# MSRI-MPI LEIPZIG SUMMER GRADUATE SCHOOL 2023

# MESSI SYSTEMS

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# PHOSHO-DEPHOSPHORYLATION: “FUTILE” CYCLE

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

$$S_1 + F \underset{\ell_{\mathrm{off}}}{\overset{\ell_{\mathrm{on}}}{\rightleftarrows}} FS_1 \overset{\ell_{\mathrm{cat}}}{\rightarrow} S_0 + F$$

$E$ and $F$ *enzymes*, $S_0$ and $S_1$ *substrates*, $S_0E$ and $S_1F$ *intermediates*

and we represent it with:
$$\begin{tikzcd} S_0 \arrow[r, bend left, "E"] & S_1 \arrow[l, bend left, "F"] \end{tikzcd}.$$

There are 6 species, 6 complexes (nodes) and 6 reactions (edges)

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# TWO SEQUENTIAL PHOSPHORYLATIONS

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

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

### WE NUMBER THE SPECIES AND THEIR CONCENTRATIONS

$x_1, x_2, x_3$ = concentrations of $S_0, S_1, S_2$

$y_1, y_2, y_3, y_4$ = concentrations of the intermediate species

$x_4$ = concentration of the kinase $E$

$x_5$ = concentration of the phosphatase $F$.

# THE DIFFERENTIAL EQUATIONS AND THE CONSERVATION LAWS

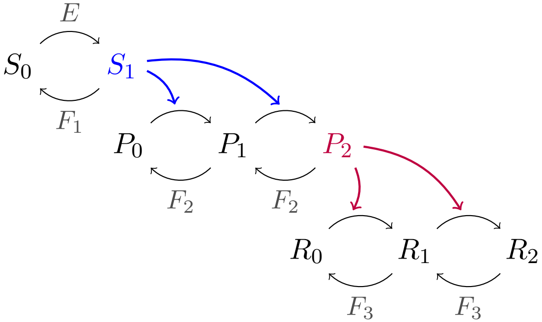
$$\begin{aligned}
\frac{dx_1}{dt} &= -k_{\mathrm{on}_0} x_1 x_4 + k_{\mathrm{off}_0} y_1 + l_{\mathrm{cat}_0} y_4 \\
\frac{dx_2}{dt} &= -k_{\mathrm{on}_1} x_2 x_4 + k_{\mathrm{cat}_0} y_1 + k_{\mathrm{off}_1} y_2 \\
&\quad -l_{\mathrm{on}_0} x_2 x_5 + l_{\mathrm{cat}_1} y_3 + l_{\mathrm{off}_0} y_4 \\
\frac{dx_3}{dt} &= k_{\mathrm{cat}_1} y_2 - l_{\mathrm{on}_1} x_3 x_5 + l_{\mathrm{off}_1} y_3 \\
\frac{dy_1}{dt} &= k_{\mathrm{on}_0} x_1 x_4 - (k_{\mathrm{off}_0} + k_{\mathrm{cat}_0}) y_1 \\
\frac{dy_2}{dt} &= k_{\mathrm{on}_1} x_2 x_4 - (k_{\mathrm{off}_1} + k_{\mathrm{cat}_1}) y_2
\end{aligned}$$

$$\begin{aligned}
\frac{dx_4}{dt} &= -k_{\mathrm{on}_0} x_1 x_4 - k_{\mathrm{on}_1} x_2 x_4 + (k_{\mathrm{off}_0} + k_{\mathrm{cat}_0}) \\
&\quad + (k_{\mathrm{off}_1} + k_{\mathrm{cat}_1}) y_2 \\
\frac{dx_5}{dt} &= -l_{\mathrm{on}_0} x_2 x_5 - l_{\mathrm{on}_1} x_3 x_5 + (l_{\mathrm{off}_1} + l_{\mathrm{cat}_1}) y \\
&\quad + (l_{\mathrm{off}_0} + l_{\mathrm{cat}_0}) y_4 \\
\frac{dy_3}{dt} &= l_{\mathrm{on}_1} x_3 x_5 - (l_{\mathrm{off}_1} + l_{\mathrm{cat}_1}) y_3 \\
\frac{dy_4}{dt} &= l_{\mathrm{on}_0} x_2 x_5 - (l_{\mathrm{off}_0} + l_{\mathrm{cat}_0}) y_4
\end{aligned}$$

$$\begin{aligned}
x_1 + x_2 + x_3 + y_1 + y_2 + y_3 + y_4 &= S_{tot} \\
x_4 + y_1 + y_2 &= E_{tot} \\
x_5 + y_3 + y_4 &= F_{tot}.
\end{aligned}$$

