On the relation between ω-limit set and boundaries of mass-action chemical reaction networks ⋆

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Abstract

ω-limit set can be used to understand the long term behavior of a dynamical system. In this paper, we use the Lyapunov function PDEs method, developed in our previous work, to study the relation between ω-limit points and boundaries for chemical reaction networks equipped with mass-action kinetics. Using the solution of the PDEs, some new checkable criteria are proposed to diagnose non ω-limit points of the network system. These criteria are successfully applied to verify that non-semilocking boundary points and some semilocking boundary points are not ω-limit points. Further, we derive the ω-limit theorem that precludes the limit cycle of some biochemical network systems. The validity of the results are demonstrated through some abstract and practical examples of chemical reaction networks.

Key words: chemical reaction network, mass-action system, boundaries, ω-limit set, Lyapunov Function PDEs.

1 Introduction

Chemical reaction networks (CRNs) are widely existing in the fields of chemistry, biology, and medicine, etc. The related studies have been applied to many fields, besides the above mentioned ones, even including those not seemly related to chemical reactions, such as electricity (Samardzija et al., 1989). Mass-action kinetics is one of the most commonly used kinetics to describe the reaction rate of chemical reactions, and the induced systems, termed as mass-action systems (MASs), often give rise to a family of nonequilibrium ordinary differential equations (ODEs). The ODEs are generally highly nonlinear, and also contain many parameters, such as the rate constants of all reactions. Due to difficult/inaccurate measurement problem to these parameters, it often requires to study the dynamical behaviors of MASs only depending on the topological structure of networks, but independent of the system parameters. Here, the dynamical behaviors mainly relate to stability, persistence, etc. The pioneering work on this topic was made by Horn and Jackson (1972), and Feinberg (1979). They defined a class of complex balanced MASs with weakly reversible network structure, and addressed well the issues on number of equilibria, locally asymptotic stability, etc. However, the globally asymptotic stability is still far from being solved. In practice, it is unnecessary to directly tackle this issue itself, but may address another issue of persistence instead. A complex balanced MAS will be globally asymptotically stable if it has persistence. Hence, the persistence study has become quite active in recent decades (Anderson, 2008; Angeli et al., 2007), but the related issues are still open problems in the field of CRNs. Certainly, persistence, as a kind of dynamical behavior, is often used to model the reaction phenomenon that no species will be used up in the course of reaction if it is present at the reaction start. The study on this topic is also interesting from the viewpoint of dynamic analysis.

In this work, we will not follow the line of studying persistence of complex balanced MASs, but launch some preparatory work about persistence of CRNs with any

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structure. As one might know, ω-limit set is a positively invariable set of the trajectory, and may be used to reflect the dynamical property of system. A MAS is persistence if the intersection of its ω-limit set and boundaries is empty. The studies on the relation between ω-limit set and boundaries of MASs are thus rather significant from the viewpoint of control theory as well as of dynamic analysis. As early as 1970s, Vasil'ev et al. (1974) proved the ω-limit set of each trajectory of a detailed balanced system to be only a single positive equilibrium or a set of boundary equilibria. Siegel and Maclean (2000) generalized this result to complex balanced MASs and use this property to derive the global asymptotic stability of a subclass of complex balanced MASs. In characterizing dynamical behaviors, Lyapunov function is a powerful tool (Blanchini and Giordano, 2014). When the networks are complex balanced, there is a canonical choice, i.e., the well-known pseudo-Helmholtz free energy function as the Lyapunov function (Horn and Jackson, 1972). However, in other cases, there is no general method to obtain a Lyapunov function, and no understanding of the space of possible Lyapunov functions for a given reaction network. Although Anderson et al. (2015) showed that the pseudo-Helmholtz free energy function can be derived from an appropriate limit of the stationary distributions for the stochastic mass-action systems, this is not a practical construction method since for almost all reaction network systems, the stationary distributions are prohibitively hard to obtain. Our early work (Fang and Gao, 2019) followed up this issue, and by connecting the microscopic and the macroscopic levels, thermodynamics and potential theory, proposed a PDE and a boundary condition for a mass-action system, referred to as the Lyapuonv Function PDEs. When the PDEs are solved, the solutions are conjectured as Lyapunov functions for the network attached. This conjecture has been proved true when the network is complex balanced, of 1-dimensional stoichiometric subspace, and a combination of the other cases, respectively. Some special networks with dimension of the stoichiometric subspace more than 2 also support the conjecture.

In this paper, we continue to utilize the Lyapunov Function PDEs, but to study the relation between ω-limit set and boundaries of each trajectory of MAS. The main contributions are listed below:

- For a MAS, based on the solution of its Lyapunov Function PDEs, two sufficient conditions are proposed to say any boundary point of system to be not ω-limit point.
- Any non-semilocking boundary point and some semilocking boundary non-equilibrium points are proved not ω-limit point.
- The ω-limit set of some MASs, especially of complex balanced MASs, is proved a set of positive equilibria or a set of boundary equilibria.
- Some practical biochemical systems are proved to have no limit cycles.

The remainder of this paper is organized as follows. Section 2 introduces some preliminaries about CRN theory and Lyapunov Function PDEs. Section 3 presents the checkable technical criteria for the ω-limit set under the framework of the Lyapunov Function PDEs, and some concrete examples are also illustrated. In Section 4, we apply our results to some kinds of real biochemical networks. Finally, Section 5 concludes the paper.

Notations: $\mathbb{R}^n, \mathbb{R}^n_{\geq 0}, \mathbb{R}^n_{>0}$ denote n-dimensional real space, non-negative real space, positive real space, respectively; $\mathscr{C}^i$ denotes the function set whose elements are ith continuously differentiable; su x denotes the support set of a vector x defined as su $x = \{S_j | x_j \neq 0\}$, $\forall x \in \mathbb{R}^n_{\geq 0}$.

2 Preliminaries

In this section we will introduce some backgrounds on CRN (Horn and Jackson, 1972; Feinberg, 1979) and the Lyapunov Function PDEs (Fang and Gao, 2019).

2.1 CRN

A CRN consists of several chemical reactions $R_i, i = 1, \cdots, r$ as shown below:

$$\sum_{j=1}^{n} \nu_{ji} S_j \longrightarrow \sum_{j=1}^{n} \nu'_{ji} S_j. \tag{1}$$

$S_j, j = 1, \cdots, n$ are all the species involved in the chemical reactions. ν_{ji}, ν'_{ji} represent the stoichiometric coefficients of S_j in the reactant and product of the i-th reaction, respectively. Thus the reaction R_i presented in (1) is equivalent to $\nu_{\cdot i} \to \nu'_{\cdot i}$ where $\nu_{\cdot i}, \nu'_{\cdot i} \in \mathbb{Z}^n_{\geq 0}$ are the vectors of ν_{ji} and ν'_{ji} called reactant and product complex of reaction R_i. Let $\mathcal{S} = \bigcup_{j=1}^{n} \{S_j\}$, $\mathcal{C} = \bigcup_{i=1}^{r} \{\nu_{\cdot i}, \nu'_{\cdot i}\}$, and $\mathcal{R} = \bigcup_{i=1}^{r} \{R_i | R_i : \nu'_{\cdot i} \to \nu_{\cdot i}\}$. The triple $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is usually used to represent a CRN. $\nu'_{\cdot i} - \nu_{\cdot i}$ called the **reaction vector** represents the concentration change of each species when the reaction R_i occurs.

