This is a scanned copy of written versions of 4.5 of 9 lectures delivered at the Mathematics Research Center, University of Wisconsin-Madison in the autumn of 1979.

Lectures on Chemical Reaction Networks

Martin Feinberg

Department of Chemical Engineering
University of Rochester
Rochester, NY 14627

Present address:
Departments of Chemical Engineering & Mathematics
The Ohio State Univerisity
140 W. 19th Avenue
Columbus, OH 43210 USA
email: feinberg.14@osu.edu

Contents

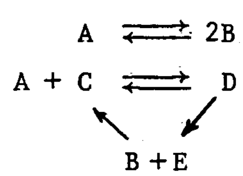
LECTURE 1: INTRODUCTION

This lecture is divided into two parts. In the first part I shall try to provide some motivation for everything that follows. In particular, I shall try to explain, at least in an informal way, how chemists and chemical engineers arrive at the differential equations they work with and how these differential equations are tied to reaction network structure. Once this is done we can begin to understand why a reasonably general theory of chemical reaction networks is necessary. Moreover, we can begin to understand why, despite the great complexity of the differential equations involved, such a theory should even be possible in principle. In the second part of this lecture I shall discuss the important but more mundane subject of notation.

1.A. Motivation

These lectures will be about a special but rather large class of ordinary differential equations — those that derive from chemical reaction networks. In order that I might provide some sense of how these equations come about it will be useful if I write down an example of a reaction network and indicate informally how it induces a system of ordinary differential equations. Then I can discuss the kinds of problems we will want to consider.

Suppose that A, B, C, D and E are chemical species, and suppose I believe that the chemical reactions occurring among these species are reasonably well reflected in the following diagram:



(1.1)

What I have written down is a diagram of a chemical reaction network. It indicates that a molecule of A can decompose into two molecules of B, that two molecules of B can react to form one molecule of A, that a molecule of A can react with a molecule of C to form a molecule of D, and so on.

Now suppose that I throw various amounts of my species into a pot. I am going to presume that the pot is stirred constantly so that its contents remain spatially homogeneous for all time, and I shall also suppose that the contents of the pot are forever maintained at fixed temperature and total volume. This, of course, is not to say that the chemical composition of the mixture within the pot will remain constant in time, for the occurrence of chemical reactions will serve to consume certain species and generate others. In fact it is the temporal evolution of the composition that we wish to investigate. With this in mind we denote the (instantaneous) values of the molar concentrations of the species by $c_A(t)$, $c_B(t)$, $c_C(t)$, $c_D(t)$ and $c_E(t)$, and we abbreviate this list of numbers by the "composition vector" $c(t)$.* Thus the picture we are thinking about, at least for the moment, looks something like that shown in Figure 1.1.†

---

*A molar concentration, say c_A, specifies the number of A molecules per unit volume of mixture. More precisely, c_A is the number of A molecules per unit volume divided by Avogardro's number, 6.023×10^{23}. We shall be somewhat more precise about what we mean by the "composition vector" in Section 1.B.

†The reactor depicted in Figure 1.1 is closed with respect to the exchange of matter with its environment. Our focus on such reactors is <u>temporary</u> and is merely intended to illustrate in a simple context how chemists and engineers formulate differential equations based upon a set of reactions believed to approximate the true chemistry. We will begin to consider "open" reactors in the next lecture (Section 2.E). There we shall indicate how open reactors can be modelled in terms of reaction networks and how the appropriate differential equations, like those for closed reactors, bear a definite relationship to reaction network structure.

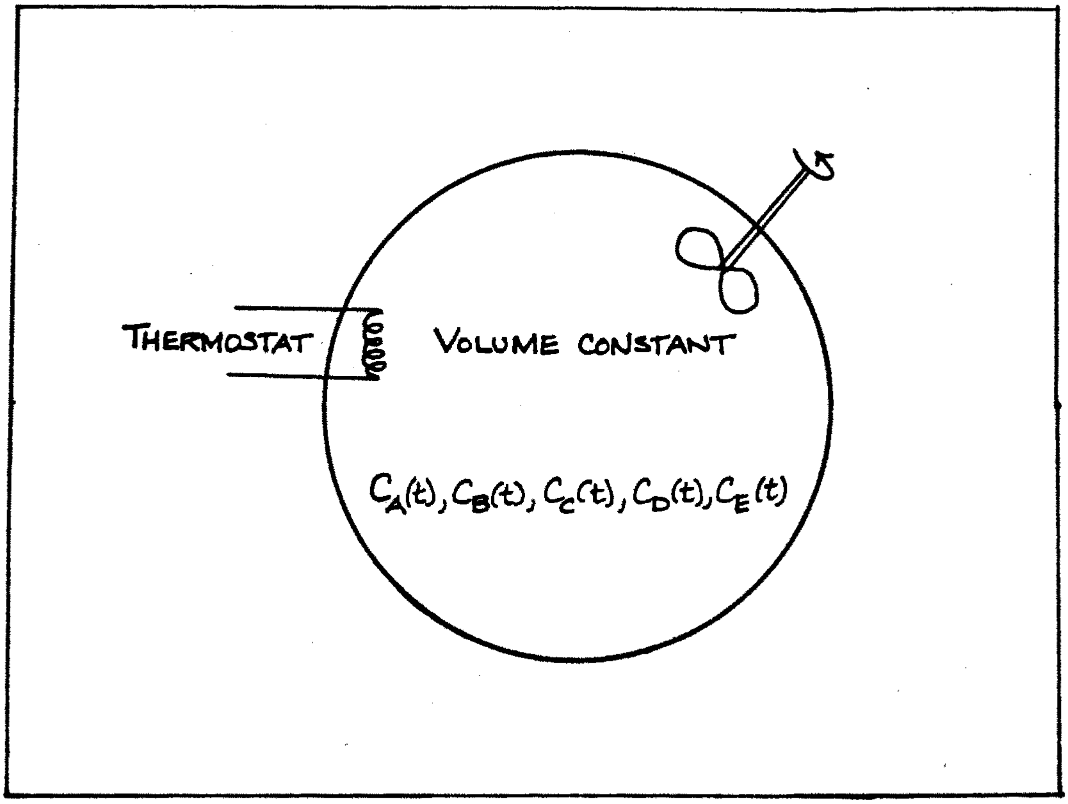


Figure 1.1

We would like to write down differential equations that describe the evolution of the five molar concentrations. Since chemical reactions are the source of composition changes, the key to understanding how to write down differential equations lies in knowing how rapidly each of the several reactions occurs. What is generally assumed is that the instantaneous occurrence rate of each reaction depends in its own way on the instantaneous mixture composition vector, c. Thus, we presume, for example, the existence of a non-negative real-valued rate function $\mathcal{K}_{A\to 2B}(\cdot)$ such that $\mathcal{K}_{A\to 2B}(c)$ is the instantaneous occurrence rate of reaction $A \to 2B$ (per unit volume of mixture) when the instantaneous mixture composition is given by the vector c.** Similarly, we presume the existence of a rate function $\mathcal{K}_{2B\to A}(\cdot)$ for the reaction $2B \to A$, a rate function $\mathcal{K}_{A+C\to D}(\cdot)$ for the reaction $A+C \to D$, and so on. A <u>kinetics</u> for a reaction network is an assignment of a rate function to each reaction in the network.

Once we presume that network (1.1) is endowed with a kinetics we are in a position to write down the system of differential equations that govern our reactor. Suppose that, at some instant, the reactor is in some composition state c. Let us begin by thinking about the instantaneous rate of change of c_A. Every time the reaction $A \to 2B$ occurs we <u>lose</u> a molecule of A, and that reaction has an occurrence rate $\mathcal{K}_{A\to 2B}(c)$. On the other hand, every time the reaction $2B \to A$ occurs we <u>gain</u> a molecule of A, and that reaction occurs at rate $\mathcal{K}_{2B\to A}(c)$. Similarly, the reactions $B+E \to A+C$ and $D \to A+C$ produce a molecule of A with each occurrence, while each occurrence of the reaction $A+C \to D$ results in the loss of a molecule of A. Thus we write

$$\dot{c}_A = -\mathcal{K}_{A\to 2B}(c) + \mathcal{K}_{2B\to A}(c) - \mathcal{K}_{A+C\to D}(c) + \mathcal{K}_{D\to A+C}(c) + \mathcal{K}_{B+E\to A+C}(c). \quad (1.2)$$

If we turn our attention to species B we notice that whenever the reaction $A \to 2B$ occurs we gain <u>two</u> molecules of B, and whenever $2B \to A$ occurs we lose <u>two</u> molecules of B. When $D \to B+E$ occurs we gain <u>one</u> B, and when $B+E \to A+C$ occurs we lose <u>one</u> B. Thus, we write

$$\dot{c}_B = 2\mathcal{K}_{A\to 2B}(c) - 2\mathcal{K}_{2B\to A}(c) + \mathcal{K}_{D\to B+E}(c) - \mathcal{K}_{B+E\to A+C}(c) \quad (1.3)$$

Continuing in this way we can write down equations for $\dot{c}_C$, $\dot{c}_D$, $\dot{c}_E$ to generate the full system of differential equations that govern our reactor:

**More precisely, $\mathcal{K}_{A\to 2B}(c)$ is the number of occurrences of $A \to 2B$ per unit time per unit volume divided by Avogadro's number.

$$
\begin{aligned}
\dot{c}_A &= -\mathcal{K}_{A\to 2B}(c) + \mathcal{K}_{2B\to A}(c) - \mathcal{K}_{A+C\to D}(c) + \mathcal{K}_{D\to A+C}(c) + \mathcal{K}_{B+E\to A+C}(c) \\
\dot{c}_B &= 2\mathcal{K}_{A\to 2B}(c) - 2\mathcal{K}_{2B\to A}(c) + \mathcal{K}_{D\to B+E}(c) - \mathcal{K}_{B+E\to A+C}(c) \\
\dot{c}_C &= -\mathcal{K}_{A+C\to D}(c) + \mathcal{K}_{D\to A+C}(c) + \mathcal{K}_{B+E\to A+C}(c) \\
\dot{c}_D &= \mathcal{K}_{A+C\to D}(c) - \mathcal{K}_{D\to A+C}(c) - \mathcal{K}_{D\to B+E}(c) \\
\dot{c}_E &= \mathcal{K}_{D\to B+E}(c) - \mathcal{K}_{B+E\to A+C}(c).
\end{aligned}
\tag{1.4}
$$

Thus far we haven't said anything about the nature of rate functions, and that is what we shall do now. More often than not chemists and engineers presume the kinetics to be of <u>mass action</u> type. With mass action kinetics one can merely look at a reaction and write down its rate function up to a multiplicative positive constant.

Here is the way things work: For the reaction $A \to 2B$ we presume that the more A there is in the reactor the more occurrences of the reaction there will be. In fact, we presume that the instantaneous occurrence rate of $A \to 2B$ is proportional to the instantaneous value of c_A. Thus, we write

$$\mathcal{K}_{A \to 2B}(c) = \alpha c_A ,$$

where α is a positive constant.

For the reaction $A+C \to D$ the situation is a little different. An occurrence requires that a molecule of A meet a molecule of C in the reactor, and we take the probability of such an encounter to be proportional to the product $c_A c_C$. Although we do not presume that every such encounter yields a molecule of D, we nevertheless take the occurrence rate of $A+C \to D$ to be given by

$$\mathcal{K}_{A+C \to D}(c) = \gamma c_A c_C ,$$

where γ is a positive constant. Similarly, an occurrence of the reaction $2B \to A$ requires that two molecules of B have an encounter, and we take

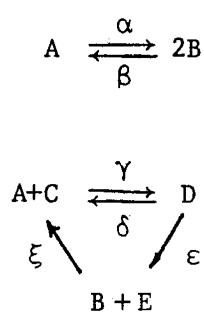
$$\mathcal{K}_{2B \to A}(c) = \beta\,(c_B)^2,$$

where β is a positive constant.

Thus, with mass action kinetics the rate functions for network (1.1) take the form

$$\begin{aligned}
\mathcal{K}_{A \to 2B}(c) &= \alpha\, c_A \\
\mathcal{K}_{2B \to A}(c) &= \beta (c_B)^2 \\
\mathcal{K}_{A+C \to D}(c) &= \gamma\, c_A c_C \\
\mathcal{K}_{D \to B+E}(c) &= \varepsilon\, c_D \\
\mathcal{K}_{D \to A+C}(c) &= \delta\, c_D \\
\mathcal{K}_{B+E \to A+C}(c) &= \xi\, c_B c_E
\end{aligned} \tag{1.5}$$

The positive numbers α, β, γ, ε, δ and ξ, called the <u>rate constants</u> for the corresponding reactions, are sometimes estimated on the basis of chemical principles or else one makes an attempt to deduce them from experiments. When a reaction network is presumed to be endowed with mass action kinetics it is the custom to indicate the rate constants (or symbols for them) alongside the corresponding reaction arrows in the network diagram. Thus for our example we might have a display like that shown in (1.6).



(1.6)

If we assume mass action kinetics for the network we have been studying, the appropriate differential equations are obtained by inserting (1.5) into (1.4):

$$\begin{aligned}
\dot{c}_A &= -\alpha c_A + \beta (c_B)^2 - \gamma c_A c_C + \delta c_D + \xi c_B c_E \\
\dot{c}_B &= 2\alpha c_A - 2\beta (c_B)^2 + \varepsilon c_D - \xi c_B c_E \\
\dot{c}_C &= -\gamma c_A c_C + \delta c_D + \xi c_B c_E \\
\dot{c}_D &= \gamma c_A c_C - (\delta+\varepsilon) c_D \\
\dot{c}_E &= \varepsilon c_D - \xi c_B c_E .
\end{aligned} \tag{1.7}$$

We have arrived at a fairly concrete system of ordinary differential equations, and we can begin to pose questions about them. Here are some of the questions we might like to ask:

(a) Does the system (1.7) admit a positive equilibrium — that is, an equilibrium at which all species concentrations are positive?

(b) Does the system (1.7) admit <u>multiple</u> positive equilibria (in a sense to be made precise in the next lecture*)?

(c) Does the system (1.7) admit an unstable positive equilibrium?

(d) Does the system (1.7) admit a periodic (positive) composition trajectory?

These are not easy questions, and the answers to them might of course depend on the particular (positive) values taken by the rate constants α, β, γ, δ, ε, and ξ . Even if we could answer these questions for <u>all</u> positive values of the rate constants what would we have accomplished?

---

*We shall want to know whether there can exist multiple positive equilibria within a <u>stoichiometric compatibility class</u>. In rough terms a stoichiometric compatibility class is a certain set of compositions which remains invariant under the flow given by (1.7).

We would have understood one model chemical system fairly well, at least with respect to certain qualitative issues.

There are, however, thousands of distinct reaction networks that might, on one occasion or another, command our attention. Each has its own system of differential equations, perhaps more complicated by far than the system we have been considering. How, then, are we to proceed? It is clear that we cannot rely forever on purely ad hoc studies of whatever systems might present themselves for examination. Even if we cast aside the long-term enormity of such an undertaking, there are still two problems that must be faced in the short run. First, questions of the kind we have posed will, for the most part, be confronted by engineers and chemists, not mathematicians. Second, it is by no means clear that mathematicians, even the most expert, are currently in a position to provide much help. The fact is that even moderately large systems of nonlinear differential equations — in particular polynomial systems like those displayed in (1.7) — remain poorly understood* in general.

It seems to me that what is required is a rather broad-based theory of those systems of differential equations that derive from reaction networks, a theory which would in some sense cuts across the fine details of individual problems to provide qualitative information about large classes of systems all at once. Moreover, we would like the results of such a theory to be of the kind that engineers and chemists can use easily in addressing questions like those we have posed.

This seems like a lot to ask, and I should try to explain why a theory of the kind I have in mind should even be possible in principle. Although we shall also be interested in the more general situation, let me temporarily restrict my attention to reaction networks endowed with mass action kinetics. Thinking back to the source of the system (1.7), we recall that it derived in a rather orderly way from the network (1.6). In fact, we knew how to write down the appropriate

*Consider, for example, the remarkable complexity of the seemingly innocuous Lorenz system [L1], which is composed of three polynomial ordinary differential equations in three variables.

differential equations (up to values of the rate constants) merely from inspection of the reaction diagram. Had we begun with a different network we would have arrived at a different system of differential equations, but again the essential shape of those equations (up to values of the rate constants) would have derived from the reaction network in a precise way. Indeed, it is the close connection between reaction network structure and the shape of the induced differential equations that lends the subject of chemical reactor theory its coherency.

This is our source of hope. If reactor behavior is determined by a system of differential equations which, in turn, is determined by the underlying reaction network in a precise way, then perhaps one can prove theorems which tie qualitative aspects of reactor behavior directly to reaction network structure.

Can this in fact be done? I hope that these lectures will help to demonstrate that one can proceed surprisingly far in this direction. In Lecture 3 I will state two theorems, one of which will _immediately_ answer all four questions that we posed about the system (1.7). The answers are _yes_, _no_, _no_, and _no_; these answers hold _for all positive values of the rate constants_ $\alpha, \beta, \gamma, \delta, \varepsilon,$ and ξ. Moreover, _these answers can be obtained merely from inspection of the reaction diagram_ (1.6); one need not even write out the differential equations. The fact is that one can delineate a large class of networks — some extremely complicated — for which the corresponding differential equations admit solutions of a very limited variety, regardless of the (positive) values the rate constants take.

Our objectives will be rather broad, and I should try to make clear what these are. Results of the kind I have just described are typical of those we are after. _We seek to classify reaction networks according to their capacity to induce differential equations which admit behavior of a specified type_. When we restrict our attention to networks endowed with mass action kinetics we will _not_ ask, for example, whether the differential equations for a particular network taken with _specified_ rate constants admit periodic orbits. Rather, we will ask if the network is such that the induced differential equations admit periodic orbits for _at least one_ set of rate constants — that is, if the _network_ has the capacity to admit periodic orbits. The network itself will be our object of study, not the network endowed with a particular set of rate constants.*

1. B. *Notation*

It is not difficult to see that the differential equations induced by a reaction network can be rather cumbersome. With this in mind I want to spend a little time talking about notation. Although the notation I shall use is quite natural to the problems we shall address, it is not entirely traditional.

With each reaction network we can associate three sets. The first is the set $\mathcal{S}$ of chemical species — {A, B, C, D, E} in network (1.1). The second is the set of objects that appear before and after the reaction arrows — {A, 2B, A+C, D, B+E} in (1.1). These objects are called the complexes of the network, and the set of complexes will be denoted by the symbol $\mathcal{C}$. The third is the set $\mathcal{R}$ of reactions — {$A \to 2B$, $2B \to A$, $A+C \to D$, $D \to A+C$, $D \to B+E$, $B+E \to A+C$} in network (1.1).

With each of these sets we shall want to associate a (finite-dimensional) vector space so that we can, for example, speak of a "vector of species concentrations" or a "vector of reaction rate constants." If m is the number of species, if n is the number of complexes and if r is the number of reactions in a network we can, of course, work in the vector spaces $\mathbb{R}^m$, $\mathbb{R}^n$, and $\mathbb{R}^r$. In this way we can speak of the "composition vector $c \in \mathbb{R}^m$," c_i being the molar concentration of the i^{th} species, $i = 1, 2,...,m$. And we can speak of the "rate constant vector $k \in \mathbb{R}^r$," k_j being the rate constant of the "j^{th} reaction," $j = 1,2,...,r$. This is what tradition would seem to require.

---

*It is perhaps worth mentioning here that, in practice, complete sets of rate constants for intricate networks are hardly ever known with great precision. It is often the case that chemists have a very good sense of what reactions are occurring but can estimate or measure rate constants only to within a considerable margin of uncertainty. For a discussion of the relationship between reaction network structure and the extent to which rate constants can be determined uniquely from certain classes of experiments see [F3] and, for more detail, [F1] and [K]. In [F1] there is also a discussion of how information about the reaction network itself can, in principle, be inferred from near-equilibrium experiments.

It turns out, however, that $\mathbb{R}^m$, $\mathbb{R}^n$, and $\mathbb{R}^r$ are somewhat awkward media in which to work. At the very least these spaces require that we number everything in sight so that we can speak of the "i^{th} species," the "j^{th} reaction," or the "k^{th} complex." Thus, we must impose an artificial ordering on each of the three sets of objects even before we begin to work, and we must carry that order around thereafter, suppressing or rearranging it whenever it becomes intrusive. There is a much better and far more natural way to do things, and that is what we shall discuss now.

We denote the real numbers by $\mathbb{R}$, the positive real numbers by $\mathbb{P}$ and the non-negative real numbers by $\bar{\mathbb{P}}$.

If $\mathcal{I}$ is a set we denote by $\mathbb{R}^{\mathcal{I}}$ the vector space of real-valued functions with domain $\mathcal{I}$. (Addition of functions and multiplication of a function by a real number are defined in the usual way.) By $\mathbb{P}^{\mathcal{I}}$ [resp., $\bar{\mathbb{P}}^{\mathcal{I}}$] we mean the subset of $\mathbb{R}^{\mathcal{I}}$ consisting of those functions which take exclusively positive [resp., non-negative] values.

Henceforth in this section we shall suppose that $\mathcal{I}$ is a <u>finite</u> set. In this case if x is a vector in $\mathbb{R}^{\mathcal{I}}$ we shall almost always use the symbol x_i to denote the number that x assigns to $i \in \mathcal{I}$. If x and y are vectors in $\mathbb{R}^{\mathcal{I}}$ we use the symbol xy to denote the vector in $\mathbb{R}^{\mathcal{I}}$ such that

$$(xy)_i = x_i y_i \quad , \quad \forall\, i \in \mathcal{I}. \tag{1.8}$$

If x is a vector in $\mathbb{R}^{\mathcal{I}}$ we denote by e^x the vector of $\mathbb{P}^{\mathcal{I}}$ such that

$$(e^x)_i = e^{x_i} \, , \quad \forall\, i \in \mathcal{I} \, . \tag{1.9}$$

For $z \in \mathbb{P}^{\mathcal{I}}$ we denote by $\ln z$ the vector of $\mathbb{R}^{\mathcal{I}}$ such that

$$(\ln z)_i = \ln z_i \, , \quad \forall\, i \in \mathcal{I}. \tag{1.10}$$

By the <u>support</u> of $x \in \mathbb{R}^I$ (denoted supp x) we mean the subset of I assigned non-zero values by x. That is,

$$\text{supp } x := \{i \in I : x_i \neq 0\}. \tag{1.11}$$

If J is a subset of I we reserve the symbol ω_J to indicate the characteristic function on J; that is, ω_J is the vector of $\mathbb{R}^I$ such that

$$(\omega_J)_i = \begin{cases} 1 \text{ if } i \in J \\ 0 \text{ if } i \notin J \end{cases}. \tag{1.12}$$

In particular, if J is the singleton $\{j\}$ then $\omega_{\{j\}}$ is the vector of $\mathbb{R}^I$ such that

$$(\omega_{\{j\}})_i = \begin{cases} 1 \text{ if } i = j \\ 0 \text{ if } i \neq j \end{cases}. \tag{1.13}$$

In this case <u>we shall write</u> ω_j <u>in place of the more formal</u> $\omega_{\{j\}}$.*

By the <u>standard basis</u> for $\mathbb{R}^I$ we mean the set

$$\{\omega_j \in \mathbb{R}^I : j \in I\}. \tag{1.14}$$

---

*This practice raises a minor possibility of confusion: While x_j is a <u>number</u> — the value assigned to $j \in I$ by $x \in \mathbb{R}^I$ — ω_j is a <u>vector</u> <u>in</u> $\mathbb{R}^I$. No confusion should result if it is remembered that a subscripted ω is <u>always</u> a vector. The symbol ω will never appear without a subscript.

This set is clearly linearly independent; and, moreover, each $x \varepsilon \mathbb{R}^I$ has a representation

$$x = \sum_{j\varepsilon I} x_j \omega_j \ . \tag{1.15}$$

Thus, (1.14) is in fact a basis for $\mathbb{R}^I$, and we have that the dimension of $\mathbb{R}^I$ is just the number of elements in the (finite) set I. Note that, for $J \subset I$, we have

$$\omega_J = \sum_{j\varepsilon J} \omega_j \ ; \tag{1.16}$$

in particular,

$$\omega_I = \sum_{j\varepsilon I} \omega_j \ . \tag{1.17}$$

We define the <u>standard scalar product</u> in $\mathbb{R}^I$ as follows: If x and z are vectors of $\mathbb{R}^I$ then

$$x \cdot z := \sum_{i\varepsilon I} x_i z_i \ . \tag{1.18}$$

Note that, with respect to this scalar product, the standard basis for $\mathbb{R}^I$ is orthonormal. Unless stated otherwise we shall always take $\mathbb{R}^I$ to be endowed with its standard scalar product. Moreover, we shall always take $\mathbb{R}^I$ to be equipped with the usual finite-dimensional vector space topology (for example, that given by the norm deriving from the standard scalar product).

We now pause to illustrate how, in very simple examples, vector spaces of the kind we have been discussing provide perhaps the most natural media in which to work.

Example 1.B.1. Let us think again about the homogeneous reactor with species A, B, C, D and E that we discussed earlier. We denote the set of species by the symbol $\mathcal{S}$; that is,

$$\mathcal{S} = \{A, B, C, D, E\}.$$

At some fixed instant the reactor contents have some fixed composition: With each species $s \in \mathcal{S}$ there is associated a (non-negative) molar concentration c_s , and we would like to represent that composition state in some vector space. But to say that there is a non-negative number associated with each species is to say that there is a function $c: \mathcal{S} \to \overline{\mathbb{P}}$ that assigns to each species its molar concentration. Now c is an element of $\overline{\mathbb{P}}^{\mathcal{S}}$, which in turn is a subset of the vector space $\mathbb{R}^{\mathcal{S}}$. We need proceed no further; c is the vector we seek.

Suppose our reactor is in composition state $c \in \overline{\mathbb{P}}^{\mathcal{S}}$. How might we interpret supp c? Recall that

$$\text{supp } c = \{s \in \mathcal{S}: c_s \neq 0\}.$$

Hence, supp c is just the set of species present in the reactor when the reactor is in composition state $c \in \overline{\mathbb{P}}^{\mathcal{S}}$.

Example 1.B.2. Let $\mathcal{R}$ denote the set of reactions in network (1.1). That is,

$$\mathcal{R} = \{A \to 2B,\ 2B \to A,\ A+C \to D,\ D \to A+C,\ D \to B+E,\ B+E \to A+C\}.$$

Now suppose that the network is endowed with mass action kinetics so that with each reaction there is associated a (positive) rate constant, and suppose also that we would like to have available a "vector of rate constants." To say that with each reaction there is associated a positive rate constant is to say that there is a function $k: \mathcal{R} \to \mathbb{P}$. Thus k is an element of $\mathbb{P}^{\mathcal{R}}$, which in turn is a subset of the vector space $\mathbb{R}^{\mathcal{R}}$. In this sense we have immediately that k is a vector of rate constants.

There is one final matter of notation we need to consider. Suppose that I is a (finite) set and that

$$\{\omega_i \in \mathbb{R}^I : i \in I\}$$

is a standard basis for $\mathbb{R}^I$. When the set I carries no algebraic structure it is sometimes the custom to replace the symbol ω_i by i itself. (See, for example, pp. 197-199 of [NSS] or pp.240-241 of [L2].) Thus, the symbol i + j becomes an abbreviation for the vector $\omega_i + \omega_j \in \mathbb{R}^I$. Similarly, 2j becomes an abbreviation for the vector $2\omega_j \in \mathbb{R}^I$.*

<u>We shall adopt this convention when (and only when) the set in question is the set $\mathcal{S}$ of chemical species</u>. Thus if, as in our example, $\mathcal{S} = \{A,B,C,D,E\}$, we can regard the symbol A+B as an abbreviation for $\omega_A + \omega_B \in \mathbb{R}^{\mathcal{S}}$, the symbol 2B as an abbreviation for $2\omega_B \in \mathbb{R}^{\mathcal{S}}$, and so on. In this way we can regard what we have called the <u>complexes</u> of a network — 2B, A, A+C, D, and B+E in network (1.1) — as <u>vectors</u> in $\mathbb{R}^{\mathcal{S}}$ (and, in particular, as vectors in $\overline{\mathbb{P}}^{\mathcal{S}}$). This view will permit an easy transition between our formal definition of a reaction network (given at the beginning of the next lecture) and the portrayal of a network in its usual diagrammatic form.

---

*In this way we develop what is sometimes called the vector space of formal linear combinations of elements of I.

Taken from a scanned copy of "Lectures on Chemical Reaction Networks," given by Martin Feinberg at the Mathematics Research Center, University of Wisconsin-Madison in the autumn of 1979.

LECTURE 2: REACTION NETWORKS, KINETICS, AND THE INDUCED DIFFERENTIAL EQUATIONS

In the first three sections of this lecture we'll make precise some of the ideas that were introduced casually in Lecture 1. Section 2.A contains our definition of a reaction network along with a small amount of auxiliary terminology. In Section 2.B we introduce the notion of a kinetics for a network, and we discuss mass action kinetics as the archetypical example. In Section 2.C we indicate in vectorial terms how a reaction system — that is, a reaction network endowed with a kinetics — induces a system of differential equations.

In Section 2.D we begin to examine some elementary connections between solutions to the differential equations for a reaction system and the structure of the underlying reaction network. These connections are hardly deep, but our awareness of them will help set the stage for the statement of substantive theorems in the next lecture.

Our discussion in Section 2.E is intended to illustrate how the mathematical framework erected in Sections 2.A-2.D is sufficiently broad as to embrace certain "open" reactors which, unlike the "closed" reactor depicted in Figure 1.1, exchange matter with the external world. The basic idea is that the influx and efflux of species can be taken into account by incorporating in a reaction network certain "funny" reactions like $A \rightarrow 2A$, $0 \rightarrow A$ ("zero reacts to A") or $A \rightarrow 0$ ("A reacts to zero"). The discussion in Section 2.E should make clear not only why it makes sense to study seemingly peculiar reaction networks but also why it is essential that we do so.

