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Impossibility of multiple steady states in a family of active membrane transport models

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Abstract To study the dynamical behavior of active membrane transport models, Vieira and Bisch proposed a complex chemical network (model 3) with two cycles. One cycle involves monomers as pump units while the other cycle uses dimers. In their work, the stoichiometric network analysis was used to study the stability of steady states and the bifurcation analysis was done through numerical methods. They concluded that the possibility of multiple steady states in the model 3 could not be discarded. Here, a zero eigenvalue analysis is applied to prove the impossibility of multiple positive steady states in the model 3. (A positive steady state is one for which all species have positive concentrations.) Moreover, the result is generalized to its family networks.

Key words Active membrane transport models · Multiple steady states · Zero eigenvalue analysis

Introduction

Biochemical cell systems can produce complex behavior, such as oscillations, multiple steady states, unstable steady states, and some chaotic attractors. Vieira and Bisch (1994) have proposed an active membrane transport model (model 3) involving both monomers and dimers as pump units. They have applied stoichiometric network analysis (Clarke 1980) to study the stability of steady states and have shown that the model 3 can produce instability. The instability could come from either a multiple steady-state bifurcation or a Hopf bifurcation. To decide the causes of the instability, numerical methods are applied for the bifurcation analysis. Although only a Hopf bifurcation has been found, in conclusion they mentioned that the possibility of multiple steady states in the model 3 could not be discarded.

It has been shown (Li 1998a) that a reaction network can admit multiple positive steady states if, and only if, for its corresponding mass action ordinary differential equations, there exists a positive steady state having a zero eigenvalue with its eigenvector in the stoichiometric subspace for the network under study. Based upon linear algebra, Li (1998a) has developed a zero eigenvalue analysis which provides a necessary and sufficient condition for the determination of such a steady state in isothermal chemical reaction networks. In this work, the analysis is applied to deny the possibility of multiple positive steady states in the model 3. Moreover, this result is easily generalized to its family networks.

Method

The zero eigenvalue analysis is presented in the Appendix. For a given reaction network, we choose an arbitrary spanning subnetwork and construct the corresponding spanning-subnetwork vectors. Following the conditions in the analysis, a system of equations and inequalities is constructed. We then solve the system. If a set of qualified solutions exists, there is a set of positive rate constants such that the corresponding isothermal, mass action differential equations for the given network admit a zero-eigenvalue positive steady state. Hence, it has capacity to admit multiple positive steady states. Otherwise, no matter what positive rate constants the system might have, the differential equations can exhibit at most one positive steady state.

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Results and discussion

The model 3 in Vieira and Bisch (1994) is

$$\begin{array}{ccccccc} A_1 & \rightleftarrows & A_2 & A_7 & \rightleftarrows A_8 \rightleftarrows & A_9 & \\ \Updownarrow & & \Updownarrow & \Updownarrow & & \Updownarrow & 2\,A_5 \rightleftarrows A_{13} \\ A_6 & & A_3 & A_{14} & & A_{10} & \\ \Updownarrow & & \Updownarrow & \Updownarrow & & \Updownarrow & A_4 + A_5 \rightleftarrows A_{12} \\ A_5 & \rightleftarrows & A_4 & A_{13} & \rightleftarrows A_{12} \rightleftarrows & A_{11} & \end{array} \tag{1}$$

Species A_1 through A_6 denote monomers A, B, C, D, E, and F; species A_7 through A_{14} denote dimers AA, AB, BB, CC, DD, DE, EE, and FF.

A spanning subnetwork of a network under consideration consists of all the irreversible reactions and one (and only one) reaction of each reversible reaction pair. A spanning subnetwork for network (1) is chosen:

$$\begin{array}{ccccccc} A_1 & \rightarrow & A_2 & A_7 & \rightarrow A_8 \rightarrow & A_9 & \\ \uparrow & & \downarrow & \uparrow & & \downarrow & 2\,A_5 \rightarrow A_{13} \\ A_6 & & A_3 & A_{14} & & A_{10} & \\ \uparrow & & \downarrow & \uparrow & & \downarrow & A_4 + A_5 \rightarrow A_{12} \\ A_5 & \leftarrow & A_4 & A_{13} & \leftarrow A_{12} \leftarrow & A_{11} & \end{array} \tag{2}$$

