

Sequential and distributive multisite phosphorylations have toric steady states

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Buenos Aires – Argentina

Raleigh, October 8, 2011

- 1 The $n(= 2)$ -site phosphorylation system
 - Notation and setting
- 2 Steady States
 - Toric steady states
- 3 Properties (sufficient conditions)
- 4 Parametrization

General setting for our study

- Biochemical reaction networks define autonomous systems of Ordinary Differential Equations (ODEs) with (in general unknown) parameters.
- We assume all kinetics are of the mass-action form.
- It is often difficult to describe the (positive) steady states.
- Our aim is to study particularly nice systems.
- This talk is based on joint work with Alicia Dickenstein, Anne Shiu and Carsten Conradi
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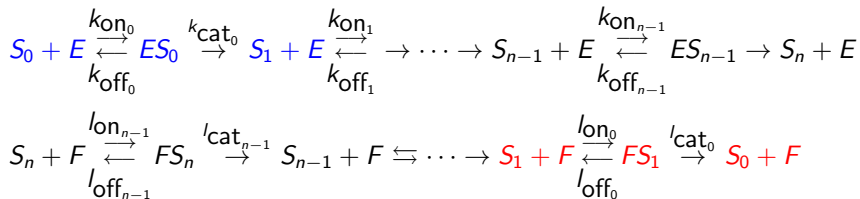
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The multisite phosphorylation network

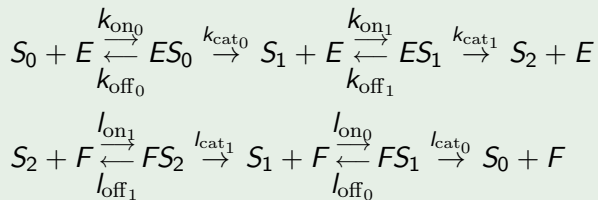
Following notation of [Wang and Sontag 2008](#),
the **n -site phosphorylation network** is:



For simplicity, we will mostly consider on these slides the case $n = 2$, although all the results hold for $n \in \mathbb{N}$.

The network.

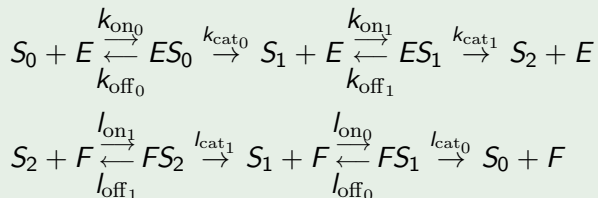
Example



- Nine ($= 3 + 4 + 2 = 3 \times n + 3$) species:
 - $S_0, S_1, S_2 \rightarrow$ substrates,
 - $ES_0, ES_1, FS_1, FS_2 \rightarrow$ intermediary species,
 - $E, F \rightarrow$ enzymes.
- Ten ($= 3 \times 2 + 4 = 4 \times n + 2$) complexes:
 - $S_0 + E, S_1 + E, S_2 + E, ES_0, ES_1, S_0 + F, S_1 + F, S_2 + F, FS_1, FS_2.$

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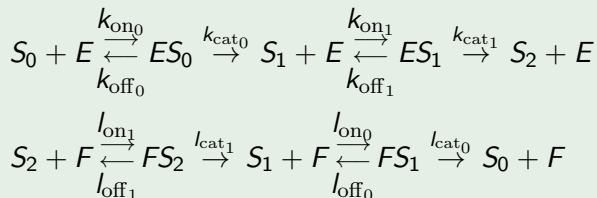
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The system.

Example

Following the notation of Wang and Sontag 2008, we write the concentration vector as

$$x = (s_0, s_1, s_2, c_0, c_1, d_1, d_2, e, f).$$

Then, the system

$$\frac{dx}{dt} = \left(\frac{dx_1}{dt}, \frac{dx_2}{dt}, \dots, \frac{dx_s}{dt} \right)^t = \left(\frac{ds_0}{dt}, \frac{ds_1}{dt}, \dots, \frac{df}{dt} \right)^t$$

can be written as:

$$\frac{dx}{dt} = \Sigma \cdot \Psi(x),$$

with Σ a 9×10 (species \times complexes) matrix and $\Psi(x)$ a column vector of length 10:

