Topics in Chemical Reaction Network Theory

by

Matthew Douglas Johnston

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Originality is claimed for the following results:

Chapter 4

- Theorem 4.3.1
- Lemma 4.3.1
- Theorem 4.3.2
- Theorem 4.3.3
- Lemma 4.3.3
- Lemma 4.3.4
- Theorem 4.3.4
- Theorem 4.3.5
- Theorem 4.3.6

Chapter 5

- Theorem 5.1.3
- Lemma 5.2.2
- Theorem 5.2.4
- Theorem 5.2.5
- Theorem 5.2.6
- Lemma 5.2.3
- Corollary 5.2.1
- Theorem 5.3.2
- Lemma 5.3.4
- Lemma 5.3.5
- Theorem 5.3.3
- Lemma 5.3.6
- Corollary 5.3.1
- Corollary 5.3.2

Chapter 6

- Lemma 6.2.2
- Theorem 6.2.3
- Corollary 6.2.1
- Corollary 6.2.2
- Theorem 6.3.2

Abstract

Under the assumption of mass-action kinetics, systems of chemical reactions can give rise to a wide variety of dynamical behaviour, including stability of a unique equilibrium concentration, multistability, periodic behaviour, chaotic behaviour, switching behaviour, and many others. In the canonical papers [25,30,33], M. Feinberg, F. Horn and R. Jackson developed so-called *Chemical Reaction Network* theory which drew a strong connection between the topological structure of the reaction graph and the dynamical behaviour of mass-action systems. A significant amount of work since that time has been conducted expanding upon this connection and fleshing out the theoretical underpinnings of the theory.

In this thesis, I focus on three topics within the scope of Chemical Reaction Network theory:

1. *Linearization*: It is known that complex balanced systems possess within each invariant space of the system a unique positive equilibrium concentration and that that concentration is locally asymptotically stable. F. Horn and R. Jackson determined this through the use of an entropy-like Lyapunov function [33]. In Chapter 4, I approach this problem through the alternative approach of linearizing the mass-action system about its equilibrium points. I show that this approach reproduces the results of F. Horn and R. Jackson and has the advantage of being able to give explicit exponential bounds on the convergence near equilibria.

2. *Persistence*: A well-known limitation of the theory introduced in [33] is that the stabilities of the positive equilibrium concentrations guaranteed by the theory are locally limited. The conjecture that the equilibrium concentrations of complex balanced systems are global attractors of their respective invariant spaces has become known as the *Global Attractor Conjecture* and has received significant attention recently. This theory has been significantly aided by the realization that trajectories not tending toward the set of positive equilibria must tend toward the boundary of the positive orthant; consequently, persistence is a sufficient condition to affirm the conjecture. In Chapter 5, I present my contributions to this problem.

3. *Linear Conjugacy*: It is known that under the mass-action assumption two reaction networks with disparate topological structure may give rise to the same set of differential equations and therefore exhibit the same qualitative dynamical behaviour. In Chapter 6, I expand the scope of networks which exhibit the same behaviour to include ones which are related by a non-trivial linear mapping. I have called this theory *Linear Conjugacy* theory. I also show how networks exhibiting a linear conjugacy can be found using the mixed integer linear programming (MILP) framework introduced by G. Szederkényi [58].

Acknowledgements

A work of this magnitude does not come together without the assistance and patience of an overwhelming number of people—far more than I could possibly list here. If I have overlooked anybody, it is only because of the limitations of time and space and in no way reflects a lack of gratitude on my part.

First and foremost, I would like to thank my parents, Bill and Betty. From my earliest years they instilled in me an unquenchable thirst for knowledge and a rigid stubbornness to see a problem through to its resolution, no matter how long it took or challenging it proved to be. No two traits could possibly have served me better for working on this project. I would not be where I am now without them.

Thanks also go out to my two younger brothers, David and Nathan. As a fellow academic, Nathan has been able to relate to my struggles when it seemed nobody else could. I often say that I have paved the way for his studies, but in truth it has almost always been the other way around. David meanwhile has kept me grounded in the real world and never let me lose sight of the things which matter the most, of the value of a close-knit family and a good home.

Thanks go to my advisor, David Siegel, who has been truly instrumental in his guidance of my academic career. With his library of textbooks—and seemingly encyclopedic knowledge of their contents—he has always been able to push me in the right direction when a problem has seemed just out of my reach. Our meetings have always left me with an appreciation for what I hope to one day become.

I would also like to thank my many collaborators and financial supporters. Thanks to Anne Shiu, Casian Pantea, David Anderson, Gheorghe Craciun, Eduardo Sontag, and János Tóth for their enlightening discussions on chemical reaction networks, and to Gabór Szederkényi for his enthusiastic collaboration. Thanks also go out to the Department of Applied Mathematics at the University of Waterloo and the National Science and Engineering Research Council of Canada for their steadfast belief in the value of this project and their consistent support of it.

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Dedication

This thesis is dedicated to my father, who always taught me to question my assumptions and to never give up without a fight.

Contents

List of Figures

Chapter 1

Introduction

The study of chemical kinetics—that is to say, the rate at which chemical reactions occur—has a long and fruitful history. Even when the formulation of each individual reaction's kinetics is well-understood, the amalgam of many such reactions into a network can lead to surprising and unpredictable dynamical results. The study of such networks has found application in such disciplines as industrial chemistry [9, 50], systems biology [48, 49, 56], enzyme kinetics [16, 52], gene regulatory networks [51], and many others.

One of the most powerful contributions to the theory of chemical kinetics is the law of mass action for interacting species, which was proposed in 1864 by C. M. Guldberg and P. Waage [27]. This 'law' says that the rate of a reaction is proportional to the product of the reactant concentrations, that is to say, the rate of a reaction catalysed by two species A and B would be given by $k[A][B]$ where $k > 0$ is some proportionality constant. This formulation has been found to be a very accurate estimator of empirical data for many reaction systems. Mass-action kinetics remains the most commonly used kinetics scheme to date although several other dynamics, such as Michaelis-Menten kinetics for

enzyme reactions [43] and Hill kinetics [29], are also widely used, especially in biological applications.

Under several simplifying assumptions, such as spatial homogeneity and a sufficiently large number of interacting molecules, the concentrations of the species can be modeled mathematically under the assumption of mass-action kinetics by a set of autonomous, polynomial ordinary differential equations. Although the models are simple, they cannot generally be solved analytically due to the non-linearity in the right-hand side, and the potential behaviours are surprisingly robust—they can exhibit periodic behaviour, chaotic behaviour, oscillatory behaviour, multistability, unboundedness, etc. [4, 14, 15, 21]. These difficulties have led to a number of alternative approaches, including separation of time scales and asymptotic analysis.

These mass-action systems have also given rise to a significant body of theoretical work. One particularly vibrant field of research has been the so-called *Chemical Reaction Network* theory developed by F. Horn, M. Feinberg, and R. Jackson in 1972 in the papers [25,30,33]. In these papers, the authors present a strong association between the topological structure of a network's reaction graph and such dynamical properties as the number and stability of equilibrium concentrations, and the possibility of periodic or chaotic behaviour. Perhaps most surprising of all is that their results depend on the structure of the graph alone and not on the associated network parameters, the reaction rate constants.

These papers also raised significant new problems. Key among these has been the question of *global stability* of a particular class of equilibrium concentrations. In [33] it is proved that for a class of chemical reaction networks called complex balanced networks there is exactly one equilibrium concentration within the interior of a particular class of invariant space of the system and that this concentration is locally asymptotically stable relative

to that invariant space; however, the authors were unable to prove that trajectories could not tend toward the boundary. Extending this stability to apply globally throughout the invariant space has been termed the *Global Attractor Conjecture* [13, 24] and has received significant attention recently [1, 3, 5, 19, 52, 54, 55]. I will present my contribution to this research problem in Chapter 5.

Another important problem which has begun to receive attention in the literature has been determining conditions under which two reaction networks with disparate network structure can give rise to the same set of differential equations and, more recently, when the flows of one network are linearly conjugate to another [18, 36]. Importantly, these theories allow us to transfer important dynamical properties (e.g. number and stability of positive equilibria, dimension of invariant spaces, etc.) from one network to another. This is particularly useful when one network has dynamical properties which are known from the reaction graph alone (e.g. complex balanced systems) while the conjugate network does not.

Approaches to this problem have been varied and largely self-contained. In their seminal paper [33], F. Horn and R. Jackson introduced an example of a complex balanced network for which the network topology could be altered without affecting the dynamics. In [6] and [7], E. Averbukh considered the case of networks which behave like reversible networks despite not having reversible network structure. Former University of Waterloo graduate student D. MacLean also considered the problem extensively in her Master's thesis [42] and unpublished research notes. The related problem of how potentially dimension-reducing transformations affect many key qualitative aspects of the dynamics of chemical reaction networks has also been studied extensively, and has been termed 'lumping' of chemical reaction networks [22, 41, 62, 64].

The most comprehensive approach to this problem, however, was taken by G. Craciun and C. Pantea in [18] where they give necessary and sufficient conditions for networks to give rise to the same dynamics (although a small oversight was corrected later by G. Szederkényi in [57]). This has given rise to several subsequent lines of research. In the papers [58], [59], [60] and [61], G. Szederkényi and his collaborators introduce mixed-integer linear programming (MILP) algorithms capable of determining complex balanced and weakly reversible alternative realizations (networks which give rise to the same dynamics) which have the greatest and fewest number of reactions given certain fixed system parameters. In [17] and [20], the authors introduce a maximum likelihood approach for determining an appropriate network structure given several candidate networks which generate the same dynamics. In [36] the authors introduce the concept of linear conjugacy, which contains the concept of realizations as a special case, and encompasses many new systems as well. I will present my contributions to this research problem, which includes the concept of linear conjugacy, in Chapter 6.

A side project of mine has been approaching the stability of the complex balanced equilibrium concentrations introduced in [33] from a linearization point of view rather than taking a Lyapunov function approach. This has not been attempted before and, while it produces no qualitative results which were not previously known, it is a comprehensive and theoretically interesting approach. Linearization also allows an exponential rate of convergence to be determined. I will present these results in Chapter 4.

Chapter 2

Background

In this chapter, the notation and important background information about chemical reaction networks which will be used throughout this thesis are introduced. In particular, the notions of the reaction graph of a chemical reaction network and mass-action kinetics—which underlie all the work contained herein—will be presented.

Due to disparity in application within the chemical kinetics literature—as well as within this thesis—it will often be necessary to represent concepts in multiple ways and with multiple notations. Throughout this thesis, we will see the central system of mass-action induced differential equations presented with not one, or two, but *four* distinct notations (one is reaction-oriented (2.3), one is complex-oriented (2.4), and two are linear-algebra-oriented (4.18) (5.10)). While this is a frequent source of confusion, effort will be put forth to explain why the disparities exist and which approaches are suitable for which applications.

2.1 Chemical Reaction Networks

In this section, the background necessary to define a chemical reaction network is introduced. We will familiarize ourselves with the concepts of chemical *species*, *complexes* and *reactions*. Two notations for representing and indexing chemical reaction networks will be introduced (the *reaction*-oriented notation of (2.1) and the *complex*-oriented notation of (2.2)). We will be careful throughout this thesis to note which scheme is being used.

The central quantities of consideration in the study of chemical kinetics are the chemical species.

Definition 2.1.1. *The **chemical species** (alternatively, **chemical reactants/products**) of a chemical reaction mechanism are the most basic elements capable of undergoing chemical change. We will denote the set of chemical species by* $\mathcal{S} = \{\mathcal{A}_i, i = 1, \ldots, m\}$ *where* $|\mathcal{S}| = m$ *is the number of distinct chemical species in the mechanism.*

Depending on the application, the nature and composition of the chemical species may very greatly. For the electrolysis of water, given by the overall equation

$$2H_2O \longrightarrow 2H_2 + O_2,$$

we are interested in the simple molecules water ($\mathcal{A}_1 = H_2O$), hydrogen ($\mathcal{A}_2 = H_2$), and oxygen ($\mathcal{A}_3 = O_2$). For other examples, the molecular composition of the species may be too complicated (or irrelevant) to be kept track of in such a manner. Many biochemical reactions fall into this category. For example, in the popular Michaelis-Menten enzyme reaction given by the equation

$$S + E \quad \leftrightarrows \quad SE \longrightarrow P + E$$

the chemical species of interest are the substrate ($\mathcal{A}_1$=S), the enzyme ($\mathcal{A}_2$=E), the substrate-enzyme complex ($\mathcal{A}_3$=SE), and the product ($\mathcal{A}_4$=P); for practical reasons, we are not interested in the molecular composition of these species [43]. It is also common to extend this notation to non-chemical applications, in which case we will just speak of the involved agents as species. For example, the famous Lotka-Volterra predator prey model is often represented as the reaction system

$$\begin{aligned} \mathrm{X} + \mathrm{Y} &\longrightarrow 2\mathrm{Y} \\ \mathrm{X} &\longrightarrow 2\mathrm{X} \\ \mathrm{Y} &\longrightarrow \mathcal{O} \end{aligned}$$

where X is the prey ($\mathcal{A}_1$=X), Y is the predator ($\mathcal{A}_2$=Y), and $\mathcal{O}$ is the null specie. The first 'reaction' represents predators eating prey, the second 'reaction' represents the growth of the prey in the absense of predation, and the final 'reaction' represents the decay of the predator in the absence of prey. In this example, it obviously makes no sense to speak of the chemical composition of the species; nevertheless, it is still sensible to think of the behaviour in terms of reactions (the predator and prey meeting constitutes a reaction!).

In building our mathematical model, we will be primarily interested in the effects of the mechanism on the chemical species. For example, in our electrolysis of water example above, we would be interested in the evolution of the concentrations of the three chemical species ($x_1 = [\mathrm{H_2O}]$, $x_2 = [\mathrm{H_2}]$, and $x_3 = [\mathrm{O_2}]$) as a result of the mechanism. We will derive reasonable equations for the rate of growth and decay of these species in a later section.

The chemical species of a system interact according to *elementary reactions*.

Definition 2.1.2. *An* ***elementary reaction*** *of a chemical reaction mechanism consists*

of a set of chemical reactants combining at a prescribed rate to form some set of chemical products. The set of elementary reactions will be denoted $\mathcal{R} = \{\mathcal{R}_i, i = 1, \ldots, r\}$ *where* $\mathcal{R}_i$ *indexes the reactant set, product set and rate constant of the* i^{th} *reaction, and* $|\mathcal{R}| = r$ *is the number of elementary reactions in the mechanism.*

It is worth noting that our definition of an elementary chemical reaction differs from the definition typically understood by chemists. Our definition is based on the most elementary component of the *mathematical* model and is not meant to imply that more elementary reaction processes do not underlie the system. For instance, the electrolysis example given above is known to have intermediate steps involving the species H^+, HO^- and e^- (free electrons). Whether we include these species, or the reactions involving them, depends on their relevance to the mathematical model we are using.

Schematically, the set of elementary reactions of a mechanism can be represented as

$$\mathcal{R}_j : \qquad \sum_{i=1}^{m} z_{ji}\mathcal{A}_i \longrightarrow \sum_{i=1}^{m} z'_{ji}\mathcal{A}_i, \qquad \text{for } j = 1, \ldots, r \tag{2.1}$$

where the terms z_{ji} and z'_{ji} are nonnegative integers called the *stoichiometric coefficients*. The vectors $\mathbf{z}_j = \left[z_{j1}\ z_{j2} \cdots z_{jm}\right]^T$ and $\mathbf{z}'_j = \left[z'_{j1}\ z'_{j2} \cdots z'_{jm}\right]^T$ are called the *stoichiometric vectors*. We can see that the three reaction systems given earlier in this section fit this reaction scheme.

The linear combination of species to the left and right of each of the reaction arrows in (2.1) are of central importance throughout the rest of this thesis.

Definition 2.1.3. *The set of species, together with their stoichiometric coefficients, on the reactant or product side of an elementary reaction are called* ***complexes****. The set of*

stoichiometrically distinct complexes will be denoted $\mathcal{C} = \{\mathcal{C}_i, i = 1, \ldots, n\}$ *where* $|\mathcal{C}| = n$ *is the number of stoichiometrically distinct complexes of the mechanism.*

In general, complexes may appear multiple times in the elementary reaction set (2.1). This observation has led many researchers to view reaction mechanisms not as a list of elementary reactions but as interactions between the n stoichiometrically distinct complexes of the system. In this setting, (2.1) is instead represented by

$$\mathcal{R}_{ij}: \qquad \mathcal{C}_i \longrightarrow \mathcal{C}_j, \qquad \text{for } i, j = 1, \ldots, n, \tag{2.2}$$

where $\mathcal{C}_i = \sum_{j=1}^{m} z_{ij}\mathcal{A}_j, i = 1, \ldots, n$ are the stoichiometrically distinct complexes of the mechanism (see [33]). We are now prepared to formally define a chemical reaction network.

Definition 2.1.4. *A* ***chemical reaction network*** *(alternatively, a* ***chemical reaction mechanism****) is given by the triplet* $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$.

Throughout most of this thesis, we will not be concerned with whether a chemical reaction network under consideration corresponds to known chemical reactions. In many cases, we will not even be concerned with whether they *could* correspond to sensible chemical reactions. As such, we should get used to thinking of chemical reaction networks as abstract mathematical constructs.

2.2 Reaction Graphs

According to (2.1), reactions are depicted as a list of simultaneously but independently occurring events, whereas according to (2.2) they are thought of as interactions between

stoichiometrically distinct complexes. Depending on the application, it may be more convenient to view reactions in one framework as opposed to the other. It is also worth noting that other graphical representations of chemical reaction networks exist (see [14, 15, 53]).

In this thesis, we will be primarily interested in the complex-oriented notation of (2.2). In this setting, we can represent chemical reaction networks as directed graphs with complexes as nodes and reactions as edges, according to the following definition.

Definition 2.2.1. *The **reaction graph** of a chemical reaction network, $\mathcal{G}(\mathcal{N})$, is given by the directed graph $G(V, E)$ with vertex set $V = \mathcal{C}$ and the directed edge set $E = \mathcal{R}$.*

Example 2.2.1. *Consider the chemical reaction network $\mathcal{N}$ given in the form of (2.1) as*

$$\begin{aligned} \mathcal{A}_1 &\longrightarrow \mathcal{A}_2 \\ \mathcal{A}_2 &\longrightarrow \mathcal{A}_3 + \mathcal{A}_4 \\ \mathcal{A}_3 + \mathcal{A}_4 &\longrightarrow \mathcal{A}_1 \\ 2\mathcal{A}_1 &\longrightarrow 2\mathcal{A}_3 \\ 2\mathcal{A}_3 &\longrightarrow 2\mathcal{A}_1. \end{aligned}$$

We can see that the network has four species and five reactions so that $m = 4$ and $r = 5$. To each reaction, we associate a reactant complex (e.g. $\mathcal{C}_3 = \mathcal{A}_3 + \mathcal{A}_4$) and a product complex (e.g. $\mathcal{C}'_3 = \mathcal{A}_1$).

We notice, however, that some of the complexes in the mechanism are repeated. For example, $\mathcal{C}'_1 = \mathcal{A}_2$ and $\mathcal{C}_2 = \mathcal{A}_2$ are stoichiometrically identical. In fact, the mechanism only has five stoichiometrically distinct complexes so that $n = 5$. Setting $\mathcal{C}_1 = \mathcal{A}_1$, $\mathcal{C}_2 = \mathcal{A}_2$, $\mathcal{C}_3 = \mathcal{A}_3 + \mathcal{A}_4$, $\mathcal{C}_4 = 2\mathcal{A}_1$, and $\mathcal{C}_5 = 2\mathcal{A}_3$, we can represent the system according to the

complex-centred reaction graph $\mathcal{G}(\mathcal{N})$ *according to Definition 2.2.1 as*

$$\begin{array}{ccc} \mathcal{A}_1 & \longrightarrow & \mathcal{A}_2 \\ & \nwarrow \quad \swarrow & \\ & \mathcal{A}_3 + \mathcal{A}_4 & \end{array} \qquad 2\mathcal{A}_1 \leftrightarrows 2\mathcal{A}_3.$$

In this setting, the network is represented as a directed graph with the distinct complexes as nodes and the reactions as directed edges. It is worth noting that $\mathcal{C}_1 = \mathcal{A}_1$ *and* $\mathcal{C}_4 = 2\mathcal{A}_1$ *are distinct complexes.*

Not surprisingly, the graph theoretical properties of reaction graphs have been exploited to produce results regarding the dynamical behaviour of chemical reaction networks [14, 15, 25, 30, 33]. We state here a few important concepts of graphs as they apply to chemical reaction networks. For a more complete introduction to directed graphs, see [11] and [12].

Definition 2.2.2. *We say* $\mathcal{C}_{\nu_0}$ *is* ***connected*** *to* $\mathcal{C}_{\nu_k}$ *if there exists a sequence of indices* (ν_{i-1}, ν_i)*,* $i = 1, \ldots, k$*, such that*

$$\mathcal{C}_{\nu_0} \longleftrightarrow \mathcal{C}_{\nu_1} \longleftrightarrow \cdots \longleftrightarrow \mathcal{C}_{\nu_{k-1}} \longleftrightarrow \mathcal{C}_{\nu_k}$$

where by $\mathcal{C}_i \longleftrightarrow \mathcal{C}_j$ *we mean that either*

$$\mathcal{C}_i \longrightarrow \mathcal{C}_j \quad \text{or} \quad \mathcal{C}_j \longrightarrow \mathcal{C}_i.$$

Definition 2.2.3. *We say there is a* ***path*** *from* $\mathcal{C}_{\nu_0}$ *to* $\mathcal{C}_{\nu_k}$ *if there exists a sequence of*

indices (ν_{i-1}, ν_i), $i = 1, \ldots, k$, *such that*

$$\mathcal{C}_{\nu_0} \longrightarrow \mathcal{C}_{\nu_1} \longrightarrow \cdots \longrightarrow \mathcal{C}_{\nu_{k-1}} \longrightarrow \mathcal{C}_{\nu_k}.$$

Definition 2.2.4. *A* ***connected component*** *or* ***linkage class*** *of a reaction graph is a maximal set of complexes* $\{\mathcal{C}_{\mu_1}, \ldots, \mathcal{C}_{\mu_k}\}$ *such that* $\mathcal{C}_{\mu_i}$ *and* $\mathcal{C}_{\mu_j}$ *are connected for* $i, j = 1, \ldots, k$. *We will let* ℓ *denote the number of distinct linkage classes* $\mathcal{L}_1, \ldots, \mathcal{L}_\ell$ *of the reaction mechanism.*

Definition 2.2.5. *A* ***strongly connected component*** *of a reaction graph is a maximal set of complexes* $\{\mathcal{C}_{\mu_1}, \ldots, \mathcal{C}_{\mu_k}\}$ *such that there is a path from* $\mathcal{C}_{\mu_i}$ *to* $\mathcal{C}_{\mu_j}$ *for all* $i, j = 1, \ldots, k$, $i \neq j$.

Since each complex is distinct, it follows that the complex set $\mathcal{C}$ of any chemical reaction network can be partitioned into distinct linkage classes $\mathcal{L}_1, \ldots, \mathcal{L}_\ell$ such that

$$\mathcal{L}_i \cap \mathcal{L}_j = \varnothing, \quad i, j = 1, \ldots, \ell, \quad i \neq j$$

and

$$\mathcal{C} = \bigcup_{i=1}^{\ell} \mathcal{L}_i.$$

We can now define two other particularly important classes of chemical reaction networks. In [25, 30, 33], the authors relate these concepts to properties of the equilibrium set of a mass-action system. These results will be discussed in Chapter 3.

Definition 2.2.6. *We say a chemical reaction network is* ***reversible*** *if for every reaction from* $\mathcal{C}_i$ *to* $\mathcal{C}_j$, *there exists a reaction from* $\mathcal{C}_j$ *to* $\mathcal{C}_i$.

Definition 2.2.7. *We say a chemical reaction network is* ***weakly reversible*** *if for every path from $\mathcal{C}_i$ to $\mathcal{C}_j$, there exists a path from $\mathcal{C}_j$ to $\mathcal{C}_i$.*

It is clear by this definition that for reversible and weakly reversible networks, the strongly connected components and linkage classes coincide. In general, this need not be the case, as can be seen by the following example.

Example 2.2.2. *Consider the network given by*

$$\begin{array}{ccc} & & \mathcal{C}_2 \rightleftarrows \mathcal{C}_3 \\ & \nearrow & \\ \mathcal{C}_1 & \longrightarrow & \mathcal{C}_4 \rightleftarrows \mathcal{C}_5. \end{array}$$

It is clear that every complex is connected so that all of the complexes belong to the same linkage class, say, $\mathcal{L} = \{\mathcal{C}_1, \mathcal{C}_2, \mathcal{C}_3, \mathcal{C}_4, \mathcal{C}_5\}$. We cannot, however, construct a path from every complex within this set to every other complex so the strongly connected components clearly constitute a further partitioning of the complexes. In this case, we have three strongly connected components, corresponding to the sets $\{\mathcal{C}_1\}$, $\{\mathcal{C}_2, \mathcal{C}_3\}$ and $\{\mathcal{C}_4, \mathcal{C}_5\}$.

So far we have only considered the properties of the reaction network which result from the interactions between complexes. We have given no consideration to how the species are embedded within the complexes. The following concepts will prove to be very important characteristics of chemical reaction networks.

Definition 2.2.8. *The* ***stoichiometric subspace*** *for a chemical reaction network (2.1)*

is the linear subspace $S \subset \mathbb{R}^m$ *such that*

$$S = span\{(\mathbf{z}_i' - \mathbf{z}_i) \mid i = 1, \ldots, r\}, \quad or$$
$$S = span\{(\mathbf{z}_j - \mathbf{z}_i) \mid (i,j) \in \mathcal{R}\}.$$

The dimension of the stoichiometric subspace will be denoted by $|S| = s$.

Definition 2.2.9. *The* ***deficiency*** *of a network is defined as*

$$\delta = n - \ell - s$$

where n *is the number of distinct complexes,* ℓ *is the number of linkage classes, and* s *is the dimension of the stoichiometric space.*

The stoichiometric subspace is crucially important in determining how the dynamics of a chemical reaction network may evolve (see Section 2.4). The deficiency is a nonnegative parameter which can often be used to restrict the behaviour of chemical reaction networks. It is worth noting that all of the components required to determine the deficiency (n, ℓ, and s) can be determined by analysis of the reaction graph alone.

Example 2.2.3. *Reconsider the network given in Example 2.2.1:*

$$\begin{array}{ccc} \mathcal{A}_1 & \longrightarrow & \mathcal{A}_2 \\ \nwarrow & & \swarrow \\ & \mathcal{A}_3 + \mathcal{A}_4 & \end{array} \qquad \textbf{(S1)}$$

$$2\mathcal{A}_1 \rightleftarrows 2\mathcal{A}_3 \qquad \textbf{(S2)}$$

As before, we make the associations $\mathcal{C}_1 = \mathcal{A}_1$, $\mathcal{C}_2 = \mathcal{A}_2$, $\mathcal{C}_3 = \mathcal{A}_3 + \mathcal{A}_4$, $\mathcal{C}_4 = 2\mathcal{A}_1$, *and* $\mathcal{C}_5 = 2\mathcal{A}_3$.

We can clearly see that the system is partitioned into two distinct sets of connected complexes, corresponding to those complexes in (S1) *and those in* (S2). *Consequently, the system has two linkage classes given by* $\mathcal{L}_1 = \{\mathcal{C}_1, \mathcal{C}_2, \mathcal{C}_3\}$ *and* $\mathcal{L}_2 = \{\mathcal{C}_4, \mathcal{C}_5\}$. *As expected, the complex set* $\mathcal{C}$ *is completely partitioned into non-overlapping linkage classes so that* $\mathcal{C} = \mathcal{L}_1 \cup \mathcal{L}_2$ *where* $\mathcal{L}_1 \cap \mathcal{L}_2 = \varnothing$.

We now consider the reversibility of the systems (S1) *and* (S2). *It is clear that system* (S1) *is not a reversible system since none of the reactions contained in the mechanism have a reverse step. We can see, however, that given any path from one complex to another (e.g.* $\mathcal{C}_1$ *to* $\mathcal{C}_2$*) there exists a path leading to the original complex (e.g.* $\mathcal{C}_2$ *to* $\mathcal{C}_3$ *to* $\mathcal{C}_1$*). Consequently, the system* (S1) *is weakly reversible.*

We can clearly see that the system (S2) *is reversible. Since every reversible mechanism is also trivially weakly reversible, the entire mechanism* (S1) *and* (S2) *is weakly reversible (but not reversible, since* (S1) *is not).*

It remains to determine the deficiency of the mechanism. The quantities we need are the number of distinct complexes (n*), the dimension of the stoichiometric subspace (*s*), and the number of linkage classes (*ℓ*). We have that* $n = 5$ *and* $\ell = 2$ *from before, so it only*

remains to determine s. We have

$$S = \text{span}\left\{\begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ -1 \\ -1 \end{bmatrix}, \begin{bmatrix} -2 \\ 0 \\ 2 \\ 0 \end{bmatrix}, \begin{bmatrix} 2 \\ 0 \\ -2 \\ 0 \end{bmatrix}\right\}$$
$$= \text{span}\left\{\begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} -2 \\ 0 \\ 2 \\ 0 \end{bmatrix}\right\}.$$

We can clearly see that $s = dim(S) = 3$ *so that the deficiency is given by*

$$\delta = n - \ell - s = 5 - 2 - 3 = 0.$$

In other words, the mechanism is a weakly reversible zero deficiency system. Such systems will be considered extensively in Section 3.4.

2.3 Mass-Action Kinetics

We are primarily interested in the time evolution of the concentrations of the chemical species as a result of a given reaction network.

In order to accomplish this, we need to derive a reasonable set of laws governing the rate of growth and depletion of the chemical species. This has been handled in various ways in the mathematical literature. Depending on the intended practical application, different

assumptions on the nature of the system are needed, which leads to different mathematical models.

In this thesis, unless otherwise stated, we will make the following model assumptions:

1. **Constant External Conditions:** The rate of a chemical reaction depends sensitively on such system properties as temperature, volume and pressure. Many enzymatic reactions, for instance, only occur within a certain temperature range and with varying efficacies within that range. We will assume throughout this thesis that the variation in these quantities is negligible throughout the course of the reactions.

2. **Continuous Mixing:** The rate of a chemical reaction depends on the spatial domain of the reaction. If pockets of higher concentration of one species or another are allowed, the rate of reaction will vary according to these spatial differences. We will assume that all of the chemical concentrations are spatially homogeneous so that we may ignore diffusive and other spatial effects. (In laboratory and industrial applications, this can be approximated by continuously stirring the mixture.)

3. **Law of Mass Action:** We still need to formulate some law by which concentrations evolve. The law of mass action is the most widely used in general chemistry. This 'law' states that the rate of a chemical reaction is proportional to the product of the reactant concentrations. This is a rough approximation of the idealization that a reaction's occurrence is proportional to the probability of the reactants occupying the same point in space (i.e. colliding). If the proportionality constant is taken to be $k > 0$ then, for a reaction catalyzed by $\mathcal{A}_1$ and $\mathcal{A}_2$, for instance, we have [rate of reaction] = $k[\mathcal{A}_1][\mathcal{A}_2]$.

We will let $x_i = [\mathcal{A}_i]$ denote the concentration of the i^{th} species and denote by $\mathbf{x} = [x_1\ x_2 \cdots x_m]^T \in \mathbb{R}^m$ the *concentration vector*.

Under these model assumptions, the reasonable system of differential equations governing the time evolution of the concentrations can be derived from (2.1). In general, for each reaction in a mass-action system there are three features which influence the dynamics: the monomial mass-action term, the proportionality constant k_i, and the net stoichiometric effect of each instance of the reaction of each species. Consequently, the governing system of differential equations is given by

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) = \sum_{i=1}^{r} k_i\ (\mathbf{z}_i' - \mathbf{z}_i)\ \mathbf{x}^{\mathbf{z}_i} \tag{2.3}$$

where $\mathbf{x}^{\mathbf{z}_i} = \prod_{j=1}^{m} x_j^{z_{ij}}$. The vectors $\{(\mathbf{z}_i' - \mathbf{z}_i) \mid i = 1, \ldots, r\}$ are called the *reaction vectors* and also factor into the stoichiometric subspace (see Definition 2.2.8). They keep track of how each species is affected by every instance of each reaction. The proportionality constants $k_i > 0$, $i = 1, \ldots, r$, are called *rate constants*. We will denote by $\mathbf{k} = [k_1\ k_2 \cdots k_r]^T \in \mathbb{R}^r_{>0}$ the *rate constant vector*.

Chemical reaction networks endowed with mass-action kinetics (2.3) will be called *mass-action systems* and will be denoted by $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$. Since mass-action kinetics is the only form of kinetics considered in this thesis, we will use $\mathcal{N}$ interchangeably to denote both the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and the mass-action system $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$.

As mentioned in the introduction of this chapter, there are multiple ways of representing the governing system of differential equations (2.3). For most of the applications in this thesis, (2.3) will *not* be the preferred representation. Rather, we will typically choose to index the mechanism according to the complex-centred notation of (2.2). With this

notation, the system of differential equations governing the time evolution of concentrations is given by

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) = \sum_{(i,j)\in\mathcal{R}} k(i,j)(\mathbf{z}_j - \mathbf{z}_i)\mathbf{x}^{\mathbf{z}_i} \tag{2.4}$$

where $\mathbf{x}^{\mathbf{z}_i} = \prod_{j=1}^{m} x_j^{z_{ij}}$. The reaction vectors are now given by the set $\{(\mathbf{z}_j - \mathbf{z}_i) \mid (i,j) \in \mathcal{R}\}$ where

$$\mathcal{R} = \{(i,j) \mid k(i,j) > 0, i,j = 1,\ldots,n\}.$$

Under these simplifying assumptions, we can represent the reaction graphs (2.1) and (2.2) respectively as the *weighted* reaction graphs

$$\mathcal{R}_i : \qquad \mathcal{C}_i \xrightarrow{k_i} \mathcal{C}_i', \qquad \text{for } i = 1,\ldots,r \tag{2.5}$$

and

$$\mathcal{R}_{ij} : \qquad \mathcal{C}_i \xrightarrow{k(i,j)} \mathcal{C}_j, \qquad \text{for } i,j = 1,\ldots,n. \tag{2.6}$$

There are two alternative ways of representing the system which will be needed in specific sections of this thesis. We will, however, refrain from introducing the relevant notations until those sections. It is also worth noting that many different assumptions on the kinetics of chemical reaction networks exist within the literature, including Michaelis-Menten kinetics [43], Hill kinetics [29], κ-variable mass-action kinetics [2, 19], S-system kinetics [48, 49], and more general kinetics [10, 56]. The reader is referred to the respective papers for a more complete introduction to these kinetics schemes.

Example 2.3.1. *Consider the reaction*

$$2\mathcal{A}_1 \xrightarrow{k} \mathcal{A}_2.$$

By our model assumptions, we may assume that the rate of the reaction depends only upon the reactant concentrations and the constant $k > 0$. By the law of mass action, we have $[\text{rate of reaction}] = k[\mathcal{A}_1][\mathcal{A}_1] = k[\mathcal{A}_1]^2$.

We have yet to consider how each instance of the reaction occurring impacts the individual species. We can readily see that each time the reaction occurs, we lose two molecules of $\mathcal{A}_1$ and gain one molecule of $\mathcal{A}_2$. We can account for this in the differential equations by adding the coefficients -2 and 1 to the individual equations.

The system is therefore governed by the system of ordinary differential equations

$$\begin{aligned} \frac{dx_1}{dt} &= -2kx_1^2 \\ \frac{dx_2}{dt} &= kx_1^2. \end{aligned}$$

The system is simple enough that we can integrate directly to arrive at the solution

$$x_1(t) = \frac{x_{10}}{2kx_{10}t + 1} \qquad x_2(t) = \frac{x_{10}}{2}\left[\frac{2kx_{10}t}{2kx_{10}t + 1}\right] + x_{20}$$

where $x_{10} = x_1(0)$ and $x_{20} = x_2(0)$. We can see immediately that as $t \to \infty$ we have $x_1(t) \to 0$ and $x_2(t) \to x_{10}/2 + x_{20}$. In other words, all of the mass gets transferred from $\mathcal{A}_1$ to $\mathcal{A}_2$, as we might expect.

2.4 Stoichiometric Compatibility Classes

Even without the benefit of specific examples, several fundamental and unique properties of mass action-systems can be readily discerned from the structure of (2.3) and (2.4). We can immediately see that concentrations evolve according to a system of autonomous non-linear, polynomial ordinary differential equations. There is a significant amount of literature on such systems [21]. Chemical reaction systems have the additional restriction that no monomial with a negative coefficient may appear in the rate equation for a concentration which does not appear in the monomial; this corresponds to the physical observation that a chemical species may not be depleted by a reaction for which it was not a reactant. This characteristic is sometimes referred to as a lack of *negative cross-effects* or the *kinetic* property of mass-action systems [21, 22, 28].

Beyond the simplest of examples, however, mass-action systems cannot be solved analytically as was done in Example 2.3.1. Consequently, a variety of analysis methods have been proposed in the literature, including quasi-steady-state approximations [45], linearization about equilibrium concentrations [56], and Lyapunov function methods [33, 42, 63].

On a more basic level, we can restrict the behaviour of trajectories by careful observation of the reaction vectors in (2.3) and (2.4). In particular, it is clear that solutions are not able to wander around freely in $\mathbb{R}^m$. The following concepts help clarify where solutions may lie. (Also see Definition 2.2.8 for the definition of the stoichiometric subspace S.)

Definition 2.4.1. *The **kinetic subspace** for a mass-action system (2.3) is the smallest linear subspace $S^* \subset \mathbb{R}^m$ such that*

$$im(\mathbf{f}(\mathbf{x})) \subseteq S^*.$$

The dimension of the kinetic subspace will be denoted by $|S^*| = s^*$.

Definition 2.4.2. *The positive* ***stoichiometric compatibility class*** *containing the initial composition* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ *is the set* $\mathsf{C}_{\mathbf{x}_0} = (\mathbf{x}_0 + S) \cap \mathbb{R}^m_{>0}$.

Definition 2.4.3. *The positive* ***kinetic compatibility class*** *containing the initial composition* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ *is the set* $\mathsf{C}^*_{\mathbf{x}_0} = (\mathbf{x}_0 + S^*) \cap \mathbb{R}^m_{>0}$.

While the stoichiometric and kinetic subspaces are related, they need not coincide, in which case we have the strict inclusion $S^* \subset S$. It is clear given the way the reaction vectors factor into (2.3) and (2.4) that we have $\mathbf{f}(\mathbf{x}) \in S^*$ and $\mathbf{f}(\mathbf{x}) \in S$ where $\mathbf{f}(\mathbf{x})$ is the right-hand side of (2.3) or (2.4). The following result clarifies the relationship between the kinetic and stoichiometric subspaces and allows us to restrict attention to $\mathsf{C}_{\mathbf{x}_0}$ for weakly reversible networks.

Lemma 2.4.1 (Corollary 1, [32])**.** *For weakly reversible mass-action systems the stoichiometric and kinetic subspaces coincide.*

The following result restricts the behaviour of solutions of (2.3) and (2.4). It can be found in [33] and [63]. A comparable result exists for kinetic compatibility classes $\mathsf{C}^*_{\mathbf{x}_0}$; however, since we will be primarily concerned with weakly reversible networks in this thesis we will restrict our attention to $\mathsf{C}_{\mathbf{x}_0}$.

Proposition 2.4.1. *Let* $\mathbf{x}(t)$ *be the solution to (2.3) with* $\mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}^m_{>0}$. *Then* $\mathbf{x}(t) \in \mathsf{C}_{\mathbf{x}_0}$ *for* $t \geq 0$.

Proof. We will prove separately that $\mathbf{x}(t) \in (\mathbf{x}_0 + S)$ for $t \geq 0$ and that $\mathbf{x}(t) \in \mathbb{R}^m_{>0}$ for $t \geq 0$.

Consider (2.3). The system is autonomous, so we can integrate from $s = 0$ to $s = t$ to get

$$\int_0^t \frac{d\mathbf{x}(s)}{ds}\, ds = \sum_{i=1}^{r} k_i(\mathbf{z}_i' - \mathbf{z}_i) \int_0^t \mathbf{x}(s)^{\mathbf{z}_i}\, ds$$

which implies

$$\mathbf{x}(t) = \mathbf{x}_0 + \sum_{i=1}^{r} k_i(\mathbf{z}_i' - \mathbf{z}_i) \int_0^t \mathbf{x}(s)^{\mathbf{z}_i}\, ds.$$

Regardless of what the integral on the right-hand side evaluates to, the sum is in the span of the reaction vectors $\mathbf{z}_i' - \mathbf{z}_i$. It follows that $\mathbf{x}(t) \in \mathbf{x}_0 + S$ for $t \geq 0$ and the first claim is proved.

We now prove $\mathbf{x}(t) \in \mathbb{R}^m_{>0}$ for $t \geq 0$. We will consider the concentration of the species x_j, $j = 1, \ldots, m$, individually. We define the following index sets:

$$\mathcal{R}_1^j = \{\mathcal{R}_i \mid \mathbf{z}_{ij} > 0\}$$
$$\mathcal{R}_2^j = \{\mathcal{R}_i \mid \mathbf{z}_{ij} = 0\}.$$

We can rewrite the j^{th} component of (2.3) with respect to these sets as

$$\frac{dx_j}{dt} = f_1(\mathbf{x}) \cdot x_j + f_2(\mathbf{x}) \tag{2.7}$$

where

$$f_1(\mathbf{x}) = \frac{1}{x_j} \sum_{\substack{i=1 \\ \mathcal{R}_i \in \mathcal{R}_1^j}}^{r} k_i(\mathbf{z}_{ij}' - \mathbf{z}_{ij})\mathbf{x}^{\mathbf{z}_i}$$
$$f_2(\mathbf{x}) = \sum_{\substack{i=1 \\ \mathcal{R}_i \in \mathcal{R}_2^j}}^{r} k_i(\mathbf{z}_{ij}' - \mathbf{z}_{ij})\mathbf{x}^{\mathbf{z}_i}.$$

Two things are worth noting about the functions $f_1(\mathbf{x})$ and $f_2(\mathbf{x})$:

1. Since $\mathbf{z}_{ij} > 0$ for $\mathcal{R}_i \in \mathcal{R}_1^j$ and $\mathbf{z}_{ij}$ is an integer, the quantity $(1/x_j)\cdot\mathbf{x}^{\mathbf{z}_i}$ is a nonnegative, finite value.

2. Since $\mathbf{z}_{ij} = 0$ for $\mathcal{R}_i \in \mathcal{R}_2^j$, it follows that $\mathbf{z}'_{ij} - \mathbf{z}_{ij} \geq 0$, and consequently that $f_2(\mathbf{x}) \geq 0$. (This is a consequence of the physical observation that a species may only be depleted as a result of a reaction if the species itself is one of the reactants.)

We can now use the integrating factor $\mu(t) = \exp\left\{-\int_0^t f_1(\mathbf{x}(s))\, ds\right\}$ on (2.7) to get

$$\begin{aligned}
& \frac{dx_j(t)}{dt} - f_1(\mathbf{x}(t)) \cdot x_j(t) = f_2(\mathbf{x}(t)) \\
\Longrightarrow \qquad & \frac{d}{dt}\left[e^{-\int_0^t f_1(\mathbf{x}(s))\, ds} x_j(t)\right] = e^{-\int_0^t f_1(\mathbf{x}(s))\, ds} f_2(\mathbf{x}(t)) \\
\Longrightarrow \qquad & x_j(t) = e^{\int_0^t f_1(\mathbf{x}(s))\, ds} x_j(0) + \int_0^t e^{-\int_0^s f_1(\mathbf{x}(r))\, dr} f_2(\mathbf{x}(s))\, ds.
\end{aligned}$$

By assumption, we have $x_j(0) > 0$ and we have already observed that $f_1(\mathbf{x})$ is well-defined and $f_2(\mathbf{x})$ is nonnegative. Since the exponential is always positive, and integrating over a nonnegative region yields a nonnegative value, we have that $x_j(t) > 0$ for all $t \geq 0$. Since the concentration x_j was chosen arbitrarily, we have $\mathbf{x}(t) \in \mathbb{R}^m_{>0}$ for all $t \geq 0$, and we are done. □

Another important class of subspace relevant to mass-action systems is the *conservation subspace*.

Definition 2.4.4. *The* ***conservation subspace*** *is given by*

$$S^\perp = \left\{\mathbf{v} \in \mathbb{R}^m \mid \langle \mathbf{v}, \mathbf{z}'_i - \mathbf{z}_i \rangle = 0, i = 1, \ldots, r\right\}.$$

Definition 2.4.5. *A chemical reaction network is said to be* ***conservative*** *if there exists a* $\mathbf{v} \in \mathbb{R}^m_{>0}$ *such that* $\mathbf{v} \in S^\perp$.

For many applications, the conservation vectors $\mathbf{v} \in S^\perp$ play a significant role in simplifying analysis of (2.3). The reason is that, since $\dot{\mathbf{x}}(t) \in S$ for all $t \geq 0$, it follows that

$$\left\langle \mathbf{v}, \frac{d\mathbf{x}(t)}{dt} \right\rangle = 0$$

for all $\mathbf{v} \in S^\perp$. This gives rise to the *conservation law*

$$\langle \mathbf{v}, \mathbf{x}(t) - \mathbf{x}_0 \rangle = 0. \tag{2.8}$$

In general, each linearly independent conservation law (2.8) allows one variable to be removed from (2.3), since any single concentration in (2.8) can by solved for as a linear combination of the others.

In many applications, this notion of a conservation law corresponds to the physical notion of conservation of mass. This is most readily seen for conservative systems. In broad strokes, reactants in a physically closed system may not appear from, or disappear into, nothing so that systems are partitioned by how much initial matter is present. While this is a convenient interpretation, however, we note that our notion of a conservation law is more general than this and can be applied to many systems where no such physical interpretation is available.

Example 2.4.1. *Reconsider the reaction from Example 2.3.1 made reversible, so that we have*

$$2\mathcal{A}_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathcal{A}_2.$$

According to (2.3), the governing system of differential equations is given by

$$\begin{aligned} \frac{dx_1}{dt} &= -2k_1x_1^2 + 2k_2x_2 \\ \frac{dx_2}{dt} &= k_1x_1^2 - k_2x_2. \end{aligned} \tag{2.9}$$

This system can no longer easily be integrated so that we are relegated to alternative methods to analyse the behaviour of the chemical concentrations. For this example, we make two crucial observations. Firstly, by Proposition 2.4.1 we have that solutions are restricted to their respective stoichiometric compatibility classes $\mathsf{C}_{\mathbf{x}_0}$. *These are translations of* S, *which is given by*

$$S = \operatorname{span}\left\{\begin{bmatrix} 2 \\ -1 \end{bmatrix}\right\}.$$

Consequently, $\mathsf{C}_{\mathbf{x}_0}$ *is a one-dimensional subset of* $\mathbb{R}^2_{>0}$.

We also notice that the equilibrium conditions coincide for the two expressions in (2.9). Specifically, we have

$$\frac{dx_1}{dt} = \frac{dx_2}{dt} = 0 \quad \text{iff} \quad x_2 = \frac{k_1}{k_2}\, x_1^2.$$

This is a one-dimensional curve in $\mathbb{R}^2_{>0}$. *More importantly, each compatibility class* $\mathsf{C}_{\mathbf{x}_0}$ *intersects this curve at exactly one point. In other words, there is precisely one equilibrium point in each compatibility class. It can be easily observed from (2.9) that trajectories above the equilibrium curve are forced downward while trajectories below the curve are forced upward so that the equilibrium point in each compatibility class is asymptotically stable (see Figure 2.1).*

We can also analyze the system by consideration of the conservation laws. For this

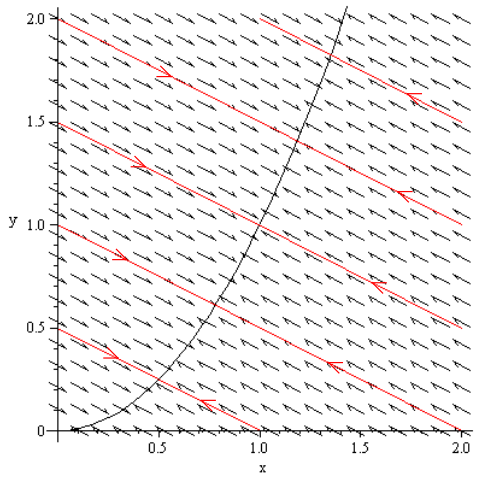

Figure 2.1: Vector field plot of (2.9) with $k_1 = k_2 = 1$. Each stoichiometric compatibility class (the translations of $x_2 = -\frac{1}{2}x_1$) intersects the equilibrium set (the parabola $x_2 = x_1^2$) precisely once.

system, we have

$$\Gamma = \text{span}\left\{\begin{bmatrix} 1 \\ 2 \end{bmatrix}\right\} = S^{\perp}.$$

By (2.8), we have

$$x_1(t) + 2x_2(t) = x_{10} + 2x_{20} \quad \Longrightarrow \quad x_2(t) = \frac{1}{2}\left(x_{10} - x_1(t)\right) + x_{20}.$$

This can be substituted into (2.9) to give

$$\begin{aligned} \frac{dx_1(t)}{dt} &= -2k_1x_1(t)^2 - k_2x_1(t) + k_2x_{10} + 2k_2x_{20} \\ x_2(t) &= \frac{1}{2}\left(x_{10} - x_1(t)\right) + x_{20}. \end{aligned}$$

As expected, the single conservation law has removed a single differential equation from

the system. The solution may now be obtained by solving for $x_1(t)$ from the remaining differential equation and applying the linear conservation law to solve for $x_2(t)$.

It is worth noting that a solution $\mathbf{x}(t)$ of (2.3) with $\mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}^m_{>0}$ may exist only on a finite interval $0 \leq t < T$. This can happen if there is an unbalanced input of a species (i.e. creation of a species with no depletion) into the system. In this case we only have $\mathbf{x}(t) \in \mathsf{C}_{\mathbf{x}_0}$ for $0 \leq t < T$.

Example 2.4.2. *Consider the system*

$$\mathcal{O} \xrightarrow{k_1} 2\mathcal{A} \xrightarrow{k_2} 4\mathcal{A}.$$

According to (2.3), the system is governed by the differential equation

$$\frac{dx}{dt} = 2k_1 + 2k_2x^2$$

which can easily be integrated to yield

$$x(t) = \sqrt{\frac{k_1}{k_2}} \tan\left(2\sqrt{k_1k_2}t + \arctan\left(\sqrt{\frac{k_2}{k_1}}x_0\right)\right).$$

This solution goes to infinity as

$$t \to T = \frac{1}{2\sqrt{k_1k_2}}\left(\frac{\pi}{2} - \arctan\left(\sqrt{\frac{k_2}{k_1}}x_0\right)\right).$$

We can see that, since $\sqrt{k_2/k_1}x_0 > 0$, we have $\arctan(\sqrt{k_2/k_1}x_0) \in (0, \pi/2)$ so that T is always a finite, positive value. Since $x(t) \to \infty$ in finite time, the solution only exists for $0 \leq t < T$.

It might be tempting to suppose that all systems with unbalanced inputs have solutions which cease to exist at some point, but this is not necessarily the case. For example, the simple system

$$\mathcal{O} \xrightarrow{k} \mathcal{A}$$

is governed by

$$\frac{dx}{dt} = k \qquad \Longrightarrow \qquad x(t) = kt + x_0.$$

While the solution grows unbounded, it does not blow up to infinity in finite time, so that the solution exists for all $t \geq 0$.

Chapter 3

Locally Stable Systems

Since mass-action systems can rarely be solved explicitly, alternative methods of analysis are frequently necessary. In this chapter, we introduce one particular type of behaviour—called *locally stable dynamics*—which is guaranteed under several well-studied conditions. We introduce and discuss two classifications of systems which are known to exhibit locally stable dynamics: detailed balanced systems and complex balanced systems.

The concept of complex-balancing of chemical reaction mechanisms was first introduced in 1972 by M. Feinberg, F. Horn and R. Jackson and has been particularly influential over the past nearly forty years (see [25, 30, 33]). As such, we will devote a significant amount of time to deriving and analyzing the results of these papers. Our considerations of the detailed balanced systems analyzed by A. Volpert in [63] will be significantly briefer.

We start by defining the type of behaviour in which we are interested.

Definition 3.0.6. *A mass-action system is said to have* ***locally stable dynamics*** *if there exists within each positive kinetic compatibility class precisely one equilibrium concentration and that concentration is locally asymptotically stable.*

We note that for the case of the weakly reversible networks considered extensively in this thesis, the kinetic and stoichiometric compatibility classes coincide by Lemma 2.4.1 so that locally stable kinetics can be redefined according to the stoichiometric compatibility classes.

Locally stable dynamics is, in some senses, the "nicest" kind of behaviour one could want. It guarantees that, regardless of our initial concentrations, the associated compatibility class has a single equilibrium point and that if we start close enough to that equilibrium point, we converge toward it.

It is important to note, however, that locally stable dynamics does not prohibit the existence of—or convergence of trajectories toward—an equilibrium concentration on the boundary of the positive compatibility class (i.e. an equilibrium where at least one concentration x_j is zero). Systems for which all trajectories starting within a compatibility class converge toward the positive equilibrium are said to have *globally stable dynamics*. They will be the main topic of consideration in Chapter 5.

In the following subsections, I introduce two classifications of mass-action systems which are known to exhibit locally stable dynamics: detailed balanced and complex balanced systems. Detailed balanced systems are a special case of complex balanced systems; however, due to their historical prominence and relatively easy formulation, I will include a full analysis of detailed balanced systems as a stepping-stone toward understanding complex balanced systems.

The Lyapunov function used to analyse both classes of systems is given by

$$L(\mathbf{x}) = \sum_{i=1}^{m} x_i(\ln(x_i) - \ln(x_i^*) - 1) + x_i^* \tag{3.1}$$

where $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ is an arbitrary equilibrium concentration. The concentration $\mathbf{x}^*$ will be called the *centre* of the Lyapunov function.

The following result corresponds to Lemma 4A and Lemma 4B in [33].

Lemma 3.0.2. *The function $L(\mathbf{x})$ given by (3.1) assumes a unique minimum in the relative interior of each $\mathsf{C}_{\mathbf{x}_0}$. Furthermore, at this minimum value we have $\nabla L(\mathbf{x}) \in S^\perp$.*

Proof. We first consider the properties of $L(\mathbf{x})$ on $\mathbb{R}^m_{>0}$. We can see that the Hessian of $L(\mathbf{x})$ is given by

$$\begin{aligned}\nabla^2 L(\mathbf{x}) &= \nabla(\nabla L(\mathbf{x})) \\ &= \nabla(\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) \\ &= \operatorname{diag}\left\{\frac{1}{x_i}\right\}_{i=1}^m.\end{aligned}$$

Since the Hessian of $L(\mathbf{x})$ is strictly positive definite for $\mathbf{x} \in \mathbb{R}^m_{>0}$, it follows that $L(\mathbf{x})$ is strictly convex. Furthermore, since $\mathsf{C}_{\mathbf{x}_0}$ is a convex subset of $\mathbb{R}^m_{>0}$, it follows that $L(\mathbf{x})$ is strictly convex on $\mathsf{C}_{\mathbf{x}_0}$.

It may still be possible that the minimum relative to $\mathsf{C}_{\mathbf{x}_0}$ is obtained along the boundary of $\mathsf{C}_{\mathbf{x}_0}$. We can see that

$$\lim_{\|\mathbf{x}\| \to \infty} L(\mathbf{x}) = \infty \tag{3.2}$$

so that $L(\mathbf{x})$ may not approach the minimum value at infinity. It may still approach the minimum somewhere on $\partial\mathbb{R}^m_{>0}$. To rule this possibility out, we approach the boundary

along an arbitrary straight line. Given $\mathbf{x}^1 \in \mathbf{R}^m_{>0}$ and $\mathbf{x}^2 \in \partial\mathbf{R}^m_{>0}$, we have that

$$\begin{aligned}\lim_{\lambda\to 1}\frac{d}{d\lambda}L(\mathbf{x}^1+\lambda(\mathbf{x}^2-\mathbf{x}^1)) &= \lim_{\lambda\to 1}\nabla L(\mathbf{x}^1+\lambda(\mathbf{x}^2-\mathbf{x}^1))\cdot(\mathbf{x}^2-\mathbf{x}^1)\\ &= \sum_{i=1}^{m}\lim_{\lambda\to 1}(\ln(x_i^1+\lambda(x_i^2-x_i^1))-\ln(x_i^*))(x_i^2-x_i^1).\end{aligned}$$

Since $\mathbf{x}^2 \in \partial\mathbb{R}^m_{>0}$, there is at least one $i_0 \in \{1,\ldots,m\}$ such that $x^2_{i_0} = 0$. For this component

$$\begin{aligned}&\lim_{\lambda\to 1}(\ln(x^1_{i_0}+\lambda(x^2_{i_0}-x^1_{i_0}))-\ln(x^*_{i_0}))(x^2_{i_0}-x^1_{i_0})\\ &\qquad = \lim_{\lambda\to 1}(\ln(x^1_{i_0}-\lambda x^1_{i_0})-\ln(x^*_{i_0}))(-x^1_{i_0}) = \infty.\end{aligned}$$

Since the rest of the elements in the sum are finite, it follows that

$$\lim_{\lambda\to 1}\frac{d}{d\lambda}L(\mathbf{x}^1+\lambda(\mathbf{x}^2-\mathbf{x}^1)) = \infty.$$

In other words, if we approach $\partial\mathbb{R}^m_{>0}$ along any straight line from the interior, the derivative explodes. It follows that the minimum of $L(\mathbf{x})$ cannot be obtained on the boundary, so that the minimum must be restricted to the relative interior of the set $\mathsf{C}_{\mathbf{x}_0}$.

The fact that $\nabla L(\mathbf{x}) \in S^\perp$ follows from the observation that $\nabla L(\mathbf{x})$ remains stationary with respect to changes within $\mathsf{C}_{\mathbf{x}_0}$. In other words, for every $(\mathbf{y}-\mathbf{x})$, $\mathbf{y} \in \mathsf{C}_{\mathbf{x}_0}$, $\mathbf{y} \neq \mathbf{x}$, we have $\nabla L(\mathbf{x})\cdot(\mathbf{y}-\mathbf{x}) = 0$ since $(\mathbf{y}-\mathbf{x}) \in S$. This is equivalent to $\nabla L(\mathbf{x}) \in S^\perp$. □

We will need the following two lemmas in our analysis of detailed balanced and complex balanced systems.

Lemma 3.0.3. *For every $a, b > 0$ we have*

$$(b-a)(\ln(a)-\ln(b)) \leq 0$$

with equality if and only if $a = b$.

Proof. We have three cases to consider.

1. If $a > b$ then $\ln(a) - \ln(b) > 0$ so that $(b-a)(\ln(a) - \ln(b)) < 0$.
2. If $a < b$ then $\ln(a) - \ln(b) < 0$ so that $(b-a)(\ln(a) - \ln(b)) < 0$.
3. If $a = b$ then $\ln(a) - \ln(b) = 0$ so that $(b-a)(\ln(a) - \ln(b)) = 0$.

The result follows. □

The following result can be found in Appendix 3 of [33]. While the result holds for any monotonically increasing function, we state it here for $\ln(x)$.

Lemma 3.0.4. *For every set $\{\alpha_1, \alpha_2, \ldots, \alpha_n\}$ satisfying $\alpha_i > 0$ for $i = 1, \ldots, n$, $n \geq 2$, we have*

$$\sum_{j=1}^{n} \alpha_j (\ln(\alpha_{j+1}) - \ln(\alpha_j)) \leq 0$$

where $\alpha_{n+1} = \alpha_1$, with equality holding if and only if

$$\alpha_1 = \cdots = \alpha_n.$$

Proof. The proof is an induction on n, the number of elements in the set.

Base case: Consider the case where $n = 2$. We have that

$$\begin{aligned}
&\sum_{j=1}^{2} \alpha_j (\ln(\alpha_{j+1}) - \ln(\alpha_j))) \\
&\qquad = \alpha_1(\ln(\alpha_2) - \ln(\alpha_1)) + \alpha_2(\ln(\alpha_1) - \ln(\alpha_2)) \\
&\qquad = (\alpha_1 - \alpha_2)(\ln(\alpha_2) - \ln(\alpha_1)).
\end{aligned}$$

It follows from Lemma 3.0.3 with $a = \alpha_2$ and $b = \alpha_1$ that this quantity is negative and equal to zero if and only if $\alpha_1 = \alpha_2$.

Inductive case: Assume that for every set $\{\alpha_1, \alpha_2 \ldots, \alpha_n\}$ with $\alpha_i > 0$, $i = 1, \ldots, n$, we have

$$\sum_{j=1}^{n} \alpha_j(\ln(\alpha_{j+1}) - \ln(\alpha_j)) \leq 0 \tag{3.3}$$

where $\alpha_{n+1} = \alpha_1$, with equality if and only if

$$\alpha_1 = \alpha_2 = \cdots = \alpha_n.$$

Now consider the set $\{\alpha_1, \ldots, \alpha_n, \alpha_{n+1}\}$ with $\alpha_i > 0$, $i = 1, \ldots, n+1$. Since we have assumed (3.3) holds for any family of n elements, we can choose α_{n+1} to be the largest element in the set $\{\alpha_1, \ldots, \alpha_{n+1}\}$ and the inductive hypothesis (3.3) to hold on the family $\{\alpha_1, \ldots, \alpha_n\}$. Consider the following sum:

$$\begin{aligned}
&\sum_{j=1}^{n+1} \alpha_j(\ln(\alpha_{j+1}) - \ln(\alpha_j)) \\
&= \sum_{j=1}^{n-1} [\alpha_j(\ln(\alpha_{j+1}) - \ln(\alpha_j))] + \alpha_n(\ln(\alpha_{n+1}) - \ln(\alpha_n)) \\
&\qquad + \alpha_{n+1}(\ln(\alpha_1) - \ln(\alpha_{n+1})).
\end{aligned}$$

We add and subtract $\alpha_n(\ln(\alpha_1) - \ln(\alpha_{n+1}))$ from the right-hand side to get

$$\begin{aligned}
&\sum_{j=1}^{n+1} \alpha_j(\ln(\alpha_{j+1}) - \ln(\alpha_j)) \\
&= \sum_{j=1}^{n-1} [\alpha_j(\ln(\alpha_{j+1}) - \ln(\alpha_j))] + \alpha_n(\ln(\alpha_1) - \ln(\alpha_n)) \\
&\qquad\qquad + (\alpha_{n+1} - \alpha_n)(\ln(\alpha_1) - \ln(\alpha_{n+1})) \\
&= \sum_{j=1}^{n} [\alpha_j(\ln(\alpha_{j+1}) - \ln(\alpha_j))] + (\alpha_{n+1} - \alpha_n)(\ln(\alpha_1) - \ln(\alpha_{n+1})).
\end{aligned}$$

We have abused the sum notation in the final line so that $\alpha_{n+1} = \alpha_1$. This sum satisfies our inductive assumption on the set $\{\alpha_1, \ldots, \alpha_n\}$. The remaining element on the right-hand side is non-positive since we have chosen α_{n+1} to be the largest element in the set. Since both the sum and the remaining term is non-positive, we can only have equality with zero if both terms are zero. By assumption, this only happens for the first term if $\alpha_1 = \cdots = \alpha_n$. The second term is zero if and only if $\alpha_{n+1} = \alpha_1$ or $\alpha_{n+1} = \alpha_n$, either of which is sufficient to imply $\alpha_1 = \alpha_2 = \cdots = \alpha_n = \alpha_{n+1}$. This completes the proof.