2.A. *Reaction Networks*

Before placing on record our definition of a reaction network I want to recall and expand upon some ideas discussed at the end of Lecture 1. We shall regard a network to be specified by its set $\mathcal{S}$ of species, by its set $\mathcal{C}$ of complexes, and by a "reacts to" relation $\mathcal{R}$ that indicates how the complexes are joined by reaction arrows. Recall that the complexes of a network are just the entities that appear at the heads and tails of the reaction arrows — A, 2B, A+C, D and B+E in network (1.1). Recall also that, in the sense of the discussion at the end of Lecture 1, we regard the complexes to be <u>vectors</u> in $\mathbb{R}^{\mathcal{S}}$. (In particular, they lie in $\overline{\mathbb{P}}^{\mathcal{S}}$.) Thus, it makes sense to add two complexes, to subtract one complex from another, to multiply a complex by a number, and to take the scalar product of a complex with any other vector of $\mathbb{R}^{\mathcal{S}}$. Moreover, it makes sense to speak of the support of a complex. For example, supp(A+B) = {A,B}, supp(2B) = {B}, supp(A) = {A}, and so on. Loosely speaking, the support of a complex is just the set of species that "appear in" that complex. We shall always use symbols like y, y' or y" to designate complexes in a reaction network.

<u>Definition 2.1.</u>* <u>A chemical reaction network</u> consists of three sets:

(i) a finite set $\mathcal{S}$, elements of which are called the <u>species</u> of the network.

(ii) a finite set $\mathcal{C}$ of distinct vectors in $\overline{\mathbb{P}}^{\mathcal{S}}$ such that

$$\bigcup_{y \in \mathcal{C}} \operatorname{supp} y = \mathcal{S} .$$

Elements of $\mathcal{C}$ are called the <u>complexes</u> of the network.

(iii) a relation $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$ such that

(a) $(y,y) \notin \mathcal{R}, \quad \forall y \in \mathcal{C}$.

(b) For each $y \in \mathcal{C}$ there exists a $y' \in \mathcal{C}$ such that $(y',y) \in \mathcal{R}$ or such that $(y,y') \in \mathcal{R}$.

Elements of $\mathcal{R}$ are called the <u>reactions</u> of the network. For each $(y,y') \in \mathcal{R}$ we say that complex y <u>reacts to</u> complex y', and we write the more suggestive $y \to y'$ in place of (y,y') if and only if y reacts to y'. The vector y [resp., y'] is called the <u>reactant complex</u> [<u>product complex</u>] of the reaction $y \to y'$.

---

*The definition of a reaction network given here is similar to but a little more restrictive than that given by Horn and me in [FH2].

Example. For network (1.1)

$\mathcal{S} = \{A,B,C,D,E\}$

$\mathcal{C} = \{A,\ 2B,\ A+C,\ D,\ B+E\} \subset \overline{\mathbb{P}}^{\mathcal{S}}$

$\mathcal{R} = \{A \to 2B,\ 2B \to A,\ A+C \to D,\ D \to A+C,\ D \to B+E,\ B+E \to A+C\}.$

Remark 2.1. The restriction imposed in item (ii) of Definition 2.1 merely requires that each element of $\mathcal{S}$ "appears in" at least one complex; that is, $\mathcal{S}$ contains no superfluous species. The conditions imposed in (iii) assert, first, that no complex reacts to itself and, second, that no complex is "isolated": each element of $\mathcal{C}$ is the product complex of some reaction or is the reactant complex of some reaction. (A complex can, of course, be the product complex for one reaction and the reactant complex for another.)

Remark 2.2. We shall reserve the symbol n to denote the number of complexes in a given network.

Remark 2.3. The component y_s (corresponding to species $s \in \mathcal{S}$) of the vector $y \in \mathcal{C}$ is usually called by chemists the stoichiometric* coefficient of species s in complex y. For example, in the complex A+C of network (1.1) the stoichiometric coefficient of A is one, the stoichiometric coefficient of C is one, and the stoichiometric coefficients of B, D, and E are zero. In the complex 2B the stoichiometric coefficient of B is two, and the stoichiometric coefficients of A,C, D and E are zero. For $y \in \mathcal{C}$ we note that supp y is the set of all species with non-zero stoichiometric coefficient in the complex y.

---

*Ugly though it is, the word "stoichiometry" has come to occupy an important place in the vocabulary of chemists and chemical engineers. Rutherford Aris, who knows about these things, traces the word back to its Greek roots — in fact, back to Plato's discussion of the material elements. He (Aris, not Plato) asserts, "Stoichiometry literally means the measurement of the elements but the word is commonly used to refer to all manner of calculations regarding the components of a chemical system... Stoichiometry is essentially the bookkeeping of the material components of the chemical system." [A] We shall use the word in this last sense.

2.B. *Kinetics*

We introduced the notion of a kinetics for a reaction network in an informal way in Lecture 1. Here we shall be a little more precise about what we mean.

Definition 2.2. A kinetics for a reaction network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ is an assignment to each reaction $y \to y' \in \mathcal{R}$ of a continuous rate function $\mathcal{K}_{y \to y'}: \overline{\mathbb{P}}^{\mathcal{S}} \to \overline{\mathbb{P}}$ such that

$$\mathcal{K}_{y \to y'}(c) > 0 \text{ if and only if } \operatorname{supp} y \subset \operatorname{supp} c\,. \tag{2.1}$$

Interpretation: In the context of Lecture 1 $\mathcal{K}_{y \to y'}(c)$ was the occurrence rate of the reaction $y \to y'$ when the (spatially homogeneous) contents of the reactor under study had composition $c \in \overline{\mathbb{P}}^{\mathcal{S}}$. There we required only that the rate functions take non-negative values. In condition (2.1) we go a little further by delineating those $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ for which the function $\mathcal{K}_{y \to y'}(\cdot)$ takes positive values. Note that, for the reaction $y \to y'$, $\operatorname{supp} y$ is just the set of species appearing in the reactant complex y. (Thus for $A+C \to D$, $\operatorname{supp}(A+C) = \{A,C\}$.) Roughly speaking, $\operatorname{supp} y$ is the set of "ingredients" required for the occurrence of $y \to y'$. On the other hand, if $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is the instantaneous composition state of the mixture, then $\operatorname{supp} c$ is the set of species which are actually present in the reactor. (Recall Example 1.B.1.) In rough terms, then, (2.1) says this: Reaction $y \to y'$ proceeds at non-zero rate (however slowly) if and only if the species appearing in the reactant complex y are actually present in the reactor. (For example, $A+C \to D$ proceeds at non-zero rate if and only if $c_A \neq 0$ and $c_C \neq 0$.)

Remark 2.4. Note that for strictly positive c — that is, for $c \in \mathbb{P}^{\mathcal{S}}$ — we have $\operatorname{supp} y \subset \operatorname{supp} c$ for all $y \in \mathcal{C}$. Thus, for $c \in \mathbb{P}^{\mathcal{S}}$ we have

$$\mathcal{K}_{y \to y'}(c) > 0 \quad \text{for all} \quad y \to y' \in \mathcal{R}\ , \tag{2.2}$$

which is to say that all reactions are "switched on".

In fact, we can describe somewhat more general circumstances under which (2.2) holds. By way of example consider the network

$$A + B \rightleftarrows C \to D\ . \tag{2.3}$$

From (2.1) it follows that (2.2) will hold if and only if $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is such that c_A, c_B and c_C are positive, even when $c_D = 0$. The key idea here is that all reactions will be switched on if and only if all species appearing in reactant complexes are present in the reactor.

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network. We denote by $\mathcal{C}_r$ the set of reactant complexes in the network:

$$\mathcal{C}_r := \{y \in \mathcal{C} : \text{There exists } y \to y' \in \mathcal{R}\}\ . \tag{2.4}$$

Moreover, we denote by $\mathcal{S}_r$ the set of reactant species — that is, the set of those species that appear in reactant complexes:

$$\mathcal{S}_r := \bigcup_{y \in \mathcal{C}_r} \operatorname{supp} y\ . \tag{2.5}$$

Then (2.2) will hold if and only if $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is such that

$$\mathcal{S}_r \subset \operatorname{supp} c\ . \tag{2.6}$$

Note that, for $c \in \mathbb{P}^{\mathcal{S}}$, (2.6) holds so that (2.2) holds as well.

Remark 2.5. I should say a few words about the role that condition (2.1) in Definition 2.2 will eventually play. We shall see in Section 2.C how the "only if" part of (2.1) guarantees that the differential equations we shall study have the natural property that, for each $s \in \mathcal{S}$, $\dot{c}_s \geq 0$ whenever $c_s = 0$. The "if" part of (2.1) will usually play a role through Remark 2.4, which characterizes the set of compositions at which all reactions proceed at non-zero rates. In such instances readers should be able to see how the "if" part of (2.1) can be dropped, provided that the set of compositions satisfying (2.6) is replaced by the set of compositions satisfying (2.2). To some extent condition (2.1) amounts to a convenience which precludes the necessity for a more "fussy" treatment.

I should perhaps also mention that there is a way of doing business somewhat different from the one we are employing here. Instead of positing a "reacts to" relation at the outset one can instead begin with rate functions and use them to define a "reacts to" relation at each $c \in \overline{\mathbb{P}}^{\mathcal{S}}$. In rough terms, one specifies $\mathcal{S}$ and $\mathcal{C}$, and then one associates a real-valued rate function $\mathcal{K}_{(y,y')}(\cdot)$ on $\overline{\mathbb{P}}^{\mathcal{S}}$ with each element $(y,y') \in \mathcal{C} \times \mathcal{C}$. These functions need not satisfy a condition such as (2.1) and, in fact, some of them can be identically zero on $\overline{\mathbb{P}}^{\mathcal{S}}$. One then says that y reacts to y' at composition $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ if $\mathcal{K}_{(y,y')}(c) \neq 0$. Thus, the "reacts to" relation becomes a local notion on $\overline{\mathbb{P}}^{\mathcal{S}}$. This slightly different viewpoint, which has some advantages, is essentially that taken in some early work by Horn and me ([H3], [F2]).

Remark 2.6. Recall from Lecture 1 that $\overline{\mathbb{P}}^{I}$ is the set of non-negative real-valued functions with domain I. Thus, each rate function is an element of $\overline{\mathbb{P}}^{(\overline{\mathbb{P}}^{\mathcal{S}})}$. Since a kinetics is an assignment to each reaction $y \to y' \in \mathcal{R}$ of a rate function $\mathcal{K}_{y \to y'}(\cdot)$, a kinetics is itself a function $\mathcal{K}: \mathcal{R} \to \overline{\mathbb{P}}^{(\overline{\mathbb{P}}^{\mathcal{S}})}$. With this in mind I shall often refer to "a kinetics $\mathcal{K}$".

Definition 2.3. A reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ is a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ endowed with a kinetics $\mathcal{K}$.

Next we consider the archetypical example, mass action kinetics.

Definition 2.4. A kinetics $\mathcal{K}$ for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is mass action if, for each $y \to y' \in \mathcal{R}$, there exists a positive number $k_{y \to y'}$ such that

$$\mathcal{K}_{y \to y'}(c) \equiv k_{y \to y'} \prod_{s \in \mathcal{S}} c_s^{y_s} . \tag{2.7}$$

The positive number $k_{y \to y'}$ is called the rate constant for the reaction $y \to y'$.

Remark 2.7. Note that in (2.7) y_s is the stoichiometric coefficient (Remark 2.3) of species s in the reactant complex y of the reaction $y \to y'$. Thus, for reaction $A+C \to D$ of network (1.1), equation (2.7) becomes

$$\begin{aligned}\mathcal{K}_{A+C \to D}(c) &\equiv k_{A+C \to D}(c_A)^1(c_B)^0(c_C)^1(c_D)^0(c_E)^0 \\ &= k_{A+C \to D}\, c_A c_C .\end{aligned}$$

Similarly,

$$\begin{aligned}\mathcal{K}_{2B \to A}(c) &\equiv k_{2B \to A}(c_A)^0(c_B)^2(c_C)^0(c_D)^0(c_E)^0 \\ &= k_{2B \to A}(c_B)^2\end{aligned}$$

And so on.

Remark 2.8. Because we will be working extensively with mass action kinetics it will be useful to introduce the special notation used by Horn and Jackson [HJ]. For c and y in $\overline{\mathbb{P}}^{\mathcal{S}}$ we define c^y as follows:

$$c^y := \prod_{s \in \mathcal{S}} c_s^{y_s} . \tag{2.8}$$

Thus, mass action rate functions take the form

$$\mathcal{K}_{y \to y'}(c) \equiv k_{y \to y'}\, c^y . \tag{2.9}$$

Remark 2.9. A mass action kinetics for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is completely specified by an assignment to each reaction $y \to y' \in \mathcal{R}$ of a positive rate constant $k_{y \to y'}$. This is to say that a mass action kinetics is specified by an element $k \in \mathbb{P}^{\mathcal{R}}$. (Recall Example 1.B.2.) Thus, notwithstanding a minor abuse of language, we shall speak of a "mass action kinetics k" and of a "mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$." In this context it will be understood that k is an element of $\mathbb{P}^{\mathcal{R}}$.

2.C. *The Differential Equations for a Reaction System*

In Lecture 1 I indicated by means of an example how one writes the differential equations for a reaction system. Here I show how the differential equations for a general reaction system can be cast in vectorial terms. We begin with the following definition:

Definition 2.5. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network. The reaction vector corresponding to reaction $y \to y' \in \mathcal{R}$ is the vector $y'-y \in \mathbb{R}^{\mathcal{S}}$.

Remark 2.10. Note that the component* of $y'-y$ corresponding to species $s \in \mathcal{S}$ is just $y'_s - y_s$, the difference between the stoichiometric coefficient of s in the product complex y' and its stoichiometric coefficient in the reactant complex y. This difference is the net number of molecules of s produced with each occurrence of the reaction $y \to y'$. Consider, for example, the reaction $A \to 2B$ in network (1.1); the corresponding reaction vector is $2B-A$. The "B^{th} component" is 2, the "A^{th} component" is -1, and the components corresponding to C, D and E are each zero.

*The components to which we refer are, of course, the components of $y'-y$ relative to the standard basis for $\mathbb{R}^{\mathcal{S}}$. Keeping in mind the "space of functions" interpretation of $\mathbb{R}^{\mathcal{S}}$, we might rephrase Remark 2.10 as follows: $y'-y$ is that function in $\mathbb{R}^{\mathcal{S}}$ that assigns to each $s \in \mathcal{S}$ the net number of molecules of s produced with each occurrence of the reaction $y \to y'$.

Definition 2.6. For a reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ the species formation rate function $f: \overline{\mathbb{P}}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$ is defined by**

$$f(c) \equiv \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(y'-y) \; . \tag{2.10}$$

That is, $f(\cdot)$ is obtained by summing the reaction vectors for the network, each multiplied by the corresponding reaction rate function.

Interpretation: If, in our homogeneous reactor, the instantaneous composition is $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ then, for each $s \in \mathcal{S}$, $f_s(c)$ gives the instantaneous rate of generation (per unit volume of mixture) of moles of species s due to the simultaneous occurrence of all reactions in $\mathcal{R}$. Note that

$$f_s(c) = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(y'_s - y_s) \; , \tag{2.11}$$

so that $f_s(c)$ is obtained by summing all the reaction occurrence rates, each weighted by the net number of molecules of s produced with each occurrence of the corresponding reaction (Remark 2.10). This is essentially the idea we used in Lecture 1.

Before proceeding further we show that, for any reaction system, the species formation rate function inherently possesses a natural property: If, for some species s, $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is such that $c_s = 0$ then, at composition c, the rate of production of s cannot be negative.

**The symbol $\mathcal{R}$ below a summation sign will always be understood to be an abbreviation for "$y \to y' \in \mathcal{R}$".

Lemma 2.1. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ be a reaction system with species formation rate function $f(\cdot)$. Then, for every $s \in \mathcal{S}$ and every $c \in \overline{\mathbb{P}}^{\mathcal{S}}$, $c_s = 0$ implies that $f_s(c) \geq 0$.

Proof. Let $\hat{c} \in \overline{\mathbb{P}}^{\mathcal{S}}$ be such that, for some $s^* \in \mathcal{S}$, $\hat{c}_{s^*} = 0$. Note that $s^* \notin \text{supp } \hat{c}$. Recall from Definition 2.2 that $\mathcal{K}_{y \to y'}(c) = 0$ when $\text{supp } y \not\subset \text{supp } c$. Thus, $\mathcal{K}_{y \to y'}(\hat{c}) = 0$ for all $y \to y' \in \mathcal{R}$ such that $y_{s^*} \neq 0$. Therefore at composition $\hat{c}$ the only reactions that might proceed at non-zero rates are those contained in the set

$$\mathcal{R}^* := \{y \to y' \in \mathcal{R} : y_{s^*} = 0\}. \tag{2.12}$$

Writing (2.7) for species s^* we obtain, for the composition $\hat{c}$,

$$\begin{aligned} f_{s^*}(\hat{c}) &= \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(\hat{c})(y'_{s^*} - y_{s^*}) \\ &= \sum_{\mathcal{R}^*} \mathcal{K}_{y \to y'}(\hat{c}) y'_{s^*}. \end{aligned} \tag{2.13}$$

Since $y'_{s^*} \geq 0$ for all $y \in \mathcal{C}$ and since rate functions take non-negative values we have $f_{s^*}(\hat{c}) \geq 0$. ///

Remark 2.11. From (2.13) it follows that $f_{s^*}(\hat{c})$ will be positive if and only if there exists $y \to y' \in \mathcal{R}$ such that $y'_{s^*} > 0$ and $\text{supp } y \subset \text{supp } \hat{c}$.

Remark 2.12. Note that in the proof of Lemma 2.1 the "if" part of condition (2.1) in Definition 2.2 plays no role. Lemma 2.1 is implicit in §1.6 of Fife's monograph [F5], where he discusses some of its consequences in the broader context of reaction-diffusion equations.*

Remark 2.13. The species formation rate function for a mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ takes the form

$$f(c) \equiv \sum_{\mathcal{R}} k_{y \to y'} c^y (y'-y) , \tag{2.14}$$

where c^y is given by (2.8).

By the differential equation for a reaction system we mean

$$\dot{c} = f(c) , \tag{2.15}$$

where the dot denotes time differentiation and $f(\cdot)$ is the species formation rate function. That is, for a reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ the corresponding differential equation is

$$\boxed{\dot{c} = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(y'-y) .} \tag{2.16}$$

---

*For his purposes Fife requires more smoothness in the rate functions than we have imposed in Definition 2.2. For much of what we shall do here continuity is enough. In dealing with mass action kinetics we shall have smoothness on $\mathbb{P}^{\mathcal{S}}$ by virtue of the functions involved. When some of the stoichiometric coefficients take values in the interval (0,1) we lose some differentiability of mass action rate functions on the boundary of $\overline{\mathbb{P}}^{\mathcal{S}}$, but this will have only minor consequences in what follows.

This, of course, is a vector differential equation which encodes the system of scalar equations

$$\dot{c}_s = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(y'_s - y_s) \ , \quad \forall s \in \mathcal{S} \ . \qquad (2.17)$$

For the network (1.1) in Lecture 1, the system (2.17) reduces to (1.4).

In particular, <u>for a mass action system</u> $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ <u>the corresponding (vector) differential equation is</u>

$$\boxed{\dot{c} = \sum_{\mathcal{R}} k_{y \to y'} \, c^y (y'-y) \ .} \qquad (2.18)$$

The individual species equations are

$$\dot{c}_s = \sum_{\mathcal{R}} k_{y \to y'} \, c^y (y'_s - y_s) \ , \quad \forall s \in \mathcal{S} \ . \qquad (2.19)$$

For the mass action system depicted in (1.6) the system (2.19) reduces to (1.7).

2.D. *An Elementary Connection between Reaction Network Structure and the Nature of Composition Trajectories*

In this section I want to explore an elementary property of the differential equations induced by a reaction system. The essential idea here is that, <u>regardless of the kinetics</u>, reaction network structure <u>alone</u> imposes restrictions on the way that composition trajectories can look. In particular, a trajectory that passes through composition $c \in \bar{\mathbb{P}}^{\mathcal{S}}$ can eventually reach composition $c' \in \bar{\mathbb{P}}^{\mathcal{S}}$ only if the pair (c', c) is compatible with certain "stoichiometrical" conditions the reaction network imposes. In very rough terms, composition trajectories are not generally free to wander in an arbitrary fashion through $\overline{\mathbb{P}}^{\mathcal{S}}$ because there are only certain directions in which the species formation rate vector can point.

To see this we consider a reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$. The species formation rate function is given by

$$f(c) = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(y' - y) \ . \tag{2.20}$$

Thus, for each $c \in \overline{\mathbb{P}}^{\mathcal{S}}$, f(c) is a non-negative linear combination of the reaction vectors for the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$. In particular, for $c \in \mathbb{P}^{\mathcal{S}}$ f(c) is a positive linear combination of the reaction vectors. (The same is true for any c satisfying (2.6).) In any case f(c) must point along the cone generated by the reaction vectors and must certainly lie in the linear subspace of $\mathbb{R}^{\mathcal{S}}$ spanned by them. This last idea serves as motivation for our next definition.

<u>Definition 2.7</u>. The <u>stoichiometric</u> <u>subspace</u> for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is the linear subspace $S \subset \mathbb{R}^{\mathcal{S}}$ defined by

$$S := \text{span}\,\{y' - y \in \mathbb{R}^{\mathcal{S}} : y \to y' \in \mathcal{R}\} \ .$$

<u>Remark 2.14</u>. By the span of the set of reaction vectors we mean of course the linear subspace of $\mathbb{R}^{\mathcal{S}}$ consisting of all real linear combinations of them. The discussion just prior to Definition 2.7 suggests that we should also have interest in the <u>stoichiometric</u> <u>cone</u> for a network, defined to be the set of all <u>non-negative</u> linear combinations of its reaction vectors. It is easy to see, however, that the stoichiometric cone and stoichiometric subspace for a network coincide when the zero vector in $\mathbb{R}^{\mathcal{S}}$ is representable as a positive linear combination of the reaction vectors, and we shall see in Lecture 5 that this last condition must be satisfied if a reaction system is to admit an equilibrium in $\mathbb{P}^{\mathcal{S}}$. Since we shall focus heavily on situations in which there does exist a positive equilibrium, there will be no distinction between the stoichiometric cone and the stoichiometric subspace in much of what we do.

Since the species formation rate function for a reaction system must take values in the stoichiometric subspace for the underlying reaction network, we shall want to know something about the size of that subspace. With this in mind we record the following definition:

Definition 2.8. The rank of a reaction network is the rank of its set of reaction vectors. That is, the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ has rank s if there exists in the set

$$\{y' - y \in \mathbb{R}^{\mathcal{S}} : y \to y' \in \mathcal{R}\} \tag{2.21}$$

a linearly independent subset containing s vectors but no linear independent subset containing $s+1$ vectors. We shall reserve the symbol s to denote the rank of a network.

Remark 2.15. From elementary considerations in linear algebra it follows that the dimension of the stoichiometric subspace for a reaction network is just the rank of the network:

$$s = \dim S \tag{2.22}$$

Example. For network (1.1) the reaction vectors are

$$\{2B-A,\ A-2B,\ D-A-C,\ A+C-D,\ B+E-D,\ A+C-B-E\} \tag{2.23}$$

The three-element subset

$$\{2B-A,\ A+C-D,\ B+E-D\} \tag{2.24}$$

is linearly independent, and any vector in (2.23) can be written as a linear combination of (2.24). Thus, $s=3$ so that the stoichiometric subspace for network (1.1) is a three-dimensional linear subspace of the five-dimensional ambient vector space $\mathbb{R}^{\mathcal{S}}$.

I have already indicated that limitations on the directions in which species formation rate vectors can point place restrictions on the way composition trajectories can evolve. The following lemma describes such a restriction.

Lemma 2.2. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ be a reaction system, and let $c: I \to \overline{\mathbb{P}}^{\mathcal{S}}$ be a solution of

$$\dot{c} = \sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(y' - y) , \tag{2.25}$$

where $I \subset \mathbb{R}$ is an interval. Then, for each $t_1, t_2 \in I$ with $t_2 > t_1$, there exists an $\alpha \in \overline{\mathbb{P}}^{\mathcal{R}}$ such that

$$c(t_2) - c(t_1) = \sum_{\mathcal{R}} \alpha_{y \to y'}(y' - y) . \tag{2.26}$$

Proof. Integrating (2.25) between t_1 and t_2 along the solution $c(\cdot)$ we obtain

$$c(t_2) - c(t_1) = \sum_{\mathcal{R}} \left(\int_{t_1}^{t_2} \mathcal{K}_{y \to y'}(c(\tau))d\tau \right)(y' - y) . \tag{2.27}$$

Noting that each integrand in (2.27) is non-negative, we set

$$\alpha_{y \to y'} = \int_{t_1}^{t_2} \mathcal{K}_{y \to y'}(c(\tau))d\tau , \quad \forall y \to y' \in \mathcal{R} . \tag{2.28}$$

In this way we obtain (2.26) from (2.27). ///

Remark 2.16. Note that if, at some instant $t^* \in [t_1,t_2]$ we have

$$\mathcal{K}_{y\to y'}(c(t^*)) > 0 \ , \ \forall \, y\to y' \in \mathcal{R} \ ,$$

then α can be taken to be strictly positive. This follows easily from the construction given in (2.28) and the continuity of the functions $\mathcal{K}_{y\to y'}(c(\cdot))$. Similarly α can be taken to be strictly positive if, for each reaction, there exists an instant in $[t_1,t_2]$ at which that reaction is "switched on".

Lemma 2.2 tells us that a composition $c' \in \overline{\mathbb{P}}^{\mathcal{S}}$ can follow a composition $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ along a solution of (2.25) only if $c'-c$ lies in the stoichiometric subspace (and, in particular, the stoichiometric cone) for the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$. Thus, if $c: I \to \overline{\mathbb{P}}^{\mathcal{S}}$ is a solution of (2.25) which passes through a composition c^0 then, for all $t \in I$, we must have

$$c(t) \in (c^0 + S) \cap \overline{\mathbb{P}}^{\mathcal{S}} \ , \tag{2.29}$$

where S is the stoichiometric subspace and

$$c^0 + S := \{c^0 + \gamma \in \mathbb{R}^{\mathcal{S}} : \gamma \in S\} \ . \tag{2.30}$$

This is to say that a composition c can lie on a trajectory passing through c^0 only if c and c^0 are "stoichiometrically compatible".

Definition 2.9. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network, and let $S \subset \mathbb{R}^{\mathcal{S}}$ be its stoichiometric subspace. Two vectors $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ and $c' \in \overline{\mathbb{P}}^{\mathcal{S}}$ are stoichiometrically compatible if $c'-c$ lies in S. Stoichiometric compatibility is an equivalence relation that induces a partition of $\overline{\mathbb{P}}^{\mathcal{S}}$ [resp., $\mathbb{P}^{\mathcal{S}}$] into equivalence classes called the stoichiometric compatibility classes [resp., positive stoichiometric compatibility classes] for the network. In particular, the stoichiometric compatibility class containing $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is the set $(c+S) \cap \overline{\mathbb{P}}^{\mathcal{S}}$, and the positive stoichiometric compatibility class containing $c \in \mathbb{P}^{\mathcal{S}}$ is the set $(c+S) \cap \mathbb{P}^{\mathcal{S}}$.

Our considerations thus far give some geometric insight into the way phase portraits are structured. A composition trajectory passing through composition c^0 must lie entirely within the stoichiometric compatibility class containing c^0. In rough terms this stoichiometric compatibility class is obtained by shifting S up to c^0 (by parallel translation) and intersecting the resulting parallel of S with $\overline{\mathbb{P}}^{\mathcal{S}}$. Some examples might be helpful.

Example 2.D.1. Consider the simple network

$$A \rightleftarrows 2B \,. \tag{2.31}$$

Here $\mathcal{S} = \{A,B\}$, and the reaction vectors are

$$\{A-2B,\ 2B-A\} \subset \mathbb{R}^{\mathcal{S}} \,.$$

The rank of the network is clearly one, and the stoichiometric subspace S is one-dimensional: it is the line in $\mathbb{R}^{\mathcal{S}}$ containg the vector $A-2B$. The stoichiometric compatibility classes are those parts of lines parallel to S that lie in $\overline{\mathbb{P}}^{\mathcal{S}}$. Regardless of the kinetics, each composition trajectory compatible with the induced differential equations lies entirely within a stoichiometric compatibility class.

For illustrative purposes we shall suppose that network (2.31) is endowed with mass action kinetics. In this case the appropriate differential equations are

$$\dot{c}_A = k_{2B\to A}(c_B)^2 - k_{A\to 2B}\, c_A$$
$$\dot{c}_B = 2k_{A\to 2B}\, c_A - 2k_{2B\to A}(c_B)^2 \tag{2.32}$$

The set of equilibrium points for (2.32) is given by those $c \in \overline{\mathbb{P}}^{\mathscr{S}}$ that satisfy

$$c_A = \frac{k_{2B\to A}}{k_{A\to 2B}}(c_B)^2 \tag{2.33}$$

The phase portrait for (2.32) is sketched in Figure 2.1.

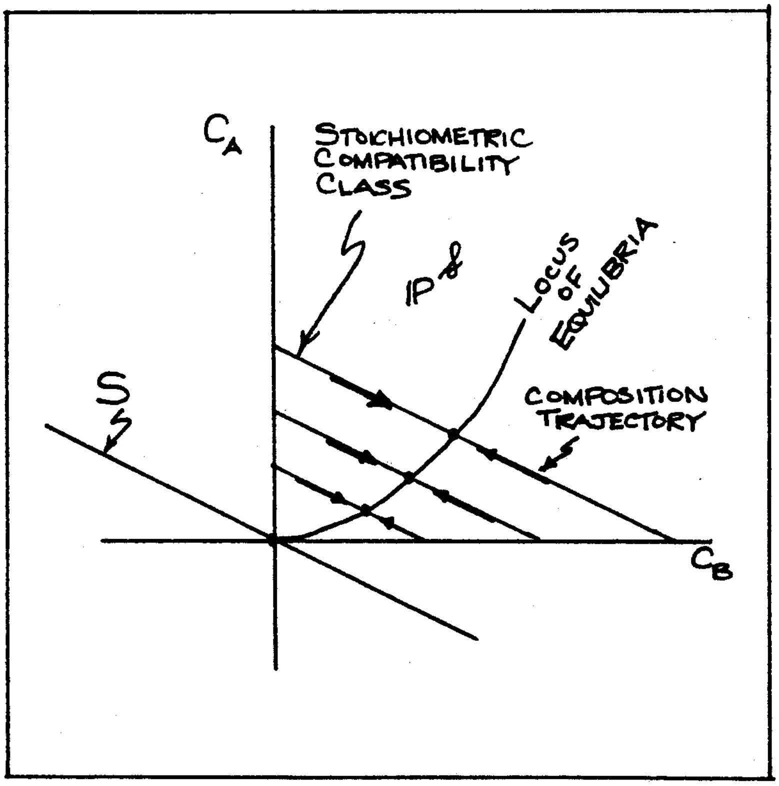
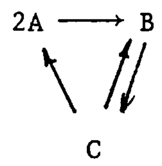


Figure 2.1

Example 2.D.2. Consider the network



(2.34)

Here $\mathcal{S} = \{A,B,C\}$, and the four reaction vectors are

$$\{B-2A,\ B-C,\ C-B,\ 2A-C\} \subset \mathbb{R}^{\mathcal{S}} .$$

The rank of the network is readily confirmed to be two so that the stoichiometric subspace S is two-dimensional. The stoichiometric compatibility classes, as indicated in Figure 2.2, are those triangles which are the intersection of parallels of S with $\overline{\mathbb{P}}^{\mathcal{S}}$. As the figure is intended to suggest, a composition trajectory must lie entirely within a stoichiometric compatibility class.