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Example

$$\Sigma = \begin{bmatrix} -k_{on0} & 0 & 0 & k_{off0} & 0 & 0 & 0 & 0 & l_{cat0} & 0 \\ 0 & -k_{on1} & 0 & k_{cat0} & k_{off1} & 0 & -l_{on0} & 0 & l_{off0} & l_{cat1} \\ 0 & 0 & 0 & 0 & k_{cat1} & 0 & 0 & -l_{on1} & 0 & l_{off1} \\ k_{on0} & 0 & 0 & -k_{off0} & -k_{cat0} & 0 & 0 & 0 & 0 & 0 \\ 0 & k_{on1} & 0 & 0 & -k_{off1} & -k_{cat1} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & l_{on0} & 0 & -l_{cat0} & -l_{off0} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & l_{on1} & 0 & -l_{cat1} & -l_{off1} \\ -k_{on0} & -k_{on1} & 0 & k_{off0} + k_{cat0} & k_{off1} + k_{cat1} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -l_{on0} & -l_{on1} & l_{cat0} + l_{off0} & l_{cat1} + l_{off1} \end{bmatrix}$$

$\Psi(\mathbf{x})$ consists of the monomials determined by the complexes in the reaction network:

$$\Psi(\mathbf{x}) = \left(\begin{array}{c} s_0 + e \\ \downarrow \\ s_0 e \end{array}, \begin{array}{c} s_1 + e \\ \downarrow \\ s_1 e \end{array}, \begin{array}{c} s_2 + e \\ \downarrow \\ s_2 e \end{array}, \begin{array}{c} ES_0 \\ \downarrow \\ c_0 \end{array}, \begin{array}{c} ES_1 \\ \downarrow \\ c_1 \end{array}, \begin{array}{c} s_0 + f \\ \downarrow \\ s_0 f \end{array}, \begin{array}{c} s_1 + f \\ \downarrow \\ s_1 f \end{array}, \begin{array}{c} s_2 + f \\ \downarrow \\ s_2 f \end{array}, \begin{array}{c} FS_1 \\ \downarrow \\ d_1 \end{array}, \begin{array}{c} FS_2 \\ \downarrow \\ d_2 \end{array} \right)^t.$$

The system is $\frac{dx}{dt} = \Sigma \cdot \Psi(x) = P(x)$, which consists of **multivariate polynomials**.

Steady States

The steady states are the (non negative) real zero locus

$$P_1(x) = \cdots = P_s(x) = 0.$$

They form the (non negative) real **variety** of the polynomial ideal $\langle P_1, \dots, P_s \rangle$.

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Toric steady states

Chemical reaction systems with toric steady states

- If the steady state ideal of the system is a **binomial ideal**, we say that the system has **toric steady states**. In this case, the steady states can be **explicitly parametrized** by monomials (or shown to be empty) and we can check for **multistationarity** (under some hypotheses).
- The chemical reaction system associated to the multisite phosphorylation of a protein by a kinase/phosphatase pair in a sequential and distributive mechanism has toric steady states.
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Steady states

Steady states

- As a steady state (x_1, x_2, \dots, x_s) satisfies

$$\Sigma\Psi(x) = 0,$$

$\Psi(x)$ belongs to the **kernel** of Σ .

Example

A basis of $\text{Ker}(\Sigma)$:

$$\begin{bmatrix} (k_{\text{off}_0} + k_{\text{cat}_0})k_{\text{on}_1}k_{\text{cat}_1}l_{\text{on}_1}l_{\text{on}_0}l_{\text{cat}_0} \\ 0 \\ 0 \\ k_{\text{on}_0}k_{\text{on}_1}k_{\text{cat}_1}l_{\text{on}_1}l_{\text{on}_0}l_{\text{cat}_0} \\ 0 \\ 0 \\ k_{\text{on}_0}k_{\text{cat}_0}k_{\text{on}_1}k_{\text{cat}_1}l_{\text{on}_1}(l_{\text{cat}_0} + l_{\text{off}_0}) \\ 0 \\ k_{\text{on}_0}k_{\text{cat}_0}l_{\text{on}_0}k_{\text{on}_1}k_{\text{cat}_1}l_{\text{on}_1} \\ 0 \end{bmatrix} \quad \begin{bmatrix} 0 \\ k_{\text{on}_0}k_{\text{cat}_0}l_{\text{on}_0}(k_{\text{off}_1} + k_{\text{cat}_1})l_{\text{on}_1}l_{\text{cat}_1} \\ 0 \\ 0 \\ k_{\text{on}_0}k_{\text{cat}_0}l_{\text{on}_0}k_{\text{on}_1}l_{\text{on}_1}l_{\text{cat}_1} \\ 0 \\ 0 \\ k_{\text{on}_0}k_{\text{cat}_0}l_{\text{on}_0}k_{\text{on}_1}k_{\text{cat}_1}(l_{\text{cat}_1} + l_{\text{off}_1}) \\ 0 \\ k_{\text{on}_0}k_{\text{cat}_0}l_{\text{on}_0}k_{\text{on}_1}k_{\text{cat}_1}l_{\text{on}_1} \end{bmatrix}$$

e_3 , e_6 .

