LYAPUNOV FUNCTIONS FOR THE STABILITY OF A CLASS OF CHEMICAL REACTION NETWORKS*

MUHAMMAD ALI AL-RADHAWI† AND DAVID ANGELI‡

Abstract. A class of Lyapunov functions is introduced for reaction networks satisfying simple graphical conditions. The Lyapunov functions piecewise linear and convex in terms of the reaction rates. The existence of such functions ensures the convergence of trajectories toward the equilibria, and guarantee the asymptotic stability of the equilibria with respect to their stoichiometric compatibility class. Examples are provided, and future directions are elaborated.

Key words. Reaction Network Dynamics, Lyapunov Functions, Asymptotic Stability.

AMS subject classifications. 37C75, 93D20, 92C42

1. Introduction.

The study of the qualitative behavior of chemical reaction networks is an area of growing interest, especially in the light of the recent challenges posed by molecular and systems biology. One of the main goals of molecular systems biology is the understanding of cell behavior and function at the level of chemical interactions, and, in particular, the characterization of qualitative features of dynamical behavior (stability, periodic orbits, chaos, etc.).

However, a major difficulty in the field of systems biology is the very large degree of uncertainty inherent in models of cellular biochemical networks. Thus, it is imperative to develop tools that are "robust" in the sense of being able to provide useful conclusions based only upon information regarding the qualitative features of the network, and not the precise values of parameters or even the specific form of reaction kinetics. Of course, this goal is often unachievable, since dynamical behavior may be subject to phase transitions (bifurcation phenomena) which are critically dependent on parameter values.

Nevertheless, and surprisingly, research by many [6], [4], [2], has resulted in the identification of classes of chemical reaction networks for which it is possible to check important dynamical properties such as stability, monotonicity, persistence, etc based on structural information only, and regardless of the parameters involved. In this work, we follow this line of research by proving stability of a wide class of chemical reaction networks.

Earlier work regarding asymptotic stability has concentrated on weakly reversible mass-action networks with deficiency zero [6]. It was shown that for this class of networks there exists a unique equilibrium in the interior of each class, which is locally asymptotically stable. This theorem is remarkable since asymptotic stability was established independently of the constants involved. It was shown later that if there are no equilibria on the boundary of the class, then global asymptotic stability of the interior equilibrium holds [11]. However, the question of global asymptotic stability remains open in general (this is the so called global attractor conjecture [5]).

*This work was supported by Leverhulme Trust under award titled "Structural conditions for oscillation in chemical reaction networks".

†Department of Electrical and Electronic Engineering, Imperial College London, London SW7 2BT, United Kingdom. Email: m.rizvi11@imperial.ac.uk

‡Department of Electrical and Electronic Engineering, Imperial College London, London SW7 2BT, United Kingdom. Also, with Dipartimento Sistemi e Informatica, University of Florence, 50139 Florence, Italy. Email: d.angeli@imperial.ac.uk.

Another approach for CRN stability is based on the notion of monotone systems [3, 2]. Once monotonicity is established, convergence theorems for monotone systems can be applied.

In this work, a more elementary approach is discussed, where Lyapunov functions are established for a certain class of CRNs prescribed by some graphical conditions. The Lyapunov functions are piecewise linear in terms of the reaction rates.

The paper is organized as follows. In Section 2, we present the main definitions and assumptions used in the paper. The main theorem and an extension are presented in Section 3. In Section 4, we present some examples, and Section 5 contains the conclusion. The proofs are presented in the Appendix.

2. Background on Chemical Reaction Networks. A Chemical Reaction Network (CRN) is defined by a set of species $\mathscr{S} = \{S_1, .., S_n\}$, and set of reactions $\mathscr{R} = \{\mathrm{R}_1, ..., \mathrm{R}_r\}$. Each chemical reaction is denoted as:

$$\mathrm{R}_i: \quad \sum_{j=1}^{n} \alpha_{ij} S_j \longrightarrow \sum_{j=1}^{n} \beta_{ij} S_j, \ i = 1, ..r, \tag{2.1}$$

