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AN ELEMENTARY PROOF OF THE EXISTENCE OF A POSITIVE EQUILIBRIUM IN REACTION NETWORKS†

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Abstract. It is interesting to know the behavior of a network from its structure. One interesting topic is to find a relation between the existence of a positive equilibrium of the reaction network and its structure. One approach to study this topic is using the concept of deficiency. In this work, we develop an algorithm and show an elementary proof of the relation based on the algorithm and deficiency.

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1. Introduction

Many systems including biological and chemical systems are studied by their mathematical models using differential equations. To construct such a model, we need to know some quantitative information like the type of reactions and the values of the parameters involved in each reaction. However, it is not easy to have the information. Thus it is important to find some relation between the functionality of a network and the network structure.

The existence of a positive equilibrium of the reaction network was studied by its structure using the concept of network deficiency ([3],[4]).

Other structure conditions based on the injectivity property have been presented in recent papers ([1],[2]) to determine whether networks have the capacity for more than one steady state.

In this paper, we present a new elementary way how to use the condition of zero deficiency in proving a theorem about the ability of a network to have a positive equilibrium. Deficiency is defined in Section 2. We define a network of

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interest and some notations, which will allow us to handle its structure mathematically. In Sections 3, we construct a new algorithm and show an elementary proof of existence of a positive equilibrium using the algorithm. The elementary proof means here a proof that does not use some theorems in linear algebra used in [3].

2. Preliminaries

In this section, we define some notations and a network of interest to handle its structure mathematically. And we also introduce Lemma 1 and Lemma 2 to be used and elementarily proved in the next section, respectively.

Definition 1. *A chemical reaction network consists of three finite sets:*

i) a set $\mathcal{S}$ of elements called the species of the network.

ii) a set $\mathcal{C}$ of functions in $\overline{\mathbb{P}}^{\mathcal{S}}$ called the complexes of the network.

iii) a relation $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$ having the following properties:

a) $(y, y) \notin \mathcal{R}$ for all $y \in \mathcal{C}$.

b) For each $y \in \mathcal{C}$, there exists $y' \in \mathcal{C}$ such that $(y, y') \in \mathcal{R}$ or $(y', y) \in \mathcal{R}$.

Here $\overline{\mathbb{P}}$ means the set of nonnegative real numbers, $\mathbb{P} = \overline{\mathbb{P}} - \{0\}$, and $\overline{\mathbb{P}}^{\mathcal{S}}$ the vector space of nonnegative real-valued functions with the domain $\mathcal{S}$. The element $(y, y') \in \mathcal{R}$ denotes a reaction $y \to y'$ called a directed arrow from y to y'.

Using Definition 1, we can assign each network to a directed graph with complexes and reactions as nodes and directed arrows, respectively. Throughout this work, a network means a chemical reaction network or its directed graph if there is no specific comment about the network.

A network is weakly reversible if each directed arrow is contained in a directed arrow circle. The network in Fig.1-(a) is weakly reversible, but the network in Fig.1-(b) is not weakly reversible because there is no directed arrow circle containing D+E→A+C.

For species A, B and positive real numbers r_a, r_b, the complex $r_aA+r_bB \in \overline{\mathbb{P}}^{\mathcal{S}}$ means $(r_aA + r_bB)(A) = r_a$, $(r_aA + r_bB)(B) = r_b$ and $(r_aA + r_bB)(s) = 0$ if $s \notin \{A, B\}$. For $y \in \mathcal{C}$, let $w_y \in \overline{\mathbb{P}}^{\mathcal{C}}$ be a characteristic function: $w_y(y_1) = 1$ if $y_1 = y$. Otherwise, $w_y(y_1) = 0$. And the symbol $[w_y]_{y_1}$ means $w_y(y_1)$. For $\alpha \in \mathbb{P}^{\mathcal{R}}$, let $\alpha_{y \to y'}$ denote the value of α at $y \to y'$. See [3] for more details and the proof of Lemma 1.

Lemma 1. *A network is weakly reversible if and only if there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ such that $\sum_{\mathcal{R}} \alpha_{y \to y'}(w_{y'} - w_y) = 0$.*

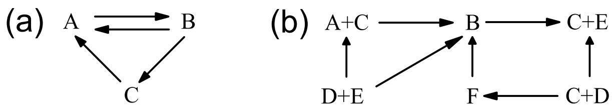

FIGURE 1. Networks (a) with three nodes and (b) six nodes.

For simplicity, we will assume $y(y^s) = 1$ for all complexes y and species y^s with $y(y^s) > 0$ without loss of generality.

