Theoretical Analysis for Dynamics of Formose Reaction based on Network Structure

Hirokazu Komatsu

Institute for Frontier Life and Medical Sciences, Kyoto University

1 Introduction

In the present paper, we consider the productivity of sugars in *formose chemical reaction networks* (FCRNs) involving the formation of the sugars from formaldehyde in two types of reactors, namely, the *batch reactor* (BR) and the *continuous stirred-tank reactor* (CSTR) [1]. Here, a BR is a closed system without the in-flow and out-flow of species in a *chemical reaction network* (CRN), while a CSTR is an open system with them [1][2].

In order to analyze the mathematical structure of FCRNs more clearly, we propose a *generalized formose chemical reaction network* (GFCRN) on the basis of characteristic network structures of the networks. By analyzing the ordinary differential equations (ODEs) that describe the dynamics of concentrations of all species in GFCRN in the two reactors, we theoretically clarify the productivity of sugars in them. In particular, in order to employ external effects to the networks, we assume time-varying kinetics for a reaction [3][4].

First, by using the techniques given in [6] and [7], we show that any positive solution to the ODE for the GFCRN in the BR converges to an equilibrium point on the boundary of positive orthant, that is, all sugars in the FCRNs cannot be produced in the BR at their steady states. Next, by giving some assumptions to the kinetics of reactions and utilizing the concept of a *semi-lockings set* of a CRN proposed in [3] and [4], we show that any positive solution to the ODE for the GFCRN in the CSTR is bounded globally in time and does not approach to the boundary of positive orthant, that is, the concentrations of all species in the network do not converge to zero. This result implies that all sugars in the FCRNs can be produced in the CSTR at their steady states, in contrast to the case of the BR.

From the above results, it is concluded that the productivity of sugars in the FCRNs in the CSTR is higher than it in the BR.

2 Chemical Reaction Networks

A *chemical reaction network* (CRN) in the sense of Feinberg [2] is mathematically defined by a triplet $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, where the elements $\mathcal{S}$, $\mathcal{C}$ and $\mathcal{R}$ are defined by

$\mathcal{S}$: the set of n *species* in the network, denoted by $\mathcal{S} := \{X_1, X_2, \ldots, X_n\}$,

$\mathcal{C}$: the set of all *complexes* y in the network,

$\mathcal{R}$: the set of all *chemical reactions* $y \to y'$ in the network.

Here a complex $y \in \mathcal{C}$ means a linear combination of species, $y = y_1 X_1 + \cdots + y_n X_n$, with coefficients of non-negative integers, $y_1, y_2, \ldots, y_n$, and a chemical reaction $y \to y'$ denotes that a complex y' is produced from y. Here we may associate y with the vector of these cofficients, $(y_1, y_2, \cdots, y_n)^T \in \mathbb{R}^n$, and y and y' are called a *reactant* and a *product*, respectively.

We consider the time-evolution of the vector composed of molar concentrations of all species in a network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. This vector is defined by $x = (x_1, x_2, \ldots, x_n)^T \in \mathbb{R}^n_{\geq 0}$. Here x_i is the molar concentration of the species $X_i \in \mathcal{S}$ and $\mathbb{R}^n_{\geq 0}$ is the non-negative orthant of $\mathbb{R}^n$. The time-evolution of x is given by the following non-autonomous ordinary differential equation (ODE) [3]:

$$\dot{x}(t) = \sum_{y \to y' \in \mathcal{R}} K_{y \to y'}(t, x(t))(y' - y), \quad t \geq 0, \tag{1}$$

where $K_{y \to y'} : [0, +\infty) \times \mathbb{R}^n_{\geq 0} \to \mathbb{R}$, which is called the *kinetics of the chemical reaction* $y \to y'$, is a non-negative continuous function on $[0, +\infty) \times \mathbb{R}^n_{\geq 0}$. Furthermore, we assume the following condition [2]–[5]: There exist functions $\overline{K}_{y \to y'}, \underline{K}_{y \to y'} : \mathbb{R}^n_{\geq 0} \to \mathbb{R}$ such that

$$\underline{K}_{y \to y'}(x) \leq K_{y \to y'}(t, x) \leq \overline{K}_{y \to y'}(x), \quad \forall x \in \mathbb{R}^n_{\geq 0}, \quad \forall t \in [0, +\infty). \tag{2}$$

Here, $\overline{K}_{y \to y'}(x)$ (resp.$\underline{K}_{y \to y'}(x)$) is a non-negative function of $C^1(\mathbb{R}^n_{\geq 0}; \mathbb{R})$ satisfying that, for any $x \in \mathbb{R}^n_{\geq 0}$, $\overline{K}_{y \to y'}(x)$ (resp.$\underline{K}_{y \to y'}(x)$) > 0 if and only if $\mathrm{supp}(y) \subset \mathrm{supp}(x)$, where $\mathrm{supp}(z)$ for $z \in \mathbb{R}^n$ is defined by a subset of $\mathcal{S}$ such that $X_i \in \mathrm{supp}(z)$ if and only if $z_i \neq 0$.

