Mass Action Reaction Networks and The Deficiency Zero Theorem

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Contents

1 Introduction

Systems of coupled chemical reactions are common in many fields, notably in biochemistry. These are usually presented symbolically, indicating the proportions in which elements combine to form other elements. For each reaction there is an associated rate used in forming the differential equations which govern the change in concentration of all elements in the system over time. The rates at which reactions occur can be difficult or even impossible to measure experimentally, however, and can vary over many orders of magnitude. In even mildly complicated systems there can be many coupled differential equations with many such reaction constants, making the rigorous examination of the system very computationally intensive at best, and unhelpful or impossible at worst. The problem and several possible solutions (including the one discussed here) are outlined in Bailey's recent article [1].

This paper presents a broader mathematical framework with which to investigate such systems, and to proves theorem which relates "topological" properties of the system – that is, properties independent of the differential equations and the reaction rates – with the stability properties of the differential equations, one of the most important and interesting goals of analyzing a network. Specifically, the following theorem will be proved:

Theorem (Deficiency Zero). *A weakly reversible mass-action reaction network with zero deficiency contains one unique equilibrium point in each positive reaction simplex.*

The conditions of weak reversibility and zero deficiency are entirely independent of the reaction constants and are easily calculable if the topology of the system is known; the definitions of both conditions are in section 5. The positive reaction simplices can be thought of as the attainable states of the system from a given starting concentration, and is defined in section 2. Mass-action kinetics is the most common kinetic model in chemistry, and its mathematical definition is given in section 4.

The purpose of this paper is twofold: the first is to present a proof of the deficiency zero theorem in its entirety, which has previously appeared in fragments (in particular, in [2], [8], and [12]). The second is to provide an introduction and overview to the mathematics of reaction network theory, with a particular focus on mass action kinetics, and as such this paper is largely self-contained (with one exception: the use of the Perron-Frobenius theorem in section 5). Otherwise, the mathematics should be comprehensible to anyone with a solid understanding of linear algebra and some multivariable real analysis. Examples are interspersed throughout to illustrate how certain concepts and proofs work; these are offset from the main text and can be skipped without losing any of the substance of the paper. For convenience, an explanation of frequently used symbols is given in appendix B.

Several general overviews of this field exist and, while not used directly, have greatly informed my understanding of the subject matter. A good overview, filled with case examples but lacking deep mathematical analysis, is found in Feinberg's two part survey [3], [4]. Horn also has a summary in [9] and [10], followed by a paper describing a simple example system in [11]. Feinberg and Horn have together written a survey [5] aimed at a more mathematical audience.

2 Fundamentals

A typical chemical reaction is written schematically as

$$\text{Reactant} \longrightarrow \text{Product}.$$

The reactant and product are each called a **complex**, which is a set of elements with associated coefficients. The elements that make up complexes are called **species**, and can be anything that participates in a reaction, typically a chemical element, molecule, or protein. The species that are on the left side of the equation are used up, and those on the right are created when the reaction occurs. The coefficient that a species takes indicates what proportion of it is created or used in the reaction, and by convention is always a non-negative integer. The goal of chemical reaction theory is to monitor how the concentration of each species changes over time. Take this example of a chemical reaction:

$$A_1 + A_2 \longrightarrow 2A_3.$$

Here, A_1, A_2, A_3 are species. The complexes are $A_1 + A_2$ and $2A_3$, which are the reactant and the product, respectively.The fundamental unit of a chemical reaction is the species, the concentration of which we are interested in monitoring. A complex is a sum of species with integer coefficients, and a reaction is a pair of complexes with an ordering (to distinguish between products and reactants). In full generality, a reaction can be written as

$$\sum_{i=1}^{m} \alpha_i A_i \longrightarrow \sum_{j=1}^{m} \beta_j A_j, \tag{2.1}$$

where $\{\alpha_i\}, \{\beta_j\}$ are sets of non-negative integers which fully determine the complexes on either side of the equation.

A reaction network is a finite set of reactions occuring simultaneously. Often, a complex participates in more than one reaction. We can combine our representations in a diagram such that all reactions are represented once and only once, as are all complexes. In this way we form a directed graph with complexes as nodes and reaction arrows as directed edges. Consider, for example, the following set of reactions:

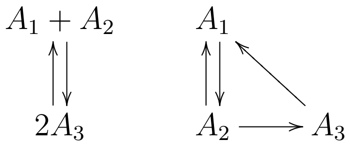
$$\begin{array}{rcl}
A_1 + A_2 & \longrightarrow & 2A_4 \\
2A_4 & \longrightarrow & A_1 + A_2 \\
A_1 & \longrightarrow & A_2 \\
A_2 & \longrightarrow & A_1 \\
A_2 & \longrightarrow & A_3 \\
A_3 & \longrightarrow & A_1
\end{array}$$

The corresponding reaction diagram is

$$\begin{tikzcd}
A_1 + A_2 \arrow[d, shift left] & A_1 \arrow[d, shift left] & \\
2A_4 \arrow[u, shift left] & A_2 \arrow[u, shift left] \arrow[r] & A_3 \arrow[ul]
\end{tikzcd}$$

In this system, there are four species A_1, A_2, A_3, A_4 and five complexes $(A_1 + A_2), (2A_4), (A_1), (A_2), (A_3)$. Note that, in this system, three of the species are also complexes, since they appear in a reaction on their own. Note also that the complexes $2A_4$ and $A_1 + A_2$ have two arrows joining them, to represent the two reactions occurring between them. Finally, it is significant that the reaction diagram is not a connected graph, but rather has two connected components. Each connected component is called a linkage class, and they will be studied in more detail in section 5.

Now, consider the similar reaction diagram



The difference between this example and the previous one is that the complex $2A_3$ replaces the complex $2A_4$. This example illustrates another important point: A_3 and $2A_3$ are different complexes; though one might be tempted to multiply all of the coefficients in the first reaction by two and then connect the graphs, this would inaccurately change the nature of the system, by suggesting, for example, that two units of A_1 must interact to form A_2, which is different than the original reaction, where a single unit of A_1 can form a unit of A_2 by itself.

These two systems may appear very similar, but the subtle difference between them is very significant in studying their dynamics. We will use these two systems in illustrative examples throughout the paper, and we will refer to the first system as system $\mathcal{A}$, and to the second as system $\mathcal{B}$.

Now, we will construct a linear algebraic structure to aid in the study of kinetic systems. In a system with m species, we call the vector space $V = \mathbb{R}^m$ the **species space**, with each coordinate representing a different species – the numbering of species is arbitrary and irrelevant to all results. Species space serves three purposes: symbolically, we can represent different parts of our system as vectors, so that we may use the tools of linear algebra and vector operations to simplify calculations and representations; we can use the vectors to keep track of the concentrations of the different species in the system so that we may easily represent the state of all species with a point; and, similarly, we can represent the rates of change of all species simultaneously.

We begin to construct a mathematical framework for analyzing reaction networks by associating a unique basis vector in V with each species. Although any basis would do, it is simplest to use the standard basis in $\mathbb{R}^m$. We denote these basis vectors in species space by $\vec{v}_i$ for the i-th species (which we will often call species i, or simply i when it is apparent that it is a species being discussed). Now a complex can be represented as a vector in species space as the sum of its constituent species multiplied by the appropriate coefficient, since this conveys the essential information about a complex: which species it contains and it what proportions. These **complex**

vectors in species space will be denoted by $\vec{y}_j$ for the j-th complex. Note that the complex vector is simply the vector with i-th entry α_i using the notation of (2.1). Each reaction can now be represented as the vector associated with the reactant complex subtracted from the vector associated with the product complex, since this shows the essential information of a reaction: the net amount of each participating species produced or used. This is called the **reaction vector** for the corresponding reaction, and, in the notation of (2.1), would be the vector with $\beta_i - \alpha_i$ for the i-th coordinate.

Example (Vector representations) Systems $\mathcal{A}$ and $\mathcal{B}$ are represented as follows:

	System $\mathcal{A}$		System $\mathcal{B}$	
	Symbol	Vector	Symbol	Vector
Species	A_1	$(1,0,0,0)$	A_1	$(1,0,0)$
	A_2	$(0,1,0,0)$	A_2	$(0,1,0)$
	A_3	$(0,0,1,0)$	A_3	$(0,0,1)$
	A_4	$(0,0,0,1)$		
Complexes	A_1	$(1,0,0,0)$	A_1	$(1,0,0)$
	A_2	$(0,1,0,0)$	A_2	$(0,1,0)$
	A_3	$(0,0,1,0)$	A_3	$(0,0,1)$
	$A_1 + A_2$	$(1,1,0,0)$	$A_1 + A_2$	$(1,1,0)$
	$2A_4$	$(0,0,0,2)$	$2A_3$	$(0,0,2)$
Reactions	$A_1 + A_2 \to 2A_4$	$(-1,-1,0,2)$	$A_1 + A_2 \to 2A_3$	$(-1,-1,2)$
	$2A_4 \to A_1 + A_2$	$(1,1,0,-2)$	$2A_3 \to A_1 + A_2$	$(1,1,-2)$
	$A_1 \to A_2$	$(-1,1,0,0)$	$A_1 \to A_2$	$(-1,1,0)$
	$A_2 \to A_1$	$(1,-1,0,0)$	$A_2 \to A_1$	$(1,-1,0)$
	$A_2 \to A_3$	$(0,-1,1,0)$	$A_2 \to A_3$	$(0,-1,1)$
	$A_3 \to A_1$	$(1,0,-1,0)$	$A_3 \to A_1$	$(1,0,-1)$

The order in which the complexes are presented here will be used throughout the examples, so that complex 1, denoted by $\vec{y}_1$, will mean A_1, and so on; so, for system $\mathcal{A}$ complex 5 will mean $2A_4$, whereas for system $\mathcal{B}$ it will mean $2A_3$.

In addition to using the vector space to give an abstract algebraic representation of our system, we can also use the species space to represent activity in the system more concretely, by letting each point represent a state of the system, with the value of each coordinate indicating the concentration of the associated species. When looking at the species space in this sense we will sometimes consider only the positive orthant of species space, V^+, where all coordinates are greater than zero, or the closure of this space, $\bar{V}^+$, where all coordinates are greater than or equal to zero. On the other hand, sometimes allowing "negative" values for concentration will be useful, such as when regarding rates of change of the system.

In this notation, we can now state that there is some continuous function $\vec{c}(t)$ returning a vector in $\bar{V}^+$ that describes the state of the system at time t. Using the constraints of the mechanism, we can write the **species formation function**, $\vec{f}(\vec{c}(t))$, describing the rate of change of the system at any given concentration. So, in mathematical notation,

$$\vec{f}(\vec{c}(t)) = \frac{d\vec{c}(t)}{dt}. \tag{2.2}$$

Since we assume that the rate of species formation is dependent *only* on concentration, we can drop the reference to time and refer to the species formation function as simply $\vec{f}(\vec{c})$.

The subspace of reaction space defined by the linear span of the reaction vectors is called S, the **stoichiometric space**, "stoichiometry" being the term in chemistry used to describe the proportions in which chemicals react. In the example above, S would be the span of the vectors $(1, 1, -2), (-1, 1, 0),$ and $(0, -1, 1)$, since all of the other reaction vectors are linearly dependent on these. The stoichiometric space can be thought of as constraints for what states the system can attain, since all changes in concentration must happen by changes occurring in the proportions dictated by the reaction vectors.