We call them b^1, b^2, b^3, b^4 , respectively.

Property 1

The partition $I_1 = \{1, 4, 7, 9\}$, $I_2 = \{2, 5, 8, 10\}$, $I_3 = \{3\}$, $I_4 = \{6\}$ of $\{1, 2, \dots, 10\}$ and the basis $b^1, b^2, b^3, b^4 \in \mathbb{R}^{10}$ of $\ker(\Sigma)$ satisfy $\text{supp}(b^i) = I_i$ (the supports are thus disjoint!).

$$\begin{array}{c}
 \left[\begin{array}{cc}
 (k_{\text{off}_0} + k_{\text{cat}_0})k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} l_{\text{on}_0} l_{\text{cat}_0} & 0 \\
 0 & k_{\text{on}_0} k_{\text{cat}_0} l_{\text{on}_0} (k_{\text{off}_1} + k_{\text{cat}_1}) l_{\text{on}_1} l_{\text{cat}_1} \\
 0 & 0 \\
 k_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} l_{\text{on}_0} l_{\text{cat}_0} & 0 \\
 0 & k_{\text{on}_0} k_{\text{cat}_0} l_{\text{on}_0} k_{\text{on}_1} l_{\text{on}_1} l_{\text{cat}_1} \\
 0 & 0 \\
 k_{\text{on}_0} k_{\text{cat}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} (l_{\text{cat}_0} + l_{\text{off}_0}) & 0 \\
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 k_{\text{on}_0} k_{\text{cat}_0} l_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} & 0 \\
 0 & k_{\text{on}_0} k_{\text{cat}_0} l_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1}
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 \hline
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 \hline
 0 & 0 \\
 \hline
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 \hline
 0 & k_{\text{on}_0} k_{\text{cat}_0} l_{\text{on}_0} k_{\text{on}_1} l_{\text{on}_1} l_{\text{cat}_1} \\
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 \hline
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 \end{array} \right]$$

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The steady state ideal is then generated by the binomials:

$$\begin{aligned} b_1^1 c_0 - b_4^1 s_0 e &= 0, & b_2^2 c_1 - b_5^2 s_1 e &= 0, \\ b_1^1 s_1 f - b_7^1 s_0 e &= 0, & b_2^2 s_2 f - b_8^2 s_1 e &= 0, \\ b_1^1 d_1 - b_9^1 s_0 e &= 0, & b_2^2 d_2 - b_{10}^2 s_1 e &= 0. \end{aligned}$$

Hence, the steady states are toric, but ... are there any positive steady states?

Property 2

For all $j \in \{1, 2, 3, 4\}$, the nonzero entries of b^j have the same sign.

$$\begin{bmatrix} (k_{\text{off}_0} + k_{\text{cat}_0})k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} l_{\text{on}_0} l_{\text{cat}_0} \\ 0 \\ 0 \\ k_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} l_{\text{on}_0} l_{\text{cat}_0} \\ 0 \\ 0 \\ k_{\text{on}_0} k_{\text{cat}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} (l_{\text{cat}_0} + l_{\text{off}_0}) \\ 0 \\ k_{\text{on}_0} k_{\text{cat}_0} l_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_1} l_{\text{on}_1} \\ 0 \end{bmatrix}$$

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This can also be checked by studying the signs of a special set of submatrices of Σ **without** needing to compute the kernel.

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- Since all steady states must satisfy the binomials shown before, the preceding Property 2 is *necessary* for the existence of positive steady states.
- In working towards sufficiency, observe that the system of binomials can be rewritten as

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- From Property 2 we know that the right-hand sides of the above equations are positive. In addition, we are interested in positive solutions $x \in \mathbb{R}_{>0}^9$, so we now apply $\ln(\cdot)$ and examine the new system:

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- Since all steady states must satisfy the binomials shown before, the preceding Property 2 is *necessary* for the existence of positive steady states.
- In working towards sufficiency, observe that the system of binomials can be rewritten as

$$\begin{aligned} \frac{c_0}{s_0 e} &= \frac{b_4^1}{b_1^1}, & \frac{c_1}{s_1 e} &= \frac{b_5^2}{b_7^2}, \\ \frac{s_1 f}{s_0 e} &= \frac{b_7^1}{b_1^1}, & \frac{s_2 f}{s_1 e} &= \frac{b_8^2}{b_5^2}, \\ \frac{d_1}{s_0 e} &= \frac{b_9^1}{b_1^1}, & \frac{d_2}{s_1 e} &= \frac{b_{10}^2}{b_2^2}. \end{aligned}$$

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$$(\ln x) \Delta = \Theta_{\kappa}$$

