Stability of steady states and algebraic parameterizations in chemical reaction networks.

Angélica Torres

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University of Copenhagen

GOAL

Given a chemical reaction network $\mathcal{G}$ under mass action kinetics, with n species and m reactions, explore the existence of a region on the space of parameters (rate constants and total amounts) such that bistability arises.

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- Chemical reaction networks.
- Stability criteria.
- Detecting bistability.

Chemical Reaction networks

$$X_1 + 2X_2 \xrightarrow{\kappa_1} 2X_1 + X_2$$

$$4X_1 + X_2 \xrightarrow{\kappa_2} 3X_1 + 2X_2$$

$$3X_1 + X_2 \xrightarrow{\kappa_3} 4X_1$$

$$2X_1 + X_2 \xrightarrow{\kappa_4} 3X_2$$

A chemical reaction network $\mathcal{G}$ is a labelled directed graph whose nodes, called *complexes*, are integer linear combinations of a set $\mathcal{S} = \{X_1, \ldots, X_n\}$ called the set of *species*.

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The concentration of the species is modelled by a polynomial system of ODEs. The coefficients $\{\kappa_1, \ldots, \kappa_m\} \subset \mathbb{R}^n_{>0}$ are called *reaction rate constants*.

$$\begin{aligned}
\dot{x}_1 =& \kappa_1 x_1 x_2^2 - \kappa_2 x_1^4 x_2 + \kappa_3 x_1^3 x_2 - 2\kappa_4 x_1^2 x_2 \\
\dot{x}_2 =& -\kappa_1 x_1 x_2^2 + \kappa_2 x_1^4 x_2 - \kappa_3 x_1^3 x_2 + 2\kappa_4 x_1^2 x_2
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Chemical Reaction networks

The steady states are the non-negative points where the vector of derivatives of the concentrations is $\dot{x} = 0$.

In our example

$$\begin{aligned}\dot{x}_1 =& \kappa_1 x_1 x_2^2 - \kappa_2 x_1^4 x_2 + \kappa_3 x_1^3 x_2 - 2\kappa_4 x_1^2 x_2 \\ \dot{x}_2 =& -\kappa_1 x_1 x_2^2 + \kappa_2 x_1^4 x_2 - \kappa_3 x_1^3 x_2 + 2\kappa_4 x_1^2 x_2\end{aligned}$$

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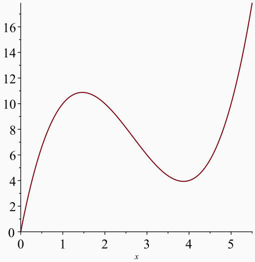
$$\begin{aligned} 0 =& \kappa_1 x_1 x_2^2 - \kappa_2 x_1^4 x_2 + \kappa_3 x_1^3 x_2 - 2\kappa_4 x_1^2 x_2 \\ 0 =& -\kappa_1 x_1 x_2^2 + \kappa_2 x_1^4 x_2 - \kappa_3 x_1^3 x_2 + 2\kappa_4 x_1^2 x_2 \end{aligned}$$

Taking $\kappa_1 = 1, \kappa_2 = 1, \kappa_3 = 8$ and $\kappa_4 = \frac{17}{4}$ the positive steady state variety is



Chemical Reaction networks

$$\dot{x}_1 = \kappa_1 x_1 x_2^2 - \kappa_2 x_1^4 x_2 + \kappa_3 x_1^3 x_2 - 2\kappa_4 x_1^2 x_2$$
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Note that $\dot{x}_1 + \dot{x}_2 = 0$. Therefore, $x_1 + x_2 = T$ through time. These linear combinations of the concentration variables are called *conservation laws*, and all points satisfying them form a *stoichiometric compatibility class*.