The differential equation corresponding to a chemical reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ with a kinetics $\mathcal{K}$ can be written as the vector form $\frac{dc}{dt} = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)\,(y' - y), c \in \overline{\mathbb{P}}^{\mathcal{S}}$ where $\mathcal{K}_{y \to y'} : \overline{\mathbb{P}}^{\mathcal{S}} \to \overline{\mathbb{P}}$ and $\mathcal{K}_{y \to y'}(c)$ is the kinetics of the reaction $y \to y'$ at c. And c^* is called a positive equilibrium if $0 = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c^*)\,(y' - y)$.

Letting $y \sim y'$ denote $y \to y'$ or $y' \to y$, this is an equivalence relation on $\mathcal{C}$ which induces equivalence classes called the linkage of classes of the network. The rank of the network is the rank of the set $\{y - y' | y \to y' \in \mathcal{R}\}$. Deficiency for a chemical reaction network is defined by $n - \ell - r$ where n, ℓ, r are the number of complexes, the number of linkage classes, and the rank of the network, respectively. More details and the proof of Lemma 2 can be found in [3].

Lemma 2. *Assume the deficiency of a network is zero. If the network is not weakly reversible, then the differential equation corresponding to the network with an arbitrary kinetics cannot have a positive equilibrium.*

3. The elementary proof of Lemma 2

In this section, we present another proof of Lemma 2 in an elementary way which does not use some linear algebra theorems in [3] but focuses on the network structure. For the elementary proof, we develop a new algorithm called Algorithm for Core Networks, which will be used to easily calculate the rank in future study.

Let y be a complex and we define two sets related to y : $S_y = \{y - \varsigma, \xi - y | \varsigma \to y,\, y \to \xi \in \mathcal{R}\} - \{\varsigma - y | \varsigma \to y, y \to \varsigma \in \mathcal{R}\}$ and $\mathcal{R}_y = \{\varsigma \to y, y \to \xi \in \mathcal{R} | y - \varsigma, \xi - y \in S_y\}$. In Fig.1-(a), $S_A = \{A - C, A - B\}$ and $\mathcal{R}_A = \{C \to A, B \to A\}$.

Definition 2. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with a complex y.*

(a) A reaction of type I(y) is a reaction $\beta \to \gamma$ in a shortest non-directed circle with two complexes y_1, y_2 such that $y_i \to y (i = 1, 2)$ or $y \to y_i (i = 1, 2)$ in $\mathcal{R}_y$. This reaction is denoted as $\beta^1 \xrightarrow[y_2]{y_1} \gamma^I$ or $\beta^1 \xrightarrow{y_i} \gamma^I$ (i=1,2).

(b) A reaction of type II(y) is a reaction $\beta \to \gamma$ in a shortest non-directed circle with two complex y_1, y_2 such that $y_1 \to y$ and $y \to y_2$ in $\mathcal{R}_y$. This reaction is denoted as $\beta^2 \xrightarrow[y_2]{y_1} \gamma^{II}$ or $\beta^2 \xrightarrow{y_i} \gamma^{II}$ (i=1,2).

For example, in Fig.1-(a), reactions of type $I(A)$ are $C^1 \xrightarrow[C]{B} A^I$, $B^1 \xrightarrow[C]{B} A^I$ and $B^1 \xrightarrow[C]{B} C^I$. The following algorithm is used to construct a network with no circle from a given network having at least one circle.

- **Algorithm for Core Networks**

Step 1. Choice of a complex y_1 from a given network N_1

Step 2. Removal of all reactions of type $I(y_1)$ from N_1

2-1. Erase $\beta_i^1 \to \gamma_i^I$ of $I(y_1)$ from $N_1 - \{\beta_\ell^1 \to \gamma_\ell^I | 1 \le \ell \le i-1\}$.

2-2. Do Step 2-1 until there is no reaction of type $I(y_1)$.

2-3. Let $E_{y_1}^1$ be the set of reactions of type $I(y_1)$ erased from N_1.

Step 3. Removal of all reactions of type $II(y_1)$ from N_1.

3-1. Erase $\beta_i^2 \to \gamma_i^{II}$ of $II(y_1)$ from $N_1 - \{\beta_\ell^2 \to \gamma_\ell^{II} | 1 \le \ell \le i-1\}$.

3-2. Do Step 3-1 until there is no arrow of type $II(y_1)$.

3-3. Let $E_{y_1}^2$ be the set of reactions of type $II(y_1)$ erased from N_1.

Step 4. Repetition of Step2 – Step3.

