

Boundedness of trajectories for weakly reversible, single linkage class reaction systems

David F. Anderson¹

June 16, 2011

Abstract

This paper is concerned with the dynamical properties of deterministically modeled chemical reaction systems with mass-action kinetics. Such models are ubiquitously found in chemistry, population biology, and the burgeoning field of systems biology. A basic question, whose answer remains largely unknown, is the following: for which network structures do trajectories of mass-action systems remain bounded in time? In this paper, we conjecture that the result holds when the reaction network is weakly reversible, and prove this conjecture in the case when the reaction network consists of a single linkage class, or connected component.

1 Introduction

Building off the work of Fritz Horn, Roy Jackson, and Martin Feinberg [8, 9, 10, 12, 13, 14] the mathematical theory termed “Chemical Reaction Network Theory” has, over the past 40 years, determined many of the basic qualitative properties of chemical reaction networks and, more generally, models of population processes. As the exact values of key system parameters, termed *rate constants* and which we will denote by κ_k , are usually difficult to find experimentally and, hence, are oftentimes unknown, the results tend to be *independent of the values of these parameters*. In large part

¹Department of Mathematics, University of Wisconsin, Madison, WI, 53706. Grant support from NSF grant DMS-1009275

motivated by the Global Attractor Conjecture [6], much of the recent attention in this field has focussed on which network structures guarantee that trajectories are *persistent*, in that they can not approach the boundary of the positive orthant along a sequence of times [1, 2, 3, 4, 6, 7, 15, 16, 17]. In this paper we consider a related question: for which network structures do trajectories of mass-action systems necessarily remain *bounded* in time? This question is similar to that of persistence in that both force us to consider extreme behaviors of the species, and, hence, the monomials of the dynamical system. Similar to the well known Persistence Conjecture (see below), we will conjecture that all trajectories of weakly reversible systems with mass-action kinetics are bounded in time. We will prove this conjecture in the case when the reaction network consists of a single linkage class, or connected component. The methods used in this paper are similar to those introduced in [1], where the Global Attractor Conjecture was shown to hold in the single linkage class case.

1.1 Formal statement of the problem

Two of the most basic questions that can be asked about a mathematical model for a chemical, or more generally a population, process are (i) must all trajectories be bounded in time and (ii) are trajectories persistent in the sense of Definition 1.1 below.

Definition 1.1. For $t \geq 0$ denoting time, let $\phi(t, x_0)$ be a trajectory to a dynamical system in \mathbb{R}^N with initial condition x_0 . A trajectory $\phi(t, x_0)$ with state space $\mathbb{R}_{\geq 0}^N$ is said to be persistent if

$$\liminf_{t \rightarrow \infty} \phi_i(t, x_0) > 0,$$

for all $i \in \{1, \dots, N\}$, where $\phi_i(t, x_0)$ denotes the i th component of $\phi(t, x_0)$. A dynamical system is said to be persistent if each trajectory with non-negative initial condition is persistent.

Thus, persistence corresponds to a non-extinction requirement. Some authors refer to dynamical systems satisfying the above condition as *strongly persistent* [20]. In their work, persistence only requires the weaker condition that $\limsup_{t \rightarrow \infty} \phi_i(t, x_0) > 0$ for each $i \in \{1, \dots, N\}$.

The following conjecture of Feinberg (see Remark 6.1.E in [9]) is one of the most well known in chemical reaction network theory. It pertains to systems

whose reaction networks are weakly reversible, or strongly connected (see Section 2), and is intimately related to the Global Attractor Conjecture [6].

Persistence Conjecture. (Version 1) Any weakly reversible reaction network with mass-action kinetics is persistent.

In [1], it was pointed out that there are really two natural conjectures pertaining to weakly reversible reaction networks with mass-action kinetics, and that these should be separated.

Definition 1.2. For $t \geq 0$ denoting time, let $\phi(t, x_0)$ be a trajectory to a dynamical system in \mathbb{R}^N with initial condition x_0 . A trajectory $\phi(t, x_0)$ is said to be bounded if

$$\limsup_{t \rightarrow \infty} |\phi(t, x_0)| < \infty.$$

A dynamical system is said to have bounded trajectories if each trajectory is bounded.

Persistence Conjecture. (Version 2) Any weakly reversible reaction network with mass-action kinetics and *bounded trajectories* is persistent.

Boundedness Conjecture. Any weakly reversible reaction network with mass-action kinetics has bounded trajectories.

Clearly, the latter two conjectures would imply the first, which would then imply the well known Global Attractor Conjecture (see [6, 9]). Note that none of the conjectures make any assumptions on the choice of rate constants, which are the natural parameters found in these systems (see Section 2). The Boundedness Conjecture stated above is quite similar to the Extended Permanence Conjecture found in [7], which conjectures that all “endotactic” systems (which include those that are weakly reversible) are *permanent*. Permanence is an even stronger condition than bounded trajectories in that all trajectories of a compatibility class (invariant manifold), regardless of initial condition, must enter a single compact subset of $\mathbb{R}_{>0}^N$. The Extended Permanence Conjecture is proven in [7] in the case when the system is two-dimensional. In Section 3.2 we briefly discuss permanence and conclude that weakly reversible, single linkage class systems are permanent if there is a $\delta > 0$ for which $\liminf_{t \rightarrow \infty} \phi_i(t, x_0) \geq \delta$ for all x_0 and all i . That is, when the system is, in some sense, *uniformly persistent*.

Each of the above mentioned conjectures remains open. In recent years there has been a great amount of energy aimed at resolving the Persistence

Conjecture, and typically that work has focused on Version 2. This focus has been quite natural as much of the motivation for the work stemmed from consideration of “complex-balanced” systems, see [8, 9], which are known to have bounded trajectories. Relatively little attention has been paid, therefore, to the related Boundedness Conjecture, as formally stated above. We will refrain from giving an exhaustive background on the work aimed at resolving the Persistence Conjectures, and instead point the interested reader to [1], where such an introduction, including most of the relevant references related to persistence and the Global Attractor Conjecture, can be found.