# Other important examples of networks

Phosphorylation cascades



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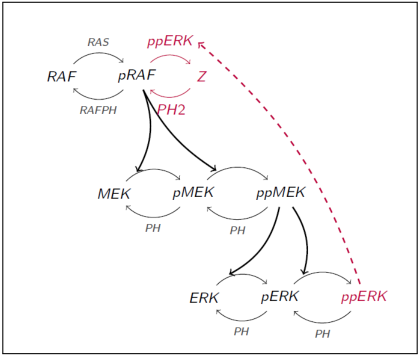
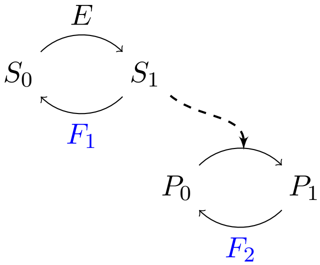
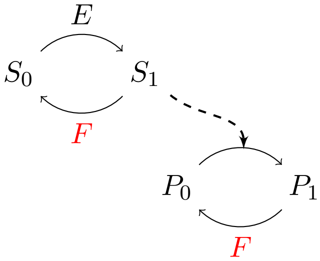
Phosphorylation cascades with retroactivity



# OTHER IMPORTANT EXAMPLES OF NETWORKS

## Different phosphatases vs same phosphatase in a cascade



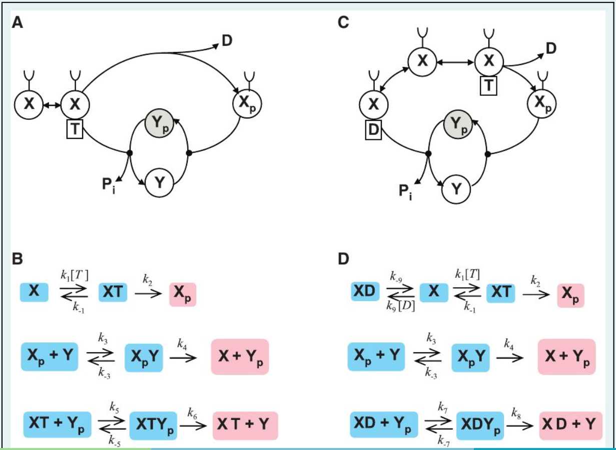


# OTHER IMPORTANT EXAMPLES OF NETWORKS

Bifunctional enzyme in E. coli, Shinar-Feinberg, Science '10

## SHINAR-FEINBERG, SCIENCE '10

$$X = \text{EnvZ}, \qquad Y = \text{OmpR}$$



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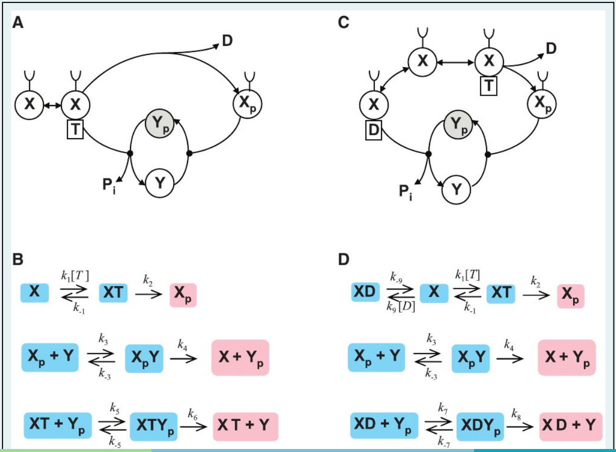
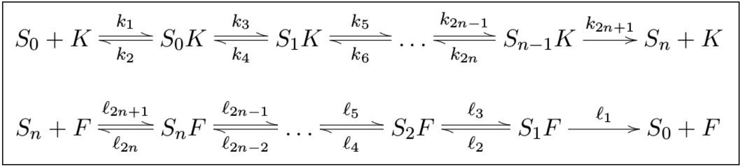