□

3.1 Equilibrium Conditions

For many mass-action systems, the behaviour of solutions can be predictably determined by the nature of the set of permissible equilibrium concentrations. Consequently, significant effort has been expended determining conditions on the equilibrium set of a system under which dynamic behaviour is qualitatively predictable. In this section, we will introduce two of the classifications of equilibrium concentrations of (2.4) which have proven useful

in the literature: detailed balanced and complex balanced equilibrium concentrations.

We start by considering a general equilibrium concentration.

Definition 3.1.1. *The concentration* $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ *is said to be an* ***equilibrium concentration*** *of (2.4) if*

$$\mathbf{f}(\mathbf{x}^*) = \sum_{(i,j)\in\mathcal{R}} k(i,j)(\mathbf{z}_j - \mathbf{z}_i)(\mathbf{x}^*)^{\mathbf{z}_i} = 0. \tag{3.4}$$

We now shift our focus to the two classes of equilibrium concentrations which will be of the most interest to us in this thesis. The formulation of detailed balanced systems presented here can be found in [63] while our formulation of complex balanced systems can be found in [33].

Definition 3.1.2. *The concentration* $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ *is said to be a* ***detailed balanced equilibrium concentration*** *of (2.4) if*

$$k(i,j)(\mathbf{x}^*)^{\mathbf{z}_i} = k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} \tag{3.5}$$

for all $i,j = 1,\ldots,n$. *A mass-action system is said to be* ***detailed balanced*** *for a given set of rate constants* $k(i,j)$ *if every positive equilibrium concentration of (2.4) is detailed balanced.*

Definition 3.1.3. *The concentration* $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ *is said to be a* ***complex balanced equilibrium concentration*** *of (2.4) if*

$$\sum_{j=1}^{n} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j=1}^{n} k(i,j) \tag{3.6}$$

for all $i = 1,\ldots,n$. *A mass-action system is said to be* ***complex balanced*** *for a given*

set of rate constants $k(i,j)$ if every positive equilibrium concentration of (2.4) is complex balanced.

The set of detailed balanced equilibrium concentrations of a mechanism will be denoted D while the set of complex balanced equilibrium concentrations will be denoted C. The set of equilibrium concentrations will be denoted E.

More intuitively, an equilibrium concentration is detailed balanced if the rate of every reaction exactly equals the rate of an opposite reaction. Similarly, an equilibrium concentration is complex balanced if, for every complex, the rate of every reaction leading into the complex exactly equals the rate leading out. Notice that all three classifications of equilibrium concentrations presented so far have represented some manner of balancing of reaction rates. For detailed balanced equilibria, we have balancing of rates across reactions; for complex balanced equilibria, we have balancing of rates across complexes; and, of course, for general equilibrium concentrations we have balancing of the rates across species.

It is also clear that the notions of detailed and complex balancing of equilibrium concentrations carry implications for the reaction graph of the system. In particular, the following results can be shown.

Lemma 3.1.1 (Lemma 2A, [30])**.** *If a mass-action system admits a detailed balanced equilibrium, then the system is reversible.*

Proof. Suppose (3.5) is satisfied and $\mathcal{C}_i \to \mathcal{C}_j$ is a reaction in the system. This implies $k(i,j) > 0$. Since (3.5) holds for all $i,j = 1,\dots,n$, and $(\mathbf{x}^*)^{\mathbf{z}_i} > 0$, it follows that

$$k(i,j)(\mathbf{x}^*)^{\mathbf{z}_i} = k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} > 0. \tag{3.7}$$

The only way (3.7) can be satisfied is if $k(j,i) > 0$. This implies $\mathcal{C}_j \to \mathcal{C}_i$ is a reaction in the system. It follows from Definition 2.2.6 that the system is reversible. □

Lemma 3.1.2. *If a mass-action system admits a complex balanced equilibrium, then the system is weakly reversible.*

Proof. Suppose (3.6) is satisfied and the reaction graph contains a path from $\mathcal{C}_a$ to $\mathcal{C}_b$, that is to say, there are complex indices $\{\nu_0, \nu_1, \ldots, \nu_l\}$ such that

$$\mathcal{C}_{\nu_{k-1}} \longrightarrow \mathcal{C}_{\nu_k}, \qquad \text{for } k = 1, \ldots, l$$

where $\nu_0 = a$ and $\nu_l = b$.

Suppose that there does not exist a path from $\mathcal{C}_b$ to $\mathcal{C}_a$. We now define the index set Σ as follows

$$\Sigma = \{k \in \{1, \ldots, n\} \mid \text{there exists a path from } \mathcal{C}_b \text{ to } \mathcal{C}_k\} \cup \{b\}.$$

From this definition, it is obvious that our assumption implies $a \notin \Sigma$.

Furthermore, we notice that all paths originating at a $\mathcal{C}_k$, $k \in \Sigma$, must necessarily lead to a $\mathcal{C}_{\tilde{k}}$, $\tilde{k} \in \Sigma$. It follows that (3.6) can be written

$$\sum_{j \in \Sigma} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} + \sum_{j \notin \Sigma} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j \in \Sigma} k(i,j)$$

for all $i \in \Sigma$. Taking the sum over $i \in \Sigma$, we have

$$\sum_{j \in \Sigma} (\mathbf{x}^*)^{\mathbf{z}_j} \sum_{i \in \Sigma} k(j,i) + \sum_{i \in \Sigma} \sum_{j \notin \Sigma} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = \sum_{i \in \Sigma} (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j \in \Sigma} k(i,j)$$

which implies

$$\sum_{i\in\Sigma}\sum_{j\notin\Sigma} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = 0. \tag{3.8}$$

Since $k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} \geq 0$ for all $i,j = 1,\ldots,n$, the only way (3.8) can be satisfied is if $k(i,j) = 0$ for all $i \notin \Sigma$ and $j \in \Sigma$. In other words, the mechanism does not permit a reaction from a complex $\mathcal{C}_i$, $i \notin \Sigma$, to a complex $\mathcal{C}_j$, $j \in \Sigma$. However, by assumption there is a path from $\mathcal{C}_a$, $a \notin \Sigma$, to $\mathcal{C}_b$, $b \in \Sigma$. In order for such a path to exist, there must exist a reaction from a complex $\mathcal{C}_i$, $i \notin \Sigma$, to a complex $\mathcal{C}_j$, $j \in \Sigma$. This is a contradiction. Consequently, our assumption that there was not a path from $\mathcal{C}_b$ to $\mathcal{C}_a$ must have been in error. Since the path chosen was arbitrary, it follows that the system is weakly reversible by Definition 2.2.7. □

It is obvious that if $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ satisfies (3.6) then $\mathbf{x}^*$ satisfies (3.5), and that if $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ satisfies either (3.6) or (3.5) then $\mathbf{x}^*$ satisfies (3.4). In other words

$$D \subseteq C \subseteq E.$$

In order to see that these inclusions can be strict, consider the following examples.

Example 3.1.1. *Consider the system*

$$\begin{aligned} \mathcal{A}_1 &\xrightarrow{\alpha} \mathcal{A}_2 \\ 2\mathcal{A}_2 &\xrightarrow{\beta} 2\mathcal{A}_1. \end{aligned} \tag{3.9}$$

The system is governed by the system of differential equations

$$\begin{aligned}\frac{dx_1}{dt} &= -\alpha x_1 + 2\beta x_2^2 \\ \frac{dx_2}{dt} &= \alpha x_1 - 2\beta x_2^2\end{aligned}$$

which has the equilibrium set

$$E = \left\{(x_1, x_2) \in \mathbb{R}^2_{>0} \mid \alpha x_1 = 2\beta x_2^2\right\}.$$

However, we can clearly see that the reaction graph (3.9) is neither reversible nor weakly reversible. Consequently, by Lemma 3.1.1 and Lemma 3.1.2, no equilibrium concentration permitted by the system may be detailed or complex balanced.

Example 3.1.2. *Consider the system*

$$\begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{\alpha} & \mathcal{A}_2 \\ & {}_{\gamma}\nwarrow \quad \swarrow_{\beta} & \\ & \mathcal{A}_3. & \end{array} \tag{3.10}$$

The system is governed by the system of differential equations

$$\begin{aligned}\frac{dx_1}{dt} &= -\alpha x_1 + \gamma x_3 \\ \frac{dx_2}{dt} &= \alpha x_1 - \beta x_2 \\ \frac{dx_3}{dt} &= \beta x_2 - \gamma x_3\end{aligned}$$

which has the equilibrium set

$$E = \left\{(x_1, x_2, x_3) \in \mathbb{R}^3_{>0} \mid \alpha x_1 = \beta x_2 = \gamma x_3\right\}.$$

This is exactly the condition required of complex balancing by Definition 3.1.3 so that $C = E$. We can see, however, that the system is only weakly reversible and not strictly reversible, so that no detailed balanced equilibrium concentrations can be permitted by Lemma 3.1.1. Consequently, the mechanism permits complex balanced equilibrium concentrations but not detailed balanced.

We may at this point surmise that the converse implications of Lemma 3.1.1 and Lemma 3.1.2 hold, that is to say, that reversibility and weak reversibility imply detailed and complex balancing of equilibrium concentrations, respectively. The following example shows that we must be careful with such intuition.

Example 3.1.3. *Consider the system*

$$\begin{array}{ccc} 2\mathcal{A}_1 & \xrightarrow{\alpha} & 2\mathcal{A}_2 \\ {\scriptstyle\gamma}\,\nwarrow & & \swarrow\,{\scriptstyle\beta} \\ & \mathcal{A}_1 + \mathcal{A}_2. & \end{array} \tag{3.11}$$

with $\alpha = 3/8$, $\beta = 1$, and $\gamma = 1$. The system is governed by the system of differential equations

$$\begin{aligned} \frac{dx_1}{dt} &= -\frac{3}{4}x_1^2 + x_2^2 + x_1x_2 \\ \frac{dx_2}{dt} &= \frac{3}{4}x_1^2 - x_2^2 - x_1x_2. \end{aligned}$$

We can see that

$$-\frac{3}{4}x_1^2 + x_2^2 + x_1x_2 = \left(x_2 - \frac{1}{2}x_1\right)\left(x_2 + \frac{3}{2}x_1\right)$$

so that

$$E = \left\{(x_1, x_2) \in \mathbb{R}^2_{>0} \mid x_2 = \frac{1}{2}x_1\right\} = \left\{\left[t, \frac{1}{2}\,t\right], t > 0\right\}.$$

The system is not reversible so that no detailed balanced equilibrium concentrations are permitted by Lemma 3.1.1. The system is weakly reversible which suggests complex balancing of equilibrium concentrations is permissible; however, in order to verify the existence of such equilibria, we still need to verify

$$\alpha(\mathbf{x}^*)^{\mathbf{z}_1} = \beta(\mathbf{x}^*)^{\mathbf{z}_2} = \gamma(\mathbf{x}^*)^{\mathbf{z}_3}$$

according to (3.6).

We can see that

$$\begin{aligned}
\alpha(\mathbf{x}^*)^{\mathbf{z}_1} &= \frac{3}{8}(x_1^*)^2 = \frac{3}{8}t^2 \\
\beta(\mathbf{x}^*)^{\mathbf{z}_2} &= (x_2^*)^2 = \frac{1}{4}t^2 \\
\gamma(\mathbf{x}^*)^{\mathbf{z}_3} &= (x_1^*)(x_2^*) = \frac{1}{2}t^2
\end{aligned}$$

so that—somewhat surprisingly—we have

$$\alpha(\mathbf{x}^*)^{\mathbf{z}_1} \neq \beta(\mathbf{x}^*)^{\mathbf{z}_2} \neq \gamma(\mathbf{x}^*)^{\mathbf{z}_3}.$$

It follows that the system permits no complex balanced equilibrium concentrations, even though the system is weakly reversible. This phenomenon will be considered in more detail

in Section 3.3 when we will reconsider this example.

3.2 Detailed Balanced Systems

In this section, we use the classification of detailed balanced equilibrium concentrations given by Definition 3.1.2 to determine properties of the system (2.4). Specifically, we prove that detailed balanced systems exhibit locally stable dynamics.

Firstly, we notice that it follows from Lemma 3.1.1 that if $(i,j) \in \mathcal{R}$ then $(j,i) \in \mathcal{R}$. Consequently, the reaction set $\mathcal{R}$ can be broken down into index pairs $\{(i,j),(j,i)\}$. We will let $\tilde{\mathcal{R}}$ denote an arbitrary subset of $\mathcal{R}$ which contains only one of the index pairs from each set $\{(i,j),(j,i)\}$.

The following result corresponds to Lemma 16 of [13]. It is also implicit in the results of [63].

Lemma 3.2.1. *Consider a mass-action system with a detailed balanced equilibrium* $\mathbf{x}^*$*. Then there exist* $\kappa_{ij} > 0$*,* $(i,j) \in \tilde{\mathcal{R}}$*, such that (2.4) can be written*

$$\frac{d\mathbf{x}}{dt} = \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right]. \tag{3.12}$$

Proof. Consider an arbitrary detailed balanced equilibrium $\mathbf{x}^*$. By Definition 3.1.2, for each pair $\{(i,j),(j,i)\}$ there exists a constant $\kappa_{ij} > 0$ such that

$$k(i,j)(\mathbf{x}^*)^{\mathbf{z}_i} = k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = \kappa_{ij}. \tag{3.13}$$

It follows that

$$k(i,j) = \frac{\kappa_{ij}}{(\mathbf{x}^*)^{\mathbf{z}_i}} \qquad \text{and} \qquad k(j,i) = \frac{\kappa_{ij}}{(\mathbf{x}^*)^{\mathbf{z}_j}}. \tag{3.14}$$

From (2.4) we have

$$\frac{d\mathbf{x}}{dt} = \sum_{(i,j)\in\mathcal{R}} k(i,j)(\mathbf{z}_j - \mathbf{z}_i)\mathbf{x}^{\mathbf{z}_i}.$$

Since $\mathcal{R}$ can be broken down into reaction pairs $\{(i,j),(j,i)\}$, we momentarily restrict our attention to just the indices i and j. Using (3.14), we have

$$\begin{aligned} &k(i,j)(\mathbf{z}_j - \mathbf{z}_i)\mathbf{x}^{\mathbf{z}_i} + k(j,i)(\mathbf{z}_i - \mathbf{z}_j)\mathbf{x}^{\mathbf{z}_j} \\ &\quad = \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} + \kappa_{ij}(\mathbf{z}_i - \mathbf{z}_j)\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j} \\ &\quad = \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right]. \end{aligned}$$

Since $\mathcal{R}$ can be broken down into these pairs, we need only consider one of the indices (i,j) or (j,i) in order to recover the original system of differential equations. In other words, it is sufficient to consider the sum over $(i,j) \in \tilde{\mathcal{R}}$. By the symmetry of the above result, it does not matter which of the indices (i,j) or (j,i) we choose in $\tilde{\mathcal{R}}$. Consequently, we have

$$\frac{d\mathbf{x}}{dt} = \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right]$$

as desired, and we are done. □

An immediate consequence of Lemma 3.2.1 is the following.

Lemma 3.2.2. *Consider a mass-action system with a detailed balanced equilibrium* $\mathbf{x}^*$.

Then, for the function $L(\mathbf{x})$ given by (3.1), we have

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} \leq 0$$

with equality if and only if

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j} \quad \textit{for all } (i,j) \in \mathcal{R}.$$

Proof. We can readily see that, for the function $L(\mathbf{x})$ given by (3.1),

$$\nabla L(\mathbf{x}) = \ln(\mathbf{x}) - \ln(\mathbf{x}^*) = \ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)$$

and by Lemma 3.2.1, (2.4) can be written

$$\frac{d\mathbf{x}}{dt} = \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right].$$

Together we have

$$\begin{aligned} \nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} &= \ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right) \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right] \\ &= \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij} \ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j - \mathbf{z}_i}\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right]. \end{aligned} \tag{3.15}$$

If we make the substitutions $a_{ij} = (\mathbf{x}/\mathbf{x}^*)^{\mathbf{z}_j}$ and $b_{ij} = (\mathbf{x}/\mathbf{x}^*)^{\mathbf{z}_i}$, (3.15) can be rewritten

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} = \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(b_{ij} - a_{ij})(\ln(a_{ij}) - \ln(b_{ij})).$$

Each element in the sum fits the form required of Lemma 3.0.3. Since $\kappa_{ij} > 0$, it follows

that

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} \leq 0.$$

Furthermore, since equality with zero can only be attained by having each term in the sum equal to zero, we have that

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} = 0 \qquad \text{iff} \qquad \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j} \quad \text{for all } (i,j) \in \mathcal{R}$$

and we are done. □

A multitude of properties of detailed balanced systems can be derived from Lemma 3.2.2. We will consider them as a single comprehensive result.

Theorem 3.2.1. *Consider a system with a detailed balanced equilibrium* $\mathbf{x}^*$*. Then the system has the following properties:*

1. *The set of positive equilibrium concentrations is given by*

$$E = \left\{\mathbf{x} \in \mathbb{R}^m_{>0} \mid (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) \in S^\perp\right\}. \tag{3.16}$$

2. *Every positive equilibrium concentration permitted by the system is a detailed balanced equilibrium concentration.*

3. *There is a unique positive detailed balanced equilibrium concentration within each positive stoichiometric compatibility class* $\mathsf{C}_{\mathbf{x}_0}$.

4. *That equilibrium concentration is locally asymptotically stable relative to* $\mathsf{C}_{\mathbf{x}_0}$.

Proof. We will prove the claims in the order they are presented.

Proof (1): Consider an equilibrium concentration $\mathbf{x}$. This implies that there is a solution of (2.4) such that $\mathbf{x}(t) \equiv \mathbf{x}$, $t \geq 0$. Along this solution, we have

$$\frac{dL(\mathbf{x}(t))}{dt} = \nabla L(\mathbf{x}(t)) \cdot \frac{d\mathbf{x}(t)}{dt} = 0$$

for all $t \geq 0$ since $\dfrac{d\mathbf{x}(t)}{dt} = \mathbf{0}$. By Lemma 3.2.2, this can happen if and only if

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j} \quad \text{for all } (i,j) \in \mathcal{R}.$$

Taking the natural logarithm of both sides and collecting terms yields

$$(\mathbf{z}_i - \mathbf{z}_j) \cdot \ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right) = (\mathbf{z}_i - \mathbf{z}_j) \cdot (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) = 0$$

for all $(i,j) \in \mathcal{R}$. Since $(i,j) \in \mathcal{R}$ implies $\mathbf{z}_i - \mathbf{z}_j \in S$, it follows that $\ln(\mathbf{x}) - \ln(\mathbf{x}^*) \in S^\perp$, and consequently $\mathbf{x} \in E$.

Now suppose $\mathbf{x} \in E$. This implies that $(\mathbf{z}_i - \mathbf{z}_j) \cdot (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) = 0$ for all $(i,j) \in \mathcal{R}$. This can be rearranged to the form

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}.$$

It follows from the form of (2.4) obtained in Lemma 3.2.1 that $\mathbf{x}$ is an equilibrium concentration, which completes the proof of Claim (1).

Proof (2): Consider an equilibrium concentration $\mathbf{x} \in \mathbb{R}^m_{>0}$. By Claim (1), this implies $\mathbf{x} \in E$ where E is given by (3.16). This implies $(\mathbf{z}_i - \mathbf{z}_j) \cdot (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) = 0$ for all $(i,j) \in \mathcal{R}$,

and consequently

$$(\mathbf{z}_i - \mathbf{z}_j) \cdot \ln(\mathbf{x}) = (\mathbf{z}_i - \mathbf{z}_j) \cdot \ln(\mathbf{x}^*) \tag{3.17}$$

for all $(i, j) \in \mathcal{R}$.

Since $\mathbf{x}^*$ is a detailed balanced equilibrium concentration, by Definition 3.1.2 we have $k(i, j)(\mathbf{x}^*)^{\mathbf{z}_i} = k(j, i)(\mathbf{x}^*)^{\mathbf{z}_j}$ for all $(i, j) \in \mathcal{R}$, from which it follows that

$$(\mathbf{z}_i - \mathbf{z}_j) \cdot \ln(\mathbf{x}^*) = \ln\left(\frac{k(j, i)}{k(i, j)}\right) \tag{3.18}$$

for all $(i, j) \in \mathcal{R}$. Combining (3.17) and (3.18), we have

$$(\mathbf{z}_i - \mathbf{z}_j) \cdot \ln(\mathbf{x}) = \ln\left(\frac{k(j, i)}{k(i, j)}\right)$$

for all $(i, j) \in \mathcal{R}$. It follows that $k(i, j)\mathbf{x}^{\mathbf{z}_i} = k(j, i)\mathbf{x}^{\mathbf{z}_j}$ for all $(i, j) \in \mathcal{R}$ and consequently $\mathbf{x} \in \mathbb{R}^m_{>0}$ is a detailed balanced equilibrium concentration. Since $\mathbf{x} \in E$ was chosen arbitrarily, Claim (2) follows.

Proof (3): From Claims (1) and (2) we have that the set of positive equilibrium points is given by

$$E = \{\mathbf{x} \in \mathbb{R}^m_{>0} \mid (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) \in S^{\perp}\}$$

and every equilibrium point is detailed balanced.

Now consider the function $L(\mathbf{x})$ given by (3.1). From Lemma 3.0.2 we have that $L(\mathbf{x})$ takes a unique minimum value relative to each positive stoichiometric compatibility class and that at this value $\nabla L(\mathbf{x}) = (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) \in S^{\perp}$. It follows immediately from the nature of E that the point $\mathbf{x} \in \mathsf{C}_{\mathbf{x}_0}$ at which this minimum attained is an equilibrium point of (2.4). Also, we can see that any other point $\mathbf{y} \in \mathsf{C}_{\mathbf{x}_0}$ lying in E would satisfy

$\nabla L(\mathbf{y}) = \ln(\mathbf{y}) - \ln(\mathbf{x}^*) \in S^{\perp}$ and therefore also be a minimal value of $L(\mathbf{y})$ relative to $\mathsf{C}_{\mathbf{x}_0}$ according to Lemma 3.0.2. This contradicts the uniqueness of the minimum value. It follows that there is a unique detailed balanced equilibrium concentration within each positive stoichiometric compatibility class, and Claim (3) is proven.

Proof (4): By Proposition 2.4.1, for any $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ we have $\mathbf{x}(t) \in \mathsf{C}_{\mathbf{x}_0}$ for all $t \geq 0$ so that we may restrict our attention to the relative topology of $\mathsf{C}_{\mathbf{x}_0}$.

By Claim (3), there is a unique positive detailed balanced equilibrium concentration $\mathbf{x}$ relative to $\mathsf{C}_{\mathbf{x}_0}$ and this equilibrium occurs at the minimum of $L(\mathbf{x})$ in the interior of the relative topology of $\mathsf{C}_{\mathbf{x}_0}$. We will let

$$L_\epsilon(\mathbf{x}) = \{\mathbf{y} \in \mathsf{C}_{\mathbf{x}_0} \mid L(\mathbf{x}) \leq Ł(\mathbf{y}) \leq L(\mathbf{x}) + \epsilon\}.$$

Since $\mathbf{x}$ is in the relative interior of $\mathsf{C}_{\mathbf{x}_0}$ and $L(\mathbf{x})$ is strictly convex, we can choose $\epsilon > 0$ sufficiently small so that $\overline{L}_\epsilon(\mathbf{x}) \cap \partial\mathsf{C}_{\mathbf{x}_0} = \varnothing$.

Now consider an arbitrary solution $\mathbf{x}(t)$ of (2.4) with $\mathbf{x}(0) = \mathbf{x}_0 \in L_\epsilon(\mathbf{x})$. We will show that for all $\delta > 0$ satisfying $\epsilon > \delta$, there is a $T > 0$ such that $\mathbf{x}(t) \in L_\delta(\mathbf{x})$ for all $t \geq T$.

We make the observation first of all that along the solution $\mathbf{x}(t)$, by Lemma 3.2.2 we have

$$\frac{dL(\mathbf{x}(t))}{dt} = \nabla L(\mathbf{x}(t)) \cdot \frac{d\mathbf{x}(t)}{dt} \leq 0.$$

This implies that, for any $\epsilon > 0$, if there exists a $T > 0$ such that $\mathbf{x}(T) \in L_\epsilon(\mathbf{x})$, then $\mathbf{x}(t) \in L_\epsilon(\mathbf{x})$ for all $t \geq T$.

We will now suppose that there does not exist a $\delta > 0$ satisfying the above conjecture. By the previous observation, this implies that $\mathbf{x}(t) \in L_\epsilon(\mathbf{x}) \setminus L_\delta(\mathbf{x})$ for all $t \geq 0$. Since

this region is bound away from $\mathbf{x}$, which is the only equilibrium concentration in the compatibility class $\mathsf{C}_{\mathbf{x}_0}$, we have by Lemma 3.2.2 that there exists an $M > 0$ such that

$$\frac{dL(\mathbf{x}(t))}{dt} = \nabla L(\mathbf{x}(t)) \cdot \frac{d\mathbf{x}(t)}{dt} < -M < 0$$

for all $t \geq 0$. It follows by integrating from 0 to T that

$$L(\mathbf{x}(T)) < L(\mathbf{x}(0)) - MT.$$

However, if we take the limit as $T \to \infty$ we have $L(\mathbf{x}(T)) \to -\infty$. This contradicts the fact that $L(\mathbf{x}(t))$ is bounded from below. Consequently, our supposition must have been in error, and it follows that for all $\delta > 0$ satisfying $\epsilon > \delta$, there is a $T > 0$ such that $\mathbf{x}(t) \in L_\delta(\mathbf{x})$ for all $t \geq T$. Since $L(\mathbf{x})$ is continuous and strictly convex on $\mathsf{C}_{\mathbf{x}_0}$, it follows that $\mathbf{x}(t)$ converges asymptotically to $\mathbf{x}$ as $t \to \infty$, which proves Claim (4). □

Example 3.2.1. *Consider the chemical reaction mechanism*

$$\mathcal{A}_1 \underset{k(2,1)}{\overset{k(1,2)}{\rightleftarrows}} \mathcal{A}_2 + \mathcal{A}_3 \underset{k(3,2)}{\overset{k(2,3)}{\rightleftarrows}} 2\mathcal{A}_3.$$

If we set $x_1 = [\mathcal{A}_1]$, $x_2 = [\mathcal{A}_2]$ and $x_3 = [\mathcal{A}_3]$, according to (2.4) the system is governed by the system of differential equations

$$\begin{aligned}
\frac{dx_1}{dt} &= -k(1,2)x_1 + k(2,1)x_2x_3 \\
\frac{dx_2}{dt} &= k(1,2)x_1 - k(2,1)x_2x_3 - k(2,3)x_2x_3 + k(3,2)x_3^2 \\
\frac{dx_3}{dt} &= k(1,2)x_1 - k(2,1)x_2x_3 + k(2,3)x_2x_3 - k(3,2)x_3^2.
\end{aligned} \tag{3.19}$$

In order to apply Theorem 3.2.1, we need to check that there is a detailed balanced equilibrium $\mathbf{x}^* \in \mathbb{R}^3_{>0}$. *From the first equation, we have*

$$\frac{dx_1}{dt} = 0 \qquad \textit{iff} \qquad k(1,2)x_1 = k(2,1)x_2x_3.$$

Substituting this into the second and third equations, we have

$$\frac{dx_2}{dt} = 0 \ \text{ and } \ \frac{dx_3}{dt} = 0 \qquad \textit{iff} \qquad k(2,3)x_2x_3 = k(3,2)x_3^2.$$

These are exactly the detailed balanced conditions expected of Definition 3.1.2 so that every positive equilibrium concentration permitted by the mechanism is detailed balanced. Consequently, we can apply Lemma 3.2.2 and Theorem 3.2.1.

It is difficult to verify directly—and in full generality—that the equilibrium set E *intersects each positive stoichiometric compatibility class* $\mathsf{C}_{\mathbf{x}_0} = (\mathbf{x}_0 + S) \cap \mathbb{R}^m_{>0}$ *exactly once. It is also difficult to directly visualize the dynamics. To make these tasks more manageable, we select* $k(1,2) = k(2,1) = k(2,3) = k(3,2) = 1$ *and* $x_{10} = x_{20} = x_{30} = 1/4$. *It is important to notice, however, that, since the arguments for the existence of detailed balanced equilibrium apply regardless of the rate constants and initial concentrations, all the results of Theorem 3.2.1 can be applied for different choices of values.*

In order to check that the compatibility class corresponding to $x_{10} = x_{20} = x_{30} = 1/4$ *intersects* E *only once, we parametrize* E *and check for points of intersection with* $(\mathbf{x}_0 + S)$. *For our system, we have*

$$S = \operatorname{span}\left\{\begin{bmatrix} -1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix}\right\}$$

and for our choice of rate constants, we can parametrize E as

$$E = \left\{ [k^2, k, k]^T, k > 0 \right\}.$$

We now solve the system of equations

$$\begin{bmatrix} x_{10} \\ x_{20} \\ x_{30} \end{bmatrix} + s \begin{bmatrix} -1 \\ 1 \\ 1 \end{bmatrix} + t \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix} = \begin{bmatrix} k^2 \\ k \\ k \end{bmatrix}$$

to get the lone admissible solution $t = 0$, $s = -3/4 + \sqrt{3}/2$ and $k = -1/2 + \sqrt{3}/2$. The corresponding equilibrium value $\mathbf{x}^*$ is

$$\mathbf{x}^* = [k^2, k, k]^T = \left[1 - \frac{\sqrt{3}}{2}, -\frac{1}{2} + \frac{\sqrt{3}}{2}, -\frac{1}{2} + \frac{\sqrt{3}}{2} \right]^T. \tag{3.20}$$

We now consider the dynamics of (3.19) given by Figure 3.1. As expected, we see that $\mathbf{x}(t)$ converges asymptotically to the equilibrium value $\mathbf{x}^*$ given by (3.20). It is also worth noting the role that the conservation law $\langle \mathbf{v}, \mathbf{x}(t) - \mathbf{x}_0 \rangle = 0$, $\mathbf{v} \in S^\perp$, plays in this analysis. We have $x_{10} = x_{20} = x_{30} = 1/4$ and can take $\mathbf{v} = [2, 1, 1]^T$ so that

$$\langle \mathbf{v}, \mathbf{x}_0 \rangle = 2x_{10} + x_{20} + x_{30} = 1.$$

The solution $\mathbf{x}(t)$ must converge to a solution satisfying the same conservation law, and indeed, at the equilibrium value $\mathbf{x}^*$ given by (3.20) we have

$$\langle \mathbf{v}, \mathbf{x}^* \rangle = 2x_1^* + x_2^* + x_3^* = 2\left(1 - \frac{\sqrt{3}}{2}\right) + \left(-\frac{1}{2} + \frac{\sqrt{3}}{2}\right) + \left(-\frac{1}{2} + \frac{\sqrt{3}}{2}\right) = 1.$$

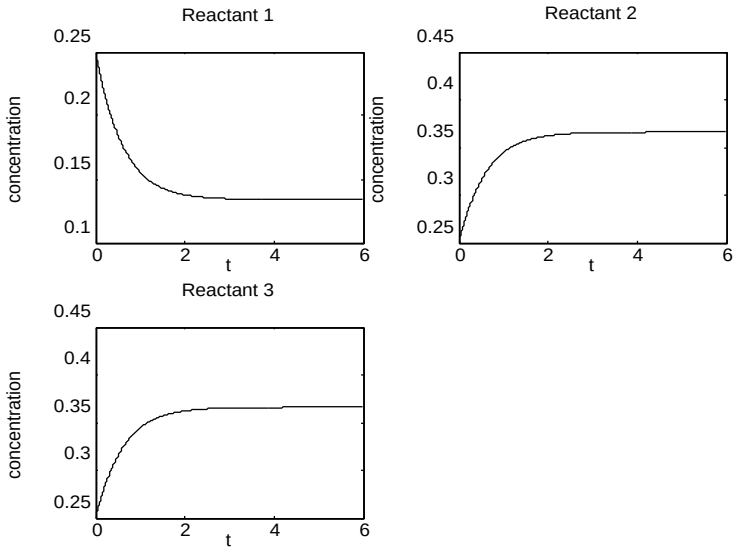

Figure 3.1: The solution $\mathbf{x}(t)$ to (3.19) for $k(1,2) = k(2,1) = k(2,3) = k(3,2) = 1$, $x_{10} = x_{20} = x_{30} = 1/4$. The solution converges to the equilibrium value given by (3.20).

We have given no consideration in this section or this example as to how to determine whether a detailed balanced equilibrium concentrations exists beyond directly checking. Further discussion of this point will be given in Section 3.4 when considering complex balanced equilibrium concentrations. Since the results contained there directly generalize to the case of detailed balancing, we do not repeat them here.

3.3 Complex Balanced Systems

In this section, we use the classification of complex balanced equilibrium concentrations given by Definition 3.1.3 to determine properties of the system (2.4). Specifically, we prove that complex balanced systems exhibit locally stable dynamics.

The methodology used in this section will be very similar to that presented in Section

3.2. Since complex balanced systems are significantly more general than detailed balanced systems, however, we will need to do more manipulation of (2.4) under the assumption of complex balancing in order to obtain a more manageable form.

In this section, we will follow closely the analysis performed in [25, 30, 33]. In [33], the authors show that a general complex balanced system can be decomposed into the direct sum of subsystems which are easier to handle, and that these subsystems—cyclic complex balanced systems—exhibit locally stable dynamics. We will omit their discussion of quasi-thermodynamic systems. We will then complete the connection between complex balancing and the reaction graph of the system derived in [25, 30]. This will culminate in the *Deficiency Zero Theorem* (Theorem 3.4.2).

3.3.1 Cyclic Complex Balanced Systems

In this subsection, we introduce and analyze a particular subset of complex balanced systems called cyclic complex balanced systems. The results contained herein will be made applicable to general complex balanced systems in Section 3.3.2.

We begin by defining a *reaction cycle*. Our definitions here are drawn from [33].

Definition 3.3.1. *A family of complex indices* $\{\nu_0, \nu_1, \ldots, \nu_l\}$, $l \geq 2$, *will be called a* ***cycle*** *if*

$$\nu_0 = \nu_l \tag{3.21}$$

but all other members of the family are distinct, and if

$$k(\nu_{j-1}, \nu_j) > 0, \quad j = 1, 2, \ldots, l$$

where l is the length of the cycle. The ***reaction cycle*** *associated with $\{\nu_0, \nu_1, \ldots, \nu_l\}$ is defined to be the corresponding set of elementary reactions*

$$\mathcal{C}_{\nu_{j-1}} \longrightarrow \mathcal{C}_{\nu_j}, \quad j = 1, 2, \ldots, l. \tag{3.22}$$

Definition 3.3.2. *We will say that a mass-action system is* ***cyclic*** *if the system consists of a single reaction cycle. For such a system, it will be understood that $l = n$.*

Throughout this section, we will only consider cyclic mass-action systems according to Definition 3.3.2. It is convenient, therefore, to index the system in consideration according to the natural ordering of the cycle, so that

$$\mathcal{C}_{j-1} \longrightarrow \mathcal{C}_j, \qquad \text{for } j = 1, \ldots, n \tag{3.23}$$

where $\mathcal{C}_0 = \mathcal{C}_n$.

Under the assumption of complex balancing of equilibrium concentrations, the following rearrangements of (2.4) can be obtained. These correspond to equations (5-10) and (5-11) of [33], respectively.

Lemma 3.3.1. *Consider a cyclic mass-action system with a complex balanced equilibrium $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. Then there exists a $\kappa > 0$ such that (2.4) can be written as either*

$$\frac{d\mathbf{x}}{dt} = \kappa \sum_{i=1}^{n} (\mathbf{z}_{i+1} - \mathbf{z}_i) \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_i} \tag{3.24}$$

or

$$\frac{d\mathbf{x}}{dt} = \kappa \sum_{i=1}^{n} \mathbf{z}_{i+1} \left[\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{i+1}} \right] \tag{3.25}$$

where $\mathbf{z}_{n+1} = \mathbf{z}_1$.

Proof. Consider an arbitrary complex balanced equilibrium $\mathbf{x}^*$. Since the system is cyclic, each complex is catalyzed by and produced as the result of exactly one reaction. In order to be complex balanced by Definition 3.1.3, therefore, according to the indexing (3.23) we have

$$k(i-1,i)(\mathbf{x}^*)^{\mathbf{z}_{i-1}} = k(i,i+1)(\mathbf{x}^*)^{\mathbf{z}_i}, \qquad \text{for all } i = 1,\dots,n$$

where $k(0,1) = k(n,1)$ and $\mathbf{z}_0 = \mathbf{z}_n$. This can only be satisfied if there exists a $\kappa > 0$ such that

$$k(1,2)(\mathbf{x}^*)^{\mathbf{z}_1} = \cdots = k(n,1)(\mathbf{x}^*)^{\mathbf{z}_n} = \kappa > 0.$$

It follows immediately that

$$k(i,i+1) = \frac{\kappa}{(\mathbf{x}^*)^{\mathbf{z}_i}}, \quad \text{for } i = 1,\dots,n.$$

Since the system is cyclic, from (2.4) and (3.23) we have

$$\begin{aligned}\frac{d\mathbf{x}}{dt} &= \sum_{i=1}^{n} k(i,i+1)(\mathbf{z}_{i+1}-\mathbf{z}_i)\mathbf{x}^{\mathbf{z}_i} \\ &= \kappa \sum_{i=1}^{n} (\mathbf{z}_{i+1}-\mathbf{z}_i)\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i}\end{aligned}$$

which is sufficient to prove (3.24).

We can also rearrange (3.24) to get

$$\begin{aligned}\frac{d\mathbf{x}}{dt} &= \kappa \sum_{i=1}^{n} (\mathbf{z}_{i+1} - \mathbf{z}_i) \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} \\ &= \kappa \left[\sum_{i=1}^{n} \mathbf{z}_{i+1} \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \sum_{i=1}^{n} \mathbf{z}_i \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i}\right] \\ &= \kappa \left[\sum_{i=1}^{n} \mathbf{z}_{i+1} \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \sum_{i=1}^{n} \mathbf{z}_{i+1} \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{i+1}}\right] \\ &= \kappa \sum_{i=1}^{n} \mathbf{z}_{i+1} \left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{i+1}}\right]\end{aligned}$$

which is sufficient to prove (3.25). □

An immediate consequence of (3.24) is the following.

Lemma 3.3.2. *Consider a cyclic mass-action system with a complex balanced equilibrium* $\mathbf{x}^*$*. Then, for the function* $L(\mathbf{x})$ *given by (3.1), we have*

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} \leq 0$$

with equality if and only if

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j} \quad \text{for all } i, j = 1, \ldots, n.$$

Proof. Consider an arbitrary complex balanced equilibrium $\mathbf{x}^*$. By (3.24) of Lemma 3.2.1, we have

$$\begin{aligned}\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} &= \kappa \cdot \ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right) \sum_{i=1}^{n} (\mathbf{z}_{i+1} - \mathbf{z}_i) \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} \\ &= \kappa \sum_{i=1}^{n} \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} \left[\ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{i+1}} - \ln\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i}\right].\end{aligned} \tag{3.26}$$

If we make the substitutions $\alpha_i = (\mathbf{x}/\mathbf{x}^*)^{\mathbf{z}_i}$, $i = 1, \ldots, n$, (3.26) can be written

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} = \kappa \sum_{i=1}^{n} \alpha_i \left[\ln(\alpha_{i+1}) - \ln(\alpha_i) \right].$$

Each element in the sum fits the form required of Lemma 3.0.4. Since $\kappa > 0$, it follows that

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} \leq 0.$$

Furthermore, since equality with zero can only be attained by having each term in the sum equal to zero, we have that

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} = 0 \qquad \text{iff} \qquad \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_i} = \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_j}$$

for all $i, j = 1, \ldots, n$, and we are done. □

Since the results of the following section will encompass any further results we could derive here, we will cease our consideration of cyclic complex balanced systems at this point.

3.3.2 General Complex Balanced Systems

In this section, we apply the results of Section 3.3.1 to general complex balanced systems.

The following result combines Lemma 6B, Lemma 6C, and Lemma 6D of [33]. This result shows that a general complex balanced system can be decomposed into a direct finite sum of cyclic complex balanced systems satisfying appropriate conditions. This allows us to rewrite (2.4) in a form which will allow us to apply Lemma 3.3.2.

Lemma 3.3.3. *Consider a mass-action system which is complex balanced at* $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. *Then there exists a* $\delta \in \mathbb{Z}_{>0}$ *and a set* $\kappa_i > 0$, $i = 1, 2, \ldots, \delta$, *such that*

$$\frac{d\mathbf{x}}{dt} = \kappa_1 \mathbf{X}_1 + \kappa_2 \mathbf{X}_2 + \cdots + \kappa_\delta \mathbf{X}_\delta \tag{3.27}$$

where

$$\mathbf{X}_i = \sum_{j=1}^{l_i} \left(\mathbf{z}_{\nu_{j+1}^{(i)}} - \mathbf{z}_{\nu_j^{(i)}} \right) \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\nu_j^{(i)}}} \tag{3.28}$$

where the set $\left\{ \nu_1^{(i)}, \nu_2^{(i)}, \ldots, \nu_{l_i}^{(i)}, \nu_{l_i+1}^{(i)} \right\}$ *is a cycle according to Definition 3.3.1.*

Proof. The proof will proceed in the following steps. We will prove firstly that every system with a complex balanced equilibrium concentration contains a reaction cycle. This corresponds to Lemma 6B of [33].

We will then show that this reaction cycle can be "removed" from the system in such a way that the remaining system is complex balanced at $\mathbf{x}^*$ and has a reduced reaction set. This corresponds to Lemma 6C of [33].

We will finally show that the system (2.4) can be decomposed into a direct finite sum of cyclic complex balanced systems of the form (3.27). This correspond to Lemma 6D of [33].

Consider a mass-action system which is complex balanced at $\mathbf{x}^*$. By Definition 3.1.3, we have

$$\sum_{j=1}^{n} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j=1}^{n} k(i,j)$$

for all $i, j = 1, \ldots, n$. By Lemma 3.1.2, we know that the reaction graph of the system is weakly reversible. Consequently, for an arbitrary path from $\mathcal{C}_i$ to $\mathcal{C}_j$ for some $i, j = 1, \ldots, n$, there is a path from $\mathcal{C}_j$ to $\mathcal{C}_i$. We know a path exists since the reaction set $\mathcal{R}$ is non-empty, so that a path from $\mathcal{C}_i$ to $\mathcal{C}_j$ to $\mathcal{C}_i$ exists for some $i, j = 1, \ldots, n$. There may, however be

repeated complexes along this path. If this is the case, we consider the path bound between the first two instances of a complex $\mathcal{C}_k$ where $\mathcal{C}_k$ is the first complex to appear twice. This path is a reaction cycle according to Definition 3.3.1.

We will let this cycle be indexed $\{\nu_1, \nu_2, \ldots, \nu_l, \nu_{l+1}\}$ where $\nu_1 = \nu_{l+1}$. It is clear that the rate terms $k(\nu_i, \nu_{i+1})(\mathbf{x}^*)^{\mathbf{z}_{\nu_i}}$, $i = 1, \ldots, l$, need not be identical along the cycle since the system is not cyclic. Since all the rate terms are positive, however, we can define

$$\kappa_1 = \min_{i=1,\ldots,l} k(\nu_i, \nu_{i+1})(\mathbf{x}^*)^{\mathbf{z}_{\nu_i}} > 0. \tag{3.29}$$

We now define two new sets of rate constants as

$$k_1(i,j) = \begin{cases} \dfrac{\kappa_1}{(\mathbf{x}^*)^{\mathbf{z}_i}}, & \text{for } (i,j) \text{ in the cycle} \\ 0, & \text{otherwise} \end{cases} \tag{3.30}$$

and

$$k'(i,j) = k(i,j) - k_1(i,j), \qquad \text{for } i,j = 1, \ldots, n. \tag{3.31}$$

To the set of rate constants $k_1(i,j)$ and $k'(i,j)$, $i,j = 1, \ldots, n$, we can associate the reaction sets $\mathcal{R}_1 = \{(i,j) \mid k_1(i,j) > 0\}$ and $\mathcal{R}' = \{(i,j) \mid k'(i,j) > 0\}$. We notice that for at least one index, we have $\kappa_1/(\mathbf{x}^*)^{\mathbf{z}_{\nu_i}} = k(\nu_i, \nu_{i+1})$ by (3.29) so that there is at least one pair (ν_i, ν_{i+1}) for which $k'(\nu_i, \nu_{i+1}) = 0$ but $k(\nu_i, \nu_{i+1}) > 0$. This implies that $|\mathcal{R}'| < |\mathcal{R}|$. In other words, after removing our reaction cycle $\mathcal{R}_1$, the remaining system has fewer reactions than the original system.

It remains to consider the properties of the systems corresponding to $\mathcal{R}_1$ and $\mathcal{R}'$. It follows from the definition of $k_1(i,j)$ and the fact that the reaction graph of $\mathcal{R}_1$ is a reaction cycle that $\mathcal{R}_1$ corresponds to a cyclic system which is complex balanced at $\mathbf{x}^*$.

Now consider $\mathcal{R}'$. Since $\mathcal{R}$ and $\mathcal{R}_1$ are complex balanced at $\mathbf{x}^*$, we have that

$$\begin{aligned}\sum_{j=1}^{n} k'(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} &= \sum_{j=1}^{n} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} - \sum_{j=1}^{n} k_1(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} \\ &= (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j=1}^{n} k(i,j) - (\mathbf{x}^*)^{\mathbf{z}_j} \sum_{j=1}^{n} k_1(i,j) \\ &= (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j=1}^{n} k'(i,j).\end{aligned}$$

This is sufficient to prove $\mathcal{R}'$ is complex balanced at $\mathbf{x}^*$ according to Definition 3.1.3.

To recap, we have that a general complex balanced system can be decomposed into two subsystems—one a cyclic complex balanced system, and the other a general complex balanced system with a smaller set of reactions. Clearly, since the remaining system ($\mathcal{R}'$ from the preceding argument) is complex balanced, we can apply the preceding argument on it to yield another cyclic complex balanced system (say, $\mathcal{R}_2$) and yet another general complex balanced system. Since the number of reactions in the remaining set is reduced by each iteration of this procedure, this process must terminate after a finite number of applications.

We are left with $k(i,j) = k_1(i,j) + k_2(i,j) + \cdots + k_\delta(i,j)$, $\delta \in \mathbb{Z}_{>0}$, $i,j = 1,\ldots,n$. Each set of rate constants $k_q(i,j)$, $i,j = 1,\ldots,n$, corresponds to a cyclic system which is complex balanced at $\mathbf{x}^*$. Since the rate constants enter (2.4) linearly, we have

$$\frac{d\mathbf{x}}{dt} = \mathbf{Y}_1 + \mathbf{Y}_2 + \cdots + \mathbf{Y}_\delta$$

where

$$\mathbf{Y}_q = \sum_{(i,j)\in\mathcal{R}_q} k_q(i,j)(\mathbf{z}_j - \mathbf{z}_i)\mathbf{x}^{\mathbf{z}_i}$$

for $q = 1,\ldots,\delta$.

Since each $\mathbf{Y}_q$ corresponds to a cyclic mass-action system which is complex balanced at $\mathbf{x}^*$, by Lemma 3.3.1 the system can be written

$$\frac{d\mathbf{x}}{dt} = \kappa_1 \mathbf{X}_1 + \kappa_2 \mathbf{X}_2 + \cdots + \kappa_\delta \mathbf{X}_\delta$$

where

$$\mathbf{X}_i = \sum_{j=1}^{l_i} \left(\mathbf{z}_{\nu_{j+1}^{(i)}} - \mathbf{z}_{\nu_j^{(i)}} \right) \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\nu_j^{(i)}}}$$

for $i = 1, \ldots, \delta$, and we are done. □

Example 3.3.1. *Consider the mechanism*

$$\begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{1} & \mathcal{A}_2 \\ {\scriptstyle 1}\uparrow & {\scriptstyle \epsilon}\swarrow\!\!\!\nearrow{\scriptstyle \epsilon} & \downarrow{\scriptstyle 1} \\ \mathcal{A}_4 & \xleftarrow[1]{} & \mathcal{A}_3 \end{array} \tag{3.32}$$

where $0 < \epsilon < 1$. *We will let* $\mathcal{C}_i = \mathcal{A}_i$, $i = 1, \ldots, 4$. *We have made the associations* $k(1,2) = 1$, $k(2,3) = 1$, $k(3,4) = 1$, $k(4,1) = 1$, $k(4,2) = \epsilon$ *and* $k(2,4) = \epsilon$.

The system is governed by the system of differential equations

$$\begin{aligned} \frac{dx_1}{dt} &= -x_1 + x_4 \\ \frac{dx_2}{dt} &= x_1 - x_2 + \epsilon x_4 - \epsilon x_2 \\ \frac{dx_3}{dt} &= x_2 - x_3 \\ \frac{dx_4}{dt} &= x_3 - x_4 - \epsilon x_4 + \epsilon x_2. \end{aligned} \tag{3.33}$$

The equilibrium condition for each species exactly corresponds to the complex balancing condition so that each equilibrium concentration is trivially complex balanced. It can be

easily determined that any equilibrium concentration satisfies $x_1^* = x_2^* = x_3^* = x_4^*$.

To follow the methodology of Lemma 3.3.3, we look for a cycle within the reaction graph (3.32). One choice is $\mathcal{A}_1 \to \mathcal{A}_2 \to \mathcal{A}_4 \to \mathcal{A}_1$, *corresponding to the cycle* $\{1, 2, 4, 1\}$. *This choice is not unique, a consideration which will be expounded upon later.*

Along this cycle we have the flux terms x_1^*, ϵx_2^*, *and* x_4^*. *Clearly, for* $0 < \epsilon < 1$ *the flux terms are not equal so that the cycle itself is not complex balanced. Instead, we choose*

$$\kappa_1 = \min\{x_1^*, \epsilon x_2^*, x_3^*\} = \epsilon x_2^*$$

where evaluation of the the minimum follows from the equilibrium condition $x_1^* = x_2^* = x_3^* = x_4^*$. *It follows from the construction in Lemma 3.3.3 that*

$$\begin{aligned} k_1(1,2) &= \epsilon & k_1(2,3) &= 0 \\ k_1(2,4) &= \epsilon & k_1(3,4) &= 0 \\ k_1(4,1) &= \epsilon & k_1(4,2) &= 0 \end{aligned} \cdot$$

We are now prepared to make our first decomposition of the system. This decomposition with yield two subsystems: $\mathcal{R}_1$, *which is the cyclic system, and* $\mathcal{R}'$, *which is the remainder upon removing* $\mathcal{R}_1$ *from our original system* $\mathcal{R}$. *We have*

$$\mathcal{R}_1: \quad \begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{\epsilon} & \mathcal{A}_2 \\ {\scriptstyle\epsilon}\uparrow & \swarrow_{\epsilon} & \\ \mathcal{A}_4 & & \end{array} \qquad \mathcal{R}': \quad \begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{1-\epsilon} & \mathcal{A}_2 \\ {\scriptstyle 1-\epsilon}\uparrow & \nearrow_{\epsilon} & \downarrow_1 \\ \mathcal{A}_4 & \xleftarrow[1]{} & \mathcal{A}_3. \end{array}$$

We can see that, as expected, our original system (3.32) can be recovered by directly summing the reactions of $\mathcal{R}_1$ *and* $\mathcal{R}'$ *together. A similar decomposition of (3.33) can be made*

since the reaction rates enter the differential equations linearly. For brevity, we will not write out the mass-action systems corresponding to $\mathcal{R}_1$ *and* $\mathcal{R}'$ *here.*

Our next task is to decompose the system $\mathcal{R}'$ *according to the same procedure outlined so far. We will leave the details as an exercise. It can be readily seen that the mass-action system corresponding to* $\mathcal{R}'$ *is complex balanced at* $x_1^* = x_2^* = x_3^* = x_4^*$ *and that* $\mathcal{A}_2 \to \mathcal{A}_3 \to \mathcal{A}_4 \to \mathcal{A}_2$ *is a cycle with minimal flow rate* $\kappa_2 = \epsilon x_3^*$*. After appropriate partitioning of the rate constants, we have that* $\mathcal{R}'$ *can be decomposed into*

$$\mathcal{R}_2: \quad \begin{array}{ccc} & & \mathcal{A}_2 \\ & {\scriptstyle\epsilon}\nearrow & \downarrow{\scriptstyle\epsilon} \\ \mathcal{A}_4 & \xleftarrow[\epsilon]{} & \mathcal{A}_3 \end{array} \qquad \mathcal{R}_3: \quad \begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{1-\epsilon} & \mathcal{A}_2 \\ {\scriptstyle 1-\epsilon}\uparrow & & \downarrow{\scriptstyle 1-\epsilon} \\ \mathcal{A}_4 & \xleftarrow[1-\epsilon]{} & \mathcal{A}_3. \end{array}$$

We can see that both $\mathcal{R}_2$ *and* $\mathcal{R}_3$ *are cyclic systems, and it can be verified directly that they are both complex balanced along* $x_1^* = x_2^* = x_3^* = x_4^*$*. As expected, the procedure has terminated after a finite number of iterations—two in this case—and yielded three cyclic systems which are complex balanced at the same equilibrium concentration. To make this*

more explicit, we notice that we can write (3.33) as

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \\ \frac{dx_3}{dt} \\ \frac{dx_4}{dt} \end{bmatrix} = \epsilon \left(\begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix} x_1 + \begin{bmatrix} 0 \\ -1 \\ 0 \\ 1 \end{bmatrix} x_2 + \begin{bmatrix} 1 \\ 0 \\ 0 \\ -1 \end{bmatrix} x_4 \right) + \epsilon \left(\begin{bmatrix} 0 \\ -1 \\ 1 \\ 0 \end{bmatrix} x_2 + \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \end{bmatrix} x_3 + \begin{bmatrix} 0 \\ 1 \\ 0 \\ -1 \end{bmatrix} x_4 \right)$$
$$+ (1-\epsilon) \left(\begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix} x_1 + \begin{bmatrix} 0 \\ -1 \\ 1 \\ 0 \end{bmatrix} x_2 + \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \end{bmatrix} x_3 + \begin{bmatrix} 1 \\ 0 \\ 0 \\ -1 \end{bmatrix} x_4 \right).$$

Each of the three bracketted expressions corresponds to one of the cyclic subsystems, $\mathcal{R}_1$, $\mathcal{R}_2$ and $\mathcal{R}_3$.

It is worth noting that decomposition procedure is not unique. It is entirely possible that a different cycle could be chosen at each iteration of the procedure, leading to entirely different systems in the decomposition (although each must be cyclic and complex balanced at the same equilibrium concentration). It is even possible for a different number of cycles to result from a distinct decomposition.

For example, consider the decomposition of $\mathcal{R}$ into

$$\mathcal{R}_1: \quad \begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{1} & \mathcal{A}_2 \\ {\scriptstyle 1}\uparrow & & \downarrow{\scriptstyle 1} \\ \mathcal{A}_4 & \xleftarrow[1]{} & \mathcal{A}_3 \end{array} \qquad \mathcal{R}_2: \quad \begin{array}{ccc} & & \mathcal{A}_2 \\ & {\scriptstyle \epsilon}\swarrow\!\!\!\nearrow{\scriptstyle \epsilon} & \\ \mathcal{A}_4 & & \end{array}$$

This is a complex decomposition which yields two subsystems instead of three! We notice,

however, that no matter how we perform the decomposition, the end result is always a set of cyclic systems, all of which are complex balanced at the same equilibrium concentrations.

It is also worth noting that the decomposition depends sensitively on the rate constants, since the rate constants play an instrumental role in determining the minimal flow rates. Choosing $\epsilon = 1$ *or* $\epsilon > 1$*—let alone fully general rate constants for each reaction—leads to dramatically different decompositions.*

We will need the following two results. The first generalizes Lemma 3.3.2 to general complex balanced systems. The second allows us to grasp the resulting vector quantities.

Lemma 3.3.4. *Consider a mass-action system with a complex balanced equilibrium* $\mathbf{x}^*$*. Then, for the function* $L(\mathbf{x})$ *given by (3.1), we have*

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} \leq 0$$

with equality if and only if, for every linkage class $\mathcal{L}_i$*,* $i = 1, \ldots, \ell$*,*

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}^{\nu_j^{(i)}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}^{\nu_k^{(i)}}}$$

for all $\mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i$*.*

Proof. Since the system is complex balanced at $\mathbf{x}^*$ it follows by Lemma 3.3.3 that the system can be decomposed into cyclic subsystems, each of which is complex balanced at $\mathbf{x}^*$. By (3.27) we have

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} = \kappa_1 \nabla L(\mathbf{x}) \cdot \mathbf{X}_1 + \cdots + \kappa_\delta \nabla L(\mathbf{x}) \cdot \mathbf{X}_\delta.$$

Since each $\mathbf{X}_i$, $i = 1, \ldots, \delta$, corresponds to a cyclic system $\mathcal{R}_i$ which is complex balanced at $\mathbf{x}^*$, it follows by Lemma 3.3.2 that, for all $i = 1, \ldots, \delta$,

$$\nabla L(\mathbf{x}) \cdot \mathbf{X}_i \leq 0$$

with equality if and only if

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_j^{(i)}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_k^{(i)}}} \tag{3.34}$$

for all $\nu_j^{(i)}, \nu_k^{(i)} \in \mathcal{R}_i$. It follows that

$$\nabla L(\mathbf{x}) \cdot \frac{d\mathbf{x}}{dt} \leq 0. \tag{3.35}$$

In order to have equality with zero, we need (3.34) to be satisfied for each cyclic subsystem $\mathcal{R}_i$, $i = 1, \ldots, \ell$; however, we can readily see that (3.34) can be extended to linkage classes since every cycle within a linkage class can be linked to every other (if they could not, they would not be in the same linkage class). It follows that equality with zero in (3.35) can only be attained if, for every $i = 1, \ldots, \ell$,

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}^{\nu_j^{(i)}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}^{\nu_k^{(i)}}}$$

for all $\mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i$, and we are done. □

Lemma 3.3.5. *Let $\mathcal{L}_i$, $i = 1, \ldots, \ell$, be the linkage classes of a chemical reaction network. Then the set of vectors*

$$\left\{\mathbf{z}_{\nu_j^{(i)}} - \mathbf{z}_{\nu_k^{(i)}} \mid \mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i, i = 1, \ldots, \ell\right\} \tag{3.36}$$

span the stoichiometric subspace S.

Proof. It is clear that every reaction vector $\mathbf{z}_i - \mathbf{z}_j$, $(i,j) \in \mathcal{R}$, is contained in the set (3.36) since $\mathcal{C}_i$ and $\mathcal{C}_j$ necessarily belong to the same linkage class so we have freedom to choose these indices. It remains to show that the set (3.36) may not exceed the span of S.

Consider an arbitrary vector $\mathbf{z}_{\nu_j^{(i)}} - \mathbf{z}_{\nu_k^{(i)}}$, $\mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i, i = 1, \ldots, \ell$. Since $\mathcal{C}_{\nu_j^{(i)}}$ and $\mathcal{C}_{\nu_k^{(i)}}$ belong to the same linkage class, it follows that there exists a chain of reactions connecting $\mathcal{C}_{\nu_j^{(i)}}$ and $\mathcal{C}_{\nu_k^{(i)}}$ of the form

$$\mathcal{C}_{\nu_k^{(i)}} = \mathcal{C}_{\mu_0} \longleftrightarrow \mathcal{C}_{\mu_1} \longleftrightarrow \cdots \longleftrightarrow \mathcal{C}_{\mu_{p-1}} \longleftrightarrow \mathcal{C}_{\mu_p} = \mathcal{C}_{\nu_j^{(i)}}$$

where by "$\longleftrightarrow$" we mean one of a forward or backward reaction. For each forward reaction, we consider the reaction vector $(\mathbf{z}_{\mu_{i+1}} - \mathbf{z}_{\mu_i}) \in S$ and for each backward reaction, we consider the negative reaction vector $-(\mathbf{z}_{\mu_i} - \mathbf{z}_{\mu_{i+1}}) = (\mathbf{z}_{\mu_{i+1}} - \mathbf{z}_{\mu_i}) \in S$. It follows that

$$\begin{aligned}\mathbf{z}_{\nu_j^{(i)}} - \mathbf{z}_{\nu_k^{(i)}} = (\mathbf{z}_{\mu_1} - \mathbf{z}_{\mu_0}) + (\mathbf{z}_{\mu_2} - \mathbf{z}_{\mu_1}) + \cdots \\ + (\mathbf{z}_{\mu_{p-1}} - \mathbf{z}_{\mu_{p-2}}) + (\mathbf{z}_{\mu_p} - \mathbf{z}_{\mu_{p-1}}) \in S.\end{aligned}$$

This completes the proof. □

We are now prepared to prove the analogous result to Theorem 3.2.1 for complex balanced systems. We will omit details of the proof where obvious similarities arise.

Theorem 3.3.1. *Consider a system with a complex balanced equilibrium $\mathbf{x}^*$. Then the system has the following properties:*

1. *The set of positive equilibrium concentrations is given by*

$$E = \{\mathbf{x} \in \mathbb{R}^m_{>0} \mid (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) \in S^\perp\}. \tag{3.37}$$

2. *Every positive equilibrium concentration permitted by the system is a complex balanced equilibrium concentration.*

3. *There is a unique positive complex balanced equilibrium concentration within each positive stoichiometric compatibility class* $\mathsf{C}_{\mathbf{x}_0}$.

4. *That equilibrium concentration is locally asymptotically stable relative to* $\mathsf{C}_{\mathbf{x}_0}$.

Proof. We will prove the claims in the order they are presented.

Proof (1): Consider an equilibrium concentration $\mathbf{x} \in \mathbb{R}^m_{>0}$. As before, this implies $\nabla L(\mathbf{x}) \cdot \dfrac{d\mathbf{x}}{dt} = 0$ which, by Lemma 3.3.4, can happen if and only if, for every linkage class $\mathcal{L}_i$, $i = 1, \ldots, \ell$,

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}^{\nu_j^{(i)}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}^{\nu_k^{(i)}}}$$

for all $\mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i$. Taking the natural logarithm of both sides and collecting terms yields

$$(\mathbf{z}_{\nu_j^{(i)}} - \mathbf{z}_{\nu_k^{(i)}}) \cdot (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) = 0.$$

Since the set of vectors $(\mathbf{z}_{\nu_j^{(i)}} - \mathbf{z}_{\nu_k^{(i)}}) \in S$ taken over $\mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i$, and all $i = 1, \ldots, \ell$, spans S by Lemma 3.3.5, it follows that $\mathbf{x} \in E$.

