Enzymatic networks and toric steady states

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Aim

- To find a graphical method for detecting toric steady states.

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We will construct some graphs from the reaction network and give some *sufficient* conditions on these graphs to guarantee toric steady states.

What are toric steady states?

(Enzymatic) Chemical Reaction Network

$$S + E \underset{k_2}{\overset{k_1}{\rightleftarrows}} Y_1 \overset{k_3}{\rightarrow} P + E$$

$$P + F \underset{k_5}{\overset{k_4}{\rightleftarrows}} Y_2 \overset{k_6}{\rightarrow} S + F$$

$\underset{\textit{mass action kinetics}}{\longrightarrow}$

Polynomial dynamical system

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x})$$

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Steady states

They are the nonnegative zeros of a set of *polynomial* equations, $f_1(\mathbf{x}) = 0, \cdots, f_s(\mathbf{x}) = 0$.

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They are the nonnegative zeros of a set of *polynomial* equations, $f_1(\mathbf{x}) = 0, \cdots, f_s(\mathbf{x}) = 0$.

Toric steady states

We say the system has *toric steady states* if the steady state ideal is a binomial ideal and it admits nonnegative zeros.

Why do we want toric steady states?

If the system has toric steady states, then

- the steady states can be explicitly parametrized by monomials (or shown to be empty).

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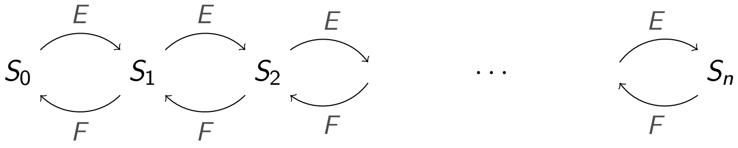
If the system has toric steady states, then

- the steady states can be explicitly parametrized by monomials (or shown to be empty).
- there are necessary and sufficient conditons that allow to decide about multistationarity and they take the form of linear inequality systems.

Known example

We showed in [–,Dickenstein,Shiu,Conradi(2012)] that the system associated to the multisite phosphorylation of a protein by a kinase/phosphatase pair in a sequential and distributive mechanism has toric steady states



Are there more?

We want to find more "seeable" examples.

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Toric steady states ⇒ rational parametrization of steady states.

The rational parameterisation theorem for multisite post-translational modification systems

Matthew Thomson [a], Jeremy Gunawardena [b,*]

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[b] Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA

M. Thomson and J. Gunawardena. J. Theor. Biol. 261, (2009), pp. 626–636.

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- They ask for $\{Enzymes\} \cap \{Substrates\} = \emptyset$ $\leadsto$ we want to consider cascades.
- We want *more* than a rational parametrization: we want *binomials*.

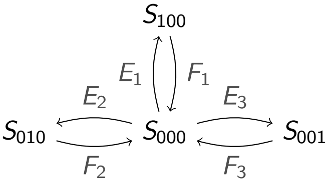
Running example

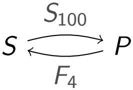
$$S_{000} + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} Y_1 \overset{k_3}{\rightarrow} S_{100} + E_1 \qquad S_{100} + F_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} Y_2 \underset{k_7}{\overset{k_6}{\rightleftarrows}} Y_3 \overset{k_8}{\rightarrow} S_{0000} + F_1$$

$$S_{000} + E_2 \underset{k_{10}}{\overset{k_9}{\rightleftarrows}} Y_4 \overset{k_{11}}{\rightarrow} S_{010} + E_2 \qquad S_{010} + F_2 \underset{k_{13}}{\overset{k_{12}}{\rightleftarrows}} Y_5 \overset{k_{14}}{\rightarrow} S_{000} + F_2$$

$$S_{000} + E_3 \underset{k_{16}}{\overset{k_{15}}{\rightleftarrows}} Y_6 \overset{k_{17}}{\rightarrow} S_{001} + E_3 \qquad S_{001} + F_3 \underset{k_{19}}{\overset{k_{18}}{\rightleftarrows}} Y_7 \overset{k_{20}}{\rightarrow} S_{000} + F_3$$

$$S + S_{100} \underset{k_{22}}{\overset{k_{21}}{\rightleftarrows}} Y_8 \overset{k_{23}}{\rightarrow} P + S_{100} \qquad P + F_4 \underset{k_{25}}{\overset{k_{24}}{\rightleftarrows}} Y_9 \overset{k_{26}}{\rightarrow} S + F_4$$