1.2 Results in this paper

In this paper we will prove that the Boundedness Conjecture holds for all systems whose network consists of a single linkage class, or connected component (see Section 2). To prove our results, we will use a method, introduced in [1], for partitioning the relevant monomials of the dynamical system along sequences of trajectory points into classes with comparable growths. This will allow us to prove that there is a Lyapunov function which decreases along all paths when $|x(t)|$ is sufficiently large.

We will prove all of our results in a slightly more general setting than mass-action kinetics in that we will allow our rate “constants” to actually be bounded functions of time. Results pertaining to systems with such a generalized mass-action kinetics are useful as these systems arise naturally when a system with standard mass-action kinetics is *projected* onto a subset of the species (see Section 3 of [1]).

The outline of the paper is as follows. In Section 2, we provide a review of the requisite definitions and terminology from chemical reaction network theory. In Section 3, we give our main results together with their proofs.

2 Preliminary concepts and definitions

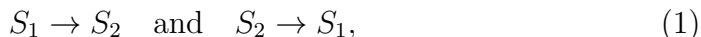
Most of the following definitions are standard in chemical reaction network theory. The interested reader should see [8] or [11] for a more detailed introduction.

Reaction networks. An example of a chemical reaction is $2S_1 + S_2 \rightarrow S_3$, where we interpret the above as saying two molecules of type S_1 combine

with a molecule of type S_2 to produce a molecule of type S_3 . For now, assume that there are no other reactions under consideration. The S_i are called chemical *species* and the linear combinations of the species found at either end of the reaction arrow, namely $2S_1 + S_2$ and S_3 , are called chemical *complexes*. Assigning the *source* (or reactant) complex $2S_1 + S_2$ to the vector $y = (2, 1, 0)$ and the *product* complex S_3 to the vector $y' = (0, 0, 1)$, we can formally write the reaction as $y \rightarrow y'$.

In the general setting we denote the number of species by N , and for $i \in \{1, \dots, N\}$ we denote the i th species as S_i . We then consider a finite set of reactions with the k th denoted by $y_k \rightarrow y'_k$, where $y_k, y'_k \in \mathbb{Z}_{\geq 0}^N$ are (non-equal) vectors whose components give the coefficients of the source and product complexes, respectively. Using a slight abuse of notation, we will also refer to the vectors y_k and y'_k as the complexes. Note that if $y_k = \vec{0}$ or $y'_k = \vec{0}$ for some k , then the k th reaction represents an input or output, respectively, to the system. Note also that any complex may appear as both a source complex and a product complex in the system. We will usually, though not always (for example, see condition 3 in Definition 2.1 below) use the prime ' to denote the product complex of a given reaction.

As an example, suppose that the entire network consists of the two species S_1 and S_2 and the two reactions



where $S_1 \rightarrow S_2$ is arbitrarily labeled as “reaction 1.” Then $N = 2$ and

$$y_1 = (1, 0), \quad y'_1 = (0, 1) \quad \text{and} \quad y_2 = (0, 1), \quad y'_2 = (1, 0).$$

Thus, the vector $(1, 0)$, or equivalently the complex S_1 , is both y_1 , the source of the first reaction, and y'_2 , the product of the second.

For ease of notation, when there is no need for enumeration we will typically drop the subscript k from the notation for the complexes and reactions.

Definition 2.1. Let $\mathcal{S} = \{S_i\}_{i=1}^N$, $\mathcal{C} = \{y\}$ with $y \in \mathbb{Z}_{\geq 0}^N$, and $\mathcal{R} = \{y \rightarrow y'\}$ denote finite sets of species, complexes, and reactions, respectively. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is called a chemical reaction network so long as the following three natural requirements are met:

1. For each $S_i \in \mathcal{S}$, there exists at least one complex $y \in \mathcal{C}$ for which $y_i \geq 1$.

2. There is no trivial reaction $y \rightarrow y \in \mathcal{R}$ for some complex $y \in \mathcal{C}$.
3. For any $y \in \mathcal{C}$, there must exist a $y' \in \mathcal{C}$ for which $y \rightarrow y' \in \mathcal{R}$ or $y' \rightarrow y \in \mathcal{R}$.

Notation: We will use each of the following choices of notation to denote a complex from \mathcal{C} : $y, y', y_i, y_j, y_k, y'_k$, etc. However, there will be other times in which we wish to denote the i th component of a complex. If the complex in question has been denoted by y_k , then we will write $y_{k,i}$. However, if the complex has been denoted by y , then we would write its i th component as y_i , which, through context, should not cause confusion with a choice of *complex* y_i . See, for example, condition 1 in Definition 2.1 above.

Definition 2.2. To each reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ we assign a unique directed graph called a reaction diagram constructed in the following manner. The nodes of the graph are the complexes, \mathcal{C} . A directed edge (y, y') exists if and only if $y \rightarrow y' \in \mathcal{R}$. Each connected component of the resulting graph is termed a linkage class of the graph.

For example, the system described in and around (1) has reaction diagram $S_1 \rightleftharpoons S_2$, which consists of a single linkage class.

Definition 2.3. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ denote a chemical reaction network. Denote the complexes of the i th linkage class by $L_i \subset \mathcal{C}$. We say $T \subset \mathcal{C}$ consists of a union of linkage classes if $T = \cup_{i \in I} L_i$ for some nonempty index set I .

Definition 2.4. The chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is said to be weakly reversible if each linkage class of the corresponding reaction diagram is strongly connected. A network is said to be reversible if $y' \rightarrow y \in \mathcal{R}$ whenever $y \rightarrow y' \in \mathcal{R}$.