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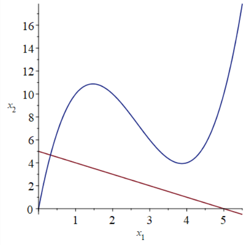

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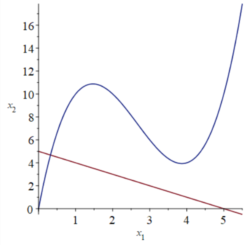

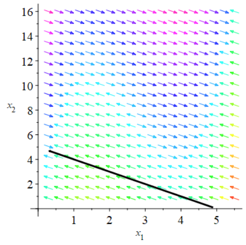

Figure 1: Conservation law $T = 5$ and vector field.

Multistationarity

The network exhibits *multistationarity* if there exist a set of reaction rate constants and total amounts, such that there are two positive steady states in one stoichiometric compatibility class.

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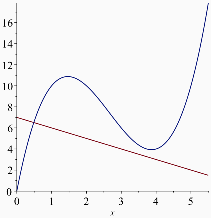

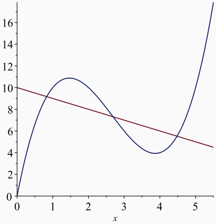

The network in our example exhibits multistationarity for the set of parameters $\{\kappa_1 = 1, \kappa_2 = 1, \kappa_3 = 8, \kappa_4 = \frac{17}{4}, T = 10\}$.

Chemical Reaction networks

- The steady states in the stoichiometric compatibility class given by T are the solutions to the system

$$
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0 =& \kappa_1 x_1 x_2^2 - \kappa_2 x_1^4 x_2 + \kappa_3 x_1^3 x_2 - 2\kappa_4 x_1^2 x_2 \\
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\end{aligned}
$$

- The function obtained by removing all the redundant steady state equations and replacing them by the conservation laws will be denoted by $F_T(x)$.

STABILITY

Consider a system of differential equations $\frac{dx}{dt} = f(x)$, with $f \in \mathcal{C}^1$, and a steady state x^*.

The steady state x^* is *asymptotically stable* if all the eigenvalues of $J_f(x^*)$ have negative real part. If one of the eigenvalues of $J_f(x^*)$ has positive real part, then x^* is *unstable*.

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In order to determine stability we will study the roots of the characteristic polynomial $p_{J_f}(\lambda)$.

Stability: Hurwitz criterion.

Let $p(x) = a_n x^n + a_{n-1}x^{n-1} + \ldots + a_1 x + a_0$ be a polynomial with $a_i \in \mathbb{R}$, $a_n > 0$ and $a_0 \neq 0$. The Hurwitz matrix associated to p is

$$H = \begin{pmatrix} a_{n-1} & a_n & 0 & 0 & \cdots & 0 \\ a_{n-3} & a_{n-2} & a_{n-1} & a_n & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & a_{6-n} & \cdots & a_2 \\ 0 & 0 & 0 & 0 & \cdots & a_0 \end{pmatrix}$$

The i-th Hurwitz determinant, is $H_i = \mathrm{det}(H_{I,I})$, with $I = \{1, \ldots, i\}$.

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Remark: $H_n = a_0 H_{n-1}$.

Stability: Our approach

1. Establish the ODEs and conservation laws of the system.

$$X_1 \xrightarrow{\kappa_1} X_2 \qquad X_2 + X_3 \xrightarrow{\kappa_2} X_1 + X_4 \qquad X_4 \xrightarrow{\kappa_3} X_3. \tag{1}$$

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The ODE system associated with the network is

$$\begin{aligned} \dot{x}_1 &= -\kappa_1 x_1 + \kappa_2 x_2 x_3 & \qquad \dot{x}_3 &= -\kappa_2 x_2 x_3 + \kappa_3 x_4 \\ \dot{x}_2 &= \kappa_1 x_1 - \kappa_2 x_2 x_3 & \qquad \dot{x}_4 &= \kappa_2 x_2 x_3 - \kappa_3 x_4. \end{aligned}$$

The conservation laws are $x_1 + x_2 = T_1$ and $x_3 + x_4 = T_2$.