For a vector $\vec{c}_0 \in V$, the coset $\vec{c}_0 + S$ intersected with $\bar{V}^+$ is called a **reaction simplex**, which we will denote $\bar{S}_{c_0}$. The set $(\vec{c}_0 + S) \cap V^+$ is called the corresponding **positive reaction simplex**, which we will denote by S_{c_0}. This can be thought of as restrictions on attainable states of the system from a given initial state $\vec{c}_0$, though not all points in S_{c_0} are actually possible; however, we do know that the "trajectory" of a system starting at concentration $\vec{c}_0$ will be confined to S_{c_0}.

Finally, we call a concentration $\vec{c}_0$ an **equilibrium concentration** if $\vec{f}(\vec{c}_0) = 0$, and the set of all equilibrium concentrations in the positive orthant, $E = \{\vec{c} \in V^+ | \vec{f}(\vec{c}) = 0\}$, the **equilibrium set**.

3 Vector Operations and Notation

For convenience, this paper makes use of certain notational conventions and uses some unusual vector operations in order to simplify the representation of otherwise complex equations, and to take advantage of some easily verifiable properties of these operations; for the most part, these vector operations are modeled after scalar equivalents, and their properties are shown to be similar to their namesakes.

The logarithm of a vector is taken coordinate-wise:

$$\ln \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix} = \begin{bmatrix} \ln x_1 \\ \ln x_2 \\ \vdots \\ \ln x_n \end{bmatrix}.$$

Taking the ratio of two vectors (both of the same dimension) is also done coordinate-wise:

$$\frac{\vec{x}}{\vec{y}} = \begin{bmatrix} \frac{x_1}{y_1} \\ \vdots \\ \frac{x_n}{y_n} \end{bmatrix}.$$

Raising a vector to the power of another vector (again, both of the same dimension) gives a scalar, by the formula

$$\vec{x}^{\vec{y}} = \begin{bmatrix} x_1 \\ \vdots \\ x_n \end{bmatrix}^{\begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix}} = \prod_{i=1}^{n} x_i^{y_i}.$$

This definition is used in defining the operation of raising a vector (n-dimensional) to the power an $n \times r$ matrix to give and r dimensional vector:

$$\vec{x}^{Y} = \begin{bmatrix} \vec{x}^{\vec{y_1}} \\ \vdots \\ \vec{x}^{\vec{y_r}} \end{bmatrix},$$

where $\vec{y_i}$ is the i-th column of the matrix Y.

Example (Vector exponents) Raising a vector $\vec{x}$ to the power of the fourth complex vector from our example systems would give

$$\vec{x}^{\vec{y}_4} = c_1 c_2.$$

These operations have properties similar to their familiar scalar counterparts, as is shown in Appendix A.

In order to make equations more readable, and to allow the reader to keep track of whether quantities within the equations are vectors or scalars, I use the convention of enclosing scalar quantities in round brackets and vector quantities in square brackets.

4 Mass Action Kinetics

It is possible to imagine any number of schemes for constructing equations that govern the rate of change of concentration in a system. The type of system that will be addressed in the rest of this paper is called **mass action kinetics**, and is the most common found in chemical systems. The idea behind mass action kinetics is that, whenever all of the components necessary for a reaction to occur collide, a reaction occurs with a certain frequency, given by the **rate constant** for that reaction. The probability of the components colliding is proportional to their concentrations, with the rate constant as the constant of proportionality. So, the rate of a certain reaction occurring is given by the equation

$$k \prod (c_i)^{\alpha_i} \tag{4.1}$$

where k is the rate constant, c_i is the concentration of the i-th species involved in the reaction, and α_i is the number of times that species appears in the reacting complex (its coefficient in the equation).

Let's examine how mass action kinetics predicts the dynamics of a system with one reaction and generalized complexes. Consider a system with m species, called $A_1, ..., A_m$. Recall from (2.1) that any reaction in the system can be written as

$$\sum_{i=1}^{m} \alpha_i A_i \xrightarrow{k} \sum_{j=1}^{m} \beta_j A_j,$$

where all α_i and β_j are non-negative integers, and k is the rate constant (it is standard chemical notation to write the rate constant above the arrow). We know the rate at which this reaction progresses at any given concentration, based on the definition in equation equation (4.1). What this means is that the rate of production of a species j (due only to contributions from this one reaction) is given by

$$\beta_j k \prod_{i=1}^{m} (c_i)^{\alpha_i}.$$

Similarly, the rate of destruction of the species j is given by

$$-\alpha_j k \prod_{i=1}^{m} (c_i)^{\alpha_i}.$$

So, the net change in the concentration of species j due to this reaction is

$$\frac{dc_j}{dt} = \beta_j k \prod_{i=1}^{m} (c_i)^{\alpha_i} - \alpha_j k \prod_{i=1}^{m} (c_i)^{\alpha_i} = (\beta_j - \alpha_j) k \prod_{i=1}^{m} (c_i)^{\alpha_i}.$$

Using the vector notation discussed in section 2, we can represent the rate of change for the entire system as

$$\frac{d\vec{c}}{dt} = \vec{R} k \prod_{i=1}^{m} (c_i)^{\alpha_i},$$

where the vector $\vec{R}$ is the vector of the reaction, defined as $\begin{bmatrix} \beta_1 - \alpha_1 \\ \vdots \\ \beta_n - \alpha_n \end{bmatrix}$.

Of course, in a general system we usually have to deal with more than one reaction. So, we denote the rate constant of the reaction from complex j to complex i by $k(i, j)$, which is zero if complex j does not react directly to form i (i.e. there is no branch from j to i in the reaction diagram), or if $i = j$. Otherwise the rate is positive. In a system with n complexes, the rate constants can be arranged in an $n \times n$ matrix, such that $k(i, j)$ is the entry in the i-th row and j-th column, is called the **rate constant matrix**, and is denoted by K.

Example (Rate constant matrices) Systems $\mathcal{A}$ and $\mathcal{B}$ would have rate constant matrices with nonzero entries in the same places, namely

$$K = \begin{bmatrix} 0 & k(1,2) & k(1,3) & 0 & 0 \\ k(2,1) & 0 & 0 & 0 & 0 \\ 0 & k(3,2) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & k(4,5) \\ 0 & 0 & 0 & k(5,4) & 0 \end{bmatrix},$$

where the complexes $(A_1), (A_2), (A_3), (A_1 + A_2), (2A_x)$ are numbered 1 through 5 in that order, and $x = 3$ for system $\mathcal{A}$, and $x = 4$ for system $\mathcal{B}$.

To deal with different species coefficients in different reactions, we will now use the notation $\alpha_{j,h}$ to denote the coefficient of species h in a reaction starting at complex j. The rate of change of concentration in the system is the sum of the contributions of all the reactions, so

$$\vec{f}(\vec{c}) = \sum_{i=1}^{n} \sum_{j=1}^{n} k(i,j) \left(\prod_{h=1}^{m} (c_h)^{\alpha_{j,h}} \right) [\vec{y}_i - \vec{y}_j], \tag{4.2}$$

where $\vec{y}_i$ is the vector representation of the i-th complex in species space. Since $\alpha_{j,h}$ represents the coefficient of species h in complex j, it is equal to the h-th component of the vector $\vec{y}_j$ by definition. Hence, we can use the notation of section 3 to rewrite (4.2) as

$$\vec{f}(\vec{c}) = \sum_{i=1}^{n} \sum_{j=1}^{n} k(i,j) \left(\vec{c}^{\vec{y}_j} \right) [\vec{y}_i - \vec{y}_j]. \tag{4.3}$$

Example (Species formation functions) The species formation functions would not look the same, and for system $\mathcal{A}$ would be

$$\vec{f}(\vec{c}) = \begin{bmatrix} k(1,2)c_2 + k(1,3)c_3 - k(2,1)c_1 + k(4,5)c_4^2 - k(5,4)c_1c_2 \\ -k(1,2)c_2 + k(2,1)c_1 - k(3,2)c_2 + k(4,5)c_4^2 - k(5,4)c_1c_2 \\ k(3,2)c_2 - k(1,3)c_3 \\ 2k(5,4)c_1c_2 - 2k(4,5)c_4 \end{bmatrix}$$

where c_i is the $i-th$ coordinate of $\vec{c}$, representing the concentration of the species A_i. For system $\mathcal{B}$ the species formation function would be

$$\vec{f}(\vec{c}) = \begin{bmatrix} k(1,2) + k(1,3)c_3 - k(2,1)c_1 + k(4,5)c_3^2 - k(5,4)c_1c_2 \\ -k(1,2)c_2 + k(2,1)c_1 - k(3,2)c_2 + k(4,5)c_3^2 - k(5,4)c_1c_2 \\ k(3,2)c_2 - k(1,3)c_3 + 2k(5,4)c_1c_2 - 2k(4,5)c_3 \end{bmatrix}.$$

Bearing in mind the definition of species space, and the vector representation of a species, we can make analogous definitions for complexes. So, in a system with m species and n complexes, we have the species space $V = \mathbb{R}^m$ and the **complex space** $W = \mathbb{R}^n$. By taking the various vector representations of complexes in species space and arranging them as the columns in an $n \times m$ matrix, we define a linear transformation from the complex space W to the species space V that takes the j-th basis vector in W to the appropriate complex vector in species space. This is called the **complex matrix** and is denoted by Y. The basis vector that represents the i-th complex is denoted by $\vec{w}_i$, and we have the identity that $Y\vec{w}_i = \vec{y}_i$, the representation of the complex in species space.

Example (Complex matrices) For system $\mathcal{A}$, we have

$$Y = \begin{bmatrix} 1 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2 \end{bmatrix}$$

and for system $\mathcal{B}$ we have

$$Y = \begin{bmatrix} 1 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 2 \end{bmatrix}.$$

We can also define a function called the **complex formation function**, denoted by $\vec{g}(\vec{c})$, which is roughly analogous to the species formation function. Like the species formation function, it takes as an argument a concentration vector in species space (note that it does not take a vector in complex space), $\vec{c}$, however the complex formation function returns a vector in complex space, with each entry corresponding to the rate of change of the corresponding complex at the given concentration. By their definitions,

$$\vec{f}(\vec{c}) = Y\vec{g}(\vec{c}). \tag{4.4}$$

The counterpart of an equilibrium point in complex space is a concentration $\vec{c_0}$ such that $\vec{g}(\vec{c_0}) = 0$. If c_0 satisfies this condition, then the system is said to be **complex balanced at** c_0; if a system is complex balanced at all equilibrium points, the system is said to be complex balanced. Note that complex balancing at $\vec{c_0}$ implies that $\vec{c_0}$ is an equilibrium point (clearly seen from (4.4), since a linear transformation of 0 is 0), but the converse is not necessarily true (if the kernel of Y is nontrivial).

Example (Nontrivial kernel of Y) In our example system $\mathcal{B}$, one could imagine a concentration at which the rate of formation of complex 3 (A_3) is twice the rate of annihilation of complex 5 ($2A_3$). In this scenario the species formation rate of species 3 would be zero, and the concentration could be an equilibrium point; however, it could not be a complex balanced point.