Now suppose $\mathbf{x} \in E$. Since the system is complex balanced, by Lemma 3.3.3 the mechanism can be decomposed into cyclic subsystems $\mathcal{R}_i$, $i = 1, \ldots, \delta$, where the cycles are

of the form $\left\{\nu_1^{(i)}, \nu_2^{(i)}, \ldots, \nu_{l_i}^{(i)}, \nu_{l_i+1}^{(i)}\right\}$. It follows from $\mathbf{x} \in E$ that, for all $i = 1, \ldots, \delta$,

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_{j+1}^{(i)}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_j^{(i)}}}$$

for all $j = 1, \ldots, l_i$. Since each cyclic subsystem (3.28) from Lemma 3.3.3 can take the form (3.25) obtained in Lemma 3.3.1, it follows that $\mathbf{x}$ is an equilibrium concentration of (2.4). This completes the proof of Claim (1).

Proof (2): Consider an equilibrium concentration $\mathbf{x} \in \mathbb{R}^m_{>0}$. By Claim (1), this implies $\mathbf{x} \in E$ where E is given by (3.37). Since the set of vectors (3.36) spans S, we have that, for all $i = 1, \ldots, \ell$, $(\mathbf{z}_{\nu_j^{(i)}} - \mathbf{z}_{\nu_k^{(i)}}) \cdot (\ln(\mathbf{x}) - \ln(\mathbf{x}^*)) = 0$ for all $\mathcal{C}_{\nu_j^{(i)}}, \mathcal{C}_{\nu_k^{(i)}} \in \mathcal{L}_i$, and consequently

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_j^{(i)}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_k^{(i)}}} \tag{3.38}$$

under the same conditions.

Since $\mathbf{x}^*$ is a complex balanced equilibrium concentration, by Definition 3.1.3 we have

$$\sum_{j=1}^{n} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j=1}^{n} k(i,j) \tag{3.39}$$

for all $i = 1, \ldots, n$. We notice, however, that in order for this condition to hold the analogous condition needs to hold for the complexes of any given linkage class $\mathcal{L}_i$, $i = 1, \ldots, \ell$. We will consider that the i^{th} linkage class $\mathcal{L}_i$ consists of the complexes $\left\{\mathcal{C}_{\nu_1^{(i)}}, \mathcal{C}_{\nu_2^{(i)}}, \ldots, \mathcal{C}_{\nu_{n_i}^{(i)}}\right\}$ where n_i is the number of complexes in $\mathcal{L}_i$. Then (3.39) holds if and only if, for every $i = 1, \ldots, \ell$,

$$\sum_{k=1}^{n_i} k(\nu_k^{(i)}, \nu_j^{(i)})(\mathbf{x}^*)^{\mathbf{z}_{\nu_k^{(i)}}} = (\mathbf{x}^*)^{\mathbf{z}_{\nu_j^{(i)}}} \sum_{k=1}^{n_i} k(\nu_j^{(i)}, \nu_k^{(i)}) \tag{3.40}$$

holds for all $j = 1, \ldots, n_i$. In other words, a mass-action system is complex balanced at $\mathbf{x}^*$ if and only if every linkage class of the system is complex balanced at $\mathbf{x}^*$.

Consider the i^{th} linkage class $\mathcal{L}_i$. We know that the system is complex balanced if and only if this linkage class is complex balanced according to (3.40). Consequently, we can decompose the rate constants relevant to $\mathcal{L}_i$, $k(\nu_j^{(i)}, \nu_k^{(i)})$, according to (3.30) and (3.54) of Lemma 3.3.3. We will let $\delta_i \in \mathbb{Z}_{>0}$ be the number of cycles in the cyclic decomposition of this subsystem and $\kappa_j > 0$, $j = 1, \ldots, \delta_i$, be the relevant constants derived via (3.30). It follows that

$$k(\nu_j^{(i)}, \nu_k^{(i)}) = \sum_{l=1}^{\delta_i} k_l(\nu_j^{(i)}, \nu_k^{(i)}) \tag{3.41}$$

where

$$k_l(\nu_j^{(i)}, \nu_k^{(i)}) = \frac{\kappa_l}{(\mathbf{x}^*)^{\mathbf{z}_{\nu_k^{(i)}}}}. \tag{3.42}$$

for each $l = 1, \ldots, \delta_i$.

Together, we have

$$\begin{aligned}
\sum_{k=1}^{n_i} k(\nu_k^{(i)}, \nu_j^{(i)})(\mathbf{x})^{\mathbf{z}_{\nu_k^{(i)}}} &= \sum_{k=1}^{n_i}\sum_{l=1}^{\delta_i} k_l(\nu_k^{(i)}, \nu_j^{(i)})(\mathbf{x})^{\mathbf{z}_{\nu_k^{(i)}}} && \text{(by 3.41)} \\
&= \sum_{k=1}^{n_i}\sum_{l=1}^{\delta_i} \kappa_l \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_k^{(i)}}} && \text{(by 3.42)} \\
&= \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_j^{(i)}}} \sum_{k=1}^{n_i}\sum_{l=1}^{\delta_i} \kappa_l && \text{(by 3.38)} \\
&= \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_j^{(i)}}} \sum_{k=1}^{n_i}\sum_{l=1}^{\delta_i} k_l(\nu_k^{(i)}, \nu_j^{(i)})(\mathbf{x}^*)^{\mathbf{z}_{\nu_k^{(i)}}} && \text{(by 3.42)} \\
&= \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_j^{(i)}}} \sum_{k=1}^{n_i} k(\nu_k^{(i)}, \nu_j^{(i)})(\mathbf{x}^*)^{\mathbf{z}_{\nu_k^{(i)}}} && \text{(by 3.41)} \\
&= (\mathbf{x})^{\mathbf{z}_{\nu_j^{(i)}}} \sum_{k=1}^{n_i} k(\nu_j^{(i)}, \nu_k^{(i)}) && \text{(by 3.39).}
\end{aligned}$$

It follows by (3.40) that $\mathbf{x}$ is a complex balanced equilibrium concentration of the mecha-

nism restricted to $\mathcal{L}_i$. Since this holds for all linkage classes $\mathcal{L}_i$, $i = 1, \ldots, \ell$, it follows that (3.39) is satisfied and consequently $\mathbf{x}$ is a complex balanced equilibrium concentration of the entire mechanism. This proves Claim (2).

Proof (3): This follows identically to the proof of Claim (3) of Theorem 3.2.1.

Proof (4): This follows identically to the proof of Claim (4) of Theorem 3.2.1, with the sole exception that $\nabla L(\mathbf{x}(t)) \cdot \dfrac{d\mathbf{x}(t)}{dt} \leq 0$ for all $t \geq 0$ follows from Lemma 3.3.4 rather than Lemma 3.2.2. □

Example 3.3.2. *Reconsider the system (3.32) given in Example 3.3.1,*

$$\begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{1} & \mathcal{A}_2 \\ {\scriptstyle 1}\uparrow & {\scriptstyle \epsilon}\nearrow\swarrow{\scriptstyle \epsilon} & \downarrow{\scriptstyle 1} \\ \mathcal{A}_4 & \xleftarrow[1]{} & \mathcal{A}_3 \end{array}$$

where $0 < \epsilon < 1$*, which can be decomposed into the cyclic subsystems* $\mathcal{R}_1$*,* $\mathcal{R}_2$ *and* $\mathcal{R}_3$ *derived previously. The system is governed by (3.33) which has equilibria along the curve* $x_1^* = x_2^* = x_3^* = x_4^*$*.*

In order to apply Theorem 3.3.1 we need to prove that the system has a complex balanced equilibrium concentration according to Definition 3.1.3. More intuitively, we need the net flow rate into each complex to balance the net flow rate out of each complex. This gives us the system of equations

$$\begin{aligned} \mathcal{C}_1 : &\qquad x_4 = x_1 \\ \mathcal{C}_2 : &\qquad x_1 + \epsilon x_4 = (1+\epsilon)x_2 \\ \mathcal{C}_3 : &\qquad x_2 = x_3 \\ \mathcal{C}_4 : &\qquad x_3 + \epsilon x_2 = (1+\epsilon)x_4. \end{aligned}$$

These conditions correspond exactly to the equilibrium conditions so that every equilibrium concentration is complex balanced.

It can be trivially seen that each positive stoichiometric compatibility class given by $(\mathbf{x}_0 + S) \cap \mathbb{R}^m_{>0}$ *where*

$$S = span\left\{\begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \end{bmatrix}\right\}$$

intersects the equilibrium curve $x_1^* = x_2^* = x_3^* = x_4^*$ *exactly once.*

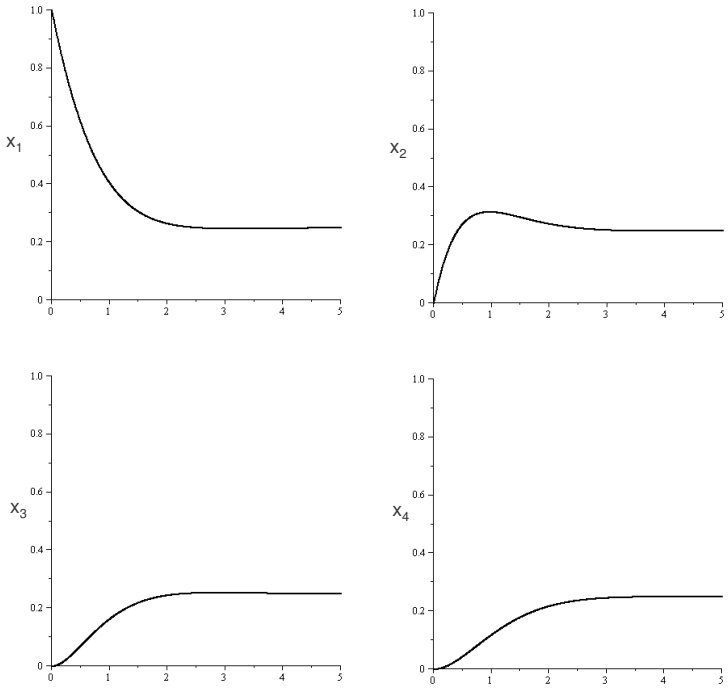

Figure 3.2: The solution $\mathbf{x}(t)$ to (3.33) for $\epsilon = 1/2$, $x_{10} = 1$, $x_{20} = x_{30} = x_{40} = 0$. The solution converges to the equilibrium value $x_1^* = x_2^* = x_3^* = x_4^* = 1/4$.

Consider the compatibility class corresponding to the equilibrium concentration $x_1^* =$

$x_2^* = x_3^* = x_4^* = 1/4$. *According to the conservation law* $\langle \mathbf{v}, \mathbf{x} - \mathbf{x}_0 \rangle = 0$ *with* $\mathbf{v} = [1, 1, 1, 1]^T$, *this corresponds to initial conditions* $\mathbf{x}_0 \in \mathbb{R}^4_{>0}$ *with* $x_{10} + x_{20} + x_{30} + x_{40} = 1$. *Numerically integrating, we can see that the system evolves toward the expected equilibrium concentration (see Figure 3.2).*

3.4 Deficiency Zero Theorem

In our discussion of complex balanced systems so far, we have seen that the assumption of complex balancing of equilibrium concentrations carries implications for the reaction graph of the system. Specifically, we have seen that complex balanced systems are weakly reversible (Lemma 3.1.2), that they can be linearly decomposed into complex balanced cyclic systems (Lemma 3.3.3), and that the complex balancing condition decomposes according to the linkage classes (see the proof of Claim (2) or Theorem 3.3.1).

What is not immediately obvious is that properties of the reaction graph carry implications for if and when the complex balancing condition on equilibrium concentrations is satisfied. In fact, in this section we will see that several easily checked conditions on the reaction graph form sufficient conditions for the complex balancing of equilibrium concentrations. Incorporating the results of Section 3.3.2, this implies that for a large class of systems we can determine the long-term dynamical properties of the system by considering conditions on the structure of the reaction graph alone. This should come as a surprise—it means we can say something about the equilibrium set of a system, and the local stability of those concentrations, without determining the equilibrium concentrations or considering the dynamics!

The results of this section are drawn primarily from the sources [13, 25, 30]. In [25]

and [30], the authors prove that weak reversibility and a deficiency of zero are sufficient conditions for the complex balancing of all equilibrium concentrations (Theorem 3.4.2). Their approach depends on abstract elements from linear algebra which will not be needed in this section. In [13], the authors relate the complex balancing condition to notions from computational algebra. Importantly for our purposes is that they provide a constructive method for determining several of the abstract quantities contained in [25] and [30]. I am also indebted to the unpublished research notes of former University of Waterloo graduate student D. MacLean who did terrific work expanding upon and clarifying the results of [25] and [30].

While all of the results contained in this section are drawn from existing literature, to the best of my knowledge the following results represent the most complete and constructive analysis of the deficiency zero condition to date.

Our analysis starts with some consideration of relevant quantities from graph theory. The definitions have been adapted according to their relevance to chemical kinetics, and in particular the reaction graph given by (2.2) where complexes represent nodes and reactions represent directed edges according to Definition 2.2.1. Whenever working with a subset of the reaction set $\mathcal{R}' \subset \mathcal{R}$, we will let $\mathcal{C}(\mathcal{R}')$ denote the set of complexes involved in reactions from the set $\mathcal{R}'$ either as a reactant or a product.

Definition 3.4.1. *A subset of the reaction set $\mathcal{T} \subset \mathcal{R}$ is said to be a* ***reaction tree*** *if, for every pair of complexes $\mathcal{C}_{\nu_0}, \mathcal{C}_{\nu_k} \in \mathcal{C}(\mathcal{T})$, there is exactly one sequence of indices $(\nu_{i-1}, \nu_i) \in \mathcal{T}$ satisfying*

$$\mathcal{C}_{\nu_0} \longleftrightarrow \mathcal{C}_{\nu_1} \longleftrightarrow \cdots \longleftrightarrow \mathcal{C}_{\nu_{k-1}} \longleftrightarrow \mathcal{C}_{\nu_k}$$

where each $\mathcal{C}_{\nu_i}$ is distinct.

It follows by this definition that the set $\mathcal{C}(\mathcal{T})$ is connected by Definition 2.2.2 and therefore all of the complexes in it belong to the same linkage class.

It should also be noted that this definition does not even permit cycles in the *undirected* graph. Definition 3.4.1 is violated regardless of the direction in which the individual reactions in the cyclic sequence flow.

Definition 3.4.2. *A reaction tree $\mathcal{T} \subset \mathcal{R}$ is said to* ***span the linkage class*** *$\mathcal{L}_i$ if $\mathcal{C}(\mathcal{T}) = \mathcal{L}_i$.*

This definition means that every complex in a linkage class is contained in the reaction tree. It is clear that no tree may exceed the complexes contained within a single linkage class. It is also clear that any reaction tree which spans a linkage class contains exactly l_i complexes in it, where l_i is the number of complexes in the linkage class $\mathcal{L}_i$.

The following definitions make use of the directed nature of reaction trees.

Definition 3.4.3. *Consider a reaction tree $\mathcal{T} \subset \mathcal{R}$. The complex $\mathcal{C}_i \in \mathcal{C}(\mathcal{T})$ is said to be a* ***sink*** *of $\mathcal{T}$ if all reactions in $\mathcal{T}$ involving $\mathcal{C}_i$ involve $\mathcal{C}_i$ as a product.*

Definition 3.4.4. *Consider a reaction tree $\mathcal{T} \subset \mathcal{R}$ and a given $\mathcal{C}_i \in \mathcal{C}(\mathcal{T})$. Then $\mathcal{T}$ is said to be an* **i-*reaction tree*** *if $\mathcal{C}_i$ is the unique sink of $\mathcal{T}$.*

An important task will be identifying i-reaction trees which span linkage classes. We will let $\mathcal{T}_j(i)$ denote the set of i-reaction trees which span the j^{th} linkage class $\mathcal{L}_j$. When the system consists of only a single linkage class (i.e. $j = 1$), we will use the shorthand $\mathcal{T}_j(i) = \mathcal{T}(i)$. The following quantities will be required throughout the rest of this section:

$$\kappa_{\mathcal{T}} = \prod_{(i_0,j_0)\in\mathcal{T}} k(i_0, j_0), \tag{3.43}$$

$$K_i = \sum_{\mathcal{T} \in \mathcal{T}_j(i)} \kappa_{\mathcal{T}}. \tag{3.44}$$

The quantities $\kappa_{\mathcal{T}}$ are the products of all the reaction rates associated with reactions in the reaction tree $\mathcal{T}$. The quantities K_i are the sum of all such products associated with i-reaction trees which span the j^{th} linkage class. It is not clear at this point why these quantities are important to chemical kinetics, but we will show in this section that they are intricately related to the complex balancing condition given by Definition 3.1.3.

Example 3.4.1. *Consider the reaction system*

$$\begin{array}{ccc} \mathcal{C}_1 & \underset{k_7}{\overset{k_1}{\rightleftarrows}} & \mathcal{C}_2 \\ {\scriptstyle k_4}\uparrow\downarrow{\scriptstyle k_6} & \searrow^{k_5} & \downarrow_{k_2} \\ \mathcal{C}_4 & \underset{k_3}{\leftarrow} & \mathcal{C}_3. \end{array} \tag{3.45}$$

We have indexed the system according to (2.1) rather than (2.2). This is done for notational simplicity and will make no difference in the analysis. This system contains only one linkage class, but the proceding analysis can be easily generalized to multiple linkage classes.

We want to determine the quantities K_i, $i = 1, \ldots, 4$. Our first point of order is to determine all of the i-reaction trees which span the complexes, that is to say, to determine the sets $\mathcal{T}(i)$ for $i = 1, \ldots, 4$.

We start by considering $i = 1$. There are two 1-reaction trees which span the complexes,

given by

$$\begin{array}{lccc} & \mathcal{C}_1 & \mathcal{C}_2 & \qquad\qquad \mathcal{C}_1 \underset{k_7}{\leftarrow} \mathcal{C}_2 \\ \mathcal{T}_1: & {}^{k_4}\uparrow & \downarrow_{k_2} & \mathcal{T}_2: \quad {}^{k_4}\uparrow \\ & \mathcal{C}_4 \underset{k_3}{\leftarrow} & \mathcal{C}_3 & \qquad\qquad \mathcal{C}_4 \underset{k_3}{\leftarrow} \mathcal{C}_3 \end{array}$$

We can now easily determine that $\kappa_{\mathcal{T}_1} = k_2k_3k_4$ *and* $\kappa_{\mathcal{T}_2} = k_3k_4k_7$ *so that* $K_1 = k_2k_3k_4+k_3k_4k_7$.

The analysis for the other complexes follows similarly. It should be noted, however, that while it is easy to verify that a particular reaction tree is in fact an i-reaction tree, it is not necessarily easy to find them all. For systems with complicated reaction graphs, computer assistance is often required.

For the other complexes, we have

$$K_2 = k_1k_3k_4$$

$$K_3 = k_1k_2k_4 + k_2k_4k_5 + k_4k_5k_7$$

$$K_4 = k_1k_2k_3 + k_3k_6k_7 + k_2k_3k_5 + k_2k_3k_6 + k_3k_5k_7.$$

The following result will be crucial to connecting reaction trees to complex balanced reaction mechanisms.

Lemma 3.4.1. *Consider an i-reaction tree* $\mathcal{T}_i$ *which spans a linkage class* $\mathcal{L}$. *Consider the reaction graph produced by adding the reaction* $\mathcal{C}_i \longrightarrow \mathcal{C}_j$, $\mathcal{C}_j \in \mathcal{L}$, *to* $\mathcal{T}_i$. *It follows that:*

1. *There exists a k-reaction tree* $\mathcal{T}_k$ *such that adding the reaction* $\mathcal{C}_k \longrightarrow \mathcal{C}_i$, $\mathcal{C}_k \in \mathcal{L}$, *to* $\mathcal{T}_k$ *produces the same reaction graph; and*

2. *There exists a j-reaction tree $\mathcal{T}_j$ such that adding the reaction $\mathcal{C}_j \longrightarrow \mathcal{C}_k$, $\mathcal{C}_k \in \mathcal{L}$, to $\mathcal{T}_j$ produces the same reaction graph.*

Proof. Let $\mathcal{T}_i$ be an i-reaction tree which spans a linkage class $\mathcal{L}$. Consider the reaction $\mathcal{C}_i \longrightarrow \mathcal{C}_j$ for some arbitrary $\mathcal{C}_j \in \mathcal{L}$. Since $\mathcal{C}_i$ is a sink it follows that this reaction is not in $\mathcal{T}_i$ by definition. Since $\mathcal{T}_i$ spans $\mathcal{L}$ and $\mathcal{C}_i$ is the unique sink of $\mathcal{T}_i$, it follows that there is a sequence of complexes and reactions such that

$$\mathcal{C}_j = \mathcal{C}_{\nu_1} \longrightarrow \mathcal{C}_{\nu_2} \longrightarrow \cdots \longrightarrow \mathcal{C}_{\nu_{l-1}} \longrightarrow \mathcal{C}_{\nu_l} = \mathcal{C}_i. \tag{3.46}$$

After adding the reaction $\mathcal{C}_i \longrightarrow \mathcal{C}_j$ we see that our new system contains a reaction cycle according to Definition 3.3.1

Consider removing the reaction $\mathcal{C}_{\nu_{l-1}} \longrightarrow \mathcal{C}_i$ from this new system. It is easy to see that the remaining system is still a tree which spans $\mathcal{L}$, since this removal breaks the only cycle and every complex in $\mathcal{L}$ is still connected to every other complex in $\mathcal{L}$. Since any reaction involving $\mathcal{C}_{\nu_{l-1}}$ as a reactant must ultimately lead to $\mathcal{C}_i$, it follows from $\mathcal{T}_i$ being a tree that $\mathcal{C}_{\nu_{l-1}} \longrightarrow \mathcal{C}_i$ is the only reaction in $\mathcal{T}_i$ involving $\mathcal{C}_{\nu_{l-1}}$ as a reactant. It follows that $\mathcal{C}_{\nu_{l-1}}$ is a sink of the new system. Furthermore, since all paths leading to $\mathcal{C}_i$ can now be extended to lead to $\mathcal{C}_{\nu_{l-1}}$, it follows that it is a unique sink. Making the association $\mathcal{C}_{\nu_{l-1}} = \mathcal{C}_k$, it follows that this system is a k-reaction tree, and we have proved claim (1).

The proof of claim (2) follows by similar reasoning. □

In other words, if we add a reaction to an i-reaction tree spanning a linkage class, we can pick another reaction to remove which produces a j-reaction tree for $i \neq j$.

We will also need the following result.

Lemma 3.4.2. *If a system is weakly reversible then for any $\mathcal{C}_i$, $i = 1, \ldots, n$, there exists at least one i-reaction tree spanning the linkage class $\mathcal{L}$ satisfying $\mathcal{C}_i \in \mathcal{L}$.*

Proof. Consider an arbitrary $\mathcal{C}_i$, $i = 1, \ldots, n$, and let $\mathcal{L}$ denote the linkage class such that $\mathcal{C}_i \in \mathcal{L}$. We will prove the claim by construction. Consider an arbitrary path

$$\mathcal{C}_i \longrightarrow \mathcal{C}_{\nu_1} \longrightarrow \cdots \longrightarrow \mathcal{C}_{\nu_{l_1-1}} \longrightarrow \mathcal{C}_j \longrightarrow \mathcal{C}_{\nu_1} \longrightarrow \cdots \longrightarrow \mathcal{C}_{\mu_{l_2-1}} \longrightarrow \mathcal{C}_i$$

for some $\mathcal{C}_j \in \mathcal{L}$. We know such a path exists because $\mathcal{C}_i$ and $\mathcal{C}_j$ belong to the same linkage class and the system is weakly reversible.

If we remove the reaction $\mathcal{C}_i \longrightarrow \mathcal{C}_{\nu_1}$ from the system, we have a reaction tree with the unique sink $\mathcal{C}_i$. Now consider a complex $\mathcal{C}_j \in \mathcal{L}$ which is not contained in the above cycle. We know that there is a path from $\mathcal{C}_j$ to $\mathcal{C}_i$ by weak reversibility. If we take the portion of this path leading from $\mathcal{C}_j$ to the first complex appearing in the reaction tree we just derived (possibly $\mathcal{C}_i$ itself), we again arrive at a reaction tree with $\mathcal{C}_i$ as its unique sink. Since we can follow this procedure until we have exhausted every complex in the linkage class, it follows that there exists an i-reaction tree spanning the linkage class containing $\mathcal{C}_i$. □

These results will prove particularly useful in proving the following. This result should be contrasted with Lemma 3A of [30] and Corollary 4 of [13]. Although our statement of the result, and the proof, differ from either of these results, they in fact address the same point. In particular, the $v_i > 0$, $i = 1, \ldots, n$, which were only guaranteed to exist by Lemma 3A of [30] can be explicitly solved for by the terms K_i introduced here as (3.44) and used in Corollary 4 of [13].

Theorem 3.4.1. *A mass-action system is weakly reversible if and only if the set* $(K_1, \ldots, K_n) \in \mathbb{R}^n_{>0}$ *defined according to (3.44) satisfies*

$$\sum_{j=1}^{n} k(j,i)K_j = K_i \sum_{j=1}^{n} k(i,j) \tag{3.47}$$

for all $i = 1, \ldots, n$.

Proof. We will prove the 'only if' claim first. Similarly to the argument used in proving Claim (2) of Theorem 3.3.1, we can partition condition (3.47) into conditions on each linkage class $\mathcal{L}_i$, $i = 1, \ldots, \ell$. Specifically, we have that (3.47) is satisfied if and only if, for every $i = 1, \ldots, \ell$,

$$\sum_{k=1}^{n_i} k(\nu_k^{(i)}, \nu_j^{(i)})K_{\nu_k^{(i)}} = K_{\nu_j^{(i)}} \sum_{k=1}^{n_i} k(\nu_j^{(i)}, \nu_k^{(i)}) \tag{3.48}$$

for all $j = 1, \ldots, n_i$, where $\left\{\mathcal{C}_{\nu_1^{(i)}}, \mathcal{C}_{\nu_2^{(i)}}, \ldots, \mathcal{C}_{\nu_{n_i}^{(i)}}\right\}$ is the set of complexes in the i^{th} linkage class and n_i is the number of such complexes.

From Lemma 3.4.2, since the system is weakly reversible we know that corresponding to every $\mathcal{C}_{\nu_j^{(i)}} \in \mathcal{L}_i$ is at least one $\nu_j^{(i)}$-reaction tree. Since the rate constants are positive, it follows that $K_{\nu_j^{(i)}} > 0$ for every $\mathcal{C}_{\nu_j^{(i)}} \in \mathcal{L}_i$.

Consider an arbitrary $\nu_k^{(i)}$-reaction tree corresponding to a term $\kappa_{\mathcal{T}}(\nu_k^{(i)})$ in the sum forming $K_{\nu_k^{(i)}}$ according to (3.44). In (3.48), these terms are multiplied by terms in the set $\left\{k(\nu_k^{(i)}, \nu_j^{(i)})\right\}_{k=1}^{n_i}$. Consider an arbitrary element in this set, $k(\nu_k^{(i)}, \nu_j^{(i)})$, $k = 1, \ldots, n_i$, and consider the product $k(\nu_k^{(i)}, \nu_j^{(i)})\kappa_{\mathcal{T}}(\nu_k^{(i)})$. This corresponds to adding a reaction $\mathcal{C}_{\nu_k^{(i)}} \longrightarrow \mathcal{C}_{\nu_j^{(i)}}$ to the given $\nu_k^{(i)}$-reaction tree. By Claim (2) of Lemma 3.4.1, it follows that there is a $\nu_j^{(i)}$-reaction tree which has the same reaction graph after adding a reaction $\mathcal{C}_{\nu_j^{(i)}} \longrightarrow \mathcal{C}_{\nu_l^{(i)}}$ for some $l = 1, \ldots, n_i$. Since the terms on the right-hand side of (3.48) exhaust all $\nu_j^{(i)}$-

reaction trees and all rate constants originating at index $\nu_j^{(i)}$, this term must lie somewhere on the right-hand side of (3.48). Since $\nu_k^{(i)}$ and $\kappa_{\mathcal{T}}(\nu_k^{(i)})$ were chosen arbitrarily, it follows that every term on the left-hand side of (3.48) necessarily lies on the right-hand side as well. Since the linkage class was also chosen arbitrarily, we have that, for all $i = 1, \ldots, \ell$,

$$\sum_{k=1}^{n_i} k(\nu_k^{(i)}, \nu_j^{(i)}) K_{\nu_k^{(i)}} \leq K_{\nu_j^{(i)}} \sum_{k=1}^{n_i} k(\nu_j^{(i)}, \nu_k^{(i)}) \tag{3.49}$$

for all $j = 1, \ldots, n_i$.

The same argument can be applied starting with $\nu_j^{(i)}$-reaction trees corresponding to terms in $K_{\nu_j^{(i)}}$ on the right-hand side of (3.48). Applying Claim (1) of Lemma 3.4.1, we have that, for all $i = 1, \ldots, \ell$,

$$\sum_{k=1}^{n_i} k(\nu_k^{(i)}, \nu_j^{(i)}) K_{\nu_k^{(i)}} \geq K_{\nu_j^{(i)}} \sum_{k=1}^{n_i} k(\nu_j^{(i)}, \nu_k^{(i)}) \tag{3.50}$$

for all $j = 1, \ldots, n_i$. Combining (3.49) and (3.50), and reverting to our original indexing, we have that

$$\sum_{j=1}^{n} k(j, i) K_j = K_i \sum_{j=1}^{n} k(i, j)$$

for all $i = 1, \ldots, n$.

The proof of the reverse implication is identical to the proof of Lemma 3.1.2. □

The condition (3.48) looks very similar to the complex balancing condition (3.6). This similarity is not superficial; however, before proceding we present some important properties which follows from (3.48). Due to significant similarities with the analogous proofs for the complex balanced systems satisfying (3.6), many details of the proofs will be omitted.

Lemma 3.4.3. *If a mass-action system is weakly reversible, then for every* $(v_1, \ldots, v_n) \in \mathbb{R}^n_{>0}$ *there exist rate constants satisfying* $k(i,j) > 0$ *for* $(i,j) \in \mathcal{R}$ *and* $k(i,j) = 0$ *for* $(i,j) \notin \mathcal{R}$ *such that, for all* $i = 1, \ldots, n$,

$$\sum_{j=1}^{n} k(j,i) v_j = v_i \sum_{j=1}^{n} k(i,j)$$

is satisfied.

Proof. We will find the rate constants explicitly.

Consider a weakly reversible mass-action system with arbitrary rate constants $k(i,j)$. By Theorem 3.4.1, the set $(K_1, \ldots, K_n) \in \mathbb{R}^n_{>0}$ satisfies

$$\sum_{j=1}^{n} k(j,i) K_j = K_i \sum_{j=1}^{n} k(i,j)$$

for all $i = 1, \ldots, n$.

Now consider an arbitrary $(v_1, \ldots, v_n) \in \mathbb{R}^n_{>0}$ and let $\tilde{k}(i,j) = (K_j/v_j) \cdot k(i,j)$ for all $i, j = 1, \ldots, n$. It follows that, for all $i = 1, \ldots, n$,

$$\sum_{j=1}^{n} \tilde{k}(j,i) v_j = \sum_{j=1}^{n} k(j,i) K_j = K_i \sum_{j=1}^{n} k(i,j) = v_i \sum_{j=1}^{n} \tilde{k}(i,j).$$

Since $(v_1, \ldots, v_n) \in \mathbb{R}^n_{>0}$ was chosen arbitrarily and the $\tilde{k}(i,j)$ satisfy the requirements, the result follows. □

Lemma 3.4.4. *Consider a weakly reversible mass-action system and let* $(v_1, \ldots, v_n) \in \mathbb{R}^n_{>0}$ *satisfy*

$$\sum_{j=1}^{n} k(j,i) v_j = v_i \sum_{j=1}^{n} k(i,j). \tag{3.51}$$

Then there exist $s^{(k)} > 0$, $k = 1, \ldots, \ell$, *such that* $v_i = s^{(k)} K_i$ *for all* i *such that* $\mathcal{C}_i \in \mathcal{L}_k$.

Proof. We will first consider what implications (3.47) and the assumption of weak reversibility have on the rate constants $k(i,j)$. The following closely mirrors the proof of Lemma 3.3.3, so some details will be glossed over.

Since the system is weakly reversible, we know that there is at least one chain of reactions which constitutes a cycle according to Definition 3.3.1. We will index this cycle $\{\nu_1, \nu_2, \ldots, \nu_l, \nu_{l+1}\}$ where l is the length of the cycle and define

$$\kappa_1 = \min_{i=1,\ldots,l} k(\nu_i, \nu_{i+1}) K_{\nu_i} > 0. \tag{3.52}$$

We now define two new sets of rate constants as

$$k_1(i,j) = \begin{cases} \dfrac{\kappa_1}{K_i}, & \text{for } (i,j) \text{ in the cycle} \\ 0, & \text{otherwise} \end{cases} \tag{3.53}$$

and

$$k'(i,j) = k(i,j) - k_1(i,j), \qquad \text{for } i,j = 1, \ldots, n. \tag{3.54}$$

As in the argument for Lemma 3.3.3, we can make associations between the set of reaction rates $k_1(i,j)$ and $k'(i,j)$, $i,j = 1, \ldots, n$, and the reaction sets $\mathcal{R}_1 = \{(i,j) \mid k_1(i,j) > 0\}$ and $\mathcal{R}' = \{(i,j) \mid k'(i,j) > 0\}$. Also as before, we have $|\mathcal{R}'| < |\mathcal{R}|$ so that the remaining system

is smaller than the original system. From linearity, we have that, for every $i = 1, \ldots, n$,

$$\begin{aligned}\sum_{j=1}^{n} k'(j,i)K_j &= \sum_{j=1}^{n} k(j,i)K_j - \sum_{j=1}^{n} k_1(j,i)K_j \\ &= K_i \sum_{j=1}^{n} k(i,j) - K_i \sum_{j=1}^{n} k_1(i,j) \\ &= K_i \sum_{j=1}^{n} k'(i,j).\end{aligned}$$

By the analogous argument to Lemma 3.1.2, this is sufficient to prove the remaining system is weakly reversible so that we can apply the same procedure to this quantity as we did to (3.48). Since the set of reactions decreases with each iteration, this process must terminate at some point, and by the above argument, each step must yield a condition of the form (3.48) corresponding to a reaction cycle.

Substituting for the $k(i,j)$ and moving everything to the left-hand side, we can write (3.51) as the condition

$$\sum_{j=1}^{n} \left(\sum_{l=1}^{\delta} k_l(j,i) \right) v_j - v_i \sum_{j=1}^{n} \left(\sum_{l=1}^{\delta} k_l(i,j) \right) = 0 \tag{3.55}$$

for all $i = 1, \ldots, n$, where the $k_l(i,j)$, $l = 1, \ldots, \delta$, are defined according to (3.53). We can break the system into the cycles $\left\{ \nu_1^{(i)}, \nu_2^{(i)}, \ldots, \nu_{l_i}^{(i)}, \nu_{l_i+1}^{(i)} \right\}$, $i = 1, \ldots, \delta$, so that (3.55) can be written as

$$\sum_{\substack{i=1 \\ \nu_j^{(i)} = l}}^{\delta} \left[k_i(\nu_{j-1}^{(i)}, \nu_j^{(i)}) v_{\nu_{j-1}^{(i)}} - k_i(\nu_j^{(i)}, \nu_{j+1}^{(i)}) v_{\nu_j^{(i)}} \right] = 0 \tag{3.56}$$

for $l = 1, \ldots, n$. It follows from (3.53) that (3.56) can be written

$$\sum_{\substack{i=1 \\ \nu_j^{(i)}=l}}^{\delta} \kappa_i \left(\frac{v_{\nu_{j-1}^{(i)}}}{K_{\nu_{j-1}^{(i)}}} - \frac{v_{\nu_j^{(i)}}}{K_{\nu_j^{(i)}}} \right) = 0$$

for $l = 1, \ldots, n$. Multiplying the l^{th} condition by the term v_l/K_l and summing over the $l = 1, \ldots, n$ conditions gives

$$\sum_{i=1}^{\delta} \kappa_i \sum_{j=1}^{l_i} \frac{v_{\nu_j^{(i)}}}{K_{\nu_j^{(i)}}} \left(\frac{v_{\nu_{j-1}^{(i)}}}{K_{\nu_{j-1}^{(i)}}} - \frac{v_{\nu_j^{(i)}}}{K_{\nu_j^{(i)}}} \right) = -\sum_{i=1}^{\delta} \frac{\kappa_i}{2} \sum_{j=1}^{l_i} \left(\frac{v_{\nu_{j-1}^{(i)}}}{K_{\nu_{j-1}^{(i)}}} - \frac{v_{\nu_j^{(i)}}}{K_{\nu_j^{(i)}}} \right)^2 = 0. \tag{3.57}$$

Since each term in the sum in (3.57) is less than or equal to zero, it follows that equality with zero in (3.57) can be obtained if and only if

$$\frac{v_{\nu_{j-1}^{(i)}}}{K_{\nu_{j-1}^{(i)}}} = \frac{v_{\nu_j^{(i)}}}{K_{\nu_j^{(i)}}}$$

for all $i = 1, \ldots, \delta$, $j = 1, \ldots, l_i$. Since all cycles in the same linkage class are connected, however, we can generalize this. If we let $\left\{ \mu_1^{(i)}, \mu_2^{(i)}, \ldots, \mu_{n_i}^{(i)} \right\}$ denote the indices of complexes in the i^{th} linkage class, where n_i is the number of complexes in this linkage class, we have that, for all $i = 1, \ldots, \ell$,

$$\frac{v_{\mu_k^{(i)}}}{K_{\mu_k^{(i)}}} = \frac{v_{\mu_j^{(i)}}}{K_{\mu_j^{(i)}}}$$

for all $j, k = 1, \ldots, n_i$. It follows that any solution $(v_1, \ldots, v_n) \in \mathbb{R}^n_{>0}$ of

$$\sum_{j=1}^{n} k(j,i) v_j = v_i \sum_{j=1}^{n} k(i,j)$$

must satisfy $v_i = s^{(k)} K_i$ for all i such that $\mathcal{C}_i \in \mathcal{L}_k$, where $s^{(k)} > 0$ is a unique constant

relative to each linkage class, and we are done. □

So far in this section, we have considered only the properties of general weakly reversible systems. We know that complex balanced systems are weakly reversible, but we have said nothing about when weakly reversible systems are complex balanced. The following two results (Theorem 3.4.2 and Theorem 3.4.3) clarify this connection.

This result should be contrasted with Theorem 4A of [30], Theorem 4.1 of [25], and Theorem 9 of [13].

Theorem 3.4.2 (Deficiency Zero Theorem)**.** *A mass-action system is complex balanced for all sets of rate constants if and only if it is weakly reversible and has a deficiency of zero (i.e.* $\delta = n - \ell - s = 0$*).*

Proof. We will prove the 'only if' statement first. Consider a system with a complex balanced equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. By Definition 3.1.3, this implies that

$$\sum_{j=1}^{n} k(j,i)(\mathbf{x}^*)^{\mathbf{z}_j} = (\mathbf{x}^*)^{\mathbf{z}_i} \sum_{j=1}^{n} k(i,j)$$

for all $i = 1, \ldots, n$. Since every complex balanced system is weakly reversible by Lemma 3.1.2, it follows by Lemma 3.4.4 that there are constants $s^{(i)} > 0$, $i = 1, \ldots, \ell$, such that

$$(\mathbf{x}^*)^{\mathbf{z}_j} = s^{(i)} K_j \tag{3.58}$$

for all j such that $\mathcal{C}_j \in \mathcal{L}_i$. If we index the i^{th} linkage class as $\left\{\mu_1^{(i)}, \mu_2^{(i)}, \ldots, \mu_{n_i}^{(i)}\right\}$, (3.58) can be written

$$\left(\mathbf{x}^*\right)^{\mathbf{z}_{\mu_j^{(i)}}} = s^{(i)} K_{\mu_j^{(i)}}$$

for $i = 1, \ldots, \ell$, $j = 1, \ldots, n_i$. It follows by taking $s^{(i)} = (\mathbf{x}^*)^{\mathbf{z}_{\mu_{n_i}^{(i)}}} / K_{\mu_{n_i}^{(i)}}$ for all $i = 1, \ldots, \ell$ that (3.58) is satisfied if and only if

$$(\mathbf{z}_{\mu_j^{(i)}} - \mathbf{z}_{\mu_{n_i}^{(i)}})^T \ln(\mathbf{x}^*) = \ln\left(\frac{K_{\mu_j^{(i)}}}{K_{\mu_{n_i}^{(i)}}}\right) \tag{3.59}$$

for all $i = 1, \ldots, \ell$, $j = 1, \ldots, n_i - 1$.

This is a set of $\sum_{i=1}^{\ell}(n_i - 1) = n - \ell$ conditions which are linear in $\ln(\mathbf{x})$. The terms on the right-hand side of (3.59) depend on the rate constants; however, from Lemma 3.4.3 we know that the $K_i > 0$, $i = 1, \ldots, n$ can be made arbitrary by an appropriate choice of rate constants. Consequently, each $\ln(K_{\mu_j^{(i)}}/K_{\mu_{n_i}^{(i)}})$ may assume an arbitrary value in $\mathbb{R}$. It follows by basic linear algebra that the system is satisfiable for all choices of rate constants if and only if the rank of the matrix with rows $(\mathbf{z}_{\mu_j^{(i)}} - \mathbf{z}_{\mu_{n_i}^{(i)}})^T$ is equal to the number of linear conditions, which is $n - \ell$. Since the vectors $(\mathbf{z}_{\mu_j^{(i)}} - \mathbf{z}_{\mu_{n_i}^{(i)}})^T$ span S, it follows that the desired condition is $\dim(S) = n - \ell$, which is equivalent to $\delta = n - \ell - s = 0$.

Since each step in the above argument holds in the reverse direction, the 'if' statement follows, and we are finished. □

This result may seem mundane at first glance, but its implications are vast. We saw in Section 3.3.2 that complex balanced systems exhibit a type of simple and predictable behaviour—all the positive compatibility classes $\mathsf{C}_{\mathbf{x}_0}$ have a unique positive equilibrium which is locally asymptotically stable relative to $\mathsf{C}_{\mathbf{x}_0}$. In this section, we have shown that a system is complex balanced at all equilibrium values if and only if it is weakly reversible system and has a deficiency of zero. In other words, we have simple conditions which negate the need to check for complex balancing of equilibrium concentrations. More surprising, these conditions have nothing to do with the dynamics of the system. They do not depend

on the rate constants. They are conditions on the *reaction graph* alone.

We will see how powerful this result is through a few examples.

Example 3.4.2. *Reconsider the mass-action system given previously in Example 2.2.1 and Example 2.2.3,*

$$\begin{array}{ccc} \mathcal{A}_1 & \overset{k(1,2)}{\longrightarrow} & \mathcal{A}_2 \\ {\scriptstyle k(3,1)}\,\nwarrow & & \swarrow\,{\scriptstyle k(2,3)} \\ & \mathcal{A}_3 + \mathcal{A}_4 & \end{array}$$

$$2\mathcal{A}_1 \underset{k(5,4)}{\overset{k(4,5)}{\rightleftarrows}} 2\mathcal{A}_3.$$

We established in Example 2.2.1 that this system is weakly reversible and in Example 2.2.3 that it has a deficiency of zero ($n = 5$, $\ell = 2$, $s = 3$, and therefore $\delta = 0$). It follows immediately from Theorem 3.4.2 that every equilibrium concentration is a complex balanced equilibrium concentration and, consequently, by Theorem 3.3.1 that the system exhibits locally stable dynamics for all choices of rate constants.

The important—and surprising—point is that the Deficiency Zero Theorem gives us the power to say this even though we have not found the equilibrium set or even bothered to write down the governing set of differential equations, much less directly analyse them!

Example 3.4.3. *Reconsider the mass-action system given previously in Example 3.3.1 and*

Example 3.3.2,

$$\begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{1} & \mathcal{A}_2 \\ {\scriptstyle 1}\uparrow & {\scriptstyle \epsilon}\swarrow\!\!\!\nearrow{\scriptstyle \epsilon} & \downarrow{\scriptstyle 1} \\ \mathcal{A}_4 & \xleftarrow[1]{} & \mathcal{A}_3 \end{array}$$

where $0 < \epsilon < 1$.

In Example 3.3.2, we determine by direct analysis that every equilibrium concentration was complex balanced and, consequently, by Theorem 3.3.1, the system exhibits locally stable dynamics. This results of this Section allow us to verify this result within significantly less strain. We can see immediately that the system is weakly reversible, that it has four complexes ($n = 4$), a single linkage class ($\ell = 1$), and the dimension of the stoichiometric space S is three ($s = 3$). It follows that the deficiency is zero ($\delta = n - \ell - s = 0$) and Theorem 3.4.2 may be applied.

It can rarely be expected, however, that conditions work out as favourably as they are required to be for Theorem 3.4.2 to be applied. The following result allows us to say something about weakly reversible systems for which the deficiency is not zero.

Theorem 3.4.3. *If a mass-action system is weakly reversible, then the deficiency corresponds to the number of conditions on the rate constants which need to be satisfied in order for the system to be complex balanced.*

Proof. In the proof of Theorem 3.4.2, we showed that the complex balancing condition (3.6) was equivalent to (3.59) holding for all $i = 1, \ldots, \ell$ and $j = 1, \ldots, n_i$ where $\left\{\mathcal{C}_{\nu_1}^{(i)}, \mathcal{C}_{\nu_2}^{(i)}, \ldots, \mathcal{C}_{\nu_{n_i}}^{(i)}\right\} = \mathcal{L}_i$.

Suppose that the vectors $(\mathbf{z}_{\mu_j^{(i)}} - \mathbf{z}_{\mu_{n_i}^{(i)}})$, $i = 1, \ldots, \ell$, $j = 1, \ldots, n_i$, are linearly dependent. This implies that there exist $c_{\mu_j^{(i)}} \in \mathbb{R}$, $i = 1, \ldots, \ell$, $j = 1, \ldots, n_i$, such that

$$\sum_{i=1}^{\ell} \sum_{j=1}^{n_i} c_{\mu_j^{(i)}} (\mathbf{z}_{\mu_j^{(i)}} - \mathbf{z}_{\mu_{n_i}^{(i)}})^T \ln(\mathbf{x}^*) = 0. \tag{3.60}$$

Combining this result with (3.59) gives us the condition

$$\prod_{i=1}^{\ell} \prod_{j=1}^{n_i} \left(\frac{K_{\mu_j^{(i)}}}{K_{\mu_{n_i}^{(i)}}} \right)^{c_{\mu_j^{(i)}}} = 1. \tag{3.61}$$

Since the $K_{\mu_j^{(i)}}$ depend on the rate constants, and can be chosen arbitrarily in accordance with Lemma 3.4.3, we can see that this constitutes a condition on the rate constants.

Since (3.59) is linear, we know that the number of linearly independent sets $c_{\mu_j^{(i)}} \in \mathbb{R}$, $i = 1, \ldots, \ell$, $j = 1, \ldots, n_i$, for which (3.60) holds corresponds to the dimension of the nullspace of the matrix with rows $(\mathbf{z}_{\mu_j^{(i)}} - \mathbf{z}_{\mu_{n_i}^{(i)}})$. This corresponds to the overall dimension minus the dimension of the row span, which is

$$(n - \ell) - \dim(S) = n - \ell - s = \delta.$$

It follows from basic linear algebra that there are δ linearly independent sets $c_{\mu_j^{(i)}} \in \mathbb{R}$, $i = 1, \ldots, \ell$, $j = 1, \ldots, n_i$, for which a condition of the form (3.61) must be satisfied in order for the system to be complex balanced. □

We can see immediately that Theorem 3.4.2 is in fact just an application of Theorem 3.4.3 taking $\delta = 0$ since this corresponds to no conditions on the rate constants. Due to the historical and applied importance of the *Deficiency Zero Theorem*, however, the result is

typically stated separately.

We already saw in an example in Section 3.1 that, while complex balanced systems are necessarily weakly reversible, not all weakly reversible systems are complex balanced. We are now prepared to revisit this example.

Example 3.4.4. *Reconsider Example 3.1.3 given by*

$$\begin{array}{ccc} 2\mathcal{A}_1 & \xrightarrow{\alpha} & 2\mathcal{A}_2 \\ & {\scriptstyle\gamma}\,\nwarrow \quad \swarrow\,{\scriptstyle\beta} & \\ & \mathcal{A}_1 + \mathcal{A}_2. & \end{array}$$

We make the associations $\mathcal{C}_1 = 2\mathcal{A}_1$, $\mathcal{C}_2 = 2\mathcal{A}_2$, *and* $\mathcal{C}_3 = \mathcal{A}_1 + \mathcal{A}_2$.

When we previously considered this example, we assigned the numerical values $\alpha = 3/8$, $\beta = 1$ *and* $\gamma = 1$ *to the rate constants and showed explicitly that the system was never complex balanced. We now have some understanding of how this situation can arise: if a weakly reversible system has a non-zero deficiency, then the system will only be complex balanced under specific conditions on the rate constants. We are now prepared to carry out the full analysis.*

Our first step is to check the deficiency of the system. We can see that the number of complexes is three ($n = 3$) *and there is only one linkage class* ($\ell = 1$). *The stoichiometric space is given by the span of the reaction vectors as follows*

$$S = span\left\{\begin{bmatrix} -2 \\ 2 \end{bmatrix}, \begin{bmatrix} 1 \\ -1 \end{bmatrix}, \begin{bmatrix} 1 \\ -1 \end{bmatrix}\right\} = span\left\{\begin{bmatrix} 1 \\ -1 \end{bmatrix}\right\}.$$

We can see that $s = dim(S) = 1$ *so that* $\delta = n - \ell - s = 1$. *It follows by Theorem 3.4.3 that a*

single condition on the rate constants α, β and γ suffices to guarantee complex balancing of equilibrium concentrations.

We now seek to find this condition. For illustrative purposes, we will carry the argument out from basic principles which carefully follows the methodology of the proof of Theorem 3.4.2.

Since the system is cyclic, the complex balancing condition on $(x_1^*, x_2^*) \in \mathbb{R}^2_{>0}$ is equivalent to

$$\alpha(x_1^*)^2 = \beta(x_2^*)^2 = \gamma x_1^* x_2^*.$$

By appropriate rearranging and taking the natural logarithm, we see that this is equivalent to the system

$$\begin{aligned} \ln(x_1^*) - \ln(x_2^*) &= \ln\left(\frac{\gamma}{\alpha}\right) \\ -\ln(x_1^*) + \ln(x_2^*) &= \ln\left(\frac{\gamma}{\beta}\right). \end{aligned}$$

This is a linearly dependent system. Summing the equations, we arrive at the condition

$$\ln\left(\frac{\gamma^2}{\alpha\beta}\right) = 0 \quad \Longrightarrow \quad \gamma^2 = \alpha\beta.$$

We can now see why our attempt failed to be complex balanced. For the values $\alpha = 3/8$, $\beta = 1$ and $\gamma = 1$, the condition $\gamma^2 = \alpha\beta$ is violated, and consequently by Theorem 3.4.3 the system is not complex balanced.

We can also arrive at this condition through consideration of the quantities K_1, K_2, K_3

defined according to (3.44). We have

$$K_1 = \beta\gamma, \quad K_2 = \alpha\gamma, \quad \textit{and} \quad K_3 = \alpha\beta.$$

The required condition from (3.61) is

$$\prod_{i=1}^{\ell}\prod_{j=1}^{n_i}\left(\frac{K_{\mu_j^{(i)}}}{K_{\mu_{n_i}^{(i)}}}\right)^{c_{\mu_j^{(i)}}} = 1.$$

For this example, we have $\ell = 1$, $n_i = n = 3$, *and* $c_1 = c_2 = 1$ *since*

$$c_1(\mathbf{z}_1 - \mathbf{z}_3) + c_2(\mathbf{z}_2 - \mathbf{z}_3) = (1)\begin{bmatrix} 1 \\ -1 \end{bmatrix} + (1)\begin{bmatrix} -1 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

It follows that the condition on the rate constants necessary and sufficient for complex balancing is

$$\left(\frac{K_1}{K_3}\right)\left(\frac{K_2}{K_3}\right) = \left(\frac{\beta\gamma}{\alpha\beta}\right)\left(\frac{\alpha\gamma}{\alpha\beta}\right) = 1 \quad \Longrightarrow \quad \gamma^2 = \alpha\beta$$

as we expected.

The natural next question is to ask how the dynamics changes when we let the rate constants slip away from the curve $\gamma^2 = \alpha\beta$. *We know that for systems satisfying this relationship, we have an equilibrium set given by (3.37), that this set has a unique intersection with each positive compatibility class, and that this intersection point is locally asymptotically stable relative to the compatibility class. We do not know, however, how many of these desirable properties—if any—are affected by perturbations in the rate constants.*

We reconsider the dynamics of the system, given by

$$\begin{aligned} \frac{dx_1}{dt} &= -2\alpha x_1^2 + \beta x_2^2 + \gamma x_1 x_2 \\ \frac{dx_2}{dt} &= 2\alpha x_1^2 - \beta x_2^2 - \gamma x_1 x_2. \end{aligned} \tag{3.62}$$

The simultaneous equilibrium condition on $\dot{x}_1$ and $\dot{x}_2$ allows us to easily determine that the equilibrium set is given by

$$x_2 = \left(\frac{-\gamma \pm \sqrt{\gamma^2 + 8\alpha\beta}}{2\beta} \right) x_1.$$

We can see that these correspond to two lines emanating from the origin, one with a positive slope, and one with a negative slope. Only the one with positive slope intersects the positive orthant, so we may ignore the one with negative slope.

Since the stoichiometric space S is one-dimensional and has a negative slope, it follows that each positive compatibility class intersects the equilibrium set exactly once. Furthermore, since $S^\perp$ is given by

$$S^\perp = \left\{ \begin{bmatrix} 1 \\ 1 \end{bmatrix} \right\}$$

we can check that

$$\ln(x_1, x_2) - \ln(x_1^*, x_2^*) \in S^\perp$$

by checking whether, for an arbitrary equilibrium concentration (x_1^*, x_2^*), we can set $\ln(x_1, x_2) - \ln(x_1^*, x_2^*) = k(1,1)$ for some $k \in \mathbb{R}$. If we take the equilibrium concentration

$$x_2^* = \frac{-\gamma + \sqrt{\gamma^2 + 8\alpha\beta}}{2\beta} x_1^*$$

we arrive at the conditions

$$x_1 = e^k x_1^* \quad \textit{and} \quad x_2 = e^k \left(\frac{-\gamma + \sqrt{\gamma^2 + 8\alpha\beta}}{2\beta} \right) x_1^*$$
$$\Longrightarrow \quad x_2 = \left(\frac{-\gamma + \sqrt{\gamma^2 + 8\alpha\beta}}{2\beta} \right) x_1.$$

This is exactly the equilibrium condition we just derived, so that the equilibrium set satisfies

$$E = \left\{ \mathbf{x} \in \mathbb{R}^m_{>0} \mid \ln(\mathbf{x}) - \ln(\mathbf{x}^*) \in S^\perp \right\}.$$

It is also easy to verify by factoring (3.62) that, for arbitrary α, β and γ, solutions above the equilibrium curve converge down toward it, while solutions below rise to it, so that the positive equilibrium concentration in each compatibility class is asymptotically stable. In other words, for this example, all of the dynamical properties guaranteed of complex balanced systems hold for this system even when complex balancing is violated! Whether this is a general property will be addressed with a further example.

Example 3.4.5. *Consider the system*

$$\begin{array}{ccc} 2\mathcal{A}_1 + \mathcal{A}_2 & \overset{k(1,2)}{\longrightarrow} & 3\mathcal{A}_1 \\ {\scriptstyle k(4,1)}\uparrow & & \downarrow{\scriptstyle k(2,3)} \\ 3\mathcal{A}_2 & \underset{k(3,4)}{\longleftarrow} & \mathcal{A}_1 + 2\mathcal{A}_2 \end{array}$$

where we make the associations $\mathcal{C}_1 = 2\mathcal{A}_1 + \mathcal{A}_2$, $\mathcal{C}_2 = 3\mathcal{A}_1$, $\mathcal{C}_3 = 3\mathcal{A}_2$, and $\mathcal{C}_4 = \mathcal{A}_1 + 2\mathcal{A}_2$. In [33], F. Horn and R. Jackson considered this sytem with the conditions $k(1,2) = k(3,4) = 1$ and $k(2,3) = k(4,1) = \epsilon$ for $\epsilon > 0$. We will do a more general analysis here before reverting to

these simplifying assumptions.

We can see that the system is weakly reversible, that there are four complexes ($n = 4$) and that there is only one linkage class ($\ell = 1$). The stoichiometric space S is given by

$$S = span\left\{\begin{bmatrix} 1 \\ -1 \end{bmatrix}, \begin{bmatrix} -2 \\ 2 \end{bmatrix}, \begin{bmatrix} -1 \\ 1 \end{bmatrix}, \begin{bmatrix} 2 \\ -2 \end{bmatrix}\right\} = span\left\{\begin{bmatrix} 1 \\ -1 \end{bmatrix}\right\}$$

so that $s = dim(S) = 1$. It follows that $\delta = n - \ell - s = 2$.

From Theorem 3.4.3, it follows that there are two conditions on the rate constants which must be satisfied in order for the system to be complex balanced. We have

$$\mathbf{z}_1 - \mathbf{z}_4 = \begin{bmatrix} 2 \\ -2 \end{bmatrix}, \quad \mathbf{z}_2 - \mathbf{z}_4 = \begin{bmatrix} 3 \\ -3 \end{bmatrix}, \quad \mathbf{z}_3 - \mathbf{z}_4 = \begin{bmatrix} 1 \\ -1 \end{bmatrix}$$

and

$$K_1 = k(2,3)k(3,4)k(4,1)$$

$$K_2 = k(1,2)k(3,4)k(4,1)$$

$$K_3 = k(1,2)k(2,3)k(4,1)$$

$$K_4 = k(1,2)k(2,3)k(3,4).$$

It follows that the linearly independent sets $c_1 = 1$, $c_2 = 0$, $c_3 = -2$, and $c_1 = 0$, $c_2 = 1$, $c_3 = -3$ satisfy (3.60) so that the conditions are

$$\left(\frac{K_1}{K_4}\right)\left(\frac{K_3}{K_4}\right)^{-2} = 1 \quad and \quad \left(\frac{K_2}{K_4}\right)\left(\frac{K_3}{K_4}\right)^{-3} = 1.$$

These can be easily simplified to

$$k(3,4)^2 = k(1,2)k(4,1) \quad \textit{and} \quad k(3,4)^3 = k(2,3)k(4,1)^2.$$

We know what happens when these conditions are satisfied since this is when the system is complex balanced, but we do not know what happens away from this set. To make this task easier, we use the conditions $k(1,2) = k(3,4) = 1$ *and* $k(2,3) = k(4,1) = \epsilon$ *for* $\epsilon > 0$*. With these restrictions, the two complex balancing conditions simplify to* $\epsilon = 1$*. For all other values, the system is not complex balanced.*

The system is governed by the differential equations

$$\begin{aligned} \frac{dx_1}{dt} &= x_1^2 x_2 - 2\epsilon x_1^3 - x_1 x_2^2 + 2\epsilon x_2^3 \\ \frac{dx_2}{dt} &= -x_1^2 x_2 + 2\epsilon x_1^3 + x_1 x_2^2 - 2\epsilon x_2^3 \end{aligned} \tag{3.63}$$

Following the analysis in [33], the equilibrium condition is $x_1^2 x_2 - 2\epsilon x_1^3 - x_1 x_2^2 + 2\epsilon x_2^3 = (x_2 - x_1)(2\epsilon x_1^2 + (2\epsilon - 1)x_1 x_2 + 2\epsilon x_2^2) = 0$*. The first bracket produces the equilibrium set* $x_2 = x_1$*, which is valid for all values of* ϵ*. The second bracket produces no real-valued equilibria over the range* $\epsilon > 1/6$*, the single degenerate curve* $x_2 = x_1$ *for* $\epsilon = 1/6$*, and two lines of equilibria over the range* $0 < \epsilon < 1/6$ *given by the relation*

$$x_2 = \left(\frac{(1 - 2\epsilon) \pm \sqrt{-12\epsilon^2 - 4\epsilon + 1}}{4\epsilon} \right) x_1.$$

We will not perform the full analysis of the dynamics here, but the results are worth summarizing. We can clearly see that, regardless of the choice of $\epsilon > 0$*, the positive compatibility classes intersect any curve of equilibria exactly once. Further analysis shows that,*

while the system is only complex balanced for $\epsilon = 1$*, it exhibits all the locally stable properties expected of complex balanced systems in the range* $\epsilon > 1/6$*. In the range* $0 < \epsilon < 1/6$*, each compatibility class has* three *equilibrium concentrations, two of which are stable, and one of which is unstable. Of particular interest is the fact that the equilibrium concentration along the curve* $x_2 = x_1$ *bifurcates from asymptotically stable to unstable as we decreased* ϵ *across* $\epsilon = 1/6$ *(see Figure 3.3). It is clear that weakly reversible systems which are not complex balanced can exhibit a wide variety of behaviour!*

The limiting case $\epsilon \to 0$ *will also be of interest in Section 5 where global stability is discussed. In this limit, trajectories begin to approach the boundary of* $\mathbb{R}^2_{>0}$ *rather than any positive equilibrium concentration. It is worth noting, also, that the system loses the property of weak reversibility in this limit as well.*

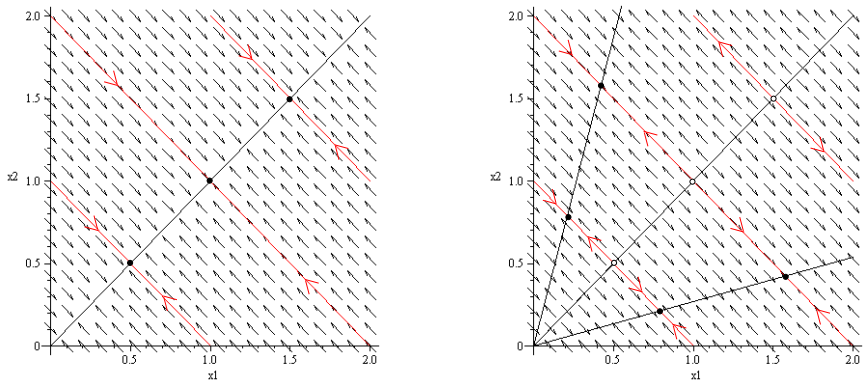

Figure 3.3: Phase portrait of the system (3.63) with $\epsilon = 1/2$ (left) and $\epsilon = 1/10$ (right). The line of equilibria $x_2 = x_1$ bifurcates as ϵ decreases through $\epsilon = 1/6$ from asymptotically stable to unstable as two new lines of equilibria emerge.