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$$J_f(\phi(x_2, x_4)) = \begin{pmatrix} -\kappa_1 & \frac{\kappa_3 x_4}{x_2} & \kappa_2 x_2 & 0 \\ \kappa_1 & -\frac{\kappa_3 x_4}{x_2} & -\kappa_2 x_2 & 0 \\ 0 & -\frac{\kappa_3 x_4}{x_2} & -\kappa_2 x_2 & \kappa_3 \\ 0 & \frac{\kappa_3 x_4}{x_2} & \kappa_2 x_2 & -\kappa_3 \end{pmatrix}$$

3. Compute the characteristic polynomial of $J_f(x^*)$, $p_{J_f}(\lambda)$, and factor λ^d, where d is the amount of conservation laws.

$$p_{J_f}(\lambda) = \lambda^4 + \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}\lambda^3 + \frac{\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4}{x_2}\lambda^2$$

$$= \lambda^2\left(\lambda^2 + \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}\lambda + \frac{\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4}{x_2}\right)$$

Stability: Our approach

4. Use the Hurwitz criterion to study the roots of the characteristic polynomial restricted to the stoichiometric compatibility class.

$$q_f(\lambda) = \lambda^2 + \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}\lambda + \frac{\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4}{x_2}$$

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The Hurwitz determinants are

$$H_1 = \frac{\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4}{x_2}$$

$$H_2 = \frac{(\kappa_2 x_2^2 + \kappa_1 x_2 + \kappa_3 x_2 + \kappa_3 x_4)(\kappa_1\kappa_2 x_2^2 + \kappa_1\kappa_3 x_2 + \kappa_3^2 x_4)}{x_2^2}$$

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For all choice of reaction rate constants and totl amounts, the steady state is asymptotically stable.

Stability: Our approach

One-site phosphorylation cycles

(1)

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$
$$S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_1F \xrightarrow{\kappa_6} S_0 + F$$

(2)

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$
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(3)

$$S_0 + E_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E_1 \xrightarrow{\kappa_3} S_1 + E_1$$
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$$S_1 + F \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_1F \xrightarrow{\kappa_9} S_0 + F$$

(4)

$$S_0 + E_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E_1 \xrightarrow{\kappa_3} S_1 + E_1$$
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$$S_1 + F_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_1F_1 \xrightarrow{\kappa_9} S_0 + F_1$$
$$S_1 + F_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_1F_2 \xrightarrow{\kappa_{12}} S_0 + F_2$$

(5) Two-site modification

$$S_0 + E_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E_1 \xrightarrow{\kappa_3} S_1 + E_1$$
$$S_1 + E_2 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_1E_2 \xrightarrow{\kappa_6} S_2 + E_2$$
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$$S_2 + F_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_2F_2 \xrightarrow{\kappa_{12}} S_1 + F_2$$

(6) Modification of two substrates

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$
$$P_0 + E \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} P_0E \xrightarrow{\kappa_6} P_1 + E$$
$$S_1 + F_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_1F_1 \xrightarrow{\kappa_9} S_0 + F_1$$
$$P_1 + F_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} P_1F_2 \xrightarrow{\kappa_{12}} P_0 + F_2$$

(7) Two layer cascade

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$
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$$P_0 + S_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} P_0S_1 \xrightarrow{\kappa_9} P_1 + S_1$$
$$P_1 + F_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} P_1F_2 \xrightarrow{\kappa_{12}} P_0 + F_2$$

We proved asymptotic stability for every set of parameters and total amounts for all these monostationary networks, except for the two layer cascade.

Downside: Computationally expensive. Some polynomials have more than one million monomials.