A set of spanning-subnetwork vectors $\{\boldsymbol{d}^{(1)}, \boldsymbol{d}^{(2)}, \ldots, \boldsymbol{d}^{(r-p-s)}\}$ is the $r-p-s$ linearly independent (nonzero) solutions to the vector equation:

$$\sum_{i \to j \in F} d_{i \to j}^{(L)} (\boldsymbol{y}_j - \boldsymbol{y}_i) = \boldsymbol{0}, \quad L = 1, 2, \ldots, r-p-s \tag{3a}$$

For network (1), $N=14$, $r=32$, $p=16$, and $s=13$, where N, r, p denote respectively the number of species, reactions, and reaction pairs, and s denotes the rank for the network (1). The elements of three spanning-subnetwork vectors $\boldsymbol{d}^{(1)}$, $\boldsymbol{d}^{(2)}$, and $\boldsymbol{d}^{(3)}$ are:

$$\begin{aligned} &d^{(1)}_{A_1 \to A_2} = 1,\ d^{(1)}_{A_2 \to A_3} = 1,\ d^{(1)}_{A_3 \to A_4} = 1,\ d^{(1)}_{A_4 \to A_5} = 1, \\ &d^{(1)}_{A_5 \to A_6} = 1,\ d^{(1)}_{A_6 \to A_1} = 1 \end{aligned} \tag{3b}$$

and $d^{(1)}_{i \to j} = 0$ for all other reactions $i \to j$ in set F,

$$\begin{aligned} &d^{(2)}_{A_7 \to A_8} = 1,\ d^{(2)}_{A_8 \to A_9} = 1,\ d^{(2)}_{A_9 \to A_{10}} = 1,\ d^{(2)}_{A_{10} \to A_{11}} = 1 \\ &d^{(2)}_{A_{11} \to A_{12}} = 1,\ d^{(2)}_{A_{12} \to A_{13}} = 1,\ d^{(2)}_{A_{13} \to A_{14}} = 1,\ d^{(2)}_{A_{14} \to A_7} = 1 \end{aligned} \tag{3c}$$

and $d^{(2)}_{i \to j} = 0$ for all other reactions $i \to j$ in set F,

$$\begin{aligned} &d^{(3)}_{A_4 \to A_5} = 1,\ d^{(3)}_{A_{12} \to A_{13}} = -1,\ d^{(3)}_{2\,A_5 \to A_{13}} = 1, \\ &d^{(3)}_{A_4 + A_5 \to A_{12}} = -1 \end{aligned} \tag{3d}$$

and $d^{(3)}_{i \to j} = 0$ for all other reactions $i \to j$ in set F.

According to the condition (i) of the analysis, the system (4) is constructed:

$\xi_1 \mu_1 + \alpha_1$ and $\xi_1 \mu_2 + \alpha_1$ are sign compatible with (s.c.w.) $\mu_2 - \mu_1$ (4a)

$\xi_1 \mu_2 + \alpha_1$ and $\xi_1 \mu_3 + \alpha_1$ are s.c.w. $\mu_3 - \mu_2$ (4b)

$\xi_1 \mu_3 + \alpha_1$ and $\xi_1 \mu_4 + \alpha_1$ are s.c.w. $\mu_4 - \mu_3$ (4c)

$\xi_1 \mu_4 + \alpha_1 + \xi_3 \mu_4 + \alpha_3$ and $\xi_1 \mu_5 + \alpha_1 + \xi_3 \mu_5 + \alpha_3$ are s.c.w. $\mu_5 - \mu_4$ (4d)

$\xi_1 \mu_5 + \alpha_1$ and $\xi_1 \mu_6 + \alpha_1$ are s.c.w. $\mu_6 - \mu_5$ (4e)

$\xi_1 \mu_6 + \alpha_1$ and $\xi_1 \mu_1 + \alpha_1$ are s.c.w. $\mu_1 - \mu_6$ (4f)

$\xi_2 \mu_7 + \alpha_2$ and $\xi_2 \mu_8 + \alpha_2$ are s.c.w. $\mu_8 - \mu_7$ (4g)