It has been proved that Eq.(1) is *non-negative* (resp. *positive*), that is, any solution $x(t)$ to Eq.(1) with an initial value $x(0) \in \mathbb{R}^n_{\geq 0}$ (resp. $x(0) \in \mathbb{R}^n_{>0}$) remains in $\mathbb{R}^n_{\geq 0}$ (resp. $\mathbb{R}^n_{>0}$) for all $t \geq 0$ [8].

3 Generalized Formose Chemical Reaction Network in Batch Reactor

We consider a *generalized formose chemical reaction network in the batch reactor*, which is given by the following CRN $(\mathcal{S}_1, \mathcal{C}_1, \mathcal{R}_1)$:

$$\mathcal{S}_1 = \{X_1, X_2, \ldots, X_n\},\ \mathcal{C}_1 = \{2X_2\} \cup \bigcup_{i=1}^{n-1} \{X_1 + X_i\} \cup \bigcup_{i=2}^{n} \{X_i\},\ \mathcal{R}_1 = \bigcup_{i=1}^{n-1} \{X_1 + X_i \to X_{i+1}\} \cup \{X_n \to 2X_2\}.$$

where $m \geq 2$ is a positive integer number, and species X_1 and X_n correspond to formaldehyde and a sugar, respectively.

By using the techniques given in [6] and [7], we have the first main result of the present paper. The proof of the theorem will be given in Section4.

Theorem 3.1 Any positive solution $x(t)$ to Eq.(1) for the CRN $(\mathcal{S}_1, \mathcal{C}_1, \mathcal{R}_1)$ with an initial value $x(0) \in \mathbb{R}^n_{>0}$ converges to an equilibrium point $\overline{x} \in \partial\mathbb{R}^n_{>0}$ on the boundary of positive orthant $\mathbb{R}^n_{>0}$. Here, $\overline{x}$ is a vector in $\partial\mathbb{R}^n_{>0}$ such that $\overline{x}_1$ and $\overline{x}_n$ are zero, and at least one of $\overline{x}_i$ $(i = 2, \ldots, n-1)$ is not zero.

4 The Proof of Theorem 3.1

First of all, we show in the following lemma that any positive solution $x(t)$ to Eq. (1) for the CRN $(\mathcal{S}_1, \mathcal{C}_1, \mathcal{R}_1)$ is bounded globally in time.

Lemma 4.1 Any positive solution $x(t)$ is bounded globally in time, that is, $\limsup_{t \to \infty} \|x(t)\| < +\infty$.

Proof Let us define a linear function $T_1 : \mathbb{R}^n_{\geq 0} \to \mathbb{R}$ defined by

$$T_1(x) := 3x_1 + 3x_n + \sum_{i=2}^{n} x_i, \quad \forall x \in \mathbb{R}^n_{\geq 0}. \tag{3}$$

Taking the time derivative of this function along the positive solution $x(t)$, we have

$$\frac{d}{dt} T_1(x(t)) = -5K_{2X_1 \to X_2}(t, x(t)) - K_{X_n \to 2X_2}(t, x(t)) - K_{X_1 + X_{n-1} \to X_n}(t, x(t)) - 3\sum_{i=2}^{n-2} K_{X_1 + X_i \to X_{i+1}}(t, x(t)), \ \forall t \geq 0,$$

which implies that $T_1(x(t)) \leq T_1(x(0))$ for all $t \geq 0$. Hence we have $0 \leq x_i(t) \leq T_1(x(0))$ for all $t \geq 0$ and $i = 1, \dots, n$. Therefore, it holds that $\limsup_{t\to\infty} \|x(t)\| < +\infty$. □

By using the linear function T_1 in the proof of this lemma, we obtain the following lemma, which guarantees the convergence of any positive solution $x(t)$ to Eq. (1) for the CRN $(\mathcal{S}_1, \mathcal{C}_1, \mathcal{R}_1)$.

