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Global stability of complex balanced mechanisms

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We prove that the ω-limit set of any solution of a complex balanced chemical reaction mechanism contains either a unique, positive complex balanced equilibrium point, or boundary complex balanced equilibrium points. Then, using this result, we are able to provide global stability results for three enzymatic mechanisms.

1. Introduction

The qualitative behavior of the solutions of chemical kinetic systems is studied extensively in [7,10,11,15,17]. In particular, it is proved by Vol'pert in [15,17] that the ω-limit set of any solution of a detailed balanced chemical reaction mechanism consists of a single positive point of detailed balanced equilibrium, or of boundary detailed balanced equilibrium points (theorem 3 in [15], and the theorem in section 3.4 in [17]). In this paper, we will present the equivalent result for complex balanced chemical reaction mechanisms. Complex balanced mechanisms were first studied by Horn, Jackson and Feinberg [7,10,11]. Furthermore, we will show that Vol'pert's theorem for detailed balanced mechanisms can be completely recovered by our result, after we prove a key relationship between detailed balanced mechanisms and complex balanced mechanisms.

In section 4, we will use our ω-limit set theorem to prove the global asymptotic stability of a subclass of complex balanced mechanisms. This is the group of complex balanced mechanisms that do not admit boundary equilibrium points. Moreover, we will show that three different enzymatic mechanisms, two of which involve inhibitors, are from this particular subclass, and hence, are globally asymptotically stable.

2. Background

The following is a short introduction to the terminology and notation of chemical kinetics. For the most part, the notation to be used has been adopted from [1,2].

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However, to concisely prove some results in this paper, we will also use the notation from [11]. Hence, in some instances below the same term will be defined with two different notations. See [6,8,11] for a complete introduction to chemical kinetics.

2.1. Chemical reaction mechanisms

In general, a chemical reaction mechanism can be represented by

$$\sum_{i=1}^{m} z_{p^-(j)i} A_i \xrightarrow{k_j} \sum_{i=1}^{m} z_{p^+(j)i} A_i \quad \text{for all } j = 1, \ldots, r, \tag{1}$$

where A_i, $i = 1, \ldots, m$, are the species involved in the r reactions of the mechanism. The linear combinations of species to the left and right of the reaction arrow are referred to as *complexes*, and $z_{p^-(j)i}$ (respectively, $z_{p^+(j)i}$) is the stoichiometric coefficient of species A_i in the reactant complex (respectively, product complex) of the jth reaction of the mechanism. Finally, k_j is rate constant of the jth reaction [1,2].

If we assume a mechanism consists of n distinct complexes, (1) can also be represented by

$$C_i \xrightarrow{k(i,j)} C_j \quad \text{for all } i, j = 1, \ldots, n, \tag{2}$$

where $C_l = \sum_{k=1}^{m} z_{lk} A_k$ is a complex, and $k(i, j)$ is the rate constant for the reaction with reactant complex C_i and product complex C_j [11]. Note that $k(i, j) = 0$ if either $i = j$, or the mechanism does not contain a reaction with C_i as the reactant and C_j as the product. Otherwise, $k(i, j) > 0$.

A chemical reaction mechanism can also be expressed as a graph theoretical digraph. See [3,9] for the definition of a digraph, and the following two definitions are from [7,10,11]:

Definition 2.1. The HJF-graph of a chemical reaction mechanism is a digraph, where the vertices represent the distinct complexes of the mechanism and the arcs indicate the reactions between the complexes.

Definition 2.2. The linkage classes of a chemical reaction mechanism are the connected components of the HJF-graph. The number of linkage classes in a mechanism will be denoted by ℓ.

If we assume the chemical reaction mechanism (1) is endowed with mass action kinetics, the evolution of its species concentrations $x_i(t)$, $i = 1, \ldots, m$, can be modeled by the system of differential equations

$$\dot{\mathbf{x}} = F(\mathbf{x}) = \sum_{j=1}^{r} \mathcal{R}_j v_j(\mathbf{x}), \tag{3}$$

where

$$\mathcal{R}_j = \mathbf{z}_{p^+(j)} - \mathbf{z}_{p^-(j)} \tag{4}$$

is the *reaction vector*, and

$$v_j(\mathbf{x}) = k_j \prod_{i=1}^{m} x_i^{z_{p^-(j)i}} \tag{5}$$

is the *rate function* of the jth reaction of the mechanism.

2.2. Equilibria

Two special types of equilibria of (3) will be considered [7,10,11]:

Definition 2.3. A concentration $\mathbf{x}^*$ will be called a complex balanced equilibrium point of (3) if and only if for every complex p of the mechanism, the sum of the rates of the reactions with p as a reactant equals the sum of the rates of the reactions with p as a product. That is,

$$\sum_{p^+(j)=p} v_j(\mathbf{x}^*) = \sum_{p^-(j)=p} v_j(\mathbf{x}^*),$$

where $v_j(\mathbf{x})$ is defined in (5). Alternatively,

$$\sum_{j=1}^{n} k(j,i)\big(\mathbf{x}^*\big)^{(j)} = \big(\mathbf{x}^*\big)^{(i)} \sum_{j=1}^{n} k(i,j) \quad \text{for all } i,\ldots,n,$$

where $(\mathbf{x}^*)^{(k)} = \prod_{i=1}^{m} (x_i^*)^{z_{ki}}$.

Definition 2.4. A concentration $\mathbf{x}^*$ will be called a detailed balanced equilibrium point of (3) if and only if the rate of the reaction $p \to p'$ equals the rate of the reaction $p' \to p$. That is, $v_{p\to p'}(\mathbf{x}^*) = v_{p'\to p}(\mathbf{x}^*)$, or alternatively,

$$k(i,j)\big(\mathbf{x}^*\big)^{(i)} = k(j,i)\big(\mathbf{x}^*\big)^{(j)} \quad \text{for all } i,j = 1,\ldots,n.$$

Remark 2.5. We will say that a chemical reaction mechanism is *complex balanced* (respectively, *detailed balanced*) if it admits a positive complex balanced equilibrium point (respectively, positive detailed balanced equilibrium point) for at least one set of positive rate constants.

Before theorems on the structural nature of complex balanced and detailed balanced mechanisms can be given, the following graph theoretical terminology and theorem are required [3]:

Definition 2.6. If $a = (u,v)$ is an arc of a digraph D, we say u is adjacent to v and v is adjacent from u.

Definition 2.7. The outdegree od(v) of a vertex v of a digraph D is the number of vertices of D that are adjacent from v.

Definition 2.8. Let u and v be (not necessarily distinct) vertices of a digraph D. A u–v walk of D is a finite, alternating sequence

$$u = u_0, a_1, u_1, a_2, \ldots, u_{n-1}, a_n, u_n = v$$

of vertices and arcs, beginning with u and ending with v, such that $a_i = (u_{i-1}, u_i)$ for $i = 1, \ldots, n$.

Definition 2.9. A vertex v is said to be reachable from a vertex u in a digraph D if D contains a u–v walk.

Definition 2.10. A digraph D is strongly connected if for every two distinct vertices of D, each vertex is reachable from the other.

Definition 2.11. If D_i is a subdigraph of D and D_i is strongly connected, then D_i is called a strong component of D.

