Proving Global Stability of Processive Phosphorylation Systems

Using Graph Reductions

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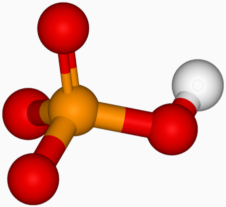


Review

From last time:

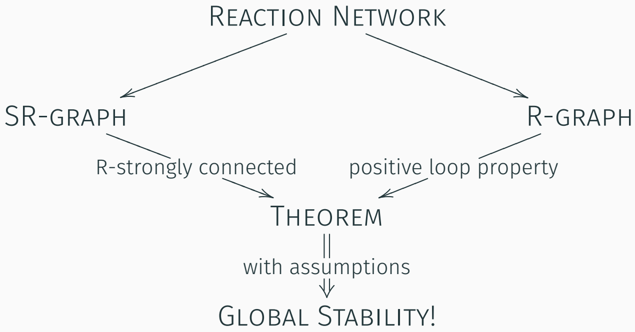
- A chemical reaction network is a graph with species, reactions and complexes

$$A + B \xrightarrow{k_1} 3A + C \xrightarrow{k_2} D$$

- Mass-action kinematics converts a network into a dynamical system
- Monotone theory is used to prove global stability

Graph Constructions

Graph Constructions



We use the setup from [1].

Graph Constructions

The SR-graph

- The **SR-graph** is a directed graph $G_{SR} = (V_{SR}, E_{SR}, L_{SR})$
- The set of vertices V_{SR} is the union of all species and reactions
- Rules governing edges and labels:
    1. If a species S is a reactant in any reaction or a product in a reversible reaction, then $\overrightarrow{SR}, \overrightarrow{RS} \in E_{SR}$.
    2. If a species S is a reactant in an irreversible reaction, then $\overrightarrow{RS} \in E_{SR}$.
    3. Let $SR \in E$. If S is a reactant, $L(S, R) := +$ and if S is a product, $L(S, R) := -$.

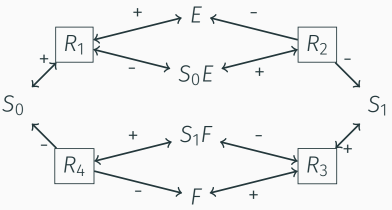
Example (1-site phosphorylation)

Chemical network

$$S_0 + E \overset{R_1}{\rightleftharpoons} S_0E \xrightarrow{R_2} S_1 + E$$

$$S_1 + F \overset{R_3}{\rightleftharpoons} S_1F \xrightarrow{R_4} S_0 + F$$

SR-graph



The R-graph

- The **R-graph** is an undirected graph $G = (V_R, E_R, L_R)$
- The set of vertices V_R is the set of reactions
- Rules governing edges:
    1. If there is a length-2 path connecting R_i and R_j in the SR-graph, then $R_iR_j \in E$
    2. Edges are labeled with the opposite of the product of the labels on the length-2 path

The R-graph

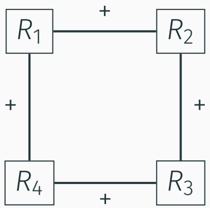
Example (1-site phosphorylation)

Chemical network

$$S_0 + E \underset{}{\overset{R_1}{\rightleftharpoons}} S_0E \xrightarrow{R_2} S_1 + E$$

$$S_1 + F \underset{}{\overset{R_3}{\rightleftharpoons}} S_1F \xrightarrow{R_4} S_0 + F$$

R-graph

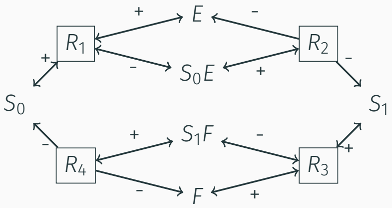


Definition

An SR-graph is *R-strongly connected* if there exists a directed path between every pair of reaction vertices.

Example (1-site phosphorylation)

SR-graph

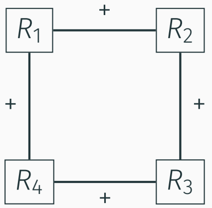


Definition

We say an R-graph has the *positive loop property* if every simple loop has an even number of negative edges.

Example (1-site phosphorylation)

R-graph



Theorem (Global Stability)

Let G be a reaction network satisfying several assumptions. Suppose

1. *the R-graph of G has the positive loop property,*
2. *the directed SR-graph of G is strongly connected,*
3. *concentrations do not not vanish asymptotically (bounded-persistence), and*
4. $\ker \Gamma \cap \operatorname{int} K \neq \emptyset$.

Then G has a unique steady state and it is a global attractor.