It is easy to see that a chemical reaction network is weakly reversible if and only if for each reaction $y \rightarrow y' \in \mathcal{R}$, there exists a sequence of complexes, $y_1, \dots, y_r \in \mathcal{C}$, such that $y' \rightarrow y_1 \in \mathcal{R}, y_1 \rightarrow y_2 \in \mathcal{R}, \dots, y_{r-1} \rightarrow y_r \in \mathcal{R}$, and $y_r \rightarrow y \in \mathcal{R}$.

Dynamics. A chemical reaction network gives rise to a dynamical system by way of a *rate function* for each reaction. That is, for each $y_k \rightarrow y'_k \in \mathcal{R}$, or simply $k \in \{1, \dots, |\mathcal{R}|\}$, we suppose the existence of a function $R_k = R_{y_k \rightarrow y'_k}$

that determines the rate of that reaction. The functions R_k are typically referred to as the *kinetics* of the system and will be denoted by \mathcal{K} , or $\mathcal{K}(t)$ in the non-autonomous case. The dynamics of the system is then given by the following coupled set of (typically nonlinear) ordinary differential equations

$$\dot{x}(t) = \sum_k R_k(x(t), t)(y'_k - y_k), \quad (2)$$

where k enumerates over the reactions and $x(t) \in \mathbb{R}_{\geq 0}^N$ is a vector whose i th component represents the concentration of species S_i at time $t \geq 0$.

Definition 2.5. *A chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ together with a choice of kinetics \mathcal{K} is called a chemical reaction system and is denoted via the quadruple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$. In the non-autonomous case where the R_k can depend explicitly on t , we will write $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$. We say that a chemical reaction system is weakly reversible if its underlying network is.*

Integrating (2) with respect to time yields

$$x(t) = x(0) + \sum_k \left(\int_0^t R_k(x(s), s) ds \right) (y'_k - y_k).$$

Therefore, $x(t) - x(0)$ remains within $S = \text{span}\{y'_k - y_k\}_{k \in \{1, \dots, R\}}$ for all time.

Definition 2.6. *The stoichiometric subspace of a network is the linear space $S = \text{span}\{y'_k - y_k\}_{k \in \{1, \dots, |\mathcal{R}|\}}$. The vectors $y'_k - y_k$ are called the reaction vectors.*

Under mild conditions on the rate functions of a system, a trajectory $x(t)$ with strictly positive initial condition $x(0) \in \mathbb{R}_{> 0}^N$ remains in the strictly positive orthant $\mathbb{R}_{> 0}^N$ for all time (see, for example, Lemma 2.1 of [18]). Thus, the trajectory remains in the relatively open set $(x(0) + S) \cap \mathbb{R}_{> 0}^N$, where $x(0) + S := \{z \in \mathbb{R}^N \mid z = x(0) + v, \text{ for some } v \in S\}$, for all time. In other words, this set is *forward-invariant* with respect to the dynamics. It is also easy to show that under the same mild conditions on R_k , $(x(0) + S) \cap \mathbb{R}_{\geq 0}^N$ is forward invariant with respect to the dynamics. The sets $(x(0) + S) \cap \mathbb{R}_{\geq 0}^N$ will be referred to as the *positive stoichiometric compatibility classes*, or simply as the *positive classes*. Note that if each of the sets $(x(0) + S) \cap \mathbb{R}_{> 0}^N$ is bounded, then all trajectories of the dynamical system are necessarily bounded also.

Therefore, the results of this paper are of interest when each positive class is an unbounded set.

The most common kinetics is that of *mass-action kinetics*. A chemical reaction system is said to have mass-action kinetics if all rate functions $R_k = R_{y_k \rightarrow y'_k}$ take the multiplicative form

$$R_k(x) = \kappa_k x_1^{y_{k,1}} x_2^{y_{k,2}} \cdots x_N^{y_{k,N}}, \quad (3)$$

where κ_k is a positive reaction rate constant and y_k is the source complex for the reaction. For $u \in \mathbb{R}_{\geq 0}^N$ and $v \in \mathbb{R}^N$, we define

$$u^v \stackrel{\text{def}}{=} u_1^{v_1} \cdots u_N^{v_N},$$

where we have adopted the convention that $0^0 = 1$, and the above is undefined if $u_i = 0$ when $v_i < 0$. Mass action kinetics can then be written succinctly as $R_k(x) = \kappa_k x^{y_k}$. Combining (2) and (3) gives the following system of differential equations

$$\dot{x}(t) = \sum_k \kappa_k x(t)^{y_k} (y'_k - y_k). \quad (4)$$

We will generalize the equation (4) slightly by allowing each κ_k to be a bounded function of time. See Definition 2.6 in [7] for a similar definition, and [5] for another recent treatment of chemical reaction systems with non-autonomous dynamics.

Definition 2.7. *We say that the non-autonomous system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$ has bounded mass-action kinetics if there exists an $\eta > 0$ such that for each $k \in \{1, \dots, |\mathcal{R}|\}$*

$$R_k(x, t) = \kappa_k(t) x^{y_k},$$

where $\eta < \kappa_k(t) < 1/\eta$ for all $t \geq 0$. Hence, the vector of concentrations satisfies

$$\dot{x}(t) = \sum_k \kappa_k(t) x(t)^{y_k} (y'_k - y_k).$$

We require some final notation. Let $v \in \mathbb{R}^N$ for some $N \geq 1$, and let $U \subset \{1, \dots, N\}$. We write $U[j]$ for the j th component of U . We then write $v|_U$ to denote the vector of size $|U|$ with

$$v|_{U,j} = (v|_U)_j \stackrel{\text{def}}{=} v_{U[j]}$$

for $j \in \{1, \dots, |U|\}$. Thus, $v|_U$ simply denotes the projection of v onto the components enumerated by U . For example, if $N = 8$ and $U = \{2, 4, 7\}$, then for any $v \in \mathbb{R}^8$, $v|_U = (v_2, v_4, v_7) \in \mathbb{R}^3$.