Definition 2.12. Let $D_1, D_2, \ldots, D_n$ be the strong components of D. Then, the condensation D^* of D is that digraph whose vertices $u_1, u_2, \ldots, u_n$ can be put in one-to-one correspondence with the strong components, where (u_i, u_j) is an arc of D^*, $i \neq j$, if and only if some vertex of D_i is adjacent to at least one vertex of D_j.

Theorem 2.13 (Theorems 15.4 and 15.8 in [3]).The condensation of every digraph contains at least one vertex of outdegree zero.

Additionally, the following chemical kinetics terminology is needed [8,10]:

Definition 2.14. A chemical reaction mechanism is said to be *weakly reversible* if in its corresponding HJF-graph, every vertex is reachable from every other vertex.

Definition 2.15. A chemical reaction mechanism is said to be *reversible* if in its corresponding HJF-graph, the vertex v being adjacent to the vertex u implies that the vertex u is adjacent to the vertex v.

We are now prepared to give two results for complex balanced and detailed balanced mechanisms. Note, if $\mathbf{x} \in \mathbb{R}^m$, by $\mathbf{x} > 0$ we mean that $x_i > 0$ for all $i = 1, \ldots, m$.

Theorem 2.16. Every complex balanced mechanism is weakly reversible.

Proof. Let **a** be a positive, complex balanced equilibrium point of the mechanism. Hence, according to definition 2.3,

$$\sum_{j=1}^{n} k(j,i)\mathbf{a}^{(j)} = \mathbf{a}^{(i)} \sum_{j=1}^{n} k(i,j)$$

for all $i = 1, \ldots, n$, or equivalently,

$$\begin{bmatrix} -\sum_{i=1}^{n} k(1,i) & k(2,1) & \ldots & k(n,1) \\ k(1,2) & -\sum_{i=1}^{n} k(2,i) & \ldots & k(n,2) \\ \vdots & \vdots & \ddots & \vdots \\ k(1,n) & k(2,n) & \ldots & -\sum_{i=1}^{n} k(n,i) \end{bmatrix} \begin{bmatrix} \mathbf{a}^{(1)} \\ \mathbf{a}^{(2)} \\ \vdots \\ \mathbf{a}^{(n)} \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{6}$$

Notice that the sum of the entries in each column of the above matrix is zero.

Now, suppose the mechanism is not weakly reversible. This implies that the HJF-graph of at least one linkage class in the mechanism is not strongly connected, and hence, the condensation, D_l^*, of that linkage class consists of more than one vertex. Furthermore, according to theorem 2.13, there exists at least one vertex, say $u \in D_l^*$, such that od$(u) = 0$.

Let S_u be the indexing set of complexes in the strongly connected subdigraph corresponding to $u \in D_l^*$, and let $k = |S_u|$. If we let $\mathbf{v}_1$ be a k-vector with entries $\mathbf{a}^{(i)}$, $i \in S_u$, and $\mathbf{v}_2$ be an $(n-k)$-vector with entries $\mathbf{a}^{(j)}$, $j \notin S_u$, then (6) can be rewritten as

$$\begin{bmatrix} A & B \\ 0 & C \end{bmatrix} \begin{bmatrix} \mathbf{v}_1 \\ \mathbf{v}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \tag{7}$$

where A is a $k \times k$ matrix with form identical to the matrix in (6). It follows then that $\mathbf{1} \cdot A\mathbf{v}_1 = \mathbf{0}$, where $\mathbf{1}$ is a k-vector with each component equal to one. Furthermore, from (7) we have

$$\mathbf{1} \cdot B\mathbf{v}_2 = \mathbf{0}, \tag{8}$$

where $\mathbf{v}_2 > \mathbf{0}$. However, $\mathbf{1} \cdot B\mathbf{v}_2 > \mathbf{0}$ due to the fact that B has nonnegative entries and at least one positive entry, since linkage classes are connected. Thus, a contradiction is reached and the proof is complete. □

Theorem 2.17. Every detailed balanced mechanism is reversible.

Proof. Follows directly from definition 2.4. □

2.3. Positivity and compatibility classes

The solutions to (3) are not able to wander freely $\mathbb{R}^m$, they are restricted in two different ways.

First of all, as proven by Vol'pert in [16,17], solutions are limited to $\overline{\mathbb{P}}^m$, where $\overline{\mathbb{P}}^m = \{\mathbf{x} \in \mathbb{R}^m \mid x_i \geqslant 0 \text{ for } i = 1, \ldots, m\}$. The statement and proof of their following result requires the use of the mechanism's corresponding Vol'pert graph. A Vol'pert graph is a finite directed bipartite graph (see [9]), where the vertex a_i represents the species A_i in the mechanism.

Theorem 2.18 (Strict positiveness). If $\mathbf{x}(t)$ is the solution to (3), together with a set of nonnegative initial concentrations on the interval $[0, \beta)$, then $x_i(t) > 0$ $(0 < t < \beta)$ for all vertices a_i that are reachable from $\mathcal{A}_0$, and $x_i(t) \equiv 0$ for all vertices a_i that are nonreachable from $\mathcal{A}_0$.

Secondly, solutions to (3) are confined to *stoichiometric compatibility classes* [8, 10]:

Definition 2.19. The stoichiometric subspace for a chemical reaction mechanism is the linear subspace $S \in \mathbb{R}^m$ defined by

$$S := \operatorname{span}\{\mathcal{R}_j \in \mathbb{R}^m\colon\ j = 1, \ldots, r\},$$

where $\mathcal{R}_j$ is defined in (4). The dimension of the stoichiometric subspace will be denoted by $\dim S$.

Definition 2.20. The stoichiometric compatibility class (respectively, positive stoichiometric compatibility class) containing the composition $\mathbf{x}^0 \in \overline{\mathbb{P}}^m$ (respectively, $\mathbf{x}^0 \in \mathbb{P}^m$) is the set $(\mathbf{x}^0 + S) \cap \overline{\mathbb{P}}^m$.

Positive stoichiometric compatibility classes can also be expressed as a system of equations called *conservation laws* [5,14]:

Definition 2.21. Conservation laws are equations of the form

$$\lambda^i \cdot \mathbf{x} = \gamma_i,$$

where $S^\perp = \operatorname{span}\{\lambda^i\colon\ i = 1, \ldots, m - \dim S\}$, and $\lambda^i \neq 0$ and $\gamma_i \in \mathbb{R}$ for all $i = 1, \ldots, m - \dim S$.

If $\lambda^i_j \geqslant 0$ and $\gamma_i > 0$ for all $i = 1, \ldots, m - \dim S$ and $j = 1, \ldots, m$, then the system of equations will be referred to as positive conservation laws.

2.4. Asymptotic stability

In [7,10,11], Horn, Jackson and Feinberg characterize a class of chemical reaction mechanisms that have a unique, positive, asymptotically stable equilibrium point in

each compatibility class. Before we can state their result, the following definition is needed:

Definition 2.22. The deficiency of a chemical reaction mechanism, δ, is defined as $\delta = n - \ell - \dim S$ where n is the number of complexes, ℓ is the number of linkage classes, and $\dim S$ is the dimension of the stoichiometric subspace.