Running example

$$S_{000} + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} Y_1 \overset{k_3}{\rightarrow} {\color{purple}S_{100}} + E_1 \qquad {\color{purple}S_{100}} + F_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} {\color{blue}Y_2} \underset{{\color{blue}k_7}}{\overset{{\color{blue}k_6}}{\rightleftarrows}} {\color{blue}Y_3} \overset{k_8}{\rightarrow} S_{0000} + F_1$$

$$S_{000} + E_2 \underset{k_{10}}{\overset{k_9}{\rightleftarrows}} Y_4 \overset{k_{11}}{\rightarrow} S_{010} + E_2 \qquad S_{010} + F_2 \underset{k_{13}}{\overset{k_{12}}{\rightleftarrows}} Y_5 \overset{k_{14}}{\rightarrow} S_{000} + F_2$$

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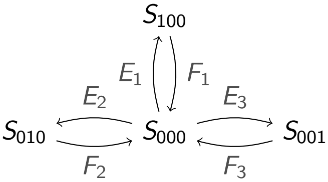
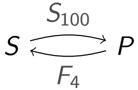
$$S + {\color{purple}S_{100}} \underset{k_{22}}{\overset{k_{21}}{\rightleftarrows}} Y_8 \overset{k_{23}}{\rightarrow} P + {\color{purple}S_{100}} \qquad P + F_4 \underset{k_{25}}{\overset{k_{24}}{\rightleftarrows}} Y_9 \overset{k_{26}}{\rightarrow} S + F_4$$





Intermediate species

The equations:

$$dy_1/dt = k_1 s_{000} e_1 - (k_2 + k_3) y_1$$

$$dy_2/dt = k_4 s_{100} f_1 - (k_5 + k_6) y_2 + k_7 y_3$$

$$dy_3/dt = k_6 y_2 - (k_7 + k_8) y_3$$

$$dy_4/dt = k_9 s_{000} e_2 - (k_{10} + k_{11}) y_4$$

$$dy_5/dt = k_{12} s_{010} f_2 - (k_{13} + k_{14}) y_5$$

$$dy_6/dt = k_{15} s_{000} e_3 - (k_{16} + k_{17}) y_6$$

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$$dy_8/dt = k_{21} s.s_{100} - (k_{22} + k_{23}) y_8$$

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The equations:

$$0 = k_1 s_{000} e_1 - (k_2 + k_3) y_1$$

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All of them are *binomials* except for...

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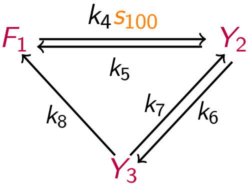
Intermediate species

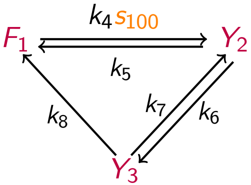
$$S_{100} + F_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} Y_2 \underset{k_7}{\overset{k_6}{\rightleftarrows}} Y_3 \overset{k_8}{\rightarrow} S_{0000} + F_1 \qquad S_{000} + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} Y_1 \overset{k_3}{\rightarrow} S_{100} + E_1$$



$$E_1 \underset{k_2 + k_3}{\overset{k_1 s_{000}}{\rightleftarrows}} Y_1$$

Intermediate species

$$S_{100}+F_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} Y_2 \underset{k_7}{\overset{k_6}{\rightleftarrows}} Y_3 \overset{k_8}{\rightarrow} S_{0000}+F_1 \qquad S_{000}+E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} Y_1 \overset{k_3}{\rightarrow} S_{100}+E_1$$



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Immediate binomial.