$\xi_2 \mu_8 + \alpha_2$ and $\xi_2 \mu_9 + \alpha_2$ are s.c.w. $\mu_9 - \mu_8$ (4h)

$\xi_2 \mu_9 + \alpha_2$ and $\xi_2 \mu_{10} + \alpha_2$ are s.c.w. $\mu_{10} - \mu_9$ (4i)

$\xi_2 \mu_{10} + \alpha_2$ and $\xi_2 \mu_{11} + \alpha_2$ are s.c.w. $\mu_{11} - \mu_{10}$ (4j)

$\xi_2 \mu_{11} + \alpha_2$ and $\xi_2 \mu_{12} + \alpha_2$ are s.c.w. $\mu_{12} - \mu_{11}$ (4k)

$\xi_2 \mu_{12} + \alpha_2 - \xi_3 \mu_{12} - \alpha_3$ and $\xi_2 \mu_{13} + \alpha_2 - \xi_3 \mu_{13} - \alpha_3$ are s.c.w. $\mu_{13} - \mu_{12}$ (4l)

$\xi_2 \mu_{13} + \alpha_2$ and $\xi_2 \mu_{14} + \alpha_2$ are s.c.w. $\mu_{14} - \mu_{13}$ (4m)

$\xi_2 \mu_{14} + \alpha_2$ and $\xi_2 \mu_7 + \alpha_2$ are s.c.w. $\mu_7 - \mu_{14}$ (4n)

$\xi_3 (2\mu_5) + \alpha_3$ and $\xi_3 \mu_{13} + \alpha_3$ are s.c.w. $\mu_{13} - 2\mu_5$ (4o)

$-\xi_3 (\mu_4 + \mu_5) - \alpha_3$ and $-\xi_3 (\mu_{12}) - \alpha_3$ are s.c.w. $\mu_{12} - \mu_4 - \mu_5$ (4p)

A vector $\boldsymbol{\mu} \in \Re^N$ is sign compatible with the stoichiometric subspace S_t if there exists in S_t a vector $\sigma (\in S_t)$ such that sign σ_L = sign μ_L, $L = 1, 2, \ldots, N$. This requirement comes from the mass conservation condition of a system. A nonzero vector $\boldsymbol{\mu} = [\mu_1, \ldots, \mu_{14}]$ is sign compatible with the stoichiometric subspace for network (1) if, and only if, the set $[\mu_1, \ldots, \mu_{14}]$ contains both a positive and negative number. We will show that there do not exist any nonzero $\boldsymbol{\mu} = [\mu_1, \ldots, \mu_{14}]$ which is sign compatible with the stoichiometric subspace for network (1) such that the Eqs. (4) are satisfied. The proof consists of several cases.

Case (1): suppose $\mu_2 > \mu_1$ and $\mu_8 > \mu_7$. Since $\mu_2 > \mu_1$, Eqs. (4a)–(4c) and Eqs. (4e)–(4f) indicate

$$\xi_1 \mu_i + \alpha_1 > 0, \quad \forall\, i = 1, \ldots, 6 \tag{5a}$$

$$\mu_4 > \mu_3 > \mu_2 > \mu_1 > \mu_6 > \mu_5 \tag{5b}$$

Equations (5a), (5b), and (4d) indicate

$$\xi_3 \mu_4 + \alpha_3 < 0 \text{ and } \xi_3 \mu_5 + \alpha_3 < 0 \tag{5c}$$

Since $\mu_8 > \mu_7$, Eqs. (4g)–(4k) and (4m)–(4n) indicate

$$\xi_2 \mu_i + \alpha_2 > 0, \quad \forall\, i = 7, \ldots, 14 \tag{5d}$$

$$\mu_{12} > \mu_{11} > \mu_{10} > \mu_9 > \mu_8 > \mu_7 > \mu_{14} > \mu_{13} \tag{5e}$$

Equations (5d), (5e), and (4l) indicate

$$\xi_3 \mu_{12} + \alpha_3 > 0 \text{ and } \xi_3 \mu_{13} + \alpha_3 > 0 \tag{5f}$$

Equations (5f), (4o), and (4p) indicate that

$$\xi_3 (2\mu_5) + \alpha_3 > 0 \text{ and } \xi_3 (\mu_4 + \mu_5) + \alpha_3 > 0 \tag{5g}$$