Theorem 2.23 (Deficiency Zero theorem). For any chemical reaction mechanism with zero deficiency, the following statements hold true:

1. If the mechanism is not weakly reversible then, for arbitrary kinetics (not necessarily mass action), the differential equations for the corresponding reaction system cannot admit either a positive equilibrium point or a cyclic composition trajectory along which all the species concentrations are positive.
2. If the mechanism is weakly reversible then, for mass action kinetics (but regardless of the positive values the rate constants take), the differential equations for the corresponding reaction system have the following properties:
   - there exists within each positive stoichiometric compatibility class precisely one positive equilibrium point;
   - that equilibrium point is asymptotically stable; and
   - there is no nontrivial cyclic composition trajectory along which all species concentrations are positive.

The proof of the Deficiency Zero involves a *Liapunov function*. The Liapunov function used is

$$H(\mathbf{x}) = \sum_{i=1}^{m} \left[x_i(\ln x_i - \ln a_i - 1) + a_i \right], \tag{9}$$

with time derivative

$$\dot{H}(\mathbf{x}) = (\ln \mathbf{x} - \ln \mathbf{a}) \cdot F(\mathbf{x}), \tag{10}$$

where $\mathbf{a} \in \mathbb{P}^m$ is a positive equilibrium point of the given mechanism. This Liapunov function is classical to chemical kinetics, and will be used in the proof of a later theorem.

In the next section we will present our major result, which provides new information on the qualitative nature of weakly reversible, deficiency zero mechanisms. It is important to note, however, that the result will hold true for the larger class of complex balanced mechanisms, of which weakly reversible, deficiency zero mechanisms are a subclass [10]:

Theorem 2.24. A necessary and sufficient condition for a mechanism to be complex balanced for any set of positive rate constants is that the following two requirements are met:

1. The mechanism is weakly reversible.
2. $\delta = 0$.

3. ω-limit set theorem

Given a weakly reversible, deficiency zero mechanism, it is known from the Deficiency Zero theorem that a solution, beginning at an initial condition sufficiently close to its uniquely compatible positive equilibrium point, will ultimately approach that positive equilibrium point. What are the dynamics of the rest of the solutions in the positive compatibility class? In this section, we will present a theorem which greatly limits the possibilities.

Before we introduce the theorem, some terminology and a theorem from [13] must first be stated.

For the general autonomous system

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \tag{11}$$

with $\mathbf{f} \in C^1(E)$ where E is an open set of $\mathbb{R}^n$, let $\psi_t : E \to E,\ t \in \mathbb{R}$, define the *flow* of the system. If $\mathbf{x}^0 \in E$, let $\mathbf{x}(t) = \psi_t(\mathbf{x}^0)$ denote the solution of (11) satisfying $\mathbf{x}(0) = \mathbf{x}^0$.

Theorem 3.1. For (11), $\mathbf{x}^0 \in E$, the ω-limit set, $\omega(\mathbf{x}^0)$, of $\psi_t(\mathbf{x}^0)$ is a closed subset of E, and if $\psi_t(\mathbf{x}^0)$ is contained in a compact subset of $\mathbb{R}^m$, then $\omega(\mathbf{x}^0)$ is a non-empty, connected, compact subset of E.

Furthermore, the following notation related to the pth complex of a chemical reaction mechanism will be used. This notation is from [2]:

$$u_p(\mathbf{x}) = \prod_{i=1}^{m} x_i^{z_{pi}}, \tag{12}$$

$$w_p(\mathbf{x}) = \sum_{p^+(j)=p} v_j(\mathbf{x}) - \sum_{p^-(j)=p} v_j(\mathbf{x}), \tag{13}$$

$$\alpha_p(\mathbf{x}, \mathbf{a}) = \prod_{i=1}^{m} \left(\frac{x_i}{a_i}\right)^{z_{pi}} = \frac{u_p(\mathbf{x})}{u_p(\mathbf{a})}, \tag{14}$$

$$\alpha_{p^-(j)}(\mathbf{x}, \mathbf{a}) = \frac{v_j(\mathbf{x})}{v_j(\mathbf{a})}, \tag{15}$$

where $v_j(\mathbf{x})$ is defined in (5).

We are now ready to present the major result, which actually pertains to the larger class of complex balanced mechanisms.

Theorem 3.2 (ω-limit set theorem). Let (1) be a complex balanced chemical reaction mechanism, and let $\mathbf{a}$ be the positive complex balanced equilibrium point admitted

by the mechanism. Then, for a solution of (3) beginning at the concentration $\mathbf{x}^0$, the ω-limit set, $\omega(\mathbf{x}^0)$, of the solution consists either of boundary points of complex balanced equilibria or of a single positive point of complex balanced equilibrium.

It is important to note that theorem 3.2 holds true for any compatibility class of a complex balanced mechanism. That is, the theorem is not restricted to positive stoichiometric compatibility classes. However, in section 4, theorem 3.2 will be applied only to positive compatibility classes in order to obtain global stability results.

The proof of theorem 3.2 requires the following lemmas and theorem:

Lemma 3.3. Let $\mathbf{x}(t)$ be a solution, and $\mathcal{L}$ be the set of linkage classes of a weakly reversible chemical reaction mechanism. Then for every linkage class $l \in \mathcal{L}$, either $v_j(\mathbf{x}) \equiv 0$ or $v_j(\mathbf{x}) > 0$ for every j where $p^{\pm}(j) \in l,\ t > 0$.

Proof. Suppose the assertion is not true. This implies that for some $t^* > 0$ and for some linkage class $l \in \mathcal{L}$,

$$v_{j^*}\big(\mathbf{x}(t^*)\big) > 0 \quad \text{and} \quad v_{j^{**}}\big(\mathbf{x}(t^*)\big) = 0,$$

where j^* and j^{**} are such that $p^{\pm}(j^*), p^{\pm}(j^{**}) \in l$. Now, according to Vol'pert in [15,16], since $v_{j^*}(\mathbf{x}) > 0$, the vertex b_{j^*} in the mechanism's corresponding Vol'pert graph will receive an index from Vol'pert's indexing method. Consequently, all a_i vertices representing species in $p^+(j^*)$ will receive an index, and furthermore, all vertices representing reactions with $p^+(j^*)$ as the reactant complex will also receive an index. Using the same argument, it follows that any b_k vertex representing a reaction in a directed arrow pathway between the complex $p_+(j^*)$ and some complex $\bar{p}$ will be indexed, implying that $v_k(\mathbf{x}) > 0$. Since the mechanism is weakly reversible, there is a directed arrow pathway between $p_+(j^*)$ and $p_-(j^{**})$. Thus, $v_{j^{**}}(\mathbf{x}) > 0$, which is a contradiction, and the proof is complete. □

Theorem 3.4. Along a nonnegative solution $\mathbf{x}(t)$ of a complex balanced mechanism, the Liapunov function (9) does not increase, and is constant if and only if $\mathbf{x}(t)$ is an equilibrium point. Additionally, if $\mathbf{x}(t)$ is an equilibrium point, then it is a complex balanced equilibrium point.

The proof of this theorem is based on the proof of theorem 2 in [2].

