \text{ constant},$$

where $\mathrm{Int}_\alpha = \{\mathbf{X_k} : X_i \to_\circ \mathbf{X_k}$ or $X_i + X_j \to_\circ \mathbf{X_k}$ for some $X_i \in \mathcal{S}^{(\alpha)}\}$.

Observation:

- Theorem 1 implies that all MESSI systems are conservative (and thus the solutions are defined for any positive time).
- Question: when these span all the linear conservation laws?
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From G to G_1 (without intermediates)

Going from G to G_1 we delete intermediates and we put an edge between two core complexes $y_i \to y_j$ if $y_1 \to_\circ y_j$ in G:

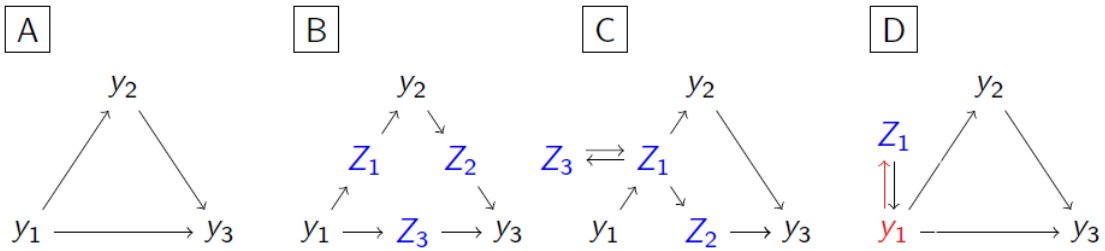

Figure: $\mathcal{S}^{(0)} \subseteq \{Z_1, Z_2, Z_3\}, \mathcal{S}^{(1)} = \{y_1, y_2, y_3\}$

In all cases $G = A, B, C, D$ (with rate constants κ), the associated digraph G_1 is A.

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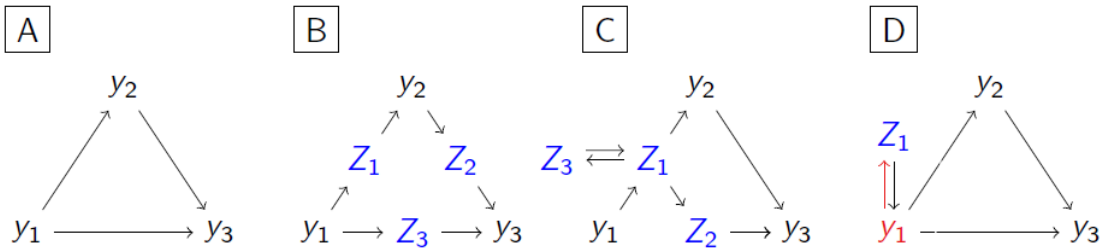

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$G_1 \to G_2$ (HIDE ENZYMES AND SWAPS IN LABELS)

G : Double seq. phospho.

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} U_1 \overset{\kappa_3}{\to} S_1 + E \underset{\kappa_5}{\overset{\kappa_4}{\rightleftarrows}} U_2 \overset{\kappa_6}{\to} S_2 + E$$

$$S_2 + F \underset{\kappa_8}{\overset{\kappa_7}{\rightleftarrows}} U_3 \overset{\kappa_9}{\to} S_1 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftarrows}} U_4 \overset{\kappa_{12}}{\to} S_0 + F$$

$\Downarrow$

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$\Rightarrow$

G_2 :

$$S_0 \underset{\tau_4\, f}{\overset{\tau_1\, e}{\rightleftarrows}} S_1 \underset{\tau_3\, f}{\overset{\tau_2\, e}{\rightleftarrows}} S_2$$

$E \rightleftarrows E, F \rightleftarrows F$ loops .

G : EnvZ – OmpR

$$X_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} X_2 \overset{\kappa_3}{\to} X_3$$

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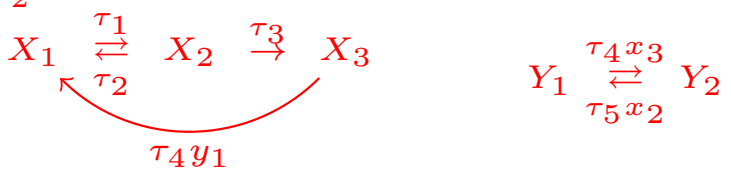

Precluding relevant boundary steady states

If we have a *minimal* partition, we define a new graph G_E, whose vertices are the sets $S^{(\alpha)}$ for $\alpha \geq 1$, and there is an edge from $S^{(\alpha)}$ to $S^{(\beta)}$ if there is a species in $S^{(\alpha)}$ on a label of an edge in G_2 between species of $S^{(\beta)}$.

