On the existence of positive steady states of deficiency-one mass action systems

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Notations

- $\mathcal{X} = \{X_1, X_2, \ldots, X_n\}$ - set of species
- $\mathcal{C} = \{C_1, C_2, \ldots, C_c\}$ - set of complexes
- $Y \in \mathbb{R}^{n \times c}$ - matrix of complexes
- $\mathcal{R}$ - set of reactions
- $\kappa = (\kappa_{ij})_{(i,j) \in \mathcal{R}}$ - rate coefficients
- $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ - mass action system
- ℓ - number of linkage classes
- t - number of terminal strong linkage classes

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Ψ, A_κ, AND THE ODE

- $$\Psi(x) = \begin{bmatrix} \prod_{s=1}^{n} x_s^{y_{s1}} \\ \prod_{s=1}^{n} x_s^{y_{s2}} \\ \vdots \\ \prod_{s=1}^{n} x_s^{y_{sc}} \end{bmatrix}$$

- $$A_\kappa = \begin{bmatrix} -\sum_{i=2}^{c} \kappa_{1i} & \kappa_{21} & \cdots & \kappa_{c1} \\ \kappa_{12} & -\left(\kappa_{21} + \sum_{i=3}^{c} \kappa_{2i}\right) & \cdots & \kappa_{c2} \\ \vdots & \vdots & \ddots & \vdots \\ \kappa_{1c} & \kappa_{2c} & \cdots & -\sum_{i=1}^{c-1} \kappa_{ci} \end{bmatrix}$$

- $$\dot{x}(\tau) = Y \cdot A_\kappa \cdot \Psi(x(\tau)), \text{ state space: } \mathbb{R}^n_{\geq 0}$$

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DEFINITION (DEFICIENCY)

$\delta = \dim(\ker Y \cap \operatorname{ran} A_\kappa)$, provided that $\ell = t$

- $E_+^\kappa = \{x \in \mathbb{R}_+^n \mid Y \cdot A_\kappa \cdot \Psi(x) = 0\}$ - positive steady states
- $\mathcal{S} = \mathrm{span}\{Y_{\cdot j} - Y_{\cdot i} \mid (i,j) \in \mathcal{R}\} \leq \mathbb{R}^n$ - stoichiometric subspace
- $(p + \mathcal{S}) \cap \mathbb{R}_{\geq 0}^n$ for $p \in \mathbb{R}_+^n$ - positive stoichiometric class

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Deficiency-One Theorem

Theorem (Martin Feinberg, 1979, 1987, 1995)

Assume

(I) $\delta_r = 0$ *or* 1 $(\forall\ r \in \overline{1,\ell})$,

(II) $\delta_1 + \cdots + \delta_\ell = \delta$, *and*

(III) $\ell = t$.

Then the following two implications hold.

$(\mathcal{C}, \mathcal{R})$ *is weakly reversible*

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$$E_+^\kappa \neq \emptyset$$

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$$|(p + \mathcal{S}) \cap E_+^\kappa| = 1 \ (\forall\ p \in \mathbb{R}_+^n)$$

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Supplement to the Deficiency-One Theorem

Assume $\ell = t = 1$ and $(\mathcal{C}, \mathcal{R})$ is *not* weakly reversible. Let

$$\mathcal{C} = \mathcal{C}' \cup^* \mathcal{C}'',$$

where $\mathcal{C}'$ is the complex set of the only terminal strong linkage class. Then

$$x \in E_+^\kappa \iff \underbrace{\begin{bmatrix} Y' & Y'' \end{bmatrix}}_{Y} \cdot \underbrace{\begin{bmatrix} A'_\kappa & * \\ 0 & A''_\kappa \end{bmatrix}}_{A_\kappa} \cdot \underbrace{\begin{bmatrix} \Psi'(x) \\ \Psi''(x) \end{bmatrix}}_{\Psi(x)} = 0.$$

Theorem (BB, 2010, 2012)

Beyond the above, assume that $\delta = 1$ and let $0 \neq h \in \ker Y \cap \operatorname{ran} A_\kappa$ be such that $\sum_{i \in \mathcal{C}''} h_i \leq 0$. Then

$$E_+^\kappa \neq \emptyset \iff \left(A''_\kappa\right)^{-1} h'' \gg 0.$$

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Special case: $(\mathcal{C}, \mathcal{R})$ is a chain

Theorem (BB, 2013)

Assume that $(\mathcal{C}, \mathcal{R})$ *is of the form*

$$C_c \underset{\kappa_{c-1,c}}{\overset{\kappa_{c,c-1}}{\rightleftarrows}} \cdots \underset{\kappa_{23}}{\overset{\kappa_{32}}{\rightleftarrows}} C_2 \xrightarrow{\kappa_{21}} C_1 .$$