Proof. According to theorem 2.16 and lemma 3.3, the linkage classes of a complex balanced mechanism can be partitioned into two groups, one with strictly positive rate functions for $t > 0$, and the other with identically zero rate functions. Let $\mathcal{L}$ be the set of all linkage classes in the mechanism, and let $\mathcal{L}' \subset \mathcal{L}$ be the set of linkage classes such that if $l \in \mathcal{L}'$ then $v_j(\mathbf{x}) > 0$ for every j where $p^{\pm}(j) \in l,\ t > 0$. Therefore, it follows that if $l \in \mathcal{L} \backslash \mathcal{L}'$, then $v_j(\mathbf{x}) \equiv 0$ for every j where $p^{\pm}(j) \in l,\ t > 0$. Furthermore, let $\{\mathcal{S}', \mathcal{L}'\}$ represent the mechanism consisting only of linkage classes from $\mathcal{L}'$, where $\mathcal{S}'$ is the set of species in the linkage classes contained in $\mathcal{L}'$.

First, suppose $\mathcal{L}' = \emptyset$. Consequently, $v_j(\mathbf{x}) \equiv 0$ for every $j = 1, \ldots, r$, and moreover, $F(\mathbf{x}) = 0$. This implies that $\mathbf{x}(t)$ is an equilibrium point of the mechanism, and that the time derivative of the Liapunov function (10) is equal to zero. Furthermore, according to definition 2.3, $\mathbf{x}(t)$ is trivially a complex balanced equilibrium point, and the proof is complete.

Next, suppose $\mathcal{L}' \neq \emptyset$. Since the reactions in $\mathcal{L}\backslash\mathcal{L}'$ contribute nothing to the rate of change of species concentrations, it follows that if we restrict the state-space of the solution to only those species in $\mathcal{S}'$, then the vector $\bar{\mathbf{x}}(t)$, where $\bar{x}_i \in \{x_j \mid A_j \in \mathcal{S}'\}$ for $i = 1, \ldots, |S'|$, is a solution of $\{\mathcal{S}', \mathcal{L}'\}$. This solution is positive for $t > 0$ according to theorem 5 in [16], since $v_j(\mathbf{x}) > 0$ for every reaction j where $p^{\pm}(j) \in l,\ l \in \mathcal{L}'$. Consequently, if we define $\overline{H}$ as a function of vectors in the state-space consisting only of species in $\mathcal{S}'$, with $\overline{H}$ having the form of (9), then the time derivative of $\overline{H}$,

$$\dot{\overline{H}}\big(\bar{\mathbf{x}}\big) = \sum_{l \in \mathcal{L}'} \sum_{p^{\pm}(j) \in l} v_j\big(\bar{\mathbf{x}}\big) \mathcal{R}_j\big(\ln \bar{\mathbf{x}} - \ln \bar{\mathbf{a}}\big), \tag{16}$$

is defined for $t > 0$, where $\bar{a}_i \in \{a_j \mid A_j \in \mathcal{S}'\}$ for $i = 1, \ldots, |\mathcal{S}'|$.

Now, using lemma 3.5 in [2], it follows that

$$\dot{\overline{H}}(\bar{\mathbf{x}}) \leqslant \sum_{l \in \mathcal{L}'} \sum_{p \in l} \alpha_p\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) w_p\big(\bar{\mathbf{a}}\big) - \frac{1}{2} \sum_{l \in \mathcal{L}'} \sum_{p^{\pm}(j) \in l} \Big[v_j\big(\bar{\mathbf{a}}\big) \min\big[\alpha_{p^+(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big), \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big)\big] \times \big(\ln \alpha_{p^+(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) - \ln \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big)\big)^2 \Big].$$

Since the original mechanism is complex balanced at $\mathbf{a}$ it follows immediately from definition 2.3 that $\{\mathcal{S}', \mathcal{L}'\}$ is complex balanced at $\bar{\mathbf{a}}$. Therefore, $w_p(\bar{\mathbf{a}}) = 0$ for every $p \in l,\ l \in \mathcal{L}'$, which gives us

$$\begin{aligned} \dot{\overline{H}}\big(\bar{\mathbf{x}}\big) &\leqslant -\frac{1}{2} \sum_{l \in \mathcal{L}'} \sum_{p^{\pm}(j) \in l} \Big[v_j(\bar{\mathbf{a}}) \min\big[\alpha_{p^+(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big), \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big)\big] \\ &\qquad \times \big(\ln \alpha_{p^+(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) - \ln \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big)\big)^2 \Big] \\ &\leqslant 0. \end{aligned} \tag{17}$$

Hence, along the positive solution $\bar{\mathbf{x}}(t)$ of $\{\mathcal{S}', \mathcal{L}'\}$, $\overline{H}(\bar{\mathbf{x}})$ does not increase for $t > 0$. Therefore, if we assume $\overline{H}$ has been extended to be continuous on the boundary of the state-space, we can conclude that the Liapunov function H does not increase along the nonnegative solution $\mathbf{x}(t)$ of $\{\mathcal{S}, \mathcal{L}\}$ for $t \geqslant 0$.

For the second part of the assertion, from (16) it is straightforward that if $\bar{\mathbf{x}}(t)$ is a positive equilibrium point of $\{\mathcal{S}', \mathcal{L}'\}$, then $\dot{\overline{H}}(\bar{\mathbf{x}}(t)) = 0$. Hence, it can be concluded from continuity that H is constant along the equilibrium point $\mathbf{x}(t)$. Finally, suppose

$\dot{\overline{H}}(\bar{\mathbf{x}}(t)) = 0$. From (17), since $v_j(\bar{\mathbf{x}}) > 0$ for every reaction j where $p^{\pm}(j) \in l,\ l \in \mathcal{L}'$, it follows that

$$\alpha_{p^+(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) = \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) \tag{18}$$

for every reaction j where $p^{\pm}(j) \in l,\ l \in \mathcal{L}'$. Therefore, since

$$w_p\big(\bar{\mathbf{x}}\big) = \sum_{p^+(j)=p} \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) v_j\big(\bar{\mathbf{a}}\big) - \sum_{p^-(j)=p} \alpha_{p^-(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) v_j\big(\bar{\mathbf{a}}\big),$$

after substituting (15) into (13), it follows from (18) that

$$\begin{aligned} w_p\big(\bar{\mathbf{x}}\big) &= \alpha_{p(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) \sum_{p^+(j)=p} v_j\big(\bar{\mathbf{a}}\big) - \alpha_{p(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) \sum_{p^+(j)=p} v_j\big(\bar{\mathbf{a}}\big) \\ &= \alpha_{p(j)}\big(\bar{\mathbf{x}}, \bar{\mathbf{a}}\big) w_p\big(\bar{\mathbf{a}}\big). \end{aligned}$$

Now, since $\bar{\mathbf{a}}$ is a complex balanced equilibrium point of $\{\mathcal{S}', \mathcal{L}'\}$, then $w_p(\bar{\mathbf{a}}) = 0$, which implies that $w_p(\bar{\mathbf{x}}) = 0$. Thus, we can conclude that $\bar{\mathbf{x}}(t)$ is a positive complex balanced equilibrium of $\{\mathcal{S}', \mathcal{L}'\}$, and moreover, from the continuity of H that $\mathbf{x}(t)$ is an equilibrium point of $\{\mathcal{S}, \mathcal{L}\}$. Furthermore, $\mathbf{x}(t)$ is a complex balanced equilibrium point since all complexes in the linkage classes contained $\mathcal{L}\backslash\mathcal{L}'$ are trivially complex balanced at $\mathbf{x}(t)$. This finishes the proof of theorem 3.4. □

Lemma 3.5. The solution $\mathbf{x}(t)$ of a complex balanced mechanism, with arbitrary nonnegative initial conditions $x_i(0) \geqslant 0,\ i = 1, \ldots, m$, exists and is bounded for $t \in [0, \infty)$.