where α_{ij}, β_{ij} are nonnegative integers called *stoichiometry coefficients*. The expression on the left-hand side is called the *reactant complex*, while the one on the right-hand side is called the *product complex*. The forward arrow refers to the idea that the transformation of reactant into product is only occurring in the direction of the arrow. If the transformation is occurring also in the opposite direction, the reaction is said to be *reversible* and it is listed as a separate reaction. For convenience, the reverse reaction of R_i is denoted as R_{-i}. Note that we allow reactant or product complex to be empty, though not simultaneously. This is used to model external inflows and outflows of the CRN. In this formulation, we do not allow autocatalytic reactions, that is reactions R_i with $\alpha_{ij} \cdot \beta_{ij} > 0$ for some species S_j.

A nonnegative concentration x_j is associated to each species S_j. Each chemical reaction R_i takes place continuously in time at a reaction rate $R_i(x_1, .., x_n) : \bar{\mathbb{R}}_+^n \to \bar{\mathbb{R}}_+$. We assume that the reaction rate satisfies the following:

1. it is a $\mathscr{C}^1$ function, i.e. continuously differentiable;
2. $x_j = 0 \Rightarrow R_i(x) = 0$, for all i such that $\alpha_{ij} > 0$;
3. it is nondecreasing with respect to its reactants, i.e

$$\frac{\partial R_i(x)}{\partial x_j} \begin{cases} \geq 0 & : \alpha_{ij} > 0 \\ = 0 & : \alpha_{ij} = 0 \end{cases}. \tag{2.2}$$

4. The inequality in (2.2) holds strictly for all $x \in \mathbb{R}_+^n$.

In addition, we sometimes require that the following holds:

5. $\forall\, x \in \mathbb{R}_+^n \ \alpha_{ij} > 0 \Rightarrow \lim_{x_j \to \infty} R_i(x) = \infty$.

A widely-used expression for the reaction rate function is the *Mass-Action kinetic* which is given by the formula:

$$R_i(x) = k_i \prod_{j=1}^{n} x_j^{\alpha_{ij}}, \tag{2.3}$$

where we used the convention $0^0 = 1$. The stoichiometry coefficients are arranged in an $n \times r$ matrix Γ called the *stoichiometry matrix*, which is defined elementwise as:

$$[\Gamma]_{ij} = \beta_{ji} - \alpha_{ji}. \tag{2.4}$$

Therefore, the dynamics of a CRN with n species and r reactions are described by a system of ordinary differential equations (ODEs) as:

$$\dot{x}(t) = \Gamma R(x(t)),\ x(0) \in \bar{\mathbb{R}}^n_+ \tag{2.5}$$

where $x(t)$ is the concentration vector evolving in the nonnegative orthant $\bar{\mathbb{R}}^n_+$, $\Gamma \in \mathbb{R}^{n\times r}$ is the stoichiometry matrix, $R(x(t)) \in \bar{\mathbb{R}}^r_+$ is the reaction rates vector.

Note that system (2.5) belongs to the class of *nonnegative systems*, i.e $\bar{\mathbb{R}}^n_+$ is forward invariant. In addition, the manifold $(\{x(0)\}+\mathrm{Im}(\Gamma))\cap\bar{\mathbb{R}}^n_+$ is forward invariant, and it is called *the positive stoichiometric compatibility class* associated with $x(0)$.

A CRN can be represented via a bipartite weighted directed graph given by the quadruple (V_S, V_R, E, W), where V_S is a set of nodes associated with species, and V_R is associated with reactions. The set of all nodes is denoted by $V = V_S \cup V_R$.
The edge set $E \subset V \times V$ is defined as follows. Whenever a certain reaction R_i belongs to the CRN:

$$\sum_{j=1}^{n} \alpha_{ij} S_j \longrightarrow \sum_{j=1}^{n} \beta_{ij} S_j,$$