The dynamics of a CRN system capturing the change of concentration of every species S_j $(j = 1, \cdots, n)$, identified by x_j, is given once the reaction rate is specified as a function $V : \mathbb{R}^n_{\geq 0} \mapsto \mathbb{R}^r_{\geq 0}$ of $x = (x_1, \cdots, x_n)^\top$. The most frequently-used model to specify the reaction rate is **mass-action kinetics**, under which the reaction rate follows power law with respect to the concentration of every species in the reactant complex, with the stoichiometric coefficients as the power. For example, for the ith reaction $\nu_{\cdot i} \to \nu'_{\cdot i}$, the reaction rate $V_i(x)$ is evaluated by

$$V_i(x) = k_i x^{\nu_{\cdot i}} \triangleq k_i \prod_{j=1}^{n} x_j^{\nu_{ji}}, \tag{2}$$

where $k_i \in \mathbb{R}_{>0}$ is the reaction rate constant.

Definition 2.1 (MAS). A CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ equipped with mass-action kinetics is called a MAS, usually represented by the quaternary $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$.

The dynamical equation of a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ can be written as

$$\frac{dx}{dt} \triangleq \dot{x}(t) = \sum_{i=1}^{r} k_i x^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i}). \tag{3}$$

For a CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, the phase space is $\mathbb{R}^n$. When studying dynamical properties of a MAS, we often need to consider the **stoichiometric subspace** $\mathscr{S}$ spanned by all reaction vectors, denoted by $\mathscr{S} = \text{span}\{\nu'_{\cdot 1} - \nu_{\cdot 1}, \cdots, \nu'_{\cdot r} - \nu_{\cdot r}\}$. Actually, the dynamical equation presented in (3) is contained in the stoichiometric subspace, thus the trajectory is uniquely determined by the initial point, and can only move within the stoichiometric compatibility class containing the initial point. The stoichiometric compatibility class is defined as follows:

Definition 2.2 (stoichiometric compatibility class). Let $x_0 \in \mathbb{R}^n_{\geq 0}$, the sets $\mathscr{S}(x_0) \triangleq \{x_0 + \xi | \xi \in \mathscr{S}\}$, $\mathscr{S}(x_0) \cap \mathbb{R}^n_{\geq 0}$ and $\mathscr{S}(x_0) \cap \mathbb{R}^n_{>0}$ are called the stoichiometric compatibility class, non-negative stoichiometric compatibility class and positive stoichiometric compatibility class of x_0, respectively.

Definition 2.3 (boundary point). For a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ governed by (3), any species concentration vector $\bar{x} \in \mathbb{R}^n_{\geq 0}$ but $\bar{x} \notin \mathbb{R}^n_{>0}$ is called a boundary point.

Remark 1 *Given a boundary point $\bar{x}$, let W represent the set of species with 0 concentration in $\bar{x}$. We define the set of boundary points with the same W as:*

$$L_W = \{x \in \mathbb{R}^n_{\geq 0} | x_i = 0 \, for \, S_i \in W; \, x_i > 0 \, for \, S_i \notin W\}.$$

Thus L_W is a boundary of $\mathbb{R}^n_{\geq 0}$ and $\partial \mathcal{R}^n_{\geq 0} = \bigcup_{W \subset \mathcal{S}} L_W$. For each stoichiometric compatibility class $\mathscr{S}_{x_0}$, the boundary of $\mathscr{S}_{x_0}$ is denoted as $F_W = \mathscr{S}(x_0) \cap L_W$.

Definition 2.4 (equilibrium and boundary equilibrium) For a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$, a concentration vector $x^* \in \mathbb{R}^n_{>0}$ is called an equilibrium if

$$\sum_{i=1}^{r} k_i (x^*)^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i}) = \mathbb{0}_n \tag{4}$$

and further a boundary equilibrium if x^* is also a boundary point.

Definition 2.5 (complex balanced equilibrium). For a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$, a concentration vector $x^* \in \mathbb{R}^n_{>0}$ is called an equilibrium if

$$\sum_{i=1}^{r} k_i (x^*)^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i}) = \mathbb{0}_n, \tag{5}$$

and a complex balanced equilibrium if

$$\sum_{\{\nu_{\cdot i} = C\}} k_i (x^*)^{\nu_{\cdot i}} = \sum_{\{\nu'_{\cdot i} = C\}} k_i (x^*)^{\nu_{\cdot i}}, \quad \forall \, C \in \mathcal{C}. \tag{6}$$

Remark 2 *At the complex balanced equilibrium point, the inflow and outflow of each complex are equal. A complex balanced equilibrium must be an equilibrium, but not vice versa. If a MAS admits an (complex balanced) equilibrium, it is called (complex) balanced MAS. If there exists a complex balanced equilibrium in a MAS, any other equilibrium (if it exists) in this MAS is also a complex balanced equilibrium (Horn and Jackson, 1972).*

For any complex balanced MAS, it requests that the network should have a weakly reversible structure, which is defined as follows.

Definition 2.6 (weakly reversible CRN). A CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is called weakly reversible if for any reaction $\nu_{\cdot i} \to \nu'_{\cdot i} \in \mathcal{R}$ there exists a series of reactions starting from $\nu'_{\cdot i}$ and ending with $\nu_{\cdot i}$, i.e., $\nu'_{\cdot i} \to \nu_{\cdot i_1} \in \mathcal{R}, \cdots, \nu_{\cdot i_m} \to \nu_{\cdot i} \in \mathcal{R}, \; m < r$.

Finally we present definitions related to ω-limit set.

Definition 2.7 (ω-*limit* point). The set of ω-*limit* points for the trajectory $x(t)$ with positive initial condition $x_0 \in \mathbb{R}^n_{>0}$ is

$$\omega(x_0) := \{x \in \mathbb{R}^n_{\geq 0} \mid x(t_N) \to x, \text{ for } t_N \to \infty\}. \tag{7}$$

Definition 2.8 (semilocking set and locking set (Anderson, 2008; Angeli et al., 2007)). For a CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, a nonempty set $W \subseteq \mathcal{S}$ is said to be a semilocking set if one species of W is in a product complex $\nu'_{\cdot i}$, there must exist a species of W in the reactant complex $\nu_{\cdot i}$. If for any reaction $\nu_{\cdot i} \to \nu'_{\cdot i}$ there exists a $S_j \in W$ in reactant complex $\nu_{\cdot i}$, then $W \subseteq \mathcal{S}$ is called a locking set.

Now we use a simple example to illustrate the above definition.

Example 1 *Consider the following CRN*

$$2S_1 \to S_2, \; S_2 + S_3 \to 2S_3.$$

The phase space is $\mathbb{R}^3$, and the corresponding boundaries are $\bigcup L_{W_i}, i = 1, \cdots, 7$, where

$$W_1 = \{S_1\}, W_2 = \{S_2\}, W_3 = \{S_3\}, W_4 = \{S_1, S_2\},$$
$$W_5 = \{S_1, S_3\}, W_6 = \{S_2, S_3\}, W_7 = \{S_1, S_2, S_3\}.$$

Now considering W_4, the species S_2 in W_4 is included in the product complex of the first reaction, the reactant complex of R_1 also contains the species S_1 in W_4. Thus W_4 is a semilocking set. Other sets can be verified similarly. So we have the semilocking set to be $\{W_3, W_4, W_5, W_7\}$, the locking set to be $\{W_3, W_4, W_5, W_7\}$, and the nonsemilocking set to be $\{W_1, W_2, W_6\}$.