Chapter 4

Linearization of Complex Balanced Systems

In this chapter, I apply the theory of linearization of nonlinear differential equations about equilibrium values to complex balanced systems introduced in Section 3.3. In addition to demonstrating the local asymptotic stability of complex balanced equilibria (Theorem 3.3.1), the results presented here are sufficient to demonstrate the local exponential convergence of solutions towards equilibrium concentrations of complex balanced systems (Theorem 4.3.6). I also complete the analysis presented in Section 2 of [9] to explicitly show the bounds of the exponential decay guaranteed by the first-order approximation of the pseudo-Helmholtz function (Lemma 4.3.5). This analysis is conducted similarly in [56]. I then compare the estimates guaranteed by our approach (Theorem 4.3.6) and that of A. Bamberger and E. Billette (Lemma 4.3.5) through an example.

This will be the only chapter of this thesis which will require the use of complex numbers. I will let $\mathbb{R}^{m\times n}$ and $\mathbb{C}^{m\times n}$ denote the set of m-times-n matrices over the real and

complex field of numbers, respectively. For $z \in \mathbb{C}$, I will let $\bar{z} \in \mathbb{C}$ denote the complex conjugate and, for $\mathbf{z} \in \mathbb{C}^n$, I will let $\bar{\mathbf{z}} \in \mathbb{C}^n$ denote the vector of complex conjugates. The magnitude of a complex number $z \in \mathbb{C}$ will be denote $|z| = \sqrt{\mathrm{Re}(z)^2 + \mathrm{Im}(z)^2}$. For $A \in \mathbb{C}^{m \times n}$, I will let $A^\dagger \in \mathbb{C}^{n \times m}$ denote the conjugate transpose of A, i.e. the matrix with entries $a^\dagger_{ij} = \bar{a}_{ji}$.

4.1 Theory of Linearization

When considering properties of a general system of autonomous differential equations of the form $\dfrac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x})$, one of the most crucial characteristics of the system is whether $\mathbf{f}(\mathbf{x})$ is *linear* or *nonlinear* in the argument $\mathbf{x} = [x_1\ x_2\ \ldots\ x_n] \in \mathbb{R}^n$.

In the simplest terms, linear systems are *easy* to analyze while nonlinear systems are *hard* to analyze. With a little understanding of integral calculus and linear algebra, linear systems are guaranteed to have a well-behaved solution which can be solved for analytically in terms of matrix exponentials—perhaps the easiest of possible solution forms—while even some of the simplest nonlinear systems to formulate are known to have no explicit solution, or to exhibit wildly complex or unpredictable behaviour. This has led to a wide range of analysis techniques for nonlinear systems, including numerical methods, asymptotic analysis, and perturbation theory, among others.

One of the most wide-spread approaches to analyzing nonlinear systems is to consider the linear systems resulting from truncating the Taylor expansion of the nonlinear system expanded about its equilibrium points. If we consider an equilibrium point $\mathbf{x}^*$ of the nonlinear system, given a suitable level of differentiability we have by Taylor's Theorem

that

$$\mathbf{f}(\mathbf{x}) = D\mathbf{f}(\mathbf{x}^*)(\mathbf{x} - \mathbf{x}^*) + O(\|\mathbf{x} - \mathbf{x}^*\|^2).$$

So long as $D\mathbf{f}(\mathbf{x}^*)$ is non-degenerate (i.e. has no zero eigenvalues), we expect that first order term to dominate the dynamics near $\mathbf{x}^*$. That is to say, near $\mathbf{x}^*$ we expect the nonlinear system to "behave like" a linear system. Many global properties about the nonlinear system can be pieced together by combining these linear pictures.

This approach will be formalized in the rest of this section, although only the results relevant to the linearization of complex balanced systems will be stated. I present the results here without proof.

Consider a general nonlinear system

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) \tag{4.1}$$

where $\mathbf{f} : \mathbb{R}^n \mapsto \mathbb{R}^n$ is at least C^2. The linear system corresponding to the linearization of (4.1) about an equilibrium concentration $\mathbf{x}^*$, $\mathbf{f}(\mathbf{x}^*) = 0$, is given by

$$\frac{d\mathbf{y}}{dt} = A\mathbf{y} \tag{4.2}$$

where $A = D\mathbf{f}(\mathbf{x}^*)$ and $\mathbf{y} = \mathbf{x} - \mathbf{x}^*$. We will let E^s, E^u, and E^c denote the stable, unstable, and centre subspaces of (4.2), respectively.

In making the connection from the linear dynamics of (4.2) to the nonlinear dynamics of (4.1), I use the following result, which has been adapted from The Center Manifold Theorem on pg. 116 of [46] and Theorem 1.1.3 on page 21 of [65]. I also reference the Stable Manifold Theorem on pg. 107 of [46].

Theorem 4.1.1. *Let* $\mathbf{f}(\mathbf{x}) \in C^r$, $r \geq 2$, *and* $\mathbf{x}^*$ *be an equilibrium of (4.1). Suppose* $D\mathbf{f}(\mathbf{x}^*)$ *has* k *eigenvalues with negative real part,* j *eigenvalues with positive real part, and* $m = n - k - j$ *eigenvalues with zero real part. Then there exists*

1. *an* m*-dimensional centre manifold* W^c_{loc} *of class* C^r *tangent at* $\mathbf{x}^*$ *to the centre subspace* E^c *of (4.2) at* $\mathbf{0}$*;*

2. *a* k*-dimensional stable manifold* W^s_{loc} *of class* C^r *tangent at* $\mathbf{x}^*$ *to the stable subspace* E^s *of (4.2) at* $\mathbf{0}$*; and*

3. *a* j*-dimensional unstable manifold* W^u_{loc} *of class* C^r *tangent at* $\mathbf{x}^*$ *to the unstable subspace* E^u *of (4.2) at* $\mathbf{0}$*.*

W^c_{loc}, W^s_{loc}, *and* W^u_{loc} *are invariant under the flow* ϕ_t *of (4.1) and* W^s_{loc} *and* W^u_{loc} *have the asymptotic properties of* E^s *and* E^u*, respectively. That is to say, solutions to (4.1) with initial conditions in* W^s_{loc} *(respectively,* W^u_{loc}*) sufficient close to* $\mathbf{x}^*$ *approach* $\mathbf{x}^*$ *at an exponential rate asymptotically as* $t \to +\infty$ *(respectively,* $t \to -\infty$*).*

4.2 Linear Algebra

In this section, we outline some basic linear algebra results which will be required in the rest of this chapter. In Section 4.2.1, we give several results regarding the definiteness of a matrix. In Section 4.2.2, we develop some important properties of the range and nullspace of a matrix, in particular how they relate to the eigenspaces corresponding to various eigenvalues. In Section 4.2.3, we introduce a particular kind of matrix, called a Laplacian matrix, which is a cornerstone for the analysis conducted in following sections.

4.2.1 Definite Matrices

In this section, I present several results regarding the definiteness of square matrices $A \in \mathbb{C}^{n\times n}$. Since all of the matrices considered in this chapter are real-valued matrices, I will quickly introduce the general theory of definiteness before simplifying to the real-valued case.

Central to the study of definiteness is the concept of a *Hermitian matrix* (for further details, see [34] and [35]).

Definition 4.2.1. *A square complex-valued matrix $A \in \mathbb{C}^{n\times n}$ is called **Hermitian** if and only if $A = A^\dagger$.*

Hermitian matrices have the nice property that the quadratic form $\mathbf{v}^\dagger A\mathbf{v}$ yields a real number for all $\mathbf{v} \in \mathbb{C}^n$ (see [34]). This allows us to define the following concepts for such matrices.

Definition 4.2.2. *A Hermitian matrix $A \in \mathbb{C}^{n\times n}$ is called **negative semidefinite** if*

$$\mathbf{v}^\dagger A\mathbf{v} \leq 0, \quad \forall\ \mathbf{v}\ \in \mathbb{C}^n. \tag{4.3}$$

*Furthermore, the matrix $A \in \mathbb{C}^{n\times n}$ is called **negative definite** if*

$$\mathbf{v}^\dagger A\mathbf{v} < 0, \quad \forall\ \mathbf{v}\ \in \mathbb{C}^n, \mathbf{v} \neq \mathbf{0}. \tag{4.4}$$

The concepts of negative semidefinite and definite matrices can be easily extended to positive semidefinite and definite matrices by switching the sign of the respective inequality.

As all the matrices considered in this chapter are real-valued, we consider *symmetric* rather than Hermitian matrices ($A \in \mathbb{R}^{n\times n}$ such that $A = A^T$). While the standard definition of definiteness is restricted to Hermitian matrices, many properties of a general real-valued matrix $A \in \mathbb{R}^{n\times n}$ can be derived by considering the *symmetric part* of A given by $\tilde{A} = \frac{1}{2}(A + A^T) \in \mathbb{R}^{n\times n}$.

When restricting attention to real-valued matrices $A \in \mathbb{R}^{n\times n}$, it is not necessary to consider the quadratic form $\mathbf{v}^\dagger A\mathbf{v}$ over $\mathbf{v} \in \mathbb{C}^n$ as is normally required. We give the following result for negative semidefinite matrices only; however, it can be easily extended to the other definiteness cases.

Lemma 4.2.1. *The symmetric part of a real-valued matrix $A \in \mathbb{R}^{n\times n}$ is negative semidefinite (i.e. satisfies (4.3)) if and only if*

$$\mathbf{x}^T A\mathbf{x} \leq 0, \quad \forall\ \mathbf{x} \in \mathbb{R}^n. \tag{4.5}$$

Moreover, equality with zero for $\mathbf{v} \in \mathbb{C}^n$ in (4.3) is satisfied if and only if equality with zero is satisfied in (4.5) for both $\mathbf{x} = Re(\mathbf{v})$ and $\mathbf{x} = Im(\mathbf{v})$.

Proof. We let $\mathbf{v}_1 = \mathrm{Re}(\mathbf{v})$ and $\mathbf{v}_2 = \mathrm{Im}(\mathbf{v})$ so that $\mathbf{v} = \mathbf{v}_1 + i\mathbf{v}_2$. The quadratic form for the symmetric part of A can be written

$$\begin{aligned}
\frac{1}{2}\mathbf{v}^\dagger(A + A^T)\mathbf{v} &= \frac{1}{2}(\mathbf{v}_1 - i\mathbf{v}_2)^T(A + A^T)(\mathbf{v}_1 + i\mathbf{v}_2) \\
&= \frac{1}{2}\left[\mathbf{v}_1^T(A + A^T)\mathbf{v}_1 + \mathbf{v}_2^T(A + A^T)\mathbf{v}_2\right] \\
&\quad + \frac{i}{2}\left[\mathbf{v}_1^T(A + A^T)\mathbf{v}_2 - \mathbf{v}_2^T(A + A^T)\mathbf{v}_1\right] \\
&= \mathbf{v}_1^T A\mathbf{v}_1 + \mathbf{v}_2^T A\mathbf{v}_2
\end{aligned}$$

where we have used the fact that, for real-valued matrices $A \in \mathbb{R}^{n\times n}$ and vectors $\mathbf{x}, \mathbf{y} \in \mathbb{R}^n$, $\mathbf{x}^T A\mathbf{y} = \mathbf{y}^T A^T \mathbf{x}$.

It is clear from this, since $\mathbf{v}_1, \mathbf{v}_2 \in \mathbb{R}^n$, that $\mathbf{x}^T A\mathbf{x} \leq 0$ for $\mathbf{x} \in \mathbb{R}^n$ implies $\mathbf{v}^\dagger(A + A^T)\mathbf{v} \leq 0$ for $\mathbf{v} \in \mathbb{C}^n$. Moreover, $\mathbf{v}_1^T A\mathbf{v}_1 = 0$ and $\mathbf{v}_2^T A\mathbf{v}_2 = 0$ is sufficient for $\mathbf{v}^\dagger(A + A^T)\mathbf{v} = 0$. We have proved the "if" statements.

We prove the "only if" conditions by contradiction. Suppose (4.5) is not satisfied, i.e. there exists a $\tilde{\mathbf{x}} \in \mathbb{R}^n$ such that $\tilde{\mathbf{x}}^T A\tilde{\mathbf{x}} > 0$. Setting $\mathbf{v}_1 = \tilde{\mathbf{x}}$ and $\mathbf{v}_2 = \mathbf{0}$ we have $\mathbf{v}^\dagger(A+A^T)\mathbf{v} > 0$ which contradicts (4.3). This completes the equivalence of (4.3) and (4.5). Now suppose equality with zero is attained for $\mathbf{v} \in \mathbb{C}^n$ in (4.3) but is not attained for the real or imaginary parts of $\mathbf{v}$ in (4.5). By the above expansion of the quadratic form, this can only happen if $\mathbf{v}_1^T A\mathbf{v}_1 + \mathbf{v}_2^T A\mathbf{v}_2 = 0$ which by (4.5) can only happen if $\mathbf{v}_1^T A\mathbf{v}_1 = \mathbf{v}_2^T A\mathbf{v}_2 = 0$, and we are done. □

This result allows us to consider the simpler quadratic form $\mathbf{x}^T A\mathbf{x}$, $\mathbf{x} \in \mathbb{R}^n$. It should be noted that, for real-valued matrices A and $\mathbf{x} \in \mathbb{R}^n$, the quadratic forms for A and that of the symmetric part $\tilde{A}$ coincide.

The definiteness of a matrix is preserved under several operations. The following properties can be easily extended to each of the notions of definiteness presented in this section; however, for our purposes it will be sufficient to consider only negative semidefinite matrices.

Theorem 4.2.1. *Let $A, A_1, A_2 \in \mathbb{R}^{n\times n}$ be symmetric and negative semidefinite, $P \in \mathbb{R}^{n\times m}$, and $\alpha > 0$. Then the following properties hold:*

1. ***Scalar multiplication**: αA is negative semidefinite.*

2. ***Subadditivity***: *$A_1 + A_2$ is negative semidefinite.*

3. ***Congruence***: *$P^T AP$ is negative semidefinite.*

Proof. By Lemma 4.2.1, it is sufficient to consider the quadratic form over $\mathbf{x} \in \mathbb{R}^n$. We can jointly prove properties 1 and 2 by considering $A_1, A_2 \in \mathbb{R}^{n\times n}$ to be negative semidefinite matrices and taking $\alpha_1, \alpha_2 > 0$. It follows that, for any $\mathbf{x} \in \mathbb{R}^n$,

$$\mathbf{x}^T(\alpha_1 A_1 + \alpha_2 A_2)\mathbf{x} = \alpha_1 \mathbf{x}^T A_1 \mathbf{x} + \alpha_2 \mathbf{x}^T A_2 \mathbf{x} \leq 0.$$

Property 3 follows from the observation that, for a negative semidefinite matrix $A \in \mathbb{R}^{n\times n}$ and any $P \in \mathbb{R}^{n\times m}$ and $\mathbf{x} \in \mathbb{R}^n$,

$$\mathbf{x}^T(P^T AP)\mathbf{x} = (P\mathbf{x})^T A(P\mathbf{x}) = \mathbf{y}^T A\mathbf{y} \leq 0$$

where $\mathbf{y} = P\mathbf{x}$. This completes the proof. □

4.2.2 Eigenspace Decomposition of $\mathbb{R}^n$

In this section, we investigate the properties of the eigenvectors associated with various eigenvalues, since they determine the behaviour of the stable, unstable, and centre manifolds locally in the linearization of a nonlinear system of differential equations about an equilibrium. Since we are only interested in solutions to (2.4) lying in $\mathbb{R}^n$, we restrict our consideration to real-valued eigenspaces.

We need to divide eigenvectors and generalized eigenvectors according to their eigenvalues: $\lambda = 0$, λ real and nonzero, and λ complex.

Definition 4.2.3. *Let $A \in \mathbb{R}^{n\times n}$ and define*

$$\begin{aligned}\Lambda_0 &= \{\lambda \mid det(A-\lambda I) = 0, \lambda \in \mathbb{R}, \lambda = 0\}\\ \Lambda_r &= \{\lambda \mid det(A-\lambda I) = 0, \lambda \in \mathbb{R}, \lambda \neq 0\}\\ \Lambda_c &= \{\lambda \mid det(A-\lambda I) = 0, \lambda \notin \mathbb{R}, \lambda \in \mathbb{C}\}.\end{aligned}$$

We define the ***generalized zero eigenspace*** N_0, ***generalized real eigenspace*** N_r, *and* ***generalized complex eigenspace*** N_c *to be*

$$N_0 = span\{\mathbf{v} \in \mathbb{R}^n \mid (A-\lambda I)^\nu \mathbf{v} = \mathbf{0}, \lambda \in \Lambda_0\} \tag{4.6}$$

$$N_r = span\{\mathbf{v} \in \mathbb{R}^n \mid (A-\lambda I)^\nu \mathbf{v} = \mathbf{0}, \lambda \in \Lambda_r\} \tag{4.7}$$

$$N_c = span\{\mathrm{Re}(\mathbf{v}), \mathrm{Im}(\mathbf{v}) \in \mathbb{R}^n \mid (A-\lambda I)^\nu \mathbf{v} = \mathbf{0}, \lambda \in \Lambda_c\} \tag{4.8}$$

where ν is the algebraic multiplicity of a given eigenvalue λ.

The following is a consequence of the real Jordan Canonical Form Theorem and can be found in [46].

Theorem 4.2.2. *For any real-valued matrix $A \in \mathbb{R}^{n\times n}$,*

$$\mathbb{R}^n = N_0 \oplus N_r \oplus N_c$$

where N_0, N_r and N_c are mutually linearly independent sets.

The following is a key result used in the next section.

Lemma 4.2.2. *Let $A \in \mathbb{R}^{n\times n}$. If the zero eigenvalue is nondeficient, then the generalized eigenspaces of A given by (4.6)-(4.8) satisfy the following:*

1. *null*$(A) = N_0$,

2. *range*$(A) = N_r \oplus N_c$.

Proof. Any eigenvector $\mathbf{v}_0$ corresponding to $\lambda_0 \in \Lambda_0$ satisfies

$$A\mathbf{v}_0 = \lambda_0 \mathbf{v}_0 = \mathbf{0}. \tag{4.9}$$

This implies $\mathbf{v}_0 \in \text{null}(A)$. Conversely, any vector $\mathbf{v}_0$ satisfying (4.9) is an eigenvector of A with a corresponding eigenvalue equal to zero, which implies $\mathbf{v}_0$ corresponds to a zero eigenvalue if and only if it is in null(A). Since the zero eigenvalue is nondeficient, there are no generalized eigenvectors to consider and the first property is proved.

Any regular eigenvector $\mathbf{v}_r$ corresponding to $\lambda_r \in \Lambda_r$ satisfies

$$A\mathbf{v}_r = \lambda_r \mathbf{v}_r.$$

This implies that

$$\mathbf{v}_r = \frac{1}{\lambda_r}\left(A\mathbf{v}_r\right) \in \text{range}(A). \tag{4.10}$$

Now consider an eigenvector $\mathbf{v}_c$ corresponding to $\lambda_c \in \Lambda_c$. There will also be a corresponding eigenvalue $\bar{\lambda}_c \in \Lambda_c$ with complex conjugate eigenvector $\bar{\mathbf{v}}_c$. We want to show that $\text{Re}(\mathbf{v}_c) \in \text{range}(A)$ and $\text{Im}(\mathbf{v}_c) \in \text{range}(A)$.

Consider the vectors

$$\mathbf{w}_1 = \frac{1}{|\lambda_c|^2}\text{Re}(\bar{\lambda}_c \mathbf{v}_c) \quad \text{and} \quad \mathbf{w}_2 = \quad \frac{1}{|\lambda_c|^2}\text{Im}(\bar{\lambda}_c \mathbf{v}_c).$$

We can see that $\mathbf{w}_1, \mathbf{w}_2 \in \mathbb{R}^n$. Furthermore, we have

$$\begin{aligned} A\mathbf{w}_1 &= \frac{1}{2|\lambda_c|^2}(\bar{\lambda}_c A\mathbf{v}_c + \lambda_c A\bar{\mathbf{v}}_c) \\ &= \frac{1}{2|\lambda_c|^2}(\bar{\lambda}_c\lambda_c\mathbf{v}_c + \lambda_c\bar{\lambda}_c\bar{\mathbf{v}}_c) \\ &= \frac{1}{2}(\mathbf{v}_c + \bar{\mathbf{v}}_c) = \mathrm{Re}(\mathbf{v}_c) \end{aligned}$$

$$\begin{aligned} A\mathbf{w}_2 &= \frac{1}{2i|\lambda_c|^2}(\bar{\lambda}_c A\mathbf{v}_c - \lambda_c A\bar{\mathbf{v}}_c) \\ &= \frac{1}{2i|\lambda_c|^2}(\bar{\lambda}_c\lambda_c\mathbf{v}_c - \lambda_c\bar{\lambda}_c\bar{\mathbf{v}}_c) \\ &= \frac{1}{2i}(\mathbf{v}_c - \bar{\mathbf{v}}_c) = \mathrm{Im}(\mathbf{v}_c). \end{aligned}$$

This implies that $\mathrm{Re}(\mathbf{v}_c) \in \mathrm{range}(A)$ and $\mathrm{Im}(\mathbf{v}_c) \in \mathrm{range}(A)$. For nondeficient λ_r and λ_c, we are done.

Now consider deficient λ_r and λ_c. We can suppose, without loss of generality, that $\mathbf{v}_1$ is a regular eigenvector from which a chain of generalized eigenvectors can be constructed. The first such generalized eigenvector, $\mathbf{v}_2$, must satisfy

$$(A - \lambda I)\mathbf{v}_2 = \mathbf{v}_1$$

where $\lambda \in \Lambda_r$ or $\lambda \in \Lambda_c$ depending on the case being considered. This implies

$$\mathbf{v}_2 = \frac{1}{\lambda}(A\mathbf{v}_2 - \mathbf{v}_1) \tag{4.11}$$

which is defined since $\lambda \neq 0$.

For real eigenvalues λ_r, it readily follows that $\mathbf{v}_2 \in \text{range}(A)$ since $\mathbf{v}_1$ satisfies $\mathbf{v}_1 \in \text{range}(A)$ by (4.10) and $A\mathbf{v}_2 \in \text{range}(A)$ by definition. This can be extended inductively to any generalized real eigenvector in the chain, and we are done.

For complex eigenvalues λ_c, we need to consider the real and imaginary parts of $\mathbf{v}_2$. We can readily see that (4.11) for complex λ_c implies

$$\begin{aligned}
\text{Re}(\mathbf{v}_2) &= \frac{1}{|\lambda_c|^2}\left[\text{Re}(\lambda_c)\left(A\text{Re}(\mathbf{v}_2) - \text{Re}(\mathbf{v}_1)\right)\right. \\
&\quad \left. +\text{Im}(\lambda_c)\left(-A\text{Im}(\mathbf{v}_2) + \text{Im}(\mathbf{v}_1)\right)\right] \\
\text{Im}(\mathbf{v}_2) &= \frac{1}{|\lambda_c|^2}\left[\text{Im}(\lambda_c)\left(A\text{Re}(\mathbf{v}_2) - \text{Re}(\mathbf{v}_1)\right)\right. \\
&\quad \left. +\text{Re}(\lambda_c)\left(A\text{Im}(\mathbf{v}_2) - \text{Im}(\mathbf{v}_1)\right)\right].
\end{aligned}$$

Since $A\text{Re}(\mathbf{v}_2)$, $A\text{Im}(\mathbf{v}_2)$, $\text{Re}(\mathbf{v}_1)$, and $\text{Im}(\mathbf{v}_1)$ are in $\text{range}(A)$, it follows by similar reasoning to the real case that $\text{Re}(\mathbf{v}_2) \in \text{range}(A)$ and $\text{Im}(\mathbf{v}_2) \in \text{range}(A)$. This can be extended inductively to any generalized complex eigenvector in the chain, and we are done.

We know from the Rank-Nullity Theorem that

$$\dim(\text{range}(A)) + \dim(\text{null}(A)) = \dim(A) = n$$

and from Lemma 4.2.2 that $\mathbb{R}^n$ is decomposed into the linearly independent spaces N_0, N_r and N_c. It follows that N_c spans $\text{null}(A)$ and $N_r \oplus N_c$ spans $\text{range}(A)$ which completes the proof. □

We now present a few results demonstrating how the range and nullspace of a matrix are changed under simple transformations.

Lemma 4.2.3. *Consider $A \in \mathbb{R}^{m\times n}$ and $B \in \mathbb{R}^{n\times k}$. Then*

$$range(AB) \subseteq range(A).$$

Furthermore, if $rank(A) = rank(AB)$ then

$$range(AB) = range(A).$$

Proof. We make use of the fact that the range of a matrix is equal to its column span. We will let $[A]_j$ denote the j^{th} column of A. The j^{th} column of AB is given by

$$[AB]_j = b_{j1}[A]_1 + b_{j2}[A]_2 + \cdots + b_{jn}[A]_n \in \text{range}(A).$$

It follows that the span of the columns $[AB]_j$ is contained in range(A) which implies range$(AB) \subseteq$ range(A).

If we also have that rank(A) = rank(AB) then range(AB) and range(A) must span the same space so range(AB) = range(A). □

Lemma 4.2.4. *Let $A \in \mathbb{R}^{n\times n}$ be arbitrary and $B \in \mathbb{R}^{n\times n}$ be an invertible matrix. Then*

1. *$null(AB) = B^{-1}null(A)$, and*
2. *$range(AB)$=$range(A)$.*

Proof. Consider $\mathbf{x} \in$ null(AB). This implies

$$AB\mathbf{x} = \mathbf{0}. \tag{4.12}$$

Since B is invertible, it has only the trivial nullspace, and therefore (4.12) implies that $B\mathbf{x} \in \text{null}(A)$. This is equivalent to $\mathbf{x} \in B^{-1}\ \text{null}(A)$ since B is invertible, which shows $\text{null}(AB) \subseteq B^{-1}\ \text{null}(A)$. It is clear that the reverse implication holds, so that $\text{null}(AB) = B^{-1}\ \text{null}(A)$.

It follows from Lemma 4.2.3 that $\text{range}(AB) \subseteq \text{range}(A)$, and since $\text{rank}(AB) = \text{rank}(A)$ by the invertibility of B, we have $\text{range}(AB) = \text{range}(A)$. This completes the proof. □

4.2.3 Laplacian Matrices

In this section, I define the Laplacian matrix of a reaction graph. The notion of a Laplacian matrix is based on that contained in [12].

I have, however, made several modifications from the standard definitions to make them specific to chemical reaction networks. In particular, I have altered the standard sign convention by assigning the *degree matrix* negative values and the *adjacency matrix* positive values. It is also worth noting that the indexing for the adjacency matrix is inverted from the order of the related reactions in the reaction graph. Consequently, the Laplacian matrix is really the negative transpose of the Laplacian in standard graph theory. For simplicity of terminology, we will simply refer to this matrix as the Laplacian. Several important properties of this Laplacian matrix will be proved.

Definition 4.2.4. *The* ***degree matrix*** *of a chemical reaction network is the matrix* $D \in \mathbb{R}^{n\times n}$ *with entries*

$$D_{ij} = \begin{cases} -\text{outdeg}(\mathcal{C}_i), & i = j \\ 0, & i \neq j \end{cases}$$

where $\text{outdeg}(\mathcal{C}_i)$ *is the number of reactions for which* $\mathcal{C}_i$ *is the reactant complex.*

Definition 4.2.5. *The* ***adjacency matrix*** *of a chemical reaction network is the matrix* $A \in \mathbb{R}^{n\times n}$ *with entries*

$$A_{ij} = \begin{cases} 1, & \text{if } \mathcal{C}_j \longrightarrow \mathcal{C}_i \in \mathcal{R} \\ 0, & \text{otherwise.} \end{cases}$$

Definition 4.2.6. *The* ***Laplacian matrix*** *of a chemical reaction network is the matrix* $L \in \mathbb{R}^{n\times n}$ *given by*

$$L = D + A.$$

The following property of Laplacian matrices corresponding to reaction cycles (see Definition 3.3.1) will be crucially important in Section 4.3.1.

Theorem 4.2.3. *The symmetric part of the Laplacian matrix* $L \in \mathbb{R}^{n\times n}$ *corresponding to a reaction cycle is negative semidefinite. Moreover,* $\mathbf{v}^\dagger \tilde{L}\mathbf{v} = 0$ *if and only if* $\mathbf{v}_1 = Re(\mathbf{v})$ *and* $\mathbf{v}_2 = Im(\mathbf{v})$ *satisfy*

$$v_{1i} = v_{1j} \quad \text{and} \quad v_{2i} = v_{2j} \quad \forall\, i,j \in \{\nu_0, \nu_1, \ldots, \nu_l\}, \tag{4.13}$$

where $\{\nu_0, \nu_1, \ldots, \nu_l\}$ *is the cycle corresponding to the reaction cycle.*

Proof. Consider the cycle $\{\nu_0, \ldots, \nu_l\}$ and let $L \in \mathbb{R}^{n\times n}$ denote the Laplacian matrix corresponding to the reaction cycle. Since Laplacian matrices are real-valued, by Lemma 4.2.1 it is sufficient to consider the properties of the real quadratic form $\mathbf{x}^T L\mathbf{x}$, $\mathbf{x} \in \mathbb{R}^n$. We have

$$\begin{aligned} \mathbf{x}^T L\mathbf{x} &= \sum_{j=1}^{l} \left(x_{\nu_j} x_{\nu_{j-1}} - x_{\nu_j}^2 \right) \\ &= -\frac{1}{2} \sum_{j=1}^{l} \left(x_{\nu_j} - x_{\nu_{j-1}} \right)^2 \leq 0 \end{aligned} \tag{4.14}$$

where $\nu_0 = \nu_l$. Clearly this is negative semidefinite and equality with zero can be satisfied if and only if $x_{\nu_1} = x_{\nu_2} = \cdots = x_{\nu_l}$, i.e. if the elements of $\mathbf{x}$ corresponding to indices of a complexes in the associated cycle are identical.

By Lemma 4.2.1 it follows from (4.14) that $\tilde{L}$ is negative semidefinite and that equality with zero is attained if and only if the real and imaginary parts of $\mathbf{v}$ satisfy (4.13). This completes the proof. □

Laplacian matrices corresponding to reaction cycles also share a connection with permutation matrices (see [34]). Given a permutation matrix $P \in \mathbb{R}^{n\times n}$, the matrix $L = P - I$, where I is the n-dimensional identity matrix, is a Laplacian matrix corresponding to a reaction cycle (or possibly multiple disjoint reaction cycles). In [40] the authors show that complex balanced systems can be decomposed in terms of permutation matrices using Birkhoff's Theorem (see pg. 527 of [34]). The decomposition contained in [40] is analogous with that contained in Section 4.3.1 of this thesis, keeping in mind the relationship between Laplacian and permutations matrices.

4.3 Dynamics of Complex Balanced Systems

In this section, I show that the asymptotic stability of complex balanced equilibrium points guaranteed by F. Horn and R. Jackson in [33] through the Lyapunov function (3.1) can also be demonstrated in the setting of linearization about equilibrium concentrations. More specifically, I show that the local stable manifold about a complex balanced concentration $\mathbf{x}^*$ lies in the compatibility class $\mathsf{C}_{\mathbf{x}_0}$ and that the local centre manifold about $\mathbf{x}^*$ lies tangent to the equilibrium set (3.16).

In addition to guaranteeing asymptotic stability, the approach of linearization provides information about the local rate of convergence of solutions to complex balanced equilibrium concentrations; namely, that the convergence must be at least exponential near $\mathbf{x}^*$. This should be contrasted with the results obtained in [9], specifically Theorem 3, Lemma 3.6, and the example contained in Section 4 of the same paper. The authors suggest through their example that the convergence is at least exponential, which confirms Theorem 3. In this Section 4.3.4, I provide confirmation that this is the case in general.

4.3.1 Linearization of Complex Balanced Systems

In this section, I will show how complex balanced systems (see Definition 3.1.3) can be decomposed as the product of matrices of the type considered in Section 4.2.3 and what the linearized form of this set of differential equations looks like.

In order to accomplish this, however, we will need to formulate the differential equations governing the mass-action system (2.3) and (2.4) in a different (but equivalent) form. We will first need to define the *stoichiometric* and *kinetics* (or *Kirchoff*) matrices, and *mass-action vector* for a chemical reaction network.

Definition 4.3.1. *The* ***stoichiometric matrix*** $Y \in \mathbb{Z}^{m\times n}$ *is the matrix with entries*

$$[Y]_{ij} = z_{ji}, \quad i = 1,\dots,m, \quad j = 1,\dots,n. \tag{4.15}$$

Definition 4.3.2. *The* ***kinetics*** *(or* ***Kirchoff****) matrix* $A_k \in \mathbb{R}^{n\times n}$ *is the matrix with entries*

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1,l\neq i}^{m} k(i,l), & \text{if} \quad i = j \\ k(j,i), & \text{if} \quad i \neq j. \end{cases} \tag{4.16}$$

Definition 4.3.3. *The **mass-action vector** $\Psi(\mathbf{x}) \in \mathbb{R}^n_{\geq 0}$ is the vector with entries*

$$\Psi_j(\mathbf{x}) = \prod_{i=1}^{m} x_i^{[Y]_{ij}}, \quad j = 1, \ldots, n. \tag{4.17}$$

Assuming mass-action kinetics, the dynamics of the specie concentrations over time is governed by the set of differential equations

$$\frac{d\mathbf{x}}{dt} = Y\ A_k\ \Psi(\mathbf{x}). \tag{4.18}$$

This formulation is equivalent to (2.3) and (2.4) and has the advantage of being amenable to linear algebra analysis. It also clearly demonstrates the structure of the chemical reaction network since the off-diagonal elements of A_k ($[A_k]_{ij}, i \neq j$) correspond to the reaction weightings. This form of mass-action kinetics will also be used extensively in Chapter 6.

In Section 3.3.2, I showed how the rate constants for a complex balanced system could be solved for in terms the complex balanced equilibrium value $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ and a positive constant $\kappa_i > 0$ specific to each cycle in the cyclic decomposition of the network (Lemma 4.2.3). This result implies the following according to the dynamics (4.18).

Theorem 4.3.1. *Consider a mass action system with kinetics matrix A_k that is complex balanced at a point $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. Then there exists a $\delta \in \mathbb{Z}_{>0}$ and $\kappa_1, \ldots, \kappa_\delta > 0$ such that*

$$A_k = (\kappa_1 L_1 + \cdots \kappa_\delta L_\delta)\, diag\{\Psi(\mathbf{x}^*)\}^{-1} \tag{4.19}$$

where L_i, $i = 1, \ldots, \delta$, are Laplacian matrices corresponding to reaction cycles and $\Psi(\mathbf{x}^*)$ is as defined in Definition 4.3.3.

Proof. The result follows immediately from the arguments of Lemma 3.3.3 applied to the kinetics matrix A_k according to Definition 4.3.2. □

It remains to linearize $\mathbf{f}(\mathbf{x})$ about the complex balanced equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. Since Y and A_k do not depend on $\mathbf{x}$ and (2.4) is linear, we have that

$$D\mathbf{f}(\mathbf{x}^*) = Y\ A_k\ D\Psi(\mathbf{x}^*) \tag{4.20}$$

where $D\mathbf{f}(\mathbf{x}^*)$ denotes the Jacobian of $\mathbf{f}(\mathbf{x})$ evaluated at the complex balanced equilibrium concentrations $\mathbf{x}^*$ (see [46]). The following result simplifies $D\Psi(\mathbf{x}^*)$.

Lemma 4.3.1. *The linearization of the mass-action vector about the equilibrium $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ satisfies*

$$D\Psi(\mathbf{x}^*) = diag\{\Psi(\mathbf{x}^*)\}\ Y^T\ X \tag{4.21}$$

where $\Psi(\mathbf{x})$ is according to Definition 4.3.3, Y is according to Definition 4.3.1, and $X = diag\left\{\left[\frac{1}{x_i^*}\right]\right\}$.

Proof. We will first derive $D\Psi(\mathbf{x})$ then evaluate at the complex balanced equilibrium $\mathbf{x}^*$. We can see that

$$\begin{aligned} D\Psi(\mathbf{x}) &= \begin{bmatrix} z_{11}(x_1^{z_{11}-1}\cdots x_m^{z_{1m}}) & \cdots & z_{1m}(x_1^{z_{11}}\cdots x_m^{z_{1m}-1}) \\ \vdots & \ddots & \vdots \\ z_{n1}(x_1^{z_{n1}-1}\cdots x_m^{z_{nm}}) & \cdots & z_{nm}(x_1^{z_{n1}}\cdots x_m^{z_{nm}-1}) \end{bmatrix} \\ &= \begin{bmatrix} \mathbf{x}^{\mathbf{z}_1} & 0 & \cdots & 0 \\ 0 & \mathbf{x}^{\mathbf{z}_2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \mathbf{x}^{\mathbf{z}_n} \end{bmatrix} \begin{bmatrix} z_{11} & z_{12} & \cdots & z_{1m} \\ z_{21} & z_{22} & \cdots & z_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ z_{n1} & z_{n2} & \cdots & z_{nm} \end{bmatrix} \begin{bmatrix} \frac{1}{x_1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \frac{1}{x_m} \end{bmatrix} \end{aligned}$$

Evaluating this at the equilibrium $\mathbf{x}^*$ gives

$$D\Psi(\mathbf{x}^*) = \operatorname{diag}\{\Psi(\mathbf{x}^*)\}\ Y^T\ X$$

where the terms are according to the statement of the Lemma, and we are done. □

Combining (4.20) and (4.21) gives the general form

$$D\mathbf{f}(\mathbf{x}^*) = Y\ A_k\ \operatorname{diag}\{\Psi(\mathbf{x}^*)\}\ Y^T\ X. \tag{4.22}$$

It is worth noting that (4.22) holds for all mass-action systems and is not dependent on the assumption of equilibrium concentrations being complex balanced.

So far in this section we have linearized $\Psi(\mathbf{x})$ and used the assumption of complex balancing to reduce the kinetics matrix A_k to eliminate the rate constants $k(i,j)$. We can now combine (4.22) and (4.19). We make the notational substitution

$$L^* = \kappa_1 L_1 + \cdots + \kappa_\delta L_\delta. \tag{4.23}$$

The final linearized form of (2.4) is

$$D\mathbf{f}(\mathbf{x}^*) = Y\ L^*\ Y^T\ X. \tag{4.24}$$

4.3.2 Dynamics of Linearized System

In this section, we consider the properties of the linear system of the form (4.2) based on the linearized form (4.24) derived in Section 4.3.1. This is given by

$$\frac{d\mathbf{y}}{dt} = Y\, L^*\, Y^T\, X\, \mathbf{y} \tag{4.25}$$

where $Y \in \mathbb{R}^{m\times n}$ is as in Definition 4.3.1, L^* is given by (4.23), and $X = \text{diag}\left\{\left[\frac{1}{x_i^*}\right]\right\}$.

It will be convenient in this section to partition the complexes according to their linkage classes. We will let $n_1, \ldots, n_\ell$ denote the number of complexes contained in each linkage class so that $n_1 + \cdots + n_\ell = n$. We also note that, since cycles necessarily do not cross linkage classes, we can associate to each Laplacian matrix L_j, $j = 1, \ldots, \delta$, in (4.23) a specific linkage class $\mathcal{L}_i$, $i = 1, \ldots, \ell$. We will let $\delta_1, \ldots, \delta_\ell$ denote the number of cycles corresponding to each linkage class such that $\delta_1 + \cdots + \delta_\ell = \delta$. We will let

$$\begin{aligned}\mathcal{D}_i = \{j \in \{1, \ldots, \delta\} \mid \text{cycle corresponding to } L_j \\ \text{is contained in } \mathcal{L}_i\}\end{aligned} \tag{4.26}$$

and note that $|\mathcal{D}_i| = \delta_i$. We will also need to restrict L^* to specific linkage classes, which we will denote by

$$L^{(i)} = \sum_{j\in\mathcal{D}_i} \kappa_j L_j \tag{4.27}$$

from which it follows that $L^* = \sum_{i=1}^{\ell} L^{(i)}$.

The analysis in this section follows from standard linear systems theory. We determine the dimension and orientation of the stable, unstable, and centre subspaces E^s, E^u, and E^c through determination of the number of eigenvalues with positive, negative, and zero real

part (counting algebraic multiplicity) and the properties of the generalized eigenvectors to which these eigenvalues correspond. The results in this section rely heavily on the results of Section 4.2.

Before we can proceed, however, we need the following preliminary results.

Lemma 4.3.2. *The matrix L^* given in (4.23) has the property that*

$$null(L^*) = span\left\{\mathbf{1}^{(1)}, \ldots, \mathbf{1}^{(\ell)}\right\} \tag{4.28}$$

where $\mathbf{1}^{(i)} \in \mathbb{R}^n$ is defined by

$$\mathbf{1}_j^{(i)} = \begin{cases} 1, & \text{if } j \in \mathcal{L}_i \\ 0, & \text{otherwise.} \end{cases} \tag{4.29}$$

Proof. Since the linkage classes are decoupled and the rows of $L_1, \ldots, L_\delta$ in (4.23) sum to zero, we can see that any vector of the form (4.29) satisfies (4.28). It remains to show that we have captured all elements of null(L^*).

Suppose $\mathbf{x} \in$ null(L^*). This means that $\mathbf{x}$ satisfies

$$L^*\mathbf{x} = \mathbf{0}$$

which implies

$$\mathbf{x}^T L^* \mathbf{x} = 0.$$

This can be expanded to

$$\kappa_1 \mathbf{x}^T L_1 \mathbf{x} + \cdots + \kappa_\delta \mathbf{x}^T L_\delta \mathbf{x} = 0. \tag{4.30}$$

Since $\mathbf{x}^T L_i \mathbf{x} \leq 0$ and $\kappa_i > 0$ for all $i = 1, \ldots, \delta$ by Theorem 4.2.3, (4.30) implies $\mathbf{x}^T L_i \mathbf{x} = 0$

for $i = 1, \ldots, \delta$. Again by Theorem 4.2.3 we know that this can happen if and only if, for the cycle $\{\nu_0, \ldots, \nu_{l_i}\}$ associated with L_i, we have $x_{\nu_1} = \cdots = x_{\nu_{l_i}}$, for $i = 1, \ldots, \delta$.

We now consider the restriction of (4.30) to linkage classes

$$\mathbf{x}^T L^{(j)} \mathbf{x} = 0, \quad j = 1, \ldots, \ell \tag{4.31}$$

where $L^{(j)}$ is as in (4.27). For whichever cycles compose this linkage class, for (4.31) to be satisfied it is a necessary condition that all of the components of $\mathbf{x}$ corresponding to elements in the cycles be identical. Since the indices of a cycle in a linkage class must overlap the indices of at least one other cycle in the same linkage class, if there is one, we must have that

$$x_\alpha = x_\beta \qquad \text{for all } \alpha, \beta \in \mathcal{L}_j.$$

We can apply this argument to each linkage class. Since the linkage classes are disjoint, this is as far as we can go. We have shown that in order for

$$\mathbf{x}^T L^* \mathbf{x} = 0$$

to be satisfied, we must have all components of $\mathbf{x}$ corresponding to indices within common linkage classes be the same. This corresponds to the span of the $\mathbf{1}^{(i)}$ vectors given in (4.29), and we are done. □

We now move on to consideration of the eigenvalues of the linearization matrix $D\mathbf{f}(\mathbf{x}^*)$ given by (4.24). The following is a pivotal result in the study of the linearized complex balanced system (4.25).

Theorem 4.3.2. *The eigenvalues of the linearization matrix $D\mathbf{f}(\mathbf{x}^*)$ given by (4.24) have nonpositive real part. Moreover, there do not exist any strictly complex eigenvalues of $D\mathbf{f}(\mathbf{x}^*)$.*

Proof. Consider $\lambda \in \sigma(Y\ L^*\ Y^T\ X)$. This implies that there exists a $\mathbf{v} \in \mathbb{C}^m$ such that

$$Y\ L^*\ Y^T\ X\ \mathbf{v} = \lambda \mathbf{v}.$$

It follows that

$$\mathbf{v}^\dagger\ X\ Y\ L^*\ Y^T\ X\ \mathbf{v} = \lambda \mathbf{v}^\dagger X \mathbf{v}. \tag{4.32}$$

We can equate the real and imaginary parts of the left- and right-hand sides of (4.32), noting that $\mathbf{v}^\dagger X \mathbf{v}$ is real-valued since X is symmetric, to get

$$\mathrm{Re}(\lambda) = \frac{\mathbf{v}^\dagger\ X\ Y\ \tilde{L^*}\ Y^T\ X\ \mathbf{v}}{\mathbf{v}^\dagger X \mathbf{v}} \tag{4.33}$$

and

$$\mathrm{Im}(\lambda) = \frac{\mathbf{v}^\dagger\ X\ Y\ \bar{L^*}\ Y^T\ X\ \mathbf{v}}{\mathbf{v}^\dagger X \mathbf{v}} \tag{4.34}$$

where $\tilde{L^*}$ is the symmetric part of L and $\bar{L^*}$ is the skew-symmetric part of L given by $\bar{L^*} = \frac{1}{2}\left(L^* - (L^*)^T\right)$.

Since X is positive definite and $\mathbf{v} \neq \mathbf{0}$, we have $\mathbf{v}^\dagger X \mathbf{v} > 0$. The numerator of (4.33) can be written

$$\mathbf{v}^\dagger (Y^T\ X)^T (\kappa_1 \tilde{L}_1 + \cdots + \kappa_\delta \tilde{L}_\delta)(Y^T\ X)\mathbf{v}.$$

We know by Theorem 4.2.3 that the $\tilde{L}_i$ are negative semidefinite for $i = 1, \ldots, \delta$. It follows immediately from the three properties of Theorem 4.2.1 that $X\ Y\ \tilde{L^*}\ Y^T\ X$ is negative

semidefinite. Since $\lambda \in \sigma(Y\ \tilde{L^*}\ Y^T\ X)$ was chosen arbitrarily, this implies that

$$\mathrm{Re}(\lambda) = \frac{\mathbf{v}^\dagger X\ Y\ \tilde{L^*}\ Y^T\ X\mathbf{v}}{\mathbf{v}^\dagger X\mathbf{v}} \leq 0$$

for all eigenvalues of $D\mathbf{f}(\mathbf{x}^*)$.

To show $D\mathbf{f}(\mathbf{x}^*)$ does not have any strictly complex eigenvalues we prove that $\mathrm{Re}(\lambda) = 0$ implies $\mathrm{Im}(\lambda) = 0$. Consider $\lambda \in \sigma(Y\ L^*\ Y^T\ X)$ such that $\mathrm{Re}(\lambda) = 0$. This can happen if and only if the numerator of (4.33) equals zero. Since $X\ Y\ \tilde{L^*}\ Y^T\ X$ is real and symmetric, by Lemma 4.2.1 this implies

$$\mathbf{v}_i^T\ X\ Y\ L^*\ Y^T\ X\ \mathbf{v}_i = 0, \quad i = 1, 2,$$

where $\mathbf{v}_1 = \mathrm{Re}(\mathbf{v})$ and $\mathbf{v}_2 = \mathrm{Im}(\mathbf{v})$. This can be rewritten

$$(Y^T\ X\ \mathbf{v}_i)^T L^* (Y^T\ X\ \mathbf{v}_i) = 0, \quad i = 1, 2,$$

and it follows from the proof of Lemma 4.3.2 that $Y^T\ X\ \mathbf{v}_i \in \mathrm{null}(L^*)$. This implies that $\mathbf{v}_i \in \mathrm{null}(X\ Y\ L^*\ Y^T\ X)$, $i = 1, 2$.

Now consider $\mathrm{Im}(\lambda)$ given by (4.34). We can expand the numerator to give

$$\mathbf{v}^\dagger\ X\ Y\ \bar{L^*}\ Y^T\ X\ \mathbf{v} = \left[\mathbf{v}_1^T\ X\ Y\ L^*\ Y^T\ X\ \mathbf{v}_2 - \mathbf{v}_2^T\ X\ Y\ L^*\ Y^T\ X\ \mathbf{v}_1\right] i.$$

Since $\mathbf{v}_i \in \mathrm{null}(X\ Y\ L^*\ Y^T\ X)$, $i = 1, 2$, it follows immediately that $\mathrm{Im}(\lambda) = 0$ and we are done. □

Since the eigenvalues of (4.24) have nonpositive real part, it follows that the unstable

manifold E^u, is empty. The remainder of the state space is divided between the stable and centre manifolds E^s and E^c, which is consistent with our expectation, based on the [33], that solutions approach complex balanced equilibrium concentrations $\mathbf{x}^*$ asymptotically relative to their compatibility classes $\mathsf{C}_{\mathbf{x}_0}$. In the rest of this section, we give more precise results on the dimension and orientation of these invariant subspaces.

We are now prepared to take a first step towards understanding the relationship between S and $S^\perp$, and E^s and E^c. The following result relates S and $S^\perp$ to the range and nullspace of $Y\ L^*\ Y^T$.

Theorem 4.3.3. *The matrix $Y\ L^*\ Y^T \in \mathbb{R}^{m\times m}$ satisfies*

$$\mathit{null}(Y\ L^*\ Y^T) = S^\perp \tag{4.35}$$

and

$$\mathit{range}(Y\ L^*\ Y^T) = S. \tag{4.36}$$

Proof. We start by proving $\text{null}(Y\ L^*\ Y^T) = S^\perp$. Take $\mathbf{v} \in \text{null}(Y\ L^*\ Y^T)$. This implies that

$$Y\ L^*\ Y^T\ \mathbf{v} = \mathbf{0} \tag{4.37}$$

which implies

$$\mathbf{v}^T\ Y\ L^*\ Y^T\ \mathbf{v} = \mathbf{x}^T\ L^*\ \mathbf{x} = 0 \tag{4.38}$$

where $\mathbf{x} = Y^T\mathbf{v}$. It follows from the argument presented in the proof of Lemma 4.3.2 that this can happen if and only if $Y^T\mathbf{v} \in \text{null}(L^*)$ where $\text{null}(L^*) = \text{span}\ \{\mathbf{1}^{(1)}, \ldots, \mathbf{1}^{(\ell)}\}$ and $\mathbf{1}^{(i)}$ has the form given in (4.29). Now consider an arbitrary linkage class $\{\mu_1, \ldots, \mu_{n_i}\} = \mathcal{L}_i$,

$i = 1, \ldots, \ell$. By Definition 4.3.1 and (4.28), $Y^T\mathbf{v} \in \text{null}(L^*)$ implies that

$$\mathbf{z}_{\mu_j}^T\mathbf{v} = s_i, \quad j = 1, \ldots, n_i \tag{4.39}$$

where s_i is a constant depending on the linkage class. With minor rearrangement, we can change this into $(n_i - 1)$ equations of the form

$$(\mathbf{z}_{\mu_j} - \mathbf{z}_{\mu_1})^T\mathbf{v} = 0, \quad j = 2, \ldots, n_i. \tag{4.40}$$

The vectors $(\mathbf{z}_{\mu_j} - \mathbf{z}_{\mu_1})$ span the stoichiometric space S restricted to the i^{th} linkage class. This derivation holds for every linkage class $i = 1, \ldots, \ell$ from which it follows that $\mathbf{v}$ lies orthogonal to a set spanning S. It follows that $\mathbf{v} \in S^\perp$. Conversely, if we take $\mathbf{v} \in S^\perp$ it follows that (4.40) and (4.39) hold and therefore that $Y^T\mathbf{v} \in \{\mathbf{1}^{(1)}, \ldots, \mathbf{1}^{(\ell)}\} = \text{null}(L^*)$. It immediately follows that $\mathbf{v} \in \text{null}(Y\ L^*\ Y^T)$ which completes the proof that $\text{null}(Y\ L^*\ Y^T) = S^\perp$.

We now prove $\text{range}(Y\ L^*\ Y^T) = S$. We start by considering $\text{range}(Y\ L^*)$. Since the range of a matrix is equivalent to the column span, we consider the form of the columns of $Y\ L^*$, and denote by $[Y\ L^*]_i$ the i^{th} column. We have

$$[Y\ L^*]_i = \sum_{(i,j)\in\mathcal{R}} \kappa(i,j)(\mathbf{z}_j - \mathbf{z}_i)$$

where $\kappa(i,j)$ is the flow rate constant of whichever cycle the reaction pair (i,j) is contained in. In other words, $[Y\ L^*]_i$ is given by a linear combination of all of the reaction vectors involving $\mathcal{C}_i$ as a reactant. It follows that $[Y\ L^*]_i \in S$ for all $i = 1, \ldots, n$. Consequently

$$\text{range}(Y\ L^*) \subseteq S.$$

Taking $A = Y\ L^*$ and $B = Y^T$, it follows from Lemma 4.2.3 that

$$\text{range}(Y\ L^*\ Y^T) \subseteq \text{range}(Y\ L^*) \subseteq S. \tag{4.41}$$

From the Rank-Nullity Theorem, we know that

$$\dim(\text{range}(A)) + \dim(\text{null}(A)) = \dim(A).$$

Taking $A = Y\ L^*\ Y^T$ we have $\dim(A)=m$ and from (4.35) that $\dim(\text{null}(A))=m - s$. This implies $\dim(\text{range}(A))=s$. It follows from Lemma 4.2.3 and (4.41) that the columns of $Y\ L^*\ Y^T$ must span S, so that

$$\text{range}(Y\ L^*\ Y^T) = S$$

and we are done. □

The following relates S and $S^\perp$ to the range and nullspace of the Jacobian $D\mathbf{f}(\mathbf{x}^*)$ given by (4.24).

Lemma 4.3.3. *The linearized matrix $D\mathbf{f}(\mathbf{x}^*) = Y\ L^*\ Y^T\ X$ satisfies*

$$\textit{range}(D\mathbf{f}(\mathbf{x}^*)) = S \tag{4.42}$$

and

$$\textit{null}(D\mathbf{f}(\mathbf{x}^*)) = X^{-1}S^\perp \tag{4.43}$$

Proof. This result follows immediately from Lemma 4.2.4 and Theorem 4.3.3 taking $A =$

$Y\ L^*\ Y^T$ and $B = X$. □

Lemma 4.3.4. *The linearized matrix $D\mathbf{f}(\mathbf{x}^*) = Y\ L^*\ Y^T\ X$ does not have a degenerate zero eigenvalue.*

Proof. Suppose A has a degenerate zero eigenvalue. This implies that there is a standard eigenvector $\mathbf{v}_1$ satisfying

$$A\mathbf{v}_1 = 0 \cdot \mathbf{v}_1 = \mathbf{0}$$

and a generalized eigenvector $\mathbf{v}_2$ satisfying

$$A\mathbf{v}_2 \neq \mathbf{0} \quad \text{and} \quad A^2\mathbf{v}_2 = \mathbf{0}.$$

We know that $\mathbf{w} = A\mathbf{v}_2 \in \text{range}(A) = S$ from Theorem 4.3.3 and that $A\mathbf{w} = \mathbf{0}$ if and only if $\mathbf{w} \in \text{null}(A) = X^{-1}S^{\perp}$ from Theorem 4.3.3. We therefore have $\mathbf{w} \in S$ and $\mathbf{w} \in X^{-1}S^{\perp}$. This implies that $\mathbf{w}^T X\mathbf{w} = 0$ which can happen if and only if $\mathbf{w} = \mathbf{0}$ since X is positive definite. This contradicts $\mathbf{w} = A\mathbf{v}_2 \neq \mathbf{0}$ and it follows that $Y\ L^*\ Y^T\ X$ cannot have a degenerate zero eigenvalue. □

We finally state the main result of this section. This result shows where the stable, unstable, and centre subspaces of (4.25) lie.

Theorem 4.3.4. *For the linearized complex balanced system (4.25) we have*

1. $E^u = \{\mathbf{0}\}$; *and*
2. $E^s = S$; *and*
3. $E^c = X^{-1}S^{\perp}$.

Proof. We know from Lemma 4.3.3 that range$(D\mathbf{f}(\mathbf{x}^*)) = S$ and null$(D\mathbf{f}(\mathbf{x}^*)) = X^{-1}S^{\perp}$, and from Lemma 4.3.4 that A does not have a degenerate zero eigenvalue. It follows by Lemma 4.2.2 that

1. $N_0 = X^{-1}S^{\perp}$; and
2. $N_r \oplus N_c = S$.

It remains to relate E^s, E^u, and E^c to N_0, N_r, and N_c. From Theorem 4.3.2 we know that $\sigma(D\mathbf{f}(\mathbf{x}^*))$ does not contain any eigenvalues with positive real part. This immediately implies that $E^u = \{\mathbf{0}\}$.

We also know from Theorem 4.3.2 that $\sigma(D\mathbf{f}(\mathbf{x}^*))$ does not contain any strictly complex eigenvalues. By definition, this implies that $N_0 = E^c$ which implies $E^c = X^{-1}S^{\perp}$. We can also easily see that this implies the elements of $N_r \oplus N_c$ have strictly negative real part, which implies $E^s = N_r \oplus N_c = S$, and we are done. □

This result implies that solutions of the linear system starting in S tend exponentially toward the origin. It is worth noting that the centre subspace E^c depends on the chosen equilibrium concentration $\mathbf{x}^*$ since X does. This will be explored more in the next section.

4.3.3 Extension to Nonlinear Dynamics

We are finally prepared to say something about the dynamics of the nonlinear system (2.4) under the assumption of complex balancing.

Theorem 4.3.5. *A complex balanced mass-action system according to Definition 3.1.3 satisfies the following properties about any positive equilibrium concentration* $\mathbf{x}^*$*:*

1. *the local stable manifold W^s_{loc} coincides locally with $\mathsf{C}_{\mathbf{x}_0}$; and*

2. *the local centre manifold W^c_{loc} coincides locally with the tangent plane to the equilibrium set (3.16) at $\mathbf{x}^*$.*

Proof. We know from Lemma 3.2.1 that all equilibrium concentrations of a complex balanced system are complex balanced equilibrium concentrations. We can therefore apply our results to all equilibrium concentrations $\mathbf{x}^* \in E$ where E is given by (3.16) by Lemma 3.2.2.

Theorem 4.1.1 and Theorem 4.3.4 imply that about any complex balanced concentration $\mathbf{x}^*$ of the nonlinear system (2.4) there exists

1. an s-dimensional stable manifold W^s_{loc} of class C^∞ which lies tangent to S; and

2. an $(m-s)$-dimensional centre manifold W^c_{loc} of class C^∞ which lies tangent to $X^{-1}S^\perp$; and

3. a zero-dimensional unstable manifold W^u_{loc} (i.e. $W^u_{loc} = \{\mathbf{0}\}$).

The third point implies that there is no unstable manifold locally about $\mathbf{x}^*$. This is what we expect from the results of F. Horn and R. Jackson [33].

The first point says that W^s_{loc} about $\mathbf{x}^*$ is locally tangent to S; however, by Proposition 2.4.1 we know the solution space $\mathbb{R}^m_{>0}$ is partitioned into compatibility classes $\mathsf{C}_{\mathbf{x}_0}$, which are affine spaces parallel to S. Since solutions may not leave $\mathsf{C}_{\mathbf{x}_0}$ and the dimensions match, the local stable manifold W^s_{loc} about $\mathbf{x}^*$ must coincide with $\mathsf{C}_{\mathbf{x}_0}$ wherever it exists. We therefore have that W^s_{loc} about $\mathbf{x}^*$ coincides with $\mathsf{C}_{\mathbf{x}_0}$.

To analyse the second point, we return to consideration of the equilibrium set (3.16) derived in [33]. We consider an arbitrary basis of $S^{\perp}$, $\{\mathbf{s}_1, \ldots, \mathbf{s}_{m-s}\}$. We can determine the orientation of the tangent plane about an equilibrium concentration $\mathbf{x}^*$ by parametrizing the equilibrium set (3.16) as

$$(\ln \mathbf{x}(\tau) - \ln \mathbf{x}^*) = \tau \mathbf{s}_i, \quad \tau \in \mathbb{R},\ i = 1, \ldots, m-s \tag{4.44}$$

and taking the limit as $\tau \to 0$. Since the set E given by (3.16) is smooth, this will give a basis for the tangent plane centered at $\mathbf{x}^*$.

Considering the components independently, (4.44) can be rewritten as $\ln x_j(\tau) - \ln x_j^* = \tau s_{ij},\ j = 1, \ldots, m-s,\ i = 1, \ldots, m$, where the s_{ij}'s are the components of $\mathbf{s}_i$. This is equivalent to $x_j(\tau) = x_j^* e^{\tau s_{ij}}$. We take the derivative with respect to τ and set $\tau = 0$ to get $x_j'(0) = x_j^* s_{ij}$. We can see that $X^{-1}\mathbf{s}_j,\ j = 1, \ldots, m-s$ forms a linearly independent basis for the tangent space $X^{-1}S^{\perp}$. This shows the local centre manifold W^c_{loc} coincides locally to the tangent plane of the equilibrium set (3.16) at $\mathbf{x}^*$, and we are done. □

4.3.4 Optimal Exponential Bound

The following result represents the amalgamation of the linearization approach taken here and the approach taken by F. Horn and R. Jackson in [33], and is the main result of this chapter. Of particular importance, this theorem represents a tightening of the convergence of complex balanced systems over the results discussed in [33] and [9].

Theorem 4.3.6. *If a mass-action system is complex balanced, then there exists within each positive compatibility class* $\mathsf{C}_{\mathbf{x}_0}$ *a unique positive equilibrium point* $\mathbf{x}^*$ *which is locally*

exponentially stable. More specifically, for any $M > 0$ satisfying

$$\max\{\mathrm{Re}(\lambda_i) \mid \mathrm{Re}(\lambda_i) < 0\} < -M < 0 \tag{4.45}$$

where λ_i are the eigenvalues of $D\mathbf{f}(\mathbf{x}^*)$, there exists a $k \geq 1$ and an $\epsilon > 0$ such that $\forall\ \mathbf{x}_0 \in \mathsf{C}_{\mathbf{x}_0} \cap B_\epsilon(\mathbf{x}^*)$,

$$\|\mathbf{x}(t) - \mathbf{x}^*\| \leq ke^{-Mt}\|\mathbf{x}_0 - \mathbf{x}^*\|, \quad \forall\ t \geq 0. \tag{4.46}$$

Proof. Consider a complex balanced system according to Definition 3.1.3. The uniqueness and stability of a positive equilibrium $\mathbf{x}^*$ relative to each compatibility class $\mathsf{C}_{\mathbf{x}_0}$ follows from Theorem 3.3.1.

The exponential stability of a complex balanced equilibrium $\mathbf{x}^*$ relative to $\mathsf{C}_{\mathbf{x}_0}$ follows from the linearization. We know from Theorem 4.3.5 that W^s coincides with $\mathsf{C}_{\mathbf{x}_0}$ locally about $\mathbf{x}^*$. Since exponential stability is guaranteed within a neighbourhood relative to W^s by Theorem 4.1.1, we have that $\mathbf{x}^*$ is locally exponentially stable relative to $\mathsf{C}_{\mathbf{x}_0}$.