The rate of change of a complex at a given concentration is the rate of creation minus the rate of annihilation, so we have

$$\vec{g}(\vec{c}) = \begin{bmatrix} \sum_{i=1}^{n} k(1,i)\vec{c}^{\vec{y}_i} \\ \vdots \\ \sum_{i=1}^{n} k(n,i)\vec{c}^{\vec{y}_i} \end{bmatrix} - \begin{bmatrix} \sum_{j=1}^{n} k(j,1)\vec{c}^{\vec{y}_1} \\ \vdots \\ \sum_{j=1}^{n} k(j,n)\vec{c}^{\vec{y}_n} \end{bmatrix} \tag{4.5}$$

Breaking this up into the components representing creation and annihilation of a species, we observe that the creation term can be simplified using notation we have already introduced; namely, we can rewrite (4.5) as

$$\vec{g}(\vec{c}) = K\vec{c}^{Y} - \sum_{j=1}^{n} \begin{bmatrix} k(j,1)\vec{c}^{\vec{y}_1} \\ \vdots \\ k(j,n)\vec{c}^{\vec{y}_n} \end{bmatrix}$$

which can be further simplified to

$$\vec{g}(\vec{c}) = K\vec{c}^{Y} - \operatorname{diag} \begin{bmatrix} \sum_{j=1}^{n} k(j,1) \\ \vdots \\ \sum_{j=1}^{n} k(j,n) \end{bmatrix} \vec{c}^{Y}, \tag{4.6}$$

where $\operatorname{diag}\vec{v}$ is the diagonal matrix whose entries are the co-ordinates of the vector $\vec{v}$. Finally, we observe that

$$\begin{bmatrix} \sum_{j=1}^{n} k(j,1) \\ \vdots \\ \sum_{j=1}^{n} k(j,n) \end{bmatrix} = K^T\vec{u}_n, \tag{4.7}$$

where $\vec{u}_n$ is the n-dimensional vector with all entries 1. So, plugging in (4.7) to (4.6), we get

$$\vec{g}(\vec{c}) = \left(K - \operatorname{diag}(K^T\vec{u}_n)\right)\vec{c}^{Y}$$

and we define the the **kinetic matrix** as

$$A = K - \operatorname{diag}(K^T \vec{u}_n). \tag{4.8}$$

It is important to note that, from it's definition, the columns of the kinetic matrix sum to zero. This will be used in the proof of Lemma 5.3.

We can now represent the complex formation vector as a matrix operation

$$\vec{g}(\vec{c}) = A\vec{c}^Y$$

and a similar representation of the species formation vector follows from (4.4),

$$\vec{f}(\vec{c}) = YA\vec{c}^Y.$$

Example (Kinetic matrices) Since the definition of the kinetic matrix depends only on the rate constant matrix K, and since we saw earlier that both of our example systems $\mathcal{A}$ and $\mathcal{B}$ have the same rate constant matrix, they both have the same kinetic matrix as well:

$$A = \begin{bmatrix} -k(2,1) & k(1,2) & k(1,3) & 0 & 0 \\ k(2,1) & -k(1,2) - k(3,2) & 0 & 0 & 0 \\ 0 & k(3,2) & -k(1,3) & 0 & 0 \\ 0 & 0 & 0 & -k(5,4) & k(4,5) \\ 0 & 0 & 0 & k(5,4) & -k(4,5) \end{bmatrix}.$$

This example illustrates the property of A that the columns sum to zero.

For system $\mathcal{A}$ we now have

$$\vec{g}(\vec{c}) = \begin{bmatrix} -k(2,1)c_1 + k(1,2)c_2 + k(1,3)c_3 \\ k(2,1)c_1 - k(1,2)c_2 - k(3,2)c_2 \\ k(3,2)c_2 - k(1,3)c_3 \\ -k(5,4)c_1c_2 + k(4,5)c_4^2 \\ k(5,4)c_1c_2 - k(4,5)c_4^2 \end{bmatrix}$$

and for system $\mathcal{B}$ the complex formation function is the same, except all incidences of c_4 are changed to c_3. The identity $\vec{f}(\vec{c}) = Y\vec{g}(\vec{c})$ can easily be checked and shown to hold.

We will now refer to the system with complex matrix Y and rate constant matrix K as $\langle Y, K\rangle$. This wholly characterizes the system, since Y gives the number of species and complexes, and the composition of the complexes, and K gives the information about which complexes react with each other and at what rate.

5 Linkage Classes and Deficiency

Up to this point, discussion has been concentrated on the "analytic" properties of chemical reaction networks; namely, the properties relating directly to the rates of change of concentration (recall from equation (2.2) that the species formation vector $\vec{f}(\vec{c})$ is part of a differential equation). Now the focus will turn to algebraic structures and relationships that define the "topology" of the reaction network. The definitions and results in this section are based on those of Feinberg [2] and Horn [8], but have been adapted significantly to the case in question.

As mentioned above, we can view a chemical reaction network as a directed graph. We say that complex i **reacts to** complex j if there is a branch beginning at node i ending at node j, and the relationship is denoted by $i \rightarrow j$ (by convention, $i \rightarrow i$). The connected components of the graph are called **linkage classes**, and if two complexes are in the same linkage class we write $i \equiv j$. This defines an equivalence relationship, and each equivalence class is called $\mathcal{L}_k$. We can make this concept more precise by defining the relation $\leftrightarrow$ as $i \leftrightarrow j$ if $i \rightarrow j$ or $j \rightarrow i$. Now we can define $\equiv$ precisely by

$$\begin{aligned} i \equiv j \qquad & \text{if there exists a set of complexes} \\ & \{\alpha_1, ..., \alpha_k\} \text{ such that } i \leftrightarrow \alpha_1 \leftrightarrow ... \leftrightarrow \alpha_k \leftrightarrow j. \end{aligned}$$

Example (Linkage classes) Both of our example systems have 2 linkage classes and, in terms of complexes, they are the same linkage classes: $\mathcal{L}_1$ contains complexes 1, 2, and 3, and $\mathcal{L}_2$ contains complexes 4 and 5. So, $\mathcal{L}_1 = \{(A_1), (A_2), (A_3)\}$ for both systems. However, complex 5 is different in each system, so for system $\mathcal{A}$, $\mathcal{L}_2 = \{(A_1 + A_2), (2A_4)\}$, but for system $\mathcal{B}$, $\mathcal{L}_2 = \{(A_1 + A_2), (2A_3)\}$.

The system is called **weakly reversible** if there exists a directed pathway from each member of a linkage class to all other members of the linkage class. Again, this can be made precise by defining another relation $\Rightarrow$, by

$$\begin{aligned} i \Rightarrow j \qquad & \text{if there exists a set of complexes} \\ & \{\alpha_1, ..., \alpha_k\} \text{ such that } i \rightarrow \alpha_1 \rightarrow ... \rightarrow \alpha_k \rightarrow j. \end{aligned}$$

Then the system is weakly reversible equivalently, if $i \Rightarrow j$ implies $j \Rightarrow i$ for all i, j.

Example (Weak reversibility) Both systems $\mathcal{A}$ and $\mathcal{B}$ are weakly reversible.

It is interesting to note that each of these definitions has an equivalent definition in terms of the rate constants $k(i,j)$. For example, complex j reacts to i if and only if $k(i,j) > 0$. Two species i and j are in the same linkage class if there exists an index set $\alpha_1, ..., \alpha_a$, where $\alpha_1 = i$ and $\alpha_a = j$, such that either $\prod_{l=1}^{a-1} k(\alpha_{l+1}, \alpha_l) > 0$ and/or $\prod_{l=1}^{a-1} k(\alpha_l, \alpha_{l+1}) > 0$. The system is weakly reversible if the existence of an index set $\{\alpha_1, ..., \alpha_a | \alpha_1 = i, \alpha_a = j, \prod_{l=1}^{a-1} k(\alpha_{l+1}, \alpha_l) > 0\}$ implies the existence of an index set $\{\beta_1, ..., \beta_a | \beta_1 = j, \beta_a = i, \prod_{l=1}^{a-1} k(\beta_{l+1}, \beta_l) > 0\}$.

The main quantity we will be concerned with is the **deficiency** of a reaction network, defined as $\delta = n - l - s$, where n is the number of complexes in the system, l is the number of linkage classes, and s is the dimension of the stoichiometric space (defined in section 2 as the linear span of all reaction vectors in a system). Clearly the deficiency is an integer; it can also be easily shown that it is non-negative, which will be the corollary of a result later in this chapter. Both the quantities n and l are immediately evident from the reaction diagram. The quantity s is also not difficult to find from the reaction diagram. Recalling the definition of the stoichiometric subspace as the span of reaction vectors, we can find s by solving for the number of linearly independent reaction vectors in the system, which can be done by writing the reaction vectors as columns of a matrix and using row reduction techniques.

An amazing property of deficiency is that it is dependent only on the complexes of the system (as defined by the matrix Y), and the linkage classes $\mathcal{L}_i$ of the system, and *not* on how the members of the linkage class react to one another. This is because the vectors in S are dependent only on linkage class. Consider two complexes i and j in the same linkage class (so $i \equiv j$). Assume that $i \not\rightarrow j$. Then there is a set $\{\alpha_1, ..., \alpha_k\}$ such that $i \rightarrow \alpha_1 \rightarrow ... \rightarrow \alpha_k \rightarrow j$. So, the vectors $[\vec{y}_{\alpha_1} - \vec{y}_i], [\vec{y}_{\alpha_2} - \vec{y}_{\alpha_1}], ..., [\vec{y}_{\alpha_k} - \vec{y}_{\alpha_{k-1}}], [\vec{y}_j - \vec{y}_{\alpha_k}]$ are all in S, as is there sum, which is $\vec{y}_j - \vec{y}_i$. So, $i \equiv j$ implies that the vector representing the elementary reaction between i and j is in S, so the dimension of S depends only on linkage classes. This gives us an immediate simplification of calculating s, since we can now find the linear independence of a smaller and simpler set of vectors when presented with a complicated reaction diagram, so long as the simplified system preserves linkage classes and complexes. Due to this property we can consider deficiency as a measure of the linear independence of "necessary" reactions; that is, if a reaction that cannot be eliminated in a simplified system is a linear combination of other reactions in the system, the deficiency will be greater than zero.

Example (Deficiency) We can now calculate the deficiencies of out example networks. We know that for both of them, $n = 5$ and $l = 2$. The question remains, what is s? Since δ depends only on linkage classes, we need not consider the systems exactly as they are written, but can look at simpler systems instead. For system $\mathcal{A}$ let's consider the system

$$A_1 \to A_2 \to A_3$$

$$A_1 + A_2 \to 2A_4,$$

which has the same linkage classes and complexes, and therefore the same value for s. The reaction vectors in this system are

$$\begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \\ 0 \end{bmatrix}, \text{ and } \begin{bmatrix} -1 \\ -1 \\ 0 \\ 2 \end{bmatrix},$$

and it is easily seen that these are all linearly independent, so $s = 3$, and the deficiency of $\mathcal{A}$ is zero. Similarly, for system $\mathcal{B}$ we can look at the reactions

$$A_1 \to A_2 \to A_3$$

$$A_1 + A_2 \to 2A_3,$$

which have reaction vectors

$$\begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix}, \text{ and } \begin{bmatrix} -1 \\ -1 \\ 2 \end{bmatrix}.$$

These are not all linearly independent, since

$$\begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix} + 2 \begin{bmatrix} 0 \\ -1 \\ 1 \end{bmatrix} = \begin{bmatrix} -1 \\ -1 \\ 2 \end{bmatrix},$$

so $s = 2$. Hence, the deficiency of system $\mathcal{B}$ is one. This is the significant difference between the two that was alluded to when they were introduced, and we will go on to show because of this certain stability properties that are guaranteed in system $\mathcal{A}$ are not in $\mathcal{B}$.