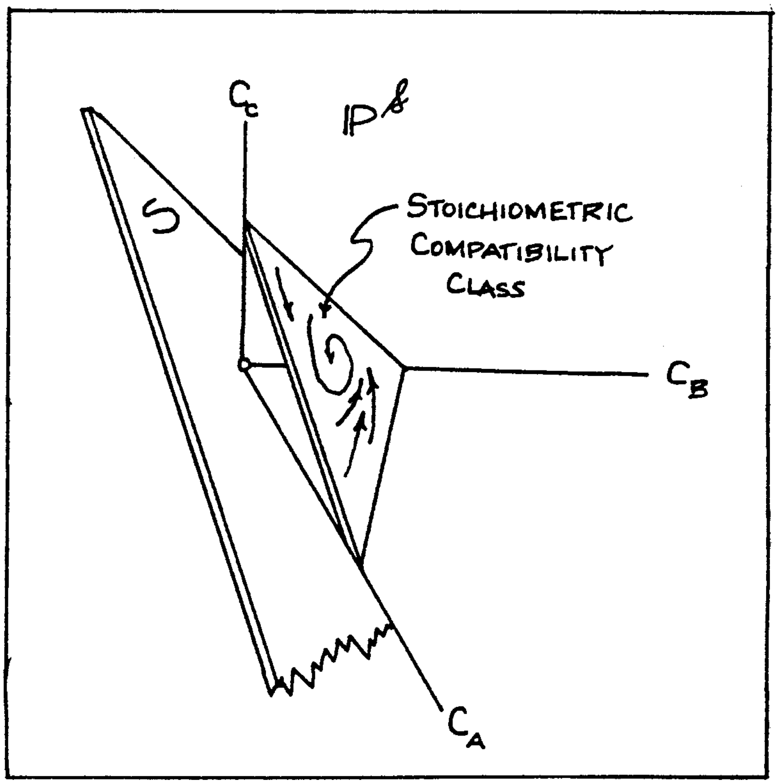


Figure 2.2

Remark 2.17. We introduced the notion of stoichiometric compatibility in anticipation of certain questions we shall raise in the next lecture. In particular, we shall be interested in the existence of multiple positive equilibria. To ask, without qualification, whether the differential equations for a reaction system admit more than one positive equilibrium is to ask a question too broadly posed, for even the very simple system discussed in Example 2.D admits a wealth of positive equilibria. The question of real interest is whether the differential equations for a reaction system can admit multiple positive equilibria within a stoichiometric compatibility class — that is, whether there can exist two or more positive equilibria which are stoichiometrically compatible with the same initial composition. (For the mass action system discussed in Example 2.D.1 the answer is no.) Similarly, when we speak of stability of an equilibrium we shall always mean stability relative to initial conditions within the stoichiometric compatibility class containing that equilibrium.

2.E. *Open Systems: Why Study "Funny" Reaction Networks?*

In this section I want to explain why, in subsequent lectures, we shall admit for consideration networks containing peculiar reactions like $A \to 2A$ or $0 \to A$ (zero reacts to A) which, at first glance, appear to be incompatible with the conservation of matter. In fact, we shall want to consider networks such as

$$\begin{aligned} A &\rightleftarrows 2B \\ A + C &\rightleftarrows B \end{aligned} \qquad (2.35)$$

which offend our sensibilities in a more subtle way: If a molecule of A can decompose into two molecules of B, then the molecular weight of a molecule of B would appear to be half that of a molecule of A. How then can a molecule of B result from a chemical combination of the heavier molecule of A with a molecule of C?

In order to understand why it makes sense to consider such peculiar networks, we must move beyond the simple picture painted at the beginning of Lecture 1 — a picture that has motivated all our considerations thus far. There we studied a homogeneous reactor (portrayed in Figure 1.1) which was closed with respect to the exchange of matter with the external world. Composition changes resulted solely from the occurrence of chemical reactions, and our differential equations were formulated accordingly.

We would also like to study homogeneous (well-stirred) reactors that are open to the influx or efflux of at least certain species. In this case we would expect composition changes to result not only from the occurrence of chemical reactions but also from the transport of various species into and out of the reactor. Consequently, these effects should also manifest themselves in the differential equations that govern the reactor's behavior. For this reason the differential equations (2.16) and (2.18) we have begun to examine might seem inappropriate to the study of open reactors, for those equations were developed in consideration of reactors in which composition changes come about by virtue of chemical reactions alone.

The fact is, however, that equations (2.16) and (2.18) are indeed suited to the study of important categories of open reactors, provided that our conception of a reaction network is suitably broadened to incorporate certain "pseudo-reactions" tailored to encode the infusion or effusion of those species supplied to or removed from a particular open reactor under study. That is, there are varieties of open reactors for which the appropriate differential equations can be viewed as deriving from a reaction network obtained by modifying or augmenting the true chemical network in such a way as to model, by means of "pseudo-reactions", various non-chemical effects.

We shall see how this works in a few examples, but before turning to them I want to make explicit the importance of our ability to subsume open reactors within the framework we have erected so far. Suppose that the possibilities suggested in Lecture 1 could be realized, that there could be developed a theory of the general mass action equation (2.18) which would, for example, indicate that the differential equations for networks of a certain large class cannot admit periodic orbits for any set of rate constants. Suppose further that a particular open system could be modelled in terms of a reaction network (composed in part of "pseudo-reactions") taken with mass action kinetics. That is, suppose (2.18), written for the model network and its kinetics, would yield precisely those differential equations one would write for the open system from first principles. Then the aforementioned theory of equation (2.18) would connect qualitative properties of these equations with the structure of the model network, and the possibility of periodic orbits for the open system under study might, for example, be decided solely on the basis of model network structure. In this way the theory would provide information not only about closed reactors but about open reactors as well.

We turn now to three examples in which we indicate how, by means of appropriately constructed model networks, certain categories of reactors are in fact describable within the framework we have already constructed. So that the basic ideas should not be obscured I have, in each case, taken the "true" chemistry to be very simple. The examples are easily generalized to situations in which the chemistry is far more complex. Moreover, in each example I have taken the kinetics of the true reactions to be mass action, and I have indicated how each reactor is describable in the context of the mass action equation (2.18). When the kinetics is not mass action, similar considerations enable one to describe each reactor in the context of the more general equation (2.16).

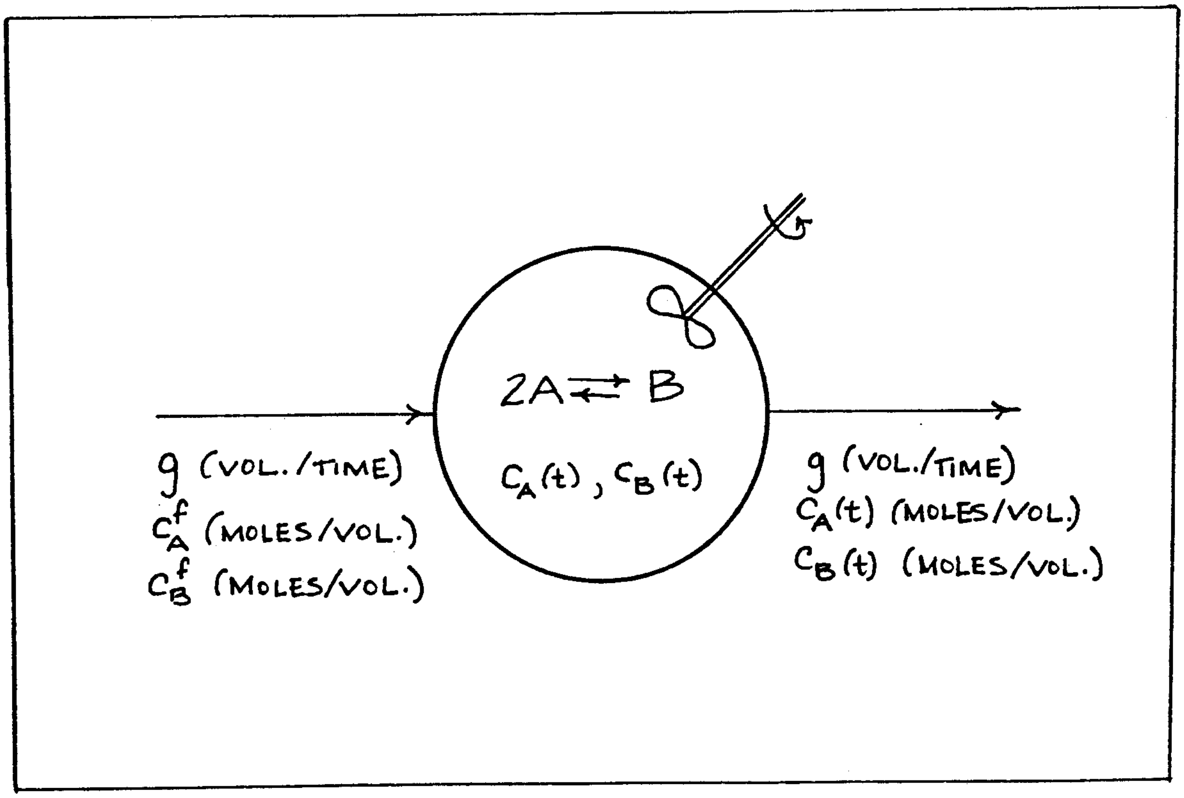
Example 2.E.1 (Continuous Flow Stirred Tank Reactors). Consider the reactor shown in Figure 2.3. The reactor contents, a liquid mixture of species A and B, are maintained homogeneous, isothermal, and of fixed volume (which, for the purposes of this example, we shall take to be unity). Feed of fixed composition is continuously supplied to the reactor at a constant volumetric flow rate g (volume/time) with molar concentrations of A and B in the feed equal to c_A^f and c_B^f, respectively. The contents of the reactor are continuously removed at volumetric flow rate g. In the reactor the only chemical reactions which occur are

$$2A \underset{k'}{\overset{k}{\rightleftarrows}} B \quad , \qquad (2.36)$$

The kinetics is mass action with rate constants as indicated in (2.36). Species balances for A and B yield the following pair of differential equations for c_A and c_B, the molar concentrations of A and B within the reactor:

$$\dot{c}_A = gc_A^f - gc_A + 2k'c_B - 2kc_A^2$$
$$\dot{c}_B = gc_B^f - gc_B = kc_A^2 - k'c_B \; . \qquad (2.37)$$

Written for the mass action system (2.36), equation (2.18) does <u>not</u> reduce to (2.37); terms corresponding to the feed and effluent are absent.



<u>Figure 2.3</u>

Consider, however, the model network (2.38):

$$2A \underset{k'}{\overset{k}{\rightleftarrows}} B \underset{g c_B^f}{\overset{g}{\rightleftarrows}} 0 \underset{g}{\overset{g c_A^f}{\rightleftarrows}} A \; . \tag{2.38}$$

The entity "0" in (2.38) is the zero complex, interpreted as the zero vector of $\mathbb{R}^{\mathcal{S}}$ (where, for our example, $\mathcal{S} = \{A,B\}$). The reactions $0 \to A$ and $0 \to B$ are adjoined to the reactions $2A \rightleftarrows B$ to reflect the infusion of A and B in the feed, and the reactions $A \to 0$ and $B \to 0$ are similarly adjoined to reflect the effusion of A and B in the exit stream. Now suppose that this model network is assigned mass action kinetics with rate constants as indicated alongside the reaction arrows in (2.38). Then (2.18), written for the mass action system depicted in (2.38), yields a vector differential equation whose component equations are precisely those displayed in (2.37).*

Thus, any results obtained for equation (2.18) which draw connections between dynamics and reaction network structure become applicable to the flow reactor we have been considering, provided it is understood that the network of interest is (2.38) rather than the simpler (2.36).

It is not difficult to see how wide varieties of continuous flow stirred tank reactors can be codified in reaction network terms by the means described here.

Example 2.E.2. (Homogeneous Reactors with Certain Species Concentrations Regarded Constant) We shall consider a reactor studied by Edelstein [E]. The reactor contents are well-stirred and are maintained at constant temperature and volume. The reactions occurring are those depicted in the network (2.39):

---

*Note that, according to the mass action prescription (2.7), the reaction $0 \to A$ with rate constant $g c_A^f$ proceeds at rate $(g c_A^f)(c_A)^0(c_B)^0 = g c_A^f$.

$$\begin{aligned} &A + L \underset{\beta}{\overset{\alpha}{\rightleftarrows}} 2A \\ &A + B \underset{\eta}{\overset{\gamma}{\rightleftarrows}} C \underset{\xi}{\overset{\varepsilon}{\rightleftarrows}} B + M \,. \end{aligned} \tag{2.39}$$

The kinetics is mass action with rate constants denoted by Greek letters alongside the corresponding reaction arrows. We shall suppose that species L and M are added to or removed from the reactor in such a manner as to keep the molar concentrations of L and M within the reactor fixed at values c_L^* and c_M^*, respectively. The differential equations for the five species concentrations within the reactor are then

$$\begin{aligned} \dot{c}_A &= \alpha c_L^* c_A - \beta c_A^2 - \gamma c_A c_B + \eta c_C \\ \dot{c}_B &= -\gamma c_A c_B + \eta c_C + \varepsilon c_C - \xi c_M^* c_B \\ \dot{c}_C &= \gamma c_A c_B - \eta c_C - \varepsilon c_C + \xi c_M^* c_B \\ \dot{c}_L &= 0 \\ \dot{c}_M &= 0 \quad . \end{aligned} \tag{2.40}$$

These are not the differential equations one would obtain by writing (2.18) for the mass action system depicted in (2.39).

However, the first three equations of (2.40) — the only ones of real interest — are induced by the mass action system

$$\begin{gathered} A \underset{\beta}{\overset{\alpha c_L^*}{\rightleftarrows}} 2A \\ A + B \underset{\eta}{\overset{\gamma}{\rightleftarrows}} C \underset{\varepsilon c_M^*}{\overset{\varepsilon}{\rightleftarrows}} B \quad . \end{gathered} \tag{2.41}$$

That is, the evolution of the molar concentrations of species A, B and C are described by the first three equations of (2.40), and these can be viewed as deriving from the model network (2.41) by means of the usual mass action formalism. Thus, any theory of equation (2.18) that draws connections between dynamics and network structure becomes applicable to the Edelstein system, so long as it is understood that the network of interest is that shown in (2.41) rather than that shown in (2.39).

This example is easily generalized to other reactors of similar type. To obtain the appropriate model network, one merely "strips away" species with time-invariant concentration from the network of true chemical reactions,* and one modifies certain rate constants in a manner suggested by the example.

---

*If all species in a particular complex have time-invariant concentrations, then the "stripping away" procedure will result in the zero complex.

Remark 2.18. The reactor considered in Example 2.E.2 is open: species L and M are added to and removed from the reactor in such a way as to maintain the concentrations of L and M within the reactor constant in time. In fact, the example — at least in the way I described it — is somewhat farfetched, for it is difficult to see how, in practical terms, control of the concentrations of L and M could be easily managed.

Nevertheless, Example 2.E.2 amounts to a formalization of a common situation that chemists really do think about. Imagine that Edelstein's reactions (2.39) are taking place in a closed reactor in which species L and M are present in amounts much larger than those of A, B and C. In such a situation it is reasonable to suppose that, for a very long time, the concentrations of L and M can be deemed constant in the differential equations for A, B and C; there simply isn't enough A, B or C available to make a dent in the amounts of L and M — at least not in the short run. In the context of this supposition and for a reasonably chosen time interval, the closed Edelstein reactor is, insofar as the dynamics of A, B and C are concerned, more or less equivalent to the physical picture I painted in Example 2.E.2; and the differential equations for A, B and C can be viewed as having been induced by the model mass action system depicted in (2.41).

Example 2.E.3. (Interconnected Cells) As shown in Figure 2.4 each of two cells contains a mixture of species A and B. The mixture in each cell is maintained homogeneous, and we shall presume that the mixture volumes are each maintained at unity and that the temperatures in the two cells are maintained at the same constant value. Species A and B diffuse from cell to cell at rates proportional to the difference in species concentration between the cells. That is, the net rate of receipt of moles of A in cell 1 is $D_A(c_{A_2} - c_{A_1})$, where D_A is a "diffusion constant" for species A, c_{A_1} is the molar concentration of A in cell 1, and c_{A_2} is the molar concentration of A in cell 2. Similarly, the net rate of receipt of moles of B in cell 1 is $D_B(c_{B_2} - c_{B_1})$. We presume also that the reactions

$$A \underset{k'}{\overset{k}{\rightleftarrows}} 2B \tag{2.42}$$

occur within each cell and that the kinetics is mass action with rate constants k and k' as indicated.

The differential equations that govern the system are

$$\begin{aligned}
\dot{c}_{A_1} &= -kc_{A_1} + k'c_{B_1}^2 + D_A(c_{A_2} - c_{A_1}) \\
\dot{c}_{B_1} &= 2kc_{A_1} - 2k'c_{B_1}^2 + D_B(c_{B_2} - c_{B_1}) \\
\dot{c}_{A_2} &= -kc_{A_2} + k'c_{B_2}^2 + D_A(c_{A_1} - c_{A_2}) \\
\dot{c}_{B_2} &= 2kc_{A_2} - 2k'c_{B_2}^2 + D_B(c_{B_1} - c_{B_2}) \ .
\end{aligned} \tag{2.43}$$

These certainly are not the differential equations induced by the mass action system (2.42), but they _are_ the differential equations induced by the _model_ network

$$\begin{gathered}
2B_1 \underset{k'}{\overset{k}{\leftrightarrows}} A_1 \underset{D_A}{\overset{D_A}{\rightleftarrows}} A_2 \underset{k'}{\overset{k}{\rightleftarrows}} 2B_2 \\
B_1 \underset{D_B}{\overset{D_B}{\rightleftarrows}} B_2
\end{gathered} \tag{2.44}$$

taken with mass action kinetics with rate constants as indicated. Thus, any theory of equation (2.18) that draws connections between dynamics and reaction network structure becomes applicable to the system considered here, _provided it is understood that the network of interest is that displayed in_ (2.44).

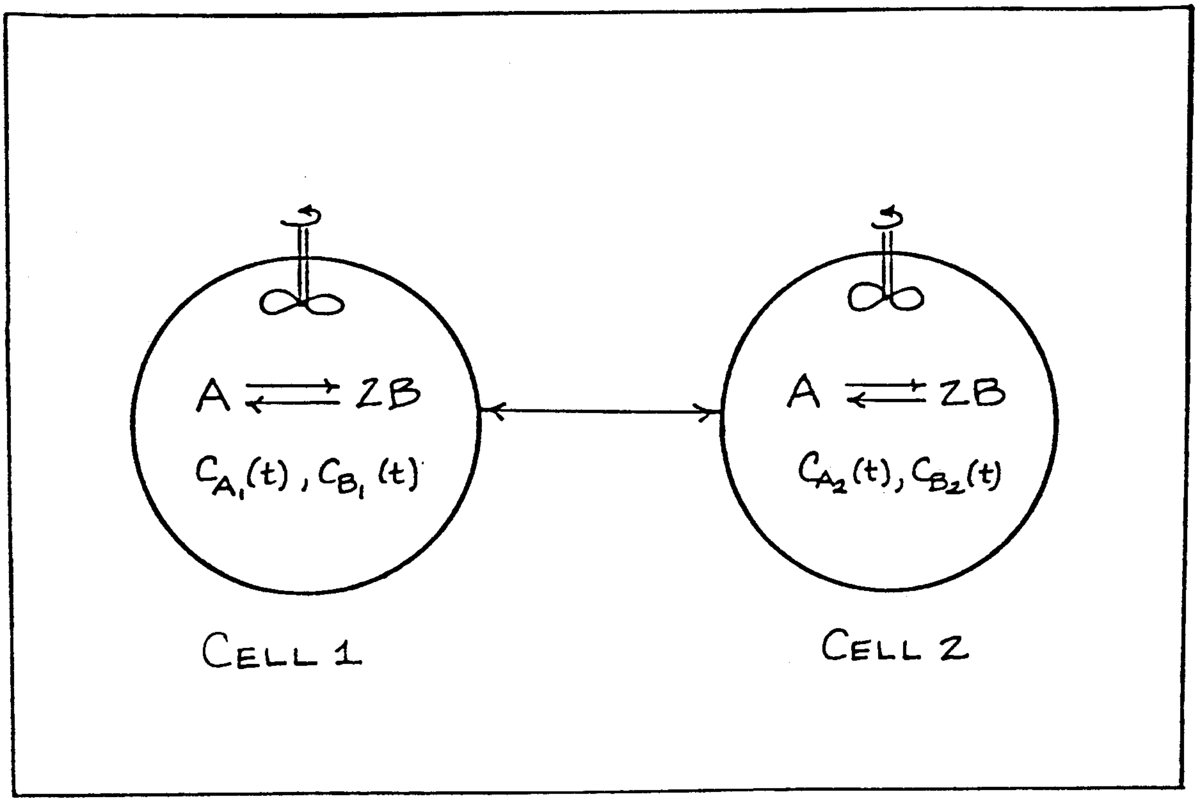


Figure 2.4

It is not difficult to see that one can let the number of cells get large and still effect a model network description in the same way. The chemistry within the cells can, of course, be considerably more complicated than we have indicated in this example. Indeed, the cells may be of the kind in Example 2.E.2 in which certain species concentrations are deemed time-invariant.

Interconnected cells have been studied from a reaction network viewpoint by Shapiro and Horn in [SH] and [S]. I will discuss their work briefly in Lecture 9, but I would strongly encourage readers interested in interconnected cells to see [SH] for a fuller summary of some striking results.

Examples 2.E.1-2.E.3 provide only a partial picture of the way in which the framework we have constructed is sufficiently broad as to accommodate a large variety of reactors by means of suitably constructed model networks. These few examples should nevertheless make clear why we would like whatever theory we generate to embrace networks which contain "funny" reactions such as $A \to 2A$ or $0 \to A$ and which apparently violate conservation of matter. Indeed, the seemingly strange network (2.35) with which we began our discussion might have resulted from the "stripping away" (in the sense of Example 2.E.2) of species D and E from the network

$$A + D \rightleftarrows 2B$$

$$A + C \rightleftarrows B + E$$

Thus, network (2.35) becomes a legitimate object of study in the context of a reactor in which the concentrations of D and E are regarded fixed.

Motivated by these considerations we shall in fact take the view that all reaction networks are legitimate objects of study. In this way we can aspire to a theory that embraces all networks we are likely to encounter, be they "true" chemical networks or model networks that describe reactors like those considered in our examples.

Remark 2.19. Although we shall consider all reaction networks as suitable objects of study, I should point out that those networks which are compatible with mass conservation have certain pleasant properties.

Following Horn and Jackson [HJ], I say that a network $\{\mathscr{S}, \mathscr{C}, \mathscr{R}\}$ is conservative if there exists a (positive) vector $M \in \mathbb{P}^{\mathscr{S}}$ contained in $S^{\perp}$, the orthogonal complement of the stoichiometric subspace for the network. This condition can be given a rough interpretation in the following way: Think of M as a vector of molecular weights, M_{s} being the molecular weight

Taken from a scanned copy of "Lectures on Chemical Reaction Networks," given by Martin Feinberg at the Mathematics Research Center, University of Wisconsin-Madison in the autumn of 1979.

LECTURE 3: TWO THEOREMS

In this lecture I shall state what I think are two remarkable theorems about the relationship between reaction network structure and qualitative properties of the induced differential equations. In rough terms, these theorems describe large classes of reaction networks, some extraordinarily intricate, for which solutions to the corresponding differential equations can only behave in a severely limited way.

Section 3.A contains a list of some major questions we would like to answer. These questions will set the stage not only for the theorems presented in this lecture but also for some results contained in subsequent lectures.

In Section 3.B I introduce in an informal way a small amount of language we shall need to discuss reaction network structure. In particular, I discuss some elementary graphical aspects of reaction networks, and then I introduce the deficiency of a network. The deficiency amounts of a non-negative integer index with which reaction networks can be classified.

In Section 3.C I state the Deficiency Zero Theorem. This theorem gives information about the very large class of networks with deficiency zero. Networks of this class can be enormously complicated and can contain hundreds of species. Very roughly, the Deficiency Zero Theorem says that the differential equations for all deficiency zero networks (taken, say, with mass action kinetics) invariably give rise to phase portraits of a certain kind: Regardless of values of the rate constants there are no unstable positive equilibria; multiple positive equilibria (within a stoichiometric compatibility class) are impossible; and there are no periodic orbits. Thus a chemist, in trying to understand a reactor in which periodic composition oscillations or multiple positive equilibria are observed, could not interpret his observations in terms of a mass action system for which the underlying reaction network has deficiency zero, no matter how intricate that network might be.

In Section 3.D I state a preliminary version of the Deficiency One Theorem. (A better version is stated in Lecture 7.) This theorem improves the Deficiency Zero Theorem to the extent that it delineates a broader class of networks which, when taken with mass action kinetics, are incapable of generating multiple positive equilibria.

Proof of the Deficiency Zero Theorem is given in Lecture 5, and proof of the Deficiency One Theorem is given in Lecture 7.

3.A. *Some Questions*

Our concern will be with the relationship between the structure of a reaction network and properties of the system of differential equations it induces. Recall that one such elementary relationship was already established in Section 2.D: For a reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$, a composition trajectory in $\overline{\mathbb{P}}^{\mathcal{S}}$ containing a point in a particular stoichiometry compatibility class lies entirely within that stoichiometric compatibility class.

We would like to know more. We would like to know in qualitative terms what happens within the stoichiometric compatibility classes, and we would like to tie that qualitative behavior to reaction network structure.

In Lecture 1 I touched upon the kinds of questions we would like to answer, and I want to go into a little more detail here. It is worth stating again that our objectives will be broad ones: We seek to classify networks according to the kind of behavior the induced differential equations might admit. Although we shall be interested in the more general situation, the discussion in this section will be confined to networks endowed with mass action kinetics.

Recall from Lecture 1 that the network itself is our object of study, not the network taken with a <u>particular</u> set of rate constants. We will <u>not</u>, for example, ask whether the differential equations for a specified mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ admit a periodic orbit. We will, however, ask if, for the <u>network</u> $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, there exists <u>some</u> $k \in \mathbb{P}^{\mathcal{R}}$ such that the differential equations induced by the mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ admit a periodic orbit. That is, we shall ask whether the <u>network</u> has the capacity to generate periodic composition oscillations.

With this in mind, I shall pose all the problems considered here in the following way: Describe the class of networks which, when taken with mass action kinetics, are such that the induced differential equations have property X regardless of values of the rate constants. Clearly, a solution to this problem provides a solution to the complementary problem: Describe the class of networks which, when taken with mass action kinetics, are such that the induced differential equations fail to have property X for some values of the rate constants. Thus if we could delineate the full class of networks that generate no periodic orbits for any set of rate constants we would then know the complementary class of networks which have the capacity to generate periodic orbits for at least one assignment of rate constants.

Theorems stated in Sections 3.C and 3.D will answer questions for some very large and intricate networks. In providing motivation for these qeustions, however, I will consider in this section only very simple "play" networks which contain two or three species. These networks are not intended to reflect real-life situations, but they will enable me to sketch equilibrium sets and phase portraits in a fairly easy way. The examples will help exhibit a variety of dynamics that different reaction networks can generate; and, more importantly, they will provide a collection of "facts" that should be fit by any theory we develop. The dynamical zoo I shall present in this section is not intended to be a good one; it contains mice and rabbits but no lions or bears. In particular, I have made no attempt to provide a simple example of a network that generates "chaotic" dynamics.*

In the examples I shall give it will be understood that the networks and rate constants displayed are those obtained after applying the modifications described in Section 2.E. For example, I will consider the "stripped" Edelstein network (2.41) rather than (2.39), for network (2.41) is the one of real interest to us. Similarly, when I talk about its rate constants it will be understood that these are the ones associated with the modified network (2.41) rather than the original.

---

*Readers might wish to see an interesting example constructed by Willamowski and Rössler [WR]. Theirs is a three-species network, only moderately intricate, that derives from consideration of a reactor like that discussed in Example 2.E.2. For suitably chosen rate constants, numerical solution of the induced differential equations is strongly suggestive of very complicated behavior.

In fact, this understanding will remain in force for the balance of these lectures. Remember that, in the spirit of Section 2.E, we admit all networks as legitimate objects of study so that whatever theory we develop can be brought to bear upon whatever model networks might present themselves in applications. Apart from a brief discussion in Lecture 6, I shall henceforth make no distinction between "true" reactions and "pseudo reactions" or between "true" rate constants and "pseudo rate constants".

I turn now to a list of some problems we would like to consider.

Problem 3.A.1. (The existence of positive equilibria). By an equilibrium for a reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ I mean a composition $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ at which the species formation function (Definition 2.6) takes the value zero. By a positive equilibrium I mean an equilibrium in $\mathbb{P}^{\mathcal{S}}$ — that is, an equilibrium at which all species concentrations are positive.

Some reaction networks (e.g., $A \to 2B$) have the property that, when taken with mass action kinetics, the induced differential equations admit no positive equilibria for some or even for any assignments of the rate constants. Any equilibria that do exist are characterized by the "extinction" of one or more species.

On the other hand, some networks (e.g., $A \rightleftarrows 2B$) taken with mass action kinetics admit at least one equilibrium in each positive stoichiometric compatibility class, regardless of values that the rate constants take. (Recall Figure 2.1 in Example 2.D.1.)