Intermediate species

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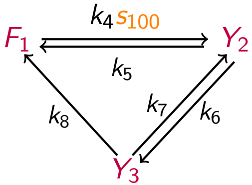

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Immediate binomial.

Binomials at s.s.:

$\rho_2 f_1 - \rho_1 y_2 = 0$

$\rho_3 f_1 - \rho_1 y_3 = 0$, where

Condition I: Strongly connected.

Intermediate species

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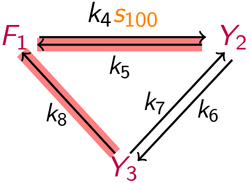

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$$\rho_1 = k_5 k_8 + k_7 k_5 + k_6 k_8 \in \mathbb{R}$$

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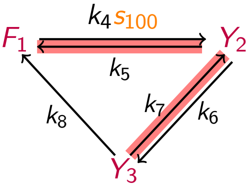

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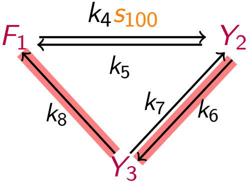

$$S_{000} + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} Y_1 \overset{k_3}{\to} S_{100} + E_1$$

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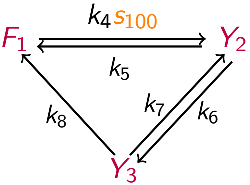

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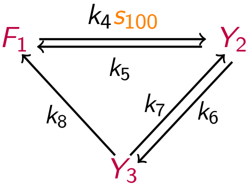

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$\rho_2 = (k_8 k_4 + k_7 k_4) s_{100} \leftarrow$monomial

Condition I: Strongly connected.

Condition II: Only one directed path from the enzyme to the each intermediate.

Intermediate species

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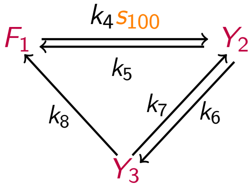

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$\rho_2 = (k_8 k_4 + k_7 k_4) s_{100}$ ←monomial

$\rho_3 = k_6 k_4 s_{100}$ ←monomial

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Intermediate species

$dy_i/dt = 0$
$1 \leq i \leq 9$

$$\Longleftrightarrow$$

$$\underbrace{\begin{aligned} \rho_1 e_1 - \rho_{e_1} y_1 &= 0 \\ \rho_2 f_1 - \rho_{f_1} y_2 &= 0 \\ \rho_3 f_1 - \rho_{f_1} y_3 &= 0 \\ \rho_4 e_2 - \rho_{e_2} y_4 &= 0 \\ \rho_5 f_2 - \rho_{f_2} y_5 &= 0 \\ \rho_6 e_3 - \rho_{e_3} y_6 &= 0 \\ \rho_7 f_3 - \rho_{f_3} y_7 &= 0 \\ \rho_8 s_{100} - \rho_{s_{1000}} y_8 &= 0 \\ \rho_9 f_4 - \rho_{f_4} y_9 &= 0 \end{aligned}}_{\text{binomials}}$$

We can solve for y_i:

$$y_2 = \frac{\rho_2}{\rho_{f_1}} f_1 = \frac{\lambda_2 s_{100}}{\rho_{f_1}} f_1 = \xi_2 s_{100} f_1, \quad \xi_2 \in \mathbb{R}$$

Enzymes and Substrates

$$de_1/dt = -dy_1/dt$$
$$de_2/dt = -dy_4/dt$$
$$de_3/dt = -dy_6/dt$$

$$df_1/dt = -(dy_2/dt + dy_3/dt)$$
$$df_2/dt = -dy_5/dt$$
$$df_3/dt = -dy_7/dt$$
$$df_4/dt = -dy_9/dt$$