Example (Networks of deficiency greater than one) It may seem, after calculating the deficiency of several networks, that all networks have deficiency of zero or one. While these may be the most common results, it is possible to construct a network of arbitrary deficiency (albeit a somewhat trivial one). The deficiency of the simple network

$$A_1 \to A_2$$

is zero; the deficiency of the system

$$\begin{array}{rcl} A_1 & \to & A_2 \\ 2A_1 & \to & 2A_2 \end{array}$$

is one, because we have added two complexes and one linkage class without changing the dimension of the stoichiometric subspace. Continuing in this vein, the deficiency of the system

$$\begin{array}{rcl} A_1 & \to & A_2 \\ 2A_1 & \to & 2A_2 \\ & \vdots & \\ (x+1)A_1 & \to & (x+1)A_2 \end{array}$$

is x, so we can construct a network of any deficiency.

With regards to our underlying linear algebraic structure, we can use these relationships to define some sets and subspaces that will be useful later. A linkage class, as defined above, is algebraically a set of indices corresponding to the complexes that are in that class. The **linkage spaces** of a system are the subspaces $W_k = \text{span}\{\vec{w}_i | i \in \mathcal{L}_k\}$.The **difference set** is the set of all vectors representing reactions between complexes in the same linkage class (whether these reactions occur in the system or not), and is called Δ, so

$$\Delta = \{\vec{w}_j - \vec{w}_i | i \equiv j\}.$$

We also define $L = \text{span}\,\Delta$. L represents the span of all reaction vectors in complex space, so, by definition $Y(L) = S$.

Lemma 5.1. *If a mass-action system has n complexes and l linkage classes, then* $\dim L = n - l$.

PROOF. Let ρ_i be equal to the number of elements of the linkage class $\mathcal{L}_i$. Since linkage classes are equivalence classes on the set of complexes, a complex belongs to one and only linkage class, so we know that $\sum_{i=1}^{l} \rho_i = n$.

We now define the difference set of a linkage class $\mathcal{L}_i$, denoted by Δ_i, by

$$\Delta_i = \{\vec{w_j} - \vec{w_k} | k, j \in \mathcal{L}_i\}.$$

Clearly, from their definitions, we have

$$\Delta = \bigcup_{i=1}^{l} \Delta_i.$$

If the set $\mathcal{L}_i$ is $\{i_1, ..., i_{\rho_i}\}$, then we can construct a basis for $\operatorname{span} \Delta_i$ by taking the set $\{\vec{w}_{i_j} - \vec{w}_{i_1} | j = 2, 3, ..., \rho_i\}$, so we have that $\dim \operatorname{span} \Delta_i = \rho_i - 1$. Now,

$$L = \bigoplus_{i=1}^{l} \operatorname{span} \Delta_i,$$

so

$$\dim L = \sum_{i=1}^{l} \dim \operatorname{span} \Delta_i = \sum_{i=1}^{l} (\rho_i - 1) = n - l,$$

concluding the proof of the lemma. □

Note that, because S is simply the image of L under the linear transformation Y, we know that $\dim L \geq \dim S$, so $n - l \geq s$ and we have shown that deficiency is non-negative.

Now we will prove an equivalent definition of deficiency in terms of dimensions of vector subspaces:

Corollary 5.2. *The deficiency of a system is equal to the dimension of the space* $\ker Y \cap L$

PROOF. Let X be the restriction of Y to L. By the properties of linear transformations,

$$\dim(\ker X) = \dim L - \dim \operatorname{im} X.$$

Of course, $\ker X = \ker Y \cap L$, and $\operatorname{im} X = YL = S$. So, it follows that

$$\dim[\ker Y \cap L] = \dim(\ker X) = \dim L - \dim \operatorname{im} X = n - l - s,$$

so the proof is complete. □

So, if the deficiency is equal to zero, it follows that

$$\ker Y \cap L = \{\vec{0}_W\}. \tag{5.1}$$

Taking the orthogonal complement of both sides of this equation gives

$$\operatorname{im} Y^T \oplus U = W, \tag{5.2}$$

where U is the span of the vectors $\vec{u_i} = \sum_{j \in \mathcal{L}_i} \vec{w_j}$, which is the orthogonal complement of L.

We are now almost prepared to show that having deficiency zero and being weakly reversible implies certain stability properties; first, however, we need a result that helps to guarantee the existence of an equilibrium point:

Lemma 5.3. *If A is the kinetic matrix of a weakly reversible mass action system, then* $\ker A$ *contains a vector $\vec{p}$ in the positive orthant of the complex space W.*

Proof. Recall from the definition of A that it is composed of two components: one representing creation of complexes, K, and one representing annihilation, $-\operatorname{diag}(K^T\vec{u}_n)$. By definition, members of a linkage class do not react with complexes outside that linkage class in either direction. Hence, the image under A of a linkage space is contained within that linkage space.

In a weakly reversible network, the linkage spaces are the minimal coordinate subspaces that have this property (where a coordinate subspace is a subspace spanned by the natural basis vectors of a space). This is true because if we choose a proper coordinate subset of a linkage space, there must be some complex outside the subset which members of the subspace react to form. Hence, no proper coordinate subset of a linkage space is invariant under the action of A. So, if we disregard the complexes outside of a linkage space W_v and consider it as $\mathbb{R}^{\rho_v}$, then the square matrices A_v that are the restrictions of A to the linkage space W_v are irreducible matrices, by the definition in [6]. (This definition of irreducibility is different but equivalent to the standard definition, which states that a matrix is irreducible if it cannot be permuted such that it has the form $\begin{bmatrix} B & 0 \\ C & D \end{bmatrix}$, where B and D are square matrices, C is any matrix, and 0 represents all zero entries.)

Define $B_v = A_v + \lambda I_v$. B_v is clearly also irreducible, and the eigenspace of B_v is equal to the kernel of A_v, since, if a vector $\vec{x}$ is in $\ker A_v$, then we have

$$B_v\vec{x} = (A_v + \lambda I_v)\vec{x} = A_v\vec{x} + \lambda I_v\vec{x} = \lambda\vec{x}.$$

Since the only entries of A, and hence A_v, that are negative are on the diagonal, we can choose λ such that all of the entries of B_v are non-negative. Because all of the entries in each column of A, and hence A_v, sum to zero, all of the entries in each column of B_v sum to λ. Now, the matrix B_v is a special case of the transition matrix of a Markov chain, in which all of the columns sum to 1. It is a common result that 1 is a maximal eigenvalue of such a matrix; by the same argument, λ is the maximal eigenvalue of B_v.

Now we can invoke the Perron-Frobenius Theorem (this is a partial statement adapted from the statement in [13], giving only the portions of the theorem needed here).

Theorem 5.4 (Perron-Frobenius). *An irreducible, non-negative $n \times n$ matrix has a real eigenvalue λ_1 with the following properties:*

1. $\lambda_1 > 0$.
2. λ_1 *is the maximal eigenvalue.*
3. λ_1 *has a positive eigenvector.*

For the complete proof of the Perron-Frobenius theorem, see [6].

Since we have constructed λ such that it is an eigenvalue of B_v satisfying the first and second points of Theorem 5.4, we know that there is some positive eigenvector $\vec{p_v}$ of B_v, which is therefore in $\ker A_v$. Obviously, each $\vec{p_v}$ is also in $\ker A$, and so is their sum, which we shall denote $\vec{p}$. Since $\vec{p}$ has all positive coordinates it is in W^+, so the proof of the lemma is complete. $\square$

Example (Proof of Lemma 5.3) We can illustrate the proof of lemma 5.3 using the kinetic matrix A of systems $\mathcal{A}$ and $\mathcal{B}$ (recalling that A is the same for both systems). We showed earlier that

$$A = \begin{bmatrix} -k(2,1) & k(1,2) & k(1,3) & 0 & 0 \\ k(2,1) & -k(1,2)-k(3,2) & 0 & 0 & 0 \\ 0 & k(3,2) & -k(1,3) & 0 & 0 \\ 0 & 0 & 0 & -k(5,4) & k(4,5) \\ 0 & 0 & 0 & k(5,4) & -k(4,5) \end{bmatrix},$$

and that the linkage classes consisted of complexes 1,2, and 3 in $\mathcal{L}_1$ and complexes 4 and 5 in $\mathcal{L}_2$. So,

$$A_1 = \begin{bmatrix} -k(2,1) & k(1,2) & k(1,3) \\ k(2,1) & -k(1,2)-k(3,2) & 0 \\ 0 & k(3,2) & -k(1,3) \end{bmatrix}$$

and

$$A_2 = \begin{bmatrix} -k(5,4) & k(4,5) \\ k(5,4) & -k(4,5) \end{bmatrix}.$$

So, we have that

$$B_1 = \begin{bmatrix} -k(2,1)+\lambda & k(1,2) & k(1,3) \\ k(2,1) & -k(1,2)-k(3,2)+\lambda & 0 \\ 0 & k(3,2) & -k(1,3)+\lambda \end{bmatrix}$$

and

$$B_2 = \begin{bmatrix} -k(5,4)+\lambda & k(4,5) \\ k(5,4) & -k(4,5)+\lambda \end{bmatrix}.$$

We can now calculate the eigenvectors of these matrices that correspond to the eigenvalue λ, and the Perron-Frobenius theorem guarantees that each matrix will have a positive eigenvector. These can be considered as vectors in the entire complex space, rather than the restriction to each linkage class, by inserting zeros in the appropriate coordinates. Then, by adding these vectors, we get a vector in W^+ that is in the kernel of A.

Now the following theorem can be proven:

Theorem 5.5. *A mass-action system that is weakly reversible and has deficiency zero has an equilibrium point in V^+, and is complex balanced at that point.*

Proof. By equation (5.2), deficiency 0 implies that the complex space $W = (\operatorname{im} Y^T \oplus U)$. Since Y^T acts on the species space V, and a basis for U is the set of l vectors $\vec{u}_j = \sum_{i \in \mathcal{L}_i} \vec{v}_i$, there is an orthogonal decomposition of any vector $\vec{w}$ in W as

$$\vec{w} = Y^T \vec{v} - \sum_{j=1}^{l} \Lambda_j \vec{u}_j \tag{5.3}$$

where $\vec{v} \in V$ and Λ_j are real numbers. Since any real number can be written as the logarithm of a positive real number, any vector in W can be written as the logarithm of a vector in W^+ and any vector in V can be written as the logarithm of a vector in V^+. Let $\vec{w} = \ln \vec{p}$ where $\vec{p}$ is the vector found in Lemma 5.3, and then choose $\vec{x} \in V^+$ and positive numbers λ_i such that $\vec{v} = \ln \vec{x}$ and $\Lambda_i = \ln \lambda_i$ in equation (5.3) above. So we can rewrite (5.3) as

$$Y^T \ln \vec{x} - \sum_{j=1}^{l} (\ln \lambda_j) \vec{u}_j = \ln \vec{p}.$$

By the identities relating the vector logarithm and the vector exponent,

$$\ln \vec{x}^Y = \ln \vec{p} + \sum_{j=1}^{l} (\ln \lambda_j) \vec{u_j}. \tag{5.4}$$

Considering the left hand side of this equation coordinate-wise and using the normal scalar identity for summing logarithms, we get

$$\ln \vec{x}^Y = \ln \sum_{j=1}^{l} (\lambda_j \vec{p_j}),$$

where $\vec{p_j}$ are the positive eigenvectors in each linkage class found in the proof of Lemma 5.3. This implies that

$$\vec{x}^Y = \sum_{j=1}^{l} \lambda_j \vec{p_j}.$$

Since $\{\vec{p_j}\}$ are all in $\ker A$, scalar multiples and sums of their scalar multiples are too. So $\vec{x}^Y$ is therefore in $\ker A$, and so the system is complex balanced at $\vec{x}$, which in turn implies that $\vec{x}$ is an equilibrium point. □