4-1. Choose a complex $y_{k+1}(k \ge 1)$ in a subnetwork N_{k+1} of N_k without both the complexes $y_i(1 \le i \le k)$ and reactions in $\bigcup_{1 \le i \le k} \left(E_{y_i}^1 \cup E_{y_i}^2\right)$

4-2. Repeat Step 2 – Step3 for y_{k+1} and N_{k+1}.

4-3. Stop this algorithm if there is no such a complex y_{k+1}.

Example 1. *In Fig.1-(b),* $E_B^1 = \{D+E \to A+C\}$ *and* $E_B^2 = \{C+E \to C+D\}$.

Definition 3. *The networks constructed by applying the above algorithm to both a given network and its linkage classes are called the core and subcore networks of the given network, respectively.*

For example, a core network is the network in Fig.1-(b) without $D + E \to B$ and $C + D \to C + E$.

For $\beta^1 \xrightarrow[\xi_2]{\xi_1} \gamma^I$ of $I(y)$ there is a relation among $\gamma^I - \beta^1$, $y - \xi_1$ and $y - \xi_2$. Similarly a relation exists among $\gamma^{II} - \beta^2$, $y - \xi$ and $\varsigma - y$ for the reaction $\beta^2 \xrightarrow[\varsigma]{\xi} \gamma^{II}$ of type $II(y)$. We need relations (1a) and (1b) in Lemma 3.

Lemma 3. *Let* $\beta^1 \underset{\xi_2}{\overset{\xi_1}{\longrightarrow}} \gamma^I$ *and* $\beta^2 \underset{\varsigma}{\overset{\xi}{\to}} \gamma^{II}$ *be reactions of type* $I(y)$ *and* $II(y)$*. Then there exist nonnegative integers* $n_i, m_j (1 \leq i, j \leq 2)$ *and complexes* $\hat{y}_i, \tilde{y}_j \in \mathcal{C} - \{y\} (1 \leq i \leq n_2, 1 \leq j \leq m_2)$ *such that*

$$\gamma^I - \beta^1 = (-1)^{n_1} (y - \xi_1) + \big\{ - (-1)^{n_1} \big\} (y - \xi_2) + \sum_{i=1}^{n_2} (\hat{y}_i - \hat{y}_{i+1}) \tag{1a}$$

and

$$\gamma^{II} - \beta^2 = (-1)^{m_1} (y - \xi) + (-1)^{m_1} (y - \varsigma) + \sum_{j=1}^{m_2} (\tilde{y}_j - \tilde{y}_{j+1}). \tag{1b}$$

Proof. Since $\beta^1 \underset{y_2}{\overset{y_1}{\longrightarrow}} \gamma^I$ is contained in a non-directed circle with y_1 and y_2, there exist a positive integer n and a sequence $\left(\gamma^I, \hat{y}_1, \cdots, \hat{y}_n, \beta^1\right)$ such that $\gamma^I \sim \hat{y}_1 \sim \cdots \sim \xi_1 \to y \leftarrow \xi_2 \sim \cdots \sim \hat{y}_n \sim \beta^1$ or $\gamma^I \sim \hat{y}_1 \sim \cdots \sim \xi_1 \leftarrow y \to \xi_2 \sim \cdots \sim \hat{y}_n \sim \beta^1$. This completes the proof of (1a). Similarly (1b) can be proved. □

In Example 1, the equations (1a) and (1b) become $(A + C) - (D + E) = (-1)^2[\{B - (D + E)\} - \{B - (A + C)\}]$ and $(C + E) - (C + D) = (-1)^2[(B - F) + \{(C + E) - B\}] + F - (C + D)$, respectively.

Lemma 4. *Assume the deficiency of a network is zero. Then the followings are true.*

(a) Each subcore network has zero deficiency.

(b) Rank of the core network is equal to the sum of ranks of subcore networks.

(c) For a complex y*,* S_y *is linearly independent.*

Proof. (a) Let the number of complexes, deficiency and rank of the given network be n, d and r, respectively. The definition of a core network implies that the deficiency and rank of the core network are also d and r, respectively. Let the number of subcore networks be ℓ, the number of complexes in each subcore network n_i, and the rank of each subcore network $r_i (1 \leq i \leq \ell)$. Then $n = \sum_{1 \leq i \leq \ell} n_i$. It follows from the definition of rank that $1 \leq r_i \leq n_i - 1$ and $\ell \leq r \leq \sum_{1 \leq i \leq \ell} r_i$. Suppose $r_i < n_i - 1$ for some i. Then

$$0 = d = n - \ell - r \geq \sum_{1 \leq i \leq \ell} n_i - \ell - \sum_{1 \leq i \leq \ell} r_i = \sum_{1 \leq i \leq \ell} (n_i - 1 - r_i) \geq n_i - 1 - r_i > 0, \tag{2}$$

which is a contradiction. Therefore $r_i = n_i - 1$ for all i, which completes the proof of (a). Using both (2) and (a), we obtain $r = \sum_{1 \leq i \leq \ell} r_i$, which is the proof of (b). To prove (c) we can construct a subcore network containing all the arrows in $\mathcal{R}_y$. Since $r_i = n_i - 1$ for all i, each subcore network is linearly independent. Therefore S_y is linearly independent. $\square$

Using the Algorithm for Core Networks, we obtain the following theorem which is the main result in this paper.