Persistence: Theorem 2 [D.-P. M.]

If there is no directed cycle in G_E, then G has no boundary steady states in any positive stoichiometric compatibility class. Thus, the network is persistent.

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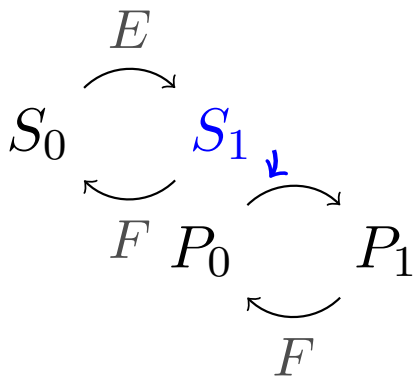

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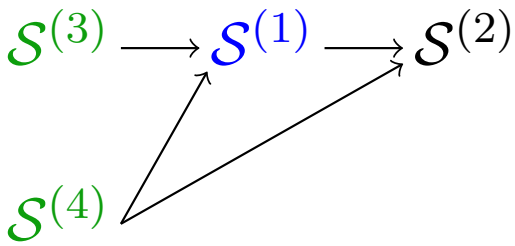

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$$\mathcal{S}^{(1)} \rightleftarrows \mathcal{S}^{(2)}$$

$x_p = X_{tot}, y_p = Y_{tot}, x = x_t = x_p y = x_T y_p = y = 0$ is a boundary steady state in the class with totals X_{tot}, Y_{tot}.

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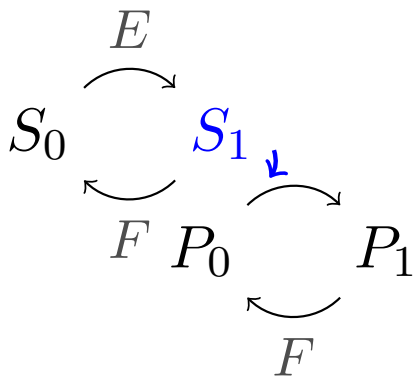

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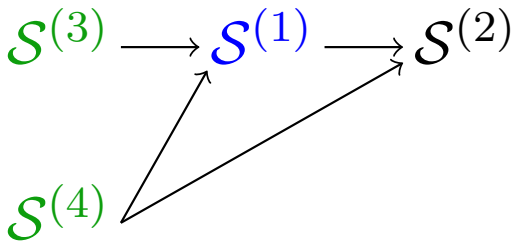

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Assume the steady state variety V is cut out by binomials with exponents in a matrix B and coefficients in $\mathbb{Q}(\kappa)$, or equivalently, it is parametrized by monomials with exponents in the dual matrix A. Let $S^\perp$ denote a matrix whose rows define the dual of the subspace $S = \langle y_j - y_i, y_i \to y_j \rangle$. If $\mathrm{rank}(S^\perp) = \mathrm{rank}(\mathrm{A}) = d$, the following statements are equivalent:

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2. For all subsets $J \subseteq [s]$ of cardinality d, the product $\det(S^\perp_J)\det(A_J)$ either is zero or has the same sign as all other nonzero products, and at least one such product is nonzero.
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- We give precise sufficient conditions for the hypotheses of Theorem 3 to hold.
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- We give precise sufficient conditions for the hypotheses of Theorem 3 to hold.
- We implemented Theorem 3 to decide if a network has the capacity for multistationarity.
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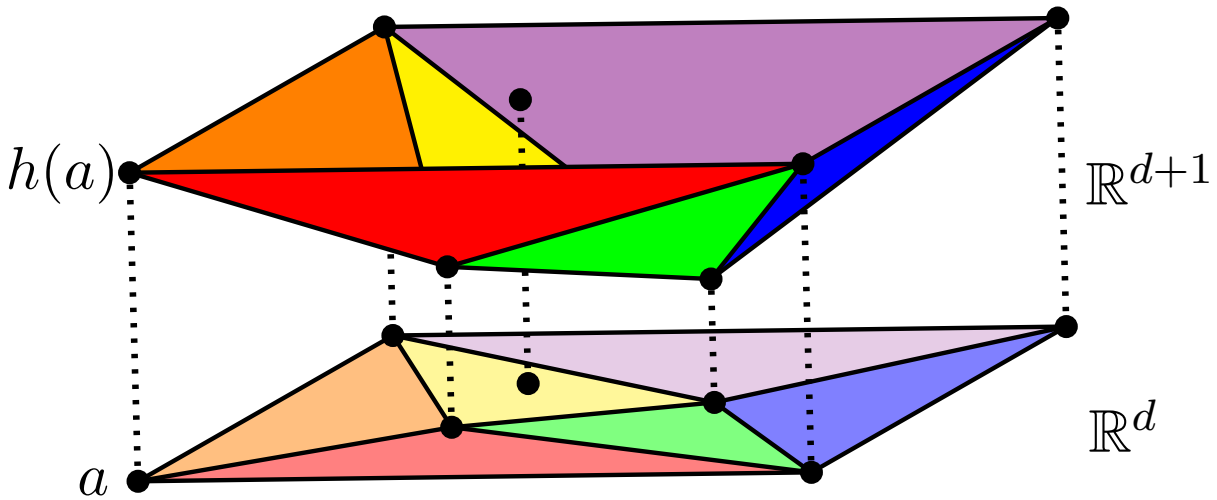
Joint work with F. Bihan and M. Giaroli

Regions of multistationarity

We devised a method to give open regions in rate constant + total amount space where multistationarity occurs for all k, T in these regions. This is based on a result by Bihan, Santos and Spaenlehauer in real algebraic geometry (arXiv:2018) which uses regular triangulations of the convex hull of the exponents occuring in $f_1, \dots, f_n$.



Coming back to the two–component system

$$
\begin{aligned}
X_1 \xrightarrow{k_1} X_2 \xrightarrow{k_2} X_3 \xrightarrow{k_3} X_4 \\
X_3 + X_5 \xrightarrow{k_4} X_1 + X_6 \\
X_4 + X_5 \xrightarrow{k_5} X_2 + X_6 \\
X_6 \xrightarrow{k_6} X_5
\end{aligned}
\tag{5}
$$

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\begin{aligned}
x_1 + x_2 + x_3 + x_4 &= T_1, \\
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Our results for the two–component system

Multstationarity parameters: Theorem 4 [B.-D.- G.]

With the previous notations, assume that the reaction rate constants and the total amounts verify the inequalities

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

Then, there exist positive constants N_1, N_2 such that for any values of γ_4 and γ_5 veryfying $\gamma_4 > N_1$ and $\frac{\gamma_5}{\gamma_4} > N_2$, the rescaling of the given parameters k_4, k_5 by $\overline{k_4} = \gamma_4\, k_4$, $\overline{k_5} = \gamma_5\, k_5$, gives raise to a multistationary system.

Other approaches to multistationarity

- Using degree theory (Brouwer's theorem): Conradi-Feliu-Mincheva-Wiuf, PLOS Computational Biology 2017.
- Using numerical or symbolic methods to detect points in different chambers of the complement of the discriminant: Harrington-Mehta-Byrne-Hauenstein 2016; Gross-Harrington-Rosen-Sturmfels, BMB 2016; Faugère-Moroz-Rouillier-Safey El Din, ISSAC 2008 and other.
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Summary

- We can use algebraic geometry to analyze system biology models.
- Algebro-geometric and combinatorial methods allows us to predict (some) dynamical behaviors of our model from the structure, without simulations and without knowing the precise reaction rate constants ...
- ... and (in some interesting cases) to "see the woods" and not only "the trees".
- In theory, we have several answers. In practice, they tend to be too complex to be understood or computed.
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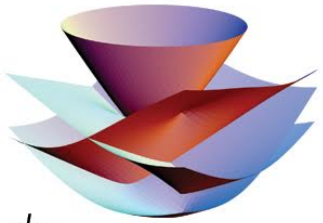

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