To obtain the estimate (4.53) for M we follow the proof of the Stable Manifold Theorem and its Corollary on pages 107-115 of [46]. We note that while this result deals with systems which can be decomposed about an equilibrium $\mathbf{x}^*$ into stable and unstable subspaces, our system is decomposed into stable and centre subspaces. We will show that the same method can be applied.

Consider the system (4.18) written as

$$\frac{d\mathbf{x}}{dt} = A(\mathbf{x} - \mathbf{x}^*) + \mathbf{F}(\mathbf{x}) \tag{4.47}$$

where $A = D\mathbf{f}(\mathbf{x}^*)$ and $\mathbf{F}(\mathbf{x})$ is the nonlinear component of $\mathbf{f}(\mathbf{x})$. The system can be

transformed into

$$\frac{d\mathbf{y}}{dt} = B(\mathbf{y} - \mathbf{y}^*) + P^{-1}\mathbf{F}(P\mathbf{y}) \tag{4.48}$$

through the transformation $P^{-1}\mathbf{x} = \mathbf{y}$ where P is the matrix with the real generalized eigenvectors of A along the columns and B is the real Jordan block matrix guaranteed under the real Jordan Canonical Form Theorem to satisfy $A = PBP^{-1}$.

We order the eigenvectors composing P so that the first $s \times s$ block of B is the Jordan canonical block corresponds to eigenvalues with negative real part. The rest of the eigenvectors correspond to the zero eigenvalue, which is nondeficient by Lemma 4.3.4. This implies that the lower block of B is identically 0. We can partition the transformed system into local stable and centre components so that we have

$$\begin{bmatrix} \dot{\mathbf{y}}_s \\ \dot{\mathbf{y}}_c \end{bmatrix} = \begin{bmatrix} Q_s & 0_{sc} \\ 0_{cs} & 0_c \end{bmatrix} \begin{bmatrix} \mathbf{y}_s \\ \mathbf{y}_c \end{bmatrix} + \begin{bmatrix} [P^{-1}\mathbf{F}(P\mathbf{y})]_s \\ [P^{-1}\mathbf{F}(P\mathbf{y})]_c \end{bmatrix} \tag{4.49}$$

where Q_s is the real Jordan block of corresponding to eigenvalues with negative real part.

We can further reduce $[P^{-1}\mathbf{F}(P\mathbf{y})]_c$. Since $\mathbf{f}(\mathbf{x}) \in S$ and $\text{range}(A) = S$ by Lemma 4.3.3, we have that $\mathbf{F}(\mathbf{x}) = \mathbf{f}(\mathbf{x}) - A(\mathbf{x} - \mathbf{x}^*) \in S$. We know that $P^{-1}P = I$. The lower $(m-s) \times s$ block of I, which is identically zero, results from the multiplication of the final $m - s$ rows of P^{-1} and the first s columns of s. Since the first s columns of P span S by construction, this implies that the rows of P^{-1} corresponding to the centre manifold map elements in S to 0. This implies $[P^{-1}\mathbf{F}(P\mathbf{y})]_c = \mathbf{0}_{(m-s)}$.

It follows from (4.49) that $\dot{\mathbf{y}}_c = \mathbf{0}_{(m-s)}$ which implies $\mathbf{y}_c(t) \equiv \mathbf{c}$, where $\mathbf{c} \in \mathbb{R}^{(m-s)}$ is a constant vector determined by the final $m - s$ components of the initial condition vector $\mathbf{y}_0 = P^{-1}\mathbf{x}_0$. These constants can be substituted into the equations for $\mathbf{y}_s$ to give the

reduced system

$$\dot{\mathbf{y}}_s = Q_s \mathbf{y}_s + [P^{-1}\mathbf{F}(P\mathbf{y})]_s \tag{4.50}$$

where the final $(m-s)$ components of $\mathbf{y}$ are constant.

We have reduced our original m-dimensional system to an s-dimensional system where the entire space is a local stable manifold. We can apply the Corollary of the Stable Manifold Theorem in [46] to ensure that for $M > 0$ satisfying

$$\max\{Re(\lambda_i) \mid Re(\lambda_i) < 0\} < -M < 0$$

there exists a $k > 1$ and an $\epsilon > 0$ such that the estimate

$$\|\mathbf{x}(t) - \mathbf{x}^*\| \leq ke^{-Mt}\|\mathbf{x}_0 - \mathbf{x}^*\|$$

holds for $\mathbf{x}_0 \in B_\epsilon(\mathbf{y}^*) \cap \mathsf{C}_{\mathbf{x}_0}$, where the evolution of $\mathbf{y}(t)$ has been transformed back to the original variables via the mapping $\mathbf{x}(t) = P\mathbf{y}(t)$. This completes the proof of Theorem 4.3.6. □

It should be noted that, while the transformation $\mathbf{x}(t) = P\mathbf{y}(t)$ is similar to the transformation $\mathbf{c}(t) = \mathbf{c}_* + T\xi(t)$ used to reduce the system in [33], there are important differences. The first s columns of the matrix T are permitted to be any orthonormal basis of S while the remaining $m-s$ columns are any orthonormal basis of $S^\perp$. By contrast, the first s columns of the matrix P, which are a basis for S, are neither required to be normalized nor orthogonal to one another. The final $m-s$ columns of P are a basis for $X^{-1}S^\perp$ rather than $S^\perp$. In both cases, however, the transformation reduces the dimension of the original m-dimensional system to an s-dimensional one.

This analysis also shares significant similarities with that carried out by A. Bamberger and E. Billette in [8]. These authors consider the first-order approximation of the Lyapunov function (3.1) considered by F. Horn and R. Jackson [33], which after adjusting notations is given by

$$H(\mathbf{x}) = (\mathbf{x} - \mathbf{x}^*)^T X (\mathbf{x} - \mathbf{x}^*). \tag{4.51}$$

They show that the time derivative of $H(\mathbf{x}(t))$ for a complex balanced system is

$$\frac{d}{dt} H(\mathbf{x}(t)) = -\sum_{i=1}^{r} k_i \mathbf{x}^{\mathbf{z}_i} \left((\mathbf{z}_i' - \mathbf{z}_i)^T X (\mathbf{x} - \mathbf{x}^*) \right)^2 + O(\mathbf{x} - \mathbf{x}^*)^3 \tag{4.52}$$

which to second-order is negative semidefinite and equal to zero if and only if $(\mathbf{x} - \mathbf{x}^*) \in X^{-1} S^{\perp}$, which lies tangent to the equilibrium set (3.16) by Theorem 4.3.5. They then show through a convexity argument that this implies the existence of a $\lambda > 0$ such that

$$0 \leq H(\mathbf{x}(t)) \leq H(\mathbf{x}(0)) e^{-\lambda t}$$

for $\mathbf{x}_0$ such that $\mathbf{x}_0 - \mathbf{x}^* \in S$.

It is not hard to show that this can be rearranged into a form satisfying (4.46) which is sufficient to prove the local exponential stability of $\mathbf{x}^*$ relative to $\mathsf{C}_{\mathbf{x}_0}$. This does not, however, give bounds on the decay parameter λ nor make any attempt to ascertain the existence of a linearly stable manifold apart from the restriction of solutions guaranteed by Proposition 2.4.1. At best, the approach taken here gives very general qualitative local behaviour about the equilibrium concentration $\mathbf{x}^*$.

Using the linear form (4.24), however, we can carry out the argument in fuller detail to obtain the following.

Lemma 4.3.5. *Let $\mathbf{x}^*$ be a complex balanced equilibrium concentration of a complex balanced mass-action system. For any $M > 0$ satisfying*

$$\alpha < -M < 0 \tag{4.53}$$

there exists an $\epsilon > 0$ such that $\forall\ \mathbf{x}_0 \in \mathsf{C}_{\mathbf{x}_0} \cap B_\epsilon(\mathbf{x}^*)$,

$$\|\mathbf{x}(t) - \mathbf{x}^*\| \leq k e^{-Mt} \|\mathbf{x}_0 - \mathbf{x}^*\|, \qquad \forall\ t \geq 0 \tag{4.54}$$

where $\alpha = \lambda_{max}(P) \min\{x_i^*\}$, $k = \sqrt{\frac{\max\{x_i^*\}}{\min\{x_i^*\}}}$, $P = X\ Y\ L^*\ Y^T\ X$, and $\lambda_{max}(P)$ is the smallest negative eigenvalue of P.

Proof. We use the function $H(\mathbf{x})$ defined in (4.51). We can take the time derivative of $H(\mathbf{x}(t))$ along solutions, using the linearized form

$$\mathbf{f}(\mathbf{x}) = Y\ L^*\ Y^T\ X\ (\mathbf{x} - \mathbf{x}^*) + O(\mathbf{x} - \mathbf{x}^*)^2,$$

to obtain

$$\frac{d}{dt} H(\mathbf{x}(t)) = 2(\mathbf{x} - \mathbf{x}^*)^T\ X\ Y\ \tilde{L^*}\ Y^T\ X\ (\mathbf{x} - \mathbf{x}^*) + O(\mathbf{x} - \mathbf{x}^*)^3. \tag{4.55}$$

Note that we can use the symmetric form of L^* since the quadratic form is the same for real-valued vectors and matrices. We will substitute $P = X\ Y\ \tilde{L^*}\ Y^T\ X$.

We know that the quadratic form equals zero if and only if $\mathbf{x} - \mathbf{x}^* \in X^{-1} S^\perp$; otherwise, it is negative. If we take $\mathbf{x} - \mathbf{x}^* \in S$ and $\|\mathbf{x} - \mathbf{x}^*\|$ sufficiently small, we can take the bound

$$\frac{d}{dt} H(\mathbf{x}(t)) \leq (2\lambda_{max}(P) + \delta) \|\mathbf{x} - \mathbf{x}^*\|^2 \tag{4.56}$$

where $\lambda_{max}(P)$ is the smallest negative eigenvalues of P and δ is the bound on the higher order terms. Clearly we can take $\|\mathbf{x}-\mathbf{x}^*\|$ small enough so that $2\lambda_{max}(P)+\delta<0$.

We can also bound $H(\mathbf{x})$ in the following way

$$\frac{1}{\max\{x_i^*\}}\|\mathbf{x}-\mathbf{x}^*\|^2 \leq H(\mathbf{x}) \leq \frac{1}{\min\{x_i^*\}}\|\mathbf{x}-\mathbf{x}^*\|^2. \tag{4.57}$$

Together, (4.56) and (4.57) imply that

$$\frac{d}{dt}H(\mathbf{x}(t)) \leq (2\lambda_{max}(P)+\delta)\min\{x_i^*\}\,H(\mathbf{x}(t)).$$

Since $H(\mathbf{x}(t)) \geq 0$, we can integrate and apply (4.57) to obtain

$$\|\mathbf{x}(t)-\mathbf{x}^*\| \leq \sqrt{\frac{\max\{x_i^*\}}{\min\{x_i^*\}}}e^{(\lambda_{max}(P)+\frac{1}{2}\delta)\min\{x_i^*\}t}\|\mathbf{x}_0-\mathbf{x}^*\|, \qquad \forall\ t\geq 0.$$

We can make δ arbitrarily small by taking $\|\mathbf{x}-\mathbf{x}^*\|$ small, from which the estimate for M follows, and we are done. □

Example 4.3.1. *Re-consider the network*

$$\begin{array}{ccc} 2\mathcal{A}_1+\mathcal{A}_2 & \overset{k(1,2)}{\longrightarrow} & 3\mathcal{A}_1 \\ {\scriptstyle k(4,1)}\uparrow & & \downarrow{\scriptstyle k(2,3)} \\ 3\mathcal{A}_2 & \underset{k(3,4)}{\longleftarrow} & \mathcal{A}_1+2\mathcal{A}_2 \end{array} \tag{4.58}$$

considered previously in Example 3.4.5. This network was first considered by F. Horn and R. Jackson under the restriction that $k(1,2) = k(3,4) = 1$ and $k(2,3) = k(4,1) = \epsilon$, in which case the system is complex balanced if and only if $\epsilon = 1$ [33]. Under less restrictive

conditions it can be shown that the general system (4.58) is complex balanced if and only if

$$k(1,2)^2 = k(2,3)k(3,4)$$

and

$$k(1,2)k(3,4) = k(2,3)k(4,1).$$

This is clearly the case for $k(1,2) = k(2,3) = k(3,4) = k(4,1) = 1$*; however, for the sake of this example we will take* $k(1,2) = 1/2$*,* $k(2,3) = 1$*,* $k(3,4) = 1/4$*,* $k(4,1) = 1/8$*.*

With these rate constants, system (4.58) is governed by the dynamics

$$\dot{x}_1 = -\dot{x}_2 = (x_2 - 2x_1)\left(\frac{1}{4}x_2^2 + \frac{1}{4}x_1x_2 + x_1^2\right) \tag{4.59}$$

which has a line of positive equilibria along $x_2 = 2x_1$ *(and these are the only real roots of (4.59)). The stoichiometric subspace is given by span*$\{[-1\ \ 1]^T\}$*. We could pick equilibrium along* $x_2 = 2x_1$ *but for illustrative purposes we choose* $x_1^* = 1/2$*,* $x_2^* = 1$*. With this choice of equilibria we can calculate the flow rate* $\kappa = 1/8$*; since system (4.58) consists of a single cycle, this flow rate applies to every reaction. Using the linearized form (4.24)*

$$D\mathbf{f}(\mathbf{x}^*) = Y\ L^*\ Y^T\ X$$

with

$$Y = \begin{bmatrix} 2 & 3 & 1 & 0 \\ 1 & 0 & 2 & 3 \end{bmatrix} \quad L^* = \kappa \begin{bmatrix} -1 & 0 & 0 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix} \quad X = \begin{bmatrix} \frac{1}{x_1^*} & 0 \\ 0 & \frac{1}{x_2^*} \end{bmatrix}$$

where $\kappa = 1/8$, $x_1^* = 1/2$, *and* $x_2^* = 1$. *We can easily compute that*

$$D\mathbf{f}(\mathbf{x}^*) = \begin{bmatrix} -\frac{5}{4} & \frac{5}{8} \\ \frac{5}{4} & -\frac{5}{8} \end{bmatrix}. \tag{4.60}$$

This can also be obtained by directly linearizing (4.59).

The linearized matrix (4.60) has the eigenvalue/eigenvector pairs $\lambda_1 = -15/8$, $\mathbf{v}_1 = [-1 \quad 1]^T$, *and* $\lambda_2 = 0$, $\mathbf{v}_2 = [1 \quad 2]^T$. *The first pair correspond to linear decay about* $\mathbf{x}^*$ *in the direction of* S, *while the second pair correspond a local centre manifold where the equilibrium set* $x_2 = 2x_1$ *cuts through the compatibility class* $\mathsf{C}_{\mathbf{x}_0}$ *are* $\mathbf{x}^*$.

To test Theorem 4.3.6, we consider system (4.58) and look to satisfy (4.46) with the values $M = 1.85$ *and* $k = 1.25$. *The results are contained in Figure 4.1(a). For an initial condition chosen sufficiently close to* $\mathbf{x}^*$, *we can see that the correspondence between the convergence of* $\mathbf{x}(t)$ *to* $\mathbf{x}^*$ *and the upper bound given by (4.46) is nearly exact.*

To test Lemma 4.3.5, I derive

$$P = X\ Y\ L^*\ Y^T\ X = \begin{bmatrix} -\frac{5}{2} & \frac{5}{4} \\ \frac{5}{4} & -\frac{5}{8} \end{bmatrix}.$$

It follows that $\lambda_{max}(P) = -\frac{25}{8}$, $\max\{x_i^*\} = 1$ *and* $\min\{x_i^*\} = \frac{1}{2}$. *It follows from (4.54) that* $k = \sqrt{2}$ *and* $\alpha = -\frac{25}{16}$. *The results are contained in Figure 4.1(b). Again, we can see that the exponential convergence holds; however, it is clear that the estimates guaranteed by Lemma 4.3.5 are not as strong as those given by the linearization approach of Theorem 4.3.6. For many examples, the estimates guaranteed by Lemma 4.3.5 are orders of magnitude apart from the optimal values.*

In Figure 4.1(c), I plot $\ln(\|\mathbf{x}(t)-\mathbf{x}^*\|)$. *Since (4.46) implies*

$$\ln(\|\mathbf{x}(t)-\mathbf{x}^*\|) \le -Mt + \ln(k\|\mathbf{x}_0-\mathbf{x}^*\|) \tag{4.61}$$

the slope of $\ln(\|\mathbf{x}(t)-\mathbf{x}^*\|)$ *as* $t \to \infty$ *gives a good approximation of the optimal value of* $-M$.

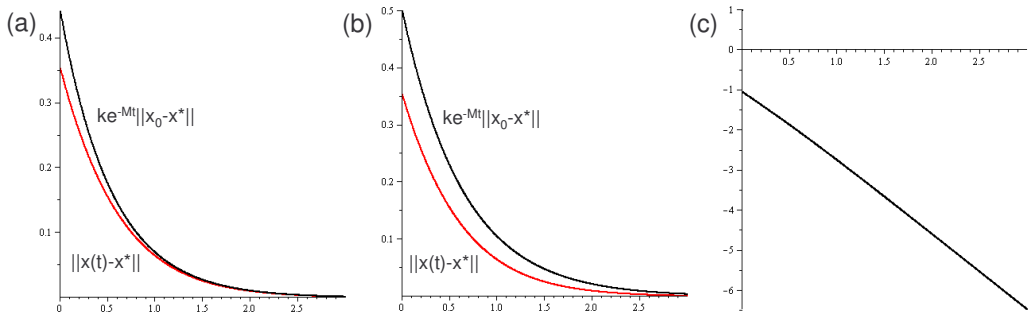

Figure 4.1: System (4.58) with $k_1 = 1/2$, $k_2 = 1$, $k_3 = 1/4$, $k_4 = 1/8$, $x_1^* = 1/2$, $x_2^* = 1$, $x_1(0) = 0.25$, and $x_2(0) = 1.25$. In (a) and (b), we can see that the solution $\mathbf{x}(t) = (x_1(t), x_2(t))$ converges toward $\mathbf{x}^* = (1/2, 1)$ at an exponential rate satisfying $\|\mathbf{x}(t)-\mathbf{x}^*\| \le ke^{-Mt}\|\mathbf{x}_0-\mathbf{x}^*\|$ with (a) $k = 1.25$, $M = 1.85$, and (b) $k = \sqrt{2}$, $M = 1.5625$. In (c), we can see that $h(t) = \ln(\|\mathbf{x}(t)-\mathbf{x}^*\|)$ becomes more linear as $t \to \infty$, as predicted by the form (5.11). The approximate slope values closely approximate the value $-M = -15/8$ as $t \to \infty$ (e.g. $h'(1) \approx -1.800320000$, $h'(2) \approx -1.866759667$, $h'(3) \approx -1.878135333$, etc.).

Chapter 5

Global Stability of Complex Balanced Systems

In this section, we present the latest research on what has come to be known as the *Global Attractor Conjecture* (Conjecture 5.1.1) and, more generally, *persistence* of chemical reaction networks. Of particular importance are Theorem 5.1.1 from Section 5.1.1 and Theorem 5.1.2 from Section 5.1.2, which significantly restrict the set of possible behaviours of trajectories violating the conjecture. Two approaches which have been taken in the literature to establishing the conjecture are presented in Section 5.2.2 and Section 5.3.1.

Our original contributions to this line of research will be contained in the remainder of the chapter. In Section 5.2, we extend the notion of dynamically non-emptiable semi-locking sets introduced in [5] to weakly dynamically non-emptiable semi-locking sets [37]. In Section 5.3.2, we extend the notion of dividing the state space of a mass-action system into strata from detailed balanced systems introduced in [13] to complex balanced systems [54]. These generalizations, as well as a few technical changes and a novel use of Farkas'

Lemma (Lemma 5.1.1 and, equivalently, Lemma 5.1.2), will allow us to broaden the scope of chemical reaction networks satisfying the global attractor conjecture.

5.1 Background

In Section 3.3 we established that complex balanced systems exhibit locally stable dynamics (see Definition 3.0.6 and Theorem 3.3.1), which means that within each positive compatibility class $\mathsf{C}_{\mathbf{x}_0}$ there is exactly one positive equilibrium concentration $\mathbf{x}^*$ and that this concentration is locally asymptotically stable relative to $\mathsf{C}_{\mathbf{x}_0}$. In other words, there is a neighbourhood of $\mathbf{x}^*$ relative to $\mathsf{C}_{\mathbf{x}_0}$ for which all trajectories originating in the neighbourhood converge toward $\mathbf{x}^*$.

Stated this way, an obvious question arises: what happens to trajectories originating *outside* of this neighbourhood? Is it possible for some trajectories to approach some other set? And, if so, what does this set look like? Or, alternatively, can the neighbourhood of convergence for $\mathbf{x}^*$ be extended to the entire compatibility class so that $\mathbf{x}^*$ is a *global* attractor for $\mathsf{C}_{\mathbf{x}_0}$?

This is a question made more interesting by the nature of the Lyapunov function $L(\mathbf{x})$ given by (3.1). By Lemma 3.3.4, we have that, along trajectories $\mathbf{x}(t)$, $\dfrac{d}{dt}L(\mathbf{x}(t)) < 0$ everywhere in $\mathsf{C}_{\mathbf{x}_0}$ unless $\mathbf{x}(t)$ is at the unique equilibrium concentration $\mathbf{x}^*$. This clearly implies that no periodic orbits or chaotic "strange attractors" may exist, and the limiting behaviour of $L(\mathbf{x})$ as $\|\mathbf{x}\| \to \infty$ implies that no trajectory may approach infinity by (3.2).

It is tempting to conclude that the unique equilibrium concentration $\mathbf{x}^*$ in $\mathsf{C}_{\mathbf{x}_0}$ is a global attractor for $\mathsf{C}_{\mathbf{x}_0}$; however, this conclusion is not warranted. The function $L(\mathbf{x})$ is not radially unbounded with respect to $\mathsf{C}_{\mathbf{x}_0}$ and consequently we cannot rule out the

possibility that trajectories tend toward the *boundary* of the set, $\partial\mathsf{C}_{\mathbf{x}_0}$. This is not an obvious point. The allure of global stability is so strong, in fact, that in their original papers on complex balanced systems, the authors Feinberg, Horn, and Jackson errantly asserted that they had proved the global stability of $\mathbf{x}^*$ relative to $\mathsf{C}_{\mathbf{x}_0}$ [25, 30, 33]! It was only later that they realized their result was in fact locally limited [31].

Nevertheless, in the nearly four decades since this work began, no example of a complex balanced system with a trajectory approaching $\partial\mathsf{C}_{\mathbf{x}_0}$ has been found. This has led many to surmise that Claim (4) of Theorem 3.3.1 can in fact be extended globally to $\mathsf{C}_{\mathbf{x}_0}$. The claim is stated most succinctly as follows (see [13, 31]).

Conjecture 5.1.1 (Global Attractor Conjecture)**.** *For any complex balanced system and any starting point* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$*, the associated complex balanced equilibrium point* $\mathbf{x}^*$ *of* $\mathsf{C}_{\mathbf{x}_0}$ *is a global attractor of* $\mathsf{C}_{\mathbf{x}_0}$*.*

As of the writing of this thesis, no fully general proof of Conjecture 5.1.1 is known. That is not to say, however, that no headway has been made on the problem; in fact, many cases are known under which this result follows [2, 13, 19, 44, 52, 54, 55]. There are also many restrictions which have been imposed upon trajectories deviating from $\mathbf{x}^*$, should such trajectories exist [1, 5, 55]. As might be expected from the preceding discussion, many of these approaches involve consideration of behaviour near $\partial\mathsf{C}_{\mathbf{x}_0}$ (or, more broadly, $\partial\mathbb{R}^m_{>0}$) since any trajectory not converging to $\mathbf{x}^*$ must converge to the boundary (in a sense to be clarified in Section 5.1.1).

In the remainder of this section, I will present the background concepts, terminology, and known results relevant to the discussion of Conjecture 5.1.1. My own results regarding Conjecture 5.1.1 will be stated in Section 5.2 and Section 5.3, which will rely heavily on

the background introduced here [37, 54].

Firstly, however, I present a few example illustrating how the concept of global stability goes hand-in-hand with the behaviour of trajectories near boundary equilibrium concentrations.

Example 5.1.1. *Consider the system*

$$2\mathcal{A}_1 + \mathcal{A}_2 \underset{k_-}{\overset{k_+}{\rightleftarrows}} \mathcal{A}_1 + 2\mathcal{A}_2.$$

It is easy to see that this system is weakly reversible and has a deficiency of zero. It follows by Theorem 3.4.2 that, regardless of the rate constants, within each positive compatibility class there is exactly one positive equilibrium concentration and that this concentration is locally asymptotically stable relative to its compatibility class.

Something more interesting happens with this example, however. If we consider the governing dynamics

$$\begin{aligned} \frac{dx_1}{dt} &= -k_+x_1^2x_2 + k_-x_1x_2^2 = x_1x_2(-k_+x_1 + k_-x_2) \\ \frac{dx_2}{dt} &= k_+x_1^2x_2 - k_-x_1x_2^2 = x_1x_2(k_+x_1 - k_-x_2) \end{aligned} \tag{5.1}$$

we see that there is a positive line of equilibria ($x_2 = (k_+/k_-)x_1$) and two lines of equilibria on the boundary of the positive orthant ($x_1 = 0$ and $x_2 = 0$). Phase plane analysis shows us that the boundary equilibria are unstable while the positive line of equilibria is stable (see Figure 5.1). It is clear, therefore, that the conditions of Theorem 3.4.2 and Theorem 3.4.3 do not prohibit the existence of equilibria on the boundary of the positive compatibility classes.

It is particularly worth noting that, since all boundary equilibria are unstable, all trajectories originating in a positive compatibility classes $\mathsf{C}_{\mathbf{x}_0}$ converge to the unique positive equilibrium concentration $\mathbf{x}^*$ in $\mathsf{C}_{\mathbf{x}_0}$ permitted by Claim 3 of Theorem 3.3.1. In other words, the local stability of $\mathbf{x}^*$ can be extended globally by consideration of behaviour near the boundary $\partial\mathbb{R}^m_{>0}$; $\mathbf{x}^*$ is a global attractor for $\mathsf{C}_{\mathbf{x}_0}$, and therefore satisfies Conjecture 5.1.1.

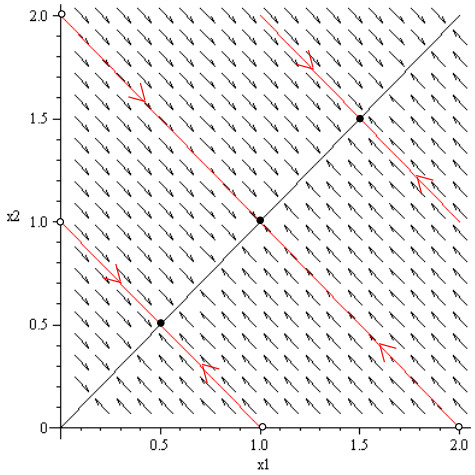

Figure 5.1: Phase portrait of the system (5.1) with $k_+ = k_- = 1$. The positive line of equilibria, $x_2 = x_1$, is asymptotically stable relative to the compatibility classes (in red) while the boundaries $x_1 = 0$ and $x_2 = 0$ are unstable.

Example 5.1.2. *Reconsider the example given in Example 3.4.5,*

$$\begin{array}{ccc} 2\mathcal{A}_1 + \mathcal{A}_2 & \xrightarrow{1} & 3\mathcal{A}_1 \\ {\scriptstyle\epsilon}\uparrow & & \downarrow{\scriptstyle\epsilon} \\ 3\mathcal{A}_2 & \xleftarrow[1]{} & \mathcal{A}_1 + 2\mathcal{A}_2 \end{array}$$

where $\epsilon > 0$ [33]. In Section 3.4, we saw that this system was complex balanced for $\epsilon = 1$, exhibited locally stable dynamics but was not complex balanced for $1/6 \leq \epsilon < 1$ and $\epsilon > 1$,

and had three lines of equilibria—two stable and one unstable—for $0 < \epsilon < 1/6$.

Now consider what happens when we take the limit $\epsilon \to 0$. *This amounts to removing the reactions corresponding to* ϵ *from the system. The remaining system is*

$$\begin{aligned} 2\mathcal{A}_1 + \mathcal{A}_2 &\xrightarrow{1} 3\mathcal{A}_1 \\ \mathcal{A}_1 + 2\mathcal{A}_2 &\xrightarrow{1} 3\mathcal{A}_2 \end{aligned} \tag{5.2}$$

which under the assumption of mass-action kinetics is governed by the system of differential equations

$$\begin{aligned} \frac{dx_1}{dt} &= x_1^2 x_2 - x_1 x_2^2 = x_1 x_2 (x_1 - x_2) \\ \frac{dx_2}{dt} &= -x_1^2 x_2 + x_1 x_2^2 = x_1 x_2 (x_2 - x_1). \end{aligned} \tag{5.3}$$

We can see immediately that there are three lines of equilibria—$x_2 = x_1$, $x_1 = 0$, *and* $x_2 = 0$*—the latter two of which lie on the boundary of the positive orthant. The positive compatibility classes cut perpendicular to the positive line of equilibria, from which it follows that each compatibility class has a single interior equilibrium concentration and two boundary equilibrium concentrations. Furthermore, a simple analysis of (5.3) shows us that the interior equilibrium concentration is* unstable *while the boundary equilibria are both stable (see Figure 5.2).*

This dynamical result is easy to understand in terms of the dynamical properties derived in Example 3.4.5. As ϵ *decreases through* $\epsilon = 1/6$, *the positive line of equilibria undergoes a pitchfork bifurcation, switching from stable to unstable and giving rise to two stable lines of equilibria. As* ϵ *approaches zero, these lines approach the* x_1 *and* x_2 *axes. They maintain their stability throughout the limit and thus, for* $\epsilon = 0$ *the axes are asymptotically stable*

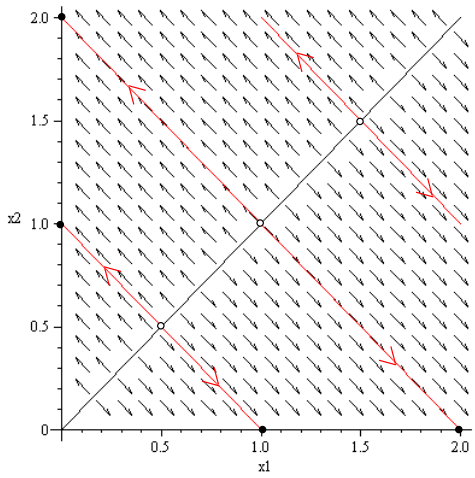

Figure 5.2: Phase portrait of the system (5.3). The positive line of equilibria, $x_2 = x_1$, is unstable relative to the compatibility classes (in red) while the boundaries $x_1 = 0$ and $x_2 = 0$ are asymptotically stable.

relative to the positive compatibility classes.

5.1.1 ω-limit Set Theorem

In this section, we present one of the most restrictive results known for trajectories of complex balanced systems not tending toward the positive equilibrium concentration [55]. We start by considering what exactly it means for a trajectory $\mathbf{x}(t)$ to "approach" or "converge to" a point $\mathbf{x}^*$ (or a set) as time goes to infinity. This is made explicit by the following concept.

Definition 5.1.1. *A point $\mathbf{x} \in \mathbb{R}^m$ is said to be an ω-**limit point** of the trajectory $\mathbf{x}(t)$ if there exists a sequence $\{t_n\}_{n=1}^{\infty}$ satisfying*

$$\lim_{n\to\infty} t_n = \infty$$

such that

$$\lim_{n\to\infty} \mathbf{x}(t_n) = \mathbf{x}.$$

Given an $\mathbf{x}_0 \in \mathbb{R}^m$*, the collection of all* ω*-limit points for the trajectory* $\mathbf{x}(t)$ *originating at* $\mathbf{x}(0) = \mathbf{x}_0$ *will be called the* ω***-limit set of*** $\mathbf{x}_0$*. This set will be denoted* $\omega(\mathbf{x}_0)$*.*

The concept of an ω-limit set is one of the foundational ones in all of dynamical systems theory (that is to say, the study of continuous variable differential equations—as studied here—*and* the study of discrete-step difference equations studied in many other applications). Since a multitude of examples can be found in virtually any textbook on dynamical systems, I omit further elaboration here. (I recommend [46] and [65].)

Since we are primarily concerned with convergence toward the boundary of the positive orthant $\partial\mathbb{R}^m_{>0}$, the following concept is particularly useful.

Definition 5.1.2. *A dynamical system with bounded trajectories is said to be* ***persistent*** *if, for every* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$*,*

$$\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing.$$

In other words, a system is persistent if no trajectory in which all variables are initially present may have any component tend toward zero (this tendency toward zero may be asymptotic or oscillatory). The concept of persistence is particularly widely used in biological modeling, where the elimination of a variable corresponds to the extinction of a species. Species which do not tend toward extinction are said to "persist". The restriction to systems with bounded trajectories is made to avoid ambiguous limiting behaviour.

In the context of chemical reaction networks, persistence means that no chemical species is exhausted as a result of the reaction system. Our primary interest in persistence is that,

since trajectories are bounded and $\mathbf{x}^*$ is the only potential strictly positive ω-limit point for complex balanced systems, Conjecture 5.1.1 holds for complex balanced systems which are persistent.

We now present a result which is of great use in the study of global stability of complex balanced networks. The proof can be found in [55].

Theorem 5.1.1 (Theorem 3.2, [55]). *Consider a complex balanced mass-action system. Then, for any $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$, the ω-limit set $\omega(\mathbf{x}_0)$ consists either of complex balanced concentrations lying on $\partial\mathbb{R}^m_{>0}$ or of a single positive point of complex balanced equilibrium.*

Theorem 5.1.1 is an important result in that it formalizes the intuition offered at the beginning of this chapter, namely, that trajectories of complex balanced systems either approach the positive complex balanced concentration or the boundary of the positive orthant. Consequently, for complex balanced systems, it is sufficient to prove that the system is persistent in order to establish Conjecture 5.1.1 holds (see also Proposition 19 of [13] and the subsequent discussion). Furthermore, the ω-limit set must consist only of complex balanced equilibrium concentrations.

5.1.2 Faces and Semi-Locking Sets

By Theorem 5.1.1 we know that trajectories of complex balanced systems may tend toward one of two things: the unique positive equilibrium concentration in the relevant compatibility class, or some set of complex balanced equilibrium concentrations on the boundary.

It is clear, consequently, that the behaviour of trajectories near the boundary of the positive orthant, $\partial\mathbb{R}^m_{>0}$, plays a very important role in determining the global stability of

$\mathbf{x}^*$ relative to its compatibility class. In particular, since trajectories of complex balanced mechanisms are bounded, it follows that persistence (see Definition 5.1.2) is a sufficient condition for the global stability of $\mathbf{x}^*$.

Another interesting question to ask if whether trajectories may tend to *anywhere* on $\partial\mathbb{R}^m_{>0}$. Can we further restrict Theorem 5.1.1 to only a subset of $\partial\mathbb{R}^m_{>0}$? And if so, what would this new set look like? Several authors have worked on this problem and, in fact, shown that ω-limit points may be restricted to an easily identifiable subset of $\partial\mathbb{R}^m_{>0}$. In this section, we summarize this work.

This line of work was begun in 2008 with the paper [5] by D. Angeli, P. DeLeenheer and E. Sontag who used Petri Net theory to prove several persistence results (which could be extended to global stability results for complex balanced systems). We, however, adopt the notation and terminology of the later paper [1] by D. Anderson since it is specific to chemical reaction networks.

In order to make the concept of persistence more manageable, we divide the boundaries of $\mathbb{R}^m_{>0}$ and $\mathsf{C}_{\mathbf{x}_0}$ into faces. For technical reasons we will only be interested in the *relative interior* of these faces, which we will define as follows. (These sets are defined similarly in [1], [5], and [13]. In [3], L_I is denoted Z_I.)

Definition 5.1.3. *Given a nonempty index set $I \subseteq \{1, 2, \ldots, m\}$, we define the sets L_I and F_I to be*

$$L_I = \{\mathbf{x} \in \mathbb{R}^m_{\geq 0} \mid x_i = 0 \text{ for } i \in I \text{ and } x_i > 0 \text{ for } i \notin I\}$$
$$F_I = \left\{\mathbf{x} \in \overline{\mathsf{C}}_{\mathbf{x}_0} \mid x_i = 0 \text{ for } i \in I \text{ and } x_i > 0 \text{ for } i \notin I\right\}$$

The set F_I can also be given as $F_I = \overline{\mathsf{C}}_{\mathbf{x}_0} \cap L_I$ or $F_I = (\mathbf{x}_0 + S) \cap L_I$.

From the vantage point of chemical kinetics, it is important to notice that $\partial\mathbb{R}^m_{>0}$ can be

directly decomposed into the relative interior of faces. That is to say, each $\mathbf{x} \in \partial\mathbb{R}^m_{>0}$ can be placed into the relative interior of exactly one face.

The following definitions are the central concept of interest in the papers [1] and [5]. Our terminology reflects [1]; in [5], semilocking sets are called siphons and locking sets are called deadlocks.

Definition 5.1.4. *Consider a nonempty set $I \subseteq \{1, 2, \ldots, m\}$. The set I is said to be a* ***semilocking set*** *if, for every reaction $\mathcal{C}_j \longrightarrow \mathcal{C}'_j$, $j = 1, \ldots, r$, which contains a species $\mathcal{A}_i$, $i \in I$, in the product complex $\mathcal{C}'_j$, there is a species $\mathcal{A}_i$, $i \in I$, in the reactant complex $\mathcal{C}_j$. A semilocking set is said to be a* ***locking set*** *if every reactant complex contains a species $\mathcal{A}_i$, $i \in I$.*

The terminology is easy to understand in light of what semilocking and locking sets imply on the dynamics of mass-action systems given by (2.4). If all of the species of a semilocking set are zero, then no species in the set may be produced under the assumption of mass-action dynamics—consequently, the semilocking set is locked into place. If every reactant complex contains an element from a semilocking, and all of those species are zero, then no reaction in the entire system may procede—the entire system is locked into place. This interpretation also gives us some hint as to how semilocking and locking sets are related to faces, since these interpretations derive from behaviour on $\partial\mathbb{R}^m_{>0}$.

Example 5.1.3. *Consider the reaction system*

$$\mathcal{A}_1 \xrightarrow{k_1} \mathcal{A}_2 \xrightarrow{k_2} \mathcal{A}_3.$$

First, let's try to find all of the semilocking sets in the system. We start by considering the product complexes and constructing our semilocking sets by working backwards.

We can see that if we want to include the complex $\mathcal{A}_3$ in our set, we must include $\mathcal{A}_2$ by the second reaction; however, to include $\mathcal{A}_2$, we must include $\mathcal{A}_1$ by the first reaction. It follows that $I_1 = \{1, 2, 3\}$ is a semilocking set.

This is not the only one, however. If we start with $\mathcal{A}_2$, we must include $\mathcal{A}_1$, but since the final reaction contains neither of these species as a product, we may stop there. It follows that $I_2 = \{1, 2\}$ is also a semilocking set.

In fact, there is one more semilocking set. It may not seem obvious, but $I_3 = \{1\}$ is also a semilocking set. Since no reaction contains $\mathcal{A}_1$ as a product, it trivially satisfies the conditions necessary to be a semilocking set.

Now consider whether any of these sets are actually locking sets. In order to be a locking set, each reactant complex must contain at least one element from a semilocking set. We can see that this is satisfied for any of our sets containing $\mathcal{A}_1$ and $\mathcal{A}_2$ so that I_1 and I_2 are locking sets but I_3 is not. Indeed, we can see from the dynamics

$$\begin{aligned}\frac{dx_1}{dt} &= -k_1 x_1 \\ \frac{dx_2}{dt} &= k_1 x_1 - k_2 x_2 \\ \frac{dx_3}{dt} &= k_2 x_2\end{aligned}$$

that if $x_1(0) = x_2(0) = x_3(0) = 0$ or $x_1(0) = x_2(0) = 0$, the entire system is locked into place, but if only $x_1(0) = 0$ then $x_1(t) = 0$ for $t \geq 0$ but $x_2(t)$ and $x_3(t)$ are free to evolve according to the second reaction.

As might be expected from our introduction to this section, we can restrict the behaviour of trajectories near $\partial\mathbb{R}^m_{>0}$ through consideration of faces and semilocking sets. The following result makes this relationship explicit. It was originally proved as Proposition 1

in [5] and later reproved as Theorem 2.5 in [1]. For completeness, we include the proof as contained in [1].

It should be noted that this result holds for all mass-action systems, not just complex balanced systems.

Theorem 5.1.2. *Consider a nonempty set $I \subseteq \{1, 2, \ldots, m\}$. If there exists a $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ such that $\omega(\mathbf{x}_0) \cap L_I \neq \varnothing$, then I is a semilocking set.*

Proof. Suppose that there exists a $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ such that $\omega(\mathbf{x}_0) \cap L_I \neq \varnothing$ but I is not a semilocking set. We will let $\mathbf{x}(t)$ denote the trajectory satisfying $\mathbf{x}(0) = \mathbf{x}_0$ and $\mathbf{y} \in \mathbb{R}^m_{\geq 0}$ denote a point satisfying $\mathbf{y} \in \omega(\mathbf{x}_0) \cap L_I$.

Since I is not a semilocking set, that implies that there is some reaction such that there is a species $\mathcal{S}_{i_0}$, $i_0 \in I$, which appears in the product complex but no species $\mathcal{S}_i$, $i \in I$, appears in the reactant complex. At the concentration $\mathbf{y}$, this reaction produces an influx of x_{i_0} while no reaction depleting x_{i_0} may proceed, so that $f_{i_0}(\mathbf{y}) > 0$. It follows by continuity that there are constants $\epsilon > 0$ and $k > 0$ such that

$$\frac{dx_{i_0}}{dt} = f_{i_0}(\mathbf{x}) > k \tag{5.4}$$

for all $\mathbf{x} \in B_\epsilon(\mathbf{y}) \cap \mathbb{R}^m_{>0}$.

Consider how $\mathbf{x}(t)$ may approach $\mathbf{y}$. Either there exists a time $\tilde{t}$ such that $\mathbf{x}(t) \in B_\epsilon(\mathbf{y}) \cap \mathbb{R}^m_{>0}$ for all $t > \tilde{t}$ or $\mathbf{x}(t)$ enters and exits $B_\epsilon(\mathbf{y}) \cap \mathbb{R}^m_{>0}$ an infinite number of times. To the first option, we notice that (5.4) implies that

$$x_{i_0}(t) > x_{i_0}(\tilde{t}) + (t - \tilde{t})k.$$

This clearly tends to infinity as t tends to infinity which violates the assumption that $\mathbf{y} \in \omega(\mathbf{x}_0)$.

It follows that $\mathbf{x}(t)$ must enter and exit $B_\epsilon(\mathbf{y}) \cap \mathbb{R}^m_{>0}$ an infinite number of times. Since the trajectory approaches $\mathbf{y}$, it follows that the trajectory must pass through the annulus $[B_\epsilon(\mathbf{y}) \setminus B_{\tilde{\epsilon}}(\mathbf{y})] \cap \mathbb{R}^m_{>0}$ an infinite number of times, where $\tilde{\epsilon}$ is any value satisfying $0 < \tilde{\epsilon} < \epsilon$. Take t_ϵ and $t_{\tilde{\epsilon}}$ to be any two times such that

$$\begin{aligned} x(t_\epsilon) &\in \partial B_\epsilon(\mathbf{y}) \cap \mathbb{R}^m_{>0} \\ x(t_{\tilde{\epsilon}}) &\in \partial B_{\tilde{\epsilon}}(\mathbf{y}) \cap \mathbb{R}^m_{>0} \\ x(t) &\in [B_\epsilon(\mathbf{y}) \setminus B_{\tilde{\epsilon}}(\mathbf{y})] \cap \mathbb{R}^m_{>0} \text{ for all } t \in (t_\epsilon, t_{\tilde{\epsilon}}). \end{aligned}$$

Since $\mathbf{f}(\mathbf{x})$ is continuous, it is bounded on the annulus so that

$$\epsilon - \tilde{\epsilon} = \|\mathbf{x}(t_\epsilon) - \mathbf{x}(t_{\tilde{\epsilon}})\| = \| \int_{t_\epsilon}^{t_{\tilde{\epsilon}}} \mathbf{f}(\mathbf{x}(s)) ds \| \leq (t_{\tilde{\epsilon}} - t_\epsilon) M$$

where M is the maximum of $\|\mathbf{f}(\mathbf{x})\|$ on the annulus. It follows that

$$t_{\tilde{\epsilon}} - t_\epsilon \geq \frac{\epsilon - \tilde{\epsilon}}{M}. \tag{5.5}$$

In other words, $\mathbf{x}(t)$ has a minimum dwell time of $(\epsilon - \tilde{\epsilon})/M$ when passing through the annulus.

Now consider the species $\mathcal{S}_{i_0}$. We have

$$\begin{aligned} x_{i_0}(t_{\tilde{\epsilon}}) &= x_{i_0}(t_\epsilon) + \int_{t_\epsilon}^{t_{\tilde{\epsilon}}} f_{i_0}(\mathbf{x}(s))ds \\ &\geq x_{i_0}(t_\epsilon) + (t_{\tilde{\epsilon}} - t_\epsilon)k \\ &\geq x_{i_0}(t_\epsilon) + \left(\frac{\epsilon - \tilde{\epsilon}}{M}\right)k \\ &\geq \left(\frac{\epsilon - \tilde{\epsilon}}{M}\right)k. \end{aligned}$$

As $\mathbf{x}(t)$ approaches $\mathbf{y}$, $\mathbf{x}(t)$ must pass through the annuluses where $\tilde{\epsilon} \to 0$; however, it is clear that

$$\tilde{\epsilon} < \left(\frac{\epsilon - \tilde{\epsilon}}{M}\right)k \leq x_{i_0}(t_{\tilde{\epsilon}})$$

for any $\tilde{\epsilon}$ sufficiently close to zero. It follows that no trajectory $\mathbf{x}(t)$ may pass through the annulus for sufficient small $\tilde{\epsilon}$. This is a contradiction, and the result follows. □

This result is particularly important for determining global stability of complex balanced systems since it is no longer necessary to prove persistence of trajectories relative to the entire boundary $\partial\mathbb{R}^m_{>0}$. Since trajectories may not tend to the relative interior of any face F_I which does not correspond to a semilocking set I, and the boundary $\partial\mathbb{R}^m_{>0}$ is completely partitioned into faces, in order to have $\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$ it is sufficient to show that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all faces F_I where I is a semilocking set.

5.1.3 Linear Functionals

An important concept in the rest of this chapter are linear functionals of the form $H(\mathbf{x}) = \langle \alpha, \mathbf{x} \rangle$ where $\alpha \in \mathbb{R}^m_{\leq 0}$ has support on the index set I. The importance of these functionals is that they gauge how "close" trajectories are to a particular set L_I.

The following result will be required to prove the original results contained in Section 5.2 and Section 5.3. In essence, it says that so long as there is a linear functional "near" every face corresponding to a semi-locking set, then the reaction network is persistent. It is proved in [54].

When we say that U is a neighbourhood of K in $\mathbb{R}^m_{\geq 0}$ we mean that U is an open covering of K restricted to $\mathbb{R}^m_{\geq 0}$.

Theorem 5.1.3. *(Theorem 3.13, [54]) Consider a general mass-action system with bounded solutions. Suppose that for every set L_I corresponding to a semi-locking set I there exists an $\alpha_I \in \mathbb{R}^m_{\leq 0}$ satisfying*

$$\begin{aligned} (\alpha_I)_i &< 0, \ \textit{for } i \in I \\ (\alpha_I)_i &= 0, \ \textit{for } i \notin I \end{aligned} \tag{5.6}$$

and the following property: for every compact subset K of L_I, there exists a neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$ such that

$$\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0 \textit{ for all } \mathbf{x} \in U. \tag{5.7}$$

Then $\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$ for all $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$.

Proof. We will let $|I|$ denote the number of elements in the set I (i.e. the number of indices i such that $x_i = 0$ for $\mathbf{x} \in L_I$).

We will prove that $\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$ by showing that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all I from $|I| = m$ to $|I| = 1$. This induction corresponds to the dimension of L_I going from 0 (the origin) to $m - 1$. Since $\partial\mathbb{R}^m_{>0}$ is completely partitioned into such sets, this is sufficient to prove the claim.

Our inductive step will consist in showing that $\omega(\mathbf{x}_0) \cap L_{\tilde{I}} \neq \varnothing$ for any semi-locking set

$\tilde{I}$ satisfying $|\tilde{I}| = k$, $1 \leq k < m$, implies $(\omega(\mathbf{x}_0) \cap \overline{L}_{\tilde{I}}) \setminus L_{\tilde{I}} \neq \varnothing$. This is sufficient to violate the inductive hypothesis that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all I such that $|I| > k$.

We take $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ to be arbitrary and fixed throughout the following induction.

Base case: Consider $|I| = m$ (i.e. $I = \mathcal{S}$) and suppose that $I = \mathcal{S}$ is a semi-locking set. We have $L_I = \{\mathbf{0}\}$ for which $K = \{\mathbf{0}\}$ is trivially a compact subset. By assumption, there exists an $\alpha_I \in \mathbb{R}^m_{<0}$ such that $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in U$ where U is some neighbourhood of K in $\mathbb{R}^m_{\geq 0}$. It follows that $\mathbf{x}(t) \in \{\mathbf{x} \in \mathbb{R}^m_{>0} \mid \langle \alpha_I, \mathbf{x} \rangle < -\delta\}$ for all $t > 0$ and some $\delta > 0$. In other words, we can make a "cut" sufficiently close to the origin such that solutions do not enter the cut out area. Consequently $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for $I = \mathcal{S}$ if I is a semi-locking set.

Since $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all I which are not semi-locking sets by Theorem 5.1.2, it follows that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for the base case $|I| = m$.

Inductive case: Consider $1 \leq k < m$ and assume that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all $|I| > k$. We will prove that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all $|I| \geq k$.

Assume $\omega(\mathbf{x}_0) \cap L_{\tilde{I}} \neq \varnothing$ for some $\tilde{I}$ such that $|\tilde{I}| = k$ and $\tilde{I}$ is a semi-locking set. Since every $\mathbf{x} \in \overline{L}_{\tilde{I}} \setminus L_{\tilde{I}}$ satisfies $\mathbf{x} \in L_I$ for some I such that $|I| > k$, the inductive hypothesis implies $(\omega(\mathbf{x}_0) \cap \overline{L}_{\tilde{I}}) \setminus L_{\tilde{I}} = \varnothing$, which is equivalent to $(\omega(\mathbf{x}_0) \cap \overline{L}_{\tilde{I}}) \subset L_{\tilde{I}}$. In order to prove the inductive step, we will show that assuming $\omega(\mathbf{x}_0) \cap L_{\tilde{I}} \neq \varnothing$ violates $(\omega(\mathbf{x}_0) \cap \overline{L}_{\tilde{I}}) \subset L_{\tilde{I}}$.

Consider the set $K = \omega(\mathbf{x}_0) \cap \overline{L}_{\tilde{I}}$. Since trajectories are bounded by assumption, $\omega(\mathbf{x}_0)$ is bounded, and consequently K is a compact set. By the inductive hypothesis, this is a subset of $L_{\tilde{I}}$ so that $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in U$ where U is some neighbourhood of K in $\mathbb{R}^m_{\geq 0}$.

Consider the linear functional $H(\mathbf{x}) = \langle \alpha_I, \mathbf{x} \rangle$. By (5.6) and (5.7), $H(\mathbf{x})$ satisfies:

1. $H(\mathbf{x}) = 0$ if and only if $\mathbf{x} \in \overline{L}_{\tilde{I}}$,

2. $H(\mathbf{x}) < 0$ for $\mathbf{x} \in \mathbb{R}^m_{>0}$, and

3. $\frac{d}{dt}H(\mathbf{x}(t)) = \langle \alpha_I, \mathbf{f}(\mathbf{x}(t))\rangle \leq 0$ for all $t > 0$ such that $\mathbf{x}(t) \in U$.

Now consider an arbitrary $\mathbf{y} \in K$. Since $\mathbf{y} \in \omega(\mathbf{x}_0)$, U is a neighbourhood of $\mathbf{y}$, and $H(\mathbf{x})$ is continuous, we can select a sequence $\{t_k\}$ ($\lim_{k\to\infty} t_k = \infty$) such that $\{\mathbf{x}(t_k)\} \subseteq U$, $\lim_{k\to\infty} \mathbf{x}(t_k) = \mathbf{y}$, and $\lim_{k\to\infty} H(\mathbf{x}(t_k)) = H(\mathbf{y}) = 0$.

By Property 3 of $H(\mathbf{x}(t))$ given above, $H(\mathbf{x}(t))$ may not increase while remaining in U and, consequently, in order to approach $\mathbf{y} \in L_{\tilde{I}}$, $\mathbf{x}(t)$ must enter and exit U an infinite number of times. Since U is relatively open in $\mathbb{R}^m_{\geq 0}$ and $\mathbf{x}(t) \in \mathbb{R}^m_{>0}$ for all $t \geq 0$ by Proposition 2.4.1, we can find a sequence $\left\{\tilde{t}_k\right\}$ corresponding to the entry points $\left\{\mathbf{x}(\tilde{t}_k)\right\} \subset (\mathbb{R}^m_{\geq 0} \setminus U)$ (i.e. $\mathbf{x}(t) \in U$ for $t \in (\tilde{t}_k, t_k)$). Because trajectories are bounded and $\mathbb{R}_{\geq 0} \setminus U$ is closed, the sequence $\left\{\mathbf{x}(\tilde{t}_k)\right\}$ has a convergent subsequence on $\mathbb{R}_{\geq 0} \setminus U$. We will denote this sequence $\left\{\mathbf{x}(\tilde{t}_{k_i})\right\}$ and let $\tilde{\mathbf{y}}$ be the point such that $\lim_{i\to\infty} \mathbf{x}(\tilde{t}_{k_i}) = \tilde{\mathbf{y}} \in \omega(\mathbf{x}_0)$. Since $H(\mathbf{x}(t))$ may not increase for $t \in (\tilde{t}_k, t_k)$ and is bounded above by zero, we have $0 > H(\mathbf{x}(\tilde{t}_k)) \geq H(\mathbf{x}(t_k))$. Since $\lim_{k\to\infty} H(\mathbf{x}(t_k)) = 0$, it follows that $\lim_{k\to\infty} H(\mathbf{x}(\tilde{t}_k)) = H(\tilde{\mathbf{y}}) = 0$, so that $\tilde{\mathbf{y}} \in \overline{L}_{\tilde{I}}$ by Property 1 of $H(\mathbf{x})$.

In total we have that $\tilde{\mathbf{y}} \in \omega(\mathbf{x}_0) \cap \overline{L}_{\tilde{I}} \cap (\mathbb{R}_{\geq 0} \setminus U) = K \cap (\mathbb{R}_{\geq 0} \setminus U)$. We recall, however, that U was a neighbourhood of K in $\mathbb{R}^m_{\geq 0}$ so that $K \cap (\mathbb{R}_{\geq 0} \setminus U) = \varnothing$. It follows that our original assumption must have been in error, so that $\omega(\mathbf{x}_0) \cap L_{\tilde{I}} = \varnothing$ for all semi-locking sets $\tilde{I}$ satisfying $|\tilde{I}| = k$.

Since $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all I which are not semi-locking sets by Theorem 5.1.2, it follows that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ if $|I| = k$, and our inductive step is shown.

Since $\partial\mathbb{R}^m_{>0}$ can be completely partitioned into sets L_I, $1 \leq |I| \leq m$, it follows that

$$\omega(\mathbf{x}_0) \cap \left[\bigcup_{1 \leq |I| \leq m} L_I \right] = \omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$$

and, since $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ was chosen arbitrarily, the result follows.

□

It remains to find the vector $\alpha \in \mathbb{R}^m_{\leq 0}$ used in the functional $H(\mathbf{x})$. An important foundational result for finding these linear functionals in Section 5.2 and Section 5.3 is the following classical result. We state two versions of the lemma as their application will be subtly different in the two sections. (We prove only the first formulation. The proof can be easily modified to capture the second formulation.)

Lemma 5.1.1 (Farkas' Lemma (1), [23])**.** *Consider $A \in \mathbb{R}^{m \times n}$. Then exactly one of the following two conditions is true:*

1. *There exists a $\mathbf{x} \in \mathbb{R}^n_{\geq 0}$, $\mathbf{x} \neq \mathbf{0}$, such that $A\mathbf{x} \leq \mathbf{0}$.*
2. *There exists a $\mathbf{y} \in \mathbb{R}^m_{>0}$ such that $A^T\mathbf{y} > \mathbf{0}$.*

Lemma 5.1.2 (Farkas' Lemma (2), [23])**.** *Consider $A \in \mathbb{R}^{m \times n}$. Then exactly one of the following two conditions is true:*

1. *There exists $\mathbf{x} \in \mathbb{R}^n_{\geq 0}$, $\mathbf{x} \notin \ker(A)$, such that $A\mathbf{x} \leq \mathbf{0}$.*
2. *There exists $\mathbf{y} \in \mathbb{R}^m_{>0}$ such that $A^T\mathbf{y} \geq \mathbf{0}$.*

Proof of version 1. Suppose both 1 and 2 are satisfied simultaneously. This implies that there are $\mathbf{x} \in \mathbb{R}^n_{\geq 0}$ and $\mathbf{y} \in \mathbb{R}^m_{>0}$ such that

$$0 < (A^T\mathbf{y})^T\mathbf{x} = \mathbf{y}^T(A\mathbf{x}) \leq 0$$

where the first inequality follows from $A^T\mathbf{y} > \mathbf{0}$ and the domain restriction on $\mathbf{x}$, and the second inequality follows from $A\mathbf{x} \leq \mathbf{0}$ and the domain restriction on $\mathbf{y}$. It follows that 1 and 2 may not be simultaneously satisfied.

Now suppose 1 is not satisfied. We will show that 2 is necessarily satisfied. We define A_i to be the i^{th} column of A and the closed and convex cone $C(A)$ to be

$$C(A) = \left\{ \mathbf{v} \in \mathbb{R}^m \;\middle|\; \mathbf{v} = \sum_{i=1}^{n} x_i A_i, x_i \geq 0, i = 1, \ldots, n \right\}.$$

Since 1 is not satisfied, it follows that the cones $C(A)$ and $\mathbb{R}^m_{\leq 0}$ intersect at only the origin. By the Hyperplane Separation Theorem, it follows that there exists a $\mathbf{y} \in \mathbb{R}^m$ such that, for every $\mathbf{v} \in C(A) \setminus \{\mathbf{0}\}$ and $\mathbf{c} \in \mathbb{R}^m_{\leq 0} \setminus \{\mathbf{0}\}$,

$$\mathbf{y}^T\mathbf{c} < 0 < \mathbf{y}^T\mathbf{v}.$$

Since the first inequality holds for all $\mathbf{c} \in \mathbb{R}^m_{\leq 0} \setminus \{\mathbf{0}\}$, it follows that $y_i > 0$ for all $i = 1, \ldots, m$, and consequently $\mathbf{y} \in \mathbb{R}^m_{>0}$. Similarly, since the second inequality applies for all $\mathbf{v} \in C(A) \setminus \{\mathbf{0}\}$, we have that for every $\mathbf{x} \in \mathbb{R}^m_{\geq 0} \setminus \{\mathbf{0}\}$,

$$0 < \mathbf{y}^T(A\mathbf{x}) = (A^T\mathbf{y})^T\mathbf{x}.$$

It follows that $(A^T\mathbf{y})_i > 0$ for all $i = 1, \ldots, n$ so that $A^T\mathbf{y} > \mathbf{0}$. Consequently, 2 is satisfied

if 1 is not.

It follows by the contrapositive that if 2 is not satisfied then 1 is satisfied. It follows that at least one of the two conditions holds; however, since both may not be satisfied simultaneous, we have that exactly one of the two propositions holds, and we are done. □

5.2 Weakly Dynamically Non-Emptiable Sets

In the paper [5], D. Angeli, P. DeLeenheer and E. Sontag consider the persistence of chemical reaction networks (see Definition 5.1.2). In this section, we summarize some of their main results. We introduce their notion of dynamically non-emptiable semi-locking sets and extend it by modifying the feasibility cone and introducing a kernel condition [54]. We also reformulate the conditions required for inclusion in the feasibility and criticality cones as matrix conditions which will allow us to prove the main original result of this section (Theorem 5.2.6).

5.2.1 Background

Many of the concepts required in previous sections and chapters will be required in this section. In particular, the notion of a conservative chemical reaction network (Definition 2.4.4), a face of the positive orthant (Definition 5.1.3), and a semi-locking set (Definition 5.1.4) will be required.

In this section, we will require an alternative formulation of mass-action kinetics. Just as (4.18) brought the complex-oriented indexing of (2.2) and (2.4) into the framework of linear algebra, the following formulation brings the reaction-oriented indexing of (2.1) and

(2.3) into the framework of linear algebra.

We define the matrix $\Gamma \in \mathbb{Z}^{m\times r}$ with entries

$$[\Gamma]_{ji} = z'_{ij} - z_{ij} \tag{5.8}$$

for $i = 1,\ldots,r$ and $j = 1,\ldots,m$ (notice the reversal of indices). We define the *reaction vector* $R(\mathbf{x}) \in \mathbb{R}^r_{\geq 0}$ according to

$$R_i(\mathbf{x}) = k_i \prod_{j=1}^{m} x_j^{z_{ij}} \tag{5.9}$$

for $i = 1,\ldots,r$. The terms $R_i(\mathbf{x})$ correspond to the *reaction rates* of chemical reactions under the assumption of mass-action kinetics.

Since $[\Gamma]_{ji}$ represents the net stoichiometric change in the j^{th} species as a result of the i^{th} reaction and $R_i(\mathbf{x})$ represents the rate of occurrence of the i^{th} reaction, it follows that $[\Gamma]_{ji}R_i(\mathbf{x})$ is the rate of change of the j^{th} species as a result of the i^{th} reaction. It follows that (2.1) is governed by the system of differential equations

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) = \Gamma R(\mathbf{x}). \tag{5.10}$$

We will also need the following concept, which is related to the concept of a *conservation vector*. (These are called *P-semiflows* in [5]. We introduce the term *semi-conservation* to emphasize the connection with chemical kinetics.)