Even if we grant that the existence or non-existence of positive equilibria is easy to decide for simple networks, this is not true of complicated networks. Ultimately one is confronted with a large system of polynomial equations in many variables (species concentrations) in which many parameters (rate constants) appear. Recall the system (1.7) of equations generated by the relatively simple mass action system (1.6).

We pose the following problem: Describe the class of networks which, when taken with mass action kinetics, induce differential equations that admit an equilibrium within each positive stoichiometric compatibility class, regardless of values of the rate constants.

Problem 3.A.2. (The uniqueness of positive equilibria). Taken with mass action kinetics, the very simple network discussed in Example 2.D.1 (Lecture 2) gives rise to precisely one equilibrium in each positive stoichiometric compatibility class, regardless of values of the rate constants. This is certainly not true of all networks (although it is true of a much larger class of networks than might be supposed).

For example, the Edelstein network (2.41), when taken with mass action kinetics, has the property that, for some values of the rate constants, the induced differential equations admit multiple positive equilibria within certain stoichiometric compatibility classes. This is the case for the rate constants shown in (3.1)

$$\begin{array}{c} A \underset{1}{\overset{8.5}{\rightleftarrows}} 2A \\ A + B \underset{1}{\overset{1}{\rightleftarrows}} C \underset{0.2}{\overset{1}{\rightleftarrows}} B \end{array} \qquad (3.1)$$

The locus of equilibrium compositions (excluding the origin) is sketched in Figure 3.1 along with two stoichiometric compatibility classes. These are parallel to the two dimensional stoichiometric subspace (not shown) containing the six reaction vectors. (The stoichiometric subspace is spanned by the reaction vectors B-C and A.) The lower stoichiometric compatibility class (the dashed rectangle) is pierced by the locus of equilibria in one point, while the higher stoichiometric compatibility class (the solid rectangle) is pierced in three points.

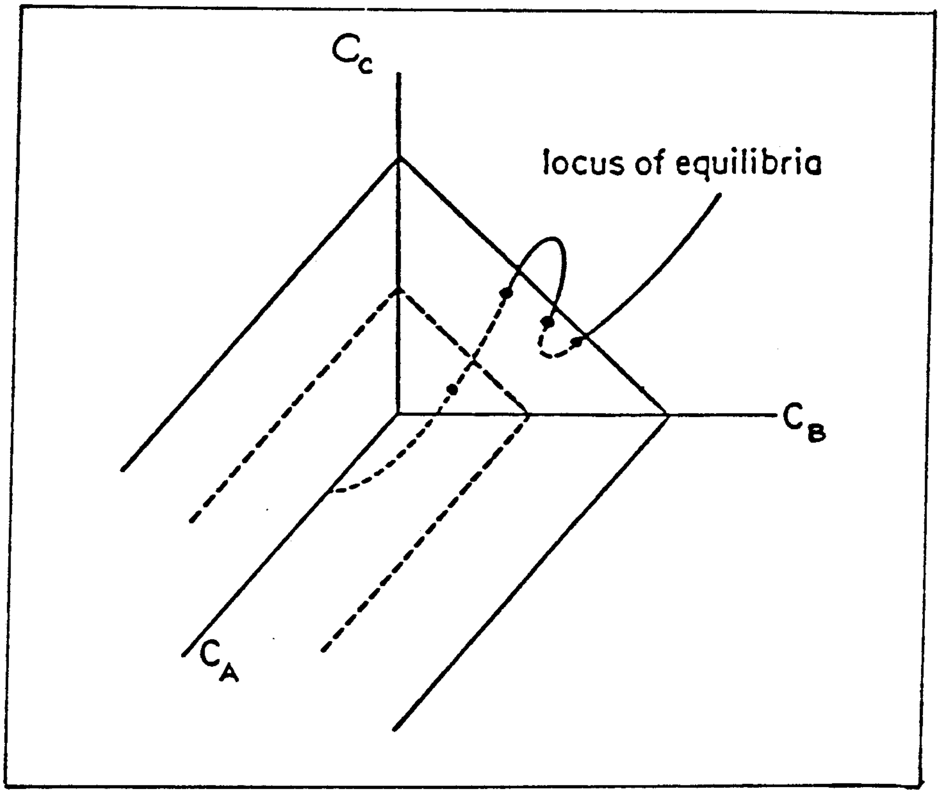


Figure 3.1

Horn and Jackson [HJ] studied another "play" network which, when taken with mass action kinetics, has the capacity to generate multiple positive equilibria. That network is displayed in (3.2):

$$\begin{array}{ccc} 3A & \xrightarrow{.1} & A + 2B \\ {\scriptstyle 1}\uparrow & & \downarrow{\scriptstyle 1} \\ 2A + B & \xleftarrow[.1]{} & 3B \end{array} \qquad (3.2)$$

For some values of the rate constants — in particular, for those shown in (3.2) — the induced differential equations give rise to three equilibria within each positive stoichiometric compatibility class. The locus of equilibria is sketched in Figure 3.2 along with some composition trajectories. The stoichiometric subspace S is one-dimensional and is spanned by the vector B-A. The positive stoichiometric compatibility classes are those parts of parallels of S that lie in the interior of the first quadrant.

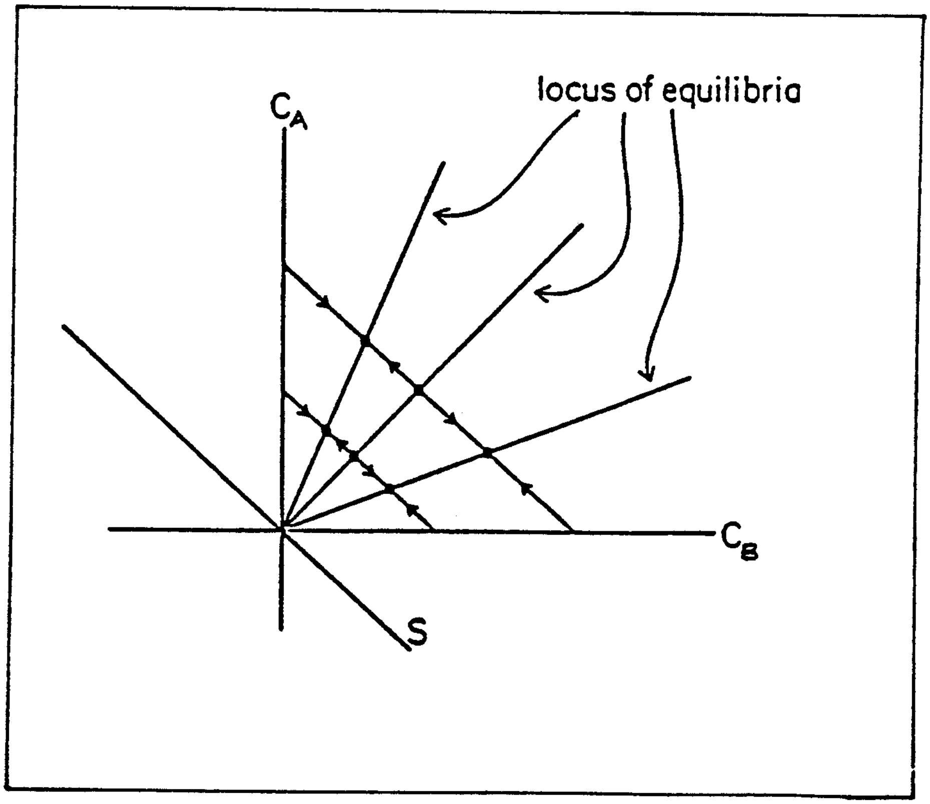


Figure 3.2

However chemically unrealistic network (3.2) might be, it turns out to be remarkably useful as a counterexample in overturning theoretical conjectures that present themselves naturally. We shall see how this works in Section 3.D.

For similar reasons I want to have available one more example of a "play" network which, when taken with mass action kinetics, has the capacity to generate multiple positive equilibria for <u>some</u> values of the rate constants. Consider the mass action system*

$$
\begin{gathered}
A \underset{.0823}{\overset{1.083}{\rightleftarrows}} 0 \underset{1.083}{\overset{1.723}{\rightleftarrows}} B \\[1em]
2A + B \underset{0.3}{\overset{1.95}{\rightleftarrows}} 3A \ .
\end{gathered}
\tag{3.3}
$$

For the network shown in (3.3) the stoichiometric subspace is two-dimensional; it is spanned by the reaction vectors A (= A-0) and B (= B-0). Thus, for this two-species network ($\mathcal{S}$ = {A,B}), the stoichiometric subspace coincides with $\mathbb{R}^{\mathcal{S}}$. (In this case there are no constraints on composition trajectories imposed solely by "stoichiometry".) There is but one positive stoichiometric compatibility class; it is identical to $\mathbb{P}^{\mathcal{S}}$.

The differential equations induced by the mass action system (3.3) admit three positive equilibria. These are shown in Figure 3.3 along with some composition trajectories.

---

*This system derives, in the sense of Example 2.E.1 (Lecture 2), from consideration of a continuous flow stirred tank reactor in which the "true" chemistry is given by the second line of (3.3) with rate constants as indicated. The volumetric flow rate of feed and effluent is 1.0823 (volume/time), and the feed composition is given by c_A^f = 0.076 (moles/volume) and c_B^f = 1.59 (moles/volume).

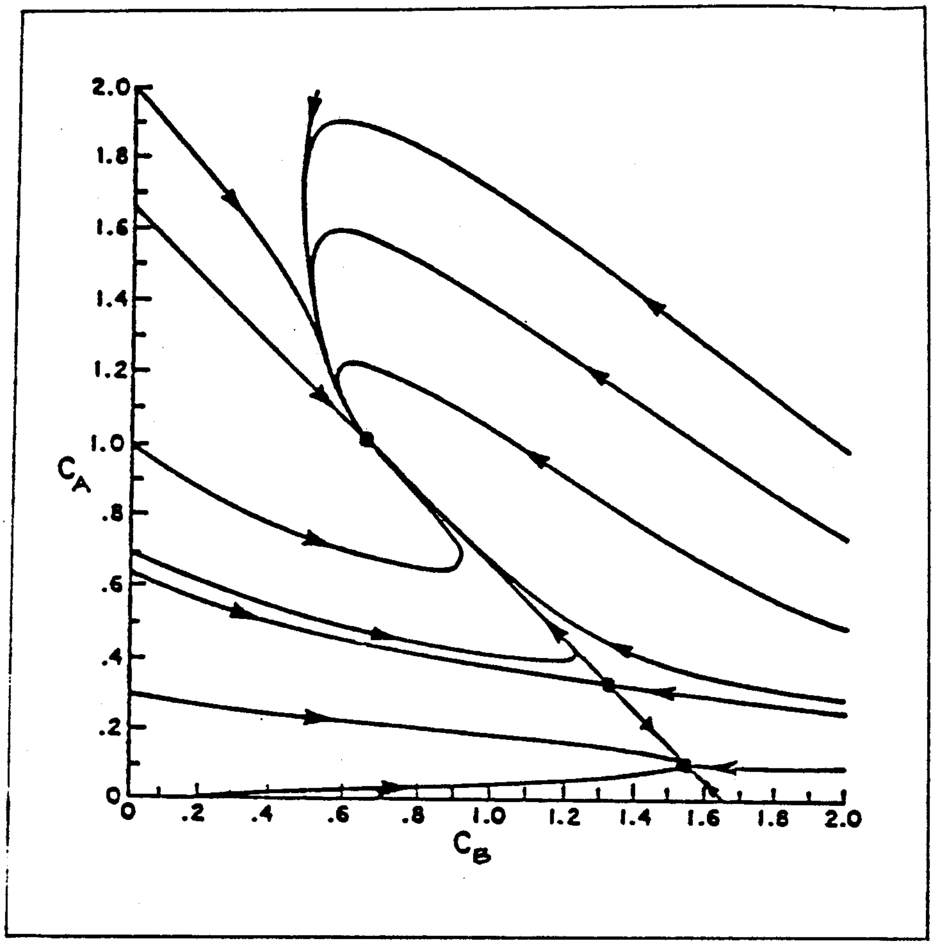


Figure 3.3

I have now provided three examples of networks which, when taken with mass action kinetics, admit multiple positive equilibria (within a stoichiometric compatibility class) for certain values of the rate constants. On the other hand there exist networks which, for every assignment of rate constants, admit precisely one equilibrium within each positive stoichiometric compatibility class. We would like to distinguish between those networks which, when endowed with mass action kinetics, have the capacity to generate multiple positive equilibria and those which do not.

Thus we pose the following problem: Describe the class of networks which, when endowed with mass action kinetics, induce differential equations that admit precisely one equilibrium within each positive stoichiometric compatibility class, regardless of values the rate constants might take.

Problem 3.A.3. (The stability of positive equilibria). Each of the mass action systems (3.1)-(3.3) not only admits multiple positive equilibria, each also admits unstable (as well as stable) positive equilibria. (For the systems (3.2) and (3.3) this can be seen in Figures 3.2 and 3.3.)

Even among those networks that admit a unique equilibrium (within each positive stoichiometric compatibility class) for every assignment of rate constants, there exist networks which have the property that, for certain values of the rate constants, the sole positive equilibrium is unstable. An example is provided by the "Brusselator" [GP] with rate constants as indicated in (3.4)*:

$$\begin{gathered} 0 \underset{1}{\overset{1}{\rightleftarrows}} A \overset{3}{\longrightarrow} B \\ 2A + B \overset{1}{\longrightarrow} 3A \end{gathered} \qquad (3.4)$$

For this two-species network, the stoichiometric subspace is two dimensional and therefore coincides with $\mathbb{R}^{\mathcal{S}}$. There is but one positive stoichiometric compatibility class; it coincides with $\mathbb{P}^{\mathcal{S}}$. It is easy to confirm that for any assignment of rate constants there is precisely one positive equilibrium. For the values shown in (3.4) the resulting equilibrium is unstable and is enclosed within a stable limit cycle. A sketch of the phase portrait is shown in Figure 3.4.

---

*In the sense of Example 2.E.2 the network shown in (3.4) has been obtained from that studied in [GP] by "stripping away" species deemed to have time-invariant concentrations.

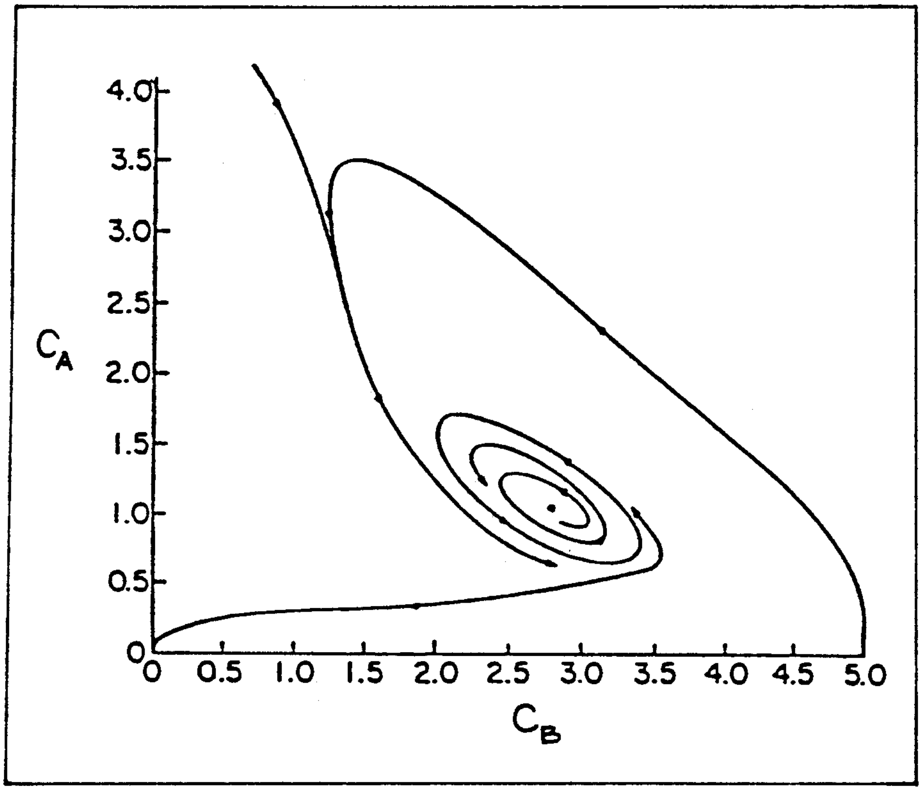


Figure 3.4

Networks (3.1)-(3.4) have the property that, for some values of the rate constants, the induced differential equations admit an unstable positive equilibrium. On the other hand, there exist networks — (2.31) is a trivial example — which, when taken with mass action kinetics, induce differential equations that admit only stable positive equilibria regardless of values of the rate constants. We would like to distinguish between those networks that have the capacity to generate unstable positive equilibria and those which do not.

We pose the following problem: Describe the class of networks which, when endowed with mass action kinetics, induce differential equations such that every positive equilibrium is stable, regardless of values the rate constants might take. (Recall that when we speak of the stability of an equilibrium we shall always mean stability relative to initial conditions in the stoichiometric compatibility class containing that equilibrium.)

Problem 3.A.4. (The existence of periodic composition cycles). As we saw in Figure 3.4, network (3.4) — when taken with mass action kinetics — has the property that, for some values of the rate constants, the induced differential equations admit periodic composition cycles. On the other hand, there exist networks which, when taken with mass action kinetics, have the property that the induced differential equations fail to admit periodic composition cycles for any assignment of rate constants. We would like to distinguish between those networks which have the capacity to generate periodic composition cycles and those which do not.

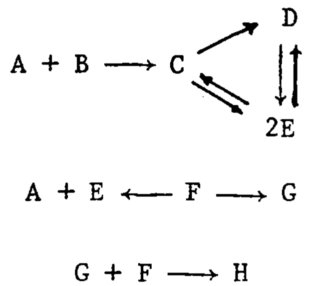
We pose the following problem: Describe the class of networks which, when endowed with mass action kinetics, induce differential equations that admit no (nonconstant) periodic composition cycles regardless of values the rate constants might take.

3.B. A Little Vocabulary

The problems we have posed are major ones. I want to present two theorems which, I think, represent substantial progress toward their resolution. In order to state them I shall require a small amount of vocabulary with which reaction network structure might be discussed. At least for now there are only three ideas we need: what we mean by the linkage classes of a network, what it means for a network to be weakly reversible, and what we mean by the deficiency of a network. The first two of these depend solely on a network's character as a graph, the precise nature of the complexes playing no essential role. The algebraic nature of the complexes will, however, influence a network's deficiency. The basic ideas, especially those associated with the graphical structure of a network, are easy to understand in an intuitive way, and in this lecture I won't be very formal about them. I will, however, give formal definitions in the next lecture when I begin to lay the groundwork for proofs.

In representing reaction networks diagrammatically I have, without saying so explicitly, always followed a certain procedure. I have displayed each complex precisely once, and then I have joined the various complexes by the appropriate reaction arrows. Whenever I speak of the reaction diagram for a network I will mean a display of this kind. One way in which we can begin talking about the structure of a reaction network is by saying some things about how its reaction diagram looks.

3.B.1. The linkage classes of a reaction network. Consider the reaction diagram (3.5). What strikes one immediately about the diagram is that



(3.5)

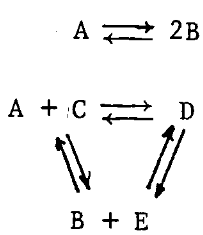
it is made up of three distinct "pieces" — one containing the complexes {A+B, C, D, 2E}, one containing the complexes {A+E, F, G} and one containing the complexes {G+F, H}. That is, if we forget about the directions in which the reaction arrows point we notice that complexes in the set {A+B, C, D , 2E} are "linked" to each other (not necessarily directly) but not to any other complex. The same is true of complexes in the set {A+E, F, G} and in the set {G+F, H} .

By inspecting the reaction diagram for any network we can discern the "pieces" of which it is composed, and we can then partition its complexes into the corresponding *linkage classes*. Thus, the linkage classes for the network depicted in (3.5) are {A+B, C, D, 2E} , {A+E, F, G} and {G+F, H}. We shall reserve the symbol ℓ for the *number of linkage classes* in a network. Clearly, ℓ is just the number of "pieces" that make up the corresponding reaction diagram.

Here are some other examples: For network (1.1) $\ell = 2$. For network (3.1) $\ell = 2$. For network (3.2) $\ell = 1$. For network (3.3) $\ell = 2$. For network (3.4) $\ell = 2$.

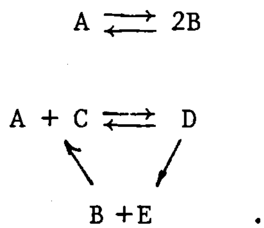
In determining the linkage classes of a network we merely ask which complexes are "linked" to which other complexes without caring about the directions in which the reaction arrows point. The directions of the reaction arrows will, however, play a role in our next idea, weak reversibility.

3.B.2. *Weak reversibility*. By a *reversible* network a chemist means one in which each reaction is accompanied by its "antireaction"; that is, if $y \to y'$ is a reaction in a reversible network then so is $y' \to y$. Thus, the network (3.6) is reversible:



(3.6)

On the other hand network (3.7), which is the same as (1.1), is not reversible:



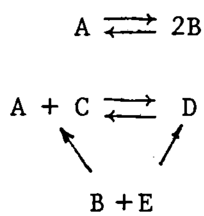
(3.7)

It turns out that reversible networks are pleasant to work with, and one can prove some nice theorems about them. It also turns out that, with almost no additional effort, one can prove these same theorems for a wider class of networks we shall call weakly reversible: A network is weakly reversible if, whenever there is a directed arrow path leading from complex y to complex y', there is also a directed arrow path leading from y' back to y. (Alternatively, a network is weakly reversible if each reaction arrow is contained within a directed arrow cycle.)

Network (3.7), while not reversible, is weakly reversible. Note, for example, that there is a directed arrow path connecting A + C to D and that there is also one leading from D back to A + C (via B + E). Note also that every reaction arrow is contained in a directed arrow cycle. (Some of these cycles are little ones containing only a pair of arrows pointing in opposite directions.)

Network (3.6) is also weakly reversible. It should be clear that every reversible network is weakly reversible. Thus, any theorems stated for weakly reversible networks apply to reversible networks as well.

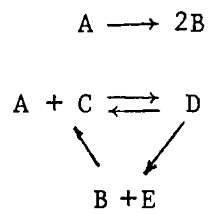
Network (3.8) is not weakly reversible:



(3.8)

There is a directed arrow path leading from complex B + E to complex D but no directed arrow path leading from D back to B + E. Note also that the reaction B + E → D is not contained in any directed arrow cycle.

Similarly, network (3.9) is not weakly reversible:



(3.9)

There is a directed arrow path connecting A to 2B but none leading from 2B back to A.

Here are some more examples: Networks (3.1) and (3.3) are reversible and, therefore, weakly reversible. Network (3.2) is weakly reversible (but not reversible). Networks (3.4) and (3.5) are neither reversible nor weakly reversible.

3.B.3. The deficiency of a reaction network. The ideas discussed in Sections 3.B.1 and 3.B.2 related solely to the structure of a network as a (directed) graph. The "stoichiometry" of the network — that is, the algebraic nature of its complexes — played no role. In our discussion of the deficiency of a network stoichiometry will play a role insofar as it influences the rank of the network (Definition 2.8). Recall that the rank of a network is the number of elements in the largest linearly independent set that can be found among its reaction vectors.

The deficiency amounts to a non-negative integer index with which reaction networks can be classified. Remember that, for a fixed reaction network, we reserved the symbol n for the number of complexes, the symbol ℓ for the number of linkage classes and the symbol s for its rank. The deficiency of a network, denoted δ, is defined by

$$\boxed{\delta := n - \ell - s\ .} \qquad (3.10)$$

We shall see in the next lecture that the deficiency of a network is never negative.

By way of example, let us calculate the deficiency of network (1.1), which is displayed again as (3.7). There are five complexes, two linkage classes, and the rank of the network is three. (We worked out the rank in the example following Definition 2.8.) Thus, the deficiency of the network is zero: $\delta = 5-2-3 = 0$. The very similar networks (3.6), (3.8) and (3.9) also have deficiency zero. For all of them $n = 5$, $\ell = 2$ and $s = 3$.

Remark 3.1. In fact, it is a simple matter to see that if $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ and $\{\mathcal{S}, \mathcal{C}, \mathcal{R}'\}$ are reaction networks with identical linkage classes then the ranks of the two networks (and hence their deficiencies) are identical as well. That is, specification of the linkage classes (rather than the precise nature of the reaction arrows) is sufficient to determine the rank.*

Let us consider some more examples. For network (3.5) $n = 9$ and $\ell = 3$. Moreover $s = 6$ since a maximal linearly independent set of reaction vectors is given by

$$\{C-(A+B),\ D-C,\ 2E-C,\ A+E-F,\ G-F,\ H-(F+G)\}\ .$$

Thus, the deficiency of network (3.5) is zero ($\delta = 9-3-6 = 0$).

*This will follow easily from (4.32), which is contained in the next lecture, and Remark 2.15.

For network (3.1) $n=5$, $\ell=2$ and $s=2$ since the pair B - C and A (= 2A-A) constitute a maximal linearly independent set of reaction vectors. (Note, for example, that the reaction vector A+B-C is the sum of B-C and A.) Thus, for network (3.1) $\delta = 5-2-2 = 1$.

For network (3.2) $n=4$, $\ell=1$ and $s=1$. (Each reaction vector is a multiple of B-A.) Thus, for network (3.2) $\delta = 4-1-1 = 2$.

For network (3.3) $n=5$, $\ell=2$ and $s=2$. (The reaction vectors A(=A-0) and B(=B-0) constitute a maximal linearly independent set.) Thus, for network (3.3) $\delta = 5-2-2 = 1$.

For network (3.4) $n=5$, $\ell=2$, and $s=2$. (The reaction vectors A(=A-0) and B-A constitute a maximal linearly independent set.) Thus, for network (3.4) $\delta = 5-2-2 = 1$.

We are now in a position to state the first of our theorems.

3.C. *The Deficiency Zero Theorem*

Basic ideas underlying the theorem I am about to state are due to Fritz Horn, Roy Jackson and me; they appeared in three articles in 1972 ([HJ], [H3], [F2].) In 1974 Horn and I published a brief description of the theorem in the engineering literature [FH1], and I reported an improved version of the theorem in 1977 [F3] along with an outline of the proof intended for graduate students in chemical engineering. Meanwhile in 1973 Horn published three articles in the Proceedings of the Royal Society which dealt with graph-theoretical aspects of the theorem [H4-6]. Some of the ideas contained in Horn's Royal Society papers are quite interesting but will not be discussed in these lectures. (For more recent work along similar lines see [W].)

Networks of deficiency zero can contain hundreds of species and hundreds of reactions. It goes without saying that the induced differential equations can be incredibly intricate. In rough terms, what the Deficiency Zero Theorem says is that, no matter how intricate these equations might be, the resulting phase portraits inevitably have a certain dull character.

Theorem 3.1. (The Deficiency Zero Theorem). Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be any reaction network of deficiency zero.

(i) If the network is not weakly reversible then, for arbitrary kinetics $\mathcal{K}$, the differential equations for the reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ cannot admit a positive equilibrium (i.e., an equilibrium in $\mathbb{P}^{\mathcal{S}}$).

(ii) If the network is not weakly reversible then, for arbitrary kinetics $\mathcal{K}$, the differential equations for the reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ cannot admit a cyclic composition trajectory containing a positive composition (i.e., a point in $\mathbb{P}^{\mathcal{S}}$).

(iii) If the network is weakly reversible (in particular, if the network is reversible) then, for any mass action kinetics $k \in \mathbb{P}^{\mathcal{R}}$, the differential equations for the mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ have the following properties: There exists within each positive stoichiometric compatibility class precisely one equilibrium; that equilibrium is asymptotically stable; and there cannot exist a nontrivial cyclic composition trajectory in $\mathbb{P}^{\mathcal{S}}$.

Remark 3.2. In fact there is more that one can say about deficiency zero networks. These additional assertions I will postpone until Lectures 5 and 6.

I want to consider how the Deficiency Zero Theorem works in some examples, and I also want to consider how it fits the facts in the case of some networks we have already discussed.

Example 3.C.1. I'll begin by recalling the very first network we discussed, (1.1) in Lecture 1. Remember that we gave the network mass action kinetics (with rate constants indicated by Greek letters in (1.6)), we wrote out the corresponding system (1.7) of differential equations, and we posed some questions about them. Despite the complexity of the system (1.7) we can now answer all the questions we posed. The network (1.1) is weakly reversible, and we have already calculated its deficiency to be zero. Thus, part (iii) of the Deficiency Zero Theorem gives the following information: Regardless of values of the rate constants there is precisely one equilibrium in each positive stoichiometric compatibility class; each of these is asymptotically stable; and there are no periodic (positive) composition trajectories.

Taken with mass action kinetics the more complicated network (3.6) induces an even more intricate system of differential equations. Nevertheless, network (3.6) is weakly reversible (in fact, reversible) and its deficiency is zero. Thus, we can make the same statements as those above.

Example 3.C.2. Next I want to consider network (3.8) which is very similar to (1.1) and (3.6). Here again the deficiency is zero, but (3.8) is not weakly reversible. Thus, the Deficiency Zero Theorem tells us that, regardless of the kinetics, the induced differential equations can admit neither a positive equilibrium nor a cyclic composition trajectory containing a positive composition. This is more or less obvious: Species E is not produced by any reaction, and, as long as species B is present, the supply of E will dwindle.

The situation for network (3.9), however, is far less transparent. Here again the deficiency is zero, and (3.9) is not weakly reversible. But now every species is both produced and consumed by chemical reactions. Nevertheless, parts (i) and (ii) of the Deficiency Zero Theorem tell us that, for any kinetics (mass action or otherwise), the induced differential equations admit no positive equilibrium nor a periodic composition trajectory containing a positive composition. (For the case of mass action kinetics the appropriate differential equations can be obtained from (1.7) by setting β equal to zero.)