Compared with the general boundary, the semilocking boundary has the following property:

Proposition 1 (Anderson, 2008) A nonempty set $W \subseteq \mathcal{S}$ in a CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is a semilocking set iff the boundary F_W is positively invariant for the dynamics (3).

ω-limit set plays an important role on the analysis of long-term dynamical properties, like persistence, global asymptotic stability etc. In this paper, we use the method of Lyapunov Function PDEs to derive some checkable criteria for ω-limit points.

2.2 Lyapunov Function PDEs

By bridging the microscopic and the macroscopic levels, and thermodynamics and potential theory, the Lyapunov Function PDEs are yielded from Chemical Master Equation (Fang and Gao, 2019). Their main use is to produce a Lyapunov function for capturing the asymptotic stability of MASs. For any MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ governed by (3), they include a first-order PDE

$$\sum_{i=1}^{r} k_i x^{\nu_{\cdot i}} - \sum_{i=1}^{r} k_i x^{\nu_{\cdot i}} \exp\{(\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)\} = 0, \quad (8)$$

and a corresponding boundary condition

$$\begin{aligned} &\lim_{x \to \bar{x}} \sum_{\text{su } \nu'_{\cdot i} \subseteq \text{su } \bar{x}} k_i x^{\nu_{\cdot i}} \exp\{(\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)\} \\ &= \lim_{x \to \bar{x}} \sum_{\text{su } \nu_{\cdot i} \subseteq \text{su } \bar{x}} k_i x^{\nu_{\cdot i}}. \end{aligned} \quad (9)$$

Note that in the above two equations $f \in \mathscr{C}^1$, $x \in \mathbb{R}^n_{>0}$, and $\bar{x} \in \mathbb{R}^n_{\geq 0}$ represents any boundary point satisfying $x - \bar{x} \in \mathscr{S}$, and su $\bar{x}$ denotes the support set of $\bar{x}$. For example, for vector $(2, 0, 1)^\top$, su $(2, 0, 1)^\top = \{\mathrm{S}_1, \mathrm{S}_3\}$.

Remark 3 *The following boundary condition is straightforward if (9) is subtracted from (8),*

$$\begin{aligned} &\lim_{x \to \bar{x}} \sum_{\text{su } \nu'_{\cdot i} \nsubseteq \text{su } \bar{x}} k_i x^{\nu_{\cdot i}} \exp\{(\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)\} \\ &= \lim_{x \to \bar{x}} \sum_{\text{su } \nu_{\cdot i} \nsubseteq \text{su } \bar{x}} k_i x^{\nu_{\cdot i}}, \ x \in \mathbb{R}^n_{>0}. \end{aligned} \quad (10)$$

(9) and (10) are referred to as the boundary condition (a) and (b) in the context, respectively.

The following proposition suggests that the solutions (if exist) of the PDEs (8) and (9) has the property of dissipation (Fang and Gao, 2019).

Proposition 2 *For a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ described by (3), let $f \in \mathscr{C}^1$ be a solution of its Lyapunov Function PDEs (8,9), then*

$$\frac{df(x)}{dt} \triangleq \dot{f}(x) \leq 0, \quad x \in \mathbb{R}^n_{>0} \quad (11)$$

with equality to hold if and only if $\nabla f(x) \perp \mathscr{S}$. Further, assume that $f \in \mathscr{C}^2$ is a solution of the PDEs. If $\exists\ D \subset \mathbb{R}^n_{>0}$ such that $\forall x \in D$ and $\forall \mu \in \mathscr{S}$ there is

$$\mu^\top \nabla^2 f(x) \mu \geq 0 \ \text{ with equality to hold } iff \ \mu = \mathbb{0}_n,$$

then for all $x \in D$, $\dot{f}(x) = 0$ if and only if x is an equilibrium of the MAS.

Fang and Gao (2019) proved that the Lyapunov Function method is valid for complex balanced MASs, all $1d$ MASs and some special MASs with dimension beyond 1. Here, we will use it to analyze the ω-limit points of some MASs.

3 Main results

In this section, we present our main results on the relation between ω-*limit* set and boundaries of MASs. The Lyapunov Function PDEs (8) and (9) might serve for analyzing any boundary point to be an ω-*limit* point or not. From the solution of dynamical equation (3), $\mathbb{R}^n_{>0}$ is the positive invariant (Siegel and Maclean, 2000), wich means it impossible for arbitrary trajectory with positive initial point to enter into a boundary of $\mathbb{R}^n$ in a finite amount of time. So we consider the situation when the starting point is on the boundary. Note that we move all proofs to lemmas to the Supplement Materials due to room limitation.

Lemma 3.1 *For a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ given by (3), the trajectory starting from a boundary point will stay in the positive stoichiometric compatibility class for infinite time or zero time.*

In the following, we use the Lyapunov Function PDEs method to derive the relationship between the ω-limit points and boundary points.

Theorem 3.2 *Consider a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ described by (3). Assume that $f \in \mathscr{C}^1$ is a nonnegative solution of its Lyapunov Function PDE (8), and $\bar{x} \in \mathbb{R}^n_{\geq 0}$ represents*

any boundary point. $\bar{x}$ is not a ω-limit point if the solution $f(x)$ satisfies

$$\overline{\lim_{x\to\bar{x}}}\,\dot{f}(x) = -\infty \text{ or } \overline{\lim_{x\to\bar{x}}}\,\dot{f}(x) \leq -M, \tag{12}$$

where $x \in \mathbb{R}^n_{>0} \cap \mathscr{S}(\bar{x})$ and M is a positive constant.

Proof. See Appendix A. □

In the case of the non-semilocking boundary points, we have

Lemma 3.3 *Consider a MAS $(\mathcal{S},\mathcal{C},\mathcal{R},k)$ with $f \in \mathscr{C}^1$ as a solution of its Lyapunov Function PDEs (8) and (9). Let $\bar{x} \in \mathbb{R}^n_{\geq 0}$ represent any boundary point of this MAS. If the set $W \triangleq \mathrm{su}^c\bar{x}$ is not a semilocking set, then $\lim_{x\to\bar{x}} \dot{f}(x) = -\infty$ where $x \in \mathbb{R}^n_{>0}$ is bounded and satisfies $x - \bar{x} \in \mathscr{S}$.*

Theorem 3.4 *Given a MAS $(\mathcal{S},\mathcal{C},\mathcal{R},k)$ in (3), $f \in \mathscr{C}^1$ is a solution of its Lyapunov Function PDEs. For each boundary point $\bar{x}$ in non-semilocking set L_W, $\bar{x}$ can not be the ω-limit point for arbitrary trajectory of this system.*