Definition 5.2.1. *Consider a nonempty set $I \subseteq \{1,2,\ldots,m\}$. A chemical reaction network*

is said to be ***conservative with respect to*** I *if there exists a* $\mathbf{c} \in \mathbb{R}^m_{\geq 0}$ *satisfying*

$$\begin{aligned} c_i &> 0, \qquad i \in I \\ c_i &= 0, \qquad i \notin I \end{aligned} \tag{5.11}$$

so that

$$\mathbf{c}^T \Gamma = \mathbf{0}^T. \tag{5.12}$$

We will call any vector $\mathbf{c} \in \mathbb{R}^m_{\geq 0}$ *satisfying (5.11) and (5.12) a* ***semi-conservation vector****.*

A key consequence of (5.12) is that multiplying on the right by $R(\mathbf{x})$ gives

$$\mathbf{c}^T \Gamma R(\mathbf{x}) = \mathbf{c}^T \frac{d\mathbf{x}}{dt} = 0 \quad \Longrightarrow \quad \mathbf{c}^T \mathbf{x}(t) = \mathbf{c}^T \mathbf{x}_0 > 0 \text{ for } \mathbf{x}_0 \in \mathbb{R}^m_{>0}. \tag{5.13}$$

In other words, the species indexed by the set I are conserved. It follows that $L_{I_0} \cap \omega(\mathbf{x}_0) \neq \varnothing$ for any subset of the boundary $L_{I_0} \subseteq \partial \mathbb{R}^m_{>0}$ where $I_0 \subseteq \mathcal{S}$ contains the support of a semi-conservative vector (since (5.13) contradicts the requirement of $L_{I_0} \cap \omega(\mathbf{x}_0) \neq \varnothing$ that $\mathbf{c}^T \mathbf{x}(t_n) \to 0$ along a subsequence of times if $I \subseteq I_0$).

In [5], the authors prove the following result. It should be noted that this applies to networks with more general kinetics than mass-action, although we refer the reader to the relevant paper for details.

Theorem 5.2.1 (Theorem 2, [5])**.** *Consider a chemical reaction network satisfying the following assumptions:*

1. *the system is conservative;*

2. *every semi-locking set contains the support of a semi-conservation vector.*

Then the system is persistent.

5.2.2 Dynamically Non-Emptiable Sets

The applicability of Theorem 5.2.1 is limited by the relative scarcity of reaction networks satisfying the condition that every semi-locking set contain the support of a semi-conservation vector. Such semi-locking sets are classified according to the following.

Definition 5.2.2. *A semi-locking set I is called **critical** if it does not contain the support of a semi-conservation vector.*

In Section 9 of [5], the authors introduce the concept of *dynamical non-emptiability* for critical semi-locking sets. This notion is dependent on the three foundational concepts: a special partial ordering on reaction rates, a structure called the *feasibility cone*, and a structure called the *criticality cone*.

Definition 5.2.3. *Consider the nonempty index set $I \subseteq \{1, 2, \ldots, m\}$. For $\mathcal{R}_i, \mathcal{R}_j \in \mathcal{R}$, we will say that $\mathcal{R}_i \preccurlyeq_I \mathcal{R}_j$ if $z_{ik} \geq z_{jk}$ for all $k \in I$ and the inequality is strict for at least one $k \in I$.*

Intuitively, the partial ordering condition given in Definition 5.2.3 gives us an estimate on the magnitudes of the reaction terms $R_i(\mathbf{x})$ near a set L_I. This is made explicit by the following result.

Lemma 5.2.1 (Lemma 4, [5])**.** *Consider a mass-action system and let $I \subseteq \{1, 2, \ldots, m\}$ be a semi-locking set. Suppose that $\mathcal{R}_i \preccurlyeq_I \mathcal{R}_j$. Then, for every $\epsilon > 0$, and each compact subset K of L_I, there exists a neighbourhood U of K in $\mathbb{R}^m_{>0}$ such that $R_i(\mathbf{x}) \leq \epsilon R_j(\mathbf{x})$ for all $\mathbf{x} \in U$.*

The concept of *dynamical non-emptiability* depends on two cones, the *feasibility cone* and *criticality cone*, which are defined as follows.

Definition 5.2.4. *The* ***feasibility cone*** *is defined to be*

$$\mathcal{F}_\epsilon(I) = \{\mathbf{v} \in \mathbb{R}^r_{\geq 0} \mid v_i \leq \epsilon v_j,\ \forall\ \mathcal{R}_i, \mathcal{R}_j \in \mathcal{R} \text{ such that } \mathcal{R}_i \preccurlyeq_I \mathcal{R}_j\}$$

where $\epsilon > 0$.

Definition 5.2.5. *The* ***criticality cone*** *is defined to be*

$$\mathcal{C}(I) = \{\mathbf{v} \in \mathbb{R}^r_{\geq 0} \mid [\Gamma \mathbf{v}]_k \leq 0,\ \forall\ k \in I\}\,.$$

We can now define *dynamical non-emptiability*, which is one of the major concepts introduced in [5].

Definition 5.2.6. *A critical semi-locking set is said to be* ***dynamically non-emptiable*** *if there exists an* $\epsilon > 0$ *such that*

$$\mathcal{F}_\epsilon(I) \cap \mathcal{C}(I) = \{\mathbf{0}\}\,.$$

The following is the main result of Section 9 of [5]. We will extend this result in Section 5.2.5. (Two sets I_1 and I_2 are *nested* if $I_1 \subset I_2$ or $I_2 \subset I_1$.)

Theorem 5.2.2 (Theorem 4, [5])**.** *Consider a conservative mass-action system satisfying the following assumptions:*

1. *all of its critical semi-locking sets are dynamically non-emptiable;*

2. there are no nested distinct critical locking sets.

Then the system is persistent.

5.2.3 Weakly Dynamically Non-Emptiable Sets

In this section, we extend the notion of dynamically non-emptiable semi-locking sets to weakly dynamically non-emptiable semi-locking sets. The definitions and results contained here can be found in [37].

Our notion of dynamical non-emptiability depends on the selection of a set $J \subseteq \mathcal{R}_I$ where

$$\mathcal{R}_I = \{(i,j) \in \{1,\dots,r\} \times \{1,\dots,r\} \mid \mathcal{R}_i \preccurlyeq_I \mathcal{R}_j\}. \tag{5.14}$$

The key modification here is that we do not necessarily need to consider *all* pairs (i,j) satisfying $\mathcal{R}_i \preccurlyeq_I \mathcal{R}_j$; often it is sufficient to consider a strict subset of these pairs of reactions. Through examples in Section 5.2.5 we will see that this modification allow us to encompass more chemical kinetics systems than we would be able to otherwise.

We will need the following two concepts.

Definition 5.2.7. *We define the* ***feasibility cone relative to*** J *to be*

$$\mathcal{F}_\epsilon(J) = \{\mathbf{v} \in \mathbb{R}^r_{\geq 0} \mid v_i \leq \epsilon v_j, \text{ for all } (i,j) \in J\}$$

where $\epsilon > 0$.

Definition 5.2.8. *We define the* ***kernel of*** I ***and*** J *to be*

$$\ker(I, J, \epsilon) = \{\mathbf{v} \in \mathbb{R}^r_{\geq 0} \mid [\Gamma \mathbf{v}]_k = 0, \text{ for all } k \in I \text{ and } v_i = \epsilon v_j, \text{ for all } (i,j) \in J\}$$

where $\epsilon > 0$.

The following notion of dynamical non-emptiability is our own. It is more general than that contained in [5] in that it makes use of the freedom to select an appropriate $J \subseteq \mathcal{R}_I$ and broadens the inclusion principle to a kernel condition. (It is clear that the standard notion of dynamical non-emptiability is included as a special case of the following by taking $J = \mathcal{R}_I$ and recognizing that $\{\mathbf{0}\} \subseteq \ker(I, J, \epsilon)$.)

Definition 5.2.9. *A critical semi-locking set* I *is said to be* ***weakly dynamically non-emptiable*** *if there exists an* $\epsilon > 0$ *and a* J *satisfying (5.14) such that*

$$\mathcal{C}(I) \cap \mathcal{F}_\epsilon(J) \subseteq \ker(I, J, \epsilon).$$

In order to relate the above conditions to Farkas' Lemma (Theorem 5.1.1) we restate them as matrix conditions. We let $n_I = |I|$ and $n_J = |J|$. We define $\Gamma_I \in \mathbb{R}^{n_I \times r}$ to be the matrix Γ with the rows $\Gamma_{k\cdot}$, $k \notin I$, removed. We define $\Gamma_J \in \mathbb{R}^{n_J \times r}$ to be the matrix where each row corresponds to a specific condition $\mathcal{R}_i \preccurlyeq_I \mathcal{R}_j$, $(i,j) \in J$, so that in that row there is a one in the i^{th} column, a $-\epsilon$ in the j^{th} column, and zeroes elsewhere. Lastly, we define $\tilde{\Gamma} \in \mathbb{R}^{(n_I + n_J) \times r}$ to be

$$\tilde{\Gamma} = \begin{bmatrix} \Gamma_I \\ \Gamma_J \end{bmatrix}.$$

The following result can be trivially seen.

Lemma 5.2.2. *The condition* $\mathcal{C}(I) \cap \mathcal{F}_\epsilon(J) \subseteq ker(I, J, \epsilon)$ *is satisfied if and only if*

$$\tilde{\Gamma}\mathbf{v} \leq \mathbf{0} \text{ for } \mathbf{v} \in \mathbb{R}^r_{\geq 0} \quad \Longrightarrow \quad \mathbf{v} \in \ker(\tilde{\Gamma}).$$

5.2.4 Connection to Facets and Non-Critical Semi-Locking Sets

In general, determining whether a semi-locking set I is weakly dynamically non-emptiable can be tedious. To this end, in this section we show that there are classes of semi-locking sets which are necessarily weakly dynamically nonemptiable: namely, semi-locking sets corresponding to facets (i.e. sets F_I of dimension $s-1$) of a weakly reversible mechanism, and semi-locking sets which are non-critical.

Facets are the central topic of consideration in [3], where the authors prove the following result.

Theorem 5.2.3 (Theorem 3.4, [3])**.** *Consider a weakly reversible mass-action system with bounded trajectories. Suppose that every semi-locking set* I *is such that* F_I *is a facet or empty. Then the system is persistent.*

The authors also connect the notion of a facet with the traditional notion of dynamical non-emptiability (Corollary 3.5, [3]). Their result, however, overstates the implications of F_I being a facet. It can be shown that semi-locking sets I corresponding to facets F_I may fail to be dynamically non-emptiable if there is a reaction $\mathcal{R}_i$ such that: (1) $\mathcal{R}_i \not\leftarrow_I \mathcal{R}_j$ for all $\mathcal{R}_j$ in the same linkage class (a connected portion of the reaction graph); and (2) $\mathcal{R}_i$ produces no stoichiometric change in the species in I. (See Example 1 of Section 5.2.5.)

We now generalize this result by showing that there is no such exemption for weak dynamical non-emptiability.

Theorem 5.2.4 (Theorem 3.8, [37]). *Consider a weakly reversible mass-action system with a semi-locking set $I \subseteq \{1, \ldots, m\}$. If F_I is a facet then I is weakly dynamically non-emptiable.*

Proof. We will follow closely the proofs of Theorem 3.2 and Corollary 3.5 contained in [3].

In their proof for Theorem 3.2, the authors show that there exist $z_j > 0$, $j \in I$, and $\gamma_i \in \mathbb{R}$, $i \in \{1, \ldots, r\}$, such that

$$\gamma_i z_j = \beta_{ij} - \alpha_{ij} \tag{5.15}$$

for all $j \in I$ and $i \in \{1, \ldots, r\}$. In other words, relative to the support of I, every reaction vector (the columns of Γ) lies within the span of a single vector which is strictly positive on the support of I. We will let $\mathbf{z} \in \mathbb{R}^{n_I}_{>0}$ denote the vector with the elements z_j, $j \in I$, indexed in order.

It follows immediately from (5.15) that every reaction in the system contributes either: (1) a net gain to all species in I, (2) a net loss to all species in I, or (3) no stoichiometric change to species in I. We can also divide the reactions according to the linkage classes $\mathcal{L}_k$, $k = 1, \ldots, \ell$. By weak reversibility each linkage class is strongly connected. We will let $R^{(k)}$ denote the reactions in the k^{th} linkage class, and $R^{(k)}_+$, $R^{(k)}_-$, and $R^{(k)}_0$ denote respectively the reactions in the k^{th} linkage class which contribute a net gain, a net loss, or no change to all species in I. We notice that $\gamma_i > 0$ for $i \in R^{(k)}_+$, $\gamma_i < 0$ for $i \in R^{(k)}_-$, and $\gamma_i = 0$ for $i \in R^{(k)}_0$. Combined with (5.15), this division gives

$$\Gamma_I \mathbf{v} = \mathbf{z} \left[\sum_{k=1}^{\ell} \left(\sum_{i \in R^{(k)}_+} \gamma_i v_i - \sum_{j \in R^{(k)}_-} |\gamma_j| v_j \right) \right]. \tag{5.16}$$

We now proceed to construct our set $J \subseteq \mathcal{R}_I$ according to (5.14). Since the system

is weakly reversible, it follows that the product complex of every reaction $\mathcal{R}_i$ is itself a reactant complex for some other reaction (which we will denote $\mathcal{R}_{i'}$) in the k^{th} linkage class. Since reactions may only produce simultaneous gain or loss to the species in I, it follows that: (1) $\mathcal{R}_{i'} \preccurlyeq_I \mathcal{R}_i$ if $i \in R_+^{(k)}$, (2) $\mathcal{R}_i \preccurlyeq_I \mathcal{R}_{i'}$ if $i \in R_-^{(k)}$, and (3) $\mathcal{R}_{i'} \not\preccurlyeq_I \mathcal{R}_i$ and $\mathcal{R}_i \not\preccurlyeq_I \mathcal{R}_{i'}$ if $i \in R_0^{(k)}$. (Notice here that $\mathcal{R}_{i'} \not\preccurlyeq_I \mathcal{R}_i$ and $\mathcal{R}_i \not\preccurlyeq_I \mathcal{R}_{i'}$ for $i \in R^{(k)}$ implies $\alpha_{ij} = \alpha_{i'j}$ for all $j \in I$, although this does not hold for general systems.)

Since the ordering relationship is transitive and can be extended throughout each linkage class by weak reversibility, it follows that the set of reactions corresponding to each linkage class $\mathcal{L}_k$ either: (1) contributes no stoichiometric change to the system (i.e. $i \in R_0^{(k)}$ for all reactions $\mathcal{R}_i$ corresponding to reactions in $\mathcal{L}_k$), or (2) contains a reaction $\mathcal{R}_{i_k}$, $i_k \in R_+^{(k)}$, such that $\mathcal{R}_j \preccurlyeq_I \mathcal{R}_{i_k}$ for all $j \in R_-^{(k)}$. We will ignore linkage classes included in case (1) since they do not affect (5.16).

We define the set

$$J = \bigcup_{\substack{k=1 \\ j \in R_-^{(k)}}}^{\ell} (j, i_k).$$

Now assume that $\Gamma_J \mathbf{v} \leq 0$. This implies that we have

$$\begin{aligned} \Gamma_I \mathbf{v} &= \mathbf{z}\left[\sum_{k=1}^{\ell}\left(\sum_{i \in R_+^{(k)} \setminus i_k} \gamma_i v_i + \gamma_{i_k} v_{i_k} - \sum_{j \in R_-^{(k)}} |\gamma_j| v_j\right)\right] \\ &\geq \mathbf{z}\left[\sum_{k=1}^{\ell}\left(\sum_{i \in R_+^{(k)} \setminus i_k} \gamma_i v_i + \left(\gamma_{i_k} - \epsilon \sum_{j \in R_-^{(k)}} |\gamma_j|\right) v_{i_k}\right)\right]. \end{aligned}$$

Regardless of the values of γ_j, $j \in R_-^{(k)}$, and $\gamma_{i_k} > 0$ for $k = 1, \ldots, \ell$, we can pick an $\epsilon > 0$ sufficient small so that $\Gamma_I \mathbf{v} \geq \mathbf{0}$ for every $\mathbf{v} \in \mathbb{R}^r_{\geq 0}$. In order to satisfy $\Gamma_I \mathbf{v} \leq \mathbf{0}$ for $\mathbf{v} \in \mathbb{R}^r_{\geq 0}$, therefore, we require $v_i = 0$ for all $i \in R_+^{(k)}$ and $i \in R_-^{(k)}$, $k = 1, \ldots, \ell$. We notice that $v_i > 0$ is

permitted for $i \in R_0^{(k)}$; however, neither Γ_I nor Γ_J contain nonzero entries in their columns corresponding to the elements in $i \in R_0^{(k)}$. It follows that $\tilde{\Gamma}\mathbf{v} \leq 0$ for $\mathbf{v} \in \mathbb{R}_{\geq 0}$ entails $\mathbf{v} \in \ker(\tilde{\Gamma})$. Since this is a sufficient condition for the weak dynamical non-emptiability of I by Lemma 5.2.2, we are done. □

In [5], the authors divide semi-locking sets according to whether they are critical or not. They first handle the case of non-critical semi-locking sets which culminates in Theorem 5.2.1. It is only in the discussion of critical semi-locking sets that they introduce the further condition of dynamical nonemptiability. Here we simplify this discussion by showing that every non-critical semi-locking set is weakly dynamically non-emptiable and therefore falls within the scope of the discussion in Section 5.2.5.

Theorem 5.2.5 (Theorem 3.9, [37])**.** *Consider a semi-locking set $I \subseteq \{1, \ldots, m\}$. If I is non-critical then it is weakly dynamically non-emptiable.*

Proof. Suppose a semi-locking set $I \subseteq \{1, \ldots, m\}$ is non-critical. This means that I corresponds to the support of a semi-conservation vector so that there exists a $\mathbf{c} \in \mathbb{R}_{\geq 0}^m$ satisfying

$$\begin{aligned} c_i &> 0, \qquad i \in I \\ c_i &= 0, \qquad i \notin I \end{aligned}$$

such that

$$\mathbf{c}^T \Gamma = \mathbf{0}^T. \tag{5.17}$$

It follows from (5.17) that there exists a $\mathbf{y} \in \mathbb{R}_{>0}^{n_I}$ such that

$$\mathbf{y}^T \Gamma_I = \mathbf{0}^T.$$

Since this implies condition 2 of Farkas' Lemma (Lemma 5.1.2) is satisfied, it follows that condition 1 must necessarily be violated. It follows that any $\mathbf{v} \in \mathbb{R}^r_{\geq 0}$ satisfying $\Gamma_I \mathbf{v} \leq 0$ must be such that $\mathbf{v} \in \ker(\Gamma_I)$. By Lemma 5.2.2, however, this is the condition for weak dynamical nonemptiability taking $J = \varnothing$ which is sufficient to prove the result. □

5.2.5 Persistence

We are now prepared to present the main result of this section. The following is a generalization of Theorem 5.2.2 and includes Theorem 5.2.1 for mass-action kinetics by Theorem 5.2.5.

Theorem 5.2.6 (Theorem 3.10, [37])**.** *Consider a mass-action system with bounded solutions. Suppose that every semi-locking set is weakly dynamically non-emptiable. Then the system is persistent.*

Proof. We know by Theorem 5.1.3 that a system with bounded solutions is persistent if, for every semi-locking set I, there is an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying

$$\alpha_i < 0, \text{ for } i \in I$$
$$\alpha_i = 0, \text{ for } i \notin I$$

so that, for every compact subset K of L_I, there exists a neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$ such that $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in U$.

By assumption, every critical semi-locking set is weakly dynamically non-emptiable, which means that there exists an $\epsilon > 0$ and a $J \subseteq \mathcal{R}_I$ such that $\mathcal{C}(I) \cap \mathcal{F}_\epsilon(J) \subseteq \ker(I, J, \epsilon)$.

By Lemma 5.2.2, this implies that

$$\tilde{\Gamma}\mathbf{v} \leq \mathbf{0}, \text{ for } \mathbf{v} \in \mathbb{R}^r_{\geq 0} \quad \Longrightarrow \quad \mathbf{v} \in \ker(\tilde{\Gamma}).$$

It follows that condition 1 of Lemma 5.1.2 is not satisfied. Consequently, in order to satisfy condition 2, there must exist a $\mathbf{c} \in \mathbb{R}^{n_I+n_J}_{>0}$ such that $\mathbf{c}^T\tilde{\Gamma} \geq \mathbf{0}^T$.

We partition $\mathbf{c} \in \mathbb{R}^{n_I+n_J}_{>0}$ so that

$$\mathbf{c} = \begin{bmatrix} \mathbf{c}_I \\ \\ \mathbf{c}_J \end{bmatrix}$$

where $\mathbf{c}_I \in \mathbb{R}^{n_I}_{>0}$ and $\mathbf{c}_J \in \mathbb{R}^{n_J}_{>0}$. From this it follows that

$$\mathbf{c}^T\tilde{\Gamma} = \mathbf{c}_I^T\Gamma_I + \mathbf{c}_J^T\Gamma_J \geq \mathbf{0}^T. \tag{5.18}$$

Multiplying through the right-hand side of (5.18) by $R(\mathbf{x})$, we have

$$\mathbf{c}_I^T\Gamma_I R(\mathbf{x}) + \mathbf{c}_J^T\Gamma_J R(\mathbf{x}) = -\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle + \mathbf{c}_J^T\Gamma_J R(\mathbf{x}) \geq 0 \tag{5.19}$$

where $\alpha \in \mathbb{R}^m_{\leq 0}$ is the vector $-\mathbf{c}_I$ extended over the support I and has zeroes elsewhere. Clearly α satisfies

$$\begin{aligned} \alpha_i &< 0 \qquad \text{for } i \in I \\ \alpha_i &= 0 \qquad \text{for } i \notin I. \end{aligned}$$

By Lemma 5.2.1, for every compact subset K of L_I and every $\epsilon > 0$, there exists a neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$ such that $\Gamma_J R(\mathbf{x}) \leq \mathbf{0}$. It follows from (5.19) that

$$\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq \mathbf{c}_J^T\Gamma_J R(\mathbf{x}) \leq 0$$

for all $\mathbf{x} \in U$.

Since this holds for every semi-locking set I by assumption, it follows by Theorem 5.1.3 that the system is persistent. □

There are several points worth emphasizing about Theorem 5.2.6 as it contrasts with Theorem 5.2.2. In our result the requirement that the system be conservative has been replaced by the more general assumption that solutions are bounded, and we do not require the assumption that there are no nested critical locking sets. Since a system being conservative implies solutions are bounded, the first is not a significant change; however, we have opened the result to non-conservative systems for which solutions can be bounded by another method, as is the case with complex balanced systems (see Section 3.3).

We have removed the distinction between critical and non-critical semi-locking sets. We do not need to make this distinction since every non-critical semi-locking set is weakly dynamically nonemptiable by Theorem 5.2.5 and therefore trivially included in Theorem 5.2.6.

For complex balanced systems, we know that persistence is a sufficient condition for global stability by Lemma 5.1.1. Consequently, we can use Theorem 5.2.6 to extend the scope of the systems satisfying the global attractor conjecture.

First, however, we need the following result.

Lemma 5.2.3 (Lemma 3.12, [37])**.** *Consider a chemical reaction network. Consider a set* $I \subseteq \{1, \ldots, m\}$ *and suppose that* $\tilde{F}_I \neq \varnothing$ *for some* $\tilde{\mathbf{x}}_0 \in \mathbb{R}^m_{>0}$*. Then, for every* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$*, either* $dim(F_I) = dim(\tilde{F}_I)$ *or* $F_I = \varnothing$*. Furthermore, for every* $\mathbf{x} \in L_I$*, there exists* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ *such that* $\mathbf{x} \in F_I$*.*

Proof. Consider the set $\tilde{L}_I = \{\mathbf{x} \in \mathbb{R} \mid x_i = 0 \text{ if } i \in I\}$. It is clear that L_I is relatively interior to $\tilde{L}_I$, i.e. $\forall\ \mathbf{x} \in L_I$, $\exists\ \epsilon > 0$ such that $B_\epsilon(\mathbf{x}) \cap \tilde{L}_I \subseteq L_I$. ($B_\epsilon(\mathbf{x})$ is the standard Euclidean ball of radius ϵ centered at $\mathbf{x}$.) Now consider the affine space $(\mathbf{x}_0 + S) \cap \tilde{L}_I$ and suppose $F_I = (\mathbf{x}_0 + S) \cap L_I \neq \varnothing$. Then, $\forall\ \mathbf{x} \in F_I$, $\exists\ \epsilon > 0$ such that $B_\epsilon(\mathbf{x}) \cap [(\mathbf{x}_0 + S) \cap \tilde{L}_I] = (\mathbf{x}_0 + S) \cap [B_\epsilon(\mathbf{x}) \cap \tilde{L}_I] \subseteq (\mathbf{x}_0 + S) \cap L_I = F_I$. Consequently, F_I is relatively interior to $(\mathbf{x}_0 + S) \cap \tilde{L}_I$. Since the dimension of $(\mathbf{x}_0 + S) \cap \tilde{L}_I$ is the same for all $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$, it follows that $\dim(F_I)$ is the same for all $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ so long as $F_I \neq \varnothing$. This proves the first claim.

Since $\tilde{F}_I \neq \varnothing$ by assumption, we can consider an arbitrary $\tilde{\mathbf{x}} \in \tilde{F}_I$. By definition, we have that $(\tilde{\mathbf{x}}_0 - \tilde{\mathbf{x}})_i > 0$ for $i \in I$ and $\tilde{\mathbf{x}}_0 - \tilde{\mathbf{x}} \in S$. Now choose an arbitrary $\mathbf{x} \in L_I$. It follows from the definition of L_I that $\mathbf{x}_0 = \mathbf{x} + \epsilon(\tilde{\mathbf{x}}_0 - \tilde{\mathbf{x}}) \in \mathbb{R}^m_{>0}$ for $\epsilon > 0$ sufficiently small. Since $\mathbf{x} \in F_I$ for $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ and $\mathbf{x} \in L_I$ was chosen arbitrarily, the second claim follows. □

This result guarantees that if $\tilde{F}_I$ is a facet (or vertex) for some $\tilde{\mathbf{x}}_0 \in \mathbb{R}^m_{>0}$, then F_I is a facet (or vertex) for any $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ so long as $F_I \neq \varnothing$. Furthermore, it guarantees that L_I can be completely partitioned into sets F_I corresponding to facets (or vertices).

We are now prepared to prove the following application of Theorem 5.2.6 to complex balanced systems. It should be noted that, while facets are weakly dynamically non-emptiable by Theorem 5.2.4, no comparable result holds for vertices (consider the origin in Example 5.2.2). Consequently, the following result cannot be attained as a simple application of Theorem 5.2.6.

Corollary 5.2.1 (Corollary 3.13, [37])**.** *Consider a complex balanced mass-action system. Suppose that every set F_I corresponding to a semi-locking set I is either a facet, a vertex, or empty, or that I is weakly dynamically non-emptiable. Then the* Global Attractor Conjecture *holds for this system.*

Proof. For complex balanced systems, $\omega(\mathbf{x}_0) \cap F_I = \varnothing$ for every F_I corresponding to a vertex (Proposition 20 of [13]) or the empty set (trivially). Also, from Corollary 3.3 of [3], we have that $\omega(\mathbf{x}_0) \cap F_I \neq \varnothing$ implies $\omega(\mathbf{x}_0) \cap \partial F_I \neq \varnothing$ for all F_I corresponding to facets; however, since ∂F_I corresponds to some $F_{\tilde{I}}$ not corresponding to a facet, this is a contradiction. It follows from Lemma 5.2.3 that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for any semi-locking set I such that F_I is a facet or a vertex for some $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$. It remains to show that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for every L_I corresponding to a weakly dynamically non-emptiable semi-locking set I.

By Theorem 5.2.6 we know that for each semi-locking set I which is weakly dynamically non-emptiable, there is an α satisfying

$$\alpha = \begin{cases} \alpha_i < 0, \text{ for } i \in I \\ \alpha_i = 0, \text{ for } i \notin I \end{cases}$$

so that, for every compact subset K of L_I, there exists a neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$ such that $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in U$. Since complex balanced systems are bounded, we are justified in using the inductive hypothesis of Theorem 5.1.3 from $|I| = m$ to $|I| = 1$ to conclude that, for all $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$, $\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$. It follows by Theorem 5.1.1 that the *Global Attractor Conjecture* holds for trajectories of such a system, and we are done. □

Example 5.2.1. *Consider the mass-action system*

$$\begin{array}{ccc} \mathcal{A}_1 & \xrightarrow{k_1} & 2\mathcal{A}_1 + \mathcal{A}_2 \\ {\scriptstyle k_3}\,\nwarrow & & \swarrow\,{\scriptstyle k_2} \\ & \mathcal{A}_1 + \mathcal{A}_2. & \end{array}$$

For this system, we have

$$\Gamma = \begin{bmatrix} 1 & -1 & 0 \\ 1 & 0 & -1 \end{bmatrix} \quad \textit{and} \quad R(\mathbf{x}) = \begin{bmatrix} k_1 x_1 \\ k_2 x_1^2 x_2 \\ k_3 x_1 x_2 \end{bmatrix}$$

and the system is governed by $\dot{\mathbf{x}} = \Gamma R(\mathbf{x})$.

We notice first of all that the system is not conservative and therefore does not fall within the scope of the systems considered in [5]. We might still be tempted to ask whether the system has semi-locking sets which are dynamically non-emptiable, so we consider the semi-locking set $I = \{1\}$. *Relative to this set, we have* $\mathcal{R}_2 \preccurlyeq_I \mathcal{R}_1$ *and* $\mathcal{R}_2 \preccurlyeq_I \mathcal{R}_3$ *so that* $\mathcal{F}_\epsilon(I) \cap \mathcal{C}(I) = \{\mathbf{0}\}$ *corresponds to finding a* $\mathbf{v} \in \mathbb{R}^3_{\geq 0}$ *such that* $v_1 - v_2 \leq 0$, $v_2 \leq \epsilon v_1$, *and* $v_2 \leq \epsilon v_3$. *This can clearly be satisfied for any* $\mathbf{v} = [0 \ 0 \ v_3]^T$ *where* $v_3 \geq 0$. *Since* $\mathcal{F}_\epsilon(I) \cap \mathcal{C}(I) \neq \{\mathbf{0}\}$, *it follows that the system contains a critical semi-locking set which is not dynamically non-emptiable.*

We notice, however, that F_I *is a facet of* $\mathsf{C}_{\mathbf{x}_0} = \mathbb{R}^2_{>0}$ *since* $s = 2$ *and* $dim(F_I) = 1$. *It follows from Theorem 5.2.4 that* I *is weakly dynamically non-emptiable. Since the system is complex balanced for all sets of rate constants and* I *is the only non-trivial semi-locking set, the* Global Attractor Conjecture *holds for this system by Corollary 5.2.1. (This result could also be attained by application of Theorem 4.6 of [3], although it should be pointed out that* F_I *is an example of a facet which is not dynamically non-emptiable in the traditional sense so that Corollary 3.5 of the same paper cannot be applied.)*

Example 5.2.2. *Consider the system*

$$\begin{array}{ccc} \mathcal{A}_1 & \underset{k_1}{\overset{k_5}{\leftrightarrows}} & 2\mathcal{A}_2 \\ {\scriptstyle k_4}\uparrow & & \downarrow{\scriptstyle k_2} \\ \mathcal{A}_2+\mathcal{A}_3 & \overset{k_3}{\leftarrow} & \mathcal{A}_1+\mathcal{A}_2. \end{array}$$

The system is governed by the dynamics $\dot{\mathbf{x}} = \Gamma R(\mathbf{x})$ *where*

$$\Gamma = \begin{bmatrix} -1 & 1 & -1 & 1 & 1 \\ 2 & -1 & 0 & -1 & -2 \\ 0 & 0 & 1 & -1 & 0 \end{bmatrix} \quad \textit{and} \quad R(\mathbf{x}) = \begin{bmatrix} k_1 x_1 \\ k_2 x_2^2 \\ k_3 x_1 x_2 \\ k_4 x_2 x_3 \\ k_5 x_2^2 \end{bmatrix}.$$

This example was first considered in [54], where the authors showed that the system is non-conservative, complex balanced for all sets of rate constants, and has only the non-trivial semi-locking set $I = \{1, 2\}$*. By the methodology presented in that paper, however, they could not find an* α *corresponding to* I *satisfying (5.6) and (5.7). Since the system is not conservative, the results of [5] cannot be applied, and since* I *is not a facet, the results of [3] cannot be applied. Here we will show that such an* α *does in fact exist by showing that* I *is weakly dynamically non-emptiable.*

We have that

$$\Gamma_I = \begin{bmatrix} -1 & 1 & -1 & 1 & 1 \\ 2 & -1 & 0 & -1 & -2 \end{bmatrix}.$$

We have $\mathcal{R}_2 \preccurlyeq_I \mathcal{R}_4$, $\mathcal{R}_3 \preccurlyeq_I \mathcal{R}_1$, $\mathcal{R}_3 \preccurlyeq_I \mathcal{R}_4$, *and* $\mathcal{R}_5 \preccurlyeq_I \mathcal{R}_4$ *so that*

$$\mathcal{R}_I = \{(2,4),(3,1),(3,4),(5,4)\}. \tag{5.20}$$

We pick the subset $J = \{(3,4)\}$ *so that*

$$\Gamma_J = \begin{bmatrix} 0 & 0 & 1 & -\epsilon & 0 \end{bmatrix}.$$

The condition $\tilde{\Gamma}\mathbf{v} \leq \mathbf{0}$ *for* $\mathbf{v} \in \mathbb{R}^5_{\geq 0}$ *is equivalent to the system* $-v_1 + v_2 - v_3 + v_4 + v_5 \leq 0$, $2v_1 - v_2 - v_4 - 2v_5 \leq 0$, *and* $v_3 - \epsilon v_4 \leq 0$ *for* $v_i \geq 0$, $i = 1, \ldots, 5$. *Taking a positive linear combination of these conditions yields* $v_2 + (1 - 2\epsilon)v_4 \leq 0$. *For* $0 < \epsilon < 1/2$, *this can be satisfied for* $v_2 \geq 0$ *and* $v_4 \geq 0$ *if and only if* $v_2 = v_4 = 0$. *It then follows from the third condition that* $v_3 = 0$. *The remaining conditions can be satisfied so long as* $v_1 = v_5 \geq 0$ *so that*

$$\mathbf{v} \in span\left\{\begin{bmatrix} 1 & 0 & 0 & 0 & 1 \end{bmatrix}^T\right\} \subseteq ker(\tilde{\Gamma}).$$

By Lemma 5.2.2, the semi-locking set I *is weakly dynamically non-emptiable. Since trajectories are bounded by virtue of the system being complex balanced, it follows from Theorem 5.2.6 that the system is persistent and from Corollary 5.2.1 that it satisfies Conjecture 5.1.1.*

In order to illustrate how the machinery of this result really works, we will complete the analysis for I *up to the point of applying Theorem 5.1.3. From Lemma 5.1.2 we have that there exists a* $\mathbf{c} \in \mathbb{R}^3_{>0}$ *such that* $\mathbf{c}^T\tilde{\Gamma} \geq \mathbf{0}^T$; *in fact, we can find it explicitly. This is satisfied*

if we choose $c_1 = 2$, $c_2 = 1$, $c_3 = 2$, *and* $0 < \epsilon < 1$, *for which values we have*

$$\mathbf{c}^T\tilde{\Gamma}R(\mathbf{x}) = \begin{bmatrix} 2 & 1 & 2 \end{bmatrix}\begin{bmatrix} -1 & 1 & -1 & 1 & 1 \\ 2 & -1 & 0 & -1 & -2 \\ 0 & 0 & 1 & -\epsilon & 0 \end{bmatrix}\begin{bmatrix} k_1x_1 \\ k_2x_2^2 \\ k_3x_1x_2 \\ k_4x_2x_3 \\ k_5x_2^2 \end{bmatrix}$$

$$= -\alpha^T\dot{\mathbf{x}} + 2(k_3x_1x_2 - \epsilon k_4x_2x_3) \geq 0$$

where $\alpha = \begin{bmatrix} -2 & -1 & 0 \end{bmatrix}^T$. *It follows that* $\alpha^T\dot{\mathbf{x}} \leq 2(k_3x_1x_2 - \epsilon k_4x_2x_3) \leq 0$ *in a neighbourhood of any compact subset of* F_I *since* $k_3x_1x_2 \leq \epsilon k_4x_2x_3$ *under the same conditions by Lemma 5.2.1. This is exactly the condition which was expected for application of Theorem 5.1.3, which completes the connection with Theorem 5.2.6.*

It is worth reemphasizing that not all sets J *satisfying (5.20) are sufficient to show that* I *is weakly dynamically non-emptiable. For instance, if we had selected* $\tilde{J} = \{(2,4),(3,1),(3,4)\}$, *we would have had*

$$\Gamma_{\tilde{J}} = \begin{bmatrix} 0 & 1 & 0 & -\epsilon & 0 \\ -\epsilon & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & -\epsilon & 0 \end{bmatrix}.$$

In this case, we can satisfy $\tilde{\Gamma}\mathbf{v} \leq \mathbf{0}$ *by choosing*

$$\mathbf{v} \in span\left\{\begin{bmatrix} 1 & 0 & 0 & 0 & 1 \end{bmatrix}^T\right\}$$

but $ker(\tilde{\Gamma}) = \{\mathbf{0}\}$. *Consequently,* $\tilde{J}$ *is insufficient to show that* I *is weakly dynamically non-emptiable.*

It is also worth noting that J is not the only choice sufficient for showing I is weakly dynamically non-emptiable. In fact, the maximal set $\tilde{J} = \mathcal{R}_I$ works with $ker(\tilde{\Gamma}) = \{\mathbf{0}\}$. (In other words, I is dynamically non-emptiable in the sense introduced in [5]! We remain unable to use Theorem 4 of [5], however, because this system is not conservative.) We can see also that it is easier to demonstrate weak dynamical non-emptiability with some choices of J than with others, an advantage which would become even more pronounced for larger systems.

Example 5.2.3. *Now consider the system*

$$\begin{array}{ccc} \mathcal{A}_1 + \mathcal{A}_2 & \overset{k_1}{\rightarrow} & 3\mathcal{A}_1 \\ {\scriptstyle k_4}\uparrow & & \downarrow{\scriptstyle k_2} \\ 2\mathcal{A}_2 & \underset{k_3}{\leftarrow} & 2\mathcal{A}_1 + \mathcal{A}_3. \end{array}$$

The system is governed by the dynamics $\dot{\mathbf{x}} = \Gamma R(\mathbf{x})$ where

$$\Gamma = \begin{bmatrix} 2 & -1 & -2 & 1 \\ -1 & 0 & 2 & -1 \\ 0 & 1 & -1 & 0 \end{bmatrix} \quad \text{and} \quad R(\mathbf{x}) = \begin{bmatrix} k_1 x_1 x_2 \\ k_2 x_1^3 \\ k_3 x_1^2 x_3 \\ k_4 x_2^2 \end{bmatrix}.$$

The system is non-conservative, complex balanced for all sets of rate constants, and has only the non-trivial semi-locking set $I = \{1, 2\}$. The system is not conservative, so the results of [5] cannot be applied, and I is not a facet, so the results of [3] cannot be applied. We consider whether I is weakly dynamically non-emptiable.

We have only the condition $\mathcal{R}_2 \preccurlyeq_I \mathcal{R}_3$ *so that* $J \subseteq \{(2,3)\}$. *Choosing the maximal such set we have*

$$\tilde{\Gamma} = \begin{bmatrix} 2 & -1 & -2 & 1 \\ -1 & 0 & 2 & -1 \\ 0 & 1 & -\epsilon & 0 \end{bmatrix}.$$

It is clear that $\mathbf{v} = \begin{bmatrix} 0 & 0 & 1 & 2 \end{bmatrix}^T$ *satisfies* $\tilde{\Gamma}\mathbf{v} \leq 0$ *but*

$$\mathbf{v} \notin \ ker(\tilde{\Gamma}) = \ span\left\{\begin{bmatrix} -\epsilon & -\epsilon & -1 & -2+\epsilon \end{bmatrix}^T\right\}$$

for any $\epsilon > 0$. *Since the condition* $\tilde{\Gamma}\mathbf{v} \leq 0$ *for* $\mathbf{v} \in \mathbb{R}^r_{\geq 0}$ *does not imply* $\mathbf{v} \in ker(\tilde{\Gamma})$ *for the trivial set* $J = \varnothing$ *either, it follows that* I *is not weakly dynamically non-emptiable and thus the results of this section cannot be applied.*

It is worth noting that persistence of this network can be demonstrated by the results contained in [2], [19], and [44], since the network contains a single linkage class, three-dimensional species space, and three-dimensional stoichiometric space, respectively.

5.3 Strata for Complex Balanced Systems

Another approach to the question of global stability can be found in [13]. In this paper, the authors G. Craciun, A. Dickenstein, A. Shui and B. Sturmfels take the novel approach of dividing the state space $\mathbb{R}^m_{>0}$ into regions, called strata, and proving that trajectories obey specific properties for as long as they remain within each strata.

In that paper, the authors considered only the behaviour of detailed balanced systems. Consequently, their definitions and results depend heavily on Definition 3.1.2. In Section

5.3.1 we will detail the results of [13]. In Section 5.3.2, we will generalize their concepts and results to complex balanced systems [54].

5.3.1 Strata for Detailed Balanced Systems

We quickly recall some of the definitions and properties relevant to the consideration of detailed balanced systems. From Lemma 3.1.1 we know that detailed balanced systems are reversible, so that if $(i,j) \in \mathcal{R}$ then $(j,i) \in \mathcal{R}$. We let $\tilde{\mathcal{R}}$ denote an arbitrary subset of $\mathcal{R}$ which contains only one of the index pairs from each set $\{(i,j),(j,i)\}$. We know from Lemma 3.2.1 that any system with a detailed balanced equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ can be written in the form

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) = \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i)\left[\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j}\right] \tag{5.21}$$

where $\kappa_{ij} > 0,\ \forall\ (i,j) \in \tilde{\mathcal{R}}$.

We will need the following preliminary definition.

Definition 5.3.1. *Consider a system with a detailed balanced equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. We will say that the subsystem $\tilde{\mathcal{R}} \subset \mathcal{R}$ is an **acyclic orientation** if it contains only one of the index pairs from $\{(i,j),(j,i)\}$ and the graph of $\tilde{\mathcal{R}}$ contains no cycles.*

We now define the notion of a stratum as it pertains to detailed balanced systems.

Definition 5.3.2. *Consider a system with a detailed balanced equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^m_{>0}$. Consider an acyclic orientation $\tilde{\mathcal{R}}$. Then the stratum associated with $\tilde{\mathcal{R}}$ is defined to be*

$$\mathcal{S} = \left\{\mathbf{x} \in \mathbb{R}^m_{>0} \;\middle|\; \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_i} > \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_j} \text{ for all } (i,j) \in \tilde{\mathcal{R}}\right\}.$$

It is clear why it is required that $\tilde{\mathcal{R}}$ be acyclic, since if there was a cycle $\{\nu_1, \nu_2, \ldots, \nu_l, \nu_{l+i}\}$ we would have some index $i_0 \in \{1, \ldots, m\}$ such that

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{i_0}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_1}} > \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_2}} > \cdots > \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_l}} > \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\nu_{l+1}}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{i_0}}.$$

Consequently, such a stratum would be empty. (It is also possible for a stratum to be empty for acyclic orientations.)

The important observation to make is that each $\mathbf{x} \in \mathbb{R}^m_{>0}$ belongs to exactly one stratum. That is to say, for each $\mathbf{x} \in \mathbb{R}^m_{>0}$, we can select a unique acyclic orientation $\tilde{\mathcal{R}}$ so that the stratum $\mathcal{S}$ associated with $\tilde{\mathcal{R}}$ contains $\mathbf{x}$. This is easy to see by considering that each $\mathbf{x} \in \mathbb{R}^m_{>0}$ produces an absolute ordering on the quantities $(\mathbf{x}/\mathbf{x}^*)^{\mathbf{z}_i}$ for $i = 1, \ldots, n$. The relevant acyclic ordering $\tilde{\mathcal{R}}$ is the one which satisfies this absolute ordering; furthermore, it must by the only one satisfying this overall ordering, since switching a single index pair in $\tilde{\mathcal{R}}$ results in a change to this absolute ordering.

In [13], the authors are able to show that, within each stratum $\mathcal{S}$, there is a linear functional which propels trajectories away from any set L_I adjacent to the stratum. The following result is contained as Lemma 17 of [13]. We have changed the signs to be consistent with a later result in Section 5.3.2.

Lemma 5.3.1. *Consider a system with a detailed balanced equilibrium concentration* $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ *and fix an acyclic orientation* $\tilde{\mathcal{R}}$*. If* $\overline{\mathcal{S}} \cap L_I \neq \varnothing$ *then there exists an* $\alpha \in \mathbb{R}^m_{\leq 0}$ *satisfying*

$$\begin{aligned} \alpha_i &< 0, \qquad \text{for } i \in I \\ \alpha_i &= 0, \qquad \text{for } i \notin I \end{aligned} \tag{5.22}$$

such that

$$\langle \mathbf{z}_i - \mathbf{z}_j, \alpha \rangle \geq 0 \tag{5.23}$$

for all $(i,j) \in \tilde{\mathcal{R}}$.

Proof. Suppose there is no $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying (5.22) and (5.23). By application of Lemma 5.1.1 on the index set I, this implies that there exists a

$$\mathbf{v} = \sum_{(i,j)\in\tilde{\mathcal{R}}} \lambda_{ij}(\mathbf{z}_i - \mathbf{z}_j), \quad \lambda_{ij} \geq 0, \quad \forall\ (i,j) \in \tilde{\mathcal{R}} \tag{5.24}$$

satisfying

$$\begin{aligned} v_i &\geq 0, \qquad \text{for all } i \in I \\ v_{i_0} &> 0, \qquad \text{for at least one } i_0 \in I. \end{aligned} \tag{5.25}$$

By assumption we have $\overline{\mathcal{S}} \cap L_I \neq \varnothing$. This implies that there exists a sequence $\{\mathbf{x}^k\} \subset \mathcal{S}$ such that $\mathbf{x}^k \to \mathbf{x} \in L_I$ as $k \to \infty$. By consideration of the quantity $(\mathbf{x}/\mathbf{x}^*)^{\mathbf{v}}$ separately for $\mathbf{x} \in L_I$ and the sequence $\{\mathbf{x}^k\}$ we will produce a contradiction.

Consider $\mathbf{x} \in L_I$. This implies $x_i = 0$ for $i \in I$. Since $v_i \geq 0$ for $i \in I$ and there exists at least one $i_0 \in I$ such that $v_{i_0} > 0$, it follows that

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{v}} = 0. \tag{5.26}$$

Now consider the sequence $\{\mathbf{x}^k\} \subset \mathcal{S}$ converging to $\mathbf{x}$. We have

$$\left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\mathbf{v}} = \left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\sum_{(i,j)\in\tilde{\mathcal{R}}} \lambda_{ij}(\mathbf{z}_i - \mathbf{z}_j)} = \prod_{(i,j)\in\tilde{\mathcal{R}}} \left[\left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\mathbf{z}_i - \mathbf{z}_j}\right]^{\lambda_{ij}}.$$

It follows from $\mathbf{x}^k \in \mathcal{S}$ and $\lambda_{ij} \geq 0$ that, for every $(i,j) \in \tilde{\mathcal{R}}$,

$$\left[\left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\mathbf{z}_i - \mathbf{z}_j}\right]^{\lambda_i} > 1, \quad \text{which implies} \quad \left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\mathbf{v}} > 1.$$

It remains to take the limit $\mathbf{x}^k \to \mathbf{x}$. The function $(\mathbf{x}/\mathbf{x}^*)^{\mathbf{v}}$ is continuous on $\mathbb{R}^m_{>0}$; furthermore, it is continuous at any $\mathbf{x} \in \partial\mathbb{R}^m_{>0}$ such that $v_i \geq 0$ if $x_i = 0$. Since $\mathbf{v}$ satisfies this for $\mathbf{x}^k \to \mathbf{x} \in L_I$, we have

$$\lim_{k\to\infty}\left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\mathbf{v}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{v}} \geq 1. \tag{5.27}$$

This contradicts (5.39). It follows that no $\mathbf{v}$ satisfying (5.37) and (5.38) exists. However, the existence of such a $\mathbf{v}$ was a direct consequence of the non-existence of an α satisfying (5.22) and (5.23), so it follows that such an α must exist. This proves our claim. □

This result allows us to prove the following, which corresponds to Corollary 18 of [13]. We have significantly modified the wording to make explicit $\langle \alpha, \mathbf{f}(\mathbf{x})\rangle \leq 0$ for all $\mathbf{x} \in \overline{\mathcal{S}}$.

Lemma 5.3.2. *Consider a detailed balanced reaction system. If $\overline{\mathcal{S}} \cap L_I \neq \varnothing$ then there exists an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying*

$$\alpha_i < 0, \text{ for } i \in I$$
$$\alpha_i = 0, \text{ for } i \notin I$$

such that $\langle \alpha, \mathbf{f}(\mathbf{x})\rangle \leq 0$ for every $\mathbf{x} \in \overline{\mathcal{S}}$.

Proof. Since $\overline{\mathcal{S}} \cap L_I \neq \varnothing$, we know by Lemma 5.3.1 that there exists an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying

$$\alpha_i < 0, \text{ for } i \in I$$
$$\alpha_i = 0, \text{ for } i \notin I$$

such that

$$\left\langle \mathbf{z}_i - \mathbf{z}_j, \alpha \right\rangle \geq 0, \quad \text{for } i = 1, \ldots, n-1. \tag{5.28}$$

According to Lemma 3.2.1 we have

$$\begin{aligned} \langle \alpha, \mathbf{f}(\mathbf{x}) \rangle &= \left\langle \alpha, \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij}(\mathbf{z}_j - \mathbf{z}_i) \left[\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_j} \right] \right\rangle \\ &= - \sum_{(i,j)\in\tilde{\mathcal{R}}} \kappa_{ij} \left[\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_j} \right] \cdot \langle \mathbf{z}_i - \mathbf{z}_j, \alpha \rangle. \end{aligned} \tag{5.29}$$

By Definition 5.3.2 we have that, for every $\mathbf{x} \in \overline{\mathcal{S}}$,

$$\left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_i} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_j} \right) \geq 0. \tag{5.30}$$

It follows immediately from (5.28), (5.45), (5.30), and the fact that $\kappa_{ij} > 0$ for every $(i,j) \in \tilde{\mathcal{R}}$ that $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in \overline{\mathcal{S}}$, and we are done. □

Lemma 5.3.2 implies that, within any stratum $\mathcal{S}$ adjacent to a set L_I, there is a linear functional $H(\mathbf{x}) = \langle \alpha, \mathbf{x} \rangle$ which pushes trajectories away, since $H(\mathbf{x})$ takes its maximum along L_I, and we have

$$\frac{d}{dt} H(\mathbf{x}(t)) = \left\langle \alpha, \frac{d}{dt} \mathbf{x}(t) \right\rangle \leq 0$$

so long as $\mathbf{x}(t) \in \mathcal{S}$.

Since this is true for every stratum and every set L_I, it is tempting to conclude that no trajectory may approach $\partial \mathbb{R}^m_{>0}$, and therefore that the unique positive equilibrium concentration permitted in each compatibility class is globally stable, but this is not warranted. Since multiple strata may intersect a given face, and each stratum may have a different

linear functional, it is conceivable that a trajectory could still approach $\partial\mathbb{R}^m_{>0}$ through creative maneouvring between the adjacent strata. More consideration of this point will be conducted in Section 5.3.2.

Despite this limitation, the following global stability result has been proved and can be found as Theorem 23 of [13]. We omit the proof.

Theorem 5.3.1. *Consider a detailed balanced system with a two-dimensional stoichiometric subspace S and bounded positive compatibility classes $\mathsf{C}_{\mathbf{x}_0}$. Then the unique positive equilibrium concentration $\mathbf{x}^*$ in $\mathsf{C}_{\mathbf{x}_0}$ is a global attractor for $\mathsf{C}_{\mathbf{x}_0}$.*

Example 5.3.1. *Consider the reaction system*

$$\mathcal{O} \underset{k_1^-}{\overset{k_1^+}{\rightleftarrows}} \mathcal{A}_1 \underset{k_2^-}{\overset{k_2^+}{\rightleftarrows}} \mathcal{A}_2.$$

This system is governed by the dynamics

$$\begin{aligned} \frac{dx_1}{dt} &= k_1^+ - (k_1^- + k_2^+)x_1 + k_2^- x_2 \\ \frac{dx_2}{dt} &= k_2^+ x_1 - k_2^- x_2 \end{aligned} \tag{5.31}$$

from which it easily follows that the system is detailed balanced at the equilibrium concentration

$$x_1^* = \frac{k_1^+}{k_1^-} \qquad x_2^* = \frac{k_1^+ k_2^+}{k_1^- k_2^-}.$$

We want to determine what the strata for this system look like. In order to do this, we find all possible acyclic orientations $\tilde{\mathcal{R}}$. For this sytem, there is no way to choose a cyclic orientation by choosing one reaction arrow from each of reaction pairs. It follows that we

have four acyclic orientations, which are given by

$$\begin{aligned}
\mathcal{R}_1 &: \quad \mathcal{O} \longrightarrow \mathcal{A}_1 \longrightarrow \mathcal{A}_2 \\
\mathcal{R}_2 &: \quad \mathcal{O} \longrightarrow \mathcal{A}_1 \longleftarrow \mathcal{A}_2 \\
\mathcal{R}_3 &: \quad \mathcal{O} \longleftarrow \mathcal{A}_1 \longrightarrow \mathcal{A}_2 \\
\mathcal{R}_4 &: \quad \mathcal{O} \longleftarrow \mathcal{A}_1 \longleftarrow \mathcal{A}_2.
\end{aligned}$$

The four corresponding strata are given by

$$\begin{aligned}
\mathcal{S}_1 &= \left\{ \mathbf{x} \in \mathbb{R}^m_{>0} \;\middle|\; 1 > \left(\frac{x_1}{x_1^*}\right) > \left(\frac{x_2}{x_2^*}\right) \right\} \\
\mathcal{S}_2 &= \left\{ \mathbf{x} \in \mathbb{R}^m_{>0} \;\middle|\; 1 > \left(\frac{x_1}{x_1^*}\right) \text{ and } \left(\frac{x_2}{x_2^*}\right) > \left(\frac{x_1}{x_1^*}\right) \right\} \\
\mathcal{S}_3 &= \left\{ \mathbf{x} \in \mathbb{R}^m_{>0} \;\middle|\; \left(\frac{x_1}{x_1^*}\right) > 1 \text{ and } \left(\frac{x_1}{x_1^*}\right) > \left(\frac{x_2}{x_2^*}\right) \right\} \\
\mathcal{S}_4 &= \left\{ \mathbf{x} \in \mathbb{R}^m_{>0} \;\middle|\; \left(\frac{x_2}{x_2^*}\right) > \left(\frac{x_1}{x_1^*}\right) > 1 \right\}.
\end{aligned} \tag{5.32}$$

We can see how trajectories behave within these strata by considering a vector field plot (see Figure 5.3).

It is clear that trajectories in each stratum adjacent to a face ($\mathcal{S}_1$, $\mathcal{S}_2$, and $\mathcal{S}_3$) are repelled from these faces. (In fact, we know no ω-limit point exists on the boundary by Theorem 5.1.2 since no face is a semilocking set. We carry out the following analysis for illustrative purposes.) We would like to be a little more explicit—we would like to find the linear functionals $H(\mathbf{x})$ which succeed in repelling trajectories from the boundaries.

Since the $\alpha \in \mathbb{R}^2_{\leq 0}$ has support on I, we can see that our options for $H(\mathbf{x})$ are limited for the strata intersecting the faces F_I where $I = \{1\}$ ($\mathcal{S}_2$) and $I = \{2\}$ ($\mathcal{S}_1$ and $\mathcal{S}_3$). In fact,

for $I = \{1\}$, our only choice is a positive scaling of

$$H(\mathbf{x}) = \langle \alpha, \mathbf{x} \rangle = [-1\ 0] \cdot [x_1\ x_2] = -x_1$$

and for $I = \{2\}$, our only choice is a positive scaling of

$$H(\mathbf{x}) = \langle \alpha, \mathbf{x} \rangle = [0\ -1] \cdot [x_1\ x_2] = -x_2.$$

It can be easily checked that $\frac{d}{dt}H(\mathbf{x}) \leq 0$ in the relevant advacent strata, but we will not perform the analysis here.

Instead, consider the face F_I corresponding to $I = \{1, 2\}$. There are two adjacent strata, $\mathcal{S}_1$ and $\mathcal{S}_2$. We notice, however, that the selection of a suitable $\alpha \in \mathbb{R}^2_{\leq 0}$ is not trivial since on the support of I we have multiple possible orientations (e.g. it may be possible that $\alpha = [-1\ -1]$ works but $\alpha = [-1\ -10]$ does not).

In order to determine which α's are admissible for the construction of our linear functionals $H(\mathbf{x})$ we consider Lemma 3.2.1. Specifically, when considering $\mathbf{x} \in \mathcal{S}_1$, we rewrite (2.4) as

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{bmatrix} = \kappa_{12} \begin{bmatrix} 1 \\ 0 \end{bmatrix} \left(1 - \left(\frac{x_1}{x_1^*}\right)\right) + \kappa_{23} \begin{bmatrix} -1 \\ 1 \end{bmatrix} \left(\left(\frac{x_1}{x_1^*}\right) - \left(\frac{x_2}{x_2^*}\right)\right) \tag{5.33}$$

and when considering $\mathbf{x} \in \mathcal{S}_2$, we rewrite (2.4) as

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{bmatrix} = \kappa_{12} \begin{bmatrix} 1 \\ 0 \end{bmatrix} \left(1 - \left(\frac{x_1}{x_1^*}\right)\right) + \kappa_{32} \begin{bmatrix} 1 \\ -1 \end{bmatrix} \left(\left(\frac{x_2}{x_2^*}\right) - \left(\frac{x_1}{x_1^*}\right)\right) \tag{5.34}$$

where $\kappa_{12} > 0$, $\kappa_{23} > 0$, and $\kappa_{32} > 0$.

It is clear that the bracketted terms are positive for $\mathbf{x}$ *in the respective strata. In order to determine an* $\alpha \in \mathbb{R}^m_{\leq 0}$ *with support on* $I = \{1, 2\}$ *such that* $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$*, we therefore need only consider the vector quantities in front of the brackets in (5.33) and (5.34). We can see, in fact, that* $\alpha = [-1 \ -1]$ *works for both (5.33) and (5.34). This implies that*

$$H(\mathbf{x}) = \langle \alpha, \mathbf{x} \rangle = [-1 \ -1] \cdot [x_1 \ x_2] = -x_1 - x_2$$

is a suitable linear functional within both $\mathcal{S}_1$ *and* $\mathcal{S}_2$.

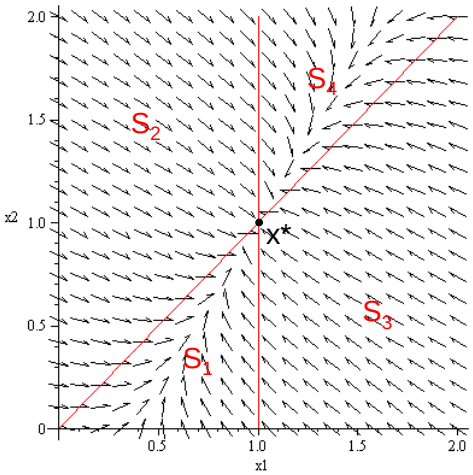

Figure 5.3: Vector field plot of (5.31) with $k_1^- = k_1^+ = k_2^- = k_2^+ = 1$. The four strata (5.32) have been overlaid.

5.3.2 General Strata

In this section, we generalize the notion of stratification to complex balanced systems. While our notion of stratification is based on that presented in [13], some differences arise. We consider a *complete* ordering of all the complexes in the system, rather than pairwise

ordering as in Definition 5.3.2, and we do not require any conditions on the reaction graph. We also keep the notion of stratification general by considering the state space $\mathbb{R}^m_{>0}$ rather than each $\mathsf{C}_{\mathbf{x}_0}$. The definitions and results contained in this section can be found in [54].

First of all, we will need to introduce the concept of a permutation operator.

Definition 5.3.3. *Consider the set $I = \{1, 2, \ldots, n\}$. The operator $\mu : I \mapsto I$ is called a* ***permutation operator*** *if it is bijective. Furthermore, we will say that the permutation operator μ implies the* ***ordering***

$$\mu(i) \succ \mu(i+1), \quad i = 1, \ldots, n-1$$

on the set $\{1, 2, \ldots, n\}$.

A permutation operator simply shuffles the elements of a set. To each such operator we can define a stratum in the following way.

Definition 5.3.4. *Given a permutation operator $\mu : I \mapsto I$ we define the* ***stratum*** *associated with μ to be*

$$\mathcal{S}_\mu = \left\{ \mathbf{x} \in \mathbb{R}^m_{>0} \;\middle|\; \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\mu(i)}} > \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\mu(i+1)}} \text{for } i = 1, \ldots, n-1 \right\}$$

where $\mathbf{x}^*$ is an arbitrary positive equilibrium concentration permitted by the system.

This is a more general notion of strata than that given by Definition 5.3.2 (i.e. for some systems, strata according to Definition 5.3.2 are further stratified by Definition 5.3.4); however, it is natural for the analysis we undertake in the remainder of this section.

Strata defined in this way have some nice properties, most importantly, that each

$\mathbf{x} \in \mathbb{R}^m_{>0}$ either belongs to a unique stratum $\mathcal{S}_\mu$ or the boundary separating one or more strata.

It is also worth noting that not every permutation generates a non-empty stratum. For example, for a system containing the complexes $\mathcal{C}_1 = \mathcal{O}, \mathcal{C}_2 = \mathcal{A}_1$, $\mathcal{C}_3 = \mathcal{A}_2$, and $\mathcal{C}_4 = \mathcal{A}_1 + \mathcal{A}_2$ there are no points satisfying

$$\frac{x_2}{x_2^*} > \frac{x_1}{x_1^*}\frac{x_2}{x_2^*} > \frac{x_1}{x_1^*} > 1$$

since the first and last conditions imply $x_1^* > x_1$ and $x_1 > x_1^*$, respectively. That is to say, for the permutation $\mu([1,2,3,4]) = [3,4,2,1]$ we have $\mathcal{S}_\mu = \varnothing$ ($\mu([1,2,3,4]) = [3,4,2,1]$ will be our short-hand for $\mu(1) = 3$, $\mu(2) = 4$, $\mu(3) = 2$, $\mu(4) = 1$). In this section, we will consider only those permutation operators μ which generate non-empty strata $\mathcal{S}_\mu$. (This is related to, although not equivalent to, the condition that $\tilde{\mathcal{R}}$ contain no cycles in Definition 5.3.2.)

Strata defined according to Definition 5.3.4 share important properties with those defined according to Definition 5.3.2. In particular, Lemma 5.3.1 can be extended by the following result.