3 Main results

Recall that for any vectors u, v such that $u \in \mathbb{R}_{\geq 0}^N$ and $v \in \mathbb{R}^N$ we define $u^v \stackrel{\text{def}}{=} u_1^{v_1} \cdots u_N^{v_N}$, where we use the convention $0^0 = 1$. For completeness, we recall the following standard definition.

Definition 3.1. For any set \mathcal{C} , we say $\{T_i\}$ is a partition of \mathcal{C} if each T_i is non-empty, $\bigcup_i T_i = \mathcal{C}$, and for all $i \neq j$, $T_i \cap T_j = \emptyset$.

The following combination of Definition 3.2 and Lemma 3.3 is a generalization of Definition 4.1 and Lemma 4.2 found in [1]. While the generalization is not made use of in the current paper, we hope that pointing out that the function f below can be nearly arbitrary will be beneficial in future work.

Definition 3.2. Let \mathcal{C} denote a finite set of vectors in \mathbb{R}^N . Let $x_n \in \mathbb{R}^N$ denote a sequence of points. For $D \subset \mathbb{R}^N$ with $\{x_n\} \subset D$, let $f : D \times \mathcal{C} \rightarrow \mathbb{R}_{>0}$. We say that \mathcal{C} is partitioned along the sequence $\{x_n\}$ with respect to f if there exists a partition, $\{T_i\}_{i=1}^P$, of \mathcal{C} , where the T_i are termed tiers, and a constant $C > 1$, such that

(i) if $y_j, y_k \in T_i$ for some $i \in \{1, \dots, P\}$, then for all n

$$\frac{1}{C}f(x_n, y_j) \leq f(x_n, y_k) \leq Cf(x_n, y_j).$$

(ii) if $y_j \in T_i$ and $y_k \in T_{i+m}$ for some $m \geq 1$, then

$$\frac{f(x_n, y_j)}{f(x_n, y_k)} \rightarrow \infty, \quad \text{as } n \rightarrow \infty.$$

When $f(x, y) = x^y$, the case considered in both this paper and [1], we will simply say that \mathcal{C} is partitioned along $\{x_n\}$.

Note that we have a natural ordering of the tiers: $T_1 \succ T_2 \succ T_3 \succ \cdots \succ T_P$, and we say T_1 is the ‘‘highest’’ tier, whereas T_P is the ‘‘lowest’’ tier.

The proof of the following lemma is a slight modification of the proof of Lemma 4.3 in [1] and is omitted.

Lemma 3.3. Let \mathcal{C} denote a finite set of vectors in \mathbb{R}^N . Let x_n be a sequence of points in $\mathbb{R}_{>0}^N$. For $D \subset \mathbb{R}^N$ with $\{x_n\} \subset D$, let $f : D \times \mathcal{C} \rightarrow \mathbb{R}_{>0}$. Then, there exists a subsequence of $\{x_n\}$ along which \mathcal{C} is partitioned with respect to f .

The following lemma, which is similar in spirit to Farkas' Lemma, states that for any set of vectors in \mathbb{R}^N , either their span includes a non-zero vector in the non-positive orthant $\mathbb{R}_{\leq 0}^N$, or there is vector normal to their span that intersects the strictly positive orthant.

Lemma 3.4 (Stiemke's Theorem, [19]). *For $i = 1, \dots, n$, let $u_i \in \mathbb{R}^m$. Either there exists a $c \in \mathbb{R}^n$ such that*

$$\left(\sum_{i=1}^n c_i u_i \right)_j \leq 0, \quad j = 1, \dots, m$$

and such that at least one of the inequalities is strict, or there is a $w \in \mathbb{R}_{> 0}^m$ such that $w \cdot u_i = 0$ for each $i \in \{1, \dots, n\}$.

Corollary 3.5. *For $i = 1, \dots, n$, let $u_i \in \mathbb{R}^m$. Let $U \subset \{1, \dots, m\}$ and $V = U^c$. Either there exists a $c \in \mathbb{R}^n$ such that*

$$\begin{aligned} \left(\sum_{i=1}^n c_i u_i \right)_j &\leq 0, \quad j \in U \\ \left(\sum_{i=1}^n c_i u_i \right)_j &\geq 0, \quad j \in V \end{aligned}$$

and such that at least one of the inequalities is strict, or there is a $w \in \mathbb{R}^m$ with

$$\begin{aligned} w_j &> 0 \text{ for } j \in U \\ w_j &< 0 \text{ for } j \in V \end{aligned}$$

such that $w \cdot u_i = 0$ for each $i \in \{1, \dots, n\}$.

Proof. Define the vector valued function $\theta : \mathbb{R}^m \rightarrow \mathbb{R}^m$ via

$$\theta(u)_j \stackrel{\text{def}}{=} \begin{cases} u_j & \text{if } j \in U \\ -u_j & \text{if } j \in V \end{cases} .$$

Applying Lemma 3.4 to the set of vectors $\theta(u_i)$ proves the result. □

Definition 3.6. *Let $w \in \mathbb{R}^N$. The set $\{i \in \{1, \dots, N\} : w_i > 0\}$ is called the positive support of w and the set $\{i \in \{1, \dots, N\} : w_i < 0\}$ is called the negative support of w . The union of the positive and negative support of w , i.e. the set $\{i \in \{1, \dots, N\} : w_i \neq 0\}$, is called the support of w .*

Definition 3.7. Let \mathcal{C} denote a finite set of vectors in \mathbb{R}^N . Let $\{T_i\}$ denote a partition of \mathcal{C} . Let $U, V \subset \{1, \dots, N\}$ with $U \cup V$ nonempty. We will say that the vector $w \in \mathbb{R}^N$ is a conservation relation that respects the triple $(U, V, \{T_i\})$ if the following two conditions hold:

1. U is the positive support of w and V is the negative support of w .
2. Whenever $y_j, y_\ell \in T_i$ for some i , we have that $w \cdot (y_j - y_\ell) = 0$.