we draw an edge from $S_j \in V_S$ to $\mathrm{R}_i \in V_R$ for all S_j's such that $\alpha_{ij} > 0$. That is, $(S_j, \mathrm{R}_i) \in E$ iff $\alpha_{ij} > 0$, and we say in this case that R_i is an *output reaction* for S_j. Similarly, we draw an edge from $\mathrm{R}_i \in V_R$ to every $S_j \in V_S$ such that $\beta_{ij} > 0$. That is, $(\mathrm{R}_i, S_j) \in E$ whenever $\beta_{ij} > 0$, and we say in this case that R_i is an *input reaction* for S_j.
A reaction R_i is called an *ancestor* of R_j if there exists a directed sequence of edges $(\mathrm{R}_i, S_{k_1}), (S_{k_1}, \mathrm{R}_{k_1}), .., (S_{k_n}, \mathrm{R}_j)$ connecting them. The set of ancestors of R_i is denoted $\mathscr{A}(\mathrm{R}_i)$.
Notice that there can not be edges connecting two reactions or two species. Finally, $W : E \to \mathbb{N}$ is the weight function which associate to each edge a positive integer as:

$$W(S_j, \mathrm{R}_i) = \alpha_{ij}, \text{ and } W(\mathrm{R}_i, S_i) = \beta_{ij}.$$

Therefore, the stoichiometry matrix Γ becomes the *incidence matrix* of the graph.

3. The Lyapunov Function.

3.1. The Main Result. Our main result is stated in this section. The proof is provided in the appendix.

THEOREM 3.1. *Given a CRN $(\mathscr{S}, \mathscr{R})$ with the associated SR-graph (V_S, V_R, E, W). Assume:*

1. *$\exists v \in \ker\Gamma$ such that $v \gg 0$, where "$\gg$" denotes entry-wise positivity,*
2. *$\forall S_i \in V_S$, there exists a unique output reaction,*
3. *$\dim(\ker\Gamma) = 1$, and*
4. *$\mathscr{A}(\mathrm{R}_i) \cap \mathscr{A}(\mathrm{R}_j) \neq \emptyset$, for all $1 \le i, j \le r$.*

Let (2.5) be the corresponding ODE with initial condition $x(0) \in \mathbb{R}^n_+$, and let $\mathscr{C}_{x_0} = (\{x(0)\}+Im(\Gamma))\cap\bar{\mathbb{R}}^n_+$ be the associated stoichiometric compatibility class. Let $E \subset \mathscr{C}_{x_0}$ be the set of equilibria for (2.5), then if $x(t)$ is bounded, $x(t) \to E$ as $t \to \infty$ (meaning that the point to set distance of $x(t)$ to E tends to 0). Furthermore, if the equilibria are isolated, then each one of them is asymptotically stable relative to $\mathscr{C}_{x_0}$.

REMARK 1. *The proof of the theorem makes use of the following Lyapunov function:*

$$V(x) = \max_{1\le i\le r} \frac{1}{q_i} R_i(x) - \min_{1\le i\le r} \frac{1}{q_i} R_i(x), \tag{3.1}$$

where $v = [q_1 \ .. \ q_n]^T \in \ker \Gamma \cap \mathbb{R}^+_n$. *Notice that* V *is piecewise linear and convex in terms of the reaction rates. We are currently investigating networks which admit more general piecewise-linear and convex in rates Lyapunov functions.*

REMARK 2. *Assumption 3 in Theorem 1 does not follow from the Assumptions 1,2. For example, the following CRN has a two-dimensional kernel:*

$$\begin{aligned} X_1 &\longrightarrow X_2 \longrightarrow X_1 + X_3, \\ 2X_3 &\longrightarrow 0 \longrightarrow X_3. \end{aligned} \tag{3.2}$$

Furthermore, Assumption 4 does not follow from the previous assumptions. For instance, consider the CRN

$$\begin{aligned} X_1 + X_2 &\longrightarrow 0 \longrightarrow X_1, \\ 0 &\longrightarrow X_2, \end{aligned} \tag{3.3}$$

where $\mathscr{A}(\mathrm{R}_2) \cap \mathscr{A}(\mathrm{R}_3) = \emptyset$.