Theorem 1. *Let a network have a positive equilibrium and zero deficiency. If y is a complex in the network, then there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ such that*

$$\sum_{\xi \in \mathcal{C}_y^0} \alpha_{\xi \to y} = \sum_{\varsigma \in \mathcal{C}_y^1} \alpha_{y \to \varsigma},$$

where $\mathcal{C}_y^0 = \{\xi \in \mathcal{C} | \xi \to y \in \mathcal{R}\}$ and $\mathcal{C}_y^1 = \{\varsigma \in \mathcal{C} | y \to \varsigma \in \mathcal{R}\}$.

Proof. Since the network has a positive equilibrium, there exists an $\alpha \in \mathbb{P}^{\mathcal{R}}$ such that $\sum_{\mathcal{R}} \alpha_{y \to y'} (y' - y) = 0$. Let y be a fixed complex in the network. We will show the equality $\sum_{\xi \in \mathcal{C}_y^0} \alpha_{\xi \to y} = \sum_{\varsigma \in \mathcal{C}_y^1} \alpha_{y \to \varsigma}$. Let the number of the complexes and linkage classes be n and ℓ, respectively. Since zero deficiency implies that the rank is $n - \ell$, we can assume without loss of generality

$$S_y \cup \{y_i' - y_i | i = \ell_1 + 1, \cdots, n\} \tag{3}$$

is linearly independent with the number of elements in S_y being $\ell_1 - \ell$. Using Step1–Step3 of the Algorithm for Core Networks with $y_1 = y$ and linear independence of the set in (3), we obtain for some constants $\tilde{\alpha}, f, g$

$$\begin{aligned} 0 &= \sum_{\mathcal{R}} \alpha_{y \to y'} (y' - y) \qquad (4) \\ &= \sum_{\xi \in \mathcal{C}_y^0} (\tilde{\alpha}_{\xi \to y} - f_{\xi y})(y - \xi) + \sum_{\varsigma \in \mathcal{C}_y^1} (\tilde{\alpha}_{y \to \varsigma} - f_{y\varsigma}) (\varsigma - y) + \sum_{i=\ell_1+1}^{n} g_{y_i y_i'} (y_i' - y_i), \end{aligned}$$

where

$$f_{\xi y} = \{\sum_{i \in \xi_I} (-1)^{\xi_i} \alpha_{\beta_i^1 \xrightarrow{\xi} \gamma_i^I}\} + \{\sum_{i \in \xi_{II}} (-1)^{\xi_i} \alpha_{\beta_i^2 \xrightarrow{\xi} \gamma_i^{II}}\},$$

$\tilde{\alpha}_{\xi \to y} = \alpha_{\xi \to y} - \alpha_{y \to \xi}$ and $\tilde{\alpha}_{y \to \varsigma} = \alpha_{y \to \varsigma} - \alpha_{\varsigma \to y}$ if $\alpha_{y \to \xi}$ and $\alpha_{\varsigma \to y}$ exist. It follows from the equation (4) and linear independence of the set in (3) that

$$\tilde{\alpha}_{\xi \to y} = f_{\xi y} \ (\xi \in \mathcal{C}_y^0) \quad \text{and} \quad \tilde{\alpha}_{y \to \varsigma} = f_{y\varsigma} \ (\varsigma \in \mathcal{C}_y^1).$$

This implies

$$\sum_{\xi \in \mathcal{C}_y^0} \tilde{\alpha}_{\xi \to y} = \sum_{\xi \in \mathcal{C}_y^0} f_{\xi y} \quad \text{and} \quad \sum_{\varsigma \in \mathcal{C}_y^1} \tilde{\alpha}_{y \to \varsigma} = \sum_{\varsigma \in \mathcal{C}_y^1} f_{y\varsigma}.$$