Proof. By theorem 2 in section 2.4 of [13], either $\mathbf{x}(t)$ exists for all $t \geqslant 0$ or $\|x(t)\|$ is unbounded. Suppose $\|x(t)\| \to \infty$ for $t \geqslant 0$. Since we are assuming $H(\mathbf{x}(t))$ has been extended to be continuous for $t \geqslant 0$, this implies that $H(\|\mathbf{x}(t)\|) \to \infty$. However, according to theorem 3.4, for $t \geqslant 0$,

$$H\big(\mathbf{x}(t)\big) \leqslant H\big(\mathbf{x}(0)\big), \quad \text{where } H\big(\mathbf{x}(0)\big) \geqslant 0.$$

Thus, a contradiction has been reached.

Now, suppose the solution is not bounded. This implies that there exists a sequence $\{t_n\},\ t_n \to \infty$, such that $\|\mathbf{x}(t_n)\| \to \infty$. Following the same argument as above, a contradiction is achieved, and the proof is complete. □

Lemma 3.6. If a chemical reaction mechanism is complex balanced, then there exists a unique, positive complex balanced equilibrium point in each compatibility class.

Proof. The result follows directly from theorem 3.4, and theorem 6A and lemma 4B in [11]. □

We are now able to prove theorem 3.2. The proof is based on the proof of theorem 4 in section 3.4 of [17].

Proof of ω-limit set theorem. According to theorem 3.4, the Liapunov function H does not increase along a nonnegative solution. As well, $H(\mathbf{x})$ is bounded from below. Thus, the limit

$$\lim_{t\to\infty} H\big(\mathbf{x}(t)\big) = H_0$$

exists. That is, $H(\mathbf{x}(t))$ approaches a constant value with increasing time.

Now, for the solution beginning at the initial concentration $\mathbf{x}^0$, let $y \in \omega(\mathbf{x}^0)$. A limit point exists as a result of lemma 3.5 and theorem 3.1. Therefore, from the continuity of H we have

$$H\big(\mathbf{x}(t)\big) \to H(y) \quad \text{as } t \to \infty,$$

which implies that $\omega(\mathbf{x}^0) \in \{\mathbf{x} \mid H(\mathbf{x}) = H_0\}$. Furthermore, since according to theorem 3.1 $\omega(\mathbf{x}^0)$ is invariant, and theorem 3.4 tells us that H remains constant only for complex balanced equilibrium points, then it can be concluded that $\omega(\mathbf{x}^0)$ consists only of complex balanced equilibrium points.

Suppose $\omega(\mathbf{x}^0)$ contains a positive complex balanced equilibrium point, $\mathbf{x}^*$. From lemma 3.6, $\mathbf{x}^*$ is the only positive equilibrium in its compatibility class. Therefore, since $\omega(\mathbf{x}^0)$ is a connected set, it follows that $\omega(\mathbf{x}^0)$ does not contain any boundary complex balanced equilibria. This completes the proof of the theorem. □

Hence, according to theorem 3.2, a solution of a complex balanced mechanism is restricted to approaching either its uniquely compatible positive equilibrium point, or its compatible boundary equilibrium points.

From theorem 3.2 we have the following corollary:

Corollary 3.7. Let (1) be a complex balanced mechanism. Then, every equilibrium point admitted by the mechanism is complex balanced.

Proof. The proof follows directly from the last part of the proof of theorem 3.2. □

Furthermore, from theorem 2.24, we obtain the following equivalent result for weakly reversible, deficiency zero mechanisms:

Corollary 3.8. Let (1) be a weakly reversible, deficiency zero chemical reaction mechanism. Then, the ω-limit set of any solution consists either of boundary points of complex balanced equilibria or of a single positive point of complex balanced equilibrium.

Proof. According to theorem 2.24, a weakly reversible, deficiency zero mechanism is complex balanced for all positive sets of rate constants, and hence, the proof follows directly from theorem 3.2. □

In the next section we will use corollary 3.8 to prove the global asymptotic stability of a certain class of weakly reversible, deficiency zero mechanisms. But

before we proceed to the next section, there is one last corollary of theorem 3.2 that we would like to present:

Corollary 3.9. Let (1) be a reversible chemical reaction mechanism that admits a positive detailed balanced equilibrium point. Then, the ω-limit set of any solution consists either of boundary points of detailed balanced equilibria or of a single positive point of detailed balanced equilibrium.

The proof of this result requires the following theorem:

Theorem 3.10. Let (1) be a complex balanced mechanism that admits a positive detailed balanced equilibrium point. Then, every complex balanced equilibrium point admitted by the mechanism is detailed balanced.

Proof. Let $\mathbf{a}$ be a positive detailed balanced equilibrium and $\mathbf{b}$ be a nonnegative complex balanced equilibrium of the mechanism. Let $\mathcal{L}$ be the set of linkage classes of the mechanism, and if $l \in \mathcal{L}$, then we will denote the number of complexes in l by n_l.

According to definition 2.4 and definition 2.3, respectively, for every linkage class $l \in \mathcal{L}$,

$$k(j,i)\mathbf{a}^{(j)} = k(i,j)\mathbf{a}^{(i)} \quad \text{for all } i,j = 1,\ldots,n_l \tag{19}$$

and

$$\sum_{j=1}^{n_l} k(j,i)\mathbf{b}^{(j)} = \mathbf{b}^{(i)} \sum_{j=1}^{n_l} k(i,j) \quad \text{for all } i = 1,\ldots,n_l, \tag{20}$$

where

$$\mathbf{a}^{(k)} = \prod_{i=1}^{m} a_i^{z_{ki}} \quad \text{and} \quad \mathbf{b}^{(k)} = \prod_{i=1}^{m} b_i^{z_{ki}}.$$

Now, if we solve for $k(j,i)$ in (19) and substitute into (20) we have

$$\sum_{j=1}^{n_l} k(i,j)\frac{\mathbf{a}^{(i)}\mathbf{b}^{(j)}}{\mathbf{a}^{(j)}} = \mathbf{b}^{(i)} \sum_{j=1}^{n_l} k(i,j) \quad \text{for all } i = 1,\ldots,n_l,$$

which can also be expressed as

$$\sum_{j=1}^{n_l} k(i,j)\mathbf{w}^{(j)} = \mathbf{w}^{(i)} \sum_{j=1}^{n_l} k(i,j) \quad \text{for all } i = 1,\ldots,n_l, \tag{21}$$

where $\mathbf{w}^{(k)} = (\mathbf{b}^{(k)}/\mathbf{a}^{(k)})$. If it can be shown that $\mathbf{w}^{(k)} = \lambda_l$ for all $k = 1,\ldots,n_l$, $\lambda_l \geqslant 0$, we will have proved the theorem.