Definition 3.8. Let $x_n \in \mathbb{R}_{>0}^N$ denote a sequence of points. We say that x_n is partially monotonic if $x_{n,i} \geq x_{n+1,i}$ for each i for which $\liminf_{n \rightarrow \infty} x_{n,i} = 0$ and if $x_{n,j} \leq x_{n+1,j}$ for each j for which $\limsup_{n \rightarrow \infty} x_{n,j} = \infty$.

Note that Definition 3.8 stands silent on the behavior of those j for which $0 < \liminf_{n \rightarrow \infty} x_{n,j} \leq \limsup_{n \rightarrow \infty} x_{n,j} < \infty$.

Theorem 3.9. Let \mathcal{C} denote a finite set of vectors in \mathbb{R}^N . Let $x_n \in \mathbb{R}_{>0}^N$ denote a partially monotonic sequence of points for which $\lim_{n \rightarrow \infty} x_{n,i} \in \{0, \infty\}$ for at least one $i \in \{1, \dots, N\}$. Let

$$U = \{i \in \{1, \dots, N\} : \lim_{n \rightarrow \infty} x_{n,i} = 0\}$$

$$V = \{j \in \{1, \dots, N\} : \lim_{n \rightarrow \infty} x_{n,j} = \infty\}.$$

Finally, suppose that \mathcal{C} is partitioned along $\{x_n\}$ with tiers T_i , for $i = 1, \dots, P$, and constant $C > 0$. Then, there is a conservation relation $w \in \mathbb{R}^N$ that respects the triple $(U, V, \{T_i\})$.

Proof. We suppose, in order to find a contradiction, that there is no conservation relation that respects the triple $(U, V, \{T_i\})$. Define the sets $W_i \subset \mathbb{R}^N$, for $i = 1, \dots, P$, and $W \subset \mathbb{R}^N$ via

$$W_i \stackrel{\text{def}}{=} \{y_j - y_k \in \mathbb{R}^N \mid y_j, y_k \in T_i\}, \quad W \stackrel{\text{def}}{=} \bigcup_{i=1}^P W_i,$$

and denote the elements of W by $\{u_k\}$. Note that if T_i consists of a single element, then W_i consists solely of the zero vector. Let $m = |U \cup V| > 0$ be the number of elements in $U \cup V$ and let $W|_{U \cup V} \subset \mathbb{R}^m$ be the restriction of W to the components associated with the index set $U \cup V$, as discussed at the end of Section 2. Denote the elements of $W|_{U \cup V}$ by $\{v_k\}$. Thus, collecting

terminology, $u_k \in \mathbb{R}^N$, whereas $v_k \in \mathbb{R}^m$, and for each $u_k \in W$, there is a corresponding $v_k \in W|_{U \cup V}$ for which $u_k|_{U \cup V} = v_k$, however the mapping $\cdot|_{U \cup V}$ need not be injective.

The set $W|_{U \cup V}$ must contain at least one nonzero vector because otherwise any non-negative vector with support $U \cup V$ would be a non-negative conservation relation that respects the triple $(U, V, \{T_i\})$, but we have assumed that no such relation exists.

Because we have assumed there is no conservation relation that respects the triple $(U, V, \{T_i\})$, we may conclude by Corollary 3.5 that there exist $c_k \in \mathbb{R}$ such that

$$\begin{aligned} \left(\sum_{v_k \in W|_{U \cup V}} c_k v_k \right)_j &\leq 0, & \text{if } j \in U \\ \left(\sum_{v_k \in W|_{U \cup V}} c_k v_k \right)_j &\geq 0, & \text{if } j \in V, \end{aligned} \tag{5}$$

and such that the inequality is strict for at least one $j \in U \cup V$.

For $v_k \in W|_{U \cup V}$, let m_k denote the number of vectors of W that reduced to it. Define the function $M : \mathbb{R}^N \rightarrow \mathbb{R}$ by

$$M(x) \stackrel{\text{def}}{=} \left[\prod_{u_k \in W} (x^{u_k})^{c_k/m_k} \right],$$

where c_k and m_k are chosen for $u_k \in W$ if $u_k|_{U \cup V} = v_k \in W|_{U \cup V}$. Note that, by construction and by the definition of partitioning along a sequence, if $u_k \in W$, then there are $y_j, y_\ell \in T_i$ for some i , such that $u_k = y_\ell - y_j$ and

$$\frac{1}{C} \leq x_n^{u_k} = \frac{x_n^{y_\ell}}{x_n^{y_j}} \leq C,$$

for all $n \geq 1$. Therefore, $M(x_n)$ is uniformly, in n , bounded both from above and below. Noting that each x_n has strictly positive components, we may take logarithms and find

$$\ln(M(x_n)) = \left(\sum_{u_k \in W} \frac{c_k}{m_k} u_k \right) \cdot \ln x_n, \tag{6}$$

where for a vector $u \in \mathbb{R}_{>0}^N$ we define

$$\ln(u) \stackrel{\text{def}}{=} (\ln(u_1), \dots, \ln(u_N)).$$

Expanding equation (6) along elements of $U \cup V$ and $(U \cup V)^c$ yields,

$$\begin{aligned} \ln(M(x_n)) &= \left(\sum_{v_k \in W|_{U \cup V}} c_k v_k|_U \right) \cdot \ln(x_n|_U) + \left(\sum_{v_k \in W|_{U \cup V}} c_k v_k|_V \right) \cdot \ln(x_n|_V) \\ &\quad + \left(\sum_{u_k \in W} \frac{c_k}{m_k} u_k|_{(U \cup V)^c} \right) \cdot \ln(x_n|_{(U \cup V)^c}). \end{aligned} \tag{7}$$