Example 3.C.3. Next I want to recall the mass action system studied by Edelstein:

$$\begin{gathered} A \underset{\beta}{\overset{\theta}{\rightleftarrows}} 2A \\ A + B \underset{\eta}{\overset{\gamma}{\rightleftarrows}} C \underset{\rho}{\overset{\varepsilon}{\rightleftarrows}} B \quad . \end{gathered} \tag{3.11}$$

The induced differential equations are

$$\begin{aligned} \dot{c}_A &= \theta c_A - \beta c_A^2 - \gamma c_A c_B + \eta c_C \\ \dot{c}_B &= (\varepsilon + \eta) c_C - \gamma c_A c_B - \rho c_B \\ \dot{c}_C &= \gamma c_A c_B - (\varepsilon + \eta) c_C + \rho c_B \quad . \end{aligned} \tag{3.12}$$

Remember that for some values of the rate constants — in particular for those shown in (3.1) — the system (3.12) admits three equilibria within a positive stoichiometric compatibility class. (One is unstable.) Network (3.11) is weakly reversible (in fact, reversible) but its deficiency is one ($n = 5$, $\ell = 2$, $s = 2$). Thus, there is no contradiction of the Deficiency Zero Theorem.

Now consider the slightly different mass action system

$$\begin{gathered} A \underset{\beta}{\overset{\theta}{\rightleftarrows}} 2A \\ A + B \underset{\eta}{\overset{\gamma}{\rightleftarrows}} C \underset{\rho}{\overset{\varepsilon}{\rightleftarrows}} 2B \quad , \end{gathered} \tag{3.13}$$

for which the induced differential equations are

$$\dot{c}_A = \theta c_A - \beta c_A^2 - \gamma c_A c_B + \eta c_C$$
$$\dot{c}_B = (2\varepsilon + \eta) c_C - \gamma c_A c_B - 2\rho c_B^2 \qquad (3.14)$$
$$\dot{c}_C = \gamma c_A c_B - (\varepsilon + \eta) c_C + \rho c_B^2$$

In very rough terms the system (3.14) is "more nonlinear" than the system (3.12): While the rate of reaction $B \to C$ in network (3.11) is proportional to c_B, the rate of reaction $2B \to C$ in network (3.13) is proportional to c_B^2. At least to the extent that they can be compared, one might expect that phase portraits for the system (3.14) should be at least as interesting as those for (3.12).

But the deficiency of the reversible network (3.13) is readily calculated to be zero ($n = 5$, $\ell = 2$, $s = 3$). Thus, for any choice of positive numbers for the Greek letters in (3.14) the system admits precisely one positive equilibrium; it is asymptotically stable; and there are no (positive) periodic solutions.

Example 3.C.4. Recall that the weakly reversible network (3.2), when taken with mass action kinetics, has the property that, for some values of the rate constants, the induced differential equations admit unstable positive equilibria and also multiple equilibria within each positive stoichiometric compatibility class. Recall that the deficiency of the network was calculated to be two ($n = 4$, $\ell = 1$, $s = 1$).

Example 3.C.5. We saw that the reversible network (3.3), taken with mass action kinetics, generates three positive equilibria (one unstable) for some values of the rate constants. The deficiency of network (3.3) was calculated to be one.

Example 3.C.6. It is not hard to show that network (3.4), taken with mass action kinetics, induces differential equations that admit precisely one positive equilibrium, regardless of values the rate constants take. For some values of the rate constants this equilibrium is unstable and is surrounded by a (positive) periodic orbit. (Recall Figure 3.4.)

The point here is that network (3.4) is not weakly reversible, but yet it has the capacity to generate a positive equilibrium and a positive composition cycle. Parts (i) and (ii) of the Deficiency Zero Theorem are not contradicted. The deficiency of network (3.4) was calculated to be one ($n = 5$, $\ell = 2$, $s = 2$).

Remark 3.3. The examples we have studied may lead some readers to draw two conclusions, neither of which should be drawn on the basis of the examples alone.

The first is that deficiency zero networks are substantially less common than those of positive deficiency. It should be kept in mind that our sample has been biased against networks of deficiency zero. Networks (3.1)-(3.4) were studied precisely because they give rise to unstable positive equilibria, multiple positive equilibria or periodic composition cycles. Thus their deficiencies could not be zero.

The second is that weakly reversible networks of non-zero deficiency invariably violate the conclusions of the Deficiency Zero Theorem, part (iii). This is false. In fact, there exist networks of positive deficiency — both weakly reversible and otherwise — which, when taken with mass action kinetics, have all the properties given by part (iii). Delineation of the full class of such networks remains a major outstanding problem.

3.D. The Deficiency One Theorem

The Deficiency Zero Theorem tells us, among other things, that all weakly reversible deficiency zero networks taken with mass action kinetics induce differential equations that admit precisely one equilibrium in each positive stoichiometric compatibility class. This holds true regardless of values the rate constants take and regardless of how complex the differential equations might be.

It turns out that there is an easily described but even broader class of networks for which the same statement can be made. This is the subject of the next theorem I want to discuss. The version I'll give in this section is a preliminary one. A better version will be stated in Lecture 7, where I shall indicate what one can say for networks which are not weakly reversible.*

Before I can state our next theorem I'll need one more idea: the deficiency of a linkage class. This is just a simple and obvious extension of ideas we have already encountered. I have already indicated how one calculates the deficiency of a reaction network. In the sense of § 3.B.1 I can also look at each of the "pieces" of which the network is composed, and I can calculate the deficiency of each "piece" separately as if it were a little network by itself. This will give a set of non-negative integers $\delta_1, \delta_2, \ldots, \delta_\ell$, one for each linkage class.

Let me be a little more formal. Suppose that $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is a reaction network with n complexes, ℓ linkage classes, and suppose that the rank of the network is s :

$$s := \text{rank}\,\{y'-y \in \mathbb{R}^{\mathcal{S}} : y \to y' \in \mathcal{R}\}. \tag{3.15}$$

Suppose also that, in the sense of § 3.B.1, I partition $\mathcal{C}$ into linkage classes $L^1, L^2, \ldots, L^\ell$. For $\theta = 1,2,\ldots,\ell$ I denote by n_θ the number of complexes in L^θ , and I define

*Readers who wish to read the more general version in Lecture 7 will be able to do so after glancing at Definitions 4.1-4.3 in Section 4.B of Lecture 4.

$$s_\theta := \text{rank}\,\{y'-y \in \mathbb{R}^{\mathcal{S}} : y \to y' \in \mathcal{R}\ ,\ y \in L^\theta\}\ . \tag{3.16}$$

That is, s_θ is the rank of the set of reaction vectors corresponding to reactions appearing in the "piece" of the network containing complexes in L^θ. I define the <u>deficiency of linkage class L^θ</u> as follows:

$$\delta_\theta := n_\theta - 1 - s_\theta\ . \tag{3.17}$$

This, of course, is just what one would compute to find the deficiency of the "θ^{th} piece", viewed as a network by itself.*

Note that

$$\begin{aligned}\sum_{\theta=1}^{\ell} \delta_\theta &= \sum_{\theta=1}^{\ell} (n_\theta - 1) - \sum_{\theta=1}^{\ell} s_\theta \\ &= n - \ell - \sum_{\theta=1}^{\ell} s_\theta \end{aligned} \tag{3.18}$$

On the other hand, the deficiency of the network as a whole is given by

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

Moreover, (3.15), (3.16) and elementary considerations in linear algebra give

$$\sum_{\theta=1}^{\ell} s_\theta \geqq s\ . \tag{3.19}$$

---

*It is not difficult to see that s_θ is also given by

$$s_\theta = \text{rank}\{y'-y \in \mathbb{R}^{\mathcal{S}} : y \in L^\theta,\ y' \in L^\theta\}\ .$$

That is, s_θ (and hence δ_θ) depend only on the set $L^\theta \subset \mathcal{C}$ and not on the precise manner in which elements of L^θ are linked by reaction arrows. For this reason it makes sense to speak of "the deficiency of linkage class L^θ" even though L^θ merely specifies a set of complexes.

Thus, we have

$$\delta \geqq \sum_{\theta=1}^{\ell} \delta_\theta \qquad (3.20)$$

with equality holding in (3.20) if and only if equality holds in (3.19).

To set the stage for the statement of our next theorem I want to characterize the class of deficiency zero networks in a somewhat different (and more awkward) way than I have so far. It will be understood that δ denotes the deficiency of a network as a whole while, for $\theta = 1,2,\ldots,\ell$, δ_θ denotes the deficiency of the θ^{th} linkage class. From (3.20) and the non-negativity of the δ_θ it should be clear that the deficiency zero networks are precisely those that satisfy both of the following conditions:

(i) $\delta_\theta = 0 \quad , \quad \theta = 1,2,\ldots,\ell$.

(ii) $\delta = \sum_{\theta=1}^{\ell} \delta_\theta$.

Thus, the Deficiency Zero Theorem permits us to make the following statement: Consider a weakly reversible network that satisfies both conditions (i) and (ii). If the network is endowed with mass action kinetics then, regardless of values of the rate constants, the induced differential equations admit precisely one equilibrium in each positive stoichiometric compatibility class.

Our next theorem asserts that this same result obtains even when condition (i) is weakened considerably: The deficiency of each linkage class can be as high as one!

Theorem 3.2 (The Deficiency One Theorem). Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with ℓ linkage classes. Let δ denote the deficiency of the network; let δ_θ denote the deficiency of the θ^{th} linkage class, $\theta = 1,2,\ldots,\ell$; and suppose that both of the following conditions are satisfied:

(i) $\delta_\theta \leqq 1$, $\theta = 1,2,\ldots,\ell$

(ii) $\delta = \sum_{\theta=1}^{\ell} \delta_\theta$.

If the network is weakly reversible (in particular, if the network is reversible) then, for any mass action kinetics $k \in \mathbb{P}^{\mathcal{R}}$, the differential equations for the mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ admit precisely one equilibrium in each positive stoichiometric compatibility class.

Remark 3.4. I should explain the sense in which Theorem 3.2 deserves to be called the Deficiency One Theorem: Networks which satisfy the hypothesis of the Deficiency Zero Theorem are precisely those which satisfy condition (ii) and for which the deficiency of no linkage class exceeds zero. By analogy, (weakly reversible) networks which satisfy the hypothesis of Theorem 3.2 are precisely those which satisfy condition (ii) and for which the deficiency of no linkage class exceeds one.

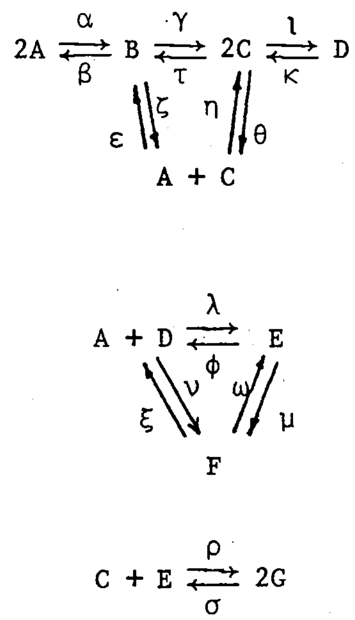
It should be clear, however, that not all (weakly reversible) deficiency one networks satisfy the hypothesis of Theorem 3.2. In particular the (weakly reversible) deficiency one networks which fail to satisfy its hypothesis are precisely those for which the deficiency of each linkage class is zero. On the other hand, it should also be clear that Theorem 3.2 gives information about certain networks with deficiency greater than one.

Theorem 3.2 has an immediate corollary:

<u>Corollary 3.3</u>. <u>Consider a weakly reversible network for which there is but one linkage class. If the network is taken with mass action kinetics then the induced differential equations can admit multiple equilibria within a positive stoichiometric compatibility class only if the deficiency of the network is two or more</u>.

In order to indicate the kind of information Theorem 3.2 and its corollary give I want to consider some examples.

<u>Example 3.D.1</u>. Consider the mass action system (3.21):



(3.21)

The differential equations for the molar concentrations of the seven species are:

$$
\begin{aligned}
\dot{c}_A &= -2\alpha c_A^2 + (2\beta+\zeta)c_B - (\varepsilon+\eta)c_A c_C + \theta c_C^2 - (\lambda+\nu)c_A c_D + \xi c_F + \phi c_E \\
\dot{c}_B &= \alpha c_A^2 - (\beta+\gamma+\zeta)c_B + \varepsilon c_A c_C + \tau c_C^2 \\
\dot{c}_C &= (2\gamma+\zeta)c_B + (\eta-\varepsilon)c_A c_C - (\theta+\iota)c_C^2 + 2\kappa c_D - \rho c_C c_E + \sigma c_G^2 \\
\dot{c}_D &= \iota c_C^2 - \kappa c_D - (\lambda+\nu)c_A c_D + \xi c_F + \phi c_E \\
\dot{c}_E &= \lambda c_A c_D - (\mu+\phi)c_E - \rho c_C c_E + \sigma c_G^2 + \omega c_F \\
\dot{c}_F &= \gamma c_A c_D + \mu c_E - (\xi+\omega)c_F \\
\dot{c}_G &= 2\rho c_C c_E - 2\sigma c_G^2
\end{aligned}
\tag{3.22}
$$

We pose the following question: Does the system (3.22) admit multiple equilibria within a positive stoichiometric compatibility class for some set of values for the rate constants? Ad hoc study of this question would require an analysis of a system of seven polynomial equations in seven variables (the species concentrations) and in which eighteen unspecified parameters (the rate constants) appear.

Yet almost immediately Theorem 3.2 tells us that for every assignment of rate constants there exists precisely one equilibrium within each positive stoichiometric compatibility class: Network (3.21) is reversible, its deficiency is one, and the deficiencies of its linkage classes are (from top to bottom) $\delta_1 = 1$, $\delta_2 = 0$ and $\delta_3 = 0$.

Example 3.D.2. Let us return once again to the Edelstein mass action system:

$$
\begin{array}{c}
A \underset{\beta}{\overset{\theta}{\rightleftarrows}} 2A \\[1em]
A + B \underset{\eta}{\overset{\gamma}{\rightleftarrows}} C \underset{\rho}{\overset{\varepsilon}{\rightleftarrows}} B
\end{array} \quad , \tag{3.23}
$$

for which the differential equations are

$$
\begin{aligned}
\dot{c}_A &= \theta c_A - \beta c_A^2 - \gamma c_A c_B + \eta c_C \\
\dot{c}_B &= (\varepsilon+\eta) c_C - \gamma c_A c_B - \rho c_B \\
\dot{c}_C &= \gamma c_A c_B - (\varepsilon+\eta) c_C + \rho c_B \quad .
\end{aligned} \tag{3.24}
$$

It will be recalled that, for values of the rate constants exhibited in (3.1), the system (3.24) admits three equilibria within a positive stoichiometric compatibility class (Figure 3.1). This is not precluded by Theorem 3.2: The deficiency of network (3.23) is one ($n = 5$, $\ell = 2$, $s = 2$), but the deficiencies of the two linkage classes are each zero. Although condition (i) of Theorem 3.2 is satisfied, condition (ii) is not.

Example 3.D.3. It is interesting to consider a perturbation of the Edelstein system obtained by adding two reactions:

$$
\begin{array}{c}
A \underset{\beta}{\overset{\theta}{\rightleftarrows}} 2A \\
\tau \downarrow\uparrow \sigma \\
A + B \underset{\eta}{\overset{\gamma}{\rightleftarrows}} C \underset{\rho}{\overset{\varepsilon}{\rightleftarrows}} B
\end{array} \quad . \tag{3.25}
$$

The corresponding differential equations are:

$$\dot{c}_A = (\theta-\tau)c_A - \beta c_A^2 - \gamma c_A c_B + (\eta+\sigma)c_C$$

$$\dot{c}_B = (\varepsilon+\eta)c_C - \gamma c_A c_B - \rho c_B \qquad (3.26)$$

$$\dot{c}_C = \gamma c_A c_B - (\varepsilon+\eta+\sigma)c_C + \rho c_B + \tau c_A \quad .$$

Whereas the Edelstein system (3.23) has the capacity to generate multiple positive equilibria within a stoichiometric compatibility class, one might expect similar behavior from the system (3.25). In particular, one might imagine that if rate constants are chosen as in (3.1) and if τ and σ are taken to be very small positive numbers then the differential equations (3.26) should admit multiple positive equilibria as do those shown in (3.24).

Yet, Corollary 3.3 tells us that this is <u>not</u> the case. The deficiency of network (3.25) is <u>one</u> ($n = 5$, $\ell = 1$, $s = 3$) and it contains but one linkage class. Thus, <u>regardless</u> of values of the rate constants there is <u>precisely one</u> positive equilibrium.* In particular, if one chooses rate constants for the Edelstein reactions as in (3.1) then, no matter how small one chooses τ and σ, the locus of equilibria shown in Figure 3.1 collapses under the perturbation, and only one point on that locus persists as an equilibrium. (The equilibrium that persists is determined by the ratio τ/σ.)

<u>Remark 3.5</u>. It is natural to conjecture that networks which satisfy the conditions of Theorem 3.2 might have <u>all</u> the properties described in part (iii) of the Deficiency Zero Theorem, not merely the existence of a unique equilibrium in each positive stoichiometric compatibility class. In fact, this is false. Paul Berner produced rate constants for network (3.25) such that the sole positive equilibrium given by Corollary 3.3 is unstable and such that numerical solution of (3.26) indicates the existence of an attractive periodic orbit on which the species concentrations are positive.

*Unlike network (3.23), the rank of network (3.25) is three so that its stoichiometric subspace coincides with $\mathbb{R}^{\mathcal{S}}$. Thus, $\mathbb{P}^{\mathcal{S}}$ is a positive stoichiometric compatibility class for network (3.25), and it is the only one.

In the next three remarks I shall provide counterexamples to show that none of the three ingredients in the hypothesis of Theorem 3.2 — weak reversibility, condition (i) and condition (ii) — can be omitted without modifying the theorem statement in some other way.

Remark 3.6. It should be clear that the absence of weak reversibility might preclude the existence of positive equilibria. What is perhaps less obvious is that the absence of weak reversibility can affect the uniqueness of equilibria within a positive stoichiometric compatibility class.

Consider the simple mass action system

$$2A \xleftarrow{\alpha} A + B \xrightarrow{\beta} 2B \ . \tag{3.27}$$

The reaction vectors are B-A and A-B so that the stoichiometric subspace is just the line spanned by B-A. The positive stoichiometric compatibility classes are just those parts of lines parallel to span (B-A) which lie in $\mathbb{P}^{\mathscr{S}}$. For the network shown in (3.27) $n=3$, $\ell=1$ and $s=1$. Thus the deficiency of the network is one and, since there is just one linkage class, conditions (i) and (ii) of Theorem 3.2 are satisfied.

The differential equations for (3.27) are

$$\begin{aligned} \dot{c}_A &= (\alpha-\beta)\, c_A c_B \\ \dot{c}_B &= (\beta-\alpha)\, c_A c_B \ . \end{aligned} \tag{3.28}$$

Note that if $\alpha \neq \beta$ there are no positive equilibria. On the other hand when $\alpha = \beta$ every composition is an equilibrium point, and there are an infinite number of equilibria within each positive stoichiometric compatibility class.

Although (3.27) satisfies both conditions (i) and (ii) of Theorem 3.2, the network is not weakly reversible, and that is the source of the problem. This example demonstrates that one cannot merely drop weak reversibility from the hypothesis of Theorem 3.2 and still hope to assert that, regardless of the rate constants, there will exist at most one equilibrium within each positive stoichiometric compatibility class.

It will turn out, however, that one can replace the weak reversibility condition in Theorem 3.2 with a substantially less stringent graphical condition* and still assert that, for all values of the rate constants, there can exist within a positive stoichiometric compatibility class at most one equilibrium. This more general result is part of the better version of the Deficiency One Theorem I shall state and prove in Lecture 7.

Remark 3.7. To see that condition (i) cannot be dropped from the hypothesis of Theorem 3.2 we need only recall the network (3.2) studied by Horn and Jackson. It is weakly reversible and, since it contains just one linkage class, condition (ii) is satisfied trivially. On the other hand the deficiency of the network is two ($n = 4$, $\ell = 1$, $s = 1$) so that condition (i) is not satisfied. Recall that when the network is taken with mass action kinetics there exist rate constants such that the induced differential equations admit three equilibria within each positive stoichiometric compatibility class (Figure 3.2).

*The condition is that each linkage class contain no more than one terminal strong linkage class. See Definitions 4.1-4.3 in the next lecture.

Remark 3.8. That condition (ii) cannot be dropped from the hypothesis of Theorem 3.2 has already been demonstrated in our discussion of Example 3.D.2. The Edelstein network (3.23) is reversible, and condition (i) is satisfied since the deficiency of each linkage class is zero. On the other hand the deficiency of the entire network is one so that condition (ii) is not satisfied. For certain values of the rate constants the system of differential equations (3.24) admits three equilibria within a positive stoichiometric compatibility class (Figure 3.1).

The situation is similar for the reversible network (3.3). There are two linkage classes, each of deficiency zero, but the deficiency of the entire network is one. Recall that for certain values of the rate constants the induced differential equations admit three positive equilibria (Figure 3.3).

Deficiency one networks arise frequently in applications, particularly in contexts like that in Example 2.E.2 (Lecture 2) wherein certain species concentrations are regarded time-invariant. As I indicated in Remark 3.4 the (weakly reversible) deficiency one networks which fail to satisfy the hypothesis of Theorem 3.2 are precisely those for which each linkage class has deficiency zero.

Unfortunately, this is a common situation. We should not, however, infer from the examples discussed in Remark 3.8 that, when taken with mass action kinetics, all (weakly reversible) deficiency one networks that violate condition (ii) invariable give rise to multiple positive equilibria for some assignment of rate constants. Consider, for example, the reversible Brusselator:

$$\begin{gathered} 0 \rightleftarrows A \rightleftarrows B \\ 2A + B \rightleftarrows 3A \; . \end{gathered} \tag{3.29}$$

The deficiency of the network is one, and the deficiency of each linkage class is zero. It is easy to confirm by ad hoc means that, for every assignment of rate constants, the induced differential equations admit precisely one positive equilibrium.

Apparently, then, some deficiency one networks which violate the hypothesis of Theorem 3.2 have the capacity to generate multiple positive equilibria when taken with mass action kinetics, but others do not. In view of the importance of deficiency one networks in applications, we would like to be able to distinguish between these in a systematic way. This will be the subject of Lecture 8.

In the next lecture we shall begin to lay the groundwork for proofs of the Deficiency Zero and Deficiency One Theorems.

Taken from a scanned copy of "Lectures on Chemical Reaction Networks," given by Martin Feinberg at the Mathematics Research Center, University of Wisconsin-Madison in the autumn of 1979.

LECTURE 4: SOME DEFINITIONS AND PROPOSITIONS

My purpose in this lecture is to accumulate some technical material that will eventually play a role in proofs of both the Deficiency Zero Theorem and the Deficiency One Theorem. Because some of the material will find no use for quite a while, this lecture will require a small amount of patience from the reader. Although I could have developed certain results at the point of first use in later lectures, there are two reasons for not proceeding in this way. First, many of the definitions, propositions and corollaries in this lecture are so strongly interrelated that there are clear advantages in having them all recorded in one place to be drawn upon as the need arises. Second, I think the price paid here for the resulting stockpile of technical material will be more than offset by a smoother, uninterrupted flow of ideas in subsequent lectures.

In Section 4.A I provide some background for the balance of this lecture. In particular, I try to supply some movitation for the questions we shall ask. In Section 4.B I discuss some properties of a reaction network that derive solely from its structure as a directed graph. Thus, in Section 4.B the nature of the reaction arrows plays the dominant role, while the precise character of the complexes sitting at the heads and tails of the reaction arrows plays virtually no role at all. In Section 4.C I begin to investigate some interplay of "stoichiometry" — that is, of the algebraic nature of the complexes — with a network's graphical structure. Finally, in Section 4.D I present a proposition which is somewhat disconnected from everything else in this lecture but which will play an important role in our study of the existence and uniqueness of positive equilibria.

Some of the definitions given in this lecture are new. Others merely serve to make formal certain ideas we have introduced in an informal way in previous lectures. Still others were actually recorded before but are repeated here for the reader's convenience.

4.A. *Some Motivation*

Before proceeding to the substantive part of this lecture I want to supply some motivation for the results we shall accumulate. In particular, I want to provide an indication of how the various objects discussed in some of the propositions (and their corollaries) will ultimately play a role in subsequent lectures.

Recall that the (vector) differential equation for a reaction system $\{\mathcal{S},\mathcal{C},\mathcal{R},\mathcal{K}\}$ is given by

$$\dot{c} = \sum_{\mathcal{R}} \mathcal{K}_{y\to y'}(c)\ (y'-y)\ . \tag{4.1}$$

In particular, the differential equation for a mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ is given by

$$\dot{c} = \sum_{\mathcal{R}} k_{y\to y'}\ c^{y}(y'-y)\ , \tag{4.2}$$

where, for each $y \in \mathcal{C}$,

$$c^{y} := \prod_{s \in \mathcal{S}} c_{s}^{y_{s}}\ . \tag{4.3}$$

From the discussion of notation in Lecture 1 it should also be recalled that

$$\{\omega_{y} \in \mathbb{R}^{\mathcal{C}} : y \in \mathcal{C}\} \tag{4.4}$$

is the standard basis for $\mathbb{R}^{\mathcal{C}}$.

I am now going to reformulate equations (4.1) and (4.2). To do this I shall require three mappings. For a network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ let $Y:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ be the linear transformation defined by its action on the standard basis for $\mathbb{R}^{\mathcal{C}}$ as follows:

$$Y\omega_{y} = y\ ,\ \forall\ y \in \mathcal{C}\ . \tag{4.5}$$

Moreover, let $\Psi: \overline{\mathbb{P}}^{\mathcal{S}} \to \overline{\mathbb{P}}^{\mathcal{C}}$ be defined by

$$\Psi(c) \equiv \sum_{y \in \mathcal{C}} c^y \omega_y \; ; \tag{4.6}$$

that is, the "y^{th} component" of $\Psi(c)$ is given by

$$\Psi_y(c) = c^y \; .$$

Finally, for each $k \in \mathbb{P}^{\mathcal{R}}$ let $A_k: \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ be the linear transformation defined by

$$A_k(x) \equiv \sum_{\mathcal{R}} k_{y \to y'} \, x_y \, (\omega_{y'} - \omega_y) \; . \tag{4.7}$$

With very little effort one can see that the differential equation (4.1) for a reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ can be written

$$\dot{c} = Y[\sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(\omega_{y'} - \omega_y)] \tag{4.8}$$

and that the differential equation (4.2) for a mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ can be written

$$\dot{c} = Y A_k \Psi(c) \; . \tag{4.9}$$

Now if we want to study the equilibrium points of the differential equation (4.8) we must ask when $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is such that the bracketed vector in (4.8) lies in the kernel of Y. Thus, it is clear that we should know something about $\ker Y$. In fact, we can go a little further: Since, for every $c \in \overline{\mathbb{P}}^{\mathcal{S}}$, the vector

$$\sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c)(\omega_{y'} - \omega_y)$$

lies in the linear subspace of $\mathbb{R}^{\mathcal{C}}$ spanned by the set

$$\{\omega_{y'} - \omega_y \in \mathbb{R}^{\mathcal{C}} : y \to y'\} \ , \tag{4.10}$$

we should pay particular attention to that part of $\ker Y$ that meets the span of (4.10). (The dimension of the intersection will turn out to be the deficiency of the network.) There is still something more that we can say: Recall that each of the rate functions in (4.8) take non-negative values and that they all take positive values on $\mathbb{P}^{\mathcal{S}}$ (Remark 2.4). Thus, we should be especially interested in that part of $\ker Y$ that contains elements of the form

$$\sum_{\mathcal{R}} \alpha_{y \to y'} (\omega_{y'} - \omega_y) \ ,$$

where the $\alpha_{y \to y'}$ are non-negative or, when we study strictly positive equilibria, where each $\alpha_{y \to y'}$ is positive.

Similarly, if we want to study the equilibrium points of the differential equation (4.9) we must ask when $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is such that $\Psi(c)$ lies in the kernel of $Y A_k$. Note that since $\Psi(\cdot)$ takes values in $\overline{\mathbb{P}}^{\mathcal{C}}$ we shall be especially interested in

$$\ker Y A_k \cap \overline{\mathbb{P}}^{\mathcal{C}} \ .$$

Note also that, when c is positive (i.e., when c lies in $\mathbb{P}^{\mathcal{S}}$), $\Psi(c)$ is also positive (i.e., $\Psi(c)$ lies in $\mathbb{P}^{\mathcal{C}}$). Thus, when we study strictly positive equilibria of (4.9) we shall want to know something about the nature of

$$\ker Y A_k \cap \mathbb{P}^{\mathcal{C}} \ .$$

Since we have the obvious inclusion

$$\ker A_k \subset \ker Y A_k \ ,$$

we can begin to study the structure of $\ker YA_k$ by first studying $\ker A_k$.

With these considerations kept in mind, the reader should have some sense of how the results we shall compile in this lecture will ultimately find use.

There is one final observation we might make. The mappings Y and Ψ for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ are heavily influenced by stoichiometry — that is, by the nature of the complexes contained in $\mathcal{C}$ — but not at all by the "reacts to" relation $\mathcal{R}$. Just the reverse is true of the mapping A_k and the set (4.10), for while $\mathcal{R}$ enters their construction in a very direct way, $\mathcal{C}$ merely plays the role of an index set. In this sense, A_k and the set (4.10) are objects that relate to the structure of a network essentially through its graphical character, and we can study these objects without paying much attention to the stoichiometrical information carried by the set $\mathcal{C}$. In fact, we shall begin by investigating how a network's graphical structure influences the nature of the set (4.10) and properties of the mapping A_k.

4.B. *Some Graphical Aspects of Reaction Networks*

The "reacts to" relation $\mathcal{R}$ gives a reaction network its character as a directed graph. The complexes play the role of the "vertices" while the reactions play the role of the (directed) "arcs." The "reacts to" relation in turn induces other relations in the set of complexes. As we explore these it will be understood that we are considering a fixed reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$.

Definition 4.1. Two complexes $y \in \mathcal{C}$ and $y' \in \mathcal{C}$ are directly linked if $y \to y'$ or if $y' \to y$. If y and y' are directly linked we write $y \leftrightarrow y'$. Two complexes $y \in \mathcal{C}$ and $y' \in \mathcal{C}$ are linked if any of the following conditions are satisfied:

(i) $y = y'$

(ii) $y \leftrightarrow y'$

(iii) $\mathcal{C}$ contains a sequence $\{y_1, y_2, \ldots, y_k\}$ such that

$$y \leftrightarrow y_1 \leftrightarrow y_2 \leftrightarrow \ldots \leftrightarrow y_k \leftrightarrow y' .$$

If y and y' are linked we write $y \sim y'$. The equivalence relation $\sim$ induces a partition of $\mathcal{C}$ into a family of equivalence classes $\{L^\theta\}$ called the linkage classes of the network. We reserve the symbol ℓ for the number of linkage classes in a network.