According to lemma 3.3, either $\mathbf{b}^{(k)} \equiv 0$ or $\mathbf{b}^{(k)} > 0$ for all $k = 1, \ldots, n_l,\ t > 0$. If $\mathbf{b}^{(k)} \equiv 0$ then $\mathbf{w}^{(k)} \equiv 0$ for all $k = 1, \ldots, n_l$, and the proof is complete. Thus, we will assume that $\mathbf{b}^{(k)} > 0$ for all $k = 1, \ldots, n_l$, which implies that $\mathbf{w}^{(k)} > 0$ for all $k = 1, \ldots, n_l$. Furthermore, we will assume that the $\mathbf{w}^{(k)}$'s are not all equal to each other, and hence, prove the result by arriving at a contradiction.

Suppose the $\mathbf{w}^{(k)}$'s have been relabeled so that

$$\mathbf{w}^{(1)} = \mathbf{w}^{(2)} = \cdots = \mathbf{w}^{(l)} > \mathbf{w}^{(l+1)} \geqslant \cdots \geqslant \mathbf{w}^{(n_l)},$$

where $1 \leqslant l \leqslant n_l$. It follows then that

$$k(i,j) = 0 \quad \text{for all } 1 \leqslant i \leqslant l,\ l < j < n_l, \tag{22}$$

in order for (21) to hold for $1 \leqslant i \leqslant l$, because otherwise

$$-\mathbf{w}^{(i)} \sum_{j=1}^{n_l} k(i,j) + \sum_{j=1}^{n_l} k(i,j)\mathbf{w}^{(j)} < \mathbf{w}^{(i)} \left[-\sum_{j=1}^{n_l} k(i,j) + \sum_{j=1}^{n_l} k(i,j) \right] = 0.$$

However, from (22) and (19), we have

$$k(j,i) = 0 \quad \text{for } 1 < i \leqslant l,\ l < j \leqslant n_l, \tag{23}$$

which together with (22) implies that the linkage class l is not connected. This is a contradiction of definition 2.2, and we are done. □

Proof of corollary 3.9. If a chemical reaction mechanism is detailed balanced, it follows immediately that the mechanism is complex balanced. Furthermore, from theorem 3.10, we know that every equilibrium point of the complex balanced mechanism is detailed balanced. Therefore, the proof of the corollary follows directly from theorem 3.2. □

4. Global stability results

If a weakly reversible, deficiency zero mechanism does not admit an equilibrium point on the boundary of the compatibility class containing the positive equilibrium $\mathbf{x}^*$, corollary 3.8 tells us that $\omega(\mathbf{x}^0) = \mathbf{x}^*$ for any compatible solution, $\psi_t(\mathbf{x}^0)$, of the mechanism. Therefore, we have the following result:

Theorem 4.1. If a weakly reversible, deficiency zero mechanism does not admit boundary equilibrium points in any positive compatibility class, then the unique positive equilibrium point in each compatibility class is globally asymptotically stable.

Proof. The result follows directly from corollary 3.8. □

It is important to emphasize that when we speak of a globally asymptotically stable positive equilibrium $\mathbf{x}^*$, we mean that it is globally stable with respect to the

concentrations in its positive compatibility class. That is, $\mathbf{x}^*$ is globally stable in $(\mathbf{x}^0 + S) \cap \overline{\mathbb{P}}^m$.

We will next apply theorem 4.1 to some particular weakly reversible, deficiency zero mechanisms. However, before we do, it is of interest to note that a result similar to theorem 4.1 is presented by Chen and Siegel in [5,14].

Assuming that their *weakly repelling condition* (condition 4.8 in [5], condition 1 in [14]) is satisfied, Chen and Siegel prove that weakly reversible, deficiency zero mechanisms are globally asymptotically stable (theorem 4.11 in [5], theorem 4 in [14]). However, the weakly repelling condition is a sufficient condition for the nonexistence of boundary equilibria. Therefore, theorem 4.1 is a generalization of the result given in [5,14].

4.1. Enzymatic mechanisms

Many reactions in biochemistry would not proceed under normal conditions without the presence of an *enzyme*. We will refer to mechanisms containing enzyme-catalyzed reactions as *enzymatic mechanisms*. To regulate the yield of an enzymatic mechanism, an *inhibitor* complex interacts with the enzyme and/or enzyme–substrate complex to prevent the reaction from going to completion [4,12]. In this section, we will give three examples of enzymatic mechanisms, two of which involve inhibitors, that are globally asymptotically stable.

In addition, note that the global stability of the single-substrate single-product enzymatic mechanism

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \cdots \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} C_n \underset{k_{-(n+1)}}{\overset{k_{n+1}}{\rightleftharpoons}} P + E,$$

given by Chen and Siegel in [14], can also be determined by the method given below.

Before we present the three enzymatic mechanisms, there is some notation that must first be introduced.

For $k = 1, \ldots, n$, let S_k represent a substrate, C_k represent an enzyme–substrate complex, P_k represent a product, and D_k represent a deactivated complex. Furthermore, let E represent an enzyme and I represent an inhibitor. In the following enzymatic mechanisms, the lower case letters will represent the concentrations corresponding to the upper case letters.

4.1.1. General enzymatic mechanism

Consider a one-enzyme, n-substrate, n-product enzymatic mechanism:

$$\begin{aligned}
S_1 + E &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P_1 + E, \\
S_2 + E &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} P_2 + E, \\
&\vdots \\
S_n + E &\underset{k_{-(2n-1)}}{\overset{k_{(2n-1)}}{\rightleftharpoons}} C_n \underset{k_{-2n}}{\overset{k_{2n}}{\rightleftharpoons}} P_n + E.
\end{aligned} \tag{24}$$

This mechanism is weakly reversible, deficiency zero, and the evolution of its species concentrations is modeled by the following system of differential equations:

$$\begin{aligned}
\dot{s}_1 &= -k_1 s_1 e + k_{-1} c_1, \\
&\vdots \\
\dot{s}_n &= -k_{(2n-1)} s_n e + k_{-(2n-1)} c_n, \\
\dot{p}_1 &= k_2 c_1 - k_{-2} p_1 e, \\
&\vdots \\
\dot{p}_n &= k_{2n} c_n - k_{-2n} p_n e, \\
\dot{c}_1 &= k_1 s_1 e - k_{-1} c_1 - k_2 c_1 + k_{-2} p_1 e, \\
&\vdots \\
\dot{c}_n &= k_{(2n-1)} s_n e - k_{-(2n-1)} c_n - k_{2n} c_n + k_{-2n} p_n e, \\
\dot{e} &= -k_1 s_1 e - \cdots - k_{(2n-1)} s_n e + k_{-1} c_1 + \cdots + k_{-(2n-1)} c_n \\
&\quad + k_2 c_1 + \cdots + k_{2n} c_n - k_{-2} p_1 e - \cdots - k_{-2n} p_n e.
\end{aligned} \tag{25}$$

To prove that the enzymatic mechanism (24) does not admit equilibrium points on the boundary of any positive compatibility class, we will need the help of the mechanism's positive conservation laws. As explained in definition 2.21, the mechanism has $\dim S^{\perp} = n + 1$ linearly independent conservation laws. To find these positive conservation laws, we simply look at (25) for nonnegative linear combinations of differential equations so that the right-hand sides of the equations add up to zero. The following are $n + 1$ such combinations:

$$\begin{aligned}
\dot{s}_1 + \dot{c}_1 + \dot{p}_1 &= 0, \\
\dot{s}_2 + \dot{c}_2 + \dot{p}_2 &= 0, \\
&\vdots \\
\dot{s}_n + \dot{c}_n + \dot{p}_n &= 0, \\
\dot{e} + \dot{c}_1 + \dot{c}_2 + \cdots + \dot{c}_n &= 0.
\end{aligned}$$

By integrating both sides of the above equations with respect to time, we obtain the following $n+1$ linearly independent, positive conservation laws for the enzymatic mechanism (24):

$$\begin{aligned}
s_1 + c_1 + p_1 &= \gamma_1 \\
s_2 + c_2 + p_2 &= \gamma_2 \\
&\vdots \\
s_n + c_n + p_n &= \gamma_n \\
e + c_1 + c_2 + \cdots + c_n &= \gamma_{n+1},
\end{aligned}$$

where $\gamma_i > 0$ for $i = 1, \ldots, n+1$, as we are only interested in solutions that exist in positive stoichiometric compatibility classes.