By construction, $x_{n,\ell}$ is bounded from both above and below for $\ell \in (U \cup V)^c$. Thus, the final term in (7) is bounded from above and below. By the inequalities in (5), where at least one term is strict, and the facts that $x_{n,i} \rightarrow 0$ for each $i \in U$ and $x_{n,i} \rightarrow \infty$ for each $j \in V$ along this subsequence, we may conclude that the sum of the first and second term, and hence $\ln(M(x_n))$ itself, is unbounded towards positive infinity as $n \rightarrow \infty$. This is a contradiction with the previously found fact that $M(x_n)$ is uniformly bounded above and below, and the result is shown. \square

3.1 Bounded trajectories in the single linkage class case

Define $V_1 : \mathbb{R}_{>0}^N \rightarrow \mathbb{R}_{\geq 0}$ by

$$V_1(z) \stackrel{\text{def}}{=} \sum_{i=1}^N [z_i(\ln(z_i) - 1) + 1]. \tag{8}$$

This is the standard Lyapunov function of chemical reaction network theory where we have chosen $\bar{x} = (1, \dots, 1)$ [8, 11]. Note that $\nabla V_1(x) = \ln x$. It is straightforward to show that V_1 is convex with a global minimum of zero at $(1, \dots, 1)$ [8]. The following is a generalization of Lemma 4.7 in [1].

Lemma 3.10. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a weakly reversible, non-autonomous mass-action system with bounded kinetics. Let $D \subset \mathbb{R}_{>0}^N$. One of the following two conditions holds:*

C1: There exists an $M > 0$, such that for any $x \in D$ for which $x_i > M$ or $x_i < 1/M$ for at least one $i \in \{1, \dots, N\}$, we have

$$\sum_k \kappa_k(t) x^{y_k} (y'_k - y_k) \cdot \ln(x) < 0, \quad \text{for all } t \geq 0.$$

C2: There exists a sequence of points $x_n \in D$ for which $\lim_{n \rightarrow \infty} x_{n,i} \in \{0, \infty\}$ for at least one i and

- (i) \mathcal{C} is partitioned along x_n with tiers $\{T_i\}_{i=1}^P$, and constant C , and*
- (ii) T_1 consists of a union of linkage classes.*

Proof. We suppose condition *C1* does not hold, and will conclude that condition *C2* must then hold. Because condition *C1* does not hold, there is a sequence of points $x_n \in D$ and times $t_n \geq 0$ for which $\lim_{n \rightarrow \infty} x_{n,i} \in \{0, \infty\}$ for at least one i and

$$\sum_k \kappa_k(t_n) x_n^{y_k} (y'_k - y_k) \cdot \ln(x_n) \geq 0. \quad (9)$$

Applying Lemma 3.3, we partition the complexes along an appropriate subsequence of $\{x_n\}$ with tiers T_i , $i = 1, \dots, P$, and constant $C > 1$. Note that this also had the effect of only considering the analogous subsequence of $\{t_n\}$.

In the following, for tier $i \in \{1, \dots, P\}$, we denote by

- $\{i \rightarrow i\}$ all reactions with both source and product complex in T_i ,
- $\{i \rightarrow i + m\}$ all reactions with source complex in T_i and product complex in T_{i+m} for $m \geq 1$,
- $\{i \rightarrow i - m\}$ all reactions with source complex in T_i and product complex in T_{i-m} for $m \geq 1$.

Defining $u/v \stackrel{\text{def}}{=} (u_1/v_1, \dots, u_N/v_N)$ for $u, v \in \mathbb{R}_{>0}^N$, we re-write the left hand

side of the inequality (9)

$$\sum_k \kappa_k(t_n) x_n^{y_k} (y'_k - y_k) \cdot \ln(x_n) = \sum_{i=1}^P \left[\sum_{\{i \rightarrow i\}} \kappa_k(t_n) x_n^{y_k} \ln \left(\frac{x_n^{y'_k}}{x_n^{y_k}} \right) \right. \quad (10)$$

$$+ \sum_{m=1}^{P-i} \sum_{\{i \rightarrow i+m\}} \kappa_k(t_n) x_n^{y_k} \ln \left(\frac{x_n^{y'_k}}{x_n^{y_k}} \right) \quad (11)$$

$$\left. + \sum_{m=1}^{i-1} \sum_{\{i \rightarrow i-m\}} \kappa_k(t_n) x_n^{y_k} \ln \left(\frac{x_n^{y'_k}}{x_n^{y_k}} \right) \right].$$

Note that, by construction, for large enough n any component in the enumeration (11) is negative, and, in fact, $\ln(x_n^{y'_k}/x_n^{y_k}) \rightarrow -\infty$ as $n \rightarrow \infty$, for these terms. The proof that the total summation above (that is, the left hand side of (10)) must also, for large enough n , be strictly negative unless condition C2 holds is now identical to the analogous portion of the proof of Lemma 4.7 in [1], and is omitted here. \square

Lemma 3.11. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a single linkage class chemical reaction network. Then, there does not exist a sequence of points $x_n \in \mathbb{R}_{>0}^N$, all in the same stoichiometric compatibility class, for which $\lim_{n \rightarrow \infty} x_{n,i} \in \{0, \infty\}$ for at least one i and*

(i) \mathcal{C} is partitioned along x_n with tiers $\{T_i\}_{i=1}^P$, and constant C , and

(ii) T_1 consists of a union of linkage classes.