Definition 4.2. A complex $y \in \mathcal{C}$ ultimately reacts to a complex $y' \in \mathcal{C}$ if any of the following conditions are satisfied:

(i) $y = y'$

(ii) $y \to y'$

(iii) $\mathcal{C}$ contains a sequence $\{y_1, y_2, \ldots, y_k\}$ such that

$$y \to y_1 \to y_2 \to \ldots \to y_k \to y' .$$

If y ultimately reacts to y' we write $y \Rightarrow y'$. Two complexes $y \in \mathcal{C}$ and $y' \in \mathcal{C}$ are strongly linked if both $y \Rightarrow y'$ and $y' \Rightarrow y$. If y and y' are strongly linked we write $y \approx y'$. The equivalence relation $\approx$ induces a partition of $\mathcal{C}$ into a family of equivalence classes $\{\Lambda^\rho\}$ called the strong linkage classes of the network.

Remark 4.1. Clearly $y \approx y'$ implies that $y \sim y'$. Thus, every strong linkage class lies within a linkage class. In fact, every linkage class is the disjoint union of strong linkage classes.

The linkage classes of a reaction network correspond to what, in graph theoretical terminology, are sometimes called the weak components of a directed graph, and the strong linkage classes correspond to what are sometimes called the strong components. (See, for example, Harary [H1].) Unfortunately, in chemical terminology the word "component" is sometimes used as a synonym for "species."

Definition 4.3. A terminal strong linkage class is a strong linkage class Λ with the property that no complex in Λ reacts to a complex not in Λ; that is, $y \in \Lambda$ and $y \to y'$ imply that y' is in Λ. We reserve the symbol t for the number of terminal strong linkage classes in a network.

An example or two might help clarify the intent of the definitions listed thus far.

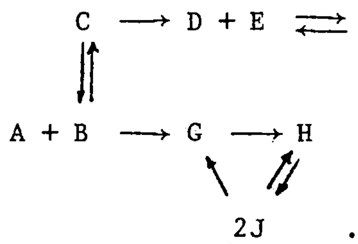
Example 4.1. Consider the network

$$A + B \longrightarrow C, \quad C \longrightarrow D + E, \quad C \rightleftarrows 2F$$

$$F + A \rightleftarrows G \quad .$$

The linkage classes are: {A+B, C, D+E, 2F} and {F+A,G}; thus, $\ell = 2$. The strong linkage classes are: {A+B},{C,2F}, {D+E} and {F+A,G}. The terminal strong linkage classes are: {D+E} and {F+A,G}; thus, $t = 2$

<u>Example 4.2.</u> Consider the network



There is but one linkage class: {C,A+B,D+E,F,G,H,2J} ; thus, $\ell = 1$. The strong linkage classes are: {C,A+B}, {D+E,F}, {G,H,2J} . The terminal strong linkage classes are: {D+E,F} and {G,H,2J}; thus, $t = 2$.

<u>Remark 4.2.</u> It should be clear that for any network each linkage class contains at least one terminal strong linkage class. Thus, $t - \ell \geq 0$; and, as Examples 4.1 and 4.2 indicate, equality may or may not obtain.

<u>Definition 4.4.</u> A reaction network is <u>reversible</u> if, for that network, the "reacts to" relation (→) is symmetric — that is, if $y' \to y$ then $y \to y'$.

Neither of the networks displayed in Examples 4.1 and 4.2 is reversible. However, the network

$$A + B \rightleftarrows C \rightleftarrows D$$

$$D + C \rightleftarrows E$$

is reversible.

Definition 4.5. A reaction network is *weakly reversible* if, for that network, any of the following (equivalent) conditions is satisfied:

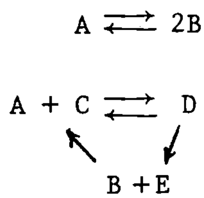
(i) The "ultimately reacts to" relation ($\Rightarrow$) is symmetric; that is, whenever $y \Rightarrow y'$ we also have $y' \Rightarrow y$.

(ii) Each reaction is contained in a directed cycle; that is, whenever $y \to y'$ we also have $y' \Rightarrow y$.

(iii) Each linkage class is a strong linkage class.

(iv) Each linkage class is a terminal strong linkage class.

It is an easy exercise to check the equivalence of (i)-(iv). Neither of the networks shown in Examples 4.1 or 4.2 is weakly reversible. Recall, however, that the network



is weakly reversible. Clearly, every reversible network is also weakly reversible, but, of course, the converse is not true.

Remark 4.3. As we shall see, the coincidence of the linkage classes and terminal strong linkage classes makes for a certain pleasantness in dealing with weakly reversible networks. Some, but not all, of the nice features a weakly reversible network enjoys derive simply from the fact that the *number* of its linkage classes is identical to the *number* of its terminal strong linkage classes (i.e., $t = \ell$). A network need not be weakly reversible for it to have this property — recall Example 4.1 — and it often happens that certain assertions that hold true for weakly reversible networks carry over (perhaps with minor modifications) to networks for which $t = \ell$.

We are now in a position to state the first of three propositions in this lecture. It will give important qualitative information about the structure of the kernel of the linear transformation A_k discussed in Section 4.A. Although I introduced A_k in consideration of a mass action system (with k the vector of rate constants), I prefer to regard Proposition 4.1 merely as a technical result about a family of linear transformations induced by a network's graphical structure. That is, in Proposition 4.1 I attribute no particular "chemical" interpretation to k. As we shall see, Proposition 4.1 acts as a "master proposition" from which several results follow, some (e.g., Corollary 4.3) having implications for reaction systems which are not necessarily mass action.

Recall from Lecture 1 that if x is an element of $\mathbb{R}^{\mathcal{C}}$ then the support of x is defined by

$$\text{supp } x := \{y \in \mathcal{C} : x_y \neq 0\}.$$

<u>Proposition 4.1. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with terminal strong linkage classes $\{\Lambda^1, \Lambda^2, \ldots, \Lambda^t\}$, let k be any vector in $\mathbb{P}^{\mathcal{R}}$, and let $A_k: \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ be the linear transformation defined by</u>

$$A_k(x) = \sum_{\mathcal{R}} k_{y \to y'}\, x_y (\omega_{y'} - \omega_y) .$$

<u>Then the kernel of A_k has a basis $\{x^1, x^2, \ldots, x^t\} \subset \overline{\mathbb{P}}^{\mathcal{C}}$ such that</u>

$$\text{supp } x^i = \Lambda^i, \quad i = 1, 2, \ldots, t .$$

Remark 4.4. Proposition 4.1, which is crucial to a lot that we shall do tells us that no matter how $k \in \mathbb{P}^{\mathcal{R}}$ is chosen the kernel of A_k maintains a definite relationship to the graphical structure of the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ from which A_k derives. In particular, ker A_k will always have dimension t, where t is the number of terminal strong linkage classes in the network. Moreover, ker A_k will have a nice basis: In that basis there will be a vector x^i corresponding to terminal strong linkage class Λ^i such that $x^i_y > 0$ for all $y \in \Lambda^i$ and $x^i_y = 0$ for all $y \notin \Lambda^i$.

Readers familiar with theorems of the Perron-Frobenius type will realize that these might provide the basis for a proof of Proposition 4.1. However, one then has the job of drawing connections between the matrix language employed, for example, in Gantmacher's book [G] and the essentially graphical language introduced thus far. Things get a little awkward. With this in mind Horn and I gave what amounts to a "from scratch" proof of Proposition 4.1 in the appendix of reference [FH2].* That proof, which is essentially graph-theoretical in spirit and which makes no use of Perron-Frobenius theorems, is a little too long to include here. Instead I refer interested readers to [FH2]. For a Perron-Frobenius argument in the narrower context of weakly reversible networks readers should see the appendix of an earlier article by Horn [H3].

In the following corollary to Proposition 4.1 we address the question of when ker A_k contains a strictly positive vector — that is, an element of $\mathbb{P}^{\mathcal{C}}$.

---

*Definition 8 in [FH2] is incorrectly constructed and should read as Definition 4.2 here. However, Definition 8 plays no role either in the statement or proof of the proposition in the appendix of [FH2], which is the same as Proposition 4.1 here apart from trivial differences in terminology and notation.

Corollary 4.2. *Let* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *be a reaction network, let* k *be any vector of* $\mathbb{P}^{\mathcal{R}}$, *and let* A_k *be as in Proposition 4.1. Then*

$$\ker A_k \cap \mathbb{P}^{\mathcal{C}}$$

is non-empty if and only if the network is weakly reversible.

Proof. Suppose the network is not weakly reversible. Then there exists a complex $\hat{y} \in \mathcal{C}$ that does not reside in any terminal strong linkage class; otherwise the linkage classes would coincide with the terminal strong linkage classes, thereby ensuring weak reversibility. Since, by virtue of Proposition 4.1, every vector in $\ker A_k$ is a linear combination of vectors with support in the terminal strong linkage classes it must be the case that $x_{\hat{y}} = 0$ for every $x \in \ker A_k$. Thus, $\ker A_k \cap \mathbb{P}^{\mathcal{C}}$ is empty.

On the other hand if the network is weakly reversible then every complex is a member of some terminal strong linkage class. In this case the sum of the basis vectors described in Proposition 4.1 is a member of $\ker A_k \cap \mathbb{P}^{\mathcal{C}}$. ///

Corollary 4.3. *Let* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *be a reaction network. There exists* $\alpha \in \mathbb{P}^{\mathcal{R}}$ *such that*

$$\sum_{\mathcal{R}} \alpha_{y \to y'} (\omega_{y'} - \omega_y) = 0 \qquad (4.12)$$

if and only if the network is weakly reversible.

Proof. First we shall prove the existence of the required α when the network is weakly reversible. Let k be any vector of $\mathbb{P}^{\mathcal{R}}$, and let A_k be as in Proposition 4.1. From the weak reversibility of the network and Corollary 4.2 we have the existence of $\hat{x} \in \ker A_k \cap \mathbb{P}^{\mathcal{C}}$. Thus,

$$\sum_{\mathcal{R}} k_{y \to y'} \hat{x}_y (\omega_{y'} - \omega_y) = 0 \quad .$$

To obtain the desired $\alpha \in \mathbb{P}^{\mathcal{R}}$ we let

$$\alpha_{y \to y'} = k_{y \to y'} \hat{x}_y \; , \quad \forall \, y \to y' \in \mathcal{R} \; .$$

Next, we shall suppose that the network is not weakly reversible, and we shall show that there can exist no $\alpha \in \mathbb{P}^{\mathcal{R}}$ that solves (4.12). Suppose that such an α exists. Let $A_\alpha : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ be as in Proposition 4.1:

$$A_\alpha(x) \equiv \sum_{\mathcal{R}} \alpha_{y \to y'} x_y (\omega_{y'} - \omega_y) \; . \tag{4.13}$$

Moreover, let $\bar{x} \in \mathbb{R}^{\mathcal{C}}$ be that vector such that $\bar{x}_y = 1$ for all $y \in \mathcal{C}$. Since α satisfies (4.12) we have from (4.13) that $A_\alpha(\bar{x}) = 0$. Thus, $\bar{x}$ lies in $\ker A_\alpha \cap \mathbb{P}^{\mathcal{C}}$, which contradicts the conclusion of Corollary 4.2. ///

Remark 4.4. In Lecture 6 we shall discuss the notion of complex balancing. This simple idea, introduced into chemical reactor theory by Horn and Jackson [HJ], has surprising and profound uses in the study of the differential equations for reactors with intricate chemistry. It happens that equation (4.12) and Corollary 4.3 have such a natural interpretation in terms of complex balancing that we would do well to give that interpretation here, at least in an informal way.

Consider a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$. For each $y \in \mathcal{C}$ let

$$\mathcal{R}_{y\to} := \{y \to y' \in \mathcal{R} : y' \in \mathcal{C}\}$$

and (4.14)

$$\mathcal{R}_{\to y} := \{y' \to y \in \mathcal{R} : y' \in \mathcal{C}\} .$$

That is, $\mathcal{R}_{y\to}$ [resp., $\mathcal{R}_{\to y}$] is the set of all reactions that have y as the reactant [product] complex. Now let α be an element of $\overline{\mathbb{P}}^{\mathcal{R}}$ (not necessarily strictly positive). The left side of (4.12) can be rearranged to give*

$$\sum_{y \in \mathcal{C}} \Big(\sum_{\mathcal{R}_{\to y}} \alpha_{y' \to y} - \sum_{\mathcal{R}_{y \to}} \alpha_{y \to y'} \Big) \omega_y . \tag{4.15}$$

Thus, α satisfies (4.12) if and only if

$$\sum_{\mathcal{R}_{\to y}} \alpha_{y' \to y} - \sum_{\mathcal{R}_{y \to}} \alpha_{y \to y'} = 0 , \forall y \in \mathcal{C} . \tag{4.16}$$

*If either $\mathcal{R}_{\to y}$ or $\mathcal{R}_{y\to}$ is empty the corresponding sum in (4.15) will be understood to be zero.

Now if, for each $y \to y' \in \mathcal{R}$, we think of $\alpha_{y \to y'}$ as a "current" flowing from complex y to complex y' then, for each $y \in \mathcal{C}$, we can think of the y^{th} component of the vector (4.15) as the net current flowing to complex y from all other complexes. Thus, (4.16) describes a condition wherein, for each complex, the total current flowing to that complex is exactly balanced by the total current flowing away from that complex. In this sense we would say that $\alpha \in \overline{\mathbb{P}}^{\mathcal{R}}$ satisfying (4.16) or, equivalently, (4.12) is complex balanced.

What Corollary (4.3) asserts is that there exists a strictly positive complex balanced α — that is, a complex balanced α in $\mathbb{P}^{\mathcal{R}}$ — if and only if the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is weakly reversible. For what amounts to a more direct proof of the "only if" part (without recourse to Proposition 4.1) see Horn's proof of Theorem 2B in [H3]; his Theorem 4B in the same article gives the "if" part as well.

In Section 4.A. I indicated why the set (4.10) will have some importance for us. Here I denote that set by the symbol Δ' : For a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ let

$$\Delta' := \{\omega_{y'} - \omega_y \in \mathbb{R}^{\mathcal{C}} : y \to y'\} \quad . \tag{4.17}$$

Since $y \to y'$ implies that y and y' are linked $(y \sim y')$ it follows that Δ' is contained in the set

$$\Delta := \{\omega_{y'} - \omega_y \in \mathbb{R}^{\mathcal{C}} : y \sim y'\} \tag{4.18}$$

and that

$$\text{span}(\Delta') \subset \text{span}(\Delta) \tag{4.19}$$

In fact, we have the following:

Lemma 4.4. For a reaction network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ let Δ' and Δ be as in (4.17) and (4.18). Then

$$\text{span}(\Delta') = \text{span}(\Delta) \ . \tag{4.20}$$

Proof. In light of (4.19) it is enough to show that span(Δ) is contained in span(Δ') or, equivalently, that Δ is contained in span(Δ'). Suppose that $\omega_{y'}-\omega_y$ is a member of Δ. Then y' and y are linked, and one of the three possibilities listed in Definition 4.1 must obtain. If $y = y'$, then $\omega_{y'}-\omega_y = 0$, and $\omega_{y'}-\omega_y$ lies in span (Δ'). If y and y' are directly linked ($y \leftrightarrow y'$) then either $y \rightarrow y'$ or $y' \rightarrow y$ so that either $\omega_y-\omega_{y'}$ or $\omega_{y'}-\omega_y$ is a member of Δ'; in either case $\omega_{y'}-\omega_y$ is a member of span(Δ'). If $\mathcal{C}$ contains a sequence $\{y_1,y_2,\ldots,y_k\}$ such that

$$y \leftrightarrow y_1 \leftrightarrow y_2 \leftrightarrow \ldots \leftrightarrow y_k \leftrightarrow y'$$

then, by the argument immediately preceding, the vectors

$$\{\omega_{y'}-\omega_{y_k},\ \omega_{y_k}-\omega_{y_{k-1}},\ldots,\omega_{y_2}-\omega_{y_1},\ \omega_{y_1}-\omega_y\}$$

are all members of span(Δ'). So then is their sum, $\omega_{y'}-\omega_y$. ///

Lemma 4.5. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a reaction network with n complexes and ℓ linkage classes, and let Δ' and Δ be defined as in (4.17) and (4.18). Then

$$\dim[\text{span}(\Delta')] = \dim[\text{span}(\Delta)] = n-\ell \ . \tag{4.21}$$

Proof. By virtue of Lemma 4.5 we need only prove the last equality in (4.21). Let $\{L^1, L^2, \ldots, L^{\ell}\}$ be the linkage classes of the network, and, for $\theta = 1,2,\ldots,\ell$, let

$$\Delta^{\theta} := \{\omega_{y'} - \omega_y \in \mathbb{R}^{\mathcal{C}} : y \in L^{\theta},\ y' \in L^{\theta}\} . \tag{4.22}$$

Then

$$\Delta = \bigcup_{\theta=1}^{\ell} \Delta^{\theta}$$

and

$$\operatorname{span}(\Delta) = \operatorname{span}(\Delta^1) \oplus \operatorname{span}(\Delta^2) \oplus \ldots \oplus \operatorname{span}(\Delta^{\ell}). \tag{4.23}$$

Now let n_θ denote the number of complexes in L^{θ}, and let those complexes be denoted $y_1, y_2, \ldots, y_{n_\theta}$. Then any element of Δ^{θ} can be written as a linear combination of the linearly independent set

$$\{\omega_{y_2} - \omega_{y_1},\ \omega_{y_3} - \omega_{y_1},\ \ldots,\ \omega_{y_{n_\theta}} - \omega_{y_1}\}.$$

Thus, $\dim \operatorname{span}(\Delta^{\theta}) = n_\theta - 1$. From (4.23) it follows that

$$\dim[\operatorname{span}(\Delta)] = \sum_{\theta=1}^{\ell} (n_\theta - 1) = n - \ell . \qquad ///$$

In preparation for our next lemma we recall from Lecture 1 some matters of notation. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with linkage classes $\{L^1, L^2, \ldots, L^{\ell}\}$. Recall that $\omega_{L^\theta} \in \mathbb{R}^{\mathcal{C}}$ is the characteristic function for the set $L^{\theta} \subset \mathcal{C}$. That is, ω_{L^θ} is the vector of $\mathbb{R}^{\mathcal{C}}$ whose y^{th} component is unity for each $y \in L^{\theta}$ and is zero for each $y \notin L^{\theta}$. Recall also that $\mathbb{R}^{\mathcal{C}}$ is endowed with the standard scalar product.

Lemma 4.6. *Let* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *be a reaction network with linkage classes* $\{L^\theta\}_{\theta=1,2,..,\ell}$, *and let* Δ *be defined as in* (4.18). *Then the set*

$$\{\omega_{L^\theta}\}_{\theta=1,2,...,\ell} \subset \mathbb{R}^{\mathcal{C}} \tag{4.24}$$

is a basis for $[\text{span}(\Delta)]^\perp$.

Proof. It is obvious that each element of (4.24) is orthogonal to each element of Δ and, therefore, to each vector of span(Δ). Moreover, the set (4.24) is clearly linearly independent. Since $\dim(\mathbb{R}^{\mathcal{C}}) = n$, where n is the number of complexes in $\mathcal{C}$, it follows from Lemma 4.5 that the dimension of the orthogonal complement of span (Δ) is $n - (n-\ell) = \ell$. Thus, (4.24) is a basis for $[\text{span}(\Delta)]^\perp$. ///

Remark 4.5. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network. From Lemma 4.6 we have that a vector $g \in \mathbb{R}^{\mathcal{C}}$ lies in span(Δ) if and only if

$$g \cdot \omega_{L^\theta} = 0 \ , \ \theta = 1,2,...,\ell \ .$$

That is, g lies in span (Δ) or, equivalently, in span(Δ') if and only if

$$\sum_{y \in L^\theta} g_y = 0 \ , \ \theta = 1,2,...,\ell \ .$$

We are now in a position to state our next corollary of Proposition 4.1. For a network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ it is clear that, for any $k \in \mathbb{P}^{\mathcal{R}}$, the linear transformation A_k takes values in span(Δ) — that is, the image of A_k lies in span(Δ). We shall be interested to know when $\text{im}\, A_k$ is identical to span(Δ).

Corollary 4.6. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network, let k be any element of $\mathbb{P}^{\mathcal{R}}$, and let $A_k : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ be as in Proposition 4.1. Then

$$\text{im}\, A_k = \text{span}(\Delta) \tag{4.25}$$

if and only if each linkage class of the network contains precisely one terminal strong linkage class. In particular, (4.25) holds if the network is weakly reversible.

Proof. Since $\text{im}\, A_k$ is contained in span(Δ) we need only examine circumstances under which the dimensions of these linear subspaces of $\mathbb{R}^{\mathcal{C}}$ are identical. From Lemma 4.5 we have that $\dim \text{span}(\Delta) = n - \ell$, where n is the number of elements in $\mathcal{C}$ and ℓ is the number of linkage classes in the network. Since $\dim (\mathbb{R}^{\mathcal{C}}) = n$, it follows from Proposition 4.1 and the standard theorem relating the dimensions of the domain, kernel and image of a linear transformation that

$$\dim (\text{im}\, A_k) = n - t\ , \tag{4.26}$$

where t is the number of terminal strong linkage classes in the network. Thus,

$$\dim \text{span}(\Delta) - \dim \text{im}\, A_k = t - \ell\ , \tag{4.27}$$

so (4.25) holds if and only if $t = \ell$ — that is, if and only if each linkage class contains precisley one terminal strong linkage class. This condition holds trivially for weakly reversible networks. ///

Remark 4.6. Note that when the graphical condition in Corollary 4.6 is satisfied, the image of A_k is in fact independent of any particular choice of $k \in \mathbb{P}^{\mathcal{R}}$; rather, im A_k depends only on the nature of the linkage classes of the network. To some extent it is this fact that makes networks for which $t = \ell$ (and weakly reversible networks in particular) relatively easy to study. When t exceeds ℓ the location of im A_k in $\mathbb{R}^{\mathcal{C}}$ will generally be influenced by k .

4.C. *Some Interplay of Stoichiometry and Graphical Structure*

The definitions and results recorded in Section 4.B pertained entirely to the graphical structure of a network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$. Our focus was exclusively on the "reacts to" relation $\mathcal{R}$, and "stoichiometry" — that is, the precise nature of the complexes in $\mathcal{C}$ — played a role only insofar as the elements of $\mathcal{C}$ provided names for the vertices of a directed graph. In what follows, however, the complexes of a network will enter our analysis in a more forceful way as we examine some interplay between the network's stoichiometry and its graphical character.

We begin by recalling some definitions from Lecture 2.

Definition 4.6. The reaction vectors for a network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ are the members of the set

$$\{y' - y \in \mathbb{R}^{\mathcal{S}} : y \to y'\}. \tag{4.28}$$

The rank of the network is the rank of its set of reaction vectors. We reserve the symbol s to denote the rank of a network. The stoichiometric subspace for the network is the span of its reaction vectors. We reserve the symbol S to denote the stoichiometric subspace of a network. (Note that $\dim S = s$.)

In the next definition we give official status to the linear transformation Y introduced in Section 4.A.

Definition 4.7. For a reaction network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ the stoichiometric map $Y:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ is that linear transformation defined by its action on the standard basis for $\mathbb{R}^{\mathcal{C}}$ as follows:

$$Y\omega_y = y\ , \quad \forall\, y \in \mathcal{C}\ . \tag{4.29}$$

Remark 4.7. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a reaction network. Since, for any pair $y, y' \in \mathcal{C}$, we have

$$y'-y = Y(\omega_{y'}-\omega_y)\ ,$$

it is clear that the set of reaction vectors for the network is given by the image of the set Δ' (defined in (4.17)) under the map Y. Thus, the stoichiometric subspace for the network is given by the image of span (Δ') under Y. In fact, we have from Lemma 4.4

$$S = Y[\text{span}(\Delta')] = Y[\text{span}(\Delta)]\ . \tag{4.30}$$

Moreover, from Corollary 4.6 and (4.30) we have the following: Let k be any element of $\mathbb{P}^{\mathcal{R}}$, and let $A_k:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ be constructed as in Proposition 4.1. Then, if each linkage class of the network contains precisely one terminal strong linkage class, the stoichiometric subspace is given by

$$S = Y[\text{im } A_k] = \text{im } YA_k \tag{4.31}$$

In particular, (4.31) holds if the network is weakly reversible.*

For future reference we also record the following easy consequence of (4.30): For any reaction network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$

$$S = \text{span}\{y'-y \in \mathbb{R}^{\mathcal{S}} : y \sim y'\}\ . \tag{4.32}$$

---

*For a more extensive discussion of conditions under which (4.31) holds see [FH2].

Now we recall our definition of deficiency:

<u>Definition 4.8.</u> The <u>deficiency</u> (denoted δ) of a reaction network is defined by

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

where n is the number of complexes in the network, ℓ is the number of linkage classes in the network, and s is the rank of the network.

In Section 4.A I indicated why, for a given network, it is worth knowing something about the intersection of the kernel of Y with span (Δ') (or, equivalently, with span(Δ)). Our next proposition ties the deficiency of the network to the dimension of that intersection [F2].

<u>Proposition 4.7. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a reaction network. If $Y:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ is the stoichiometric map for the network, if</u>

$$\Delta := \{\omega_{y'} - \omega_y \in \mathbb{R}^{\mathcal{C}} : y \sim y'\} ,$$

<u>and if δ is the deficiency of the network, then</u>

$$\delta = \dim[\ker Y \cap \mathrm{span}(\Delta)] .$$

<u>In particular, if the deficiency of the network is zero then</u>

$$\ker Y \cap \mathrm{span}(\Delta) = \{0\} .$$

Proof. Let $\bar{Y}$: span(Δ) $\to \mathbb{R}^{\mathcal{S}}$ be the restriction of Y to span(Δ). Then, from the standard theorem relating the dimensions of the domain, kernel, and image of a linear transformation, we have

$$\dim \operatorname{span}(\Delta) = \dim \ker \bar{Y} + \dim \operatorname{im} \bar{Y} \ . \tag{4.36}$$

From Lemma 4.5 we have dim span(Δ) = $n - \ell$. Moreover,

$$\operatorname{im} \bar{Y} = Y[\operatorname{span}(\Delta)] \ ,$$

which, from Remark 4.6, is just S, the stoichiometric subspace of the network. But dim S = s, where s is the rank of the network. Finally,

$$\ker \bar{Y} = \ker Y \cap \operatorname{span}(\Delta) \ .$$

Thus, rearrangement of (4.36) gives

$$\dim[\ker Y \cap \operatorname{span}(\Delta)] = n - \ell - s = \delta. \qquad ///$$

Remark 4.8. We note in passing that Proposition 4.7 ensures that the deficiency of any reaction network is non-negative.

Remark 4.9. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network, and let

$$g = \sum_{y \in \mathcal{C}} g_y \omega_y \tag{4.33}$$

be an element of $\mathbb{R}^{\mathcal{C}}$. In Remark 4.5 we observed that g lies in span(Δ) if and only if

$$\sum_{y \in L^\theta} g_y = 0 \ , \quad \theta = 1,2,\ldots,\ell, \tag{4.34}$$

where $\{L^1, L^2, \ldots, L^\ell\}$ are the linkage classes of the network. If Y is the stoichiometric map for the network then we can operate on both sides of (4.33) to see that g lies in $\ker Y$ if and only if

$$\sum_{y \in \mathcal{C}} g_y y = 0 \ . \tag{4.35}$$

Thus, g lies in $\ker Y \cap \text{span}(\Delta)$ if and only if it satisfies both (4.34) and (4.35). If the deficiency of the network is zero we have from Proposition 4.7 that the only solution to (4.34) and (4.35) is the trivial $g = 0$. If the deficiency of the network is one we have the existence of a non-zero g that solves (4.34) and (4.35), and the only other solutions are scalar multiples of g.

At the beginning of the next lecture we shall want to know when the reaction vectors of a network are such that strictly positive linear combination of them can give the zero vector. That is, we shall want to know when, for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ such that

$$\sum_{\mathcal{R}} \alpha_{y \to y'}(y'-y) = 0 \, .$$

We begin to address this question in our first corollary of Proposition 4.7.

Corollary 4.8. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network. Then $\alpha \in \mathbb{R}^{\mathcal{R}}$ satisfies the equation

$$\sum_{\mathcal{R}} \alpha_{y \to y'}(y'-y) = 0 \tag{4.37}$$

if it satisfies the equation

$$\sum_{\mathcal{R}} \alpha_{y \to y'}(\omega_{y'} - \omega_y) = 0 \, . \tag{4.38}$$

Moreover, if the deficiency of the network is zero then α satisfies (4.37) *only* if it also satisfies (4.38).

Proof. Drawing upon the stoichiometric map for the network, we can rewrite equation (4.37) as follows:

$$Y\left[\sum_{\mathcal{R}} \alpha_{y \to y'}(\omega_{y'} - \omega_y)\right] = 0 \, . \tag{4.39}$$

Thus, if $\alpha \in \mathbb{R}^{\mathcal{R}}$ solves (4.38) it also solves (4.37). To prove the last part of the corollary we suppose that α solves (4.37) and, therefore, (4.39). Since the quantity in brackets on the left side of (4.39) is clearly a member of span (Δ) we must have the inclusion

$$\sum_{\mathcal{R}} \alpha_{y \to y'}(\omega_{y'} - \omega_y) \in \ker Y \cap \operatorname{span}(\Delta) \tag{4.40}$$

If the deficiency of the network is zero then Proposition 4.7 ensures that the set on the right side of (4.40) contains only the zero vector of $\mathbb{R}^{\mathcal{C}}$. Thus, α satisfies (4.38). ///

Corollary 4.8 is stated in terms of α in $\mathbb{R}^{\mathcal{R}}$, not necessarily in $\mathbb{P}^{\mathcal{R}}$ or even $\overline{\mathbb{P}}^{\mathcal{R}}$. Next we focus on strictly positive solutions of (4.37).

Corollary 4.9. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a reaction network of deficiency zero. Then there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ that satisfies

$$\sum_{\mathcal{R}} \alpha_{y \to y'}(y'-y) = 0 \qquad (4.37)$$

if and only if the network is weakly reversible.