Theorem 4.2. The enzymatic mechanism (24) admits no boundary equilibrium points in any positive compatibility class.

Proof. To prove this theorem we will assume that the mechanism admits an equilibrium point, denoted by $(s_1^*, \ldots, s_n^*, p_1^*, \ldots, p_n^*, c_1^*, \ldots, c_n^*, e^*)$, where a particular component of the equilibrium is equal to zero. Then, using the positive conservation laws and theorem 2.18 we will arrive at a contradiction. This will be done for each component of the equilibrium point.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $s_k^* = 0$.
$\Rightarrow c_k^* = 0$ (from theorem 2.18),
$\Rightarrow p_k^* > 0$ (from conservation laws),
$\Rightarrow e^* = 0$ (from theorem 2.18),
$\Rightarrow \exists j,\ j \neq k$, such that $c_j^* > 0$ (from conservation laws),
$\Rightarrow e^* > 0$ (from theorem 2.18).
Contradiction.

Due to the symmetry of the mechanism, $p_k^*,\ k = 1, \ldots, n$, is not equal to zero.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $c_k^* = 0$.
$\Rightarrow s_k^* > 0$ or $p_k^* > 0$ (from conservation laws),
$\Rightarrow e^* = 0$ (from theorem 2.18),
$\Rightarrow \exists j,\ j \neq k$, such that $c_j^* > 0$ (from conservation laws),
$\Rightarrow e^* > 0$ (from theorem 2.18).
Contradiction.

Suppose $e^* = 0$.
$\Rightarrow c_k^* = 0,\ \forall k,\ k = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Therefore, there are no boundary equilibrium points admitted by (24) and the proof is complete. □

Theorem 4.3. The enzymatic mechanism (24) has a unique positive equilibrium point in each positive compatibility class that is globally asymptotically stable.

Proof. The result follows directly from theorem 4.2 and theorem 4.1. □

4.2. General enzymatic mechanism with uncompetitive inhibitor

Consider a one-enzyme, n-substrate, n-product enzymatic mechanism that is regulated by an *uncompetitive inhibitor*. The uncompetitive inhibitor binds to the enzyme–substrate complex in each of the n reactions, rendering them inactive [12]:

$$
\begin{aligned}
&S_1 + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P_1 + E,\\
&S_2 + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} P_2 + E,\\
&\qquad\vdots\\
&S_n + E \underset{k_{-(2n-1)}}{\overset{k_{(2n-1)}}{\rightleftharpoons}} C_n \underset{k_{-2n}}{\overset{k_{2n}}{\rightleftharpoons}} P_n + E,\\
&C_1 + I \underset{k_{-(2n+1)}}{\overset{k_{(2n+1)}}{\rightleftharpoons}} D_1,\\
&C_2 + I \underset{k_{-(2n+2)}}{\overset{k_{(2n+2)}}{\rightleftharpoons}} D_2,\\
&\qquad\vdots\\
&C_n + I \underset{k_{-(3n)}}{\overset{k_{(3n)}}{\rightleftharpoons}} D_n.
\end{aligned}
\tag{26}
$$

This mechanism is weakly reversible, deficiency zero, and has the following $\dim S^{\perp} = n + 2$ positive conservation laws. These positive conservation laws were found by applying the method used in section 4.1.1:

$$
\begin{aligned}
s_1 + p_1 + c_1 + d_1 &= \gamma_1,\\
s_2 + p_2 + c_2 + d_2 &= \gamma_2,\\
&\vdots\\
s_n + p_n + c_n + d_n &= \gamma_n,\\
e + c_1 + c_2 + \cdots + c_n + d_1 + d_2 + \cdots + d_n &= \gamma_{n+1},\\
i + d_1 + d_2 + \cdots + d_n &= \gamma_{n+2},
\end{aligned}
$$

where $\gamma_i > 0$ for $i = 1, \ldots, n + 2$, as we are only interested in solutions that exist in positive stoichiometric compatibility classes.

Theorem 4.4. The enzymatic mechanism (26) admits no boundary equilibrium points in any positive compatibility class.

Proof. Assuming the mechanism admits an equilibrium point, denoted by $(s_1^*, \ldots, s_n^*, p_1^*, \ldots, p_n^*, c_1^*, \ldots, c_n^*, d_1^*, \ldots, d_n^*, i^*, e^*)$, the proof of this theorem is identical in form to the proof of theorem 4.2.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $s_k^* = 0$.
$\Rightarrow c_k^* = 0$ (from theorem 2.18),
$\Rightarrow d_k^* = 0$ (from theorem 2.18),
$\Rightarrow p_k^* > 0$ (from conservation laws),
$\Rightarrow e^* = 0$ (from theorem 2.18),
$\Rightarrow c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18),
$\Rightarrow d_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Due to the symmetry of the mechanism, $p_k^*,\ k = 1, \ldots, n$, is not equal to zero.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $c_k^* = 0$.
$\Rightarrow d_k^* = 0$ and [($s_k^* = 0$ and $p_k^* = 0$) or $e^* = 0$] (from theorem 2.18).
If $d_k^* = 0$ and $s_k^* = 0$ and $p_k^* = 0$,
contradiction of conservation laws.
If $d_k^* = 0$ and $e^* = 0$,
$\Rightarrow c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18),
$\Rightarrow d_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Suppose $e^* = 0$.
$\Rightarrow c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18),
$\Rightarrow d_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $d_k^* = 0$.
$\Rightarrow c_k^* = 0$ or $i^* = 0$ (from theorem 2.18).
If $c_k^* = 0$,
$\Rightarrow e^* = 0$ or ($s_k^* = 0$ and $p_k^* = 0$) (from theorem 2.18).
If $s_k^* = 0$ and $p_k^* = 0$,
contradiction of conservation laws.
If $e^* = 0$,
$\Rightarrow c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18),
$\Rightarrow d_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.
If $i^* = 0$,
$\Rightarrow d_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Suppose $i^* = 0$.
$\Rightarrow d_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Therefore, there are no boundary equilibrium points admitted by (26) and the proof is complete. □

Theorem 4.5. The enzymatic mechanism (26) has a unique positive equilibrium point in each positive compatibility class that is globally asymptotically stable.