Example (Proof of Theorem 5.5) System $\mathcal{A}$ is deficiency zero and weakly reversible, so it satisfies the hypothesis of Theorem 5.5. Let the vector $\vec{p}$ given by Lemma 5.3 have coordinates as follows:

$$\vec{p} = \begin{bmatrix} p_1 \\ p_2 \\ p_3 \\ p_4 \\ p_5 \end{bmatrix}$$

so the restrictions of these to each linkage class are

$$\vec{p_1} = \begin{bmatrix} p_1 \\ p_2 \\ p_3 \\ 0 \\ 0 \end{bmatrix} \text{ and } \vec{p_2} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ p_4 \\ p_5 \end{bmatrix}.$$

So, using equation (5.4), we have

$$\begin{aligned}
\ln \vec{x}^Y &= \ln \vec{p} + (\ln \lambda_1)\vec{u_1} + (\ln \lambda_2)\vec{u_2} \\
&= \begin{bmatrix} \ln p_1 \\ \ln p_2 \\ \ln p_3 \\ \ln p_4 \\ \ln p_5 \end{bmatrix} + \begin{bmatrix} \ln \lambda_1 \\ \ln \lambda_1 \\ \ln \lambda_1 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ \ln \lambda_2 \\ \ln \lambda_2 \end{bmatrix} \\
&= \begin{bmatrix} \ln(\lambda_1 p_1) \\ \ln(\lambda_1 p_2) \\ \ln(\lambda_1 p_3) \\ \ln(\lambda_2 p_4) \\ \ln(\lambda_2 p_5) \end{bmatrix} \\
&= \ln \left(\begin{bmatrix} \ln(\lambda_1 p_1) \\ \ln(\lambda_1 p_2) \\ \ln(\lambda_1 p_3) \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ \ln(\lambda_2 p_4) \\ \ln(\lambda_2 p_5) \end{bmatrix} \right) \\
&= \ln(\lambda_1 \vec{p_1} + \lambda_2 \vec{p_2}).
\end{aligned}$$

Now, we can remove the logarithms from both sides (this can be done by taking the exponential coordinate-wise on both sides of the equation). Since both $\vec{p_1}$ and $\vec{p_2}$ are in the kernel of A, linear combinations of them are as well, so $\vec{x}^Y$ is in the kernel of A, and hence $\vec{x}$ is an equilibrium point and the system is complex balanced at that point.

System $\mathcal{B}$ does not satisfy the hypothesis of Theorem 5.5, since it has deficiency one. This means that we can not use the identity $W = (\operatorname{im} Y^T \oplus U)$, since $\operatorname{im} Y^T \oplus U$ is some two dimensional space, and it may not intersect the positive orthant of W at all. Hence, this proof for existence of a complex balanced equilibrium point does not apply to networks of deficiency one.

6 Quasithermostatic and Quasithermodynamic Systems

At this point, several conditions on systems will be introduced, in order to construct a Lyapunov function on our system. This will be used with the results of sections 7 and 8 to show that complex balancing at one point implies complex balancing at all equilibrium points, and the uniqueness of this point within each reaction reaction simplex $\bar{S}_{c_0}$, which is defined as the coset of the stoichiometric space S containing the concentration $\vec{c_0}$, and represents the attainable states of a system starting at concentration $\vec{c_0}$. The definitions and proofs are from Horn and Jackson [12].

A system is **Quasi-thermostatic (QTS)** if and only if there exists some vector $\vec{a} \in V^+$ such that the set $E' = \{\vec{c} \in V^+ | [\ln \vec{c} - \ln \vec{a}] \in S^\perp\}$ is equal to the equilibrium set E. The function is then called **QTS with respect to** $\vec{a}$. This is equivalent to the condition

$$[\ln \vec{c} - \ln \vec{a}] \cdot \vec{x} = 0 \text{ for any } \vec{x} \in S, \text{ if and only if } \vec{c} \in E. \tag{6.1}$$

It follows immediately from the definition that $\vec{a}$ itself is an equilibrium concentration. Note that it is sufficient to show that this holds for a set of $\vec{x}_i$ which spans S.

Example (Quasi-thermostatic systems) It is difficult to characterize what the QTS condition means in general, other than saying it imposes certain regularity constraints on the set of equilibrium points; exactly what these conditions are, however, will vary. Take, for example, the simplest possible system:

$$A_1 \to A_2$$

In this example system the QTS states that a vector $\vec{c}$ is an equilibrium if and only if it satisfies the equation

$$x_1 \ln c_1 - x_1 \ln a_1 + x_2 \ln c_2 - x_2 \ln a_2 = 0,$$

which is simply equation (6.1) expanded and written in coordinates. Now, the stoichiometric subspace of this system is spanned by the vector $\begin{bmatrix} 1 \\ -1 \end{bmatrix}$. Using this and the standard logarithm identities, we can simplify the condition to be

$$\ln \frac{c_1}{a_1} - \ln \frac{c_2}{a_2} = 0,$$

so a point is an equilibrium if and only if $\vec{c} = \alpha \vec{a}$ for any constant α and some fixed $\vec{a}$.

More complicated conditions are possible, such as in the system

$$\begin{aligned} A_1 + A_2 &\to 2A_3 \\ A_4 &\to A_5 \end{aligned}$$

which leads to the restrictions

$$\frac{c_1}{a_1}\frac{c_2}{a_2} = \left(\frac{c_3}{a_3}\right)^2 \text{ and } \frac{c_4}{a_4} = \frac{c_5}{a_5}.$$

Because of this dependence on the topology of the system, it is very difficult to form a precise descriptive picture of what QTS means in general other than that it restricts the equilibrium set; however, the mathematical reasoning behind the definition will become clear in section 8.

A further restriction on the dynamic behavior of a system is the quasi-thermodynamic condition. A system is **Quasi-thermodynamic (QTD) with respect to $\vec{a}$** if and only if it is QTS with respect to $\vec{a}$ and, for all vectors $\vec{c} \in V^+$, $\vec{c} \notin E$,

$$\Big([\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}(\vec{c})\Big) < 0,$$

where $\vec{f}(\vec{c})$ is the species formation vector at $\vec{c}$.

The **pseudo-Helmholtz function (PHF) with respect to $\vec{a}$** is defined as

$$H(\vec{c}) = \sum_{j=1}^{m} \big((\ln c_j - \ln a_j - 1)c_j\big)$$

where c_j is the j-th component of the vector $\vec{c}$ (and likewise with a_j).

The PHF is constructed such that it has the following properties:

1. H is continuous in $\bar{V}^+$
2. H is strictly convex in $\bar{V}^+$
3. $H(\vec{c}) = ([\ln \vec{c} - \ln \vec{a} - \vec{e}_v] \cdot \vec{c})$, $\vec{c} \in V^+$, where $\vec{e}_v$ is the vector in V with all entries equal to 1, and H is continuously differentiable in V^+ with $\vec{\nabla} H(\vec{c}) = [\ln \vec{c} - \ln \vec{a}]$.
4. If $\vec{c}_1 \in \partial\bar{V}^+$, $\vec{c}_2 \in V^+$, then $\vec{c}_2 + \lambda[\vec{c}_1 - \vec{c}_2] \in V^+$ for $0 \leq \lambda < 1$ and $\lim\limits_{\lambda \to 1} \frac{d}{d\lambda} H(\vec{c}_2 + \lambda[\vec{c}_1 - \vec{c}_2]) = \infty$.
5. $\lim\limits_{|\vec{c}| \to \infty} H(\vec{c}) = \infty$.

Generally, when a QTS system, QTD system, or PHF is discussed, the "with respect to $\vec{a}$" will be dropped, and it should be understood that such a vector $\vec{a}$ is still associated with the system.

Lemma 6.1. *In any reaction simplex $\bar{S}_{c0}$ the PHF (with respect to any $\vec{a}$) assumes its minimum relative to the simplex at a unique concentration in the positive orthant.*

Proof. Since the reaction simplex is closed, existence of a minimum follows from property 5 of the PHF, since this condition ensures that the PHF cannot become infinitesimally small on the unbounded portion of the simplex.

The simplex is the intersection of two convex sets, so it too is convex. Property 2 of the PHF asserts that H is a strictly convex function, and thus can only assume its minimum relative to a reaction simplex (which is convex) at one point, giving uniqueness.

Finally, property 4 of the PHF assures that it does not assume its minimum on the boundary, since this property that, at arbitrary closeness to the boundary, the PHF is increasing. Hence, the minimum is in the interior of the simplex, and therefore in the positive orthant. □

Lemma 6.2. *For a QTS system each reaction simplex $\bar{S}_{c0}$ contains precisely one equilibrium.*

Proof. Let $\vec{c}_*$ be the minimum of the PHF in the reaction simplex (proven to exist above), which is located on the interior to the simplex. Relative to the displacements within the simplex, $\vec{c}_*$ must be a stationary point, meaning that the gradient of H at $\vec{c}_*$ must be orthogonal to all vectors $[\vec{c} - \vec{c}_*]$, $\vec{c} \in \bar{S}_{c0}$. This is equivalent to the condition $\vec{\nabla} H(\vec{c}_*) \in S^{\perp}$. Now, by property 3 of the PHF, and because $\vec{c}_* \in V^+$, we have

$$\vec{\nabla} H(\vec{c}_*) = [\ln \vec{c}_* - \ln \vec{a}].$$

By the definition of QTS, it follows that $\vec{c}_* \in E$, proving the existence of an equilibrium point in a QTS system.

Uniqueness follows by essentially reversing the procedure above: consider an equilibrium point $\vec{c}_*$. By the definition of QTS, $[\ln \vec{c}_* - \ln \vec{a}] \in S^{\perp}$, so the PHF is stationary relative to displacements in the simplex at this point. Since the PHF is strictly convex function, and a strictly convex function can only have one stationary point, $\vec{c}_*$ is the only equilibrium point. □

It should be noted that, while the definition of the PHF may seem confusing and unintuitive, it was simply constructed so that the lemmas of this section could be proved; it has no significance outside of this function.

7 Reaction Cycles

Our focus will now temporarily shift to a certain class of systems, for which some powerful results will be derived. In the next section, we will show how these results can be expanded to apply to generalized mass action systems. The results and arguments in these two sections are after Horn and Jackson [12].

An ordered set of complex indices $v_0, v_1, ..., v_l$ is called an **l-cycle** if:

1. $v_0 = v_l$
2. $v_i \neq v_j$ unless $i = 0$ and $j = l$
3. $k(v_j, v_{j-1}) > 0, 1 \leq j \leq l$; that is, complex v_{j-1} in the cycle reacts to form complex v_j of the cycle for all j.

When dealing with l-cycles, we will assume that the subscripts of the elements of the cycle are taken to be modulo l, so that, for example $v_{l+1} = v_1$.

We call the system $\langle Y, K \rangle$ cyclic if there is an n-cycle in the system; that is, if there exists some l-cycle containing all the complexes of the system. Note that weak reversibility is necessary for cyclicness, but not sufficient. Necessity follows from the fact that, for any pair of complexes v_j and v_k in a cyclic system we have both index sets such that $\prod_{i=j}^{k-1} k(v_{i+1}, v_i) > 0$ and such that $\prod_{i=k}^{j-1} k(v_{i+1}, v_i) > 0$ (recalling that the subscripts are taken modulo l), so that the definition of weakly reversible in terms of reaction constants is satisfied. The fact that it is not sufficient can be easily seen from the fact that a cyclic system can only have one linkage class, since $k(i, j) = 0$ for i, j in different linkage classes.