Proof. The result directly derives from Theorem 3.2.□

Example 2 *A MAS takes the reaction route as*

$$2S_1 \xrightarrow{k_1} S_1 + S_2, 2S_2 \xrightarrow{k_2} S_2 + S_3, 2S_3 \xrightarrow{k_3} S_3 + S_1.$$

where the reaction rate constants are $k_1 = k_2 = k_3 = 1$. It is not difficult to check that for this MAS any nonzero boundary point is a non-semilocking boundary point. The origin is excluded since it is not likely to be an ω-limit point due to mass conservation of this network. (Fang and Gao, 2019) has proved that the following function given by

$$f(x) = 2x^\top \mathrm{Ln}\left(\frac{x}{x^*}\right) - 2\mathbb{1}_3^\top(x - x^*), \quad x \in \mathbb{R}^n_{>0},$$

is a nonnegative solution of the Lyapunov Function PDEs of the MAS, where $x^* = (1,1,1)^\top$ is an interior equilibrium. Attached to the current MAS, we can compute the limit of its time derivative

$$\begin{aligned}\lim_{x\to\bar{x}} \dot{f}(x) = \lim_{x\to\bar{x}} 2[&\left(-x_1^2 + x_3^2\right)\ln x_1 + \left(x_1^2 - x_2^2\right)\ln x_2 \\ &+ \left(x_2^2 - x_3^2\right)\ln x_3]\end{aligned}$$

Clearly, for any nonzero boundary point $\bar{x}$, if $\bar{x} - x^* \in \mathscr{S}$, we have $\lim_{x\to\bar{x}} \dot{f}(x) = -\infty$. This means that each boundary point can not be the ω-limit point of an arbitrary trajectory of this MAS.

Above results illustrate that non-semilocking boundary points cannot be ω-limit points from the perspective of Lyapunov Function PDEs. The following part is dedicated to the study of semilocking boundary points.

Lemma 3.5 *Given a MAS $(\mathcal{S},\mathcal{C},\mathcal{R},k)$ with the dynamics of (3), let its Lyapunov Function PDEs (8) and (9) admit a solution $f \in \mathscr{C}^1$. Then for any semilocking boundary point $\bar{x} \in \mathbb{R}^n_{\geq 0}$ we have*

$$\begin{aligned}\overline{\lim_{x\to\bar{x}}}\,\dot{f}(x) &= \overline{\lim_{x\to\bar{x}}} \sum_{i=1}^{r} k_i x^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x) \\ &\leq \underbrace{\overline{\lim_{x\to\bar{x}}} \sum_{\substack{\mathrm{su}\ \nu_{\cdot i} \subseteq \mathrm{su}\ \bar{x} \\ \mathrm{su}\ \nu'_{\cdot i} \subseteq \mathrm{su}\ \bar{x}}} k_i x^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)}_{F_1(x)} \\ &+ \underbrace{\overline{\lim_{x\to\bar{x}}} \sum_{\substack{\mathrm{su}\ \nu_{\cdot i} \subseteq \mathrm{su}\ \bar{x} \\ \mathrm{su}\ \nu'_{\cdot i} \nsubseteq \mathrm{su}\ \bar{x}}} k_i x^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)}_{F_2(x)} \\ &+ \underbrace{\overline{\lim_{x\to\bar{x}}} \sum_{\substack{\mathrm{su}\ \nu_{\cdot i} \nsubseteq \mathrm{su}\ \bar{x} \\ \mathrm{su}\ \nu'_{\cdot i} \subseteq \mathrm{su}\ \bar{x}}} k_i x^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)}_{F_3(x)} \\ &+ \underbrace{\overline{\lim_{x\to\bar{x}}} \sum_{\substack{\mathrm{su}\ \nu_{\cdot i} \nsubseteq \mathrm{su}\ \bar{x} \\ \mathrm{su}\ \nu'_{\cdot i} \nsubseteq \mathrm{su}\ \bar{x}}} k_i x^{\nu_{\cdot i}} (\nu'_{\cdot i} - \nu_{\cdot i})^\top \nabla f(x)}_{F_4(x)} \\ &= F_1(x) + F_3(x) + F_4(x).\end{aligned}$$

The above result may simplify the computation of $\lim_{x\to\bar{x}} \dot{f}(x)$ when $\bar{x}$ is a semilocking boundary point. We then use it to analyze the non-equilibriums in the semilocking set and further derive the ω-limit set theorem of some kinds of chemical reaction systems.

Theorem 3.6 *For a MAS $(\mathcal{S},\mathcal{C},\mathcal{R},k)$ governed by (3), assume its Lyapunov Function PDEs (8), (9) admit a nonnegative solution $f \in \mathscr{C}^2$. Then for any semilocking boundary non-equilibrium point $\bar{x} \in \mathbb{R}^n_{\geq 0}$ of this network, $\bar{x}$ is not an ω-limit point if the Hessian matrix of $f(x)$ is a positive definite diagonal matrix.*

Proof. See Appendix B. □

Theorem 3.7 (ω-limit Theorem) Consider a MAS $(\mathcal{S},\mathcal{C},\mathcal{R},\mathcal{K})$ given in (3). If the solution f of its Lyapunov Function PDEs is a positive definite diagonal matrix, then the ω-limit set of each bounded solution of this system is a set of positive equilibria or a set of boundary equilibria.

Proof. $f(x(t))$ along the trajectory $x(t)$ begins with x_0 is monotone decreasing, but it is also bounded below,

thus $\lim_{t\to+\infty} f(x) = F_0$. $\omega(x_0) \in \{x|f(x) = F_0\}$ is contained in a bounded, closed set(compact). Thus $\omega(x_0)$ is invariant and connected. Because $\dot{f}(x) = 0$ iff x is an equilibrium, the ω-limit set only contains equilibria. From the connected property, the ω-limit set can not contain both positive equilibrium and boundary equilbiria. Thus ω-limit set is a set of positive equilibria or a set of boundary equilibria. □

Note that the direct application of Theorem 3.7 is to complex balanced MASs which can derive the result in (Siegel and Maclean, 2000).

Corollary 1 *Assume a MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ described by (3) is complex balanced. Then the ω-limit set of each trajectory is a single positive equilibrium or a set of boundary equilibria.*

Proof. It has been proved (Fang and Gao, 2019) that the well-known pseudo-Helmholtz free energy function (Horn and Jackson, 1972), given by

$$f(x) = \sum_{j=1}^{n} x_j \left(\ln x_j - \ln x_j^* - 1\right) + x_j^*, \quad x \in \mathbb{R}^n_{>0}$$

is a nonnegative solution of the corresponding Lyapunov function PDEs, where $x^* \in \mathbb{R}^n_{>0}$ is an equilibrium in the complex balanced system. Note that the eqilibrium x^* should be chosen such that $x^* - \bar{x} \in \mathscr{S}$, which must be existing since each positive stoichiometric compatibility class must contain and only contains an equilibrium (Horn and Jackson, 1972). Clearly, $f \in \mathscr{C}^2$ and its Hessian matrix, written as $\nabla^2 f(x) = \mathrm{diag}\{1/x_1, \cdots, 1/x_n\}$, is a positive definite diagonal matrix. The result is straightforward based on Theorem 3.7. □

But it can also be used in non-complex balanced network as the following example.