# EXAMPLE: PROCESSIVE PHOSPHORILATIONS

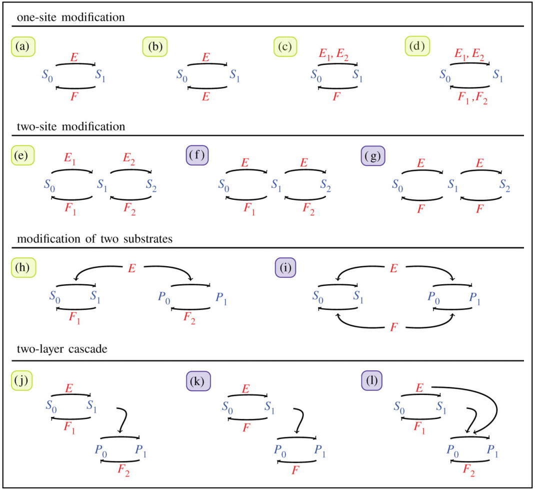


$$S_0 + K \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_0K \underset{k_4}{\overset{k_3}{\rightleftharpoons}} S_1K \underset{k_6}{\overset{k_5}{\rightleftharpoons}} \dots \underset{k_{2n}}{\overset{k_{2n-1}}{\rightleftharpoons}} S_{n-1}K \xrightarrow{k_{2n+1}} S_n + K$$

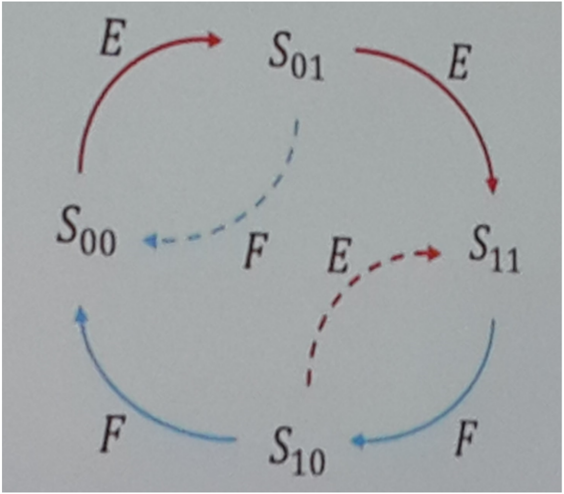
$$S_n + F \underset{\ell_{2n}}{\overset{\ell_{2n+1}}{\rightleftharpoons}} S_nF \underset{\ell_{2n-2}}{\overset{\ell_{2n-1}}{\rightleftharpoons}} \dots \underset{\ell_4}{\overset{\ell_5}{\rightleftharpoons}} S_2F \underset{\ell_2}{\overset{\ell_3}{\rightleftharpoons}} S_1F \xrightarrow{\ell_1} S_0 + F$$

C. CONRADI AND A. SHIU. *A global convergence result for processive multisite phosphorylation systems, 2015.*

# Small motifs ([Alon'07, Feliu-Wiuf'12])



# Shvartsman's enzymatic network



# A common structure [P.Millán-D.'18: The structure of MESSI biological systems]

## MESSI systems

We identified with Mercedes Pérez Millán a **common structure** in many popular biological networks that describe Modifications of type Enzyme-Substrate or Swap with Intermediates, which allows us to prove general results valid in all these networks. MESSI systems include **all** the previous ones.

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# DEFINITION OF A MESSI SYSTEM

A MESSI network is a chemical reaction network satisfying the following properties. When endowed with mass-action kinetics, we have a MESSI system.

- There exists a **partition** of the set $\mathcal{S}$ of species:

$$\mathcal{S} = \underbrace{\mathcal{S}^{(0)}}_{\textbf{intermediates}} \bigsqcup \underbrace{\mathcal{S}^{(1)} \bigsqcup \mathcal{S}^{(2)} \bigsqcup \cdots \bigsqcup \mathcal{S}^{(M)}}_{\textbf{non-intermediates or core}}.$$

- There are two types of complexes: intermediates (consisting of a single intermediate species) and **non-intermediates or core** (consisting of one or two core species, but if there are two, they belong to *distinct* $\mathcal{S}^{(\alpha)}$).
- Notation: $\rightarrow_\circ =$ reacts via a path of intermediates.

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**Examples:** All the examples we mentioned, all the linear ones . . . plus many other common biochemical models.

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### ENZYMES AND SWAPS

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## Conserved quantities: Theorem 1

A MESSI system has one (independent) linear conservation relation associated to each of the subsets $S^{(\alpha)}, 1 \leq \alpha \leq M$, in the partition of the species set corresponding to non-intermediate species:

$$\sum_{\mathbf{X_i} \in \mathcal{S}^{(\alpha)}} x_i + \sum_{\mathbf{X_k} \in \mathrm{Int}_\alpha} x_k = \text{ constant},$$

where $\mathrm{Int}_\alpha = \{\mathbf{X_k} : X_i \rightarrow_\circ \mathbf{X_k} \text{ or } X_i + X_j \rightarrow_\circ \mathbf{X_k} \text{ for some } X_i \in \mathcal{S}^{(\alpha)}\}$.