Example (Cyclic systems and weak reversibility) Neither of our example systems $\mathcal{A}$ or $\mathcal{B}$ are cyclic, but either one of their linkage classes considered as a system by itself would be cyclic. Using these examples one might conjecture that all linkage classes of a weakly reversible system can be written as a cyclic system;

however, this is not the case. Consider as a counter-example the following system

$$\begin{tikzcd}
A_1 \arrow[r] & A_2 \arrow[dl] \\
A_3 \arrow[u] \arrow[r] & A_4 \arrow[u]
\end{tikzcd}$$

which is weakly reversible, but is not cyclic since any cycle that contained all of the complexes would have to contain nonterminal repeated indices.

Recalling the definition from (4.3), we see the species formation vector of a cyclic system is given by

$$\vec{f}(\vec{c}) = \sum_{j=1}^{l} \left(k(v_j, v_{j-1}) \vec{c}^{\,\vec{y}_{v_{j-1}}} \right) \left[\vec{y}_{v_j} - \vec{y}_{v_{j-1}} \right]$$

and the rate of formation of complex v_j is given by

$$g^{v_j}(\vec{c}) = \left(k(v_j, v_{j-1}) \vec{c}^{\,\vec{y}_{v_{j-1}}} - k(v_{j+1}, v_j) \vec{c}^{\,\vec{y}_{v_j}} \right).$$

By the definition of complex balancing, a cyclic system is complex balanced at $\vec{a} \in V^+$ if and only if, for all j,

$$\begin{aligned}
k(v_j, v_{j-1}) \left(\vec{a}^{\,\vec{y}_{v_{j-1}}} \right) - k(v_{j+1}, v_j) \left(\vec{a}^{\,\vec{y}_{v_j}} \right) &= 0 \\
\Leftrightarrow k(v_j, v_{j-1}) (\vec{a}^{\,\vec{y}_{v_{j-1}}}) &= k(v_{j+1}, v_j) (\vec{a}^{\,\vec{y}_{v_j}})
\end{aligned}$$

so all $k(v_j, v_{j-1})$ are equal, and we have

$$k(v_j, v_{j-1}) (\vec{a}^{\,\vec{y}_{v_{j-1}}}) = \kappa \text{ for some positive constant } \kappa. \tag{7.1}$$

Now, for a cyclic system that is complex balanced at a, we can rewrite the species formation vector as

$$\vec{f}(\vec{c}) = \kappa \sum_{j=1}^{l} \left(\left[\frac{\vec{c}}{\vec{a}} \right]^{\vec{y}_{v_{j-1}}} \right) \left[\vec{y}_{v_j} - \vec{y}_{v_{j-1}} \right] \tag{7.2}$$

and equivalently for complex formation we have

$$g^{v_j}(\vec{c}) = \kappa \left(\left[\frac{\vec{c}}{\vec{a}} \right]^{\vec{y}_{v_{j-1}}} - \left[\frac{\vec{c}}{\vec{a}} \right]^{\vec{y}_{v_j}} \right). \tag{7.3}$$

Proposition 7.1. *If a cyclic mass action system is complex balanced at* $\vec{a} \in V^{+}$*, then it is quasi-thermodynamic with respect to* $\vec{a}$*.*

Before Proposition 7.1 can be proven, the following inequality is needed:

Lemma 7.2. *If* $\varphi : X \to \mathbb{R}, X \subseteq \mathbb{R}$ *is strictly increasing, and* $\xi_0, \xi_1, ..., \xi_l \in X$ *such that* $\xi_0 = \xi_l$*, then*

$$\sum_{j=1}^{l} \xi_{j-1} \left(\varphi(\xi_j) - \varphi(\xi_{j-1})\right) \leq 0 \tag{7.4}$$

with equality holding if and only if $\xi_0 = \xi_1 = ... = \xi_l$*.*

Proof. Define $\Phi_l : X^l \to \mathbb{R}$ by

$$\Phi_l(\xi_1, ..., \xi_l) = \sum_{j=1}^{l} (\xi_{j-1}(\varphi(\xi_j) - \varphi(\xi_{j-1})), \tag{7.5}$$

where $\xi_0 = \xi_l$. So, the statement of the lemma becomes

$$\Phi_l(\xi_1, ..., \xi_l) \leq 0 \text{ for all } \xi_j \in X$$

and that equality occurs if and only if all $\xi_1 = ...\xi_l$.

The proof is by induction on l. For $l = 2$,

$$\Phi_2(\xi_1, \xi_2) = (\xi_2 - \xi_1)\left(\varphi(\xi_1) - \varphi(\xi_2)\right). \tag{7.6}$$

If $\xi_1 > \xi_2$, then $(\xi_2 - \xi_1) < 0$ and $(\varphi(\xi_1) - \varphi(\xi_2)) > 0$ by the fact that φ is strictly increasing. If $\xi_1 < \xi_2$, then $(\xi_2 - \xi_1) > 0$ and $(\varphi(\xi_1) - \varphi(\xi_2)) < 0$, again by the fact that φ is strictly increasing. So, if $\xi_1 \neq \xi_2$, then equation 7.6 is clearly negative. If $\xi_1 = \xi_2$, then it is clearly zero, so the lemma is true for $l = 2$.

Assume the lemma is valid for l. Consider a set of real numbers $\xi_1, ..., \xi_{l+1}$. Since it is finite, this set has a maximum; since Φ_{l+1} is invariant under cyclic permutations, assume without loss of generality that ξ_{l+1} is this maximum. From the definition 7.5 we see that only one term of the sum includes ξ_{l+1}, so we can write

$$\Phi_{l+1}(\xi_1, ...\xi_{l+1}) = \Phi_l(\xi_1, ..., \xi_l) + (\xi_{l+1} - \xi_l)\left((\varphi(\xi_l) - \varphi(\xi_{l+1})\right). \tag{7.7}$$

Our induction hypothesis states that the first term on the right hand side is non-positive; because we chose $\xi_{l+1} \geq \xi_l$, the second term is non-positive because φ is strictly increasing.

Since both these terms are non-positive, if $\Phi_{l+1} = 0$, both of the terms on the right hand side of equation 7.7 must be zero. The induction hypothesis states that, if $\Phi_l(\xi_1, ...\xi_l) = 0$, then $\xi_1 = ... = \xi_l$. If the second term equals zero, then $\xi_l = \xi_{l+1}$. So, for equality to hold, $\xi_1 = ... = \xi_{l+1}$. So, the lemma is true by induction. □

PROOF OF PROPOSITION 7.1. If the system is complex balanced at $\vec{a}$, then by cyclicness, using the equality given in equation (7.2),

$$\begin{aligned} [\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}(\vec{c}) &= \left[\ln \frac{\vec{c}}{\vec{a}}\right] \cdot \vec{f}(\vec{c}) \\ &= \kappa \left[\ln \frac{\vec{c}}{\vec{a}}\right] \cdot \left[\sum_{j=1}^{l} \left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_{j-1}}}\right) [\vec{y}_{v_j} - \vec{y}_{v_{j-1}}]\right] \end{aligned}$$

for any $\vec{c} \in V^+$, and distributing the inner product across the sum gives

$$\kappa \sum_{j=1}^{l} \left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_{j-1}}}\right) \left(\left[\ln \frac{\vec{c}}{\vec{a}}\right] \cdot [\vec{y}_{v_j} - \vec{y}_{v_{j-1}}]\right). \tag{7.8}$$

Using the distributive property of the inner product a second time, and applying the properties of the vector form of the logarithm, equation (7.8) can be written as

$$\kappa \sum_{j=1}^{l} \left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_{j-1}}}\right) \left(\ln\left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_j}}\right) - \ln\left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_{j-1}}}\right)\right). \tag{7.9}$$

Now, the logarithm is a strictly increasing function, the arguments it takes are $\left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_0}}\right), ..., \left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_l}}\right)$, and $\left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_0}}\right) = \left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_l}}\right)$, so the result of equation (7.9) satisfies the conditions of lemma 7.2. Since $\kappa > 0$, this gives

$$\left([\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}(\vec{c})\right) \leq 0 \text{ for } \vec{c} \in V^+ \tag{7.10}$$

with equality holding if and only if

$$\left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_{j-1}}}\right) = \left(\left[\frac{\vec{c}}{\vec{a}}\right]^{\vec{y}_{v_j}}\right) \text{ for all } j. \tag{7.11}$$

This condition for equality implies that

$$[\ln \vec{c} - \ln \vec{a}] \cdot [y_{v_j} - y_{v_{j-1}}] = 0. \tag{7.12}$$

Note that the set of all $[y_{v_j} - y_{v_{j-1}}]$ spans the stoichiometric space, so, by the definition in equation (6.1), showing that equality occurs in (7.10) if and only if $\vec{c}$ is an equilibrium concentration is equivalent to the system being QTS. Once this has been demonstrated, QTD follows immediately because equation 7.10 guarantees that the inner product is negative when equality does not hold.

So, consider an equilibrium concentration for the system $\vec{c}$. By definition, $\vec{f}(\vec{c}) = \vec{0}$, so equality holds in (7.10). This shows that equilibrium concentration implies equality in (7.10). Now, assume that (7.12) holds for a concentration $\vec{c}$. This implies that (7.11) holds, so (7.10) holds, and the proof of Proposition 7.1 is complete. $\square$

The next result follows from the last quite easily:

Lemma 7.3. *If a cyclic mass action system is complex balanced at any concentration in the positive species space, it is complex balanced at all equilibrium concentrations, or, equivalently,* $\ker Y$ *is trivial.*

Proof. If the system is complex balanced at $\vec{a} \in V^+$, and $\vec{c} \in E$, then (7.11) holds, so (7.3) shows that complex formation is zero for all j; hence the system is complex balanced at $\vec{c}$. $\square$

8 Generalization to non-cyclic systems

The purpose of this section is to prove that the results of the preceding section are valid not only for cyclic systems, but for general mass action systems as well. This will be done by decomposing of general systems into cyclic systems.

First, we will introduce the concept of a **chain of complexes**. A chain of complexes can be thought of as a generalization of the l-cycles of the previous section; it, too, is an ordered set of complex indices, which we will denote by $\mu_0, ..., \mu_p$, without the first and second restrictions on l-cycles. That is, $k(\mu_j, \mu_{j-1}) > 0$ for all $j = 1, ..., p$, but μ_0 does not have to equal μ_p, and indices may be repeated. As in l-cycles, p is called the length of the chain. μ_0 is called the initial complex of the chain, and μ_p is called the terminal complex. Since $k(\mu_i, \mu_i) = 0$ no two adjacent complexes may be equal.

A chain is called **long** if $p \geq n$, where n is the number of complexes in the system. A long chain has at least $n+1$ complexes in it (since there is a 0-th member of the chain), so at least one complex index must appear twice.