Example 3 *A MAS follows*

$$S_1 \xrightarrow{k_1} S_2,\ 2S_2 \xrightarrow{k_2} S_2 + S_1,\ 2S_1 + S_3 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} 2S_3\,.$$

By setting $k_1 = k_2 = k_3 = k_4 = 1$, we can verify that the function

$$f(x) = x_1 \ln x_1 - x_1 + 2(x_2 \ln x_2 - x_2) + x_3 \ln x_3 - x_3 + 4$$

is a nonnegative solution of its corresponding PDE. Its time derivative is

$$\begin{aligned}\dot{f}(x) = (-x_1 + x_2^2 - 2x_1^2 x_3 + 2x_3^2) \ln x_1 \\ +2(x_1 - x_2^2) \ln x_2 + (x_1^2 x_3 - x_3^2) \ln x_3,\end{aligned}$$

and Hessian matrix is $\nabla^2 f(x) = \mathrm{diag}(1/x_1, 2/x_2, 1/x_3)$ which is obviously a positive diagonal matrix in $\mathbb{R}^3_{>0}$.

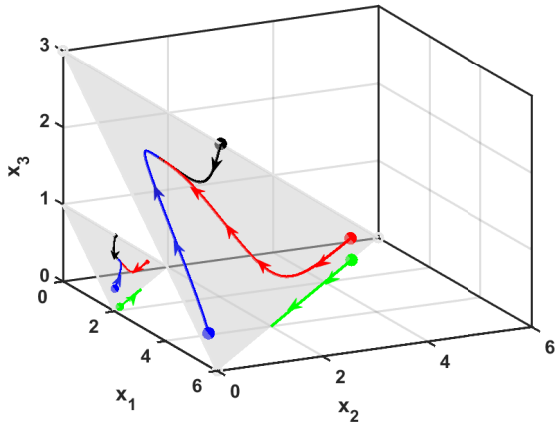

Fig. 1. Chemical stoichiometric compatibility classes and trajectories of the system in Example 3.

Hence, from Theorem 3.6 all semilocking boundary nonequilibrium points in this MAS are not ω-limit points.

We exhibit more details here. For simplicity, consider a representative semilocking boundary point $\bar{x} = (\bar{x}_1, \bar{x}_2, 0)^\top$, where $\bar{x}_1, \bar{x}_2 > 0$ and $W \triangleq \mathrm{su}^c\bar{x} = \{S_3\}$, then we have

$$\begin{aligned}&\lim_{x\to\bar{x}} \dot{f}(x) = \lim_{x\to\bar{x}} (-x_1 + x_2^2 - 2x_1^2 x_3 + 2x_3^2) \ln x_1 \\ &+ \lim_{x\to\bar{x}} 2(x_1 - x_2^2) \ln x_2 + (x_1^2 x_3 - x_3^2) \ln x_3 \\ &= -(\bar{x}_1 - \bar{x}_2^2)(\ln \bar{x}_1 - 2 \ln \bar{x}_2).\end{aligned}$$

Therefore, if $\bar{x}_1 \neq \bar{x}_2^2$, which suggests $\bar{x}$ is not a boundary equilibrium from the dynamical equation, then $\lim_{x\to\bar{x}} \dot{f}(x) < 0$. $\bar{x}$ is not an ω-limit point. Because this network is a conserved network with a conservation law $(1, 1, 2)$, each trajectory of this network is bounded. So Theorem 3.7 tells us the ω-limit set of each trajectory is a positive equilibriums set or a boundary equilibriums set.

Figure 1 shows two stoichiometric compatibility classes with eight different trajectories. The small and large triangles are non-negative stoichiometric compatibility classes

$$\begin{aligned}&SCC1 : \{(x_1, x_2, x_3) | x_1 + x_2 + 2x_3 = 2, x_i \geq 0\}; \\ &SCC2 : \{(x_1, x_2, x_3) | x_1 + x_2 + 2x_3 = 6, x_i \geq 0\};\end{aligned}$$

respectively. In Fig. 1, the black and green trajectories start from different boundaries, while the red and blue ones begin with positive initial points. All the trajectories with positive initial points converge to positive equilibriums. These dynamical behaviors shown in the figure is consistent with the result in Theorem 3.7. Thus from the Theorem 3.7, there does not exist limit cycle in this system.

4 Applications

In this section, we apply our results to some real biochemical networks which are obviously not complex balanced even not weakly reversible.

Example 4 (PAK-1 network) *p21-activited kinase 1(PAK-1) is involved in a variety of biological processes such as tumor cell proliferation, apoptosis and invasion(Hong et al., 2021). The following network can be seen as a simplified model of PAK-1:*

$$2E \xrightarrow{k_1} E + P_1, E \xleftarrow{k_2} P_1 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} P_2 . \tag{13}$$

Let x_1, x_2, x_3 denote the concentration of species E, P_1, P_2, the following function

$$f(x) = \sum_{2,3}(x_i \ln x_i - x_i - x_i^* \ln x_i^* + x_i^*) + 2(x_1 \ln x_1 - x_1 - x_1^* \ln x_1^* + x_1^*)$$

with $x^* = (x_1^*, x_2^*, x_3^*) = \left(\sqrt{\frac{k_2 k_4}{k_1}}, k_4, k_3\right)$ is the solution of its corresponding PDE. The Hessian matrix of this function

$$\nabla^2 f(x) = \operatorname{diag}\left(\frac{2}{x_1}, \frac{1}{x_2}, \frac{1}{x_3}\right) \tag{14}$$

is a positive diagonal matrix. The ω-limit points of all trajectories can only be equilibria.

Above biological system is actually a CBP network(complex balanced produced network) proposed by us in (Wu et al., 2020; Lu et al., 2022). Each CBP network can be generated by a corresponding complex balanced network and diagonal matrix $Q = \operatorname{diag}(q_1, \cdots, q_n)$. CBP networks are generally not weakly reversible structure. Actually, not only the PAK1 network satisfies the theorem 3.7 conditions, but all CBP networks satisfy. See Remark 4 below for details.

Remark 4 *PAK-1 network (13) can be produced by the following network*

$$2E \underset{k_2}{\overset{\frac{1}{4}k_1}{\rightleftharpoons}} P_1 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} P_2 , \tag{15}$$

And the corresponding matrix $Q = \operatorname{diag}(2, 1, 1)$. The solution of Lyapunov Function PDE of CBP networks is generalized pseudo-Helmholtz free energy(Wu et al., 2020) in the following form:

$$f(x) = \sum_{j=1}^{n} q_j x_j \left(\ln x_j - \ln x_j^* - 1\right) + x_j^*, \quad x \in \mathbb{R}^n_{>0}.$$

Clearly, $f \in \mathscr{C}^2$ and its Hessian matrix, written as $\nabla^2 f(x) = \operatorname{diag}(q_1/x_1, \cdots, q_n/x_n)$ is a positive definite diagonal matrix. Then we can derive that all boundary nonequilibria are not ω-limit points straightforward based on Theorem 3.6.

It should be noted that the Lyapunov functions for PAK-1 network, and also for networks in **Examples 2** and **3** are all the logarithmic Lyapunov function. They have similar form to the Lyapunov function used for Lotka Volterra systems. The result is actually not surprising due to the closeness of the two classes of systems. Essentially, they are closely related to polynomial systems. Besides PAK-1 network, many practical networks also satisfy the conditions in Theorem 3.7, thus being precluded to have the limit cycle.