Using (1a) in Lemma 3 and (4), we obtain

$$
\begin{aligned}
\sum_{\xi\in\mathcal{C}_y^0} f_{\xi y} &= \sum_{\xi\in\mathcal{C}_y^0}\left\{\sum_{i\in\xi_I}(-1)^{\xi_i}\alpha_{\beta_i^1\xrightarrow[\xi_i^0]{\xi}\gamma_i^I}\right\}+\sum_{\xi\in\mathcal{C}_y^0}\left\{\sum_{i\in\xi_{II}}(-1)^{\xi_i}\alpha_{\beta_i^2\xrightarrow[\varsigma_i]{\xi}\gamma_i^{II}}\right\}\\
&= \frac{1}{2}\sum_{i\in\cup\xi_I}(-1)^{\xi_i}\left(\alpha_{\beta_i^1\xrightarrow[\xi_i^0]{\xi}\gamma_i^I}-\alpha_{\beta_i^1\xrightarrow[\xi]{\xi_i^0}\gamma_i^I}\right)+\sum_{\xi\in\mathcal{C}_y^0}\left\{\sum_{i\in\xi_{II}}(-1)^{\xi_i}\alpha_{\beta_i^2\xrightarrow[\varsigma_i]{\xi}\gamma_i^{II}}\right\}\\
&= \sum_{\xi\in\mathcal{C}_y^0}\left\{\sum_{i\in\xi_{II}}(-1)^{\xi_i}\alpha_{\beta_i^2\xrightarrow[\varsigma_i]{\xi}\gamma_i^{II}}\right\}.
\end{aligned}
$$

Similarly

$$
\sum_{\varsigma\in\mathcal{C}_y^1} f_{y\varsigma} = \sum_{\varsigma\in\mathcal{C}_y^1}\left\{\sum_{i\in\varsigma_{II}}(-1)^{\varsigma_i}\alpha_{\beta_i^2\xrightarrow[\xi_i]{\varsigma}\gamma_i^{II}}\right\}.
$$

Since (1b) in Lemma 3 and (4) imply

$$
\{(-1)^{\varsigma_i}\alpha_{\beta_i^2\xrightarrow[\xi_i]{\varsigma}\gamma_i^{II}} \mid \varsigma\in\mathcal{C}_y^1\ ,\ i\in\varsigma_{II}\} = \{(-1)^{\xi_i}\alpha_{\beta_i^2\xrightarrow[\varsigma_i]{\xi}\gamma_i^{II}} \mid \xi\in\mathcal{C}_y^0,\ i\in\xi_{II}\},
$$

we obtain

$$
\sum_{\xi\in\mathcal{C}_y^0}\tilde{\alpha}_{\xi\to y} = \sum_{\xi\in\mathcal{C}_y^0} f_{\xi y} = \sum_{\varsigma\in\mathcal{C}_y^1} f_{y\varsigma} = \sum_{\varsigma\in\mathcal{C}_y^1}\tilde{\alpha}_{y\to\varsigma},
$$

which implies the proof. □

Using Theorem 1, we obtain the following theorem.

Theorem 2. *If a network has a positive equilibrium and zero deficiency, then the network is weakly reversible.*

Proof. Theorem 1 implies that for any complex y, there exists $\alpha\in\mathbb{P}^{\mathcal{R}}$ such that $\sum\limits_{\varsigma\in\mathcal{C}_y^1}(-\alpha_{y\to\varsigma})+\sum\limits_{\xi\in\mathcal{C}_y^0}\alpha_{\xi\to y}=0$. That means,

$$
\left[\sum_{\varsigma\in\mathcal{C}_y^1}\alpha_{y\to\varsigma}(w_\varsigma-w_y)+\sum_{\xi\in\mathcal{C}_y^0}\alpha_{\xi\to y}(w_y-w_\xi)\right]_y = 0.
$$

Since for any complex y,

$$
\left[\sum_{\mathcal{R}}\alpha_{y_1\to y_2}(w_{y_1}-w_{y_2})\right]_y = \left[\sum_{\varsigma\in\mathcal{C}_y^1}\alpha_{y\to\varsigma}(w_\varsigma-w_y)+\sum_{\xi\in\mathcal{C}_y^0}\alpha_{\xi\to y}(w_y-w_\xi)\right]_y,
$$

we obtain

$$\left[\sum_{\mathcal{R}} \alpha_{y_1 \to y_2} \left(w_{y_1} - w_{y_2}\right)\right]_y = 0.$$

Thus there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ such that $\sum_{\mathcal{R}} \alpha_{y \to y'} \left(w_{y'} - w_y\right) = 0$, which completes the proof. □

Remark 1. *Theorem 2 implies that if a network is not weakly reversible, then the network can not have a positive equilibrium under the assumption of zero deficiency.*

Remark 2. *Using Algorithm for Core Networks, we can easily calculate the rank of a network, which is a topic for future study.*

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