$$\begin{aligned}
ds_{100}/dt &= -\, dy_8/dt + k_3 y_1 - k_4 s_{100} f_1 + k_5 y_2 \\
ds_{000}/dt &= -\, k_1 s_{000} e_1 + k_2 y_1 + k_8 y_3 - k_9 s_{000} e_2 + k_{10} y_4 + k_{14} y_5 - \\
&\quad -\, k_{15} s_{000} e_3 + k_{16} y_6 + k_{20} y_7 \\
ds_{010}/dt &= -\, k_{12} s_{010} f_2 + k_{13} y_5 + k_{11} y_4 \\
ds_{001}/dt &= -\, k_{18} s_{001} f_3 + k_{19} y_7 + k_{17} y_6 \\
ds/dt &= -\, k_{21} s.s_{100} + k_{22} y_8 + k_{26} y_9 \\
dp/dt &= -\, k_{24} p f_4 + k_{25} y_9 + k_{23} y_8
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All of them are *binomials* except for...

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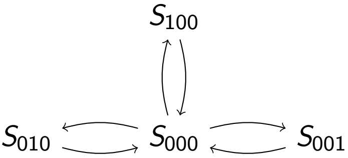
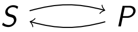
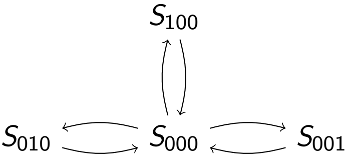
$$ds_{100}/dt = -dy_8/dt + k_3\xi_1 s_{000}e_1 - (k_4 - k_5\xi_2)s_{100}f_1$$
$$ds_{000}/dt = -(k_1 - k_2\xi_1)s_{000}e_1 + k_8\xi_3 s_{100}f_1 - (k_9 - k_{10}\xi_4)s_{000}e_2 + + k_{14}\xi_5 s_{010}f_2 - (k_{15} - k_{16}\xi_6)s_{000}e_3 + k_{20}\xi_7 s_{001}f_3$$
$$ds_{010}/dt = -(k_{12} - k_{13}\xi_5)s_{010}f_2 + k_{11}\xi_4 s_{000}e_2$$
$$ds_{001}/dt = -(k_{18} - k_{19}\xi_7)s_{001}f_3 + k_{17}\xi_6 s_{000}e_3$$
$$ds/dt = -(k_{21} - k_{22}\xi_8)s.s_{100} + k_{26}\xi_9 pf_4$$
$$dp/dt = -(k_{24} - k_{25}\xi_9)pf_4 + k_{23}\xi_8 s.s_{100}$$

~~Enzymes~~ and Substrates



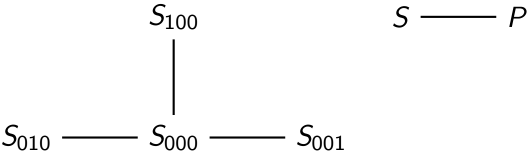


~~Enzymes~~ and Substrates



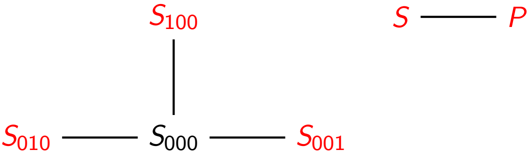
Condition III: multiple directed edges are *not allowed*

~~Enzymes~~ and Substrates



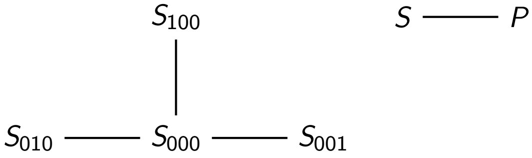
Condition III: multiple directed edges are *not allowed*
Condition IV(a): reversible + forest

~~Enzymes~~ and Substrates



Condition III: multiple directed edges are *not allowed*
Condition IV(a): reversible + forest

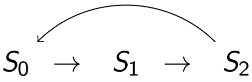
~~Enzymes~~ and Substrates



Condition III: multiple directed edges are *not allowed*

Condition IV(a): reversible + forest

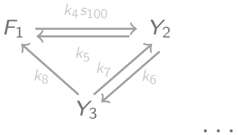
Condition IV(b): outdegree, indegree ≤ 1



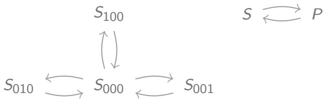
Theorem

Theorem
Given an enzymatic chemical reaction network $G = (V, \mathcal{R}, k_i)$. Assume Conditions I and II hold for each digraph G_T and Condition III holds for G, if the digraph G_S satisfies either Condition IV(a) or Condition IV(b), then the mass action system arising from G has toric steady states.