Lemma 5.3.3 (Lemma 3.4, [54])**.** *If $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$ then there exists an $\alpha \in \mathbb{R}^m$ satisfying*

$$\begin{aligned} \alpha_i &< 0, \ \textit{for } i \in I \\ \alpha_i &= 0, \ \textit{for } i \notin I \end{aligned} \tag{5.35}$$

and

$$\langle \mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)}, \alpha \rangle \geq 0, \quad \textit{for } i = 1, \ldots, n-1. \tag{5.36}$$

Proof. Suppose there is no $\alpha \in \mathbb{R}^m$ satisfying (5.35) and (5.36). By application of Farkas' Lemma (Lemma 5.1.1) on the index set I, this implies that there exist $\lambda_i \geq 0$, $i = 1, \ldots, n-1$

such that

$$\mathbf{v} = \sum_{i=1}^{n-1} \lambda_i \left(\mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)} \right) \tag{5.37}$$

satisfies

$$\begin{aligned} v_i &\geq 0, \qquad \text{for all } i \in I \\ v_{i_0} &> 0, \qquad \text{for at least one } i_0 \in I. \end{aligned} \tag{5.38}$$

By assumption we have $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$. This implies that there exists a sequence $\{\mathbf{x}^k\} \subset \mathcal{S}_\mu$ such that $\mathbf{x}^k \to \mathbf{x} \in L_I$ as $k \to \infty$. By consideration of the quantity $(\mathbf{x}/\mathbf{x}^*)^{\mathbf{v}}$ separately for $\mathbf{x} \in L_I$ and the sequence $\{\mathbf{x}^k\}$ we will produce a contradiction.

Consider $\mathbf{x} \in L_I$. This implies $x_i = 0$ for $i \in I$. Since $v_i \geq 0$ for $i \in I$ and there exists at least one $i_0 \in I$ such that $v_{i_0} > 0$, it follows that

$$\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{v}} = 0. \tag{5.39}$$

Now consider the sequence $\{\mathbf{x}^k\} \subset \mathcal{S}_\mu$ converging to $\mathbf{x}$. We have

$$\left(\frac{\mathbf{x}^k}{\mathbf{x}^*} \right)^{\mathbf{v}} = \left(\frac{\mathbf{x}^k}{\mathbf{x}^*} \right)^{\sum_{i=1}^{n-1} \lambda_i (\mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)})} = \prod_{i=1}^{n-1} \left[\left(\frac{\mathbf{x}^k}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)}} \right]^{\lambda_i}.$$

It follows from $\mathbf{x}^k \in \mathcal{S}_\mu$ and $\lambda_i \geq 0$ that, for $i = 1, \ldots, n-1$,

$$\left[\left(\frac{\mathbf{x}^k}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)}} \right]^{\lambda_i} > 1, \quad \text{which implies} \quad \left(\frac{\mathbf{x}^k}{\mathbf{x}^*} \right)^{\mathbf{v}} > 1.$$

It remains to take the limit $\mathbf{x}^k \to \mathbf{x}$. The function $(\mathbf{x}/\mathbf{x}^*)^{\mathbf{v}}$ is continuous on $\mathbb{R}^m_{>0}$; furthermore, it is continuous at any $\mathbf{x} \in \partial\mathbb{R}^m_{>0}$ such that $v_i \geq 0$ if $x_i = 0$. Since $\mathbf{v}$ satisfies this for

$\mathbf{x}^k \to \mathbf{x} \in L_I$, we have

$$\lim_{k\to\infty}\left(\frac{\mathbf{x}^k}{\mathbf{x}^*}\right)^{\mathbf{v}} = \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{v}} \geq 1. \tag{5.40}$$

This contradicts (5.39). It follows that no $\mathbf{v}$ satisfying (5.37) and (5.38) exists. However, the existence of such a $\mathbf{v}$ was a direct consequence of the non-existence of an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying (5.35) and (5.36), so it follows that such an α must exist. This proves our claim.

□

5.3.3 Cyclic Complex Balanced Systems

In this section, we consider the properties of cyclic complex balanced systems (see Definition 3.3.1).

The following result allows us to rearrange the governing system of differential equations given by (3.24) into a form which will be convenient in light of our conception of strata. Since we are dealing with strata, we will need to recall the definition of a permutation operator (Definition 5.3.3).

It is important to notice the difference between $\mu(j+1)$ and $\mu(j)+1$: the increment $\mu(j+1)$ is made with respect to the implied ordering given by the permutation μ, while the increment $\mu(j)+1$ is made with respect to the original ordering of the cycle.

Theorem 5.3.2 (Theorem 3.8, [54])**.** *Given a cyclic complex balanced system and an arbitrary permutation operator μ, the system (2.4) can be written*

$$\frac{d\mathbf{x}}{dt} = \kappa \sum_{i=1}^{n-1}\left[\sum_{j=1}^{i}\mathbf{s}_{\mu(j)}\right]\left(\left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\mu(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*}\right)^{\mathbf{z}_{\mu(j+1)}}\right) \tag{5.41}$$

where $\mathbf{s}_{\mu(j)} = \mathbf{z}_{\mu(j)+1} - \mathbf{z}_{\mu(j)}$.

Proof. We notice first of all that, since the system is cyclic, we have

$$\sum_{i=1}^{n} \mathbf{s}_{\mu(i)} = \sum_{i=1}^{n} \mathbf{s}_i = \sum_{i=1}^{n} \left(\mathbf{z}_{i+1} - \mathbf{z}_i \right) = \mathbf{0}$$

which immediately implies $\kappa \sum_{i=1}^{n} \mathbf{s}_{\mu(i)} \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(n)}} = \mathbf{0}$.

Subtracting this from (3.24), which is the form of (2.3) justified by Lemma 3.3.1, we have

$$\begin{aligned} \frac{d\mathbf{x}}{dt} &= \kappa \sum_{i=1}^{n-1} \mathbf{s}_{\mu(i)} \left[\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(i)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(n)}} \right] \\ &= \kappa \sum_{i=1}^{n-1} \mathbf{s}_{\mu(i)} \left[\sum_{j=i}^{n-1} \left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j+1)}} \right) \right] \\ &= \kappa \sum_{i=1}^{n-1} \left[\sum_{j=1}^{i} \mathbf{s}_{\mu(j)} \right] \left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(i)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(i+1)}} \right) \end{aligned}$$

and the result is shown. □

It is clear from (5.41) that the vectors $\sum_{j=1}^{i} \mathbf{s}_{\mu(j)}$, $i = 1, \ldots, n-1$, play an intricate role in determining the dynamics of a system within a given stratum. The following result allows us to further understand the nature of these vectors.

Lemma 5.3.4 (Lemma 3.9, [54]). *For every permutation operator μ and every $k = 1, 2, \ldots, n-1$, there exist $\lambda_j \in \mathbb{Z}_{\leq 0}$, $j = 1, 2, \ldots, n-1$, such that*

$$\sum_{j=1}^{k} \mathbf{s}_{\mu(j)} = \sum_{j=1}^{n-1} \lambda_j \left(\mathbf{z}_{\mu(j)} - \mathbf{z}_{\mu(j+1)} \right)$$

where $\mathbf{s}_{\mu(j)} = \mathbf{z}_{\mu(j)+1} - \mathbf{z}_{\mu(j)}$.

Proof. Consider a permutation operator μ and fix a $k \in \{1, 2, \ldots, n-1\}$. Consider

$$\mathbf{s}_{\mu(k)} = \mathbf{z}_{\mu(k)+1} - \mathbf{z}_{\mu(k)}.$$

Clearly, there exists a $t_1 \in \{1, 2, \ldots, n\}$ such that $\mu(k) + 1 = \mu(t_1)$. We need to consider where $\mu(t_1)$ lies in the ordering implied by μ relative to $\mu(k)$, in particular, whether (1) $\mu(t_1) \succ \mu(k)$, or (2) $\mu(t_1) \prec \mu(k)$. We will use an iterative process on the vectors $\mathbf{s}_{\mu(j)}$, $j = 1, \ldots, k$, to show that the case $\mu(t_1) \succ \mu(k)$ eventually leads us in a natural way to consideration of an index t_{i_0} satisfying $\mu(t_{i_0}) \prec \mu(k)$.

Case 1: If $\mu(t_1) \succ \mu(k)$ then $\mathbf{s}_{\mu(t_1)}$ is a term in the sum $\sum_{j=1}^{k} \mathbf{s}_{\mu(j)}$. It follows that

$$\begin{aligned} \mathbf{s}_{\mu(k)} + \mathbf{s}_{\mu(t_1)} &= \left(\mathbf{z}_{\mu(k)+1} - \mathbf{z}_{\mu(k)}\right) + \left(\mathbf{z}_{\mu(t_1)+1} - \mathbf{z}_{\mu(t_1)}\right) \\ &= \mathbf{z}_{\mu(t_1)+1} - \mathbf{z}_{\mu(k)} \end{aligned} \tag{5.42}$$

since $\mu(k) + 1 = \mu(t_1)$. We now repeat this process. We know that there exists a $t_2 \in \{1, 2, \ldots, n\}$ such that $\mu(t_1) + 1 = \mu(t_2)$ and, as before, either $\mu(t_2) \succ \mu(k)$ or $\mu(t_2) \prec \mu(k)$. If $\mu(t_2) \succ \mu(k)$, we add $\mathbf{s}_{\mu(t_2)}$ to the cumulative sum (5.42). We can continue doing this until we arrive at an index i_0 for which $\mu(t_{i_0-1}) + 1 = \mu(t_{i_0}) \prec \mu(k)$, yielding

$$\mathbf{s}_{\mu(k)} + \sum_{i=1}^{i_0-1} \mathbf{s}_{\mu(t_i)} = \mathbf{z}_{\mu(t_{i_0})} - \mathbf{z}_{\mu(k)}. \tag{5.43}$$

We know such a terminal index exists because the cyclic nature of the system guarantees each index $\mu(t_i - 1) + 1 = \mu(t_i) \succ \mu(k)$ is unique, so that a distinct vector $\mathbf{s}_{\mu(t_i)}$ is chosen during each iteration. Since $k < n$ and the cycle is of length n, this process must reach an index $\mu(t_{i_0} - 1) + 1 = \mu(t_{i_0}) \prec \mu(k)$ eventually.

Case 2: If $\mu(t_{i_0}) \prec \mu(k)$, we can interpolate (5.43) as follows:

$$\begin{aligned}\mathbf{s}_{\mu(k)} + \sum_{i=1}^{i_0-1} \mathbf{s}_{\mu(t_i)} &= \mathbf{z}_{\mu(t_{i_0})} - \mathbf{z}_{\mu(k)} \\ &= \left(\mathbf{z}_{\mu(t_{i_0})} - \mathbf{z}_{\mu(t_{i_0}-1)}\right) + \cdots + \left(\mathbf{z}_{\mu(k+1)} - \mathbf{z}_{\mu(k)}\right) \\ &= -\left(\mathbf{z}_{\mu(k)} - \mathbf{z}_{\mu(k+1)}\right) - \cdots - \left(\mathbf{z}_{\mu(t_{i_0}-1)} - \mathbf{z}_{\mu(t_{i_0})}\right).\end{aligned} \tag{5.44}$$

Notice that if our initial reindexing $\mu(k)+1 = \mu(t_1)$ yielded $\mu(t_1) \prec \mu(k)$, we can take $t_{i_0} = t_1$ in the above argument. This amounts to interpolating $\mathbf{s}_{\mu(k)} = \mathbf{z}_{\mu(t_1)} - \mathbf{z}_{\mu(k)}$ directly.

We return now to consideration of the entire sum $\sum_{j=1}^{k} \mathbf{s}_{\mu(j)}$. Since a distinct vector $\mathbf{s}_{\mu(t_i)}$ is chosen in each application of the argument for Case 1, we can divide this sum into those elements $\mathbf{s}_{\mu(j)}$ considered in (5.44) and those not. For those elements not yet considered, the same argument can be applied starting with the lowest remaining index, which will yield another sum of the form (5.44). This will remove some of the remaining vectors $\mathbf{s}_{\mu(j)}$ from the sum. Since there are a finite number of complexes, this process must terminate at some point. Clearly, any sum of vectors of the form given in (5.44) has non-positive integer coefficients for the terms $\mathbf{z}_{\mu(j)} - \mathbf{z}_{\mu(j+1)}$, so that the existence of $\lambda_j \in \mathbb{Z}_{\leq 0}$ is guaranteed. Since μ and $k \in \{1, 2, \ldots, n-1\}$ were chosen arbitrarily, the result follows.

□

The results to this point are sufficient to prove the following result. This should be contrasted with Corollary 18 of [13].

Lemma 5.3.5 (Lemma 3.10, [54])**.** *Consider a cyclic complex balanced system and an*

arbitrary permutation operator μ. *If* $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$ *then there exists an* $\alpha \in \mathbb{R}^m_{\leq 0}$ *satisfying*

$$\alpha_i < 0, \ \textit{for } i \in I$$
$$\alpha_i = 0, \ \textit{for } i \notin I$$

such that $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ *for every* $\mathbf{x} \in \overline{\mathcal{S}}_\mu$.

Proof. Since $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$, we know by Lemma 5.3.3 that there exists an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying

$$\alpha_i < 0, \ \text{for } i \in I$$
$$\alpha_i = 0, \ \text{for } i \notin I$$

such that

$$\left\langle \mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)}, \alpha \right\rangle \geq 0, \quad \text{for } i = 1, \ldots, n-1.$$

According to Theorem 5.3.2 we have

$$\begin{aligned} \langle \alpha, \mathbf{f}(\mathbf{x}) \rangle &= \left\langle \alpha, \kappa \sum_{i=1}^{n-1} \left[\sum_{j=1}^{i} \mathbf{s}_{\mu(j)} \right] \left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j+1)}} \right) \right\rangle \\ &= \kappa \sum_{i=1}^{n-1} \left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j+1)}} \right) \cdot \left\langle \alpha, \sum_{j=1}^{i} \mathbf{s}_{\mu(j)} \right\rangle. \end{aligned} \tag{5.45}$$

For every $\mathbf{x} \in \overline{\mathcal{S}}_\mu$, by Definition 5.3.4 we have

$$\left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu(j+1)}} \right) \geq 0. \tag{5.46}$$

Now consider $\langle \alpha, \sum_{j=1}^{i} \mathbf{s}_{\mu(j)} \rangle$. We know from Lemma 5.3.4 that there exist $\lambda_j \in \mathbb{Z}_{\leq 0}$,

$j = 1, 2, \ldots, n-1$, such that

$$\sum_{j=1}^{i} \mathbf{s}_{\mu(j)} = \sum_{j=1}^{n-1} \lambda_j (\mathbf{z}_{\mu(j)} - \mathbf{z}_{\mu(j+1)}).$$

We also know by Lemma 5.3.3 that $\left\langle \mathbf{z}_{\mu(j)} - \mathbf{z}_{\mu(j+1)}, \alpha \right\rangle \geq 0$. Together, these facts imply that for every $i = 1, 2, \ldots, n-1$,

$$\left\langle \alpha, \sum_{j=1}^{i} \mathbf{s}_{\mu(j)} \right\rangle = \sum_{j=1}^{n-1} \lambda_j \left\langle \mathbf{z}_{\mu(j)} - \mathbf{z}_{\mu(j+1)}, \alpha \right\rangle \leq 0. \tag{5.47}$$

It follows immediately from (5.45), (5.46), (5.47) and the fact that $\kappa > 0$ that $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for every $\mathbf{x} \in \overline{\mathcal{S}}_\mu$, and we are done.

□

5.3.4 General Complex Balanced Systems

In this section, we extend Lemma 5.3.5 to general complex balanced systems. We follow the methodology employed by F. Horn and R. Jackson and reproduced in Section 3.3.2 in generalizing from cyclic complex balanced systems to general complex balanced systems [33].

Theorem 5.3.3 (Theorem 3.12, [54])**.** *Consider a complex balanced system and an arbitrary permutation operator μ. If $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$ then there exists an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisying*

$$\alpha_i < 0, \text{ for } i \in I$$
$$\alpha_i = 0, \text{ for } i \notin I$$

such that $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for every $\mathbf{x} \in \overline{\mathcal{S}}_\mu$.

Proof. Consider a permutation operator μ satisfying $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$. By Lemma 5.3.3 there exists an $\alpha \in \mathbb{R}^m_{\leq 0}$ satisfying

$$\begin{aligned} \alpha_i &< 0, \text{ for } i \in I \\ \alpha_i &= 0, \text{ for } i \notin I \end{aligned} \tag{5.48}$$

and

$$\langle \mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)}, \alpha \rangle \geq 0, \quad \text{for } i = 1, \ldots, n-1. \tag{5.49}$$

The form of α from (5.48) is what we need for the theorem. We now want to use (5.49) to determine the sign of $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle$.

Since the system is complex balanced, by Lemma 3.3.3 we have

$$\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle = \kappa_1 \langle \alpha, \mathbf{X}_1 \rangle + \cdots + \kappa_\delta \langle \alpha, \mathbf{X}_\delta \rangle$$

where the κ_i are positive constants determined by the rate constants and the $\mathbf{X}_i$ have the form (3.28). Each $\mathbf{X}_i$ corresponds to a cycle in the cyclic decomposition of the system where the i^{th} cycle is indexed $\left\{\nu_1^{(i)}, \nu_2^{(i)}, \ldots, \nu_{l_i}^{(i)}, \nu_1^{(i)}\right\}$. The overall ordering

$$\mu(1) \succ \mu(2) \succ \cdots \succ \mu(n) \tag{5.50}$$

implies an ordering on the complex indices $\left\{\nu_1^{(i)}, \ldots, \nu_{l_i}^{(i)}\right\}$. We can do this by simply removing the elements from (5.50) which do not correspond to indices in the set $\left\{\nu_1^{(i)}, \ldots, \nu_{l_i}^{(i)}\right\}$ whilst otherwise preserving the ordering.

Now consider a single term $\langle \alpha, \mathbf{X}_i \rangle$, $i = 1, \ldots, \delta$. Firstly, we reindex the complexes so that the relevant cycle is $\{1, 2, \ldots, l_i, 1\}$. We let μ_i denote the permutation operator which preserves the ordering implied by μ on this reduced index set, after reindexing. (For

example, consider a system with five complexes and the cycle $\{2,4,1,2\}$. Consider the permutation operator $\mu([1,2,3,4,5]) = [2,5,3,1,4]$. Then we reindex the cycle so that we have $\{1,2,3,1\}$ and $\mu_i([1,2,3]) = [1,3,2]$ since $2 \succ 1 \succ 4$ in the original ordering implied by μ.)

Since $\mathbf{X}_i$ is cyclic and complex balanced, we can apply all of the results used in the proof of Lemma 5.3.5 to get

$$\langle \alpha, \mathbf{X}_i \rangle = \sum_{i=1}^{l_i-1} \left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu_i(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu_i(j+1)}} \right) \cdot \left\langle \alpha, \sum_{j=1}^{i} \mathbf{s}_{\mu_i(j)} \right\rangle \tag{5.51}$$

where $\mathbf{s}_{\mu_i(j)} = \mathbf{z}_{\mu_i(j)+1} - \mathbf{z}_{\mu_i(j)}$. Since the ordering of the complexes corresponding to elements in the i^{th} cycle satisfy (5.50), we have

$$\left(\left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu_i(j)}} - \left(\frac{\mathbf{x}}{\mathbf{x}^*} \right)^{\mathbf{z}_{\mu_i(j+1)}} \right) \geq 0$$

for all $\mathbf{x} \in \overline{\mathcal{S}}_\mu$. Similarly, we can apply Lemma 5.3.4 to show that

$$\left\langle \alpha, \sum_{j=1}^{i} \mathbf{s}_{\mu_i(j)} \right\rangle = \sum_{j=1}^{l_i-1} \lambda_j \left\langle \mathbf{z}_{\mu_i(j)} - \mathbf{z}_{\mu_i(j+1)}, \alpha \right\rangle \leq 0 \tag{5.52}$$

where $\lambda_j \in \mathbb{Z}_{\leq 0}$ for $j = 1, 2, \ldots, l_i - 1$. This implies $\kappa_i \langle \alpha, \mathbf{X}_i \rangle \leq 0$. Since we can carry out this procedure for all $i = 1, \ldots, \delta$, we have

$$\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle = \kappa_1 \langle \alpha, \mathbf{X}_1 \rangle + \cdots + \kappa_\delta \langle \alpha, \mathbf{X}_\delta \rangle \leq 0$$

and we are done.

□

5.3.5 Applications

Several global stability results follow immediately from Theorem 5.3.3. In particular, this theorem is sufficient to guarantee solutions of (2.4) do not approach the boundary for general complex balanced systems if they remain within a single stratum. This is clear because, if we take $T \geq 0$ to be the final time that a trajectory $\mathbf{x}(t)$ enters the relevant stratum, the linear functional $H(\mathbf{x}(t)) = \langle \alpha, \mathbf{x}(t) \rangle$, where α satisfies (5.35), must satisfy $H(\mathbf{x}(t)) \leq H(\mathbf{x}(T)) < 0$ for all $t > T$ since $\frac{d}{dt} H(\mathbf{x}(t)) = \langle \alpha, \mathbf{f}(\mathbf{x}(t)) \rangle \leq 0$ for all $t > T$ by Theorem 5.3.3. This contradicts the observation that, if $\mathbf{x}(t)$ converges to $\mathbf{x}^* \in L_I$ then

$$\lim_{t \to \infty} H(\mathbf{x}(t)) = H(\mathbf{x}^*) = 0.$$

If multiple strata $\mathcal{S}_\mu$ intersect a given set L_I, however, we cannot guarantee the existence of a common α satisfying $\langle \alpha, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ simultaneously within all such strata. Consequently, we cannot rule out the possibility that trajectories approach the boundary through creative maneouvering between strata.

This difficulty, however, does not always arise. In cases where there is a common α "near" each L_I, trajectories are pushed away from the boundary according to Theorem 5.1.3. The following lemma relates this result to the methodology of Section 5.3.4.

Lemma 5.3.6 (Lemma 3.14, [54])**.** *Let M_I denote the set of permutation operators μ such that $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$ for a fixed I. Then, for every compact subset K of L_I, there exists a neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$ such that*

$$U \subseteq \bigcup_{\mu \in M_I} \overline{\mathcal{S}}_\mu.$$

Proof. Suppose there is a compact subset K of L_I such that, for every neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$, $U \subseteq \cup_{\mu \in M_I} \overline{\mathcal{S}}_\mu$ is violated. It follows that there exists a sequence $\{\mathbf{x}^k\} \subseteq \cup_{\mu \notin M_I} \overline{\mathcal{S}}_\mu$ such that $\mathbf{x}^k$ approaches L_I as $k \to \infty$. Since K is compact, we may select the sequence so that $\mathbf{x}^k \to \mathbf{x}$ for some specific $\mathbf{x} \in L_I$.

Since there are finite strata, we can select a subsequence $\{\mathbf{x}^{k_i}\} \subseteq \mathcal{S}_\mu$ for a fixed $\mu \notin M_I$; however, this implies $\lim_{i \to \infty} \mathbf{x}^{k_i} = \mathbf{x} \in \overline{\mathcal{S}}_\mu \cap L_I$. This contradicts $\mu \notin M_I$. Consequently, our assumption was in error, and $U \subseteq \cup_{\mu \in M_I} \overline{\mathcal{S}}_\mu$ for some neighbourhood U of K in $\mathbb{R}^m_{\geq 0}$. The result follows. □

Given Lemma 5.3.6 and Theorem 5.1.3, we can see that (5.7) corresponds to the existence of a common α_I existing in all strata adjacent to a given set L_I, which is the desired condition. In general, however, it is difficult to verify this condition directly. The following result gives testable conditions from which (5.7) follows. It also answers the question of global stability.

Corollary 5.3.1 (Corollary 3.15, [54])**.** *Consider a complex balanced system. Let M_I denote the set of permutation operators μ such that $\overline{\mathcal{S}}_\mu \cap L_I \neq \varnothing$ for a fixed I. Suppose that for every fixed I, $1 \leq |I| < m$, corresponding to a semi-locking set one of Condition 1 or Condition 2 given below is satisfied. Then the unique positive complex balanced equilibrium $\mathbf{x}^*$ of $\mathsf{C}_{\mathbf{x}_0}$ is a global attractor for $\mathsf{C}_{\mathbf{x}_0}$.*

Condition 1: *We will say Condition 1 is satisfied if there exists an $\alpha_I \in \mathbb{R}^m_{\leq 0}$ satisfying (5.6) such that, for all $i = 1, 2, \ldots, n-1$ and all $\mu \in M_I$,*

$$\langle \mathbf{z}_{\mu(i)} - \mathbf{z}_{\mu(i+1)}, \alpha_I \rangle \geq 0.$$

Condition 2: *Consider the cycles* $\left\{\nu_1^{(i)}, \nu_2^{(i)}, \ldots, \nu_{l_i}^{(i)}, \nu_1^{(i)}\right\}$, $i = 1, 2, \ldots, \delta$, *in the cyclic decomposition of a complex balanced system according to Lemma 3.3.3. We will reindex each cycle to* $\{1, 2, \ldots, l_i, 1\}$ *and let* μ_i, $i = 1, \ldots, \delta$, *denote the appropriately reindexed permutation operator restricted to the complexes in the* i^{th} *cycle. We will say Condition 2 is satisfied if there exists an* $\alpha_I \in \mathbb{R}^m_{\leq 0}$ *satisfying (5.6) such that, for all* $i = 1, 2, \ldots, \delta$ *and all* $\mu \in M_I$,

$$\left\langle \sum_{j=1}^{k} \mathbf{s}_{\mu_i(j)}, \alpha_I \right\rangle \leq 0, \qquad \text{for } k = 1, 2, \ldots, l_i - 1,$$

where $\mathbf{s}_{\mu_i(j)} = \mathbf{z}_{\mu_i(j)} - \mathbf{z}_{\mu_i(j)+1}$.

Proof. The proof will proceed in the following steps. We will prove firstly that Condition 1 or 2 is sufficient to show $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in \cup_{\mu \in M_I} \overline{\mathcal{S}}_\mu$. We then show by Lemma 5.3.6 that the such systems satisfy the hypotheses of Theorem 5.1.3 so that $\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$. We then show that for complex balanced systems this is enough to prove the global stability of the positive equilibrium concentration in each positive compatibility class.

Consider a complex balanced system. We know that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all sets L_I corresponding to non-semi-locking sets I by Lemma 5.3.3. We also know that for complex balanced systems we have $\omega(\mathbf{x}_0) \cap \{\mathbf{0}\} = \varnothing$ (see Proposition 20 of [13], for one proof). That is to say, we need only consider sets L_I corresponding to semi-locking sets I such that $1 \leq |I| < m$.

It is clear by the proof of Theorem 5.3.3 that either Condition 1 (by (5.52)) or Condition 2 (by (5.51)) is sufficient to prove that $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in \cup_{\mu \in M_I} \overline{\mathcal{S}}_\mu$. This implies by Lemma 5.3.6 that for every compact subset K of L_I there is a neighbourhood U of K in

$\mathbb{R}^m_{\geq 0}$ such that $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ for all $\mathbf{x} \in U$. We know that solutions of (2.4) are bounded for complex balanced systems since, for the function

$$L(\mathbf{x}) = \sum_{i=1}^{m} x_i(\ln(x_i) - \ln(x_i^*) - 1) + x_i^*, \tag{5.53}$$

we have $\frac{d}{dt}L(\mathbf{x}(t)) < 0$ for all $t \geq 0$ and $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ [33]. It follows by Theorem 5.1.3 that $\omega(\mathbf{x}_0) \cap L_I = \varnothing$ for all such sets L_I. Since we have considered all sets L_I, it follows that $\omega(\mathbf{x}_0) \cap \partial\mathbb{R}^m_{>0} = \varnothing$.

Since our system is complex balanced, it follows by Theorem 3.3.1 that there is precisely one equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ in each positive stoichiometric compatibility class $\mathsf{C}_{\mathbf{x}_0}$. Since there are no ω-limit points on the boundary of the positive orthant, by Theorem 5.1.1 it follows that the only ω-limit point is the positive equilibrium concentration. It follows that $\mathbf{x}^*$ is a global attractor for $\mathsf{C}_{\mathbf{x}_0}$ and we are done. □

Since Condition 1 implies Condition 2 by Lemma 5.3.4, but the converse does not necessarily hold, it is typically preferable to check Condition 2. In the following section, our approach will be to define a set P of vectors $\sum_{j=1}^{k} \mathbf{s}_{\mu_i(j)}, i = 1, \ldots, \delta, k = 1, \ldots, l_i - 1$, and check Condition 2 relative to this set.

The following result corresponds to Corollary 4.5 of [3]. It is a generalization of Theorem 23 of [13] (stated Theorem 5.3.1 here) to complex balanced systems.

Corollary 5.3.2 (Corollary 3.16, [54])**.** *Consider a complex balanced mass-action system whose stoichiometric subspace S is two-dimensional. Then the unique positive complex balanced equilibrium $\mathbf{x}^*$ of $\mathsf{C}_{\mathbf{x}_0}$ is a global attractor for $\mathsf{C}_{\mathbf{x}_0}$.*

Proof. With application of Corollary 5.3.1, the proof follows identically to the proof of

Theorem 23 contained in [13]. We also notice that since trajectories of any complex balanced system are bounded by $L(\mathbf{x}(t)) \leq L(\mathbf{x}_0)$ for all $t \geq 0$, we may remove the assumption of boundedness. □

Example 5.3.2. *The following example is given in [3] as an example of a three-dimensional complex balanced system for which a general method of guaranteeing global stability is not known. The system considered is*

$$\mathcal{A}_1 \leftrightarrows \mathcal{A}_2 \leftrightarrows \mathcal{A}_1 + \mathcal{A}_2 \leftrightarrows \mathcal{A}_1 + \mathcal{A}_3. \tag{5.54}$$

We assign $\mathcal{C}_1 = \mathcal{A}_1$, $\mathcal{C}_2 = \mathcal{A}_2$, $\mathcal{C}_3 = \mathcal{A}_1 + \mathcal{A}_2$, *and* $\mathcal{C}_4 = \mathcal{A}_1 + \mathcal{A}_3$, *and* $x_1 = [\mathcal{A}_1]$, $x_2 = [\mathcal{A}_2]$, *and* $x_3 = [\mathcal{A}_3]$. *The system is complex balanced at all equilibrium concentrations so we need not consider the rate constants. The compatibility class* $\mathsf{C}_{\mathbf{x}_0} = \mathbb{R}^3_{>0}$ *is three-dimensional and the only non-trivial semi-locking set is* $I = \{1, 2\}$ *so that we need only consider the set* L_I *corresponding to this index set.*

We will show that all strata such that $\overline{\mathcal{S}}_\mu \cap L_{\{1,2\}} \neq \varnothing$ *have a common* $\alpha_I \in \mathbb{R}^m_{\leq 0}$ *satisfying (5.6) and Condition 2 of Corollary 5.3.1. There are six* μ *such that* $\overline{\mathcal{S}}_\mu \cap L_{\{1,2\}} \neq \varnothing$*:*

(1) $\mu([1,2,3,4]) = [2,4,1,3]$
(2) $\mu([1,2,3,4]) = [4,2,1,3]$
(3) $\mu([1,2,3,4]) = [4,1,2,3]$
(4) $\mu([1,2,3,4]) = [2,1,4,3]$
(5) $\mu([1,2,3,4]) = [1,2,4,3]$
(6) $\mu([1,2,3,4]) = [1,4,2,3]$.

Since the vectors $\sum_{j=1}^k \mathbf{s}_{\mu_i(j)}$ *are the vector coefficients of the bracketed strata terms in (5.41), it is instructive to rewrite the system of differential equations (2.4) implied by the network (5.54) according to Theorem 5.3.2. (This analysis is not, however, required to determine the set of all admissible vectors* $\sum_{j=1}^k \mathbf{s}_{\mu_i(j)}$*.) We will carry out the analysis for*

one stratum and leave the rest as an exercise.

The first stratum is given by

$$\mathcal{S}_\mu = \left\{ \mathbf{x} \in \mathbb{R}^3_{>0} \;\middle|\; \frac{x_2}{x_2^*} > \frac{x_1}{x_1^*} \cdot \frac{x_3}{x_3^*} > \frac{x_1}{x_1^*} > \frac{x_1}{x_1^*} \cdot \frac{x_2}{x_2^*} \right\}. \tag{5.55}$$

Since the system can be decomposed into the cycles $\{1,2,1\}$*,* $\{2,3,2\}$*, and* $\{3,4,3\}$*, according to Lemma 3.27 and Theorem 5.3.2, the system (2.4) can be written*

$$\begin{aligned} \frac{d\mathbf{x}}{dt} = \kappa_1 \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix} \left(\frac{x_2}{x_2^*} - \frac{x_1}{x_1^*} \right) + \kappa_2 \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \left(\frac{x_2}{x_2^*} - \frac{x_1}{x_1^*} \cdot \frac{x_2}{x_2^*} \right) \\ + \kappa_3 \begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix} \left(\frac{x_1}{x_1^*} \cdot \frac{x_3}{x_3^*} - \frac{x_1}{x_1^*} \cdot \frac{x_2}{x_2^*} \right) \end{aligned} \tag{5.56}$$

where $\mathbf{x}^* = [x_1^*, x_2^*, x_3^*]^T$ *is the unique positive complex balanced equilibrium point and* κ_1*,* κ_2 *and* κ_3 *are positive constants determined by the rate constants. In* $\mathcal{S}_\mu$ *the bracketed terms of (5.56) are strictly positive so that the sign of* $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle$ *is determined by the vector terms alone. Consider a vector* $\alpha_I \in \mathbb{R}^3_{\leq 0}$ *satisfying (5.6) for which*

$$\alpha_I = \lambda_1(-1,0,0) + \lambda_2(-1,-1,0), \qquad \lambda_1 \geq 0, \lambda_2 \geq 0.$$

For any such α_I *we have* $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$*, which is sufficient to show the linear function* $H(\mathbf{x}(t)) = \langle \alpha_I, \mathbf{x}(t) \rangle$ *repels trajectories from the set* $L_{\{1,2\}}$ *in the first stratum.*

A similar analysis can be carried out in the five other strata. Removing repetition, the

set of admissible vectors $\sum_{j=1}^{k} \mathbf{s}_{\mu(j)}$ *is*

$$P = \left\{ \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix}, \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 1 \\ -1 \end{bmatrix} \right\}.$$

Since $\alpha_I = (-1, -1, 0)$ *satisfies* $\langle \alpha_I, \mathbf{v} \rangle \leq 0$ *for all* $\mathbf{v} \in P$*, we have that* $\langle \alpha_I, \mathbf{f}(\mathbf{x}) \rangle \leq 0$ *for all* $\mathbf{x} \in \overline{\mathcal{S}}_\mu$ *where* $\mathcal{S}_\mu$ *is such that* $\overline{\mathcal{S}}_\mu \cap L_{\{1,2\}} \neq \varnothing$*. It follows by Corollary 5.3.1 that* $\mathbf{x}^*$ *is a global attractor for* $\mathsf{C}_{\mathbf{x}_0} = \mathbb{R}^3_{>0}$ *and we are done.*

Chapter 6

Linear Conjugacy of Chemical Reaction Networks

In this chapter we introduce the concept of *linearly conjugate* reaction networks. The primary result of Section 6.2 is Theorem 6.2.3 which gives conditions under which two networks are linearly conjugate [36]. In Section 6.3 we adapt the mixed-integer linear programming framework introduced by G. Szederkényi in the series of papers [58–61] to consider linear conjugate network and refine the procedure for determining weakly reversible networks [38]. We illustrate the important points with examples.

6.1 Background

In the typical analysis of chemical reaction networks, we are given a network and asked to analyse its qualitative behaviour based on some set of kinetic assumptions. We are also often asked the inverse problem, that is to say, we are often given kinetic information and

asked to determine the network structure.

This immediately gives rise to the following question: Is the network structure unique? Or is it possible for two *different* networks to give rise to the same dynamics? Consider the following example, which was originally given in the paper [18] by G. Craciun and C. Pantea.

Example 6.1.1. *Consider the networks*

$$\mathcal{N}: \qquad \begin{aligned} \mathcal{A}_1 &\xrightarrow{2/9} \mathcal{A}_2 + \mathcal{A}_3 \\ \mathcal{A}_1 &\xrightarrow{1/6} 2\mathcal{A}_2 \\ \mathcal{A}_1 &\xrightarrow{11/18} 2\mathcal{A}_4 \end{aligned} \tag{6.1}$$

and

$$\mathcal{N}': \qquad \begin{aligned} \mathcal{A}_1 &\xrightarrow{5/9} \mathcal{A}_2 + \mathcal{A}_4 \\ \mathcal{A}_1 &\xrightarrow{1/9} 2\mathcal{A}_3 \\ \mathcal{A}_1 &\xrightarrow{1/3} 2\mathcal{A}_4. \end{aligned} \tag{6.2}$$

It can be easily checked that under the assumption of mass-action kinetics, both (6.1) and (6.2) give rise to the following system of differential equations

$$\frac{dx_1}{dt} = -x_1, \qquad \frac{dx_2}{dt} = \frac{5}{9}x_1, \qquad \frac{dx_3}{dt} = \frac{2}{9}x_1, \qquad \frac{dx_4}{dt} = \frac{11}{9}x_1 \tag{6.3}$$

according to (2.3).

In other words, (6.1) and (6.2) give rise to exactly the same dynamics! If the only information we were provided was kinetic information of the form (6.3) we would not

be able to determine whether (6.1) or (6.2) was the correct network structure—even *in principle*. Within the literature, this fact is sometimes referred to as the "fundamental dogma of chemical kinetics" [20, 58, 59].

This realization has given rise to the following terms.

Definition 6.1.1. *Two reaction networks $\mathcal{N}$ and $\mathcal{N}'$ are said to be* ***dynamically equivalent*** *if they generate the same mass-action kinetics (2.3).*

Definition 6.1.2. *The reaction networks $\mathcal{N}$ will be called a* ***realization*** *of the kinetics (2.3) if $\mathcal{N}$ gives rise to the system (2.3) under the assumption of mass-action kinetics. In the case that two networks $\mathcal{N}$ and $\mathcal{N}'$ give rise to the same mass-action kinetics (2.3) (i.e. they are dynamically equivalent) we will say that $\mathcal{N}'$ is an alternative realization of $\mathcal{N}$, or vice-versa.*

The most comprehensive study of realizations has been conducted in [18] wherein G. Craciun and C. Pantea consider conditions under which two networks can produce the same dynamics. G. Craciun, C. Pantea and G. Rempala have followed up upon this work by presenting results which attempt to quantify which networks with equivalent dynamics are most likely to correspond to the physically realized network [20]. Other related work can be found in E. Averbukh [6], F. Horn and R. Jackson [33], F. Krambeck [39], D. MacLean [42], J. Tóth, G. Li, H. Rabitz and A. Tomlin [62], and J. Wei and J. Kuo [64].

An important aspect of the study of dynamically equivalent networks is that, if one network has known dynamics and the other system does not, then the system with unknown dynamics inherits the known dynamics of the first. This is particularly powerful when the network with known dynamics has dynamics known from the reaction structure alone as in networks satisfying the Deficiency Zero Theorem (Theorem 3.4.2).

This also gives rise to the follow up question: Is it possible to relate the dynamics of two networks when the kinetics *differ* from one another? That is to say, can we relate important properties such as persistence, number and stability of equilibrium points, dimensions of kinetic and stoichiometric subspaces, etc., between networks which do not generate identical mass-action systems (2.3)?

This was the question which we posed in the paper [36], the results of which we summarize in Section 6.2. In that paper, we attempted to bring these known results on realizations together into a unified framework and language. We chose to borrow from dynamical systems theory in calling two networks which exhibit the same qualitative dynamics *conjugate* networks [46, 65]. More specifically, we have called two networks conjugate if there is a mapping which takes trajectories of one network into trajectories of the other. For networks where the governing differential equations for two networks are identical, the required conjugacy mapping is the identity. We go further than the results of [18] with Theorem 6.2.3 by giving conditions on the network for which a non-trivial mapping is required to demonstrate conjugacy.

Another important question is, given a specified network, can we actually *find* a network which is conjugate to it? The papers [18] and [36] present conditions under which two networks can be shown to be conjugate but they provide no mechanism by which a second network with conjugate dynamics can be found. This is an important problem since, if a network with unknown dynamics can be shown to be conjugate to a network with known dynamics, the dynamical properties of the second network will apply to the first as well. Consequently, for networks with unknown dynamics, if possible, we would like to be able to find networks which are conjugate to it with known dynamics.

Significant headway on this problem has been made recently by G. Szederkényi. In [58],

he proposed a mixed-integer linear programming (MILP) algorithm capable of determining sparse and dense realizations of a given kinetics (i.e. networks with the fewest and greatest number of reactions for a fixed complex set). This work has been continued in a series of papers which address specific supplemental conditions which can be imposed upon the networks. With K. Hangos and T. Péni, he considers the problem of determining when networks have equivalent dynamics to a detailed or complex balanced network for specific rate constant choices [59, 60], and with K. Hangos and Z. Tuza he considers conditions which guarantee weak reversibility [61].

In Section 6.3, we summarize these results and present the results of our own collaboration with G. Szederkényi [38]. In particular, we extend the MILP framework of his series of papers to include the notion of linear conjugacy which we will present in Section 6.2. We also show how weak reversibility can be formulated as a linear constraint within this framework, which is an important improvement over the results of [61].

6.2 Linearly Conjugate Networks

In this section we introduce the a concept which guarantees that two mass-action systems have the same qualitatively behaviour despite disparate reaction network structure. Our approach to this problem is to show that there is a suitably nice mapping between the flows of (2.3) for one network and another. In the standard theory of differential equations, the notion of equivalence between trajectories is captured in the well-studied concept of *conjugacy* (see [46, 65]).

Consider two general systems of autonomous ordinary differential equations

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t)), \qquad \mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}^n \tag{6.4}$$

$$\frac{d\mathbf{y}(t)}{dt} = \mathbf{g}(\mathbf{y}(t)), \qquad \mathbf{y}(0) = \mathbf{y}_0 \in \mathbb{R}^n \tag{6.5}$$

and associate to them the flows $\Phi(\mathbf{x}_0, t)$ and $\Psi(\mathbf{y}_0, t)$, respectively. We now introduce the concepts relevant to the conjugacy of systems (6.4) and (6.5) (see [65]).

Definition 6.2.1. *The function* $\mathbf{h} : \mathbb{R}^n \mapsto \mathbb{R}^n$ *is called a* $\mathbf{C}^k$-***diffeomorphism*** *if all partial derivatives of* $\mathbf{h}(\mathbf{x})$ *and* $\mathbf{h}^{-1}(\mathbf{x})$ *exist up to the* k^{th} *order.*

Definition 6.2.2. *The systems (6.4) and (6.5) are said to be* $\mathbf{C}^k$-***conjugate*** *if there exists a* $\mathbf{C}^k$*-diffeomorphism* $\mathbf{h} : \mathbb{R}^n \mapsto \mathbb{R}^n$ *such that* $\mathbf{h}(\Phi(\mathbf{x}_0, t)) = \Psi(\mathbf{h}(\mathbf{x}_0), t)$ *for all* $\mathbf{x}_0 \in \mathbb{R}^n$ *and* $t \geq 0$.

The notion of *conjugacy* is generally considered a strong condition in that it requires the $\mathbf{C}^k$-diffeomorphism $\mathbf{h}(\mathbf{x})$ to not only map orbits of one system into another but also to exactly preserve the parametrization of time. Due to how stringent this requirement typically is, researchers often use the weaker notion of *equivalence*, whereby orbits are again mapped into orbits but only the orientation of time is preserved; the exact parametrization of time is left undetermined. In our study of mass-action systems, however, we will be able to satisfy the standard notion of conjugacy.

We now move the notion of $\mathbf{C}^k$-conjugacy to the framework of chemical reaction networks. It should be noted that conjugacy is a special case of chemical *lumping* introduced by J. Wei and J. Kuo in [64] and developed further by J. Tóth, G. Li, H. Rabitz and A. Tomlin in [62]. In their notion of lumping, several species are grouped together to (potentially) reduce the dimension of the kinetic system; conjugacy is implied in the case when

the dimension is not reduced. The notion of linear conjugacy is specifically considered by Gy. Farkas in [22], although our main result (Theorem 6.2.3) goes further in presenting verifiable conditions under which conjugacy holds. Several other results also related to conjugacy exist within the literature [6, 18, 39, 42, 58, 59].

We define the reaction network $\mathcal{N}' = (\mathcal{S}, \mathcal{C}', \mathcal{R}')$ as consisting of the reaction set

$$\mathcal{R}'_i: \qquad \sum_{j=1}^{m} \tilde{z}_{ij}\mathcal{A}_j \longrightarrow \sum_{j=1}^{m} \tilde{z}'_{ij}\mathcal{A}_j, \qquad i = 1, \ldots, \tilde{r} \tag{6.6}$$

or, alternatively,

$$\mathcal{R}'_i: \qquad \tilde{\mathcal{C}}_i \longrightarrow \tilde{\mathcal{C}}'_i, \qquad i = 1, \ldots, \tilde{r}. \tag{6.7}$$

The associated mass-action system will be denoted $(\mathcal{S}, \mathcal{C}', \mathcal{R}', \mathbf{k}')$ where the rate constants are given by $\tilde{k}_i > 0$, $i = 1, \ldots, \tilde{r}$. We will let $\Phi(\mathbf{x}_0, t)$ denote the flow associated with the mass-action kinetics (2.3) for $\mathcal{N}$ and $\Psi(\mathbf{y}_0, t)$ denote the flow associated with the mass-action kinetics (2.3) for $\mathcal{N}'$. We will adopt the convention of referring to $\mathcal{N}$ as the *original network* and $\mathcal{N}'$ as the *target network*.

Note that, while we follow the notation of [18] in denoting any second network by $\mathcal{N}' = (\mathcal{S}, \mathcal{C}', \mathcal{R}')$, we distinguish the relevant components of the second network using tildés to avoid confusion with the vectors $\mathbf{z}'_i$ from the first system. Also notice that the networks $\mathcal{N}$ and $\mathcal{N}'$ are allowed to have not only different complexes and reactions, but different *numbers* of complexes and reactions; the number of species $|\mathcal{S}| = m$, however, is required to be the same.

We are now prepared to define our notion of conjugacy of chemical reaction networks.

Definition 6.2.3. *Consider two mass-action systems $\mathcal{N}$ and $\mathcal{N}'$. We will say $\mathcal{N}$ and $\mathcal{N}'$ are* $\mathbf{C}^k$***-conjugate*** *if there exists a $\mathbf{C}^k$-diffeomorphism $\mathbf{h} : \mathbb{R}^m_{>0} \mapsto \mathbb{R}^m_{>0}$ such that $\mathbf{h}(\Phi(\mathbf{x}_0, t)) =$*

$\Psi(\mathbf{h}(\mathbf{x}_0), t)$ *for all* $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$.

Definition 6.2.4. *We will say* $\mathcal{N}$ *and* $\mathcal{N}'$ *are* ***linearly conjugate*** *if they are* $\mathbf{C}^\infty$*-conjugate and the diffeomorphism* $\mathbf{h} : \mathbb{R}^m_{>0} \mapsto \mathbb{R}^m_{>0}$ *is linear.*

We will focus on the notion of linear conjugacy. Note that any linear diffeomorphism is necessarily $\mathbf{C}^\infty$ so that any linear conjugacy is a $\mathbf{C}^\infty$-conjugacy. The following results clarify the form the linear mapping $\mathbf{h} : \mathbb{R}^m_{>0} \mapsto \mathbb{R}^m_{>0}$ may take and the implications of conjugacy. It should be contrasted with Lemma 1 and Theorem 1 of [22].

Lemma 6.2.1. *A linear, bijective mapping* $\mathbf{h} : \mathbb{R}^m_{>0} \mapsto \mathbb{R}^m_{>0}$ *may consist of at most positively scaling and reindexing of coordinates.*

Proof. Consider a linear, bijective mapping $\mathbf{h} : \mathbb{R}^m_{>0} \mapsto \mathbb{R}^m_{>0}$. Since $\mathbf{h}(\mathbf{x})$ is linear, it can be represented $\mathbf{h}(\mathbf{x}) = A\mathbf{x}$ where $A \in \mathbb{R}^{m \times m}$ and since $\mathbf{h}(\mathbf{x})$ is bijective, it has an inverse $\mathbf{h}^{-1}(\mathbf{x}) = A^{-1}\mathbf{x}$. Since the mappings are from $\mathbb{R}^m_{>0}$ to $\mathbb{R}^m_{>0}$, all entries in A and A^{-1} must be non-negative and every row of A and A^{-1} must contain at least one non-zero entry.

Suppose there is a row of A with more than one non-zero entry. Since A and A^{-1} may contain no negative numbers, in order to satisfy $A\ A^{-1} = I$ this implies that there are at least two rows of A^{-1} which contain zeroes in the same $m - 1$ columns. Such an A^{-1}, however, would have a zero determinant and therefore be non-invertible, which is a contradiction.

It follows that each row of A has precisely one positive entry. Since A is invertible it follows that each column of A also has precisely one positive entry so that A is a positively weighted permutation matrix. In terms of the transformation $\mathbf{h}(\mathbf{x}) = A\mathbf{x}$ this means the mapping may only positively scale and re-index the components of the vector $\mathbf{x}$, which completes the proof. □

Lemma 6.2.2. *If a mass-action system $\mathcal{N}$ is linearly conjugate to a mass-action system $\mathcal{N}'$ and $\mathcal{N}'$ exhibits locally stable dynamics, then $\mathcal{N}$ exhibits locally stable dynamics.*

Proof. The result follows trivially from Lemma 6.2.1 and Definition 6.2.3. □

It is worth noting that other qualitative properties of mass-action systems are also preserved by linear conjugacy (multistability, persistence, boundedness, etc.). Some aspects of qualitative equivalence of $\mathcal{N}$ and $\mathcal{N}'$ can, however, fail for non-linear conjugacies (see [62]).

6.2.1 Known Results

In this section, we give a brief summary of the results which are, to the best of our knowledge, the only attempts to demonstrate conjugacy of two mass-action systems.

For the first few results considered, conjugacy is demonstrated by showing an exact equivalence between the governing differential equations (2.3) for $\mathcal{N}$ and $\mathcal{N}'$. This phenomenon is called *macro-equivalence* in [33] and *confoundability* in [18]. In [58] and the related literature, two networks with identical dynamics are called two *realizations* of the same reaction kinetic differential equations (see Definition 6.19). We will also consider the notion of *lumping* introduced in [64] and further developed in [62], which allows for non-trivial conjugacies and also dimension reduction.

The most thorough study of realizations to date has been conducted by G. Craciun and C. Pantea [18]. In that paper, the authors considered the problem of experimentally assigning values to rate constants to systems with linearly dependent reactions flowing from the same reactant complexes. The following is a corrected version of their main result. We will let $\mathcal{C}_{react}$ denote the set of reactant complexes in either the complex set $\mathcal{C}$ or the complex set $\mathcal{C}'$.

Theorem 6.2.1 (Theorem 4.4 (corrected), [18])**.** *There exist rate constants choices such that the mass-action systems $\mathcal{N}$ and $\mathcal{N}'$ are conjugate with $\mathbf{h}(\mathbf{x}) = \mathbf{x}$ if and only if $C_{\mathcal{R}}(\mathcal{C}^0) \cap C_{\mathcal{R}'}(\mathcal{C}^0) \neq \varnothing$ for every complex $\mathcal{C}^0 \in \mathcal{C}_{react}$, where*

$$C_{\mathcal{R}}(\mathcal{C}^0) = \left\{ \sum_{i=1}^{r} \alpha_i (\mathbf{z}_i' - \mathbf{z}_i) \mid \alpha_i > 0 \text{ if } \mathbf{z}_i = \mathbf{z}^0, \alpha_i = 0 \text{ otherwise} \right\}. \tag{6.8}$$

This theorem gives necessary and sufficient conditions for two chemical reaction networks $\mathcal{N}$ and $\mathcal{N}'$ to admit rate constant vectors which generate the same set of governing differential equations (2.3). It is clear that conjugacy follows according to Definition 6.2.3. It should be noted, however, that conjugacy may only hold for specific choices of the rate constants. (The original result in [18] overlooked the possibility that the net flow from a reactant complex in either $\mathcal{N}$ or $\mathcal{N}'$ could equal zero. It was noted by G. Szederkényi in [57] that conjugacy could hold for networks with different reactant complexes so long as the corresponding outflows cancel in (2.3).)

Averbukh also considers conditions which relate the dynamics of an undetermined network $\mathcal{N}$ to a network $\mathcal{N}'$ with known dynamics. In particular, he presents conditions under which a general network has the same dynamics as a detailed balanced network (Theorem 2 of [6]). This is a powerful result since detailed balanced networks are known to exhibit locally stable dynamics [33, 63].

Conjugacy is also considered by F. Krambeck in Section 6 of [39] for detailed balanced systems where it is referred to as *non-uniqueness* of the rate constants. F. Horn and R.

Jackson briefly consider conjugate systems in [33]. Their primary example is the network

$$\mathcal{N}: \quad \begin{array}{ccc} 2\mathcal{A}_1 + \mathcal{A}_2 & \xrightarrow{1} & 3\mathcal{A}_1 \\ {\scriptstyle \epsilon}\uparrow & & \downarrow{\scriptstyle \epsilon} \\ 3\mathcal{A}_2 & \xleftarrow{1} & \mathcal{A}_1 + 2\mathcal{A}_2 \end{array}$$

where $\epsilon > 0$. (This was previously considered as Example 3.4.5.) They show that the network exhibits locally stable dynamics for $\epsilon \geq 1/6$ and that the network possesses the same mass-action kinetics (2.3) as a complex balanced network $\mathcal{N}'$ for $\epsilon \geq 1/2$. The Master's thesis of D. MacLean also contains specific examples of networks which are conjugate to complex balanced systems [42]. This connection with complex balanced systems is made more explicit in her unpublished research notes, to which much of the inspiration for the idea of linear conjugacy is indebted.

Another related strain of research has been conducted on the concept of chemical *lumping*. In [64], J. Wei and J. Kuo introduced the notion of lumping for monomolecular reactions. This was extended to general kinetics and transformations by J. Tóth, G. Li, H. Rabitz and A. Tomlin in [62]. They give the following definition, which is based on the following set-up.

Consider two general systems of autonomous ordinary differential equations

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t)), \qquad \mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}^n \tag{6.9}$$

$$\frac{d\mathbf{y}(t)}{dt} = \mathbf{g}(\mathbf{y}(t)), \qquad \mathbf{y}(0) = \mathbf{y}_0 \in \mathbb{R}^m \tag{6.10}$$

where $m \leq n$ and $\mathbf{f} : \mathbb{R}^n \mapsto \mathbb{R}^n$ and $\mathbf{g} : \mathbb{R}^m \mapsto \mathbb{R}^m$ are continuously differentiable. Associate to these systems the flows $\Phi(\mathbf{x}_0, t)$ and $\Psi(\mathbf{y}_0, t)$, respectively.

Definition 6.2.5. *Suppose there exist positive integers n and m such that $m \leq n$, a $\mathbf{C}^2$ transformation $\mathbf{h} : \mathbb{R}^n \mapsto \mathbb{R}^m$ satisfying $\mathbf{h}(\mathbf{0}) = \mathbf{0}$, and a $\mathbf{C}^1$ transformation $\mathbf{u} : \mathbb{R}^n \mapsto \mathbb{R}^{n-m}$. Consider the transformation*

$$\hat{\mathbf{h}}(\mathbf{x}) = \begin{bmatrix} \mathbf{h}(\mathbf{x}) \\ \mathbf{u}(\mathbf{x}) \end{bmatrix}.$$

*We will say that (6.9) is **exactly lumpable** into (6.10) via the transformation $\mathbf{y} = \mathbf{h}(\mathbf{x})$ if*

1. $\mathbf{h}(\Phi(\mathbf{x}_0, t)) = \Psi(\mathbf{h}(\mathbf{x}_0), t)$ *for all* $\mathbf{x}_0 \in \mathbb{R}^n$,
2. *The Jacobian of* $\hat{\mathbf{h}}(\mathbf{x})$ *is nonsingular for all* $\mathbf{x} \in \mathbb{R}^n$, *and*
3. $\lim_{\|\mathbf{x}\| \to \infty} \|\hat{\mathbf{h}}\| = \infty$.

In other words, a system is lumpable into another system if there is a (potentially dimension-reducing) transformation for which the kinetics of the second system depends solely on the lumped variables of the transformation. In the case where $m = n$ (i.e. the dimension of the system is not reduced) the notions of lumping and conjugacy coincide aside from small technical requirements (e.g. condition 3 above). The following result is also provided in [62].

Theorem 6.2.2. *The system (6.9) is exactly lumpable into the system (6.10) via the non-degenerate transformation $\mathbf{h}(\mathbf{x})$ if and only if*

$$\mathbf{g}(\mathbf{h}(\mathbf{x})) = \mathbf{h}'(\mathbf{x})\mathbf{f}(\mathbf{x})$$

for all $\mathbf{x} \in \mathbb{R}^n$.

In [62], the authors prove that many dynamical properties of dynamical systems are transferred to their corresponding lumped systems. The case where $\mathbf{h}(\mathbf{x})$ is linear is considered by Gy. Farkas in [22]. Our approach here will be different in focusing on how the reaction graph is alterred for conjugate networks.

6.2.2 Original Results

In this section, we present our main original result regarding linear conjugacy of chemical reaction networks. In Section 6.2.3, we show how Theorem 6.2.3 can broaden the scope of weakly reversible networks theory through several illustrative examples.

Theorem 6.2.3 (Theorem 3.2, [36]). *Consider two mass-action systems $\mathcal{N}$ and $\mathcal{N}'$. Suppose that for the rate constants $k_i > 0$, $i = 1, \ldots, r$, there exist constants $b_i > 0$, $i = 1, \ldots, \tilde{r}$, and $c_j > 0$, $j = 1, \ldots, m$, such that, for every $\mathcal{C}^0 \in \mathcal{C}_{react}$,*

$$\sum_{\substack{i=1 \\ \mathcal{C}_i = \mathcal{C}^0}}^{r} k_i(\mathbf{z}_i' - \mathbf{z}_i) = T \sum_{\substack{i=1 \\ \tilde{\mathcal{C}}_i = \mathcal{C}^0}}^{\tilde{r}} b_i(\tilde{\mathbf{z}}_i' - \tilde{\mathbf{z}}_i) \tag{6.11}$$

where $T = diag\{c_j\}_{j=1}^{m}$. Then $\mathcal{N}$ is linearly conjugate to $\mathcal{N}'$ with rate constants

$$\tilde{k}_i = b_i \prod_{j=1}^{m} c_j^{\tilde{z}_{ij}}, \qquad i = 1, \ldots \tilde{r}. \tag{6.12}$$

It is important to note that the reactant complex set for $\mathcal{C}$ *need not* be the same as that of $\mathcal{C}'$. When $\mathcal{C}^0 \in \mathcal{C}_{react}$ is not an element of the reactant complex set of $\mathcal{C}$, we will consider the summation on the left-hand side of (6.11) to be empty, and similarly for the

right-hand side of (6.11) when $\mathcal{C}^0$ is not an element of the reactant complex set of $\mathcal{C}'$, i.e.

$$\sum_{\substack{i=1\\ \mathcal{C}_i=\mathcal{C}^0}}^{r} k_i(\mathbf{z}'_i - \mathbf{z}_i) = \mathbf{0} \quad \text{and} \quad \sum_{\substack{i=1\\ \tilde{\mathcal{C}}_i=\mathcal{C}^0}}^{\tilde{r}} b_i(\tilde{\mathbf{z}}'_i - \tilde{\mathbf{z}}_i) = \mathbf{0},$$

respectively. In order to satisfy (6.11), therefore, if one system contains a reactant complex not contained in the other, it is necessary for the origin to lie in the cone generated by the reaction vectors flowing from that reactant complex in the other system.

Proof. Let $\Phi(\mathbf{x}_0, t)$ correspond to the flow of the mass-action system (2.3) associated to the reaction network $\mathcal{N}$ given by (2.1). Consider the linear mapping $\mathbf{h}(\mathbf{x}) = T^{-1}\mathbf{x}$ where $T = \text{diag}\{c_j\}_{j=1}^m$. Now define $\Psi(\mathbf{y}_0, t) = T^{-1}\Phi(\mathbf{x}_0, t)$ so that $\Phi(\mathbf{x}_0, t) = T\Psi(\mathbf{y}_0, t)$.

Since $\Phi(\mathbf{x}_0, t)$ is a solution of (2.3) for the reaction set (2.1), we have

$$\begin{aligned}
\Psi'(\mathbf{y}_0, t) &= T^{-1}\Phi'(\mathbf{x}_0, t) \\
&= T^{-1}\sum_{i=1}^{r} k_i(\mathbf{z}'_i - \mathbf{z}_i)\ \Phi(\mathbf{x}_0, t)^{\mathbf{z}_i} \\
&= T^{-1}\sum_{\mathcal{C}^0 \in \mathcal{C}_{react}} \sum_{\substack{i=1\\ \mathcal{C}_i=\mathcal{C}^0}}^{r} k_i(\mathbf{z}'_i - \mathbf{z}_i)\ \Phi(\mathbf{x}_0, t)^{\mathbf{z}^0} \\
&= T^{-1}\sum_{\mathcal{C}^0 \in \mathcal{C}_{react}} T \sum_{\substack{i=1\\ \tilde{\mathcal{C}}_i=\mathcal{C}^0}}^{\tilde{r}} b_i(\tilde{\mathbf{z}}'_i - \tilde{\mathbf{z}}_i)(T\ \Psi(\mathbf{y}_0, t))^{\mathbf{z}^0} \\
&= \sum_{i=1}^{\tilde{r}} \left(b_i \prod_{j=1}^{m} c_j^{\tilde{z}_{ij}} \right) (\tilde{\mathbf{z}}'_i - \tilde{\mathbf{z}}_i)\ \Psi(\mathbf{y}_0, t)^{\tilde{\mathbf{z}}_i}.
\end{aligned}$$

It is clear that $\Psi(\mathbf{y}_0, t)$ is the flow of (2.3) for the reaction network (6.6) with rate constants given by (6.12). We have that $\mathbf{h}(\Phi(\mathbf{x}_0, t)) = \Psi(\mathbf{h}(\mathbf{x}_0), t)$ for all $\mathbf{x}_0 \in \mathbb{R}^m_{>0}$ and $t \geq 0$ where $\mathbf{y}_0 = \mathbf{h}(\mathbf{x}_0)$ since $\mathbf{y}_0 = \Psi(\mathbf{y}_0, 0) = T^{-1}\Phi(\mathbf{x}_0, 0) = T^{-1}\mathbf{x}_0$. It follows that the networks $\mathcal{N}$ and $\mathcal{N}'$ are linearly conjugate by Definition 6.2.4, and we are done. □

This result gives conditions under which two mass-action systems $\mathcal{N}$ and $\mathcal{N}'$ are linearly conjugate. This is a particularly useful result when the qualitative properties of the original network are obscure while the behaviour of the target network is well understood.

With the exception of the scaling matrix T, condition (6.11) is very similar to the cone intersection condition in Theorem 6.2.1 where the constants $k_i > 0$, $i = 1, \ldots, r$, and $b_i > 0$, $i = 1, \ldots, \tilde{r}$, correspond to the magnitudes of the cone generators (i.e. the reaction vectors). If we allow k_i and b_i to vary we have

$$C_{\mathcal{R}}(\mathcal{C}^0) = \left\{ \sum_{\substack{i=1 \\ \mathcal{C}_i = \mathcal{C}^0}}^{r} k_i(\mathbf{z}'_i - \mathbf{z}_i) \mid k_i > 0, i = 1, \ldots, r \right\}$$

and

$$C_{\mathcal{R}'}(\mathcal{C}^0) = \left\{ \sum_{\substack{i=1 \\ \tilde{\mathcal{C}}_i = \mathcal{C}^0}}^{\tilde{r}} b_i(\tilde{\mathbf{z}}'_i - \tilde{\mathbf{z}}_i) \mid b_i > 0, i = 1, \ldots, \tilde{r} \right\}$$

according to (6.8).