Stability: Our approach

As a second example, consider the **Gene transcription network**, that is known to be multistationary.

$$X_1 \xrightarrow{\kappa_1} X_1 + P_1 \qquad X_2 \xrightarrow{\kappa_2} X_2 + P_2$$

$$P_1 \xrightarrow{\kappa_3} 0 \qquad P_2 \xrightarrow{\kappa_4} 0$$

$$X_2 + P_1 \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} X_2P_1 \qquad 2P_2 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} P_2P_2$$

$$X_1 + P_2P_2 \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} X_1P_2P_2$$

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$$X_1 + P_2P_2 \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} X_1P_2P_2$$

We denote the concentration variables as x_1 =X_1, x_2 =X_2, x_3=P_1, x_4= P_2, x_5 = $\mathrm{X}_2\mathrm{P}_1$, x_6 = $\mathrm{P}_2\mathrm{P}_2$, and $X_7 = X_1P_2P_2$.

Stability: Our approach

The system of ODEs is

$$\dot{x}_1 = -\kappa_9 x_1 x_6 + \kappa_{10} x_7 \qquad \dot{x}_5 = \kappa_5 x_2 x_3 - \kappa_6 x_5$$

$$\dot{x}_2 = -\kappa_5 x_2 x_3 + \kappa_6 x_5 \qquad \dot{x}_6 = \kappa_7 x_4^2 - \kappa_9 x_1 x_6 - \kappa_8 x_6 + \kappa_{10} x_7$$

$$\dot{x}_3 = -\kappa_5 x_2 x_3 + \kappa_1 x_1 - \kappa_3 x_3 + \kappa_6 x_5 \qquad \dot{x}_7 = \kappa_9 x_1 x_6 - \kappa_{10} x_7$$

$$\dot{x}_4 = -2\kappa_7 x_4^2 + \kappa_2 x_2 - \kappa_4 x_4 + 2\kappa_8 x_6,$$

and the conservations laws are

$$x_1 + x_7 = T_1 \qquad \text{and} \qquad x_2 + x_5 = T_2.$$

Stability: Our approach

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and the conservations laws are

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A positive parameterization of the steady states is

$$x_1 = \frac{\kappa_2\kappa_3\kappa_6 x_5}{\kappa_1\kappa_4\kappa_5 x_4}, x_2 = \frac{\kappa_4 x_4}{\kappa_2}, x_3 = \frac{\kappa_6 x_5 \kappa_2}{\kappa_4\kappa_5 x_4}, x_6 = \frac{\kappa_7 x_4^2}{\kappa_8}, x_7 = \frac{\kappa_9\kappa_2\kappa_3\kappa_6 x_5 x_4 \kappa_7}{\kappa_1\kappa_4\kappa_5\kappa_8\kappa_{10}}$$

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For this network the characteristic polynomial $p_{J_f}(\lambda)$ has degree 7.

After factoring λ^2 we apply the Hurwitz criterion to a polynomial of degree 5.

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We found that H_1, H_2, H_3 and H_4 are rational functions with positive coefficients.

$$H_5 = -\frac{\kappa_6\kappa_3\left(\kappa_2\kappa_7\kappa_9 x_4^2 x_5 - \kappa_4\kappa_7\kappa_9 x_4^3 - \kappa_2\kappa_8\kappa_{10} x_5 - \kappa_4\kappa_8\kappa_{10} x_4\right)}{x_4} H_4$$

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This network is multistationary. Is it bistable?

Stability: Our approach

In this network the solutions of $F_T(x) = 0$ are in one to one correspondence with the roots of

$$F_{T,1}(\varphi(x_1)) = \frac{1}{(\kappa_1\kappa_5 x_1 + \kappa_3\kappa_6)^2\kappa_4^2\kappa_8\kappa_{10}}\Big[\kappa_1^2\kappa_4^2\kappa_5^2\kappa_8\kappa_{10}x_1^3 + (-T_1\kappa_1^2\kappa_4^2\kappa_5^2\kappa_8\kappa_{10} + 2\kappa_1\kappa_3\kappa_4^2\kappa_5\kappa_6\kappa_8\kappa_{10})x_1^2 +$$

$$(T_2^2\kappa_2^2\kappa_3^2\kappa_6^2\kappa_7\kappa_9 - 2T_1\kappa_1\kappa_3\kappa_4^2\kappa_5\kappa_6\kappa_8\kappa_{10} + \kappa_3^2\kappa_4^2\kappa_6^2\kappa_8\kappa_{10})x_1 - T_1\kappa_3^2\kappa_4^2\kappa_6^2\kappa_8\kappa_{10}\Big]$$

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This is a univariate polynomial of degree 3.