Lemma 8.1. *If a long chain exists in $\langle Y, K\rangle$ then there also exists at least one cycle in $\langle Y, K\rangle$.*

Proof. Choose indices μ_α and μ_β ($\beta > \alpha$) such that $\mu_\alpha = \mu_\beta$ and the set $\mu_\alpha, ..., \mu_{\alpha+1}, ..., \mu_\beta$ contains no repeated indices other than the initial and terminal members. Such a subset must exist, since at least one index is repeated, and $\mu_\alpha \neq \mu_{\alpha+1}$. A cycle can now be constructed by setting $v_0 = \mu_\alpha, v_1 = \mu_{\alpha+1}, ..., v_l = \mu_{\alpha+l} = \mu_\beta$. $\square$

Lemma 8.2. *If $\langle Y, K\rangle$ is complex balanced at some concentration $\vec{a}$ and $K \neq 0$, then there exists a long chain, and therefore a cycle, in $\langle Y, K\rangle$.*

Proof. By non-triviality of K, there exists some nonzero $k(i,j)$. Since the system is complex balanced at $\vec{a}$, we have that the rate of creation and the rate of consumption of complex i must be equal at concentration $\vec{a}$:

$$\sum_{v=1}^{n} k(i,v)\left(\vec{a}^{\vec{y}_v}\right) = \sum_{u=1}^{n} k(u,i)\left(\vec{a}^{\vec{y}_i}\right)$$

Since we know that the left hand side of the equation is positive, the right hand side must be as well, so there is at least one complex h such that $k(h,i) > 0$. Now, set $j = \mu_0, i = \mu_1, h = \mu_2$. This is a chain of length 2. This process can be repeated, to show that the fact that $k(h,i) > 0$ implies nonzero $k(l,h)$, thus adding $l = \mu_3$ to the chain, and can be iterated to form a chain of any length. So, any non-trivial system that is complex balanced at some point contains chains of all lengths. $\square$

The following lemma is the fundamental result that allows the decomposition of general mass action systems into cyclic systems; it states that any system can be broken down into a cyclic and a noncyclic component, and that the noncyclic component is in some way "smaller" than the original system, allowing this process to be iterated such that it does not continue indefinitely.

Lemma 8.3. *If $\langle Y, K\rangle, (K \neq 0)$ is complex balanced at $\vec{a}$, then there exist rate constant matrices K_1 and K_1' such that*

1. *$K = K_1 + K_1'$.*
2. *$\langle Y, K_1 \rangle$ is cyclic and complex balanced at $\vec{a}$.*
3. *$\langle Y, K_1' \rangle$ is complex balanced at $\vec{a}$, and the number of nonzero elementary reactions (the number of nonzero entries in the matrix K_1') is strictly less than the number in $\langle Y, K \rangle$.*

PROOF. Lemma 8.2 gives that there exists a cycle in $\langle Y, K \rangle$. Let $v_1, ..., v_l$ be the indices of this cycle. Now, define

$$\kappa_1 = \min_{j=1,...l} \left(k(v_j, v_{j-1}) \left(\vec{a}^{\vec{y}_{v_{j-1}}} \right) \right)$$

and

$$k_1(p,q) = \begin{cases} \frac{\kappa_1}{\left(\vec{a}^{\vec{y}_{v_{j-1}}}\right)} & \text{if } (p,q) = (v_j, v_{j-1}), j = 1, ..., l, \\ 0 & \text{if } (p,q) \neq (v_j, v_{j-1}). \end{cases} \tag{8.1}$$

This definition is to ensure that

$$k_1(p,q) \leq k(p,q)$$

with the equality holding for at least one nonzero value of $k_1(p,q)$. Now, if we define

$$k_1'(p,q) = k(p,q) - k_1(p,q)$$

and use the above inequality, we get that

$$k_1'(p,q) \geq 0 \text{ for all } (p,q),$$

and the kernel of k_1' has more elements than the kernel of k.

Now, let K_1 be the matrix with (i,j)-th entry $k_1(i,j)$, and K_1' be the matrix with (i,j)-th entry $k_1'(i,j)$. So, $K = K_1 + K_1'$, as desired.

From the definition of k_1, it follows that $\langle Y, K_1 \rangle$ is cyclic; furthermore, k_1 is constructed such that $k(v_j, v_{j-1})(\vec{a}^{\vec{y}_{v_{j-1}}}) = \kappa_1$, a constant, so by equation (7) $\langle Y, K_1 \rangle$ is complex balanced at $\vec{a}$, so the second part of the lemma is true.

The fact that the kernel of k_1' is greater than and includes that of k is equivalent to the statement that the number of nonzero entries in K_1' is less than the number in K. The fact that $\langle Y, K_1' \rangle$ is complex balanced at $\vec{a}$ follows immediately from the definition of k_1' as the difference between k and k_1. The fact that these two systems are complex balanced means that $\vec{a}^Y$ is in the kernel of the kinetic matrix of both systems. The kinetic matrix is defined entirely in terms of the matrices K and K_1, repectively, and the definitions are linear in K and K_1. It follows the kinetic matrix for $\langle Y, K_1' \rangle$ is simply the difference of the kinetic matrices of $\langle Y, K \rangle$ and $\langle Y, K_1' \rangle$, so $\vec{a}^Y$ is also in the kernel of the kinetic matrix for $\vec{a}^Y$, and hence the system is complex balanced at $\vec{a}$. $\square$

As mentioned above, the goal of this lemma is to iterate it, in order to be able to decompose all systems into cyclic subsystems. The following corollary makes that idea precise:

Corollary 8.4. *If $\langle Y, K \rangle, (K \neq 0)$ is complex balanced at $\vec{a}$, then there exist rate constant matrices $K_1, K_2, ...K_\omega$ such that*

1. $K = \sum_{i=1}^{\omega} K_i$.
2. *$\langle Y, K_i \rangle$ is cyclic and complex balanced at $\vec{a}$, for all $i = 1, ..., \omega$.*

PROOF. Simply repeat the process described in the proof of Lemma 8.3 until the matrix $K_i' = 0$; decompose K_1' into K_2 and K_2', etc. Due to part 3 of the lemma, the number of nonzero entries in K_i' is strictly less than the number of nonzero entries in K_{i-1}', and since the number of entries in the matrices is finite, it must eventually be zero (in fact, we can put an upper bound on ω at m^2). $\square$

Example (Cyclic decomposition) Our example systems can be decomposed quite easily, by separating the matrix K into linkage classes. However, the more complicated construction of Lemma 8.3 and Corollary 8.4 is needed in systems such as the one described in the previous example, where a linkage class in and of itself is noncyclic.

Now, everything that has been proven thus far can be combined to prove the first result that applies to general mass action systems, a generalization of Proposition 7.1 and Lemma 7.3

Theorem 8.5. *If a mass action system is complex balanced at a concentration $\vec{a}$, then it is complex balanced at all equilibrium concentrations, and is quasi-thermodynamic with respect to all equilibrium concentrations.*

PROOF. Let $\langle Y, K \rangle$ be a mass action system complex balanced at $\vec{a}$. Break down K into $K_1, ..., K_\omega$ as described in Lemma 8.4 such that $\langle Y, K_1 \rangle$,

..., $\langle Y, K_\omega \rangle$ are all cyclic mass action systems. Now, use the definition of the species formation vector to define $\vec{f}_i(\vec{c}), i = 1, ..., \omega$ for each of these systems. Due to the first part of Lemma 8.4, the rate constants of the subsystems sum to give the rate constant of the original system, so

$$\vec{f}(\vec{c}) = \sum_{i=1}^{\omega} \vec{f}_i(\vec{c}). \tag{8.2}$$

Therefore, we can take the dot product on both sides of this equation, giving

$$[\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}(\vec{c}) = \sum_{j=1}^{\omega} [\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}_i(\vec{c}). \tag{8.3}$$

To each term in the sum we can apply equation (7.10) from the proof of Proposition 7.1, since each $\langle Y, K_i \rangle$ satisfies the hypothesis of the proposition. This gives

$$[\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}_i(\vec{c}) \leq 0, \vec{c} \in V^+,$$

for all i, so, by (8.2),

$$[\ln \vec{c} - \ln \vec{a}] \cdot \vec{f}(\vec{c}) \leq 0, \vec{c} \in V^+, \tag{8.4}$$

Now, assume that $\vec{c^*} \in E$; so $\vec{f}(\vec{c^*}) = 0$ and equality holds in (8.4), which implies that equality must hold for all $\vec{f}_i(\vec{c^*})$ in (7.10), so $\vec{c^*}$ is in the equilibrium set of all the subsystems $\langle Y, K_i \rangle$. By Lemma 7.3, this implies that $\langle Y, K_i \rangle$ is complex balanced at $\vec{c^*}$, as well. This, in turn, implies that $\langle Y, K \rangle$ is complex balanced at $\vec{c^*}$, since the complex formation vector is just the sum of the complex formation vectors in the subsystems.

Now, $\langle Y, K_i \rangle$ is QTD with respect to $\vec{a}$ by Proposition 7.1, so $[\ln \vec{c^*} - \ln \vec{a}]$ is orthogonal to all elementary reaction vectors in $\langle Y, K_i \rangle$, for all i. However, the stoichiometric space S of $\langle Y, K \rangle$ is simply the linear span of the union of the elementary reaction vectors in $\langle Y, K_i \rangle$, so it follows that $[\ln \vec{c^*} - \ln \vec{a}] \in S^\perp$ if $\vec{c^*} \in E$. The converse is clearly true as well, since if $[\ln \vec{c^*} - \ln \vec{a}] \in S^\perp$, then it is orthogonal to all elementary reaction vectors in $\langle Y, K_i \rangle$, and since each $\langle Y, K_i \rangle$ is QTS this implies that c^* is in the equilibrium set for $\langle Y, K_i \rangle$, and hence in E.

So, we have shown that $\langle Y, K \rangle$ is QTS with respect to $\vec{a}$. Finally, we have that $\langle Y, K \rangle$ is QTD, because the equality in equation (8.4) can only occur when the corresponding equality holds for all $\langle Y, K_i \rangle$; since each of these subsystems is QTD, this only occurs when $\vec{c}$ is in the equilibrium set for each $\langle Y, K_i \rangle$, which in turn implies $\vec{c} \in E$. $\square$

9 The Deficiency Zero Theorem

Finally, the principal theorem of this paper can be proven.

Theorem 9.1 (Deficiency Zero). *A weakly reversible mass-action reaction network with deficiency zero contains one unique equilibrium point in each positive reaction simplex.*

Proof. The existence of an equilibrium point is given by Theorem 5.5, as is the fact that the system is complex balanced at all equilibrium points. The fact that this equilibrium point is complex balanced implies that all equilibrium points are complex balanced, and that the system is quasi-thermodynamic with respect to all of the equilibrium points, by Theorem 8.5. Quasi-thermodynamic implies quasi-thermostatic, so Lemma 6.2 tells us that each reaction simplex contains precisely one equilibrium. □

It may seem that the invocation of Theorem 5.5 is superfluous, since Lemma 6.2 implies existence; however, Theorem 8.5 requires that the system be complex balanced at an equilibrium point, so we must prove that the system admits equilibria before it can be applied.

With the aid of a lemma, we will be able to expand the scope of this result by giving a partial converse.

Lemma 9.2. *If a system contains a concentration at which it is complex balanced, then it is weakly reversible.*

Proof. Let $\vec{c_0}$ be a concentration at which the system is complex balanced. So, by the definition of complex balanced and from equation (4.5), we get the equation

$$\sum_{i=1}^{n}\begin{bmatrix} k(1,i)\vec{c_0}^{\vec{y}_i} \\ \vdots \\ k(n,i)\vec{c_0}^{\vec{y}_i} \end{bmatrix} = \sum_{i=1}^{n}\begin{bmatrix} k(i,1)\vec{c_0}^{\vec{y}_1} \\ \vdots \\ k(i,n)\vec{c_0}^{\vec{y}_n} \end{bmatrix},$$

so

$$\sum_{i=1}^{n} k(j,i)\vec{c_0}^{\vec{y}_i} = \sum_{i=1}^{n} k(i,j)\vec{c_0}^{\vec{y}_j} \tag{9.1}$$

for each j.