REMARK 3. *The boundedness of solutions can be guaranteed, for instance, by a having a strictly positive conservation law, i.e some vector* $w \in \mathbb{R}^n_+$ *such that* $w^T\Gamma = 0$, *or by verifying the persistence of the network via known methods [1], combined with assumption 5 in §2 (in this latter case boundedness of reaction rates guarantees boundedness of all reactants).*

REMARK 4. *If stoichiometry classes are compact and contain only isolated equilibria, then there is a unique asymptotically stable equilibrium in each stoichiometric compatibility class. This follows by the Poicaré-Hopf Theorem, and by the fact that the index of an isolated asymptotically stable equilibrium equals one [9, p. 340].*

3.2. Extension to Reversible Reactions. Theorem 1 can be extended to allow the addition of the reverse of certain reactions. Note that adding the reverse of an irreversible reaction increases the dimension of the kernel of Γ so that the original result would not normally apply.

THEOREM 3.2. *Given a CRN* $(\mathscr{S}, \mathscr{R})$ *with the associated graph* (V_S, V_R, E, W) *that satisfies the conditions of Theorem 3.1. Let* $V_{R'} \subset V_R$ *be the set of reactions* R_i *that satisfy: if* $(\mathrm{R}_i, S_j) \in E$ *and* $(\mathrm{R}_k, S_j) \in E$ *then* $i = k$, *i.e the set of reactions* R_i *that are the only input reaction for all of its product species. Let* $(\mathscr{S}, \tilde{\mathscr{R}})$ *be the CRN constructed by adding reverse reactions for reactions belonging to* $V_{R'}$.
Let (2.5) *be the corresponding ODE with initial condition* $x(0) \in \mathbb{R}^n_+$, *and let* $\mathscr{C}_{x_0} = (\{x(0)\} + Im(\Gamma)) \cap \bar{\mathbb{R}}^n_+$ *be the associated stoichiometric compatibility class. Let* $E \subset \mathscr{C}_{x_0}$ *be the set of equilibria for* (2.5), *then if* $x(t)$ *is bounded,* $x(t) \to E$ *as* $t \to \infty$ *(meaning that the point to set distance of* $x(t)$ *to* E *tends to* 0*). Furthermore, if the equilibria are isolated, then each one of them is asymptotically stable relative to* $\mathscr{C}_{x_0}$.

REMARK 5. *Theorem 3.2 uses the following Lyapunov function:*

$$V(x) = \max_{1 \le i \le r} \frac{1}{q_i}(R_i(x) - R_{-i}(x)) - \min_{1 \le i \le r} \frac{1}{q_i}(R_i(x) - R_{-i}(x)). \tag{3.4}$$

4. Examples. The following CRNs are examples for which Theorem 3.1 is applicable,

$$\begin{aligned} X_1 &\longrightarrow X_2, \\ 2X_2 &\longrightarrow X_1 + X_3, \\ X_3 &\longrightarrow X_2, \end{aligned} \tag{4.1}$$

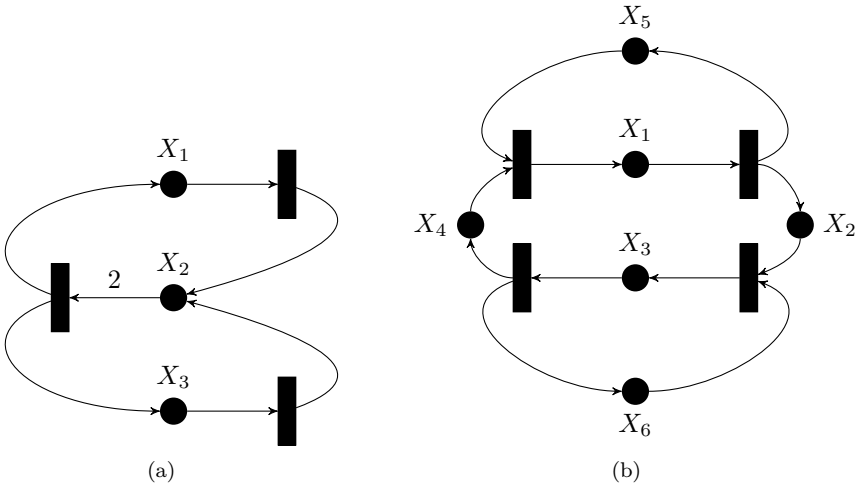

FIG. 4.1. *Examples where Theorem 1 is applicable.*

and

$$\begin{aligned} X_4 + X_5 &\longrightarrow X_1 \longrightarrow X_2 + X_5, \\ X_2 + X_6 &\longrightarrow X_3 \longrightarrow X_4 + X_6, \end{aligned} \tag{4.2}$$