There is a maximum of 3 positive steady states in each stoichiometric compatibility class.

Detecting bistability

If the solutions of $0 = F_T(x)$ can be reduced to the study of one univariate polynomial $(F_{T,j} \circ \varphi)(x_i)$, then, for a steady state $x^* = \varphi(x_i)$ the following relation holds

$$\det(J_{F_T}(x^*)) = (-1)^{i+j}(F_{T,j} \circ \varphi)'(x_i)\det(J_{F_T}(x^*)_{J,I}).$$

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$$(-1)^s a_0 = (-1)^{i+j}(F_{T,j} \circ \varphi)'(x_i) \det(J_{F_T}(x^*)_{J,I}).$$

If additionally

- the sign of $\det(J_{F_T}(\varphi(x_i))_{J,I})$ is independent of $x_i > 0$ and is nonzero, and
- All the Hurwitz determinants of $p_{J_f(\varphi(x_i))}$ are positive, except for $H_n = a_0 H_{n-1}$.

Then the positive solutions $z_1 < \cdots < z_\ell$ of $F_{T,j}(\varphi(x_i)) = 0$, satisfy that, either $\varphi(z_1), \varphi(z_3), \ldots$ are asymptotically stable and $\varphi(z_2), \varphi(z_4), \ldots$ are unstable, or the other way around.

Stability

Back to the Gene transcription network:

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- Reduce the solutions of $F_T(x) = 0$ to one polynomial.

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- Sign of $\det(J_{F_T}(\varphi(x_i))_{J,I})$ independent of x_i.

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$$\det(J_{F_T}(\varphi(x_i))_{J,I}) = -(\kappa_1\kappa_5 x_1 + \kappa_3\kappa_6)\kappa_4\kappa_8\kappa_{10}$$

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We conclude that $a_0 = -(F_{T,j} \circ \varphi)'(x_1)\det(J_{F_T}(x^*)_{J,I})$.

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We conclude that $a_0 = -(F_{T,j} \circ \varphi)'(x_1) \det(J_{F_T}(x^*)_{J,I})$.

If $(F_{T,j} \circ \varphi)(x_1)$ has 3 different positive roots $z_1 < z_2 < z_3$, then z_1 and z_3 are asymptotically stable and z_2 is unstable.

Bistability

In other multistationary networks...

Allosteric kinase

$$E_1 + S_0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} E_1S_0 \xrightarrow{\kappa_3} E_1 + S_1$$

$$E_2 + S_0 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} E_2S_0 \xrightarrow{\kappa_6} E_2 + S_1$$

$$S_1 \xrightarrow{\kappa_7} S_0 \qquad E_1 \underset{\kappa_9}{\overset{\kappa_8}{\rightleftharpoons}} E_2 \qquad E_1S_0 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} E_2S_0$$

Two layer cascade 1

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$

$$S_1 + F \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_1F \xrightarrow{\kappa_6} S_0 + F$$

$$P_0 + S_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} P_0S_1 \xrightarrow{\kappa_9} P_1 + S_1$$

$$P_1 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} P_1F \xrightarrow{\kappa_{12}} P_0 + F$$

Two site modification

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$

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$$S_2 + F_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_2F_2 \xrightarrow{\kappa_{12}} S_1 + F_2$$

Bistability

Two site phosphorylation

$$E + S_0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} E + S_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_1E \xrightarrow{\kappa_9} S_2 + E$$

$$F + S_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_2F \xrightarrow{\kappa_{12}} F + S_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_1F \xrightarrow{\kappa_6} F + S_0$$