Example 5 *Now we consider the following simple autocatalytic network*

$$2S_1 + S_2 \xrightarrow{k_{2,3}} 3S_1 , \ S_1 + 2S_2 \xrightarrow{k_{1,3}} 3S_2 ,$$
$$S_1 \underset{k_{2,1}}{\overset{k_{1,1}}{\rightleftharpoons}} S_2 , \ 2S_1 \xleftarrow{k_{2,2}} S_1 + S_2 \xrightarrow{k_{1,2}} 2S_2 .$$

Such networks are often used to simulate the foraging process of ants (Khaluf et al., 2017). Choosing reaction rate constants as $k_{1,3} = k_{2,3} = k_{1,2} = 1, k_{2,2} = 3, k_{2,1} = 2, k_{1,1} = 4$, it is easy to verify that the following function is the solution of its Lyapunov function PDE

$$f(x) = \int_1^{x_1} \ln \frac{6s}{s^2 + 3s + 2} ds + \int_1^{x_2} \ln \frac{6s}{s^2 + s + 4} ds.$$

The Hessian matrix of above f is also positive diagonal in chemical stoichiometric compatibility class $\{x_1 + x_2 = 2\}$, thus the ω-limit points in this stoichiometric compatibility class can only be the positive equilibria $(1, 1)^\top$ or the set of boundary equilibria from the Theorem 3.7.

5 Conclusion

This article has made a systematic study on the relation between ω-limit points and boundary points of MASs through the Lyapunov Function PDEs method. Based on the solution of the PDEs, we develop some criteria (sufficient conditions) to say the boundary point of the MAS to be not ω-limit point. Furthermore, we prove the sufficient conditions are valid in ruling out two types of boundary points, i.e., any non-semilocking boundary point and some semilocking boundary non-equilibrium points, to become ω-limit points. As a complementary result, we also present the ω-limit theorem that characterizes the ω-limit set of some MASs, especially of the well-known complex balanced MASs, only likely to be a set of positive equilibria or a set of boundary equilibria. All of the results indicate that the Lyapunov Function PDEs method is a powerful and practical tool to diagnose the relation between ω-limit points and boundaries

of MAS. Note that ω-limit points are often used to characterize persistence, so the PDEs method is exhibiting large potential in capturing the dynamical behaviors of MASs, not only stability (Fang and Gao, 2019; Wu et al., 2020; Lu et al., 2022) but also persistence.

Acknowledgements

This work was funded by the National Nature Science Foundation of China under Grant No. 12071428 and 62111530247, and the Zhejiang Provincial Natural Science Foundation of China under Grant No. LZ20A010002.

Appendix: Detailed proofs of some results

A. Proof of Theorem 3.2

Proof. For any initial point $x(0) \in \mathbb{R}^n_{>0} \cap \mathscr{S}(\bar{x})$, we have $f(x(0)) \geq 0$ and

$$f(x(t)) = f(x(0)) + \int_0^t \dot{f}(x(s))ds. \tag{16}$$

In the following, we use rebuttals of evidence to continue the proof. Assume that $\bar{x}$ is a ω-*limit* point under the given initial conditions. Under this assumption and the conditions of $f \in \mathscr{C}^1$ and $\overline{\lim_{x\to\bar{x}}} \dot{f}(x) = -\infty$ (or $-M$), we can find a positive constant M_0 and a ϵ-neighbourhood of $\bar{x}$ ($\epsilon > 0$), denoted by $N_\epsilon(\bar{x})$, for any trajectory $x(t)$ starting from $x(0)$ such that $\dot{f}(x) < -M_0, \forall x \in N_\epsilon(\bar{x})$, and its residence time in $N_\epsilon(\bar{x})$ is infinite, i.e.,

$$T_\epsilon = \lim_{t\to+\infty} \int_0^t \mathbb{1}_{\{x(s)\in N_\epsilon(\bar{x})\}} ds = +\infty. \tag{17}$$

If we cannot find such a $N_\epsilon(\bar{x})$ supporting (17), consider another ϵ'-neighbourhood of $\bar{x}$ ($\epsilon' > \epsilon$), denoted by $N_{\epsilon'}(\bar{x})$, in which $\lim_{x\to\bar{x}} \dot{f}(x) < -M_0'$ ($M_0' > 0$), and denote the residence time for the trajectory $x(t)$ to stay in $N_{\epsilon'}(\bar{x})$ by

$$T_{\epsilon'} = \lim_{t\to+\infty} \int_0^t \mathbb{1}_{\{x(s)\in N_{\epsilon'}(\bar{x})\}} ds.$$

If $T_{\epsilon'} = +\infty$, then replace ϵ in (17) by ϵ'. If $T_{\epsilon'}$ is finite, then from the infinite time that the trajectory $x(t)$ stays in the positive stoichiometric compatibility class of $x(0)$, we get that the time for $x(t)$ to stay out of $N_{\epsilon'}(\bar{x})$ is infinite. Define an area Ω by

$$\Omega \triangleq \{x \in \mathbb{R}^n_{>0} | \epsilon \leq \|x - \bar{x}\| \leq \epsilon'\},$$

which is obviously a bounded region. Since $\bar{x}$ is assumed to be a ω-limit point of the trajectory $x(t)$, for any $t_1 > 0$ we can find $t_2 > t_1$ such that $x(t_2) \in N_\epsilon(\bar{x})$. This together with the trajectory staying out of $N_{\epsilon'}(\bar{x})$ for infinite time suggests that the trajectory will pass through the region Ω infinite times. Note that $g(x)$ is a continuous function about x and the trajectory $x(t)$ is bounded, so $g(x)$ is bounded and $\exists\ M_1 > 0$ such that $\|g(x)\|_\infty \leq M_1, \forall x \in \Omega$. Denote the time for the trajectory to enter into Ω at a certain time by t_a and to leave Ω by t_b, then we have

$$\epsilon' - \epsilon \leq \|x(t_b) - x(t_a)\| = \| \int_{t_a}^{t_b} g(x(s))ds\| \leq (t_b - t_a)M_1$$
$$\Rightarrow t_b - t_a \geq \frac{\epsilon' - \epsilon}{M_1},$$

where $g(x(t)) = \dot{x}(t)$. This means that it at least needs the time of $(\epsilon' - \epsilon_1)/M_1$ for the trajectory to stay in Ω. Since the trajectory passes through Ω infinite times, so its residence time in Ω will be infinite if the time trends to infinity. This is inconsistent with $T_{\epsilon'}$ being finite. Therefore, if we assume $\bar{x} \in \omega(x(0))$, there must exist a $N_\epsilon(\bar{x})$ such that $\lim_{x\to\bar{x}} \dot{f}(x) < -M_0$ and $T_\epsilon = +\infty$. By taking limit on both sides of (16), we get

$$\lim_{t\to+\infty} f(x(t)) = f(x(0)) + \lim_{t\to+\infty} \int_0^t \dot{f}(x(s))ds$$
$$\leq f(x(0)) - M_0 \lim_{t\to+\infty} \int_0^t \mathbb{1}_{\{x(s)\in N_\epsilon(\bar{x})\}} ds = -\infty,$$

where the second inequality holds since $\dot{f}(x) \leq 0$(See Proposition 2). This result is contrary to $f(x) \geq 0$. Hence, the assumption $\bar{x} \in \omega(x(0))$ is not true. □