## Observation:

- Theorem 1 implies that all MESSI systems are conservative (and thus the solutions are defined for any positive time).
- Question: when these span all the linear conservation laws?
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# FROM $G$ TO $G_1$ (WITHOUT INTERMEDIATES)

Going from $G$ to $G_1$ we delete intermediates and we put an edge between two core complexes $y_i \to y_j$ if $y_1 \to_\circ y_j$ in $G$:

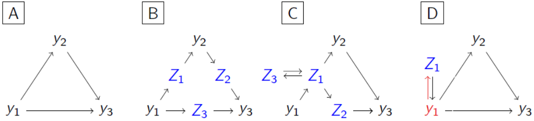

FIGURE: $\mathcal{S}^{(0)} \subseteq \{Z_1, Z_2, Z_3\}, \mathcal{S}^{(1)} = \{y_1, y_2, y_3\}$

In all cases $G = A, B, C, D$ (with rate constants $\kappa$), the associated digraph $G_1$ is $A$.

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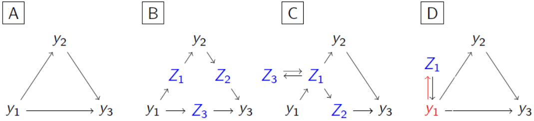

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# RELATION BETWEEN THE STEADY STATES OF $(G, \kappa)$ AND $G_1(\tau, \kappa)$

### PROJECTING THE STEADY STATES

The rational map sending the rate constants $\kappa$ in $G$ to the rate constants $\tau(\kappa)$ in $G_1$ verifies that the steady states of the mass-action chemical reaction systems defined by $G$ with rate constants $\kappa$ and $G_1$ with rate constants $\tau(\kappa)$, are in one-to-one correspondence via the projection $\pi(u, x) = x$, where $u$ is the vector of concentrations of the intermediate species and $x$ is the vector of concentrations of the core species.

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# $G_1 \to G_2$ (HIDE ENZYMES AND SWAPS IN LABELS)

**G : Double seq. phospho.**

$$S_0 + E \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} U_1 \overset{\kappa_3}{\to} S_1 + E \underset{\kappa_5}{\overset{\kappa_4}{\rightleftarrows}} U_2 \overset{\kappa_6}{\to} S_2 + E$$

$$S_2 + F \underset{\kappa_8}{\overset{\kappa_7}{\rightleftarrows}} U_3 \overset{\kappa_9}{\to} S_1 + F \underset{\kappa_{11}}{\overset{\kappa_{10}}{\rightleftarrows}} U_4 \overset{\kappa_{12}}{\to} S_0 + F$$

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$$\Rightarrow$$

$G_2$ :

$$S_0 \underset{\tau_4\, f}{\overset{\tau_1\, e}{\rightleftarrows}} S_1 \underset{\tau_3\, f}{\overset{\tau_2\, e}{\rightleftarrows}} S_2$$

$E \rightleftarrows E$, $F \rightleftarrows F$ loops .

**G : EnvZ − OmpR**

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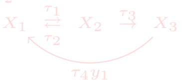

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$$\begin{tikzcd}
X_1 \arrow[r, shift left, "\tau_1"] & X_2 \arrow[l, shift left, "\tau_2"] \arrow[r, "\tau_3"] & X_3 \arrow[ll, bend left, "\tau_4 y_1"]
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# $MG_2, G_2$ AND $G_2^\circ$

- $G_1 \to MG_2$ produces in general a multigraph with loops.
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# AN IMPORTANT PROPERTY

### PERSISTENCE

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If we have a *minimal* partition, we define a new graph $G_E$, whose vertices are the sets $S^{(\alpha)}$ for $\alpha \geq 1$, and there is an edge from $S^{(\alpha)}$ to $S^{(\beta)}$ if there is a species in $S^{(\alpha)}$ on a label of an edge in $G_2$ between species of $S^{(\beta)}$.

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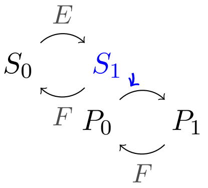
# EXAMPLES



$\mathcal{S}^{(1)} = \{S_0, S_1\}$,
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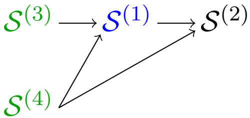

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G: EnvZ-OmpR $S^{(0)}$, $S^{(1)} = \{X, XT, X_p\}$, $S^{(2)} = \{Y, Y_p\}$.