Equations (5c), (5f), and (5g) imply $\xi_3 \neq 0$. Let ξ_3 be a positive real number. These equations lead to

$$\left\{ \begin{array}{c} \mu_{12} \\ \mu_{13} \\ 2\mu_5 \\ \mu_4 + \mu_5 \end{array} \right\} > \frac{-\alpha_3}{\xi_3} > \left\{ \begin{array}{c} \mu_4 \\ \mu_5 \end{array} \right\} \tag{5h}$$

Equation (5h) indicates that μ_4, μ_5, μ_{12}, and μ_{13} are all positive. From Eqs. (5b) and (5e), we conclude that $\mu_1, \ldots, \mu_{14}$ are all positive. This $\boldsymbol{\mu}$ is not sign compatible with the stoichiometric subspace for network (1). If ξ_3 is a negative real number, it follows that $\mu_1, \ldots, \mu_{14}$ are all negative, which is still not sign compatible with the stoichiometric subspace for network (1). For this case, we conclude that no sign compatible solution satisfies Eq. (4).

Case (2): suppose $\mu_1 > \mu_2$ and $\mu_8 > \mu_7$. Since $\mu_1 > \mu_2$, Eqs. (4a)–(4c) and Eqs. (4e)–(4f) indicate

$$\xi_1 \mu_i + \alpha_1 < 0, \quad \forall\, i = 1, \ldots, 6 \tag{6a}$$

$$\mu_4 < \mu_3 < \mu_2 < \mu_1 < \mu_6 < \mu_5 \tag{6b}$$

Equations (6a), (6b), and (4d) indicate

$$\xi_3 \mu_4 + \alpha_3 > 0 \text{ and } \xi_3 \mu_5 + \alpha_3 > 0 \tag{6c}$$

Since $\mu_8 > \mu_7$, Eqs. (5d)–(5f) are still true for this case. Eqs. (5f), (4o), and (4p) indicate

$$\mu_{13} > 2\mu_5 \text{ and } \mu_4 + \mu_5 > \mu_{12} \tag{6d}$$

Equations (6b) and (6d) lead to $\mu_{13} > 2\mu_5 > \mu_4 + \mu_5 > \mu_{12}$, which is contrary to Eq. (5e). For this case, there does not exist any solution to Eq. (4).

The procedure in case (1) can also be used to deny the existence of sign compatible solutions to Eq. (4) for $\mu_1 > \mu_2$ and $\mu_7 > \mu_8$, and for $\mu_1 = \mu_2$ and $\mu_7 = \mu_8$. The procedure in case (2) can also be applied to deny the possibility of solutions to Eq. (4) for $\mu_1 < \mu_2$ and $\mu_7 \geq \mu_8$, for $\mu_1 > \mu_2$ and $\mu_7 = \mu_8$, and for $\mu_1 = \mu_2$ and $\mu_7 \neq \mu_8$. Thus, the applications of the zero eigenvalue analysis prove that, taken with mass action kinetics, network (1) cannot admit either a zero-eigenvalue positive steady state or multiple positive steady states, no matter what positive rate constants the system might have.

The network (7) below represents an extension of the network (1):

$$\begin{array}{lll} \mathrm{M}_1 \rightleftarrows \mathrm{M}_2 & \mathrm{D}_1 \rightleftarrows \mathrm{D}_2 & \\ \mathrm{M}_2 \rightleftarrows \mathrm{M}_3 & \mathrm{D}_2 \rightleftarrows \mathrm{D}_3 & \\ \quad\vdots & \quad\vdots & 2\,\mathrm{M}_{x+1} \rightleftarrows \mathrm{D}_{y+1} \\ \mathrm{M}_x \rightleftarrows \mathrm{M}_{x+1} & \mathrm{D}_y \rightleftarrows \mathrm{D}_{y+1} & \mathrm{M}_x + \mathrm{M}_{x+1} \rightleftarrows \mathrm{D}_y \\ \quad\vdots & \quad\vdots & \\ \mathrm{M}_{x+i} \rightleftarrows \mathrm{M}_1 & \mathrm{D}_{y+j} \rightleftarrows \mathrm{D}_1 & \end{array} \tag{7}$$