Proof. Note that in the one linkage class case T_1 can only consist of a union of linkage classes if $T_1 \equiv \mathcal{C}$. We suppose, in order to find a contradiction, that there is a sequence, $\{x_n\}$, all in the same stoichiometric compatibility class, for which $\lim_{n \rightarrow \infty} x_{n,i} \in \{0, \infty\}$ for at least one i and

(i) \mathcal{C} is partitioned along x_n with tiers $\{T_i\}_{i=1}^P$, and constant C , and

(ii) T_1 consists of a union of linkage classes.

Perhaps after restricting ourselves to a sub-sequence, we may choose x_n to be partially monotonic (recall Definition 3.8). Let

$$U = \{i \in \{1, \dots, N\} : \lim_{n \rightarrow \infty} x_{n,i} = 0\}$$

$$V = \{j \in \{1, \dots, N\} : \lim_{n \rightarrow \infty} x_{n,j} = \infty\}.$$

Note that $U \cup V$ is nonempty by construction. By Theorem 3.9 there is a conservation relation $w \in \mathbb{R}_{\geq 0}^N$ that respects the triple $(U, V, \{T_i\})$.

For each $j \in V$, $w_j < 0$ and $x_{n,j} \rightarrow \infty$. Thus, if V is nonempty, $w \cdot x_n \rightarrow -\infty$, as $n \rightarrow \infty$. If V is empty, then U is necessarily nonempty and, by construction, $w \cdot x_n \rightarrow 0$, as $n \rightarrow \infty$. However, because $T_1 \equiv \mathcal{C}$, we have that $w \cdot (y'_k - y_k) = 0$ for all $y_k \rightarrow y'_k \in \mathcal{R}$. Thus, as the x_n are all in the same stoichiometric compatibility class, we have that $w \cdot x_n$ is a constant. This shows that we can not have $w \cdot x_n \rightarrow -\infty$, as $n \rightarrow \infty$, and so V must be empty. However, by our construction we may then conclude that $w_i \geq 0$ for all i , and $w_i > 0$ for at least one i . Hence, $w \cdot x_n > 0$, and not zero. \square

We now have our main result.

Theorem 3.12. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a single linkage class, weakly reversible, non-autonomous mass-action system with bounded kinetics. Then, $\limsup_{t \rightarrow \infty} |\phi(t, x_0)| < \infty$ for each $x_0 \in \mathbb{R}_{> 0}^N$. That is, the system has bounded trajectories.*

Proof. Letting D be a non-empty positive stoichiometric compatibility class, in the statement of Lemma 3.10, we conclude by combining Lemmas 3.10 and 3.11 that there is an $M > 0$ so that for any $x \in D$ with $|x| > M$, we have

$$\sum_k \kappa_k(t) x^{y_k} (y'_k - y_k) \cdot \ln(x) < 0, \quad \text{for all } t \geq 0.$$

Therefore,

$$\frac{\partial}{\partial t} V_1(\phi(t, x_0)) < 0, \tag{12}$$

whenever $|\phi(t, x_0)| > M$. Let $B_{x_0} = \sup\{V_1(x) : |x| = M \text{ or } x = x_0\}$. Inequality (12) shows that $V_1(\phi(t, x_0)) \leq B_{x_0}$ for all $t \geq 0$, which when combined with the fact that $V_1(x) \rightarrow \infty$ as $|x| \rightarrow \infty$, proves the result. \square

3.2 Permanence

Note that Lemma 3.10 and, in particular, equation (12) do not give a rate at which V_1 is decreasing. Hence, we can not conclude in general that all trajectories contained within a given stoichiometric compatibility class enter a single compact subset of $\mathbb{R}_{\geq 0}^N$. That is, we can not conclude that trajectories are permanent in the sense of Definition 3.13 below. This is quantified above by the explicit dependence of B_{x_0} upon x_0 . However, we may strengthen our results slightly.

Definition 3.13. For $t \geq 0$ denoting time, let $\phi(t, x_0)$ be a trajectory to a dynamical system in \mathbb{R}^N with initial condition x_0 . The system is said to be permanent if there is a $\rho > 0$ such that for every $x_0 \in \mathbb{R}_{\geq 0}^N$,

$$\rho < \liminf_{t \rightarrow \infty} \phi_i(t, x_0) \leq \limsup_{t \rightarrow \infty} \phi_i(t, x_0) < 1/\rho$$

for all $i \in \{1, \dots, N\}$.

Lemma 3.14. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a weakly reversible, non-autonomous mass-action system with bounded kinetics. Let $D \subset \mathbb{R}_{> 0}^N$ be such that $\text{dist}(D, \partial\mathbb{R}_{> 0}^N) > \delta$, for some $\delta > 0$. One of the following two conditions holds:

C1: For any $\epsilon > 0$, there exists an $M = M_{\epsilon, \delta} > 0$ such that for any $x \in D$ with $|x| > M$, we have

$$\sum_k \kappa_k(t) x^{y_k} (y'_k - y_k) \cdot \ln(x) < -\epsilon, \quad \text{for all } t \geq 0.$$

C2: There exists a sequence of points $x_n \in D$ that satisfies $\lim_{n \rightarrow \infty} |x_n| = \infty$ and

- (i) \mathcal{C} is partitioned along x_n with tiers $\{T_i\}_{i=1}^P$, and constant C , and
- (ii) T_1 consists of a union of linkage classes.