Phosphorylation of two substrates

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Two layer cascade 2

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$$P_0 + S_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} P_0S_1 \xrightarrow{\kappa_9} P_1 + S_1$$

$$P_0 + E \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} P_0E \xrightarrow{\kappa_{12}} P_1 + E$$

$$P_1 + F_2 \underset{\kappa_{14}}{\overset{\kappa_{13}}{\rightleftharpoons}} P_1F_2 \xrightarrow{\kappa_{15}} P_0 + F_2$$

Bistability

If it is not possible to apply the procedure directly, We use two reduction techniques that preserve multistationarity and stability properties

- Removal and addition of reactions that preserve the conservation laws. In particular, removing reversible reactions.

$$\mathrm{C}_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \mathrm{C}_2 \quad \text{can be transformed into} \quad \mathrm{C}_1 \xrightarrow{\tau} \mathrm{C}_2$$

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- Adding or removing intermediates

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We were able to detect bistability with the following reductions

Bistability

Allosteric kinase

$$E_1 + S_0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} E_1S_0 \xrightarrow{\kappa_3} E_1 + S_1$$

$$E_2 + S_0 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} E_2S_0 \xrightarrow{\kappa_6} E_2 + S_1$$

$$S_1 \xrightarrow{\kappa_7} S_0 \qquad E_1 \underset{\kappa_9}{\overset{\kappa_8}{\rightleftharpoons}} E_2 \qquad E_1S_0 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} E_2S_0$$

Two layer cascade 1

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} S_1 + E$$

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$$S_2 + F_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_2F_2 \xrightarrow{\kappa_{12}} S_1 + F_2$$

Reduced Allosteric kinase

$$E_1 + S_0 \xrightarrow{\tau_1} E_1S_0 \xrightarrow{\tau_2} E_1 + S_1$$

$$E_2 + S_0 \xrightarrow{\tau_3} E_2 + S_1 \qquad E_2 + S_0 \xrightarrow{\tau_6} E_1S_0$$

$$S_1 \xrightarrow{\tau_4} S_0 \qquad E_1 \xrightarrow{\tau_5} E_2$$

Reduced two layer cascade 1

$$S_0 + E \xrightarrow{\tau_1} S_1 + E$$

$$S_1 + F \xrightarrow{\tau_2} S_0 + F$$

$$P_0 + S_1 \xrightarrow{\tau_3} P_0S_1 \xrightarrow{\tau_4} P_1 + S_1$$

$$P_1 + F \xrightarrow{\tau_5} P_1F \xrightarrow{\tau_6} P_0 + F$$

Two site modification reduced

$$S_0 + E \xrightarrow{\tau_1} S_0E \xrightarrow{\tau_2} S_1 + E$$

$$S_1 + E \xrightarrow{\tau_3} S_1E \xrightarrow{\tau_4} S_2 + E$$

$$S_1 + F_1 \xrightarrow{\tau_5} S_0 + F_1$$

$$S_2 + F_2 \xrightarrow{\tau_6} S_1 + F_2$$

Bistability

Two site phosphorylation

$$E + S_0 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} S_0E \xrightarrow{\kappa_3} E + S_1 \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} S_1E \xrightarrow{\kappa_9} S_2 + E$$

$$F + S_2 \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftharpoons}} S_2F \xrightarrow{\kappa_{12}} F + S_1 \underset{\kappa_5}{\overset{\kappa_4}{\rightleftharpoons}} S_1F \xrightarrow{\kappa_6} F + S_0$$

Phosphorylation of two substrates

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Two layer cascade 2

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Two site phosphorylation reduced

$$E + S_0 \xrightarrow{\tau_1} S_0E \xrightarrow{\tau_2} E + S_1 \xrightarrow{\tau_3} S_2 + E$$

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$$S_0 + E \xrightarrow{\tau_1} S_1 + E$$

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$$P_1 + F_2 \xrightarrow{\tau_5} P_0 + F_2$$

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Thank you

THANK YOU!