Proof. This is an immediate consequence of Corollaries 4.3 and 4.8. ///

Remark 4.10. A network which has a non-zero deficiency may admit a strictly positive solution to (4.37) even if the network is not weakly reversible. For example, the network

$$2A \longrightarrow A + B \longleftarrow 2B$$

is not weakly reversible and has a deficiency of one ($n = 3$, $\ell = 1$, $s = 1$). Equation (4.37) takes the form

$$\alpha_{2A \to A+B}(A+B - 2A) + \alpha_{2B \to A+B}(A+B - 2B) = 0 .$$

A strictly positive solution is given by $\alpha_{2A \to A+B} = 1$, $\alpha_{2B \to A+B} = 1$.

Taken together, Corollaries 4.8 and 4.9 tell us that for all weakly reversible networks of deficiency zero there will exist strictly positive solutions to (4.37) and that all such solutions will also satisfy (4.38). In our next corollary we address the situation for weakly reversible networks of non-zero deficiency.

Corollary 4.10. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a weakly reversible network of non-zero deficiency. Then there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ that satisfies (4.38) and, therefore, (4.37). Moreover, there exists $\bar{\alpha} \in \mathbb{P}^{\mathcal{R}}$ that satisfies (4.37) but not (4.38).

Proof. The existence of $\alpha \in \mathbb{P}^{\mathcal{R}}$ satisfying (4.38) is given by Corollary 4.3. Since the deficiency of the network is non-zero it follows from Proposition 4.7 that there exists a non-zero vector g in

$$\ker Y \cap \operatorname{span}(\Delta) .$$

From Lemma 4.4 we have that $\operatorname{span}(\Delta) = \operatorname{span}(\Delta')$. Consequently, g lies in $\operatorname{span}(\Delta')$ so that there exists $\beta \in \mathbb{R}^{\mathcal{R}}$ satisfying

$$g = \sum_{\mathcal{R}} \beta_{y\to y'}(\omega_{y'}-\omega_y) . \tag{4.41}$$

Now let $\alpha \in \mathbb{P}^{\mathcal{R}}$ solve (4.38) and choose $\lambda \in \mathbb{P}$ to be sufficiently large so that

$$\bar{\alpha} := \beta + \lambda\, \alpha \tag{4.42}$$

is a member of $\mathbb{P}^{\mathcal{R}}$. From (4.41) and (4.38) it follows that

$$g = \sum_{\mathcal{R}} \bar{\alpha}_{y\to y'}(\omega_{y'}-\omega_y) . \tag{4.43}$$

Since g is non-zero, (4.43) ensures that $\bar{\alpha}$ does not satisfy (4.38). To see that $\bar{\alpha}$ satisfies (4.37) we need only recall that g lies in $\ker Y$; acting with Y on both sides of (4.43) we obtain

$$0 = \sum_{\mathcal{R}} \bar{\alpha}_{y\to y'}(y'-y) . \qquad ///$$

Remark 4.11. Corollaries (4.8)-(4.10) lend themselves to interpretation in terms of complex balancing (Remark 4.4). Recall that for a network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ we said that an element $\alpha \in \bar{\mathbb{P}}^{\mathcal{R}}$ is complex balanced if it satisfies (4.38). Our focus on non-negative α in Remark 4.4 was merely intended to facilitate a "physical" interpretation of the complex balancing condition. Henceforth we shall say that any element $\alpha \in \mathbb{R}^{\mathcal{R}}$ (not necessarily non-negative) that satisfies (4.38) is complex balanced. With this in mind, we can then state the following: For a network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$:

(i) All complex balanced $\alpha \in \mathbb{R}^{\mathcal{R}}$ are solutions of (4.37). [Corollary 4.8]

(ii) If the deficiency of the network is zero then all $\alpha \in \mathbb{R}^{\mathcal{R}}$ that solve (4.37) are complex balanced. [Corollary 4.8]

(iii) If the network is not weakly reversible then, regardless of its deficiency, there exists no complex balanced $\alpha \in \mathbb{P}^{\mathcal{R}}$. [Corollary 4.3]

(iv) If the network is not weakly reversible and its deficiency is zero then there exists no $\alpha \in \mathbb{P}^{\mathcal{R}}$ that solves (4.37). [Corollary 4.9]

(v) If the network is weakly reversible then, regardless of its deficiency, there exists a complex balanced $\alpha \in \mathbb{P}^{\mathcal{R}}$ that solves (4.37). [Corollaries 4.8-4.10]

(vi) If the network is weakly reversible and its deficiency is non-zero then there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ that solves (4.37) and is not complex balanced. [Corollary 4.10]

Ideas like these, which turn out to be surprisingly important, were studied in [F2] and [H3].

In Section 4.A I attempted to provide a small amount of motivation for the collection of results we have assembled thus far. There I indicated why for a mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$, it would be helpful to know something, about the nature of $\ker YA_k$, where Y is the stoichiometric map for the network and A_k is the linear transformation constructed as in Proposition 4.1. In fact, Proposition 4.1 was motivated by the idea that $\ker A_k$ is <u>part</u> of $\ker YA_k$. In our next corollary we show that for networks of deficiency zero, $\ker A_k$ is <u>all</u> of $\ker YA_k$.

Corollary 4.11. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network of deficiency zero, and let k be any element of $\mathbb{P}^{\mathcal{R}}$. If $Y: \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ is the stoichiometric map for the network and $A_k: \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ is as in Proposition 4.1 then*

$$\ker Y A_k = \ker A_k \ .$$

Proof. Since $\ker A_k$ is obviously contained in $\ker Y A_k$ we need only show that $\ker Y A_k$ is contained in $\ker A_k$. For $x \in \ker Y A_k$ we have

$$A_k x \in \ker Y \ .$$

Since A_k takes values in span(Δ), where Δ is defined for the network by (4.18), we have in fact the inclusion

$$A_k x \in \ker Y \cap \text{span}(\Delta) \ .$$

Thus, from Proposition 4.7, $A_k x = 0$ so that x is contained in $\ker A_k$, and we have $\ker Y A_k = \ker A_k$. ///

Remark 4.12. Corollary 4.11 tells us that, for a zero deficiency network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, the structure of $\ker Y A_k$ is precisely that given by Proposition 4.1, regardless of the value that $k \in \mathbb{P}^{\mathcal{R}}$ takes. In particular, $\dim \ker Y A_k$ is equal to the number of terminal strong linkage classes in the network. If each linkage class contains precisely one terminal strong linkage class then, obviously, $\dim \ker Y A_k$ is equal to the number of linkage classes. This last statement admits a generalization for networks of arbitrary deficiency:

Corollary 4.12. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network for which each linkage class contains precisely one terminal strong linkage class, and let k be any element of $\mathbb{P}^{\mathcal{R}}$. If Y is the stoichiometric map for the network, if A_k is as in Proposition 4.1, if δ is the deficiency of the network and if ℓ is the number of its linkage classes then

$$\dim(\ker YA_k) = \ell + \delta. \tag{4.44}$$

In particular, (4.44) holds if the network is weakly reversible.

Proof. For the linear transformation $YA_k: \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ we have the standard relationship between the dimensions of the domain, kernel and image. Since $\dim \mathbb{R}^{\mathcal{C}} = n$ (the number of complexes) we have

$$\dim \ker YA_k = n - \dim \operatorname{im} YA_k . \tag{4.45}$$

Because each linkage class contains precisely one terminal strong linkage class we know (Remark 4.7) that $\operatorname{im} YA_k = S$, where S is the stoichiometric subspace of the network. Moreover, $\dim S = s$, where s is the rank of the network. Thus, from (4.45),

$$\begin{aligned} \dim \ker YA_k &= n - s \\ &= \ell + (n - \ell - s) \\ &= \ell + \delta. \end{aligned}$$

///

Remark 4.13. For networks having more terminal strong linkage classes than linkage classes equation (4.44) need not hold. In fact, it need not hold even when the number of linkage classes in (4.44) is replaced by the number of strong terminal linkage classes. For such networks dim ker YA_k may depend on the particular $k \in \mathbb{P}^{\mathcal{R}}$ with which A_k is constructed. Consider, for example, the network

$$2A \longleftarrow A + B \longrightarrow 2B \ , \qquad (4.46)$$

for which there are two terminal strong linkage classes — {2A} and {2B} — and one linkage class, {2A, A+B, 2B}. It is not difficult to show that, for $k_{A+B \to 2A} = k_{A+B \to 2B}$, dim ker $YA_k = 3$ while, for $k_{A+B \to 2A} \neq k_{A+B \to 2B}$, dim ker $YA_k = 2$.

The problem with network (4.46) is that, for at least certain values of k, im YA_k need not coincide with S, the stoichiometric subspace of the network. (Recall that this coincidence played a role in the proof of Corollary 4.12.) An extensive discussion of the relationship between im YA_k and S for networks in general is given in [FH2]. From results contained there it is not difficult to show that, for any network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ and for all $k \in \mathbb{P}^{\mathcal{R}}$, one has

$$\ell + \delta \leq \dim \ker YA_k \leq t + \delta \ , \qquad (4.47)$$

where δ is the deficiency, ℓ is the number of linkage classes, and t is the number of terminal strong linkage classes. Moreover, for <u>all</u> $k \in \mathbb{P}^{\mathcal{R}}$ strict inequality holds in the lower estimate of (4.47) provided that $t - \ell > \delta$ (or, equivalently, $n - t - s < 0$, where n is the number of complexes). Note that for (4.46) $\delta = 1$, $\ell = 1$ and $t = 2$ so that this condition is not satisfied.

4.D. A Proposition Concerning the Nature of Equilibria

Before closing this lecture I shall need one more proposition. Because it is somewhat disconnected from those results we have accumulated so far I should provide some additional motivation for what we are about to do. I begin by recalling some definitions stated in Lecture 2.

Definition 4.9. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a reaction network, and let $S \subset \mathbb{R}^{\mathcal{S}}$ be its stoichiometric subspace. Two vectors $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ and $c' \in \overline{\mathbb{P}}^{\mathcal{S}}$ are stoichiometrically compatible if $c'-c$ lies in S. Stoichiometric compatibility is an equivalence relation that induces a partition of $\overline{\mathbb{P}}^{\mathcal{S}}$ [resp., $\mathbb{P}^{\mathcal{S}}$] into equivalence classes called the stoichiometric compatibility classes [resp., positive stoichiometric compatibility classes] for the network. In particular, the stoichiometric compatibility class containing $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is the set $(c+S) \cap \overline{\mathbb{P}}^{\mathcal{S}}$, and the positive stoichiometric compatibility class containing $c \in \mathbb{P}^{\mathcal{S}}$ is the set $(c+S) \cap \mathbb{P}^{\mathcal{S}}$.

In proving parts of both theorems stated in Lecture 3 I shall have to show that, under certain circumstances, the differential equations for a mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R}, k\}$ admit precisely one equilibrium point in each positive stoichiometric compatibility class. To do this I will show that, under the given circumstances, the set of all positive equilibrium points is identical to the set

$$E: = \{c \in \mathbb{P}^{\mathcal{S}} : \ln c - \ln c^* \in S^{\perp}\}, \tag{4.48}$$

where c^* is a fixed element of $\mathbb{P}^{\mathcal{S}}$, where $S^{\perp}$ is the orthogonal complement (relative to the standard scalar product in $\mathbb{R}^{\mathcal{S}}$) of the stoichiometric subspace for the network, and where $\ln c$ is that vector of $\mathbb{R}^{\mathcal{S}}$ defined by

$$(\ln c)_s = \ln c_s \quad , \quad \forall s \in \mathcal{S} . \tag{4.49}$$

Thus, to show that each positive stoichiometric compatibility class contains precisely one equilibrium it will be useful to know that the set E meets each positive stoichiometric compatibility class in precisely one point.

Uniqueness is easy: Suppose that c' and c are stoichiometrically compatible and are members of E . From stoichiometric compatibility we have that

$$c' - c \in S \, , \tag{4.50}$$

and, from (4.48), it follows easily that

$$\ln c' - \ln c \in S^{\perp} \, . \tag{4.51}$$

Thus, from (4.50) and (4.51) we have

$$0 = (c'-c) \cdot (\ln c' - \ln c) = \sum_{s \in \mathcal{S}} (c'_s - c_s)(\ln c'_s - \ln c_s) \, . \tag{4.52}$$

Since the function $\ln: \mathbb{P} \to \mathbb{R}$ is strictly monotonically increasing, (4.52) can hold only if, for all $s \in \mathcal{S}$, $c'_s = c_s$ — that is, only if $c' = c$.

It is somewhat more difficult to show that each positive stoichiometric compatibility class in fact meets E. The argument I shall give is essentially a variation of that given by Horn and Jackson [HJ, Section 4]. The result we seek will emerge as a consequence of our next proposition. In preparation for its statement we review some matters of notation. If x is a member of $\mathbb{R}^{\mathcal{S}}$, then $e^x \in \mathbb{P}^{\mathcal{S}}$ is defined by

$$(e^x)_s = e^{x_s} \, , \quad \forall s \in \mathcal{S} \, .$$

If x and y are members of $\mathbb{R}^{\mathcal{S}}$, then $x\,y \in \mathbb{R}^{\mathcal{S}}$ is defined by

$$(xy)_s = x_s y_s \ , \quad \forall\, s \in \mathcal{S} \ .$$

In particular, for $a \in \mathbb{R}^{\mathcal{S}}$ and $x \in \mathbb{R}^{\mathcal{S}}$ we have

$$(a\,e^x)_s = a_s e^{x_s} \ , \quad \forall\, s \in \mathcal{S} \ .$$

In Proposition 4.13 $\mathbb{R}^{\mathcal{S}}$ is endowed with the standard scalar product.

Proposition 4.13. Let $\mathcal{S}$ be any finite set, let $\mathbb{R}^{\mathcal{S}}$ be the vector space generated by $\mathcal{S}$, let S be a linear subspace of $\mathbb{R}^{\mathcal{S}}$, and let a and b be elements of $\mathbb{P}^{\mathcal{S}}$. There exists a (unique) vector $\mu \in S^{\perp}$ such that

$$a\,e^{\mu} - b$$

is an element of S.

Proof. Let $\phi\colon \mathbb{R}^{\mathcal{S}} \to \mathbb{R}$ be defined by

$$\phi(x) := \sum_{s \in \mathcal{S}} (a_s\, e^{x_s} - b_s x_s) \ . \tag{4.53}$$

Straightforward computation shows that the gradient of ϕ at x is given

$$\nabla\phi(x) = a\,e^x - b \tag{4.54}$$

and that the Hessian of ϕ at x, $H(x)\colon \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$, is given by

$$H(x)\gamma \equiv (a\,e^x)\gamma \ . \tag{4.55}$$

Moreover, for each $x \in \mathbb{R}^{\mathcal{S}}$, $H(x)$ is positive-definite: For all non-zero $\gamma \in \mathbb{R}^{\mathcal{S}}$

$$\gamma \cdot H(x)\gamma = \gamma \cdot a e^{x}\gamma = \sum_{s \in \mathcal{S}} a_s e^{x_s}(\gamma_s)^2 > 0 . \tag{4.56}$$

Thus, the function ϕ is strictly convex.

Next we wish to show that, for any non-zero $x \in \mathbb{R}^{\mathcal{S}}$,

$$\lim_{\alpha \to \infty} \phi(\alpha x) = \infty . \tag{4.57}$$

Note that

$$\phi(\alpha x) = \sum_{s \in \mathcal{S}} (a_s e^{\alpha x_s} - \alpha\, b_s x_s) \tag{4.58}$$

Note also that, for $x_s \neq 0$, the positivity of a_s and b_s give

$$\lim_{\alpha \to \infty} (a_s\, e^{\alpha x_s} - \alpha\, b_s x_s) = \infty , \tag{4.59}$$

while for $x_s = 0$ we have

$$(a_s\, e^{\alpha x_s} - \alpha\, b_s x_s) = a_s ,\ \forall\, \alpha \in \mathbb{R} . \tag{4.60}$$

Thus, for $x \neq 0$, (4.58)-(4.60) imply (4.57).

Now let $\bar{\phi}: S^{\perp} \to \mathbb{R}$ be the restriction of ϕ to $S^{\perp}$. Since ϕ is continuous and convex so is $\bar{\phi}$. Thus, the continuity of $\bar{\phi}$ and a standard result for convex functions give that the set

$$C := \{x \in S^{\perp} : \bar{\phi}(x) \leq \bar{\phi}(0)\} \tag{4.61}$$

is closed, convex (and obviously contains the zero vector). Moreover, it follows from (4.57) that C contains no half-line with end-point 0. Since, in a finite-dimensional vector space, every unbounded closed convex set containing 0 must contain a half-line with end-point 0 — see [SW], p.105 — it follows that C is bounded and therefore compact.

Thus, there exists $\mu \in C$ such that

$$\bar{\phi}(\mu) \leq \bar{\phi}(x) \ , \ \forall \, x \in C \ . \tag{4.62}$$

In fact, from the definition of C we have

$$\bar{\phi}(\mu) \leq \bar{\phi}(x) \ , \ \forall \, x \in S^{\perp} \ . \tag{4.63}$$

Thus, for all $\gamma \in S^{\perp}$,

$$\begin{aligned} 0 &= \frac{d}{d\theta} \bar{\phi}(\mu + \theta\gamma) \Big|_{\theta=0} \\ &= \frac{d}{d\theta} \phi(\mu + \theta\gamma) \Big|_{\theta=0} \\ &= \nabla\phi(\mu) \cdot \gamma \end{aligned}$$

It follows that $\nabla\phi(\mu)$ must lie in S so that, from (4.54), we have the inclusion

$$a \, e^{\mu} - b \in S \ . \tag{4.64}$$

Thus, $\mu \in S^{\perp}$ satisfies the requirement of the proposition.

To prove uniqueness we presume that $\mu' \in S^{\perp}$ also satisfies the inclusion

$$a \, e^{\mu'} - b \in S \ . \tag{4.65}$$

From (4.64) and (4.65) we have

$$a(e^{\mu'} - e^{\mu}) \in S ,$$

and, since $\mu'-\mu$ lies in $S^{\perp}$, we must have

$$0 = (\mu'-\mu) \cdot [a(e^{\mu'}-e^{\mu})] = \sum_{s \in \mathcal{S}} a_s(\mu'_s-\mu_s)(e^{\mu'_s}-e^{\mu_s}). \tag{4.66}$$

Since each a_s is positive and since the exponential function is strictly monotonically increasing, (4.66) can hold only if, for all $s \in \mathcal{S}$, $\mu'_s = \mu_s$ — that is, only if $\mu' = \mu$. ///

Remark 4.14. There is an interesting observation that can be made here. With $\mathbb{R}^{\mathcal{S}}$ and S as in Proposition 4.13 it is a standard result in linear algebra that any $b \in \mathbb{R}^{\mathcal{S}}$ has a unique representation

$$b = x_1 + x_2 , \; x_1 \in S^{\perp} , \; x_2 \in S .$$

Taking $a_s = 1$ for all $s \in \mathcal{S}$ in Proposition 4.13, we obtain a similar (but deeper) result: Any positive $b \in \mathbb{R}^{\mathcal{S}}$ — that is, any $b \in \mathbb{P}^{\mathcal{S}}$ — admits a unique representation

$$b = e^{\mu_1} + \mu_2 \;\; , \;\; \mu_1 \in S^{\perp}, \mu_2 \in S .$$

Corollary 4.14. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with stoichiometric subspace $S \subset \mathbb{R}^{\mathcal{S}}$. For any $c^* \in \mathbb{P}^{\mathcal{S}}$ the set

$$E: = \{c \in \mathbb{P}^{\mathcal{S}} : \ln c - \ln c^* \in S^{\perp}\}$$

meets each positive stoichiometric compatibility class in precisely one point.

Proof. Let p be an arbitrary element of $\mathbb{P}^{\mathcal{S}}$. We shall show that E meets the positive stoichiometric compatibility class containing p in precisely one point. That there can be at most one such point was proved in the discussion prior to the statement of Proposition 4.13. To prove the existence of such a point we note that Proposition 4.13 ensures the existence of $\mu \in S^{\perp}$ such that

$$c^* e^{\mu} - p \in S . \tag{4.67}$$

Now let $c \in \mathbb{P}^{\mathcal{S}}$ be defined by

$$c: = c^* e^{\mu} . \tag{4.68}$$

From (4.67), (4.68), and Definition 4.9 it is clear that c lies in the positive stoichiometric compatibility class containing p. Taking logarithms of both sides of (4.68) we obtain

$$\ln c - \ln c^* = \mu \in S^{\perp} \tag{4.69}$$

Thus, c lies in E as well. ///

Having assembled a reasonable "bag of tools", we turn now to proof of the Deficiency Zero Theorem.

Taken from a scanned copy of "Lectures on Chemical Reaction Networks," given by Martin Feinberg at the Mathematics Research Center, University of Wisconsin-Madison in the autumn of 1979.

LECTURE 5: PROOF OF THE DEFICIENCY ZERO THEOREM

Although our proof of the Deficiency Zero Theorem will be fairly clean, the course we'll take is a little indirect. Readers will notice that, in a few places, we study networks of arbitrary deficiency, showing that, when special conditions prevail, the corresponding differential equations have exceptionally nice properties. Only then do we prove that those special conditions prevail automatically for networks of deficiency zero. In this way we can begin to accumulate certain results which, while especially pertinent to deficiency zero networks, have some bearing on networks of higher deficiency as well. These results will ultimately find use in subsequent lectures.

Recall that, for a reaction system $\{\mathcal{S},\mathcal{C},\mathcal{R},\mathcal{K}\}$, the induced (vector) differential equation is

$$\dot{c} = \sum_{\mathcal{R}} \mathcal{K}_{y\to y'}(c)(y'-y) \ . \qquad (5.1)$$

In particular, for a mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ the (vector) differential equation is

$$\dot{c} = \sum_{\mathcal{R}} k_{y\to y'}\, c^{y}(y'-y) \ , \qquad (5.2)$$

where

$$c^{y} := \prod_{s\in\mathcal{S}} c_s^{y_s} \ . \qquad (5.3)$$

For the convenience of the reader we repeat the Deficiency Zero Theorem here:

Theorem 5.1 (The Deficiency Zero Theorem). Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be any reaction network of deficiency zero.

(i) If the network is not weakly reversible then, for arbitrary kinetics $\mathcal{K}$, the differential equations for the reaction system $\{\mathcal{S},\mathcal{C},\mathcal{R},\mathcal{K}\}$ cannot admit a positive equilibrium (i.e., an equilibrium in $\mathbb{P}^{\mathcal{S}}$).

(ii) If the network is not weakly reversible then, for arbitrary kinetics $\mathcal{K}$, the differential equations for the reaction system $\{\mathcal{S},\mathcal{C},\mathcal{R},\mathcal{K}\}$ cannot admit a cyclic composition trajectory containing a positive composition (i.e., a point in $\mathbb{P}^{\mathcal{S}}$).

(iii) If the network is weakly reversible then, for any mass action kinetics $k \in \mathbb{P}^{\mathcal{R}}$, the differential equations for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ have the following properties: There exists within each positive stoichiometric compatibility class precisely one equilibrium; that equilibrium is asymptotically stable; and there cannot exist a nontrivial cyclic composition trajectory in $\mathbb{P}^{\mathcal{S}}$.

Remark 5.1. Once we have proved Theorem 5.1 in Section 5.A and make comments on the proof in Section 5.B we shall, in Section 5.C, indicate how the statement of the theorem can be sharpened.

5.A. *Proof*

Our proof of Theorem 5.1 will be divided into three parts. First we shall prove the relatively easy parts (i) and (ii). Second, we shall prove part (iii) on the basis of the assumption that the differential equations for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ admit a positive equilibrium (not necessarily one in each positive stoichiometric compatibility class). Finally, we will prove that the differential equations do indeed admit a positive equilibrium.

5.A.1 *Proof of parts (i) and (ii).*

We begin with the following lemma (for networks of arbitrary deficiency endowed with arbitrary kinetics).

Lemma 5.2. The differential equations for a reaction system $\{\mathcal{S},\mathcal{C},\mathcal{R},\mathcal{K}\}$ admit an equilibrium in $\mathbb{P}^{\mathcal{S}}$ or a cyclic trajectory containing a point in $\mathbb{P}^{\mathcal{S}}$ only if there exists $\alpha \in \mathbb{P}^{\mathcal{R}}$ that satisfies the equation

$$\sum_{\mathcal{R}} \alpha_{y \to y'}(y'-y) = 0 . \tag{5.4}$$

Proof. Suppose that $c^* \in \mathbb{P}^{\mathcal{S}}$ is an equilibrium for (5.1). Then

$$\sum_{\mathcal{R}} \mathcal{K}_{y \to y'}(c^*)(y'-y) = 0 . \tag{5.5}$$

Since $\operatorname{supp} c^* = \mathcal{S}$ we have

$$\operatorname{supp} y \subset \operatorname{supp} c^* \quad , \quad \forall y \in \mathcal{C} . \tag{5.6}$$

Thus, from our definition of a kinetics (Lecture 2) we have

$$\mathcal{K}_{y \to y'}(c^*) > 0 \quad , \quad \forall \, y \to y' \in \mathcal{R} \; . \tag{5.7}$$

Let $\alpha \in \mathbb{P}^{\mathcal{R}}$ be defined by

$$\alpha_{y \to y'} := \mathcal{K}_{y \to y'}(c^*) \quad , \quad \forall \, y \to y' \in \mathcal{R} \; . \tag{5.8}$$

From (5.5) it follows that α satisfies (5.4).

Now let $\bar{c}:[0,T] \to \bar{\mathbb{P}}$ be a solution of (5.1) such that $\bar{c}(0) = \bar{c}(T)$. Since, from the definition of a kinetics, each of the rate functions $\mathcal{K}_{y \to y'}(\cdot)$ takes non-negative values and is continuous, it follows that, for each $y \to y' \in \mathcal{R}$, the composite function $\mathcal{K}_{y \to y'}(\bar{c}(\cdot))$ takes non-negative values and is continuous. Integrating (5.1) with respect to time over the interval $[0,T]$ we obtain

$$0 = \sum_{\mathcal{R}} \left[\int_0^T \mathcal{K}_{y \to y'}(\bar{c}(t))dt \right](y'-y) \; . \tag{5.9}$$

Note that each of the integrals in (5.9) is non-negative. Now suppose that there exists $t_1 \in [0,T]$ such that $\bar{c}(t_1)$ is a member of $\mathbb{P}^{\mathcal{S}}$. Then, from an argument virtually identical to that given at the beginning of this proof, we have

$$\mathcal{K}_{y \to y'}(\bar{c}(t_1)) > 0 \quad , \quad \forall \, y \to y' \in \mathcal{R} . \tag{5.10}$$

This and the continuity of the $\mathcal{K}_{y \to y'}(\bar{c}(\cdot))$ ensure that each of the integrals in (5.9) is in fact positive. Letting $\alpha \in \mathbb{P}^{\mathcal{R}}$ be defined by

$$\alpha_{y \to y'} := \int_0^T \mathcal{K}_{y \to y'}(\bar{c}(t))dt \; , \tag{5.11}$$

we see from (5.9) that α satisfies (5.4). ///

To complete the proof of parts (i) and (ii) of Theorem 5.1 we merely combine Lemma 5.2 with Corollary 4.9, which asserts that if $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ is a deficiency zero network which is not weakly reversible then there can exist no $\alpha \in \mathbb{P}^{\mathcal{R}}$ that satisfies (5.4). ///

5.A.2. *Proof of part (iii), given the existence of an equilibrium in $\mathbb{P}^{\mathcal{S}}$.*

At the outset we will focus on a fixed mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R}, k\}$ without supposing that the network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ is of deficiency zero. Recall from Lecture 2 that the species formation rate function $f\colon \overline{\mathbb{P}}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$ for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ is given by

$$f(c) \equiv \sum_{\mathcal{R}} k_{y \to y'} c^{y}(y'-y) \ . \tag{5.12}$$

Thus, the differential equation (5.2) is just

$$\dot{c} = f(c) \ . \tag{5.13}$$

Recall also from Lecture 4 (Section 4.A) that the species formation rate function can be cast in the form

$$f(c) \equiv Y A_k \Psi(c) \quad , \tag{5.14}$$

where $Y\colon \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ is the stoichiometric map for the network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$, where $A_k\colon \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ is constructed for the mass action kinetics $k \in \mathbb{P}^{\mathcal{R}}$ as in Proposition 4.1, and where $\Psi\colon \overline{\mathbb{P}}^{\mathcal{S}} \to \overline{\mathbb{P}}^{\mathcal{C}}$ is given by

$$\Psi(c) \equiv \sum_{y \in \mathcal{C}} c^{y} \omega_{y} \ , \tag{5.15}$$

$\{\omega_y \in \mathbb{R}^{\mathcal{C}} : y \in \mathcal{C}\}$ denoting the standard basis for $\mathbb{R}^{\mathcal{C}}$.

If $c^* \in \overline{\mathbb{P}}^{\mathscr{S}}$ is an equilibrium of (5.13) — that is, if $f(c^*) = 0$ — then, from (5.14), we must have the inclusion

$$\Psi(c^*) \in \ker Y A_k \ .$$

It *may* happen that we have in fact the stronger inclusion

$$\Psi(c^*) \in \ker A_k \ . \qquad (5.16)$$

Now if there exists a positive equilibrium, $c^* \in \mathbb{P}^{\mathscr{S}}$, satisfying the special condition (5.16) then, surprisingly enough, one can say quite a bit about the quality of solutions to (5.13). This was first observed by Horn and Jackson [HJ], but some of the arguments I give [F3] are rather different from theirs.