where in both cases $q_i = 1, i = 1, .., r$ in (3.1). Figure 4.1(a,b) shows the associated graphs for them, respectively.
Note that both networks have deficiency one so stability can not be deduced via the methodology of [6]. Also, results of [2] can not be applied for the first network since X_2 has two input reactions. Nevertheless, by deficiency one theory [7], it can be shown that there is a unique equilibrium in each invariant manifold for both networks. Hence, by Theorem 3.1, the unique equilibrium is asymptotically stable relative to its invariant manifold.

Furthermore, Theorem 3.2 can be used to prove the asymptotic stability of the following network:

$$\begin{aligned} X_1 &\longrightarrow X_2, \\ 2X_2 &\longleftrightarrow X_1 + X_3, \\ X_3 &\longrightarrow X_2, \end{aligned}$$

where the reverse of the second reaction in (4.1) has been added, however, the theorem does not guarantee the existence of Lyapunov function if the reverse of the other two reactions are added. In contrast, the reverse of any of the reactions in the network (4.2) can be added to it.

5. Conclusion. In this paper, a new class of Lyapunov functions have been introduced for a wide class of CRNs satisfying simple graphical conditions. The Lyapunov functions are of simple structure, namely, they are piecewise linear and convex in terms of the reaction rates. The existence of such functions ensures the convergence of trajectories toward the equilibria, and guarantee the asymptotic stability of the equilibria with respect to their stoichiometric compatibility class.

For future work, the authors are currently working to characterize the class of CRNs that admit a piecewise linear in rates Lyapunov function, and algorithms to construct them.

Appendix: Proofs. *Proof of Theorem 1:* Define the functions, $M, m : \mathbb{R}^r_+ \to \mathbb{R}$, as follows:

$$M(R) = \max_{1\leq i\leq r} \frac{1}{q_i} R_i, \qquad m(R) = \min_{1\leq i\leq r} \frac{1}{q_i} R_i.$$

We let

$$\overline{R}(x) = M(R(x)), \qquad \underline{R}(x) = m(R(x)),$$

and introduce the candidate Lyapunov function:

$$V(x) = \overline{R}(x) - \underline{R}(x).$$

Notice that, by definition, $V(x) \geq 0$. Moreover, V is convex and piecewise linear in reaction rates.
We need to show that $V(x) = 0$ if and only if x is an equilibrium. Indeed, $V(x) = 0$ iff $\frac{1}{q_1} R_1(x) = \cdots = \frac{1}{q_r} R_r(x)$, which, by assumptions 1 and 3, is equivalent to $R(x) \in \ker \Gamma$. The last statement is equivalent to x being an equilibrium.

To show that $V(x)$ is nonincreasing along the system trajectories, we proceed by showing that both $\overline{R}(x(t))$ and $\underline{R}(x(t))$ are monotone functions of time. Taking Dini derivatives along solutions of (2.5) yields

$$\begin{aligned} D^+\overline{R}(x(t)) &:= \limsup_{h\to 0} \frac{\overline{R}(x(t+h)) - \overline{R}(x(t))}{h} = \limsup_{h\to 0} \frac{M(R(x(t+h))) - M(R(x(t)))}{h} \\ &= \limsup_{h\to 0} \frac{M(R(x(t)) + h\dot{R}(x(t)))) - M(R(x(t)))}{h}, \end{aligned} \tag{5.1}$$

where the last equality follows from Taylor's expansion and considering that $M(R)$ is a Lipschitz function. Similarly for $\underline{R}(x(t))$ we see that:

$$\begin{aligned} D^-\underline{R}(x(t)) &:= \liminf_{h\to 0} \frac{\underline{R}(x(t+h)) - \underline{R}(x(t))}{h} \\ &= \liminf_{h\to 0} \frac{m(R(x(t)) + h\dot{R}(x(t)))) - m(R(x(t)))}{h}. \end{aligned} \tag{5.2}$$