Consider a subset $\mathcal{N}$ of complex indices such that, if $i \in \mathcal{N}$, $i \to j$ implies that $j \in \mathcal{N}$. Summing over elements of $\mathcal{N}$ in equation (9.1) gives

$$\sum_{j\in\mathcal{N}}\sum_{i=1}^{n} k(j,i)\vec{c_0}^{\vec{y}_i} = \sum_{j\in\mathcal{N}}\sum_{i=1}^{n} k(i,j)\vec{c_0}^{\vec{y}_j}.$$

Clearly,

$$\sum_{j\in\mathcal{N}}\sum_{i\in\mathcal{N}} k(j,i)\vec{c_0}^{\vec{y}_i} = \sum_{j\in\mathcal{N}}\sum_{i\in\mathcal{N}} k(i,j)\vec{c_0}^{\vec{y}_j}$$

is true, since the left and right hand sums are the same. Combining these two equations gives

$$\sum_{j\in\mathcal{N}}\sum_{i\in\mathcal{N}'} k(j,i)\vec{c_0}^{\vec{y}_i} = \sum_{j\in\mathcal{N}}\sum_{i\in\mathcal{N}'} k(i,j)\vec{c_0}^{\vec{y}_j}, \tag{9.2}$$

where $\mathcal{N}'$ is the set of all complex indices not in $\mathcal{N}$. However, by the definition of $\mathcal{N}$, the right hand side of equation (9.2) is zero, since no complexes in $\mathcal{N}$ react with complexes outside of $\mathcal{N}$. That means that the left hand side of the equation is also zero, so the conditions on $\mathcal{N}$ imply that, if $i \in \mathcal{N}$ and $j \to i$, then $j \in \mathcal{N}$ as well.

Now, for a complex j, define the set j_+ as

$$j_+ = \{v | j \Rightarrow v\}.$$

This set satisfies the properties of $\mathcal{N}$ above, so if $i \to j$, then $i \in j_+$. Conversely, assume $i \Rightarrow j$; then, transitivity of the operation $\Rightarrow$ implies that $j \Rightarrow i$; since this is true for all j, the system is weakly reversible. □

The following partial converse to Theorem 9.1 follows:

Theorem 9.3. *A zero deficiency system that is not weakly reversible has no equilibrium concentration in the positive orthant of species space.*

PROOF. Assume that the theorem is false, and $\vec{c_0}$ is an equilibrium point. Then $Y\vec{g}(\vec{c_0}) = 0$, so $\vec{g}(\vec{c_0}) \in \ker Y$. Also, recalling the definition of L as the span of the difference set of vectors in the same linkage class, $\vec{g}(\vec{c_0}) \in L$. So, $\vec{g}(\vec{c_0}) \in (\ker Y \cup L)$. However, in equation (5.1), we saw that having deficiency zero implied that $\ker Y \cup L = \vec{0}_W$, so $\vec{g}(\vec{c_0}) = \vec{0}$, and the system is therefore complex balanced at $\vec{c_0}$. However, by lemma 9.2, the system is therefore weakly reversible, which violates the hypothesis of the theorem. □

10 Conclusions and Applications

Theorems 9.1 and 9.3 give powerful tools for analyzing chemical reaction networks. The question arises as to whether or not deficiency zero is a rare condition on networks; as it happens, it seems that many networks that are encountered experimentally, or even those that are created combinatorically, have deficiency zero. Weak reversibility also isn't a terribly onerous condition; if a network is not weakly reversible, there must be some sort of "sink" - a complex that is being produced but not being used up, or a complex that is being used up but not produced - that would preclude an equilibrium in positive species space, so one would not expect an equilibrium in such a system. An argument could be made that *all* systems are weakly reversible, since, technically, all chemical reactions are bidirectional; however, this argument is flawed in this case, since many reverse reactions occur so infrequently that the mass-action approximations do not apply.

Considering the frequency with which the conditions are satisfied, one might wonder why the majority of networks don't exhibit the stability guaranteed by the theorems. The answer is that the scenarios in which the model takes place are fairly idealized. Conditions such as the environment being well-mixed (i.e. spatially independent) are difficult to find in nature, and even the model that is the basis of the work, the mass-action model, may not hold in many systems. Also, the theorem only accounts for the existence and uniqueness of equilibrium points in each positive reaction simplex, saying nothing about points on the boundary (namely, points where one or more species has concentration zero). However, it has been conjectured in [3] that no attracting equilibrium points exist on the boundary, and non counterexamples have been found.

The theorems were originally formulated to rule out systems that exhibit so-called "exotic" behavior - namely, multiple positive equilibria or sustained oscillations. However, it is the hope of the author that the theorems could also be used to account for robustness of certain systems to perturbations in various environmental factors, since these factors are generally considered to be encoded in the reaction rate constants.

This paper has generally presumed that all participants and reactions in a network are known, and only the measuring of rate constants is troublesome. However, this is certainly not always the case, and in biological systems it is quite frequent to not know all of the participants in a reaction network. Work is being done to formulate algorithms that would take known information about a network and propose possible nodes and reactions that are missing. Bearing both of the above applications in mind, deficiency could be used to aid such programs, if it is known whether or not the system reaches a positive equilibrium or not.

The hope of the author is to apply these theorems to explain the behavior of some real biological systems that appear to exhibit an unusual amount of stability, since many perturbations in a network can be considered to be "encoded" in the rate constants. One such network was described recently by Goulian et al [7]. The network described therein exhibits stability, both experimentally and theoretically, as can be shown through manipulation of the differential equations and taking certain approximations. However, the network is also deficiency zero and weakly reversible, and hence the results of this paper apply, giving a possible alternate explanation for the mechanism's robustness. Further work must be done to investigate this hypothesis, and perhaps find other examples of robust networks that can be explained in this manner.

Appendix

A Vector logarithms, ratios, and exponents

This appendix demonstrates that the relationships between the vector versions of the logarithm, ratio, and exponent operations hold as expected from the scalar counterparts.

Let $\vec{x}, \vec{y}, \vec{z}$ be n-dimensional vectors with components $\{x_1, ..., x_n\}$, $\{y_1, ..., y_n\}$, and $\{z_1, ..., z_n\}$. Using the definitions given above, we have

$$\ln \frac{\vec{x}}{\vec{y}} = \begin{bmatrix} \ln \frac{x_1}{y_1} \\ \vdots \\ \ln \frac{x_n}{y_n} \end{bmatrix} = \begin{bmatrix} \ln x_1 - \ln y_1 \\ \vdots \\ \ln x_n - \ln y_n \end{bmatrix} = \begin{bmatrix} \ln x_1 \\ \vdots \\ \ln x_n \end{bmatrix} - \begin{bmatrix} \ln y_1 \\ \vdots \\ \ln y_n \end{bmatrix} = \ln \vec{x} - \ln \vec{y}$$

and

$$\ln\left(\vec{x}^{\vec{y}}\right) = \ln \prod_{i=1}^{n} x_i^{y_i} = \sum_{i=1}^{n} \ln(x_i^{y_i}) = \sum_{i=1}^{n} y_i \ln x_i = \begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix} \cdot \begin{bmatrix} \ln x_1 \\ \vdots \\ \ln x_n \end{bmatrix} = \vec{y} \cdot \ln \vec{x},$$

as well as
$$\left[\frac{\vec{x}}{\vec{y}}\right]^{\vec{z}} = \prod_{i=1}^{n}\left(\frac{x_i}{y_i}\right)^{z_i} = \prod_{i=1}^{n}\frac{x_i^{z_i}}{y_i^{z_i}} = \frac{\prod_{i=1}^{n} x_i^{z_i}}{\prod_{i=1}^{n} y_i^{z_i}} = \frac{\vec{x}^{\vec{z}}}{\vec{y}^{\vec{z}}}.$$
So, all identities hold as they should.

This is also true for raising a vector to the power of a matrix. Let Z be an $n \times m$ matrix with $\vec{z}(i)$ as the i-th column. Then

$$\ln \vec{x}^{Z} = \ln \begin{bmatrix} \vec{x}^{\vec{z_1}} \\ \vdots \\ \vec{x}^{\vec{z_m}} \end{bmatrix} = \begin{bmatrix} \ln \vec{x}^{\vec{z_1}} \\ \vdots \\ \ln \vec{x}^{\vec{z_m}} \end{bmatrix} = \begin{bmatrix} \vec{z_1} \cdot \ln \vec{x} \\ \vdots \\ \vec{z_m} \cdot \vec{x_m} \end{bmatrix} = Z^{T} \ln \vec{x}.$$

Note that it is the transpose of the matrix acting on the logarithm of the vector; this makes sense, since the result of the operation $\vec{x}^{Y}$ is an m-dimensional vector, so the logarithm is also m-dimensional. However, $\ln \vec{x}$ is n-dimensional, so the matrix acting on it must be an $m \times n$ matrix, as is Z^{T}, not an $n \times m$ matrix, such as Z.

B Frequently Used Symbols

$\vec{a}$	A concentration vector, either the vector at which a QTS, QTD, or PHF is centered (see section 6) or a vector at which a system is complex balanced (see sections 7 and 8).
A	The kinetic matrix of the system, defined in equation (4.8).
A_i	The i-th species of a system.
$\vec{c}$	A vector representing a concentration. Sometimes appears with a subscript to distinguish it from a generalized as a concentration with particular significance.
δ	The deficiency of a system, defined as $n - l - s$.
Δ	The difference set of a system is a subspace of complex space defined as the set of the vectors that are the difference between two complex vectors, where the complexes are in the same linkage class, written as $\{\vec{w_j} - \vec{w_i} \mid i \equiv j\}$.
Δ_i	The difference set of the linkage class $\mathcal{L}_i$, defined as $\{\vec{w_j} - \vec{w_k} \mid j, k \in \mathcal{L}_i\}$.

$\vec{f}(\vec{c})$	The species formation function of a system, which maps from species space to species space to give a vector showing the rate of change in the concentration of each species at a given concentration. Originally defined by equation (2.2), with several equivalent definitions derived in section 4.
$\vec{g}(\vec{c})$	The complex formation function of a system, which maps from species space to complex space to give a vector showing the net rate of change for each complex at a given concentration. Originally derived in equation (4.5).
k	Used as a rate constant in a general reaction.
$k(i,j)$	The rate constant of the reaction from complex j to complex i.
K	The rate constant matrix of a system, defined as the matrix with entries $k(i,j)$.
l	The number of linkage classes in a system.
L	The linear span of Δ.
$\mathcal{L}_i$	A linkage class, defined as a set of complex indices such that $i \equiv j$ for all pairs in the set. Each complex index is in one and only one linkage class.
m	The number of species in a system.
n	The number of complexes in a system.
s	The dimension of the stoichiometric space S.
S	The stoichiometric space of system, defined as the span of reaction vectors in the system. So $S = \text{span}\{\vec{y}_j - \vec{y}_i \mid i \to j\}$.
$\vec{v}_i$	The species vector for the i-th species, which is simply the i-th natural basis vector in species space ($\mathbb{R}^m$).
V	Species space, which is simply $\mathbb{R}^m$ in a system with m species.
V^+	The positive orthant of species space, or $\{\vec{x} \in V \mid x_1, ..., x_m > 0\}$, where x_i is the i-th coordinate of the vector $\vec{x}$.

$\bar{V}^+$	The closure of V^+, or $\{\vec{x} \in V \| x_1, ..., x_m \geq 0\}$.
$\vec{w}_i$	The complex vector for the i-th complex in complex space, which is simply the i-th natural basis vector of $\mathbb{R}^n$.
W	Complex space, which is simply $\mathbb{R}^n$ in a system with n complexes.
$\vec{y}_i$	The complex vector for the i-th complex in species space, which is the sum of the species vectors multiplies by their coefficients in complex i, or, equivalently, $Y\vec{w}_i$.
Y	The linear transformation from complex space to species space with $\vec{y}_i$ as the i-th column, which takes $\vec{w}_i$ to $\vec{y}_i$.

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