where species M and D represent monomer and dimer, respectively. For network (1), we have $x=4$, $y=6$, $i=j=2$. The extension network (7) also has $r-p-s=3$ and three spanning-subnetwork vectors. Hence, its corresponding system of inequalities and equations, constructed according to the zero eigenvalue analysis, is structurally similar to Eq. (4). It also consists of variables ξ_1 and α_1 for reactions in the monomer cycle, variables ξ_2 and α_2 for reactions in the dimer cycle, and variables ξ_3 and α_3 for the other two reversible reaction pairs outside the cycles. From the above discussion, the sign compatibility propagates around the monomer and the dimer cycles no matter how many reactions they might contain. One can easily extend the result of network (1) to deny the possibility of multiple positive steady states in the extension model (7).

The zero eigenvalue analysis provides a necessary and sufficient condition for the determination of multiple positive steady states in complex isothermal reaction networks. Most of the biological systems belong to this catalog. The deficiency zero theorem (Horn 1972; Horn and Jackson 1972; Feinberg 1987), the deficiency one theorem (Feinberg 1987), and algorithm (Feinberg 1988) give important results about complex reaction networks. Since both networks (1) and (7) have deficiency one, the deficiency zero theorem cannot be applied. The deficiency one theorem and algorithm cannot be applied to networks with cycles, which is the class to which the networks (1) and (7) belong. The stoichiometric network analysis (Clarke 1980) has been used to show that the network (1) exhibits an unstable steady state (Vieira and Bisch 1994). However, an unstable steady state may go to boundary (some species have zero concentrations), explosion (some species have infinite concentrations), another stable steady state, stable limit cycle, or other chaotic attractors. It needs further numerical analysis. The zero eigenvalue analysis used in this work can directly answer the question of multiple steady states.

Several models simulating active membrane transport have been proposed (Weissmüller and Bisch 1993; Vieira and Bisch 1994). They are suitable for the applications of the analysis. The steady state multiplicity in a family of complex allosteric models for glycolysis is determined by the zero eigenvalue analysis, while the possibility of multiple steady states can be overlooked for a simplified model by the use of a quasisteady state assumption (Li, 1998b).

Appendix: theoretical framework

Zero eigenvalue analysis

Consider an N-species reaction network with reaction set R and stoichiometric subspace S_t. Suppose the network has rank s and r reactions with p reversible reaction pairs. Let the reaction set for an arbitrary spanning subnetwork be F and let $\{\boldsymbol{d}^{(1)}, \boldsymbol{d}^{(2)}, \ldots, \boldsymbol{d}^{(r-p-s)}\}$ be a set of corresponding spanning-subnetwork vectors. Then the corresponding isothermal mass action differential equations for the given network have the capacity to admit a positive steady state having a zero eigenvalue with its corresponding eigenvector in the stoichiometric subspace S_t if, and only if, there exists a nonzero vector $\boldsymbol{\mu} \in \Re^N$ which is sign compatible with S_t and also numbers $\xi_1, \xi_2, \ldots, \xi_{r-p-s}, \alpha_1, \alpha_2, \ldots, \alpha_{r-p-s}$ satisfying the following two conditions:

(i) For every reversible reaction $y_i \rightleftarrows y_j \in R$ with $y_i \to y_j \in F$

$$\sum_{L=1}^{r-p-s} [\xi_L (\boldsymbol{y}_i \cdot \mu) + \alpha_L]\, d_{i\to j}^{(L)} \quad \text{and}$$

$$\sum_{L=1}^{r-p-s} [\xi_L (\boldsymbol{y}_j \cdot \mu) + \alpha_L]\, d_{i\to j}^{(L)}$$

are sign compatible with $(\boldsymbol{y}_j - \boldsymbol{y}_i) \cdot \boldsymbol{\mu}$ (the symbol "$\cdot$" means the standard dot product.

(ii) For every irreversible reaction $y_i \to y_j \in R$

$$\sum_{L=1}^{r-p-s} \xi_L \, d_{i\to j}^{(L)} > 0 \quad \text{and} \quad \sum_{L=1}^{r-p-s} [\xi_L \, (\boldsymbol{y}_i \cdot \boldsymbol{\mu}) + \alpha_L] \, d_{i\to j}^{(L)} = 0$$

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