Let $I_x = \{i : \frac{1}{q_i} R_i(x) = \overline{R}(x)\}$, $J_x = \{j : \frac{1}{q_j} R_j(x) = \underline{R}(x)\}$. Define $\dot{\overline{R}}(x(t)) := \max_{i\in I_x} \frac{1}{q_i} \dot{R}_i(x(t))$, and $\dot{\underline{R}}(x(t)) := \min_{i\in J_x} \dot{R}_i(x(t))$. Also, $i^\star(x) := \arg\max_{i\in I_x} \dot{R}_i(x)$ [1], and $j^\star(x) := \arg\min_{j\in J_x} \frac{1}{q_j} \dot{R}_j(x)$. Now, it follows from (5.1) and (5.2) that, $D^+\overline{R}(x(t)) = \dot{\overline{R}}(x(t))$ and $D^-\underline{R}(x(t)) = \dot{\underline{R}}(x(t))$ and therefore $D^+V(x(t)) \leq \dot{\overline{R}}(x(t)) -$

[1] If it is not unique, we choose arbitrary one.

$\dot{\underline{R}}(x(t))$. Moreover, by assumption 2, we can perform the following computation:

$$\begin{aligned}
\dot{\overline{R}}(x) &= \frac{1}{q_{i^\star(x)}} \frac{\partial R_{i^\star(x)}}{\partial x} \Gamma R(x) \\
&= \frac{1}{q_{i^\star(x)}} \sum_{\ell:\alpha_{i^\star(x)\ell}>0} \frac{\partial R_{i^\star(x)}}{\partial x_\ell} \left(-\alpha_{i^\star(x)\ell} R_{i^\star(x)}(x) + \sum_{i \neq i^\star(x)} \beta_{i\ell} R_i(x) \right) \\
\dot{\underline{R}}(x) &= \frac{1}{q_{j^\star(x)}} \frac{\partial R_{j^\star(x)}}{\partial x} \Gamma R(x) \\
&= \frac{1}{q_{j^\star(x)}} \sum_{\ell:\alpha_{j^\star(x)\ell}>0} \frac{\partial R_{j^\star(x)}}{\partial x_\ell} \left(-\alpha_{j^\star(x)\ell} R_{j^\star(x)}(x) + \sum_{i \neq j^\star(x)} \beta_{i\ell} R_i(x) \right) \qquad (5.3)
\end{aligned}$$

Since $v \in \ker \Gamma$, then $-\alpha_{i^\star \ell} = \sum_{i \neq i^\star} \frac{q_{i^\star}}{q_i} \beta_{i\ell}$. Hence,

$$-\alpha_{i^\star \ell} R_{i^\star}(x) + \sum_{i \neq i^\star} \beta_{i\ell} R_i(x) \leq \sum_{i \neq i^\star} \frac{q_{i^\star}}{q_i} \beta_{i\ell} R_{i^\star}(x) + \sum_{i \neq i^\star} \beta_{i\ell} \frac{q_i}{q_{i^\star}} R_{i^\star}(x) = 0.$$

By a similar argument for the second term and by (2.2) we get $\dot{\overline{R}}(x) \leq 0$ and $\dot{\underline{R}}(x) \geq 0$ and as a consequence $D^+V(x(t)) \leq 0$, which implies that V is nonincreasing along the system trajectories [8, §41].

By assumption the solution $x(t)$ is bounded, so the ω-limit set $\omega(x(0))$ is non-empty and compact. Moreover, by monotonicity of $\overline{R}(x(t))$ and $\underline{R}(x(t))$ it is contained in the intersection of two level sets of $\overline{R}$ and $\underline{R}$. We use the Krasovskii-LaSalle principle [8, §55] to show convergence to equilibria.