Proof. The proof is essentially the same as for Lemma 3.10. We first suppose condition *C1* does not hold. Let $\epsilon > 0$. By our assumption, there must be a sequence of points $x_n \in D$ and times $t_n \geq 0$ such that $\lim_{n \rightarrow \infty} |x_n| = \infty$ and

$$\sum_k \kappa_k(t_n) x_n^{y_k} (y'_k - y_k) \cdot \ln(x_n) \geq -\epsilon.$$

The proof is now exactly the same as for Lemma 3.10, except that you recognize that for any $y \in T_1$, we necessarily have that $x_n^y \rightarrow \infty$, as $n \rightarrow \infty$. Therefore, the terms in the summation in (11) not only dominate the others, but force the expression to $-\infty$ as $n \rightarrow \infty$, thereby concluding the proof. \square

Corollary 3.15. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$, with $\mathcal{S} = \{S_1, \dots, S_N\}$, be a single linkage class, weakly reversible, non-autonomous mass-action system with

bounded kinetics. Let P be a positive stoichiometric compatibility class and suppose there is a $\delta > 0$ so that

$$\liminf_{t \rightarrow \infty} \phi_i(t, x_0) > \delta, \quad \text{for all } i \in \{1, \dots, N\} \text{ and all } x_0 \in P.$$

Then, there is a $\rho > 0$ such that for any $x_0 \in P$

$$\rho < \liminf_{t \rightarrow \infty} \phi_i(t, x_0) \leq \limsup_{t \rightarrow \infty} \phi_i(t, x_0) < 1/\rho$$

for all $i \in \{1, \dots, N\}$. That is, the system is permanent.

Proof. The lower bound follows by our assumption. The upper bound follows from Lemmas 3.14 (with D equal to P restricted to those x a distance of at least δ away from the boundary), 3.11, and similar arguments as in the proof of Theorem 3.12. The only real difference in the proof is that the analog of equation (12) is

$$\frac{\partial}{\partial t} V_1(\phi(t, x_0)) < -\epsilon,$$

whenever $|\phi(t, x_0)| > M$, giving us the needed force to guarantee $|\phi(t, x_0)|$ decreases below some $1/\rho$. \square

Note that the $M = M_{\epsilon, \delta} > 0$ of Lemma 3.14, and hence in the proof of Corollary 3.15, explicitly depends upon δ . Therefore, it is not sufficient in the statement of Corollary 3.15 to assume the existence of a different $\delta = \delta_{x_0} > 0$ for each x_0 . Thus, the main results of [1] pertaining to weakly reversible networks (with arbitrary deficiency) are not strong enough to guarantee permanence using the above methods.

References

- [1] D. F. Anderson, *A proof of the global attractor conjecture in the single linkage class case*, to appear in SIAM J. Appl. Math. Available at <http://arxiv.org/abs/1101.0761>.
- [2] D. F. Anderson and A. Shiu, *The dynamics of weakly reversible population processes near facets*, SIAM J. Appl. Math. **70** (2010), no. 6, 1840–1858.

- [3] D. Angeli, P. De Leenheer, and E. D. Sontag, *A Petri net approach to the study of persistence in chemical reaction networks*, in *Biology and Control Theory: Current Challenges*, Lecture Notes in Control and Inform. Sci. 357, I. Queinnec, S. Tarbouriech, G. Garcia, and S.-I. Niculescu, eds., Springer-Verlag, Berlin (2007), 181–216.
- [4] David Angeli, Patrick De Leenheer, and Eduardo Sontag, *A petri net approach to the study of persistence in chemical reaction networks*, *Math. Biosci.* **210** (2007), no. 2, 598–618.
- [5] ———, *Persistence results for chemical reaction networks with time-dependent kinetics and no global conservation laws*, *SIAM Appl. Math.* **71** (2011), no. 1, 128–146.
- [6] G. Craciun, A. Dickstein, A. Shiu, and B. Sturmfels, *Toric dynamical systems*, *J. Symb. Comp.* **44** (2009), 1551–1565.
- [7] G. Craciun, F. Nazarov, and C. Pantea, *Persistence and permanence of mass-action and power-law dynamical systems*, submitted, available at arXiv:1010.3050v1.
- [8] M. Feinberg, *Lectures on chemical reaction networks*, Delivered at Math. Res. Cent., U. Wisc.-Mad. Available for download at <http://www.che.eng.ohio-state.edu/~feinberg/LecturesOnReactionNetworks>, 1979.
- [9] ———, *Chemical reaction network structure and the stability of complex isothermal reactors - I. the deficiency zero and deficiency one theorems, review article 25*, *Chem. Eng. Sci.* **42** (1987), 2229–2268.
- [10] M. Feinberg and F. J. M. Horn, *Dynamics of open chemical systems and the algebraic structure of the underlying reaction network*, *Chem. Eng. Sci.* **29** (1974), 775 – 787.
- [11] J. Gunawardena, *Chemical reaction network theory for in-silico biologists*, Available for download at <http://vcp.med.harvard.edu/papers/crnt.pdf>, 2003.
- [12] F. J. M. Horn, *Necessary and sufficient conditions for complex balancing in chemical kinetics*, *Arch. Rat. Mech. Anal.* **49** (1972), no. 3, 172–186.

- [13] ———, *The dynamics of open reaction systems*, SIAM-AMS Proceedings **VIII** (1974), 125–137.
- [14] F. J. M. Horn and R. Jackson, *General mass action kinetics*, Arch. Rat. Mech. Anal. **47** (1972), 81–116.
- [15] M. D. Johnston and D. Siegel, *A stratum approach to global stability of complex balanced systems*, to appear in Dyn. Syst. Available on arxiv:1008.1622.
- [16] ———, *Weak dynamic non-emptiability and persistence of chemical kinetic systems*, available on arxiv:1009.0720.
- [17] C. Pantea, *On the persistence and global stability of mass-action systems*, submitted.
- [18] E. D. Sontag, *Structure and stability of certain chemical networks and applications to the kinetic proofreading of t-cell receptor signal transduction*, IEEE Trans. Auto. Cont. **46** (2001), no. 7, 1028–1047.
- [19] E. Stiemke, *Über positive Lösungen homogener linearer Gleichungen*, Mathematische Annalen **76** (1915), 340–342.
- [20] Y. Takeuchi, *Global dynamical properties of Lotka-Volterra systems*, World Sci. Pub., 1996.