Graph Reductions

Removing Intermediates

To remove an **intermediate** Y, the following two conditions must be met:

(I1) Y consists of exactly one species and does not appear in any other complex

(I2) there exist unique complexes y and y' such that

- either $y \rightarrow Y$ or $y \leftrightharpoons Y$ is a reaction
- either $Y \rightarrow y'$ or $Y \leftrightharpoons y'$ is a reaction
- shared species in y and y' (represented by e) have the same weights
- $y - e \rightarrow y' - e, \quad y' - e \rightarrow y - e, \quad y - e \leftrightharpoons y' - e$ and $y' - e \leftrightharpoons y - e$ are *not* reactions

Removing Intermediates

From the network $G = (\mathcal{S}, \mathcal{C}, \mathcal{R})$, we construct the reduced network $G^* = (\mathcal{S}^*, \mathcal{C}^*, \mathcal{R}^*)$.

We define $\mathcal{R}^* := \mathcal{R}_c^* \cup \mathcal{R}_Y^*$, where $\mathcal{R}_Y^*$ is the subset of reactions in $\mathcal{R}$ that do not have Y as a product or reactant and

$$R_Y^* := \begin{cases} \{y - e \leftrightharpoons y' - e\}, & \text{if } y \leftrightharpoons Y, Y \leftrightharpoons y' \in \mathcal{R} \\ \{y - e \rightarrow y' - e\}, & \text{if } y \rightarrow Y \in \mathcal{R}, \text{or } Y \rightarrow y' \in \mathcal{R} \end{cases} . \quad (1)$$

Example (1-site phosphorylation)

$$S_0 + E \underset{}{\overset{R_1}{\rightleftharpoons}} S_0E \xrightarrow{R_2} S_1 + E$$

$$S_1 + F \underset{}{\overset{R_3}{\rightleftharpoons}} S_1F \xrightarrow{R_4} S_0 + F$$

Removing Intermediates

Example (1-site phosphorylation)

$$R_1^* : \; S_0 \longrightarrow S_1$$

$$R_2^* : \; S_1 \longrightarrow S_0$$

Removing Intermediates

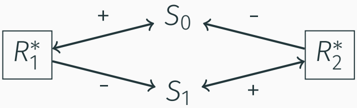
Example (1-site phosphorylation)

Chemical network

$$R_1^* : S_0 \longrightarrow S_1$$

$$R_2^* : S_1 \longrightarrow S_0$$

SR-graph



R-graph

Theorem (Invariance Under Removing Intermediates)

Let G be a reaction network some basic network assumptions. Suppose G^* is a reaction network obtained from G by successive removal of intermediates. Then

1. *the directed SR-graph of G^* is R-strongly connected if, and only if, the directed SR-graph of G is strongly connected,*
2. *the R-graph of G^* has the positive loop property if, and only if, the R-graph of G has the positive loop property,*
3. *G^* is bounded persistent if and only if G is bounded persistent*
4.
5. $ker\, \Gamma^* \cap int\, K^* \neq \emptyset \iff ker\, \Gamma \cap int\, K \neq \emptyset.$

n-site Processive Phosphorylation

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

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

This model captures systems that are reversible, irreversible and have product inhibition.

Last time we showed that the n-site model is globally stable.

Generalized Processive Phosphorylation

$$
\begin{array}{ccccccccccc}
P_1 + E_1 & \rightleftharpoons & C_{11} & \rightleftharpoons & C_{12} & \rightleftharpoons & \dots & \rightleftharpoons & C_{1n_1} & \rightleftharpoons & P_2 + E_1 \\
P_2 + E_2 & \rightleftharpoons & C_{21} & \rightleftharpoons & C_{22} & \rightleftharpoons & \dots & \rightleftharpoons & C_{2n_2} & \rightleftharpoons & P_3 + E_2 \\
\vdots & & & & & & \vdots & & & & \vdots \\
P_m + E_m & \rightleftharpoons & C_{m1} & \rightleftharpoons & C_{m2} & \rightleftharpoons & \dots & \rightleftharpoons & C_{mn_m} & \rightleftharpoons & P_1 + E_m
\end{array}
$$

Theorem (ME)

The dynamical system of the generalized model arising from mass-action kinematics has a unique positive steady state and it is a global attractor.

Generalized Processive Phosphorylation

$$
\begin{array}{ccccccccccc}
P_1 + E_1 & \rightleftharpoons & C_{11} & \rightleftharpoons & C_{12} & \rightleftharpoons & \dots & \rightleftharpoons & C_{1n_1} & \rightleftharpoons & P_2 + E_1 \\
P_2 + E_2 & \rightleftharpoons & C_{21} & \rightleftharpoons & C_{22} & \rightleftharpoons & \dots & \rightleftharpoons & C_{2n_2} & \rightleftharpoons & P_3 + E_2 \\
\vdots & & & & & & \vdots & & & & \vdots \\
P_m + E_m & \rightleftharpoons & C_{m1} & \rightleftharpoons & C_{m2} & \rightleftharpoons & \dots & \rightleftharpoons & C_{mn_m} & \rightleftharpoons & P_1 + E_m
\end{array}
$$