Let $\tilde{x}(t)$ denote any solution of (2.5) which is contained in $\omega(x(0))$. By finiteness of the set of reactions, there exists $i^\star$ and $j^\star$ and an open subset of $\mathbb{R}$, $\mathcal{T}$,[2] such that $\frac{1}{q_{i^\star}} R_{i^\star}(\tilde{x}(t)) = \overline{R}(\tilde{x}(t))$ and $\frac{1}{q_{j^\star}} R_{j^\star}(\tilde{x}(t)) = \underline{R}(\tilde{x}(t))$ for all $t \in \mathcal{T}$. As $\overline{R}(\tilde{x}(t))$ and $\underline{R}(\tilde{x}(t))$ are constant, by (5.3) and assumption 4 in §2 we get $\dot{\tilde{x}}_\ell(t) = 0$ for all ℓ such that $\alpha_{i^\star \ell} > 0$, $\alpha_{j^\star \ell} > 0$ and all $t \in \mathcal{T}$. Therefore, $\alpha_{i^\star \ell} R_{i^\star}(\tilde{x}) = \sum_{i \neq i^\star} \beta_{i\ell} R_i(\tilde{x})$, and since $\frac{1}{q_i} R_i(\tilde{x}(t)) \leq \frac{1}{q_{i^\star}} R_{i^\star}(\tilde{x}(t))$, then $\frac{1}{q_{i^\star}} R_i(\tilde{x}(t)) = \overline{R}(\tilde{x}(t))$ for all i such that there is ℓ with $\beta_{i\ell} > 0$, $\alpha_{i^\star \ell} > 0$ and all $t \in \mathcal{T}$. A similar argument can be carried out for $\underline{R}(\tilde{x}(t))$. By induction, it follows that $\frac{1}{q_{i^\star}} R_i(\tilde{x}(t)) = \overline{R}(\tilde{x}(t))$ if $\mathrm{R}_i \in \mathscr{A}(\mathrm{R}_{i^\star})$ for $t \in \mathcal{T}$. Similarly, $\frac{1}{q_{j^\star}} R_j(\tilde{x}(t)) = \underline{R}(\tilde{x}(t))$ if $\mathrm{R}_j \in \mathscr{A}(\mathrm{R}_{j^\star})$. Since $\mathscr{A}(\mathrm{R}_{i^\star}) \cap \mathscr{A}(\mathrm{R}_{j^\star}) \neq \phi$, we get $\overline{R}(\tilde{x}(t)) = \underline{R}(\tilde{x}(t))$ for all $t \in \mathcal{T}$ and since $\mathcal{T}$ is an open set this implies that $\tilde{x}(t) \in E$. In particular $\omega(x(0)) \subset E$. ■

Proof of Theorem 3.2: Define the functions, $M, m : \mathbb{R}^r_+ \to \mathbb{R}$, as follows:

$$M(R) = \max_{1 \leq i \leq r} \frac{1}{q_i} (R_i(x) - R_{-i}(x)), \qquad m(R) = \min_{1 \leq i \leq r} \frac{1}{q_i} (R_i(x) - R_{-i}(x)),$$

where $R_{-i}(x) \equiv 0$ if $\mathrm{R}_{-i} \notin \tilde{\mathscr{R}}$. The definitions of $\overline{R}, \underline{R}, V$ are identical to the ones in the proof of Theorem 1.
Note the $V(x) \geq 0$. Furthermore, it can be shown easily that $\{x | V(x) = 0\} =$

[2] Let $\mathcal{T}_i = \{t | \overline{R}(\tilde{x}(t)) = R_i(\tilde{x}(t))\}$, $i = 1, .., r$, then $\mathcal{T}_i$ are closed and $\bigcup_i \mathcal{T}_i = \mathbb{R}$. The existence of an open set $\mathcal{T}$ and $i^\star$ follows by the Baire Category Theorem [10].

$\{x|R(x) \in \ker \Gamma\}$ = the set of equilibria of (2.5).