The following two results can be obtained from Theorem 6.2.3 by allowing the rate constants of the original network $\mathcal{N}$ to vary. In these results we let $T = \text{diag}\{c_j\}_{j=1}^{m}$ and consider $c_j > 0$, $j = 1, \ldots, m$, to be fixed.

Corollary 6.2.1 (Corollary 3.1, [36]). *Consider two mass-action systems $\mathcal{N}$ and $\mathcal{N}'$. Then there exist rate constant vectors $\mathbf{k} \in \mathbb{R}^r_{>0}$ and $\mathbf{k}' \in \mathbb{R}^{\tilde{r}}_{>0}$ such that $\mathcal{N}$ and $\mathcal{N}'$ are conjugate with $\mathbf{h}(\mathbf{x}) = T^{-1}\mathbf{x}$ if and only if for every $\mathcal{C}^0 \in \mathcal{C}_{react}$ we have $C_{\mathcal{R}}(\mathcal{C}^0) \cap [T\, C_{\mathcal{R}'}(\mathcal{C}^0)] \neq \varnothing$.*

Corollary 6.2.2 (Corollary 3.2, [36]). *Consider two mass-action systems $\mathcal{N}$ and $\mathcal{N}'$. Then for every rate constant vector $\mathbf{k} \in \mathbb{R}^r_{>0}$ there exists a rate constant vector $\mathbf{k}' \in \mathbb{R}^{\tilde{r}}_{>0}$ such that $\mathcal{N}$ is conjugate to $\mathcal{N}'$ with $\mathbf{h}(\mathbf{x}) = T^{-1}\mathbf{x}$ if and only if for every $\mathcal{C}^0 \in \mathcal{C}_{react}$ we have*

$C_{\mathcal{R}}(\mathcal{C}^0) \subseteq [T\, C_{\mathcal{R}'}(\mathcal{C}^0)]$.

Proof. The forward implications follow directly from Theorem 6.2.3.

To prove the only if portions of the results, notice that the assumption of conjugacy with $\mathbf{h}(\mathbf{x}) = T^{-1}\mathbf{x}$ implies that

$$\Psi'(\mathbf{y}_0, t) = \sum_{\mathcal{C}^0 \in \mathcal{C}_{react}} \sum_{\substack{i=1 \\ \mathcal{C}_i = \mathcal{C}^0}}^{r} T^{-1} \left(k_i \prod_{j=1}^{m} c_j^{z_{ij}} \right) (\mathbf{z}'_i - \mathbf{z}_i)\ \Psi(\mathbf{y}_0, t)^{\mathbf{z}_0} \tag{6.13}$$

while we have

$$\Psi'(\mathbf{y}_0, t) = \sum_{\mathcal{C}^0 \in \mathcal{C}_{react}} \sum_{\substack{i=1 \\ \mathcal{C}_i = \mathcal{C}^0}}^{\tilde{r}} \tilde{k}_i (\tilde{\mathbf{z}}'_i - \tilde{\mathbf{z}}_i)\ \Psi(\mathbf{y}_0, t)^{\mathbf{z}_0} \tag{6.14}$$

from (2.3). In order to have equality between (6.13) and (6.14) we require that

$$\sum_{\substack{i=1 \\ \mathcal{C}_i = \mathcal{C}^0}}^{r} \left(k_i \prod_{j=1}^{r} c_j^{z_{ij}} \right) (\mathbf{z}'_i - \mathbf{z}_i) = T \sum_{\substack{i=1 \\ \mathcal{C}_i = \mathcal{C}^0}}^{\tilde{r}} \tilde{k}_i (\tilde{\mathbf{z}}'_i - \tilde{\mathbf{z}}_i)$$

for every $\mathcal{C}^0 \in \mathcal{C}_{react}$. The desired cone conditions follow immediately from the conditions on the rate constants vectors $\mathbf{k} \in \mathbb{R}^r_{>0}$ and $\mathbf{k}' \in \mathbb{R}^{\tilde{r}}_{>0}$. □

6.2.3 Examples

In Section 6.2.2, the results depended on having two given networks $\mathcal{N}$ and $\mathcal{N}'$ to compare. In standard practice, however, we have only a single network $\mathcal{N}$ whose dynamics are unknown and we need to find the target network $\mathcal{N}'$ whose dynamics are understood.

In this section, we will consider a particularly broad and well-understood class of such target networks in weakly reversible networks. Since it is known that weakly reversible

systems are complex balanced for at least some values of the rate constants (Theorem 3.4.3), and therefore exhibit locally stable dynamics for those rate constants values, it is a reasonable starting point when considering a network $\mathcal{N}$ which seems to exhibit locally stable dynamics to search for weakly reversible target networks $\mathcal{N}'$ to which it could be conjugate.

In practice, however, there are many sensitivities which can arise in choosing a suitable target network $\mathcal{N}'$ which is weakly reversible. We will illustrate the applicability, and limitations, of Theorem 6.2.3 to such cases through four examples. The first is an example where linear conjugacy to a weakly reversible network which exhibits locally stable dynamics can be universally shown. The second is an example where linear conjugacy to a weakly reversible network can only be shown for certain choices of the rate vector $\mathbf{k} \in \mathbb{R}^r_{>0}$. This is also an example where S^* and S do not always coincide for the original network $\mathcal{N}$. The third is an example where linear conjugacy to a weakly reversible network holds universally but conditions on $\mathbf{k} \in \mathbb{R}^r_{>0}$ are still required to guarantee locally stable dynamics. This example also demonstrates how these conditions can be reduced by creatively "splitting" a reaction in the target network $\mathcal{N}'$. The fourth is an example where a "phantom" reactant complex is used to demonstrate linear conjugacy to a weakly reversible network.

Our general technique in this section will be to search for weakly reversible target networks $\mathcal{N}'$ which involve the same reactant complexes as the original network $\mathcal{N}$.

Example 6.2.1. *Consider the chemical reaction network $\mathcal{N}$ given by*

$$\mathcal{N}: \qquad \begin{array}{c} \mathcal{A}_1 + 2\mathcal{A}_2 \xrightarrow{k_1} \mathcal{A}_1 + 3\mathcal{A}_2 \xrightarrow{k_2} \mathcal{A}_1 + \mathcal{A}_2 \xrightarrow{k_3} 3\mathcal{A}_1 \\ 2\mathcal{A}_1 \xrightarrow{k_4} \mathcal{A}_2. \end{array}$$

A quick analysis of (2.3) reveals that $\mathcal{N}$ appears to exhibit locally stable dynamics which suggests the network may be conjugate to a complex balanced network. We want to find a weakly reversible network $\mathcal{N}'$ such that we can apply Theorem 6.2.3. To start, we can consider networks with reactions flowing between the complexes in the reactant set of $\mathcal{N}$, which is

$$\{\mathcal{A}_1 + 2\mathcal{A}_2, \mathcal{A}_1 + 3\mathcal{A}_2, \mathcal{A}_1 + \mathcal{A}_2, 2\mathcal{A}_1\}.$$

Many such networks can be eliminated for failing to be weakly reversible, leaving a relatively small set of possibilities. One such possibility is the network $\mathcal{N}'$ given by

$$\mathcal{N}': \qquad \begin{array}{c} \mathcal{A}_1 + 2\mathcal{A}_2 \underset{\tilde{k}_2}{\overset{\tilde{k}_1}{\rightleftarrows}} \mathcal{A}_1 + 3\mathcal{A}_2 \\ \mathcal{A}_1 + \mathcal{A}_2 \underset{\tilde{k}_4}{\overset{\tilde{k}_3}{\rightleftarrows}} 2\mathcal{A}_1. \end{array}$$

In order for $\mathcal{N}$ and $\mathcal{N}'$ to be conjugate, we need to find $b_i > 0$, $c_j > 0$, $i = 1, \ldots, 4$, $j = 1, 2$, such that

$$\begin{aligned}
k_1 \begin{bmatrix} 0 \\ 1 \end{bmatrix} &= b_1 \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix} \begin{bmatrix} 0 \\ 1 \end{bmatrix} \\
k_2 \begin{bmatrix} 0 \\ -2 \end{bmatrix} &= b_2 \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix} \begin{bmatrix} 0 \\ -1 \end{bmatrix} \\
k_3 \begin{bmatrix} 2 \\ -1 \end{bmatrix} &= b_3 \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix} \begin{bmatrix} 1 \\ -1 \end{bmatrix} \\
k_4 \begin{bmatrix} -2 \\ 1 \end{bmatrix} &= b_4 \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix} \begin{bmatrix} -1 \\ 1 \end{bmatrix}.
\end{aligned}$$

It can be easily found that $b_1 = k_1$, $b_2 = 2k_2$, $b_3 = k_3$, $b_4 = k_4$, $c_1 = 2$, $c_2 = 1$ works.

It follows from (6.12) that $\mathcal{N}$ is conjugate to $\mathcal{N}'$ with rate constants given by $\tilde{k}_1 = 2k_1$, $\tilde{k}_2 = 4k_2$, $\tilde{k}_3 = 2k_3$ and $\tilde{k}_4 = 4k_4$. We know that the network $\mathcal{N}'$ is deficiency zero which implies by Theorem 3.4.2 and Theorem 3.3.1 that it exhibits locally stable dynamics for every set of rate constants $\tilde{k}_i$, $i = 1, \ldots, 4$. It follows that the original network $\mathcal{N}$ exhibits locally stable dynamics for all sets of rate constants k_i, $i = 1, \ldots, 4$. It could also be noted that $C_{\mathcal{R}}(\mathcal{C}^0) = T\, C_{\mathcal{R}'}(\mathcal{C}^0)$ for every $\mathcal{C}^0 \in \mathcal{C}_{react}$ so that $\mathcal{N}$ and $\mathcal{N}'$ satisfy the hypotheses of Corollary 6.2.2 and therefore conjugacy holds unconditionally.

Example 6.2.2. *Consider the chemical reaction network $\mathcal{N}$ given by*

$$\mathcal{N}: \qquad \mathcal{A}_2 \overset{k_1}{\longleftarrow} \mathcal{A}_1 \overset{k_2}{\longleftarrow} 2\mathcal{A}_2 \overset{k_3}{\longrightarrow} 3\mathcal{A}_1.$$

The only weakly reversible target network involving the same reactant complex set as $\mathcal{N}$ is

$$\mathcal{N}': \qquad \mathcal{A}_1 \underset{\tilde{k}_2}{\overset{\tilde{k}_1}{\rightleftarrows}} 2\mathcal{A}_2.$$

In order to satisfy (6.11), we need to find $b_1 > 0$, $b_2 > 0$, $c_1 > 0$, and $c_2 > 0$ such that

$$\begin{aligned} k_1 \begin{bmatrix} -1 \\ 1 \end{bmatrix} &= b_1 \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix} \begin{bmatrix} -1 \\ 2 \end{bmatrix} \\ k_2 \begin{bmatrix} 1 \\ -2 \end{bmatrix} + k_3 \begin{bmatrix} 3 \\ -2 \end{bmatrix} &= b_2 \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix} \begin{bmatrix} 1 \\ -2 \end{bmatrix} \end{aligned} \tag{6.15}$$

while satisfying (6.12) requires

$$\tilde{k}_1 = b_1 c_1, \qquad \textit{and} \qquad \tilde{k}_2 = b_2 c_2^2. \tag{6.16}$$

The system (6.15) corresponds to satisfying $k_1 = b_1 c_1$, $k_1 = 2b_1 c_2$, $k_2 + 3k_3 = b_2 c_1$, *and* $k_2 + k_3 = b_2 c_2$. *From the first two equations, we have* $c_1/c_2 = 2$ *while from the last two we have* $c_1/c_2 = (k_2 + 3k_3)/(k_2 + k_3)$, *which implies (6.15) can be satisfied if and only if* $k_2 = k_3$. *With this restriction, the system can be satisfied for* $b_1 = k_1$, $b_2 = 2k_2 = 2k_3$, $c_1 = 2$, $c_2 = 1$. *It follows from (6.16) that* $\tilde{k}_1 = 2k_1$ *and* $\tilde{k}_2 = 2k_2 = 2k_3$.

It is known that $\mathcal{N}'$ *is complex balanced, and therefore exhibits locally stable dynamics, for all values of* $\tilde{k}_1 > 0$ *and* $\tilde{k}_2 > 0$*; however, because we required a condition on the rate constants of* $\mathcal{N}$ *in order for condition (6.15) to be satisfied,* $\mathcal{N}$ *does not exhibit locally stable dynamics unconditionally. In fact, it exhibits locally stable dynamics only for* $k_2 = k_3$. *For* $k_2 > k_3$, *all trajectories tend to the origin, while for* $k_3 > k_2$ *all trajectories become unbounded.*

It is worth noting that the kinetic subspace S^* *is two-dimensional for* $\mathcal{N}$ *for all rate constants values except* $k_2 = k_3$ *when it collapses to a single dimension and we have the strict inclusion* $S^* \subset S$. *Since* $\mathcal{N}'$ *is weakly reversible, we always have* $S^* = S$ *for* $\mathcal{N}'$ *by Lemma 2.4.1 and we notice that this is always one-dimensional. The systems will only be conjugate when the dimensions of the kinetics compatibility classes match, which only occurs when* $k_2 = k_3$.

It could also be noted that $C_{\mathcal{R}}(\mathcal{C}^0) \cap [T\, C_{\mathcal{R}'}(\mathcal{C}^0)] \neq \varnothing$ *for every* $\mathcal{C}^0 \in \mathcal{C}_{react}$ *but* $C_{\mathcal{R}}(\mathcal{C}^0) \notin [T\, C_{\mathcal{R}'}(\mathcal{C}^0)]$ *for* $\mathcal{C}^0 = 2\mathcal{A}_2 \in \mathcal{C}_{react}$. *Consequently, the networks* $\mathcal{N}$ *and* $\mathcal{N}'$ *satisfy the hypotheses of Corollary 6.2.1 but not Corollary 6.2.2; linear conjugacy with* $\mathbf{h}(\mathbf{x}) = T^{-1}\mathbf{x}$

cannot therefore be guaranteed for all rate constant vectors $\mathbf{k} \in \mathbb{R}^3_{>0}$.

Example 6.2.3. *Consider the chemical reaction network* $\mathcal{N}$ *given by*

$$\begin{aligned} & \mathcal{A}_1 + 2\mathcal{A}_2 \xrightarrow{\epsilon} \mathcal{A}_1 \\ \mathcal{N}: \qquad & 2\mathcal{A}_1 + \mathcal{A}_2 \xrightarrow{1} 3\mathcal{A}_2 \\ & \mathcal{A}_1 + 3\mathcal{A}_2 \xrightarrow{1} \mathcal{A}_1 + \mathcal{A}_2 \xrightarrow{1} 3\mathcal{A}_1 + \mathcal{A}_2 \end{aligned}$$

for $\epsilon > 0$.

We search for target networks $\mathcal{N}'$ *with reactions flowing between the complexes in the reactant set of* $\mathcal{N}$*, which is*

$$\{\mathcal{A}_1 + 2\mathcal{A}_2, 2\mathcal{A}_1 + \mathcal{A}_2, \mathcal{A}_1 + 3\mathcal{A}_2, \mathcal{A}_1 + \mathcal{A}_2\}.$$

Many such networks can be eliminated for failing to be weakly reversible, leaving a relatively small set of possibilities. We will choose the network $\mathcal{N}'$ *given by*

$$\begin{array}{lccc} & \mathcal{A}_1 + 2\mathcal{A}_2 & \xrightarrow{\tilde{k}_1} & \mathcal{A}_1 + \mathcal{A}_2 \\ \mathcal{N}': & {\scriptstyle \tilde{k}_4}\uparrow \quad & {\scriptstyle \tilde{k}_5}\nearrow & \quad \downarrow{\scriptstyle \tilde{k}_2} \\ & \mathcal{A}_1 + 3\mathcal{A}_2 & \xleftarrow[\tilde{k}_3]{} & 2\mathcal{A}_1 + \mathcal{A}_2 \end{array}$$

where we have chosen to "split" the reaction flowing from the reactant complex $\mathcal{A}_1 + 3\mathcal{A}_2$ *into two weighted reactions. The utility of this technique will become apparent momentarily.*

In order to satisfy (6.11) we need to find constants $b_i > 0$, $c_j > 0$, $i = 1, \ldots, 5$, $j = 1, 2$,

such that

$$\epsilon\begin{bmatrix} 0 \\ -2 \end{bmatrix} = b_1\begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix}\begin{bmatrix} 0 \\ -1 \end{bmatrix}$$

$$\begin{bmatrix} 2 \\ 0 \end{bmatrix} = b_2\begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix}\begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$\begin{bmatrix} -2 \\ 2 \end{bmatrix} = b_3\begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix}\begin{bmatrix} -1 \\ 2 \end{bmatrix}$$

$$\begin{bmatrix} 0 \\ -2 \end{bmatrix} = \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix}\left(b_4\begin{bmatrix} 0 \\ -1 \end{bmatrix} + b_5\begin{bmatrix} 0 \\ -2 \end{bmatrix}\right).$$

We will choose the solution set $b_1 = 2\epsilon$, $b_2 = b_3 = 1$, $b_4 = 2(1-t)$, $b_5 = t$, $c_1 = 2$, $c_2 = 1$ *where* $0 \leq t < 1$ *is a weighting constant. This gives rise to the rate constants* $\tilde{k}_1 = 4\epsilon$, $\tilde{k}_2 = 2$, $\tilde{k}_3 = 4$, $\tilde{k}_4 = 4(1-t)$ *and* $\tilde{k}_5 = 2t$ *according to (6.12).*

There is one condition on the rate constants of $\mathcal{N}'$ *in order for the mass-action system to be complex balanced. That condition is*

$$\epsilon = \frac{1-t}{\sqrt{2-t}}.$$

Each $0 \leq t < 1$ *corresponds to specific network* $\mathcal{N}'$ *which is conjugate to* $\mathcal{N}$*. Consequently, we can guarantee that* $\mathcal{N}$ *is conjugate to a complex balanced system, and therefore exhibits locally stable dynamics, for the range of values* $0 < \epsilon \leq 1/\sqrt{2}$*. Notice that if we had not split the reaction flowing from the complex* $\mathcal{A}_1 + 3\mathcal{A}_2$ *and instead had all of the weight represented in* $\tilde{k}_4$*, we would have only been able to show that* $\mathcal{N}$ *exhibits locally stable dynamics for* $\epsilon = 1/\sqrt{2}$*.*

It can be checked empirically that locally stable dynamics appears to be exhibited for $\mathcal{N}$ *for all values* $\epsilon > 0$. *There is a unique positive equilibrium concentration given by* $(x_1^*, x_2^*) = (1, -\epsilon/2 + \sqrt{(\epsilon/2)^2 + 1})$ *which is locally asymptotically stable for all* $\epsilon > 0$ *according to standard linearization theory. It is not our claim, therefore, that this theory represents a complete classification of locally stable dynamics, even for networks which exhibit locally stable dynamics for some values of the rate constants.*

Example 6.2.4. *Consider the chemical reaction network* $\mathcal{N}$ *given by*

$$\mathcal{A}_1 \xrightarrow{k_1} 2\mathcal{A}_1 + 2\mathcal{A}_2 \xrightarrow{k_2} \mathcal{A}_2 \xrightarrow{k_3} \mathcal{A}_1 + \mathcal{A}_2.$$

A quick analysis (2.3) reveals that $\mathcal{N}$ *appears to exhibit locally stable dynamics which suggests that the network may be lienarly conjugate to a complex balanced network; however, there is no weakly reversible network* $\mathcal{N}'$ *involving the same reactant complexes as* $\mathcal{N}$ *which serves as an obvious candidate to satisfy the requirements of Theorem 6.2.3.*

We recall, though, that Theorem 6.2.3 did not require the target network $\mathcal{N}'$ *to use the same reactant complexes as* $\mathcal{N}$. *We can have a reactant complex* $\mathcal{C}^0$ *from the reactant complex set of* $\mathcal{C}'$ *which is not in the reactant complex set of* $\mathcal{C}$ *so long as*

$$\sum_{\substack{i=1 \\ \tilde{\mathcal{C}}_i = \mathcal{C}^0}}^{\tilde{r}} b_i(\tilde{\mathbf{z}}_i' - \tilde{\mathbf{z}}_i) = \mathbf{0}.$$

One possible target network $\mathcal{N}'$ *which makes use of such a "phantom" reactant complex is*

given by

$$\mathcal{N}': \qquad \begin{array}{ccc} \mathcal{A}_1 + \mathcal{A}_2 & \underset{\tilde{k}_6}{\overset{\tilde{k}_3}{\leftrightarrows}} & \mathcal{A}_2 \\ {\scriptstyle \tilde{k}_4}\downarrow \quad {\scriptstyle \tilde{k}_5}\searrow & & \uparrow{\scriptstyle \tilde{k}_2} \\ \mathcal{A}_1 & \underset{\tilde{k}_1}{\longrightarrow} & 2\mathcal{A}_1 + 2\mathcal{A}_2. \end{array} \tag{6.17}$$

Since the reactions corresponding to $\tilde{k}_1$, $\tilde{k}_2$ and $\tilde{k}_3$ in $\mathcal{N}$ are the same as those for k_1, k_2, and k_3 in $\mathcal{N}$, we set $c_1 = c_2 = 1$, $b_1 = k_1$, $b_2 = k_2$, and $b_3 = k_3$. Since the complex $\mathcal{A}_1 + \mathcal{A}_2$ is not a reactant complex in $\mathcal{C}$, in order to satisfy (6.11) it is required that

$$\tilde{k}_4 \begin{bmatrix} 0 \\ -1 \end{bmatrix} + \tilde{k}_5 \begin{bmatrix} 1 \\ 1 \end{bmatrix} + \tilde{k}_6 \begin{bmatrix} -1 \\ 0 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

This can be satisfied if $\tilde{k}_4 = \tilde{k}_5 = \tilde{k}_6 = t$ for any $t > 0$.

The network $\mathcal{N}'$ is weakly reversible and has a deficiency of one ($\delta = n - \ell - s = 4 - 1 - 2 = 1$). According to Theorem 3.4.3 there is one condition on the rate constants required for the network to be complex balanced. That condition in terms of the rate constants of $\mathcal{N}$ is

$$6t^3 = k_1 k_2 k_3.$$

Since every value of $t > 0$ corresponds to a valid conjugate network $\mathcal{N}'$, this is no restriction at all. It follows that the original network $\mathcal{N}$ is conjugate to a complex balanced system for all choices of rate constants and therefore universally exhibits locally stable dynamics.

In other words, we are able to demonstrate the network $\mathcal{N}$ is universally conjugate to a complex balanced network $\mathcal{N}'$, and therefore possesses very predictable dynamics, by adding a "phantom" reactant complex which contributes no dynamical information to the mass-

action kinetics (2.3). It should be noted, however, that in order for the target network $\mathcal{N}'$ satisfying (6.11) to be weakly reversible it is necessary that any such phantom reactant complex at least appear in the set of product reactants of $\mathcal{N}$. (This example is further considered in Example 6.3.5 where the use of a "phantom" reactant is not required.)

6.3 Dynamical Equivalence as an Optimization Problem

Theorem 6.2.3 is powerful in that it gives verifiable conditions under which two networks are linearly conjugate and therefore exhibit the same qualitative dynamics. This is useful when two networks are specified. In all of the examples in Section 6.2.3, however, the target networks $\mathcal{N}'$ were carefully selected to illustrate how the dynamics of a known system can be transferred to a system with unknown dynamics. No intuition for finding such a suitably well-behaved target network $\mathcal{N}'$ was provided.

An immediate question is raised: In the case where only one reaction network is specified, is there a general mechanism by which we can find conjugate networks? In particular, can we find a target network within a broader class of networks with well-known and suitably well-behaved dynamics (e.g. complex balanced networks, weakly reversible networks, etc.)?

The related problem of determining alternate realizations of a given dynamics has been attempted from within an optimization framework by G. Szederkényi. In [58] he gives a mixed-integer linear programming (MILP) algorithm for finding sparse and dense realizations (i.e. realizations with the fewest and greatest number of reactions). In [59]

and [60], together with K. Hangos and T. Pena he extends the algorithm to determine sparse and dense detailed and complex balanced realizations. In [61], together with K. Hangos and Z. Tzusa he gives an algorithm for determining weakly reversible realizations.

In this section, I summarize the results of these papers. I then show this approach can be extended to linear conjugacy. Finally, I show how weak reversibility can be introduced as a linear constraint [38].

Throughout this section, I will use the complex-oriented notation of (2.2) and the complex-oriented mass-action kinetics schemes (2.4) and (4.18).

6.3.1 Sparse and Dense Realizations

The problem of algorithmically determining alternate realizations of a given kinetics was first addressed by G. Szederkényi in [58]. He considers the problem of determining realizations satisfying the following definitions.

Definition 6.3.1. *A realization $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of a given kinetics scheme (4.18) is called* ***sparse*** *if $|\mathcal{R}| \leq |\mathcal{R}'|$ for all other realizations $\mathcal{N}' = (\mathcal{S}, \mathcal{C}, \mathcal{R}')$.*

Definition 6.3.2. *A realization $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ of a given kinetics scheme (4.18) is called* ***dense*** *if $|\mathcal{R}| \geq |\mathcal{R}'|$ for all other realizations $\mathcal{N}' = (\mathcal{S}, \mathcal{C}, \mathcal{R}')$.*

That is to say, a realization is sparse if it contains the minimum number of reactions required to generate the kinetics (4.18) for a fixed complex set while a realization is dense if it contains the maximal number of reactions for a fixed complex set.

That the complex set must be fixed is necessary for both theoretical and applied reasons. In terms of application, we must search for realizations over the set of available complexes,

and if this is not a bounded set this process will never terminate. More interestingly, however, is the observation that for some networks there is no upper limit for the number of complexes involved in a realization and hence no well-defined dense realization. Consider the following example.

Example 6.3.1. *Consider the reaction network*

$$\mathcal{N}: \quad \mathcal{O} \xrightarrow{k} \mathcal{A}.$$

Under the assumption of mass-action kinetics, this network gives rise to the dynamics

$$\frac{dx}{dt} = k \tag{6.18}$$

according to (4.18).

Now consider the networks of the form

$$\mathcal{N}': \quad \mathcal{O} \xrightarrow{k/(i\cdot n)} i\mathcal{A}, \qquad i = 1, \ldots, n,$$

for $n \geq 1$. It is easy to check that this set of networks generates the kinetics scheme (4.18) for all $n \geq 1$ so that they are dynamically equivalent. We can see that as n grows, however, the number of complexes and the number of reactions grows with n so that realizations of (6.18) exist involving an arbitrary number of complexes and reactions. It follows that no dense realization is defined.

Consequently, for any algorithm searching for realizations of a particular kinetics, and in particular dense realizations, it is important to specify the complex set. This raises the

question of which complexes from the original network $\mathcal{N}$ should be included in the search for a suitable target network $\mathcal{N}'$.

In [58], G. Szederkényi fixed the stoichiometric matrix $Y \in \mathbb{Z}_{\geq 0}^{m \times n}$ to contain only the (source or product) complexes contained in the network $\mathcal{N}'$. Since fixing Y also fixes the mass-action vector $\Psi(\mathbf{x})$, the only variables remain in the kinetics matrix A_k, so that the problem of finding an alternative realization $\mathcal{N}$ of $\mathcal{N}'$ then becomes one of finding a kinetics matrix A_k such that

$$Y \cdot A_k \cdot \Psi(\mathbf{x}) = Y \cdot A_k' \cdot \Psi(\mathbf{x}).$$

If we set $M = Y \cdot A_k'$ and impose that A_k be a kinetics matrix, dynamical equivalence can be guaranteed by the conditions

$$\textbf{(DE)} \quad \begin{cases} Y \cdot A_k = M \\ \sum_{i=1}^{n} [A_k]_{ij} = 0, \quad j = 1, \ldots, n \\ [A_k]_{ij} \geq 0, \quad i, j = 1, \ldots, n, \; i \neq j \\ [A_k]_{ii} \leq 0, \quad i = 1, \ldots, n. \end{cases} \tag{6.19}$$

A sparse (respectively, dense) realization is given by a matrix A_k satisfying (6.19) with the most (respectively, least) off-diagonal entries which are zeroes. A correspondence between the non-zero off-diagonal entries in A_k and a positive integer value can be made by considering the binary variables $\delta_{ij} \in \{0, 1\}$ which will keep track of whether a reaction is 'on' or 'off', i.e. we have

$$\delta_{ij} = 1 \leftrightarrow [A_k]_{ij} > \epsilon, \quad i, j = 1, \ldots, n, \;\; i \neq j$$

for some sufficient small $0 < \epsilon \ll 1$, where the symbol '$\leftrightarrow$' denotes the logical relation 'if and only if'. This proposition logic constraint for the structure of a network can be accomplished with the constraint

$$0 \leq \epsilon\delta_{ij} \leq [A_k]_{ij} \leq u_{ij}\delta_{ij}, \qquad i,j = 1,\ldots,n, i \neq j \tag{6.20}$$

where $u_{ij} > 0$ for $i,j = 1,\ldots,n, i \neq j$. These constraints (6.20) can be reformulated as the following linear mixed-integer constraints (see, for example, [47]):

$$\textbf{(S)} \begin{cases} 0 \leq [A_k]_{ij} - \epsilon\delta_{ij}, \quad i,j = 1,\ldots,n, \;\; i \neq j \\ 0 \leq -[A_k]_{ij} + u_{ij}\delta_{ij}, \quad i,j = 1,\ldots,n, \;\; i \neq j \\ \delta_{ij} \in \{0,1\}, \quad i,j = 1,\ldots,n, i \neq j. \end{cases} \tag{6.21}$$

The number of reactions present in the network corresponding to A_k is then given by the sum of the δ_{ij}'s so that the problem of determining a sparse network corresponds to satisfying the objective function

$$\textbf{(Sparse)} \begin{cases} \text{minimize} \quad \displaystyle\sum_{i,j=1,i\neq j}^{n} \delta_{ij} \end{cases} \tag{6.22}$$

over the constraint sets (6.19) and (6.21). Finding a dense network corresponds to maximizing the same function, which can also be stated as a minimization problem as

$$\textbf{(Dense)} \begin{cases} \text{minimize} \quad \displaystyle\sum_{i,j=1,i\neq j}^{n} -\delta_{ij}. \end{cases} \tag{6.23}$$

Example 6.3.2. *Consider the reaction network*

$$\mathcal{N}: \quad 2\mathcal{A}_1 \xrightarrow{1} 2\mathcal{A}_2 \xrightarrow{1} \mathcal{A}_1 + \mathcal{A}_2.$$

According to (4.18) this generates the kinetics

$$\begin{aligned} \frac{dx_1}{dt} &= -2x_1^2 + x_2^2 \\ \frac{dx_2}{dt} &= 2x_1^2 - x_2^2. \end{aligned} \tag{6.24}$$

We want to find the sparse and dense realizations capable of generating (6.24). We have the matrices

$$M = \begin{bmatrix} -2 & 1 & 0 \\ 2 & -1 & 0 \end{bmatrix}, \qquad Y = \begin{bmatrix} 2 & 0 & 1 \\ 0 & 2 & 1 \end{bmatrix}$$

so the relevant constraint set is

$$\begin{array}{lll} 2[A_k]_{11} + [A_k]_{31} = -2 & 0 \le [A_k]_{12} - \epsilon\delta_{12} & 0 \le -[A_k]_{12} + u_{12}\delta_{12} \\ 2[A_k]_{12} + [A_k]_{32} = 0 & 0 \le [A_k]_{13} - \epsilon\delta_{13} & 0 \le -[A_k]_{13} + u_{13}\delta_{13} \\ 2[A_k]_{13} + [A_k]_{33} = 1 & 0 \le [A_k]_{21} - \epsilon\delta_{21} & 0 \le -[A_k]_{21} + u_{21}\delta_{21} \\ 2[A_k]_{21} + [A_k]_{31} = 0 & 0 \le [A_k]_{23} - \epsilon\delta_{23} & 0 \le -[A_k]_{23} + u_{23}\delta_{23} \\ 2[A_k]_{22} + [A_k]_{32} = 2 & 0 \le [A_k]_{31} - \epsilon\delta_{31} & 0 \le -[A_k]_{31} + u_{31}\delta_{31} \\ 2[A_k]_{23} + [A_k]_{33} = 1 & 0 \le [A_k]_{32} - \epsilon\delta_{32} & 0 \le -[A_k]_{31} + u_{31}\delta_{31} \end{array} \tag{6.25}$$

$$\begin{aligned} [A_k]_{11} + [A_k]_{21} + [A_k]_{31} &= 0 \\ [A_k]_{12} + [A_k]_{22} + [A_k]_{32} &= 0 \\ [A_k]_{13} + [A_k]_{32} + [A_k]_{33} &= 0 \end{aligned}$$

over the decision variables

$$[A_k]_{12}, [A_k]_{13}, [A_k]_{21}, [A_k]_{23}, [A_k]_{31}, [A_k]_{32} \geq 0$$

$$[A_k]_{11}, [A_k]_{22}, [A_k]_{33} \leq 0$$

$$\delta_{12}, \delta_{13}, \delta_{21}, \delta_{23}, \delta_{31}, \delta_{32} \in \{0, 1\}\,.$$

Running the MILP optimization problem with the optimization package GLPK with bounds $\epsilon = 0.1$ *and* $u_{ij} = 10$, $i, j = 1, \ldots, n$, *yields the sparse and dense realizations given in Figure 6.1. We can see that any network involving the complex set* $2\mathcal{A}_1$, $\mathcal{A}_1 + \mathcal{A}_2$ *and* $2\mathcal{A}_2$ *must involve at least two reactions and can contain up to six. It is interesting to note that the original network also contained only two reactions and therefore also qualifies as a sparse network. This illustrates the fact that the structure of sparse networks is not necessarily unique.*

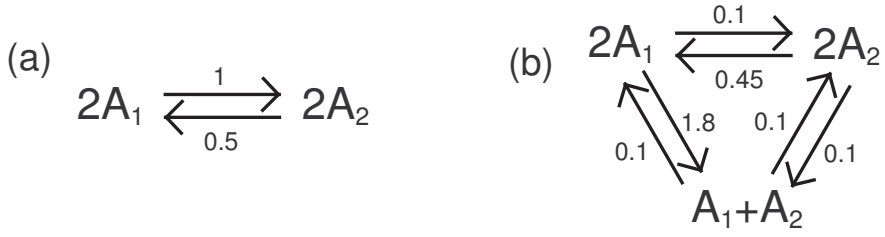

Figure 6.1: Sparse (a) and dense (b) networks which generate the kinetics scheme (6.24).

6.3.2 Generating Realizations

It is often useful to generate realizations $\mathcal{N}$ from polynomial systems of the form

$$f_i(\mathbf{x}) = \sum_{j=1}^{r_i} m_{ij} \prod_{k=1}^{n} x_k^{b_{jk}}, \quad i = 1, \ldots, m \tag{6.26}$$

where r_i is the number of polynomials in the i^{th} expression. That is to say, given a polynomial system (6.26), we are often interested in algorithmically producing a reaction network $\mathcal{N}$ which *could* be responsible for the given kinetic output, if one exists. Such a network could then be used as the starting point for subsequent network and dynamical analysis.

Such an algorithm is presented in [28] and reproduced in [59]. In the algorithm which follows, we let $\mathbf{e}_i$ denote the i^{th} standard basis vector in $\mathbb{R}^m$.

Algorithm 1 (from [28], reproduced in Section 2.3 of [59]): For each $i = 1, \ldots, n$ and for each $j = 1, \ldots, r_i$ do

1. $C_j = B_j + \text{sign}(m_{ij}) \cdot \mathbf{e}_i$
2. Add the following reaction to the graph of the realization

$$\sum_{k=1}^{n} b_{jk} \mathcal{A}_k \longrightarrow \sum_{k=1}^{n} c_{jk} \mathcal{A}_k$$

   with reaction rate coefficient $|m_{ij}|$, where $C_j = [c_{j1} \cdots c_{jn}]$.

Algorithm 1 essentially dictates that, for each monomial in the set of differential equations (6.26) we add a reaction corresponding to either an increase or decrease in the i^{th}

species, depending on the sign of the coefficient, and then assign the reaction its rate according to the magnitude of that coefficient. It is easy to see that a reaction network generated in this fashion, if one exists, generates a polynomial system (6.26) according to the mass-action assumption (4.18)

There is no reason to believe that the reaction network produced by Algorithm 1 will be well-structured or physically sensible, but the algorithm is guaranteed to produce a reaction network if the system was indeed generated by a chemical reaction network operating under the assumption of mass-action kinetics. Such networks have the restriction over general polynomial differential equations that there may be no negative cross-effects [28] (i.e. no equation $f_i(\mathbf{x})$ may have a negative coefficient corresponding to a term which does not contain x_i since this would correspond to a reaction "using up" a species which did not appear as a reactant for the given reaction).

Example 6.3.3. *Consider the set of polynomial differential equations*

$$\begin{aligned} \dot{x}_1 &= x_1x_2^2 - 2x_1^2 + x_1x_3^2 \\ \dot{x}_2 &= -x_1^2x_2^2 + x_1x_3^2 \\ \dot{x}_3 &= x_1^2 - 3x_1x_3^2 \end{aligned} \tag{6.27}$$

considered in [38]. We want to find a reaction network $\mathcal{N}$ which generates the dynamics (6.27) according to Algorithm 1. We will systematically consider the monomials in order.

Consider the monomial $x_1x_2^2$ which has a coefficient of 1. Since the coefficient is positive, has magnitude 1, and the term appears in the expression for x_1, we add an $\mathcal{A}_1$ to the complex $\mathcal{A}_1 + 2\mathcal{A}_2$ to get the reaction

$$\mathcal{A}_1 + 2\mathcal{A}_2 \xrightarrow{1} 2\mathcal{A}_1 + 2\mathcal{A}_2.$$

Now consider the monomial $-x_1^2x_2^2$ which has a coefficient of -1. Since the coefficient is negative, has magnitude 1, and the term appears in the expression for x_2, we subtract an $\mathcal{A}_2$ from the complex $2\mathcal{A}_1 + 2\mathcal{A}_2$ to get the reaction

$$2\mathcal{A}_1 + 2\mathcal{A}_2 \xrightarrow{1} 2\mathcal{A}_1 + \mathcal{A}_2.$$

The rest of the monomials can be analyzed similarly. The end result of the algorithm is the network

$$\begin{array}{ccccc} \mathcal{A}_1 + 2\mathcal{A}_2 & \xrightarrow{1} & 2\mathcal{A}_1 + 2\mathcal{A}_2 & \xrightarrow{1} & 2\mathcal{A}_1 + \mathcal{A}_2 \\ & & \mathcal{A}_1 \xleftarrow{2} 2\mathcal{A}_1 \xrightarrow{1} 2\mathcal{A}_1 + \mathcal{A}_3 & & \\ 2\mathcal{A}_1 + 2\mathcal{A}_3 & \xleftarrow{1} & \mathcal{A}_1 + 2\mathcal{A}_3 & \xrightarrow{1} & \mathcal{A}_1 + \mathcal{A}_2 + 2\mathcal{A}_3 \\ & & \downarrow_3 & & \\ & & \mathcal{A}_1 + \mathcal{A}_3. & & \end{array}$$

It is easy to see that this network generates the kinetics (6.27) under the assumption of mass-action kinetics (4.18).

6.3.3 Complex Balancing as a Linear Constraint

We are typically interested in more important information than simply whether there is or is not an alternative realization of a kinetics scheme (4.18). Ideally we would like the realization we find to tell us dynamical information about the original network, e.g. whether the system is persistent, how many equilibria there are, what their stabilities are, etc. Consequently, it is useful to restrict our search space to classes of networks which are known to exhibit the behaviour we suspect the original network to exhibit.

Since complex balanced networks exhibit locally stable dynamics (see Definition 3.0.6

and Theorem 3.3.1), for networks which appear to exhibit locally stable dynamics it is often desirable to restrict our search space to complex balanced networks. This requires a reformulation of our complex balancing condition (3.6). In matrix form, and considering the mass-action kinetic form (4.18), we have that a system is complex balanced at $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ if and only if

$$A_k \, \Psi(\mathbf{x}^*) = \mathbf{0}. \tag{6.28}$$

We can now formulate the complex balancing condition as a linear constraint. If we let $\mathbf{x}^* \in \mathbb{R}^m_{>0}$ be an equilibrium concentration of the original network, we can impose complex balancing by introducing the set of constraints

$$\textbf{(CB)} \quad \left\{ \quad \sum_{j=1}^{m} [A_k]_{ij} \Psi_j(\mathbf{x}^*) = 0, \quad i = 1, \ldots, n. \right. \tag{6.29}$$

Example 6.3.4. *Reconsider the network given in Example 6.3.2. We determined a sparse and dense realization involving the complexes* $2\mathcal{A}_1$, $\mathcal{A}_1 + \mathcal{A}_2$, *and* $2\mathcal{A}_2$ *(see Figure 6.1). It is easy to check that the sparse network is complex balanced. From the differential equations (6.24) we have that the equilibrium set is given by* $x_2^* = \sqrt{2}x_1^*$ *so that we have* $\Psi_1(\mathbf{x}^*) = (x_1^*)^2$, $\Psi_2(\mathbf{x}^*) = (x_2^*)^2 = 2(x_1^*)^2$ *and* $\Psi_3(\mathbf{x}^*) = (x_1^*)(x_2^*) = \sqrt{2}(x_1^*)^2$. *Complex balancing follows by (6.28) because*

$$\begin{bmatrix} -1 & 0.5 & 0 \\ 1 & -0.5 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} (x_1^*)^2 \\ 2(x_1^*)^2 \\ \sqrt{2}(x_1^*)^2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

For the dense network given in Figure 6.1(b) we can see that

$$\begin{bmatrix} -1.9 & 0.45 & 0.1 \\ 0.1 & -0.55 & 0.1 \\ 1.8 & 0.1 & -0.2 \end{bmatrix} \begin{bmatrix} (x_1^*)^2 \\ 2(x_1^*)^2 \\ \sqrt{2}(x_1^*)^2 \end{bmatrix} \neq \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

so that the network is not complex balanced. We can impose that the realizations be complex balanced by imposing the conditions

$$[A_k]_{11} + 2[A_k]_{12} + \sqrt{2}[A_k]_{13} = 0$$
$$[A_k]_{21} + 2[A_k]_{22} + \sqrt{2}[A_k]_{23} = 0$$
$$[A_k]_{31} + 2[A_k]_{32} + \sqrt{2}[A_k]_{33} = 0$$

according to (6.29) (the $(x_1^*)^2$'s factor out if they are included). Appending these constraints to (6.25) yields the network given in Figure 6.2). It can be verified that the network is complex balanced, and therefore satisfies all of the properties given in Theorem 3.3.1, by checking that

$$\begin{bmatrix} -1.05 & 0.45 & \frac{3}{40}\sqrt{2} \\ 0.95 & -0.55 & \frac{3}{40}\sqrt{2} \\ 0.1 & 0.1 & -\frac{3}{20}\sqrt{2} \end{bmatrix} \begin{bmatrix} (x_1^*)^2 \\ 2(x_1^*)^2 \\ \sqrt{2}(x_1^*)^2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

6.3.4 Weak Reversibility as a Linear Constraint

We know from Theorem 3.4.3 that weakly reversible networks always possess the capacity for locally stable dynamics (see Definition 3.0.6). Consequently, it is very desireable to be able to restrict our attention to networks which are weakly reversible.

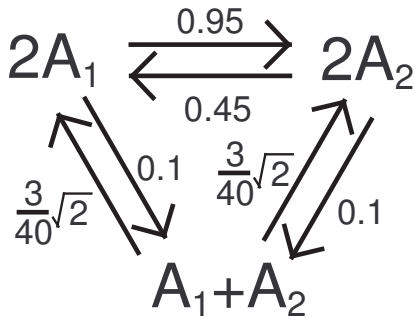

Figure 6.2: A complex balanced dense realization of the kinetics scheme (6.24).

In [61] the authors introduce an algorithm for determining dense weakly reversible realizations of a given kinetics. The algorithm is based on the fact that there are no cycles involving elements in different strongly connected components of a reaction network [11], and that for a fixed complex set the structure of the dense realization of a network is unique and contains the structures of all other possible realizations as sub-graphs (Theorem 3.1 of [60]). Omitting technical details, the algorithm can be summarized as:

1. Define the matrices Y and M and initialize $\mathcal{K} = \{\varnothing\}$.

2. Force the edges in $\mathcal{K}$ to be excluded and compute a dense realization A_k.

3. Check whether A_k is weakly reversible (if so, end algorithm and return A_k).

4. Find all edges in A_k which lead from one strongly connected component to another and add them to $\mathcal{K}$.

5. Check whether these edges may be removed (if so, repeat steps (2)-(4); if not, end algorithm and return $A_k = 0$).

The algorithm has the drawbacks that it can only compute dense realizations and not sparse ones, and that it requires potentially multiple MILP optimizations which are known to be NP-hard. In this section we show that the requirement of weak reversibility can be formulated as a linear constraint.

We require the following classical result about weakly reversible networks, which is modified from Theorem 3.1 of [26] and Proposition 4.1 of [24]:

Theorem 6.3.1. *Let A_k be a kinetics matrix and let Λ_i, $i = 1, \ldots, \ell$, denote the support of the i^{th} linkage class. Then the reaction graph corresponding to A_k is weakly reversible if and only if there is a basis of $ker(A_k)$, $\{\mathbf{b}^{(1)}, \ldots, \mathbf{b}^{(\ell)}\}$, such that, for $i = 1, \ldots, \ell$,*

$$\mathbf{b}^{(i)} = \begin{cases} b_j^{(i)} > 0, & j \in \Lambda_i \\ b_j^{(i)} = 0, & j \notin \Lambda_i. \end{cases}$$

An immediate consequence of Theorem 6.3.1 is that there is a vector $\mathbf{b} \in \mathbb{R}^m_{>0} \cap \ker(A_k)$ if and only if the reaction graph corresponding to A_k is weakly reversible. In other words, we can guarantee weak reversibility by imposing the condition

$$A_k \cdot \mathbf{b} = \mathbf{0} \tag{6.30}$$

for some $\mathbf{b} \in \mathbb{R}^n_{>0}$. This, however, is a nonlinear constraint in the k_{ij}'s and b_j's. In order to make it linear, we consider the matrix $\tilde{A}_k$ with entries

$$[\tilde{A}_k]_{ij} = [A_k]_{ij} \cdot b_j. \tag{6.31}$$

It is clear from (6.31) that $\tilde{A}_k$ encodes a kinetics matrix and that $\mathbf{1} \in \mathbb{R}^m$ (the m-dimensional

vector containing only ones) lies in $\ker(\tilde{A}_k)$. Moreover, it is easy to see that $\tilde{A}_k$ encodes a weakly reversible network if and only if A_k corresponds to a weakly reversible network. We can therefore check weak reversibility of the chemical reaction network corresponding to A_k with the linear conditions

$$\textbf{(WR')} \quad \begin{cases} \sum_{i=1}^{n} [\tilde{A}_k]_{ij} = 0, \quad j = 1, \ldots, n \\ \sum_{i=1}^{n} [\tilde{A}_k]_{ji} = 0, \quad j = 1, \ldots, n \\ [\tilde{A}_k]_{ij} \geq 0, \quad i, j = 1, \ldots, n, \; i \neq j \\ [\tilde{A}_k]_{ii} \leq 0, \quad i = 1, \ldots, n. \end{cases} \tag{6.32}$$

By solving for the diagonal elements of $\tilde{A}_k$, the set of constraints (6.32) can be simplified to

$$\textbf{(WR)} \quad \begin{cases} \sum_{i=1, i\neq j}^{n} [\tilde{A}_k]_{ij} = \sum_{i=1, i\neq j}^{n} [\tilde{A}_k]_{ji}, \quad j = 1, \ldots, n \\ [\tilde{A}_k]_{ij} \geq 0, \quad i, j = 1, \ldots, n, \; i \neq j. \end{cases} \tag{6.33}$$

No condition comparable to $Y \cdot A_k = M$ exists for the matrix $\tilde{A}_k$ so that we are left to optimize with respect to the internal entries of both A_k and $\tilde{A}_k$. Given appropriate choices of $0 < \epsilon \ll 1$ and $u_{ij} > 0$, $i, j = 1, \ldots, n$, $i \neq j$, we can impose

$$\textbf{(WR-S)} \quad \begin{cases} 0 \leq [\tilde{A}_k]_{ij} - \epsilon\delta_{ij}, \quad i, j = 1, \ldots, n, \;\; i \neq j \\ 0 \leq -[\tilde{A}_k]_{ij} + u_{ij}\delta_{ij}, \quad i, j = 1, \ldots, n, \;\; i \neq j \end{cases} \tag{6.34}$$

as well as (6.21) to ensure that both A_k and $\tilde{A}_k$ contain zero and non-zero entries in the same places so that they correspond to reaction graphs with the same structure.

Example 6.3.5. *Reconsider the network $\mathcal{N}$ given by*

$$\mathcal{A}_1 \xrightarrow{1} 2\mathcal{A}_1 + 2\mathcal{A}_2 \xrightarrow{1} \mathcal{A}_2 \xrightarrow{1} \mathcal{A}_1 + \mathcal{A}_2 \tag{6.35}$$

which was originally considered in Example 6.2.4.

It is clear that no realization could contain fewer than three reactions since there are three source complexes. Consequently this is an example of a sparse realization. It is not, however, a weakly reversible network. We saw that the weakly reversible network given in (6.17) was linearly conjugate to $\mathcal{N}$ with conjugacy constants $c_1 = c_2 = 1$ (i.e. they are alternative realizations of one another) but we might still wonder if there is a weakly reversible realizations with fewer than six reactions.

Solving for the sparse weakly reversible realization in GLPK with the constraints (6.19), (6.21), (6.33) and (6.34) gives the network in Figure 6.3. We can see that the sparse weakly reversible realizations in fact contains four reactions.

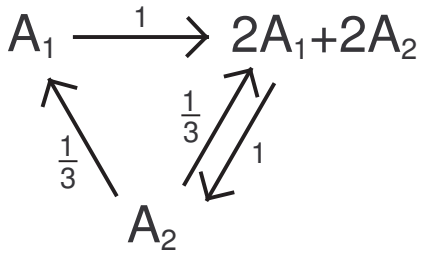

Figure 6.3: Sparse weakly reversible network which generates the same mass-action kinetics as (6.35).

6.3.5 Linear Conjugacy as a Linear Constraint

In Section 6.2 we were introduced to the concept of *linear conjugacy* of chemical reaction networks. In this section we will extend the MILP optimization framework introduced so far in Section 6.3 to include the possibility of networks related by a non-trivial linear conjugacy.

The notation we will use in this section will be different than that used in Section 6.2. As a result, we will prove agian the main result of that section, Theorem 6.2.3, with this new notation.

Theorem 6.3.2. *Consider two mass-action systems $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ and $\mathcal{N}' = (\mathcal{S}, \mathcal{C}', \mathcal{R}')$ and let Y be the stoichiometric matrix corresponding to the complexes in either network. Consider a kinetics matrix A_k corresponding to $\mathcal{N}$ and suppose that there is a kinetics matrix A_b with the same structure as $\mathcal{N}'$ and a vector $\mathbf{c} \in \mathbb{R}^m_{>0}$ such that*

$$Y \cdot A_k = T \cdot Y \cdot A_b \tag{6.36}$$

where $T = diag\{\mathbf{c}\}$. Then $\mathcal{N}$ is linearly conjugate to $\mathcal{N}'$ with kinetics matrix

$$A'_k = A_b \cdot diag\{\Psi(\mathbf{c})\}. \tag{6.37}$$

Proof. Let $\Phi(\mathbf{x}_0, t)$ correspond to the flow of (4.18) associated to the reaction network $\mathcal{N}$. Consider the linear mapping $\mathbf{h}(\mathbf{x}) = T^{-1} \cdot \mathbf{x}$ where $T = \text{diag}\{\mathbf{c}\}$. Now define $\tilde{\Phi}(\mathbf{y}_0, t) = T^{-1} \cdot \Phi(\mathbf{x}_0, t)$ so that $\Phi(\mathbf{x}_0, t) = T \cdot \tilde{\Phi}(\mathbf{y}_0, t)$.

Since $\Phi(\mathbf{x}_0, t)$ is a solution of (4.18) we have

$$\begin{aligned}
\tilde{\Phi}'(\mathbf{y}_0, t) &= T^{-1} \cdot \Phi'(\mathbf{x}_0, t) \\
&= T^{-1} \cdot Y \cdot A_k \cdot \Psi(\Phi(\mathbf{x}_0, t)) \\
&= T^{-1} \cdot T \cdot Y \cdot A_b \cdot \Psi(T \cdot \tilde{\Phi}(\mathbf{y}_0, t)) \\
&= Y \cdot A_b \cdot \operatorname{diag}\{\Psi(\mathbf{c})\} \cdot \Psi(\tilde{\Phi}(\mathbf{y}_0, t)).
\end{aligned}$$

It is clear that $\tilde{\Phi}(\mathbf{y}_0, t)$ is the flow of (4.18) corresponding to the reaction network $\mathcal{N}'$ with the kinetics matrix given by (6.37). We have that $\mathbf{h}(\Phi(\mathbf{x}_0, t)) = \tilde{\Phi}(\mathbf{h}(\mathbf{x}_0), t)$ for all $\mathbf{x}_0 \in \mathbb{R}^n_{>0}$ and $t \geq 0$ where $\mathbf{y}_0 = \mathbf{h}(\mathbf{x}_0)$ since $\mathbf{y}_0 = \tilde{\Phi}(\mathbf{y}_0, 0) = T^{-1} \cdot \Phi(\mathbf{x}_0, 0) = T^{-1} \cdot \mathbf{x}_0$. It follows that the networks $\mathcal{N}$ and $\mathcal{N}'$ are linearly conjugate and we are done. □

This result give conditions for two networks to be linearly conjugate, and therefore exhibit the same qualitative dynamics, but says nothing as far as how to find a linearly conjugate network when only a single network is provided.

However, we can easily extend the MILP framework to include linear conjugacy. This can be accomplished by replacing the set of constraints (6.19) with

$$\textbf{(LC)} \quad \begin{cases} Y \cdot A_b = T^{-1} \cdot M \\ \sum_{i=1}^{n} [A_b]_{ij} = 0, \quad j = 1, \ldots, n \\ [A_b]_{ij} \geq 0, \quad i, j = 1, \ldots, n, \; i \neq j \\ [A_b]_{ii} \leq 0, \quad i = 1, \ldots, n \\ \epsilon \leq c_j \leq 1/\epsilon, \quad j = 1, \ldots, m \end{cases} \tag{6.38}$$

where $M = Y \cdot A_k$, T =diag$\{\mathbf{c}\}$, and $0 < \epsilon \ll 1$, and replacing the set of constraints (6.21) by

$$\textbf{(LC-S)} \quad \begin{cases} 0 \leq [A_b]_{ij} - \epsilon\delta_{ij}, \quad i,j = 1,\ldots,n, \;\; i \neq j \\ 0 \leq -[A_b]_{ij} + u_{ij}\delta_{ij}, \quad i,j = 1,\ldots,n, \;\; i \neq j \\ \delta_{ij} \in \{0,1\}, \quad i,j = 1,\ldots,n, i \neq j, \end{cases} \tag{6.39}$$

where $u_{ij} > 0$ for $i,j = 1,\ldots,n, i \neq j$.

A_b has the same structure as the kinetics matrix A'_k corresponding to the conjugate network, and this matrix has the same structure as the matrix $\tilde{A}_k$ given by (6.31) (replacing A_k by A'_k). Consequently, the problem of determining a sparse or dense weakly reversible network which is linearly conjugate to a given kinetics can be given by optimizing either (6.22) or (6.23), respectively, over the constraint sets (6.38), (6.39), (6.33), and (6.34). The kinetics matrix A'_k for the linearly conjugate network is given by (6.37).

Example 6.3.6. *Reconsider the kinetics scheme*

$$\begin{aligned} \dot{x}_1 &= x_1x_2^2 - 2x_1^2 + x_1x_3^2 \\ \dot{x}_2 &= -x_1^2x_2^2 + x_1x_3^2 \\ \dot{x}_3 &= x_1^2 - 3x_1x_3^2 \end{aligned} \tag{6.40}$$

given in Example 6.3.3. Using the algorithm given in Section 6.3.2 (see also [28] and [59]), we determined a kinetic realization involving the complexes

$$C_1 = A_1 + 2A_2, C_2 = 2A_1 + 2A_2, C_3 = 2A_1 + A_2,$$

$$C_4 = 2A_1, C_5 = A_1, C_6 = 2A_1 + A_3, C_7 = A_1 + 2A_3$$

$$C_8 = 2A_1 + 2A_3, C_9 = A_1 + A_2 + 2A_3, C_{10} = A_1 + A_3.$$

With this fixed complex set, we can carry out the MILP optimization procedure outlined in this section to find sparse and dense weakly reversible networks which are linearly conjugate to a network with kinetics (6.40). We have

$$Y = \begin{bmatrix} 1 & 2 & 2 & 2 & 1 & 2 & 1 & 2 & 1 & 1 \\ 2 & 2 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 2 & 2 & 2 & 1 \end{bmatrix}$$

and

$$M = \begin{bmatrix} 1 & 0 & 0 & -2 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & -3 & 0 & 0 & 0 \end{bmatrix}.$$

With the bounds $\epsilon = 1/20$ and $u_{ij} = 20$ for $i, j = 1, \ldots, 10$, $i \neq j$, the algorithm gives us the sparse network given in Figure 6.4(a) (conjugacy constants $c_1 = 20$, $c_2 = 2$, and $c_3 = 5$) and the dense network given in Figure 6.4(b) (conjugacy constants $c_1 = 20/3$, $c_2 = 20/33$, and $c_3 = 5/3$). It is interesting to note that the sparse and dense networks utilize different complexes and that the ratio of conjugacy constants differ between the sparse and dense networks. It is worth noting that the sparse realization is also deficiency zero so that the Deficiency Zero Theorem (Theorem 3.4.2) can be applied [25, 30, 33]. Consequently, solutions of (6.40) satisfy all of the stringent dynamical restrictions typically reserved for complex balanced systems.

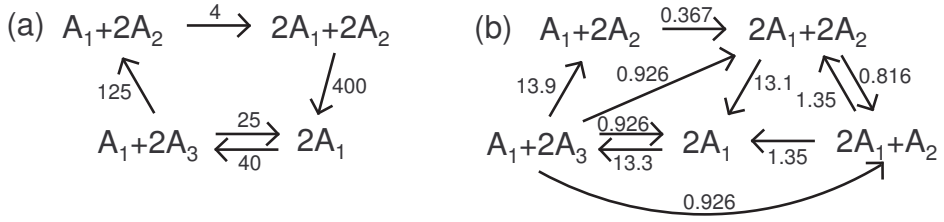

Figure 6.4: Weakly reversible networks which are linearly conjugate to a network with the kinetics (6.3.6). The network in (a) is sparse while the network in (b) is dense. The parameter values in (b) have been rounded to three significant figures.

Chapter 7

Conclusions and Future Work

In this thesis, I have presented a number of original results on topics pertaining to chemical reaction network theory.

In Chapter 4, a number of results were demonstrated using the method of linearization about equilibrium points. Theorem 4.3.5 shows that the results of F. Horn and R. Jackson contained in [33] can be reproduced in the setting of linearization about equilibrium values. In particular, it was shown that the local stable manifold about a complex balanced equilibrium concentration corresponds to the relevant stoichiometric compatibility class, and the centre manifold corresponds to the tangent plane to the equilibrium curve as it meets that compatibility class. Theorem 4.3.6 shows that the convergence toward a complex balanced equilibrium concentration is exponential in nature and the decay constant can be taken to be arbitrarily close to the slowest converging subspace of the corresponding linear problem.

In Chapter 5, the question of persistence of chemical reaction networks was investigated. Theorem 5.2.6 shows that a chemical reaction network for which all sets I corresponding

to semi-locking sets are weakly dynamically non-emptiable is persistent. This is a generalization of Theorem 4 of [5]. It was shown that weak dynamical non-emptiability captures more persistent chemical reaction networks than the notion introduced in that paper. Theorem 5.3.3 shows that any stratum which intersects a boundary of the positive orthant $\mathbb{R}^m_{>0}$ has a linear functional which pushes trajectories away from that portion of the boundary while trajectories remain within the stratum. Supplemental conditions were provided which guarantee persistence (Corollary 5.3.1).

In Chapter 6, the concept of two chemical reaction networks being linearly conjugate was introduced (Definition 6.2.4 and Theorem 6.2.3). Importantly, linearly conjugate networks exhibit the same qualitative dynamics even if their network structures differ significantly. The linear constraint set (6.38) was added to the mixed-integer linear programming procedure introduced by G. Szederkényi in [59] to allow the algorithm to search for linearly conjugate networks instead of simply dynamically equivalent ones. Additionally, the linear constraint sets (6.33) and (6.34) were introduced. These constraints provide a single step procedure for determining weakly reversible chemical reaction networks which are linearly conjugate to a given network. They represent a significant improvement in computational efficiency over the algorithm introduced in [61].

There are a number of open problems within the scope of these topics which would be ideal grounds for future work.

1. Linearization (Chapter 4)

    - It is worth noting that the linearized form (4.20) does not depend on the corresponding chemical reaction network being complex balanced. Expanding this approach to networks which are not complex balanced could potentially be very

insightful.

- We have only considered linearization about strictly positive equilibrium concentrations. Applying this approach to equilibrium concentrations lying on $\partial\mathbb{R}^m_{>0}$ would give us information about the dynamical behaviour on faces, and also information about how trajectories behave near the boundary.

2. Global Stability and Persistence (Chapter 5)

   - Significant work has been conducted recently on the *Global Attractor Conjecture* (Conjecture 5.1.1). It is now known to hold, for instance, when the reaction network contains only one linkage class [2], when there are only three species [19], and when the stoichiometric compatibility classes are three-dimensional [44]. The general case, however, remains unproved.

3. Linear Conjugacy (Chapter 6)

   - We have only considered *linear* conjugacies and *mass-action* kinetics. Adapting the methodology outlined here to nonlinear conjugacies and kinetic schemes other than mass-action (e.g. Michaelis-Menten or Hill kinetics) could yield potentially powerful results.
   - The computational procedure outlined for determining linearly conjugate networks depended on the rate constants for the original network being specified. Consequently, we may be overlooking behaviours admitted by the network as a result of poor rate constant selection. Expanding the algorithm to search over the rate constant values of the original network as well as those of the target network would be an insightful step forward.

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