Assume that $\delta = 1$. *Let* $0 \neq h \in \ker Y \cap \operatorname{ran} A_\kappa$ *be such that* $\sum_{i=2}^{c} h_i \leq 0$. *Let us define* $\vartheta_2, \ldots, \vartheta_c$ *by the recursion*

$$\vartheta_2 = -\frac{1}{\kappa_{21}} \sum_{i=2}^{c} h_i \text{ and}$$

$$\vartheta_j = \frac{\kappa_{j-1,j}}{\kappa_{j,j-1}} \vartheta_{j-1} - \frac{1}{\kappa_{j,j-1}} \sum_{i=j}^{c} h_i, \quad j = 3, \ldots, c.$$

Then $E_+^\kappa \neq \emptyset \iff \vartheta_j > 0 \ (\forall j \in \{2, 3, \ldots, c\})$.

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Assume that $(\mathcal{C},\mathcal{R})$ *is of the form*

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Assume that $\delta = 1$. *Let* $0 \neq h \in \ker Y \cap \operatorname{ran} A_\kappa$ *be such that* $\sum_{i=2}^{c} h_i \leq 0$. *Then*

(A) $\exists\ \kappa : \mathcal{R} \to \mathbb{R}_+$ *such that* $E_+^\kappa \neq \emptyset$ *if and only if* $\sum_{i=2}^{c} h_i < 0$ *and*

(B) $\forall\ \kappa : \mathcal{R} \to \mathbb{R}_+$ *we have* $E_+^\kappa \neq \emptyset$ *if and only if*

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THEOREM (BB, 2013)

Assume that $\ell = t = 1$ *and* $\delta = 1$. *Assume also that* $(\mathcal{C}, \mathcal{R})$ *is not weakly reversible and let*

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Then there exists $\kappa : \mathcal{R} \to \mathbb{R}_+$ *such that* $E_+^\kappa \neq \emptyset$ *if and only if*

$$\sum_{i \in \widetilde{\mathcal{C}}} h_i < 0 \text{ for all } \emptyset \neq \widetilde{\mathcal{C}} \subsetneq \mathcal{C} \text{ with } \varrho^{\text{in}}(\widetilde{\mathcal{C}}) = \emptyset,$$

where $\varrho^{\text{in}}(\widetilde{\mathcal{C}})$ *is the set of reactions that enter* $\widetilde{\mathcal{C}}$.

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TO THE PROOF: EXISTENCE OF POSITIVE h-TRANSSHIPMENTS

THEOREM

Assume that (V, A) is a weakly connected directed graph and $h : V \to \mathbb{R}$ is such that $\sum_{i \in V} h_i = 0$. Then there exists $z : A \to \mathbb{R}_+$ with $\mathrm{excess}_z = h$ if and only if

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- $U(i) = \{k \in \mathcal{C}'' \mid \text{each } k \rightsquigarrow \mathcal{C}' \text{ path crosses } i\}$,
- $\mathcal{C}''(j) = \{k \in \mathcal{C}'' \mid \text{there exist both } k \rightsquigarrow j \text{ and } j \rightsquigarrow k \text{ path}\}$
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- let $\mathcal{J} \subseteq \mathcal{C}''$ be such that
  - for all $j \in \mathcal{C}''$ we have $|\mathcal{C}''(j) \cap \mathcal{J}| = 1$ and
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- $\mathcal{C}''(j) = \{k \in \mathcal{C}'' \mid \text{there exist both } k \rightsquigarrow j \text{ and } j \rightsquigarrow k \text{ path}\}$
- $U(\mathcal{C}''(j)) = \{k \in \mathcal{C}'' \mid \text{each } k \rightsquigarrow \mathcal{C}' \text{ path crosses } \mathcal{C}''(j)\}$
- $W(j) = \left\{ k \in \mathcal{C}'' \;\middle|\; \begin{array}{l} \text{there exist paths } k \rightsquigarrow j \text{ and } k \rightsquigarrow \mathcal{C}' \\ \text{that intersect each other only in } k \end{array} \right\}$
- let $\mathcal{J} \subseteq \mathcal{C}''$ be such that
  - for all $j \in \mathcal{C}''$ we have $|\mathcal{C}''(j) \cap \mathcal{J}| = 1$ and
  - for all $j \in \mathcal{J}$ we have $\varrho^{\text{out}}(j) \cap \varrho^{\text{out}}(\mathcal{C}''(j)) \neq \emptyset$.