The definitions of $\dot{\overline{R}}(x), \underline{\dot{R}}(x), i^\star(x), j^\star(x)$ are analogous to corresponding one in the proof of Theorem 1. Hence,

$$\dot{\overline{R}}(x) = \frac{1}{q_{i^\star}} \sum_{\ell:\alpha_{i^\star\ell}>0} \frac{\partial R_{i^\star}}{\partial x_\ell} \left(-\alpha_{i^\star\ell}(R_{i^\star}(x) - R_{-i^\star}(x)) + \sum_{i\neq i^\star} \beta_{i\ell}(R_i(x) - R_{-i}(x)) \right)$$
$$- \frac{1}{q_{i^\star}} \sum_{\ell:\beta_{i^\star\ell}>0} \frac{\partial R_{-i^\star}}{\partial x_\ell} \left(-\beta_{i^\star\ell}(R_{-i^\star}(x) - R_{i^\star}(x)) + \sum_{i\neq i^\star} \alpha_{i\ell}(R_{-i}(x) - R_i(x)) \right),$$

$$\underline{\dot{R}}(x) = \frac{1}{q_{j^\star}} \sum_{\ell:\beta_{j^\star\ell}>0} \frac{\partial R_{j^\star}}{\partial x_\ell} \left(-\beta_{j^\star\ell}(R_{j^\star}(x) - R_{-j^\star}(x)) + \sum_{j\neq j^\star} \alpha_{j\ell}(R_i(x) - R_{-i}(x)) \right)$$
$$- \frac{1}{q_{j^\star}} \sum_{\ell:\alpha_{j^\star\ell}>0} \frac{\partial R_{-j^\star}}{\partial x_\ell} \left(-\alpha_{j^\star\ell}(R_{-j^\star}(x) - R_{j^\star}(x)) + \sum_{j\neq j^\star} \beta_{j\ell}(R_{-i}(x) - R_i(x)) \right),$$

where having a single negative coefficient in every bracket follows from the additional assumption in the statement of the theorem.

Therefore, using a similar argument to the one in the proof of Theorem 1 it can be seen that $\dot{\overline{R}}(x) \leq 0$. Similarly, $\underline{\dot{R}}(x) \geq 0$ and $D^+V(x(t)) \leq 0$.

By assumption the solution $x(t)$ is bounded, so the ω-limit set $\omega(x(0))$ is non-empty and compact. Moreover, by nondeacresingness of $\overline{R}(x(t))$ and $\underline{R}(x(t))$ it is contained in the intersection of two level sets of $\overline{R}$ and $\underline{R}$.

A similar argument to the one in proof of Theorem 1 can be carried out to to show convergence to equilibria via the Krasovskii-LaSalle principle. The details are omitted to avoid repetition.

REFERENCES

[1] D. Angeli, P. De Leenheer, and E. Sontag, *A petri net approach to persistence analysis in chemical reaction networks*, in Biology and Control Theory: Current Challenges, I. Queinnec, S. Tarbouriech, G. Garcia, and S.I. Niculescu, eds., Springer, 2007, pp. 181–216.

[2] ———, *Graph-theoretic characterizations of monotonicity of chemical networks in reaction coordinates*, Journal of mathematical biology, 61 (2010), pp. 581–616.

[3] D. Angeli and E.D. Sontag, *Translation-invariant monotone systems, and a global convergence result for enzymatic futile cycles*, Nonlinear Analysis: Real World Applications, 9 (2008), pp. 128–140.

[4] B.L Clarke, *Stability of complex reaction networks*, in Advances in Chemical Physics, Volume 43, I. Prigogine and S.A Rice, eds., John Wiley & Sons, 1980, pp. 1–215.

[5] G. Craciun, A. Dickenstein, A. Shiu, and B. Sturmfels, *Toric dynamical systems*, Journal of Symbolic Computation, 44 (2009), pp. 1551–1565.

[6] M. Feinberg, *Chemical reaction network structure and the stability of complex isothermal reactors–I. the deficiency zero and deficiency one theorems*, Chemical Engineering Science, 42 (1987), pp. 2229–2268.

[7] ———, *Chemical reaction network structure and the stability of complex isothermal reactors–II. multiple steady states for networks of deficiency one*, Chemical engineering science, 43 (1988), pp. 1–25.

[8] W. Hahn, *Stability of motion*, Springer-Verlag, New York, 1967.

[9] M.A Krasnosel'skiĭ and P.P. Zabreĭko, *Geometrical methods of nonlinear analysis*, Springer-Verlag, 1984.

[10] H.L Royden, *Real Analysis*, Prentice Hall, 3rd ed., 1988.

[11] E.D. Sontag, *Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction*, IEEE Transactions on Automatic Control, 46 (2001), pp. 1028–1047.