Lemma 4.2 For any positive solution $x(t)$, the following limits exist:

$$\lim_{t\to\infty} \int_0^t K_{X_1+X_i\to X_{i+1}}(s, x(s))ds, \quad i = 1, \dots, n-1, \quad \lim_{t\to\infty} \int_0^t K_{X_n\to 2X_2}(s, x(s))ds, \tag{4}$$

$$\lim_{t\to\infty} \int_0^t \underline{K}_{X_1+X_i\to X_{i+1}}(x(s))ds, \quad i = 1, \dots, n-1, \quad \lim_{t\to\infty} \int_0^t \underline{K}_{X_n\to 2X_2}(x(s))ds. \tag{5}$$

Proof Integrating (10) from 0 to t, we have

$$T_1(x(0) \geq \int_0^t K_{X_n\to 2X_2}(s, x(s))ds, \int_0^t K_{X_1+X_i\to X_{i+1}}(s, x(s))ds, \quad i = 1, \dots, n-1, \quad \forall t \geq 0. \tag{6}$$

Moreover from the assumption (2) of the kinetics for a reaction we obtain

$$T_1(x(0) \geq \int_0^t \underline{K}_{X_n\to 2X_2}(x(s))ds, \int_0^t \underline{K}_{X_1+X_i\to X_{i+1}}(x(s))ds, \quad i = 1, \dots, n-1, \quad \forall t \geq 0. \tag{7}$$

Hence we see from monotonically increasing of these integral functions (6) and (7) with respect to t that (4) and (5) hold. □

The convergence of any positive solution $x(t)$ to Eq.(1) for the CRN $(\mathcal{S}_1, \mathcal{C}_1, \mathcal{R}_1)$ is proven, immediately.

Corollary 4.1 For any positive solution $x(t)$, the following limits exist: $\lim_{t\to\infty} x_i(t) = \overline{x}_i$, $i = 1, \dots, n$, where $\overline{x} = (\overline{x}_1, \dots, \overline{x}_n)$ is a non-zero vector in $\mathbb{R}^n_{\geq 0}$.

Next, we determine the convergence values $\overline{x}_i$ $(i = 1, \dots, n)$. In order to show that the variables $x_i(t)$ $(i = 1, n)$ converge to zero as $t \to +\infty$, we start with proving the following lemma.

Lemma 4.3 For any positive solution $x(t)$, it holds that

$$\lim_{t\to\infty} \underline{K}_{X_1+X_i\to X_{i+1}}(x(t)) = 0, \; i = 1, \dots, n-1, \quad \lim_{t\to\infty} \underline{K}_{X_n\to 2X_2}(x(t)) = 0. \tag{8}$$

Proof We see from Lemma 6.1 and the assumption of a function $\underline{K}_{y\to y'}(x)$ that for all $y \to y' \in \mathcal{R}_1$, $\sup_{t\geq 0} \left| d\underline{K}_{y\to y'}(x(t))/dt \right| < +\infty$. Therefore, from Barbalat's lemma [6] and Lemma 4.2 the limit (8) holds. □

Together with this lemma and the assumption (i) of a function $K_{y\to y'}(t, x)$, we have the following theorem with respect to the convergence of the variables $x_i(t)$ $(i = 1, n)$.

Theorem 4.1 For any positive solution $x(t)$, it holds that $\lim_{t\to\infty} x_i(t) = 0$, $i = 1, n$.
Proof Let us consider the case of $i = 1$. We assume that $\limsup_{t\to\infty} x_1(t) \neq 0$. This means that there exists a sequence $\{t_l\}_{l\in\mathbb{N}}$ satisfying $\lim_{l\to\infty} t_l = +\infty$ such that $\lim_{l\to\infty} x_1(t_l) = \limsup_{t\to\infty} x_1(t) > 0$. Hence, we see from continuity of the function $\underline{K}_{2X_1\to X_2}(x(t))$ with respect to t that $\lim_{l\to\infty} \underline{K}_{2X_1\to X_2}(x(t_l)) > 0$, which is a contradiction with (8).
The other variable x_n can be proved in the same way as the above, hence the proof is omitted here. □

Finally, we show at least one of the limits of the variables x_i $(i = 2, \dots, n-1)$ is not zero.

Theorem 4.2 For any positive solution $x(t)$, at least one of the limits $\lim_{t\to\infty} x_i(t)$, $i = 2, \ldots, n-1$ is not zero.