$(\mathcal{C}, \mathcal{R})$ IS OF GENERAL FORM ($\forall\ \kappa$)

THEOREM (BB, 2013)

Assume that $\ell = t = 1$ *and* $\delta = 1$. *Assume also that* $(\mathcal{C}, \mathcal{R})$ *is not weakly reversible and let*

$$\mathcal{C} = \mathcal{C}' \cup^* \mathcal{C}'',$$

where $\mathcal{C}'$ *is the set of complexes in the only terminal strong linkage class. Let*

$$0 \neq h \in \ker Y \cap \operatorname{ran} A_\kappa \textit{ be such that } \sum_{k \in \mathcal{C}''} h_k \leq 0.$$

Then we have $E_+^\kappa \neq \emptyset$ *for all* $\kappa : \mathcal{R} \to \mathbb{R}_+$ *if and only if*

- *for all* $i \in \mathcal{C}''$ *we have* $\sum_{k \in U(i)} h_k \leq 0$ *and*
- *for all* $j \in \mathcal{J}$ *with* $W(j) \subseteq \mathcal{C}''(j)$, *we have* $\sum_{k \in U(\mathcal{C}''(j))} h_k < 0$.

$(\mathcal{C}, \mathcal{R})$ IS OF GENERAL FORM $(\forall\ \kappa)$

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To the proof: Matrix-Tree Theorem

Theorem (William Thomas Tutte, 1948)

The signed determinant corresponding to the ijth element of A_κ is

$$(-1)^{c-1} \cdot \sum_{\widetilde{A} \in T(j)} \left(\prod_{a \in \widetilde{A}} \kappa_a \right).$$

Theorem

Let $Q \subseteq \{1, 2, \ldots, c\}$ and $i, j \in \{1, 2, \ldots, c\} \setminus Q$. Then the determinant of the matrix obtained from A_κ by deleting the rows corresponding to $Q \cup \{i\}$ and the columns corresponding to $Q \cup \{j\}$ is

$$(-1)^{i+j} \cdot (-1)^{c-|Q|-1} \cdot \sum_{\widetilde{A} \in T^{ij}(Q \cup \{j\})} \left(\prod_{a \in \widetilde{A}} \kappa_a \right).$$

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Further mass action systems with $\delta = 1$

Theorem (BB, 2013)

Assume that

(i) $\delta = 1$ *and*

(ii) $(\mathcal{C}, \mathcal{R})$ *is weakly reversible.*

Then

$$|(p + \mathcal{S}) \cap E_+^\kappa| \geq 1 \ (\forall\, p \in \mathbb{R}_+^n).$$

Moreover, if $\ell \leq 2$ *then* $|(p + \mathcal{S}) \cap E_+^\kappa| < \infty \ (\forall\, p \in \mathbb{R}_+^n)$.

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To the proof: a power function

Assume that $\ell = t = 1$ and let $\overline{y} \in \mathbb{R}^{\mathcal{C}}_{\geq 0}$, $y^* \in \mathbb{R}^{\mathcal{C}}_{\geq 0}$, and $h \in \mathbb{R}^{\mathcal{C}} \backslash \{0\}$ be such that $A_\kappa \overline{y} = 0$, $A_\kappa y^* = h$,

$$\text{for all } j \in \mathcal{C} \text{ we have } j \in \mathcal{C}' \text{ if and only is } \overline{y}_j > 0,$$
$$\text{for all } j \in \mathcal{C} \backslash \mathcal{C}' \text{ we have } y^*_j > 0, \text{ and}$$
$$\text{there exists } j \in \mathcal{C}' \text{ such that } y^*_j = 0.$$

Define $\beta^* \in \mathbb{R}$ and the function $p : (\beta^*, \infty) \to \mathbb{R}_+$ by

$$\beta^* = \max\left\{ -\frac{\overline{y}_i}{y^*_i} \;\middle|\; i \in \mathcal{C} \text{ and } y^*_i > 0 \right\} \text{ and}$$
$$p(\beta) = \prod_{i \in \mathcal{C}} (\beta y^*_i + \overline{y}_i)^{h_i} \quad (\beta \in (\beta^*, \infty)),$$

respectively.