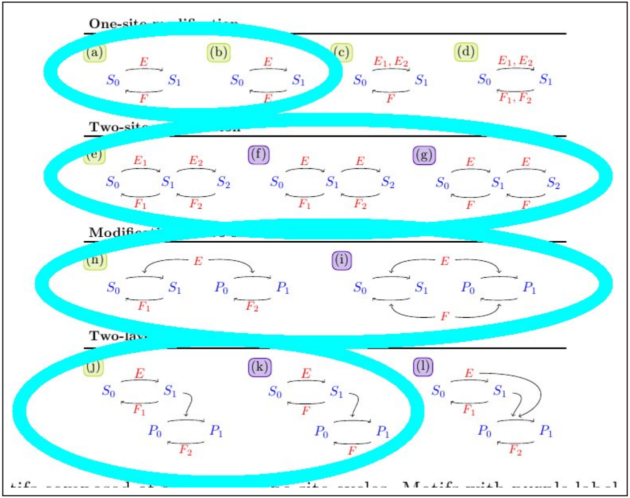
G_T



G_S



More examples

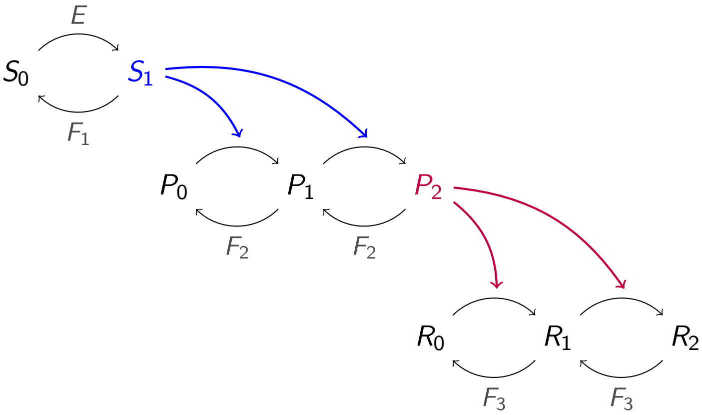


E. Feliu and C. Wiuf. *Enzyme sharing as a cause of multistationarity in signaling systems.*

J. Roy. Soc. Interf., 9:71, (2012), pp. 1224–1232.

Another relevant example

Cascades such as the MAPK/ERK pathway:



G_T and G_S:

G_T:

$$E \underset{k_2+k_3}{\overset{k_1 S_0}{\rightleftarrows}} Y_1 \qquad F_1 \underset{k_5+k_6}{\overset{k_4 S_1}{\rightleftarrows}} Y_2$$

$$Y_3 \underset{k_8+k_9}{\overset{k_7 P_0}{\leftrightarrows}} S_1 \underset{k_{11}+k_{12}}{\overset{k_{10} P_1}{\rightleftarrows}} Y_4$$

$$Y_5 \underset{k_{14}+k_{15}}{\overset{k_{13} P_2}{\leftrightarrows}} F_2 \underset{k_{17}+k_{18}}{\overset{k_{16} P_1}{\rightleftarrows}} Y_6$$

$$Y_7 \underset{k_{20}+k_{21}}{\overset{k_{19} R_0}{\leftrightarrows}} P_2 \underset{k_{23}+k_{24}}{\overset{k_{22} R_1}{\rightleftarrows}} Y_8$$

$$Y_9 \underset{k_{26}+k_{27}}{\overset{k_{25} R_2}{\leftrightarrows}} F_3 \underset{k_{29}+k_{30}}{\overset{k_{28} R_1}{\rightleftarrows}} Y_{10}$$

G_S:

S_0 —— S_1

P_0 —— P_1 —— P_2

R_0 —— R_1 —— R_2

Thanks for your attention!