Proof We assume that $\lim_{t\to\infty} x_i(t) = 0$ for all $i = 2, \ldots, n-1$. Now, let us define the linear function $T_2 : \mathbb{R}^n \to \mathbb{R}$ by $T_2(x) := \sum_{i=2}^{n} x_i$ for all $x \in \mathbb{R}^n_{\geq 0}$. Taking the time derivative of this function T_2 along the positive solution $x(t)$ from Lemma 4.2, we have

$$\lim_{t\to\infty} T_2(x(t)) = T_2(0) + \lim_{t\to\infty} \int_0^t K_{2X_1\to X_2}(s, x(s))ds + \sum_{i=2}^{n} \lim_{t\to\infty} \int_0^t K_{X_{2i}\to 2X_i}(s, x(s))ds > 0. \tag{9}$$

Now we see from continuity of the function $T_2(x(t))$ with respect to t that $\lim_{t\to\infty} T_2(x(t)) = 0$, which is a contradiction with (9).

Therefore at least one of the limits $\lim_{t\to\infty} x_i(t)$, $i = 2, \ldots, n-1$ is not zero. □

The proof of Theorem 3.1 is completed from Thereoms 4.1 and 4.2

5 Generalized Formose Chemical Reaction Network in Continuous Stirred-Tank Reactor

We consider a *generalized formose chemical reaction network in the continuous stirred-tank reactor* $(\mathcal{S}_2, \mathcal{C}_2, \mathcal{R}_2)$ given by

$$\mathcal{S}_2 := \mathcal{S}_1, \quad \mathcal{C}_2 := \mathcal{C}_1 \cup \{0,\ X_1\}, \quad \mathcal{R}_2 := \mathcal{R}_1 \cup \{0 \to X_1\} \cup \bigcup_{i=1}^{n} \{\ X_i \to 0\ \}.$$

where 0 denotes the zero complex, of which entries are all zeros. Here, we assume that the function $K_{0\to X_1}(t, x) = \alpha_{0\to X_1}(t)$, where a continuous function $\alpha_{0\to X_1}(t)$ satisfies that there exist constants $\underline{M}_{0\to X_1}, \overline{M}_{0\to X_1} > 0$ such that $\underline{M}_{0\to X_1} < \alpha_{0\to X_1}(t) < \overline{M}_{0\to X_1}$ for all $t \geq 0$, and the function $\underline{K}_{X_i\to 0}(x)$ satisfies that $\lim_{x_i\to+\infty} \underline{K}_{X_i\to 0}(x) = +\infty$ as $x_i \to +\infty$.

The second main result of the present paper is in the following theorem, the proof of which will be given in Section6.

Theorem 5.1 Any positive solution $x(t)$ to Eq.(1) for the CRN $(\mathcal{S}_2, \mathcal{C}_2, \mathcal{R}_2)$ with an initial value $x(0) \in \mathbb{R}^n_{>0}$ is bounded globally in time. Moreover, the following inequality holds: $\liminf_{t\to\infty} x_i(t) > 0$, $i = 1, \ldots, n$.

6 The Proof of Theorem 5.1

First, we show the first part of Theorem 5.1 that any positive solution $x(t)$ to Eq.(1) for the CRN $(\mathcal{S}_2, \mathcal{C}_2, \mathcal{R}_2)$ is bounded globally in time.

Theorem 6.1 Any positive solution $x(t)$ is bounded globally in time.

Proof Taking the time derivative of the function T_1 defined by (3) along the positive solution $x(t)$, we have

$$\frac{d}{dt} T_1(x(t)) \leq -\sum_{i=1}^{n} K_{X_i\to 0}(t, x(t)) + 3\alpha_{0\to X_1}(t) \leq -\sum_{i=1}^{n} \underline{K}_{X_i\to 0}(x(t)) + \overline{\alpha}, \quad \forall t \geq 0, \tag{10}$$

where we put $\overline{\alpha} := 3 \sup_{t\geq 0} \alpha_{0\to X_1}(t)$.