Proof. The result follows directly from theorem 4.4 and theorem 4.1. □

4.3. General enzymatic mechanism with competitive inhibitor

Consider a one-enzyme, n-substrate, n-product enzymatic mechanism that is regulated by a *competitive inhibitor*. The competitive inhibitor competes with the substrate to bind to the enzyme. When the inhibitor is successful in binding with the enzyme, the

enzyme can no longer react with the substrate to form the enzyme–substrate complex, and thus, the enzyme becomes inactive [12]:

$$\begin{aligned}
&S_1 + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P_1 + E,\\
&S_2 + E \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} P_2 + E,\\
&\qquad\vdots\\
&S_n + E \underset{k_{-(2n-1)}}{\overset{k_{2n-1}}{\rightleftharpoons}} C_n \underset{k_{-2n}}{\overset{k_{2n}}{\rightleftharpoons}} P_n + E,\\
&E + I \underset{k_{-(2n+1)}}{\overset{k_{(2n+1)}}{\rightleftharpoons}} D.
\end{aligned} \tag{27}$$

This mechanism is weakly reversible, deficiency zero, and has the following $\dim S^{\perp} = n + 2$ positive conservation laws. These positive conservation laws were found by applying the method used in section 4.1.1:

$$\begin{aligned}
s_1 + p_1 + c_1 &= \gamma_1,\\
s_2 + p_2 + c_2 &= \gamma_2,\\
&\vdots\\
s_n + p_n + c_n &= \gamma_n,\\
i + d &= \gamma_{n+1},\\
e + d + c_1 + c_2 + \cdots + c_n &= \gamma_{n+2},
\end{aligned}$$

where $\gamma_i > 0$ for $i = 1, \ldots, n + 2$, as we are only interested in solutions that exist in positive stoichiometric compatibility classes.

Theorem 4.6. The enzymatic mechanism (27) admits no boundary equilibrium points in any positive compatibility class.

Proof. Assuming the mechanism admits an equilibrium point, denoted by $(s_1^*, \ldots, s_n^*, p_1^*, \ldots, p_n^*, c_1^*, \ldots, c_n^*, d_1^*, \ldots, d_n^*, i^*, e^*)$, the proof of this theorem is identical in form to the proof of theorem 4.2.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $s_k^* = 0$.
$\Rightarrow c_k^* = 0$ (from theorem 2.18),
$\Rightarrow p_k^* > 0$ (from conservation laws),
$\Rightarrow e^* = 0$ (from theorem 2.18),
$\Rightarrow d^* = 0$ and $c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Due to the symmetry of the mechanism, $p_k^*,\ k = 1, \ldots, n$, is not equal to zero.

Suppose $\exists k,\ k = 1, \ldots, n$, such that $c_k^* = 0$.
$\Rightarrow e^* = 0$ or ($p_k^* = 0$ and $s_k^* = 0$) (from theorem 2.18).
If $e^* = 0$,
$\Rightarrow c_j^* = 0,\ \forall j = 1, \ldots, n$, and $d^* = 0$ (from theorem 2.18).
Contradiction of conservation laws.
If $p_k^* = 0$ and $s_k^* = 0$,
contradiction of conservation laws.

Suppose $i^* = 0$.
$\Rightarrow d^* = 0$ (from theorem 2.18).
Contradiction of conservation laws.

Suppose $e^* = 0$.
$\Rightarrow d^* = 0$ and $c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Suppose $d^* = 0$.
$\Rightarrow i^* > 0$ (from conservation laws).
$\Rightarrow e^* = 0$ (from theorem 2.18).
$\Rightarrow c_j^* = 0,\ \forall j = 1, \ldots, n$ (from theorem 2.18).
Contradiction of conservation laws.

Therefore, there are no boundary equilibrium points admitted by the enzymatic mechanism (27), and the proof is complete. □

Theorem 4.7. The enzymatic mechanism (27) has a unique positive equilibrium point in each positive compatibility class that is globally asymptotically stable.

Proof. The result follows directly from theorem 4.6 and theorem 4.1. □

4.4. Enzymatic mechanism with noncompetitive inhibitor

There are three basic types of inhibition; competitive inhibition (section 4.2), uncompetitive inhibition (section 4.3), and *noncompetitive inhibition* [4].

A noncompetitive inhibitor deactivates both the enzyme and the enzyme–substrate complex, giving the following mechanism [12]:

$$\begin{aligned} S + E &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} P + E, \\ C_1 + I &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} C_3 + S, \\ E + I &\underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} C_3. \end{aligned} \tag{28}$$

However, mechanism (28) has a deficiency of one. Thus, even though it can be shown that the mechanism does not admit a boundary equilibrium point in any positive compatibility class, theorem 4.1 cannot be used to determine the mechanism's dynamics. The dynamics of mechanism (28) are, therefore, left for future research.

References

[1] A. Bamberger and E. Billette, Quelques extensions d'un théorème de Horn et Jackson, C.R. Acad. Sci. Paris Sér. I Math. 319(12) (1994) 1257–1262.
[2] A. Bamberger and E. Billette, Contribution à l'étude mathématique des états stationnaires dans les systèmes de réactions chimiques, Technical report 42, Institut Français du Pétrole (January 1995).
[3] M. Behzad, G. Chartrand and L. Lesniak-Foster, *Graphs and Digraphs* (Prindle, Weber and Schmidt International Series, 1979).
[4] P.D. Boyer, H. Lardy and K. Myräck, *The Enzymes*, 2nd edition, Vol. 1 (Academic Press, 1959).
[5] Y.F. Chen, Chemical kinetics systems with regular dynamics, Master's Thesis, University of Waterloo (1992).
[6] P. Erdi and J. Toth, *Mathematical Models of Chemical Reactions* (Princeton University Press, 1989).
[7] M. Feinberg, Complex balancing in general kinetic systems, Arch. Rational Mech. Anal. 49 (1972) 187–194.
[8] M. Feinberg, Lectures on chemical reaction networks, Unpublished lectures given at the Mathematics Research Center, University of Wisconsin (1979).
[9] R. Gould, *Graph Theory* (Benjamin/Cummings, 1988).
[10] F. Horn, Necessary and sufficient conditions for complex balancing in chemical kinetics, Arch. Rational Mech. Anal. 49 (1972) 172–186.
[11] F. Horn and R. Jackson, General mass action kinetics, Arch. Rational Mech. Anal. 47 (1972) 187–194.
[12] L.A. Moran and K.G. Scrimgeour, *Biochemistry*, 2nd edition (Patterson, 1994).
[13] L. Perko, *Differential Equations and Dynamical Systems* (Springer-Verlag, 1993).
[14] D. Siegel and Y.F. Chen, Global stability of deficiency zero chemical networks, Canad. Appl. Math. Quart. 2(3) (1994) 413–434.
[15] V.M. Vasil'ev, A.I. Vol'pert and S.I. Khudyaev, A method of quasi-stationary concentrations for the equations of chemical kinetics, Comput. Math. Math. Phys. 13(3) (1974) 187–206.
[16] A.I. Vol'pert, Differential equations on graphs, Math. USSR–Sb. 17(4) (1972) 571–582.
[17] A.I. Vol'pert and S.I. Hudjaev, *Analysis in Classes of Discontinuous Functions and Equations of Mathematical Physics* (Nijhoff, Dordrecht, 1985) chapter 12.