■ Where

$$\ln x = (\ln(s_0), \ln(s_1), \ln(s_2), \ln(c_0), \ln(c_1), \ln(d_1), \ln(d_2), \ln(e), \ln(f)),$$



$$\Delta = [e_4 - e_8 - e_1 \mid e_9 + e_2 - e_8 - e_1 \mid e_6 - e_8 - e_1 \mid e_5 - e_8 - e_2 \mid \\ e_9 + e_3 - e_8 - e_2 \mid e_7 - e_8 - e_2],$$

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$$\Theta_{\kappa} = \left(\ln \frac{b_4^1}{b_1^1}, \ln \frac{b_7^1}{b_1^1}, \ln \frac{b_9^1}{b_1^1}, \ln \frac{b_5^2}{b_2^2}, \ln \frac{b_8^2}{b_2^2}, \ln \frac{b_{10}^2}{b_2^2} \right).$$

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Property 3

The linear system $(\ln x) \Delta = \Theta_{\kappa}$ has a real solution $(\ln x) \in \mathbb{R}^5$.

Call U the matrix with integer entries whose columns form a basis of the kernel of Δ :

$$\Delta U = \mathbf{0} .$$

Basic Linear Algebra implies that equation $(\ln x) \Delta = \Theta_{\kappa}$ has a solution, if and only if

$$\Theta_{\kappa} U = 0 .$$

It is straightforward to check that, in our case, Δ has rank 6 and hence full rank. Thus the system has a real solution.

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Parametrization

- Recall $I_1 = \{1, 4, 7, 9\}$, $I_2 = \{2, 5, 8, 10\}$.
- Let $A \in \mathbb{Z}^{w \times 9}$ be a matrix of maximal rank w such that
$$\ker(A) = \langle y_1 - y_4, y_1 - y_7, y_1 - y_9, y_2 - y_5, y_2 - y_8, y_2 - y_{10} \rangle.$$
- Let A_i denote the i -th column of A .
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- Then all positive solutions $x \in \mathbb{R}_{>0}^9$ to the binomial system can be written as

$$x = \left(\tilde{x}_1 t^{A_1}, \tilde{x}_2 t^{A_2}, \dots, \tilde{x}_9 t^{A_9} \right),$$

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Example

In our case:

$$A = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 \\ 0 & 1 & 2 & 1 & 2 & 1 & 2 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix} .$$

We have the following particular solution:

$$s_0 = e = f = 1, \quad s_1 = \frac{b_7^1}{b_1^1}, \quad s_2 = \frac{b_8^2 b_7^1}{b_1^1 b_2^2}, \quad c_0 = \frac{b_4^1}{b_1^1}, \quad c_1 = \frac{b_5^2 b_7^1}{b_1^1 b_2^2}, \quad d_1 = \frac{b_9^1}{b_1^1}, \quad d_2 = \frac{b_{10}^2 b_7^1}{b_1^1 b_2^2} .$$

Therefore we obtain the following 3-dimensional parametrization of the steady state locus:

$$\mathbb{R}_{>0}^3 \rightarrow \mathbb{R}_{>0}^9$$

$$(t_1, t_2, t_3) \mapsto \left(t_1, \frac{b_7^1}{b_1^1} t_1 t_2, \frac{b_8^2 b_7^1}{b_1^1 b_2^2} t_1 t_2^2, \frac{b_4^1}{b_1^1} t_1 t_2 t_3, \frac{b_5^2 b_7^1}{b_1^1 b_2^2} t_1 t_2^2 t_3, \frac{b_9^1}{b_1^1} t_1 t_2 t_3, \frac{b_{10}^2 b_7^1}{b_1^1 b_2^2} t_1 t_2^2 t_3, t_2 t_3, t_3 \right) .$$

$$t_1 = s_0, \quad t_2 = e/f, \quad t_3 = f$$

For the n -site phosphorylation system we have

$$\Sigma_n \in \mathbb{R}^{(3n+3) \times (4n+2)}.$$

It holds that $\text{rank}(\Sigma_n) = 3n$ or equivalently, the space of conservation relations has dimension 3.

Explicit (and natural) conservation relations show that **each invariant polyhedron** of any trajectory (starting at a point in the positive orthant) is **bounded** and there are **no** boundary steady states (but none of this is used in the following result)

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Conclusions

- We found sufficient conditions for a chemical reaction network to have toric steady states.
- Steady states of chemical reaction networks with toric steady states can be explicitly parametrized with monomials.
- Multistationarity (for some parameters) can be checked.
- Good estimates for the number of steady states (for given parameters) in a stoichiometric compatibility class?
- Stability of these steady states?

Thanks!