B. Proof of Theorem 3.6.

Proof. Since $\bar{x} \in \mathbb{R}^n_{\geq 0}$ is a semilocking boundary non-equilibrium point in the MAS, from Lemma 3.5 we have

$$\overline{\lim_{x\to\bar{x}}} \dot{f}(x) \leq F_1(x) + F_3(x) + F_4(x).$$

In addition, we have

$$\lim_{x\to\bar{x}} \sum_{\text{su } \nu_{\cdot i}\subseteq \text{su } \bar{x}} k_i x^{\nu_{\cdot i}} = \lim_{x\to\bar{x}} \sum_{\substack{\text{su } \nu_{\cdot i}\subseteq \text{su } \bar{x} \\ \text{su } \nu'_{\cdot i}\subseteq \text{su } \bar{x}}} k_i x^{\nu_{\cdot i}} + \sum_{\substack{\text{su } \nu_{\cdot i}\subseteq \text{su } \bar{x} \\ \text{su } \nu'_{\cdot i}\nsubseteq \text{su } \bar{x}}} k_i x^{\nu_{\cdot i}}$$
$$= \lim_{x\to\bar{x}} \sum_{\substack{\text{su } \nu_{\cdot i}\subseteq \text{su } \bar{x} \\ \text{su } \nu'_{\cdot i}\subseteq \text{su } \bar{x}}} k_i x^{\nu_{\cdot i}}$$
$$= \lim_{x\to\bar{x}} \sum_{\substack{\text{su } \nu_{\cdot i}\subseteq \text{su } \bar{x} \\ \text{su } \nu'_{\cdot i}\subseteq \text{su } \bar{x}}} k_i x^{\nu_{\cdot i}} + \lim_{x\to\bar{x}} \sum_{\substack{\text{su } \nu_{\cdot i}\nsubseteq \text{su } \bar{x} \\ \text{su } \nu'_{\cdot i}\subseteq \text{su } \bar{x}}} k_i x^{\nu_{\cdot i}}$$
$$= \lim_{x\to\bar{x}} \sum_{\text{su } \nu'_{\cdot i}\subseteq \text{su } \bar{x}} k_i x^{\nu_{\cdot i}},$$

which together with the boundary condition (a) (9) yields

$$\begin{aligned}&\lim_{x\to\bar{x}}\sum_{\text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}} k_i x^{\nu_{\cdot i}}\\&=\lim_{x\to\bar{x}}\sum_{\text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}} k_i x^{\nu_{\cdot i}}\exp\{(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)\}\end{aligned}$$

By performing the Taylor expansion of $\exp\Lambda_i \triangleq \exp\{(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)\}$ with respect to zero, we get

$$\lim_{x\to\bar{x}}\left(\sum_{\text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}} k_i x^{\nu_{\cdot i}}\Lambda_i+\sum_{\text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}} k_i x^{\nu_{\cdot i}}\frac{e^{\alpha_i}}{2}\Lambda_i^2\right)=0$$

where $\alpha_i\in\mathbb{R}$ lies between 0 and Λ_i. Further, we obtain

$$\begin{aligned}\overline{\lim_{x\to\bar{x}}}\sum_{\text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}} k_i x^{\nu_{\cdot i}}\Lambda_i \le \underbrace{-\overline{\lim_{x\to\bar{x}}}\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\frac{e^{\alpha_i}}{2}\Lambda_i^2}_{H_1(x)}\\ \underbrace{-\overline{\lim_{x\to\bar{x}}}\sum_{\substack{\text{su }\nu_{\cdot i}\not\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\frac{e^{\alpha_i}}{2}\Lambda_i^2}_{H_2(x)},\end{aligned}$$

i.e., $F_1(x)+F_3(x)\le H_1(x)+H_2(x)$. Obviously, $H_1(x)\le 0$ and $H_2(x)\le 0$.

We are only concerned with $H_1(x)$ to follow the proof. Denote $W=\text{su}^c\,\bar{x}$, which is a semilocking set. Naturally, under the conditions of su $\nu'_{\cdot i}\subseteq$ su $\bar{x}$ and su $\nu_{\cdot i}\subseteq$ su $\bar{x}$, $\nu'_{ji}-\nu_{ji}=0, j\in W$. For simplicity but without loss of generality, we assume $W=\{m+1,\ \cdots,\ n\}$ where $m<n$. Then under the mentioned conditions, we have

$$(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)=\sum_{j=1}^{m}(\nu'_{ji}-\nu_{ji})\nabla_j f(x).$$

Since $\Delta f(x)$ is a diagonal matrix, i.e.,

$$\frac{\partial^2 f}{\partial x_{j_1}\partial x_{j_2}}=0=\frac{\partial\nabla_{j_1}f}{\partial x_{j_2}},$$

$\nabla_{j_1}f(x)$ does not contain x_{j_2} if $j_1\in W$ while $j_2\notin W$. By letting $x_\perp$ and $\bar{x}_\perp$ denote the first m components of x and $\bar{x}$, respectively, we thus get $-H_1(x)$ equal to

$$\begin{aligned}&=\overline{\lim_{x_\perp\to\bar{x}_\perp}}\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x_\perp^{\nu_{\cdot i}}\frac{e^{\alpha_i}}{2}\left(\sum_{j=1}^{m}(\nu'_{ji}-\nu_{ji})\nabla_j f(x_\perp)\right)^2\\&=\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i \bar{x}_\perp^{\nu_{\cdot i}}\frac{e^{\alpha_i}}{2}\left(\sum_{j=1}^{m}(\nu'_{ji}-\nu_{ji})\nabla_j f(\bar{x}_\perp)\right)^2.\end{aligned}$$

If $H_1(x)=0$, which implies $\nabla f(\bar{x}_\perp)\perp(\nu'_{\cdot i}-\nu_{\cdot i})$ for all su $\nu_{\cdot i}\subseteq$ su $\bar{x}$ and su $\nu'_{\cdot i}\subseteq$ su $\bar{x}$, we obtain

$$\begin{aligned}&\lim_{x\to\bar{x}}\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\\&=\lim_{x\to\bar{x}}\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\exp[(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)]\end{aligned}\tag{18}$$

Combining the boundary condition (a) (9), we further have

$$\lim_{x\to\bar{x}}\sum_{\substack{\text{su }\nu_{\cdot i}\not\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\exp[(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)]=0.\tag{19}$$

This result also applies to other semilocking boundary non-equilibrium points, denoted by $\bar{x}^*$, satisfying su $\bar{x}=$ su $\bar{x}^*$. The main reason is that the change of $\exp\{(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)\}$ from $x\to\bar{x}$ to $x\to\bar{x}^*$ in (19) will not change the limit value, which can be easily verified when we make the following decomposition

$$\begin{aligned}&(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)\\&=\sum_{j=1}^{m}(\nu'_{ji}-\nu_{ji})\nabla_j f(x_j)+\sum_{j=m+1}^{n}(\nu'_{ji}-\nu_{ji})\nabla_j f(x_j)\end{aligned}$$