Generalized Processive Phosphorylation

$$
\begin{array}{ccccccccccccc}
P_1 + E_1 & \rightleftharpoons & C_{12} & \rightleftharpoons & \dots & \rightleftharpoons & C_{1n_1} & \rightleftharpoons & P_2 + E_1 \\
P_2 + E_2 & \rightleftharpoons C_{21} \rightleftharpoons & C_{22} & \rightleftharpoons & \dots & \rightleftharpoons & C_{2n_2} & \rightleftharpoons & P_3 + E_2 \\
\vdots & & & & \vdots & & & & \vdots \\
P_m + E_m & \rightleftharpoons C_{m1} \rightleftharpoons & C_{m2} & \rightleftharpoons & \dots & \rightleftharpoons & C_{mn_m} & \rightleftharpoons & P_1 + E_m
\end{array}
$$

Generalized Processive Phosphorylation

$$
\begin{array}{ccccccccccc}
P_1 + E_1 & \rightleftharpoons & & & & & & & C_{1n_1} & \rightleftharpoons & P_2 + E_1 \\
P_2 + E_2 & \rightleftharpoons & C_{21} & \rightleftharpoons & C_{22} & \rightleftharpoons & \ldots & \rightleftharpoons & C_{2n_2} & \rightleftharpoons & P_3 + E_2 \\
\vdots & & & & & & \vdots & & & & \vdots \\
P_m + E_m & \rightleftharpoons & C_{m1} & \rightleftharpoons & C_{m2} & \rightleftharpoons & \ldots & \rightleftharpoons & C_{mn_m} & \rightleftharpoons & P_1 + E_m
\end{array}
$$

Processive Phosphorylation

Generalized Processive Phosphorylation

$$
\begin{array}{ccccccccccc}
 & & & & P_1 & \rightleftharpoons & P_2 & & & & \\
P_2 + E_2 & \rightleftharpoons & C_{21} & \rightleftharpoons & C_{22} & \rightleftharpoons & \dots & \rightleftharpoons & C_{2n_2} & \rightleftharpoons & P_3 + E_2 \\
\vdots & & & & & & \vdots & & & & \vdots \\
P_m + E_m & \rightleftharpoons & C_{m1} & \rightleftharpoons & C_{m2} & \rightleftharpoons & \dots & \rightleftharpoons & C_{mn_m} & \rightleftharpoons & P_1 + E_m
\end{array}
$$

Generalized Processive Phosphorylation

$$P_1 \rightleftharpoons P_2$$

$$P_2 \rightleftharpoons P_3$$

$$\vdots \qquad\qquad \vdots$$

$$P_m \rightleftharpoons P_1$$

Generalized Processive Phosphorylation

$$
\begin{aligned}
P_1 &\rightleftharpoons P_2 \\
P_2 &\rightleftharpoons P_3 \\
\vdots & \qquad \vdots \\
P_m &\rightleftharpoons P_1
\end{aligned}
$$

Generalized Processive Phosphorylation

$$
\begin{aligned}
P_1 &\rightleftharpoons P_3 \\
P_3 &\rightleftharpoons P_4 \\
\vdots & \qquad \vdots \\
P_m &\rightleftharpoons P_1
\end{aligned}
$$

Generalized Processive Phosphorylation

$$P_1 \rightleftharpoons P_m$$

$$P_m \rightleftharpoons P_1$$

Generalized Processive Phosphorylation

$$R_1^* : \; P_1 \rightleftharpoons P_m$$

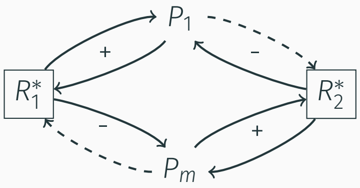
$$R_2^* : \; P_m \rightleftharpoons P_1$$

Chemical network

$$R_1^* : \; P_1 \longrightarrow P_m$$

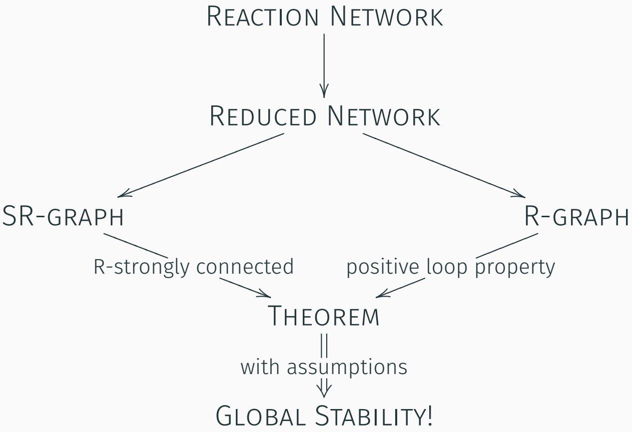
$$R_2^* : \; P_m \longrightarrow P_1$$

SR-graph



R-graph

Graph Constructions



Thank You!

References

[1] M. M. de Freitas, C. Wiuf, and E. Feliu. Intermediates and generic convergence to equilibria. 2016.