Let us define a subset $B \subset \mathbb{R}^n$ by $B := \left\{ x \in \mathbb{R}^n_{\geq 0} \mid g(x) \leq \overline{\alpha} \right\}$, where $g(x) := \sum_{i=1}^{n} \underline{K}_{X_i\to 0}(x)$. Since it follows from the assumption of a function $\underline{K}_{X_i\to 0}(x)$ that $g(0) = 0$ and $g(x) \to +\infty$ as $\|x\| \to +\infty$, the subset B is non-empty and compact on $\mathbb{R}^n$. Putting $\overline{T}_1 := \max_{x\in B} T_1(x) < +\infty$ we see that $0 \leq$

$T_1(x(t)) \leq \max\{\overline{T}_1, T_1(x(0))\}$ for all $t \geq 0$. Hence we have $0 \leq x_i(t) \leq \max\{\overline{T}_1, T_1(x(0))\}$ for all $t \geq 0$ and $i = 1, \ldots, n$, which implies that $\limsup_{t\to\infty} \|x(t)\| < +\infty$. □

Next, in order to prove the second part of Theorem 5.1, we give the definition of a *semi-locking set* of a CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and a lemma [3]

Definition 6.1 For a network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, a non-empty subset $\mathcal{W}$ of $\mathcal{S}$ is called a *semi-locking set* if $\mathcal{W} \cap \mathrm{supp}(y) \neq \emptyset$ for any reaction $y \to y' \in \mathcal{R}$ such that $\mathcal{W} \cap \mathrm{supp}(y') \neq \emptyset$.

Lemma 6.1 Consider the Eq. (1) for $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. Let $W \subset \mathcal{S}$ be a non-empty subset. If there exists an initial value $x(0) \in \mathbb{R}^n_{>0}$ such that $\omega(x(0)) \cap L_{\mathcal{W}} \neq \emptyset$, then $\mathcal{W}$ is a semi-locking set. Here $\omega(x(0))$ is an omega limit set of $x(0)$, and $L_{\mathcal{W}}$ is a subset of $\mathbb{R}^n$ defined by $L_{\mathcal{W}} := \{\, x \in \mathbb{R}^n \mid x_i = 0 \Leftrightarrow X_i \in \mathcal{W} \,\}$.

Theorem 6.2 For any positive solution $x(t)$, it holds that $\liminf_{t\to\infty} x_i(t) > 0$, $i = 1, \ldots, n$.
Proof Theorem 6.1 means that the omega-limit set $\omega(x(0))$ is a non-empty, compact and invariant subset of $\mathbb{R}^n_{\geq 0}$ [6]. Moreover, we see that $(\mathcal{S}_2, \mathcal{C}_2, \mathcal{R}_2)$ does not have a semi-locking set, and hence it follows from Lemma 6.1 that $\omega(x(0)) \subset \mathbb{R}^n_{>0}$. Therefore, since any positive solution $x(t)$ approaches to $\omega(x(0))$ as $t \to +\infty$ [6], from the compactness of $\omega(x(0))$, the proof of Theorem 6.2 is completed. □

The proof of Theorem 5.1 is completed from Thereoms 6.1 and 6.2.

References

[1] W. P. Huskey and I. R. Epstein, Autocatalysis and apparent bistability in the formose reaction, Journal of the American Chemical Society, Vol. 111, No. 9, pp.3157–3163 (1989).

[2] M. Feinberg, Foundation of chemical reaction network theory, Springer, New York (2019).

[3] D. Angeli, P. D. Leenheer and E. D. Sontag, Persistence results for chemical reaction networks with time-dependent kinetics and no global conservation laws, SIAM Journal on Applied Mathematics, Vol.71, No.1, pp. 128–146 (2011).

[4] D. F. Anderson, A proof of the global attractor conjecture in the single linkage class, SIAM Journal on Applied Mathematics, Vol. 71, No. 4, pp.1487-1508 (2011).

[5] M. A. Al-Radhawi and D. Angeli, New approach to the stability of chemical reaction networks: piecewise linear in rates Lyapunov functions, IEEE Transactions on Automatic Control, Vol. 61, No. 1, pp. 76–89 (2016).

[6] H. K.Khalil, Nonlinear Systems Third Edition, Prentice Hall (2002).

[7] H. Komatsu and H. Nakajima, Stability analysis of non-weakly reversible single linkage class chemical reaction networks, Proc. 2018 IEEE Conference on Decision and Control, pp. 4815–4820 (2018).

[8] E.D. Sontag, Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-Cell receptor signal transduction, IEEE Transactions on Automatic Control, Vol. 61, No. 7, pp.1028–1047 (2001).

Hirokazu Komatsu
Institute for Frontier Life and Medical Sciences, Kyoto University
53 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan
E-mail address : komatsu134711@gmail.com