Clearly, the second term in the right hand of the above equation will keep unchanged from $x\to\bar{x}$ to $x\to\bar{x}^*$ since the last $n-m$ entries of $\bar{x}$ and $\bar{x}^*$ are the same. Although the first term will change, both $\bar{x_j}^*$ and $\bar{x_j}$ are specific positive bounded values for $j=1,\cdots,m$, which will lead to $f(\bar{x_j})$ and $f(\bar{x_j}^*)$ bounded. Therefore, the first term will keep bounded for any boundary points satisfying su $\bar{x}=$ su $\bar{x}^*$. Namely, (19) holds for any $\bar{x}^*$ with $\text{su}^c\,\bar{x}^*=W$. We thus can generalize (18) into

$$\begin{aligned}&\lim_{\substack{x_j>0,j=1,\cdots,m\\ x_j\to 0,j=m+1,\cdots,n}}\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\\&=\lim_{\substack{x_j>0,j=1,\cdots,m\\ x_j\to 0,j=m+1,\cdots,n}}\sum_{\substack{\text{su }\nu_{\cdot i}\subseteq\text{su }\bar{x}\\ \text{su }\nu'_{\cdot i}\subseteq\text{su }\bar{x}}} k_i x^{\nu_{\cdot i}}\exp[(\nu'_{\cdot i}-\nu_{\cdot i})^\top\nabla f(x)],\end{aligned}$$

which is actually equivalent to

$$\sum_{\substack{\text{su } \nu_{\cdot i}\subseteq \text{su } \bar{x} \\ \text{su } \nu'_{\cdot i}\subseteq \text{su } \bar{x}}} k_i x_\perp^{\tilde{\nu}_{\cdot i}} - k_i x_\perp^{\tilde{\nu}_{\cdot i}} \exp[(\tilde{\nu}'_{\cdot i} - \tilde{\nu}_{\cdot i})^\top \nabla \tilde{f}(x)] = 0.$$

Here, $\tilde{\nu}_{\cdot i}$, $\tilde{\nu}'_{\cdot i}$ and $\nabla\tilde{f}(x)$ are the first m entries of $\nu_{\cdot i}$, $\nu'_{\cdot i}$ and $\nabla f(x)$, respectively. Now we define another MAS $(\tilde{\mathcal{S}}, \tilde{\mathcal{C}}, \tilde{\mathcal{R}}, \tilde{k})$ with $\tilde{\mathcal{S}} = \{S_1, \cdots, S_m\}$, $\tilde{\mathcal{R}} = \{\nu_{\cdot i} \to \nu'_{\cdot i} |\ \text{su } \nu_{\cdot i}, \text{su } \nu'_{\cdot i} \subseteq \{1, \cdots, m\}\}$, $\tilde{\mathcal{C}} = \{\text{complexes in } \tilde{\mathcal{R}}\}$ and $\tilde{k}$ as the projection of $k \in \mathbb{R}^{\mathcal{R}}$ into $\mathbb{R}^{\tilde{\mathcal{R}}}$. Then, according to the new MAS, (5) may be rewritten as

$$\sum_{\tilde{\mathcal{R}}} \tilde{k}_i x_\perp^{\tilde{\nu}_{\cdot i}} = \sum_{\tilde{\mathcal{R}}} \tilde{k}_i x_\perp^{\tilde{\nu}_{\cdot i}} \exp\{(\tilde{\nu}'_{\cdot i} - \tilde{\nu}_{\cdot i})^\top \nabla \tilde{f}(x)\}.$$

Note that $\triangle f(x)$ is a diagonal matrix, so $\nabla\tilde{f}(x)$ is independent of x_j when $j = m+1, \cdots, n$. Denote the function whose gradient with respect to $x_\perp$ is $\nabla\tilde{f}(x)$ by $\tilde{f}(x)$, then $\tilde{f}(x)$ is only related to $x_\perp$. Therefore, $\tilde{f}(x)$ is a solution of (5), i.e., the Lyapunov Function PDE of the MAS $(\tilde{\mathcal{S}}, \tilde{\mathcal{C}}, \tilde{\mathcal{R}}, \tilde{k})$. Also, note that $\triangle\tilde{f}(x)$ is positive definite, which together with the assumption of $H_1(x) = 0$ suggests that $\bar{x}_\perp$ is a positive equilibrium point in $(\tilde{\mathcal{S}}, \tilde{\mathcal{C}}, \tilde{\mathcal{R}}, \tilde{k})$ (based on Proposition 2). Therefore, $\bar{x}$ is a boundary equilibrium point in the MAS $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$, which is contradict to the condition that $\bar{x}$ is a boundary non-equilibrium point. We thus have $H_1(x) < 0$, i.e., $\exists\, M > 0$ such that $F_1(x) + F_3(x) < -M$. From the proof of Lemma 3.3, we have $F_4(x) \le 0$, so $\overline{\lim_{x\to\bar{x}}} \dot{f}(x) \le -M$. Further from Lemma 3.2, we get that $\bar{x}$ is not an *ω-limit* point. □

References

Anderson, D. F., Craciun, G., Gopalkrishnan, M., & Wuif, C. (2015). Lyapunov functions, Stationary distributions, and non-equilibrium potential for reaction networks. *Bulletin of Mathematical Biology*, 77(9), 1744-1767.

Anderson, D. F. (2008). Global Asymptotic Stability for A Class of Nonlinear Chemical Equations. *SIAM Journal on Applied Mathematics*, 68(5), 1464–1476.

Angeli, D., Leenheer, P. D., & Sontag, E. D. (2007). A petri net approach to the study of persistence in chemical reaction networks. *Mathematical Biosciences*, 210(2), 98–618.

Blanchini, F., Giordano, G. (2014). Piecewise-linear Lyapunov functions for structural stability of biochemical networks. *Automatica*, 50(10), 2482-2493.

Fang, Z., & Gao, C. H. (2019). Lyapunov function partial differential equations for chemical reaction networks: some speccial cases. *SIAM Journal on Applied Dynamical Systems*, 18(2), 1163–1199.

Feinberg, M. (1979). Lectures on chemical reaction networks. University of Wisconsin-Madison;available online at http://www.che.eng.ohio-state.edu/feinberg/LecturesOnReactionNetworks.

Hong, H., Kim, J., Al-Radhawi, M. A., Sontag, E. D., & Kim, J. (2021). Derivation of stationary distributions of biochemical reaction networks via structure transformation. *Communications Biology*, 4(620).

Horn, F., & Jackson, R. (1972). General mass action kinetics. *Archive for Rational Mechanics and Analysis*, 47(2), 81–116.

Khaluf, Y., Pinciroli, C., Valentini, G., & Hamann, H. (2017). The impact of agent density on scalability in collective systems: noise-induced versus majority-based bistability. *Swarm Intelligence*, 11(2), 155–179.

Lu, Y. F., Gao, C. H., & Dochain, D. (2022). Lyapunov function PDEs to the stability of some complex balancing derivative and compound networks. *IEEE Transactions on Automatic Control*, DOI: 10.1109/TAC.2021.3115889.

Samardzija, N., Greller, L., & Wasserman, E. (1989). Nonlinear chemical kinetic schemes derived from mechanical and electrical dynamical systems. *The Journal of Chemical Physics*, 90(4), 2296– 2304.

Siegel, D., & MacLean, D. (2000). Global stability of complex balanced mechanisms. *Journal of Mathematical Chemistry*, 27(3), 89–110.

Vasil'ev, V. M., Vol'pert, A. I., & Khudyaev, S. I. (1974). A method of quasi-stationary concentrations for the equations of chemical kinetics. *Computational Mathematics and Mathematical Physics*, 13(3), 187–206.

Wu, S., Lu, Y. F., & Gao, C. H. (2020). Lyapunov function pdes for stability analysis of a class of chemical reaction networks. *IFAC-PapersOnLine*, 53(2), 11509-11514.

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