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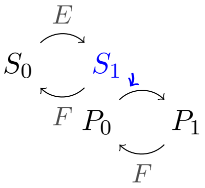

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## DECIDING MULTISTATIONARITY: REMINDER

Assume the steady state variety $V$ is cut out by binomials with exponents in a matrix $B$ and coefficients in $\mathbb{Q}(\kappa)$, or equivalently, it is parametrized by monomials with exponents in the dual matrix $A$. Let $W$ denote a matrix whose rows define the dual of the subspace $S = \langle y_j - y_i, y_i \to y_j \rangle$. If $\mathrm{rank}(W) = \mathrm{rank}(\mathrm{A}) = d$, the following statements are equivalent:

1. There is at most a single positive solution in $V \cap x(0) + S$ for any $x(0)$ in the positive orthant (monostationarity), for any choice of rate constants $\kappa$.
2. For all subsets $J \subseteq [s]$ of cardinality $d$, the product $\det(W) \det(A_J)$ either is zero or has the same sign as all other nonzero products, and at least one such product is nonzero.

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# s-toric MESSI systems

**Definition**

A *structurally toric*, or *s-toric MESSI system*, is a MESSI system whose digraph $G$ satisfies the following conditions:

- $(\mathcal{C}')$: For every intermediate complex $U_k$ there exist a *unique* core complex $y_{(k)}$ such that $y_{(k)} \to_\circ U_k$ in $G$.
- $(\mathcal{C}'')$: The associated multidigraph $MG_2$ does not have parallel edges and the digraph $G_2$ is weakly reversible.
- $(\mathcal{C}''')$: …

**Intermediates satisfy binomial equations at s.s.**

Given a MESSI network $G$ that satisfies condition $(\mathcal{C}')$, there are (explicit) rational functions $\mu_k \in \mathbb{Q}(\kappa), 1 \leq k \leq p$, such that for any steady state $x \in \mathbb{R}^n_{>0}$ of the associated MESSI network $G_1$, the steady state $\pi^{-1}(x) = (u(x), x)$ of $G$ is given by a monomial map:

$$u_k(\mathbf{x}) = \mu_k \, \mathbf{x}^{y_{(k)}}, \quad k = 1, \dots, p. \tag{2}$$

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# EXPLICIT BINOMIALS

### COMBINATORIALLY CONSTRUCTED

Any s-toric MESSI system is toric. Moreover, we can choose explicit binomials with coefficients in $\mathbb{Q}(\kappa)$ which describe the positive steady states.

### HYPOTHESES FOR THE QUOTED MULTITATIONARITY RESULT ARE SATISFIED

Let $G$ be an s-toric MESSI network. Assume that the partition is minimal with $m$ subsets of core species and the associated digraph $G_E$ has no directed cycles. Then,

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Let $G$ be the underlying digraph of a MESSI system satisfying condition $\mathcal{C}'$.

Assume that the associated digraph $G_E$ has no directed cycles, the underlying undirected graph of the associated graph $G_2^\circ$ is a forest (an acyclic graph), and $MG_2$ has no parallel edges.

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# RATIONAL PARAMETRIZATIONS

- A wide class of MESSI systems admit a rational parametrization.
- It is shown by [Feliu-Wiuf'13] that the values of the intermediate species at steady state can be rationally written in terms of the core species, in an algorithmic way.
- The following result extends Theorem 4 in [Thomson-Gunawardena'09].

# RATIONAL PARAMETRIZATIONS

## THEOREM

*Let $G$ be the underlying digraph of a MESSI system. Assume that the associated digraph $G_2$ is weakly reversible and the associated digraph $G_E$ has no directed cycles. Then, $V_{>0}(I_f)$ admits a rational parametrization, which can be algorithmically computed.*

*More explicitly, it is possible to define levels for the subsets $\mathcal{S}^{(\alpha)}, \alpha \geq 1$, according to indegree. Then, given any choice of one index $i_\alpha$ in each $\mathcal{S}^{(\alpha)}$, the concentration of any core species $x_i$ in $\mathcal{S}^{(\alpha)}$ can be rationally expressed in an effective way in terms of $x_{i_\alpha}$ and the variables $x_{i_\beta}$ for which the indegree of $\mathcal{S}^{(\beta)}$ is strictly smaller than the indegree of $\mathcal{S}^{(\alpha)}$.*

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