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To the proof: a power function

Lemma

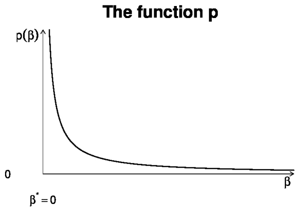
Let $p : (\beta^*, \infty) \to \mathbb{R}_+$ be as in the previous slide. Then

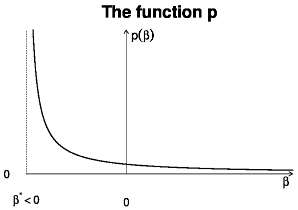
(A) $\lim_{\beta \to \beta^* + 0} p(\beta) = \infty$,

(B) $\lim_{\beta \to \infty} p(\beta) = 0$,

(C) *the derivative of p is negative on (β^*, ∞), and*

(D) $p : (\beta^*, \infty) \to \mathbb{R}_+$ *is a bijection.*





To the proof: the Bolzano Theorem in 2 dimensions

Theorem

Assume that $f : [0,1]^2 \to \mathbb{R}^2$ *is continuous and*

$f_2 \leq 0$

$f_1 \geq 0$ $\quad$ $f_1 \leq 0$

$f_2 \geq 0$

Then $\exists\, x \in [0,1]^2$ *with* $f(x) = \boldsymbol{0} \in \mathbb{R}^2$.

To the proof: the Bolzano Theorem in n dimensions

Theorem

Assume that $f : [0,1]^n \to \mathbb{R}^n$ *is continuous and*

$$(\forall\, x \in \partial[0,1]^n)(\forall\, i \in \overline{1,n})[x_i = 0 \Rightarrow f_i(x) \geq 0] \text{ and}$$
$$(\forall\, x \in \partial[0,1]^n)(\forall\, i \in \overline{1,n})[x_i = 1 \Rightarrow f_i(x) \leq 0].$$

Then $\exists\, x \in [0,1]^n$ *with* $f(x) = \mathbf{0} \in \mathbb{R}^n$.

Can the previous theorem be generalised substantially?

Conjecture (Jian Deng, Martin Feinberg, Chris Jones, Adrian Nachman)

Assume that $(\mathcal{C}, \mathcal{R})$ *is weakly reversible. Then*

$$1 \leq |(p + \mathcal{S}) \cap E_+^\kappa| < \infty \ (\forall\, p \in \mathbb{R}_+^n).$$

Remark

Once the above conjecture is proved, the set

$$E_0^\kappa = \{x \in \partial \mathbb{R}_{\geq 0}^n \mid Y \cdot A_\kappa \cdot \Psi(x) = 0\}$$

can also be described.

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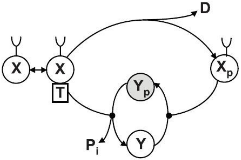
An EnvZ-OmpR model in which ATP (resp. ADP) is the cofactor in phospho-OmpR dephosphorylation

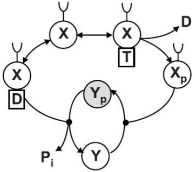


$$\mathrm{X} \underset{k_{-1}}{\overset{k_1[T]}{\rightleftharpoons}} \mathrm{XT} \xrightarrow{k_2} \mathrm{X_p}$$

$$\mathrm{X_p + Y} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{X_pY} \xrightarrow{k_4} \mathrm{X + Y_p}$$

$$\mathrm{XT + Y_p} \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \mathrm{XTY_p} \xrightarrow{k_6} \mathrm{XT + Y}$$

`cofactor: ATP`



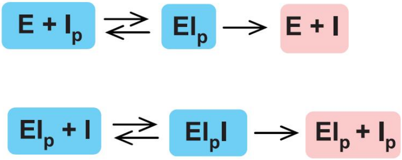
$$\mathrm{XD} \underset{k_9[D]}{\overset{k_{-9}}{\rightleftharpoons}} \mathrm{X} \underset{k_{-1}}{\overset{k_1[T]}{\rightleftharpoons}} \mathrm{XT} \xrightarrow{k_2} \mathrm{X_p}$$

$$\mathrm{X_p + Y} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{X_pY} \xrightarrow{k_4} \mathrm{X + Y_p}$$

$$\mathrm{XD + Y_p} \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} \mathrm{XDY_p} \xrightarrow{k_8} \mathrm{XD + Y}$$

`cofactor: ADP`

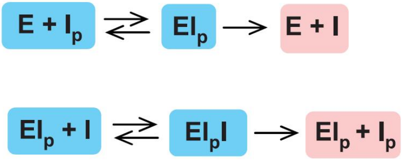
IDHKP-IDH system (phosphorylation of the enzyme isocitrate dehydrogenase by a bifunctional kinase-phosphatase)



For these three systems, we have

- $\delta_1 = \delta_2 = 0 (= \delta_3)$ and $\delta = 1$ and
- $(\mathcal{C}, \mathcal{R})$ is *not* weakly reversible.

IDHKP-IDH SYSTEM (PHOSPHORYLATION OF THE ENZYME ISOCITRATE DEHYDROGENASE BY A BIFUNCTIONAL KINASE-PHOSPHATASE)



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CONTACT INFORMATION

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