Sequential and distributive multisite phosphorylations have toric steady states

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Overview

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 [http://arxiv.org/abs/1102.1590]

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The multisite phosphorylation network

Following notation of Wang and Sontag 2008,
the **n-site phosphorylation network** is:

$$S_0 + E \underset{k_{\text{off}_0}}{\overset{k_{\text{on}_0}}{\rightleftarrows}} ES_0 \overset{k_{\text{cat}_0}}{\rightarrow} S_1 + E \underset{k_{\text{off}_1}}{\overset{k_{\text{on}_1}}{\rightleftarrows}} \rightarrow \cdots \rightarrow S_{n-1} + E \underset{k_{\text{off}_{n-1}}}{\overset{k_{\text{on}_{n-1}}}{\rightleftarrows}} ES_{n-1} \rightarrow S_n + E$$

$$S_n + F \underset{l_{\text{off}_{n-1}}}{\overset{l_{\text{on}_{n-1}}}{\rightleftarrows}} FS_n \overset{l_{\text{cat}_{n-1}}}{\rightarrow} S_{n-1} + F \leftrightarrows \cdots \rightarrow S_1 + F \underset{l_{\text{off}_0}}{\overset{l_{\text{on}_0}}{\rightleftarrows}} FS_1 \overset{l_{\text{cat}_0}}{\rightarrow} S_0 + F$$

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

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

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

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

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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

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

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:

The system.

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Example

$$\Sigma = \begin{bmatrix} -k_{\text{on}_0} & 0 & 0 & k_{\text{off}_0} & 0 & 0 & 0 & 0 & l_{\text{cat}_0} & 0 \\ 0 & -k_{\text{on}_1} & 0 & k_{\text{cat}_0} & k_{\text{off}_1} & 0 & -l_{\text{on}_0} & 0 & l_{\text{off}_0} & l_{\text{cat}_1} \\ 0 & 0 & 0 & 0 & k_{\text{cat}_1} & 0 & 0 & -l_{\text{on}_1} & 0 & l_{\text{off}_1} \\ k_{\text{on}_0} & 0 & 0 & -k_{\text{off}_0} - k_{\text{cat}_0} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_{\text{on}_1} & 0 & 0 & -k_{\text{off}_1} - k_{\text{cat}_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & l_{\text{on}_0} & 0 & -l_{\text{cat}_0} - l_{\text{off}_0} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & l_{\text{on}_1} & 0 & -l_{\text{cat}_1} - l_{\text{off}_1} \\ -k_{\text{on}_0} & -k_{\text{on}_1} & 0 & k_{\text{off}_0} + k_{\text{cat}_0} & k_{\text{off}_1} + k_{\text{cat}_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -l_{\text{on}_0} & -l_{\text{on}_1} & l_{\text{cat}_0} + l_{\text{off}_0} & l_{\text{cat}_1} + l_{\text{off}_1} \end{bmatrix}$$

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

$$\Psi(\mathbf{x}) = (\overset{S_0+E}{\overset{\downarrow}{s_0e}}, \overset{S_1+E}{\overset{\downarrow}{s_1e}}, \overset{S_2+E}{\overset{\downarrow}{s_2e}}, \overset{ES_0}{\overset{\downarrow}{c_0}}, \overset{ES_1}{\overset{\downarrow}{c_1}}, \overset{S_0+F}{\overset{\downarrow}{s_0f}}, \overset{S_1+F}{\overset{\downarrow}{s_1f}}, \overset{S_2+F}{\overset{\downarrow}{s_2f}}, \overset{FS_1}{\overset{\downarrow}{d_1}}, \overset{FS_2}{\overset{\downarrow}{d_2}})^t.$$

The system is $\frac{dx}{dt} = \Sigma.\Psi(x) = P(x)$, 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 $\langle P_1, \ldots, P_s \rangle$.

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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.
- This result is implicit in [Wang and Sontag, 2008] and it is a particular case of [Thomson and Gunawardena, 2009].

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Steady states

Steady states

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

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

$\Psi(x)$ belongs to the kernel of Σ.

Example

A basis of $Ker(\Sigma)$:

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

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 $\{1,2,\ldots,10\}$ and the basis $b^1, b^2, b^3, b^4 \in \mathbb{R}^{10}$ of $\ker(\Sigma)$ satisfy $\mathrm{supp}(b^i) = I_i$ (the supports are thus disjoint!).

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

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The steady state ideal is then generated by the binomials:

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

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.

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

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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

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

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

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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 $x \in \mathbb{R}^9_{>0}$, so we now apply $\ln(\cdot)$ and examine the new system:

- Since all steady states must satisfy the binomials shown before, the preceding Property 2 is *necessary* for the existence of positive steady states.
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$$(\ln x)\,\Delta = \Theta_\kappa$$

- Where

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

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

- and

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

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Property 3

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

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.
- Let $\tilde{x} \in \mathbb{R}^9_{>0}$ be a positive steady state of the chemical reaction system.

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Parametrization

- Then all positive solutions $x \in \mathbb{R}^9_{>0}$ to the binomial system can be written as

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

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  for some $t \in \mathbb{R}^w_{>0}$.
- In particular, the positive steady state locus has dimension w and can be parametrized by monomials in the concentrations.

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:

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

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

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

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

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

For the *n*-site phosphorylation system we have

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

It holds that $\mathrm{rank}(\Sigma_n) = 3n$ 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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The n-site phosphorylation system has toric steady states. The steady state locus has dimension 3 and can be explicitly parametrized by monomials.

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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!