Throughout our discussion it will be understood that the functions f, Y, A_k and Ψ are constructed as above for the fixed mass action system $\{\mathscr{S}, \mathscr{C}, \mathscr{R}, k\}$ under consideration. Logarithms of positive vectors are taken component-wise as in Lecture 1. Many of our results will derive from the following proposition:

Proposition 5.3. Let $\{\mathscr{S}, \mathscr{C}, \mathscr{R}, k\}$ *be a mass action system with stoichiometric subspace* $S \subset \mathbb{R}^{\mathscr{S}}$ *and species formation rate function* $f: \overline{\mathbb{P}}^{\mathscr{S}} \to \mathbb{R}^{\mathscr{S}}$. *If there exists* $c^* \in \mathbb{P}^{\mathscr{S}}$ *such that*

$$A_k \Psi(c^*) = 0 \ , \qquad (5.17)$$

then

$$f(c) \cdot (\ln c - \ln c^*) \leq 0 \ , \quad \forall c \in \mathbb{P}^{\mathscr{S}} \ . \qquad (5.18)$$

Moreover, for $c \in \mathbb{P}^{\mathscr{S}}$ *the following are equivalent:*

(i) $f(c) \cdot (\ln c - \ln c^*) = 0$

(ii) $\ln c - \ln c^*$ *lies in* $S^{\perp}$

(iii) $A_k \Psi(c) = 0$

(iv) $f(c) = 0.$

Remark 5.2. Since c^* in Proposition 5.3 is strictly positive ($c^* \in \mathbb{P}^{\mathcal{S}}$) it follows that $\Psi(c^*)$ is strictly positive ($\Psi(c^*) \in \mathbb{P}^{\mathcal{C}}$), whereupon (5.17) requires that A_k have a strictly positive vector in its kernel. Thus, from Corollary 4.2, the hypothesis of Proposition 5.3 can be satisfied only if the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is weakly reversible.

Proof of Proposition 5.3. Let $\mu : \mathbb{P}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$ be defined by

$$\mu(c) := \ln c - \ln c^* \ . \tag{5.19}$$

From (5.3) it is easy to confirm that, for $c \in \mathbb{P}^{\mathcal{S}}$,

$$c^y = (c^*)^y e^{y \cdot \mu(c)} \ , \quad \forall\, y \in \mathcal{C} \ . \tag{5.20}$$

Therefore, from (5.12) and (5.20) we have for all $c \in \mathbb{P}^{\mathcal{S}}$

$$f(c) = \sum_{\mathcal{R}} k_{y \to y'} (c^*)^y e^{y \cdot \mu(c)} (y' - y) \ . \tag{5.21}$$

From (5.19) and (5.21) we have for all $c \in \mathbb{P}^{\mathcal{S}}$

$$f(c) \cdot (\ln c - \ln c^*) = \sum_{\mathcal{R}} k_{y \to y'} (c^*)^y e^{y \cdot \mu(c)} (y' \cdot \mu(c) - y \cdot \mu(c)) \ . \tag{5.22}$$

Now the exponential function has the following well-known property: For any α' and α in $\mathbb{R}$

$$e^{\alpha}(\alpha' - \alpha) \le e^{\alpha'} - e^{\alpha} \tag{5.23}$$

with equality holding if and only if $\alpha' = \alpha$. Using the estimate (5.23) termwise in (5.22) we obtain

$$f(c) \cdot (\ln c - \ln c^*) \leq \sum_{\mathcal{R}} k_{y \to y'} (c^*)^y (e^{y' \cdot \mu(c)} - e^{y \cdot \mu(c)}) \ , \ \forall c \in \mathbb{P}^{\mathcal{S}} \tag{5.24}$$

with equality holding if and only if

$$\mu(c) \cdot (y'-y) = 0 \ , \quad \forall \ y \to y' \in \mathcal{R} \ . \tag{5.25}$$

Using the orthonormality of the standard basis for $\mathbb{R}^{\mathcal{C}}$, we can rewrite the right side of (5.24) as

$$[\sum_{\mathcal{R}} k_{y \to y'} (c^*)^y (\omega_{y'} - \omega_y)] \cdot \sum_{y'' \in \mathcal{C}} e^{y'' \cdot \mu(c)} \omega_{y''} \tag{5.26}$$

But the term in brackets in (5.26) is just $A_k \Psi(c^*)$ which, by hypothesis, is just the zero vector of $\mathbb{R}^{\mathcal{C}}$. Thus, the right side of (5.24) vanishes for all $c \in \mathbb{P}^{\mathcal{S}}$ so that (5.24) is equivalent to (5.18).

To show that (i) and (ii) are equivalent we note that equality holds in (5.24) and, therefore, in (5.18) if and only if $c \in \mathbb{P}^{\mathcal{S}}$ satisfies (5.25). Since the stoichiometric subspace for the network is just the span of its reaction vectors, (5.25) is equivalent to the inclusion

$$\ln c - \ln c^* = \mu(c) \in S^{\perp} \ . \tag{5.27}$$

Next we show that (ii) implies (iii). From Remark 5.2 we know that the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is weakly reversible so that its terminal strong linkage classes coincide with its linkage classes, which we denote $L^1, L^2, \ldots, L^{\ell}$. Moreover, we have from Proposition 4.1 the existence of a basis $\{x^1, x^2, \ldots, x^{\ell}\} \subset \overline{\mathbb{P}}^{\mathcal{C}}$ for $\ker A_k$ such that

$$\operatorname{supp} x^{\theta} = L^{\theta} \ , \quad \theta = 1, 2, \ldots, \ell \ . \tag{5.28}$$

Thus, from (5.17), $\Psi(c^*) \in \mathbb{P}^{\mathcal{C}}$ has a representation of the following kind: There exist (positive) numbers $\lambda_1,\ldots,\lambda_\ell$ such that

$$\begin{aligned}\Psi(c^*) &= \sum_{y\in\mathcal{C}} (c^*)^y \omega_y \\ &= \sum_{\theta=1}^{\ell} \Big(\sum_{y\in L^\theta} (c^*)^y \omega_y\Big) \\ &= \sum_{\theta=1}^{\ell} \lambda_\theta x^\theta \ . \end{aligned} \tag{5.29}$$

The second equation in (5.29) follows from the fact that $\mathcal{C}$ is the disjoint union of the linkage classes. From (5.28) and the third equation of (5.29) it follows easily that

$$\sum_{y\in L^\theta} (c^*)^y \omega_y = \lambda_\theta x^\theta \ , \quad \theta = 1,2,\ldots,\ell \tag{5.30}$$

This is to say that the set

$$\{ \sum_{y\in L^\theta} (c^*)^y \omega_y \in \overline{\mathbb{P}}^{\mathcal{C}} : \theta = 1,2,\ldots,\ell \} \tag{5.31}$$

is also a basis for $\ker A_k$. Now suppose that $c \in \mathbb{P}^{\mathcal{S}}$ is such that (ii) holds or, equivalently, that

$$\mu(c) \in S^{\perp} \ , \tag{5.32}$$

where $\mu(c)$ is as in (5.19). From (5.32) and (4.32) we have that $y'\cdot\mu(c) = y\cdot\mu(c)$ whenever y' and y are linked. That is, there exist numbers $\xi_1,\ldots,\xi_\ell$ such that

$$y \cdot \mu(c) = \xi_\theta \quad , \quad \forall\, y \in L^\theta \ . \tag{5.33}$$

From (5.15) and (5.20) we have

$$\begin{aligned}
\Psi(c) &= \sum_{y \in \mathcal{C}} c^y \omega_y \\
&= \sum_{y \in \mathcal{C}} (c^*)^y \, e^{y \cdot \mu(c)} \, \omega_y \\
&= \sum_{\theta=1}^{\ell} \Big(\sum_{y \in L^\theta} (c^*)^y \, e^{y \cdot \mu(c)} \, \omega_y \Big) \\
&= \sum_{\theta=1}^{\ell} e^{\xi_\theta} \Big(\sum_{y \in L^\theta} (c^*)^y \, \omega_y \Big) \ .
\end{aligned} \tag{5.34}$$

Since (5.31) is a basis for $\ker A_k$ it follows from (5.34) that $A_k \Psi(c) = 0$.

That (iii) implies (iv) follows immediately from (5.14). That (iv) implies (i) is trivial. ///

Corollary 5.4. Under the hypothesis of Proposition 5.3 the differential equations for the mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ admit precisely one equilibrium in each positive stoichiometric compatibility class.

Proof. From the equivalence of (ii) and (iv) in Proposition 5.3 the set of equilibria in $\mathbb{P}^{\mathcal{S}}$ coincides with the set

$$E = \{c \in \mathbb{P}^{\mathcal{S}} : \ln c - \ln c^* \in S^\perp\} \ . \tag{5.35}$$

From Corollary 4.14 this set meets each positive stoichiometric compatibility class in precisely one point. ///

Remark 5.4. Under the hypothesis of Proposition 5.3 we have, from the equivalence of (iii) and (iv), that every equilibrium in $\mathbb{P}^{\mathcal{S}}$ satisfies (iii). Thus, any positive equilibrium satisfies the condition imposed on c^* in the hypothesis of Proposition 5.3, and any of them might have served as c^* in the statement of the proposition. With this in mind we can, when the hypothesis of Proposition 5.3 is satisfied, think of c^* as a fixed but arbitrary positive equilibrium for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$.

Remark 5.5. Under the hypothesis of Proposition 5.3 we have from Corollary 5.4 a great deal of information about the nature of equilibrium points for the differential equations of the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$. Now we would like dynamical information as well. We shall proceed by means of Liapunov functions.

For fixed $c^* \in \mathbb{P}^{\mathcal{S}}$ let $h:\mathbb{P}^{\mathcal{S}} \to \mathbb{R}$ be defined by

$$h(c) \equiv \sum_{s\in\mathcal{S}} [c_s(\ln c_s - \ln c_s^* - 1) + c_s^*] \ . \tag{5.36}$$

Clearly,

$$h(c^*) = 0 \ . \tag{5.37}$$

Moreover, from the strict concavity of the logarithm function we have, for each $s \in \mathcal{S}$ and each $c_s > 0$,

$$\ln c_s - \ln c_s^* \geq \frac{1}{c_s}(c_s - c_s^*) \tag{5.38}$$

with equality holding if and only if $c_s = c_s^*$. From this we obtain

$$h(c) > 0 \quad , \quad c \neq c^* \ . \tag{5.39}$$

Moreover, straightforward computation gives

$$\nabla h(c) \equiv \ln c - \ln c^* \; . \tag{5.40}$$

From (5.40) the Hessian of h at $c \in \mathbb{P}^{\mathcal{S}}$, $G(c): \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$, is given by

$$G(c)\gamma = \frac{\gamma}{c} \; , \quad \forall \gamma \in \mathbb{R}^{\mathcal{S}} \; , \tag{5.41}$$

where $(\gamma/c)_s = \gamma_s/c_s$. Note that for all $c \in \mathbb{P}^{\mathcal{S}}$ and all non-zero $\gamma \in \mathbb{R}^{\mathcal{S}}$

$$\gamma \cdot G(c)\gamma = \sum_{s \in \mathcal{S}} \gamma_s^{\,2}/c_s > 0 \; . \tag{5.42}$$

Thus, the Hessian of h is positive-definite at each $c \in \mathbb{P}^{\mathcal{S}}$ so that h is strictly convex.

We are now in a position to state our next corollary of Proposition 5.3.

Corollary 5.5. *Under the hypothesis of Proposition 5.3 and with* c^* *as in that proposition, let* $h: \mathbb{P}^{\mathcal{S}} \to \mathbb{R}$ *be as in (5.36). Then, for all* $c \in \mathbb{P}^{\mathcal{S}}$,

$$\nabla h(c) \cdot f(c) \le 0 \tag{5.43}$$

with equality holding if and only if $f(c) = 0$.

Proof. This is an immediate consequence of (5.40) and Proposition 5.3. ///

Remark 5.6. Suppose that the hypothesis of Proposition 5.3 holds, that c^* is as in that proposition and that $h(\cdot)$ is as in (5.36). In rough terms Corollary 5.5 tells us that, for any positive solution $c(\cdot)$ of (5.2), the function $h(c(\cdot))$ is non-increasing along that solution and is decreasing except at equilibrium points. That is,

$$\begin{aligned}\frac{d}{dt} h(c(t)) &= \nabla h(c(t)) \cdot \dot{c}(t) \\ &= \nabla h(c(t)) \cdot f(c(t)) \\ &\leq 0 \qquad (5.44)\end{aligned}$$

with equality holding if and only if $\dot{c}(t) = f(c(t)) = 0$.

Corollary 5.6. Under the hypothesis of Propositon 5.3 the differential equations for the mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ admit no nontrivial cyclic composition trajectories in $\mathbb{P}^{\mathcal{S}}$.

Proof. Suppose that $c:[0,T] \to \mathbb{P}^{\mathcal{S}}$ is a nonconstant solution of (5.2) such that $c(0) = c(T)$. With c^* as in Proposition 5.3 let $h:\mathbb{P}^{\mathcal{S}} \to \mathbb{R}$ be as in (5.36). Then

$$\begin{aligned}h(c(T)) - h(c(0)) &= \int_0^T \frac{d}{dt} h(c(t))dt \\ &= \int_0^T \nabla h(c(t)) \cdot f(c(t))dt \qquad (5.45)\end{aligned}$$

From Corollary 5.5 we have that the integrand is non-positive and, since the solution is nonconstant, that the integrand is negative at some $t \in [0,T]$. This and the continuity of $\nabla h(c(\cdot)) \cdot f(c(\cdot))$ give us

$$h(c(T)) < h(c(0)). \qquad (5.46)$$

But this contradicts the supposition that $c(T) = c(0)$. ///

Corollary 5.7. Under the hypothesis of Proposition 5.3 each equilibrium in $\mathbb{P}^{\mathcal{S}}$ for the differential equations of the system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ is asymptotically stable (relative to initial conditions in the positive stoichiometric compatibility class containing that equilibrium.)

Proof. Let $c^* \in \mathbb{P}^{\mathcal{S}}$ be as in Proposition 5.3. Note that c^* is an equilibrium and is the only equilibrium in the positive stoichiometric compatibility class containing c^* (Corollary 5.4). Recall (Lecture 2) that composition trajectories having a point in the stoichiometric compatibility class containing c^* lie entirely within it. Note also that the positive stoichiometric compatibility class containing c^* is open in the relative topology on the stoichiometric compatibility class containing c^*. Now let $h: \mathbb{P}^{\mathcal{S}} \to \mathbb{R}$ be as in (5.36), and let $\bar{h}$ be the restriction of h to the positive stoichiometric compatibility class containing c^*. From (5.37), (5.39), Corollary 5.5 and Remark 5.6 it follows that $\bar{h}$ is a strict Liapunov function for c^* on the positive stoichiometric compatibility class containing it. (See, for example, Hirsch and Smale [HS].) Thus, c^* is asymptotically stable relative to initial conditions in its positive stoichiometric compatibility class. From Remark 5.4 it follows that the same argument can be made for any equilibrium in $\mathbb{P}^{\mathcal{S}}$. ///

Remark 5.7. From Corollaries 5.4, 5.6, and 5.7 we now have that any mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ which admits a positive equilibrium c^* satisfying

$$A_k \Psi(c^*) = 0 \tag{5.47}$$

will have the property that its differential equations have all the qualities described in part (iii) of the Deficiency Zero Theorem. Thus far in Section 5.A.2 we have placed no restriction on the deficiency of the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ under discussion. The connection with deficiency zero networks comes from the following:

Proposition 5.8. Suppose that the differential equations for a mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ admit an equilibrium in $\mathbb{P}^{\mathcal{S}}$. If the network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ has deficiency zero then the hypothesis of Proposition 5.3 is satisfied.

Proof. Let $c^* \in \mathbb{P}^{\mathcal{S}}$ be an equilibrium. Then, from the discussion preceding Proposition 5.3, we must have

$$\Psi(c^*) \in \ker Y A_k \ . \tag{5.48}$$

Since the network has deficiency zero Corollary 4.11 gives

$$\ker Y A_k = \ker A_k \tag{5.49}$$

Thus, (5.47) holds. ///

Remark 5.8. Let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be a network of deficiency zero. For any $k \in \mathbb{P}^{\mathcal{R}}$, Remark 5.7 and Proposition 5.8 tell us that the differential equations for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ will have all the properties described in Theorem 5.1, part (iii), so long as those differential equations admit a positive equilibrium. From part (i) of Theorem 5.1 (or, alternatively, from Remark 5.2 and Proposition 5.8) we know that no such equilibrium can exist if the network is not weakly reversible. If, however, the network is weakly reversible and we can show that, for any $k \in \mathbb{P}^{\mathcal{R}}$, the differential equations for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ admit even one equilibrium in $\mathbb{P}^{\mathcal{S}}$, then part (iii) of the Deficiency Zero Theorem will have been proved. This we do in Section 5.A.3.

5.A.3. Proof of the existence of a positive equilibrium. We will follow the line of argument in [H3], which in turn draws on ideas in [F2]. Our purpose is to show that if $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ is a weakly reversible deficiency zero network then, for any $k \in \mathbb{P}^{\mathcal{R}}$, the differential equations for the mass action system $\{\mathcal{S},\mathcal{C},\mathcal{R},k\}$ admit an equilibrium in $\mathbb{P}^{\mathcal{S}}$. If $Y:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ is the stoichiometric map for the network and if, for fixed but arbitrary $k \in \mathbb{P}^{\mathcal{R}}$, $A_k: \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ is as in Proposition 4.1, we seek $c^* \in \mathbb{P}^{\mathcal{S}}$ such that

$$Y A_k \Psi(c^*) = 0 , \tag{5.50}$$

where $\Psi:\overline{\mathbb{P}}^{\mathcal{S}} \to \overline{\mathbb{P}}^{\mathcal{C}}$ is given by

$$\Psi(c) \equiv \sum_{y \in \mathcal{C}} c^y \omega_y \tag{5.51}$$

with

$$c^y \equiv \prod_{s \in \mathcal{S}} c_s^{y_s} . \tag{5.52}$$

Since, from Corollary 4.11, we have for zero deficiency networks

$$\ker Y A_k = \ker A_k , \tag{5.53}$$

we must in fact seek $c^* \in \mathbb{P}^{\mathcal{S}}$ such that

$$\Psi(c^*) \in \ker A_k . \tag{5.54}$$

In the spirit of Section 5.A.2 we shall find it useful to begin by considering an arbitrary weakly reversible network $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ (of arbitrary deficiency) and by finding conditions on $k \in \mathbb{P}^{\mathcal{R}}$ such that there exists $c^* \in \mathbb{P}^{\mathcal{S}}$ satisfying (5.54). (That we need only consider weakly reversible networks follows from Remark 5.2.) Then we will show that for weakly reversible deficiency zero networks these conditions are satisfied for all $k \in \mathbb{P}^{\mathcal{R}}$.

By way of preparation we let $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ be an arbitrary network (not necessarily weakly reversible) for which $Y:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ is the stoichiometric map. The <u>transpose</u> of Y is that linear transformation $Y^T:\mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{C}}$ such that

$$(Y^T z) \cdot x = z \cdot Y x \ , \quad \forall z \in \mathbb{R}^{\mathcal{S}} \ , \forall x \in \mathbb{R}^{\mathcal{C}} \ . \tag{5.55}$$

It is easy to confirm that

$$Y^T z \equiv \sum_{y \in \mathcal{C}} (y \cdot z)\omega_y \ . \tag{5.56}$$

Let $L^1, L^2, \ldots, L^\ell$ be the linkage classes of $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$. Recall that, for $\theta = 1,2,\ldots,\ell$, ω_{L^θ} is the characteristic function on L^θ ; that is,

$$\omega_{L^\theta} = \sum_{y \in L^\theta} \omega_y \ , \quad \theta = 1,2,\ldots,\ell \ . \tag{5.57}$$

We turn now to an easy but important consequence of Proposition 4.7.

<u>Lemma 5.8</u>. <u>Let</u> $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$ <u>be a reaction network of deficiency</u> δ , <u>and let</u> n <u>be the number of complexes in</u> $\mathcal{C}$. <u>If</u> $Y:\mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ <u>is the stoichiometric map for the network and</u> $L^1, L^2, \ldots, L^\ell$ <u>are its linkage classes, then</u>

$$\dim[\operatorname{im} Y^T + \operatorname{span}(\omega_{L^1}, \omega_{L^2}, \ldots, \omega_{L^\ell})] = n - \delta \ . \tag{5.58}$$

<u>In particular, if</u> $\delta = 0$ <u>then</u>

$$\operatorname{im} Y^T + \operatorname{span}(\omega_{L^1}, \omega_{L^2}, \ldots, \omega_{L^\ell}) = \mathbb{R}^{\mathcal{C}} \ . \tag{5.59}$$

Proof. With $\Delta \subset \mathbb{R}^{\mathcal{C}}$ as in Proposition 4.7 we have from that proposition

$$\dim[\ker Y \cap \text{span}(\Delta)] = \delta \quad . \tag{5.60}$$

Since $\dim \mathbb{R}^{\mathcal{C}} = n$ we have from (5.60)

$$\dim[\ker Y \cap \text{span}(\Delta)]^{\perp} = n - \delta \quad . \tag{5.61}$$

However,

$$[\ker Y \cap \text{span}(\Delta)]^{\perp} = (\ker Y)^{\perp} + (\text{span}(\Delta))^{\perp} \quad . \tag{5.62}$$

From the well known relationship between the kernel of a linear transformation and the image of its transpose we have

$$(\ker Y)^{\perp} = \text{im } Y^{T} \; . \tag{5.63}$$

Moreover, from Lemma 4.6

$$[\text{span}(\Delta)]^{\perp} = \text{span}(\omega_{L^1}, \omega_{L^2}, \ldots, \omega_{L^\ell}) \; . \tag{5.64}$$

Combining (5.61)-(5.64) we obtain (5.58). When $\delta = 0$ (5.58) tells us that the linear subspace of $\mathbb{R}^{\mathcal{C}}$ on the left of (5.59) has the same dimension as $\mathbb{R}^{\mathcal{C}}$ and therefore must coincide with it. ///

Lemma 5.8 will be used in conjunction with our next proposition, which deals with an arbitrary <u>weakly</u> <u>reversible</u> network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$. In its statement it will be understood that $L^1, \ldots, L^\ell$ are the linkage classes of the network, that Y is the stoichiometric map for the network, that $\Psi(\cdot)$ is as in (5.51) and that, for $k \in \mathbb{P}^{\mathcal{R}}$, A_k is as in Proposition 4.1. Since the network is weakly reversible its linkage classes coincide with its terminal strong linkage classes so that, from Proposition 4.1, $\ker A_k$ has a (non-negative) basis $\{x^1, x^2, \ldots, x^\ell\} \subset \overline{\mathbb{P}}^{\mathcal{C}}$ such that

$$\operatorname{supp} x^\theta = L^\theta \quad , \quad \theta = 1,2,\ldots,\ell \ . \tag{5.65}$$

Since the union of the linkage classes is $\mathcal{C}$ it follows from (5.65) that

$$\sum_{\theta=1}^{\ell} x^\theta$$

is positive — that is, a member of $\mathbb{P}^{\mathcal{C}}$. Recall that if I is a set (be it $\mathcal{S}$ or $\mathcal{C}$) and if p is a member of $\mathbb{P}^I$, then $\ln p \in \mathbb{R}^I$ is defined by

$$(\ln p)_i = \ln(p_i) \quad , \quad \forall\, i \in I \ . \tag{5.66}$$

Similarly, for $z \in \mathbb{R}^I$ the vector $e^z \in \mathbb{P}^I$ is defined by

$$(e^z)_i = e^{z_i} \ , \quad \forall\, i \in I \ . \tag{5.67}$$

Proposition 5.9. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a weakly reversible network (of arbitrary deficiency), let k be an element of $\mathbb{P}^{\mathcal{R}}$, and let $\{x^1, x^2, \ldots, x^\ell\} \subset \overline{\mathbb{P}}^{\mathcal{C}}$ be a basis for $\ker A_k$ as in Proposition 4.1. The following are equivalent:

(i) There exists $c^* \in \mathbb{P}^{\mathcal{S}}$ such that

$$\Psi(c^*) \in \ker A_k \ . \tag{5.68}$$

(ii) $\ln\left(\sum_{\theta=1}^{\ell} x^\theta\right)$ is contained in $\operatorname{im} Y^T + \operatorname{span}(\omega_{L^1}, \omega_{L^2}, \ldots, \omega_{L^\ell})$. (5.69)

Proof. Condition (ii) is obviously equivalent to:

(iii) There exist $z \in \mathbb{R}^{\mathcal{S}}$ and numbers $\{-\xi_1, -\xi_2, \ldots, -\xi_\ell\} \subset \mathbb{R}$ such that

$$\ln\left(\sum_{\theta=1}^{\ell} x^\theta\right) = Y^T z - \sum_{\theta=1}^{\ell} \xi_\theta \omega_{L\theta} . \tag{5.70}$$

With $z \in \mathbb{R}^{\mathcal{S}}$ and $\{\xi_1, \ldots, \xi_\ell\}$ as in (iii), we can take $c^* \in \mathbb{P}^{\mathcal{S}}$ and $\{\lambda_1, \ldots, \lambda_\ell\} \subset \mathbb{P}$ to be given by

$$c^* = e^z \tag{5.71}$$

and

$$\lambda_\theta = e^{\xi_\theta} , \quad \theta = 1, 2, \ldots, \ell \tag{5.72}$$

to see that (iii) is equivalent to:

(iv) There exist $c^* \in \mathbb{P}^{\mathcal{S}}$ and $\{\lambda_1, \ldots, \lambda_\ell\} \subset \mathbb{P}$ such that

$$\begin{aligned} Y^T \ln c^* &= \ln\left(\sum_{\theta=1}^{\ell} x^\theta\right) + \sum_{\theta=1}^{\ell} (\ln \lambda_\theta)\omega_{L\theta} \\ &= \ln\left(\sum_{\theta=1}^{\ell} \lambda_\theta x^\theta\right) . \end{aligned} \tag{5.73}$$

From (5.56) we have

$$Y^T \ln c^* = \sum_{y \in \mathcal{P}} (y \cdot \ln c^*)\, \omega_y \,, \tag{5.74}$$

and from (5.52) it follows that

$$y \cdot \ln c^* = \ln (c^*)^y \,, \quad \forall\, y \in \mathcal{P} \,. \tag{5.75}$$

Combining (5.74) and (5.75) we obtain

$$\begin{aligned} Y^T \ln c^* &= \sum_{y \in \mathcal{P}} [\ln (c^*)^y] \omega_y \\ &= \ln \Big(\sum_{y \in \mathcal{P}} (c^*)^y \omega_y \Big) \\ &= \ln \Psi(c^*) \,. \end{aligned} \tag{5.76}$$

Thus, we can combine (5.76) with (5.73) and take exponentials to assert that (iv) is equivalent to:

(v) <u>There exist</u> $c^* \in \mathbb{P}^{\mathcal{S}}$ <u>and</u> $\{\lambda_1, \ldots, \lambda_\ell\} \subset \mathbb{P}$ <u>such that</u>

$$\Psi(c^*) = \sum_{\theta=1}^{\ell} \lambda_\theta\, x^\theta \,. \tag{5.77}$$

Since $\{x^1,\ldots,x^\ell\}$ is a basis for $\ker A_k$, (v) clearly implies (i). That (i) implies (v) (with <u>positive</u> λ_θ in (5.77)) follows easily from the special nature of the basis $\{x^1,\ldots,x^\ell\}$ and the fact that, for $c^* \in \mathbb{P}^{\mathcal{S}}$, $\Psi(c^*)$ is a member of $\mathbb{P}^{\mathcal{C}}$. ///

<u>Remark 5.9</u>. In Proposition 5.9 there are, of course, an infinite supply of bases for $\ker A_k$ having the special properties given in Proposition 4.1. If, however, condition (ii) is satisfied for one choice of such a basis it will be satisfied for any other choice of such a basis: It is easy to confirm that if $\{x^1,\ldots,x^\ell\}$ and $\{\bar{x}^1,\ldots,\bar{x}^\ell\}$ are two such bases, then

$$\ln\left(\sum_{\theta=1}^{\ell} x^\theta\right) \quad \text{and} \quad \ln\left(\sum_{\theta=1}^{\ell} \bar{x}^\theta\right)$$

will differ by an element of

$$\operatorname{span}(\omega_{L^1},\omega_{L^2},\ldots,\omega_{L^\ell}) .$$

<u>Remark 5.10</u>. Condition (ii) of Proposition 5.9 requires that the vector

$$\ln\left(\sum_{\theta=1}^{\ell} x^\theta\right) \in \mathbb{R}^{\mathcal{C}} \tag{5.78}$$

lie in the linear subspace

$$\operatorname{im} Y^T + \operatorname{span}(\omega_{L^1},\omega_{L^2},\ldots,\omega_{L^\ell}) \subset \mathbb{R}^{\mathcal{C}} . \tag{5.79}$$

Since $\{x^1,x^2,\ldots,x^\ell\}$ is a basis for $\ker A_k$, the values that might be taken by (5.78) will be influenced by the particular value of $k \in \mathbb{P}^{\mathcal{R}}$. On the other hand the linear subspace (5.79) <u>depends only on the network</u> $\{\mathcal{S},\mathcal{C},\mathcal{R}\}$.

We are now coming to the end of the road:

Corollary 5.10. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *be any weakly reversible network of deficiency zero, and let* k *be any element of* $\mathbb{P}^{\mathcal{R}}$. *With* A_k *as in Proposition 4.1 and with* $\Psi(\cdot)$ *as in (5.51) there exists* $c^* \varepsilon\, \mathbb{P}^{\mathcal{S}}$ *such that*

$$A_k \Psi(c^*) = 0 \ .$$

That is, the differential equations for the mass action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ *admit an equilibrium in* $\mathbb{P}^{\mathcal{S}}$, *and that equilibrium satisfies the hypothesis of Proposition 5.3.*

Proof. For deficiency zero networks Lemma 5.8 tells us that the linear subspace (5.79) is in fact *all* of $\mathbb{R}^{\mathcal{C}}$. Thus, for *any* $k \ \varepsilon\ \mathbb{P}^{\mathcal{R}}$, condition (ii) of Proposition 5.9 is satisfied trivially. So, then, is the equivalent condition (i). ///

With Corollary 5.10 we have achieved the final objective set in Remark 5.8. This completes our proof of Theorem 5.1.

of species s. If, in a constant volume homogeneous reactor, c_s is the instantaneous molar concentration of species s (which, it will be recalled, is proportional to the number of molecules of s per unit volume), then $M_s\, c_s$ gives the instantaneous mass (per unit volume) of s in the reactor. Thus, if $c \in \overline{\mathbb{P}}^{\mathcal{S}}$ is the instantaneous reactor composition then

$$M \cdot c = \sum_{s \in \mathcal{S}} M_s\, c_s$$

gives the instantaneous total mass (per unit reactor volume) of all species appearing in the network.

Now if $\mathcal{K}$ is a kinetics for the network and $f(\cdot)$ is the species formation rate function for the reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$, we have, for any $c \in \overline{\mathbb{P}}^{\mathcal{S}}$,

$$M \cdot \dot{c} = M \cdot f(c) = 0 . \tag{2.45}$$

The second equation in (2.45) holds because M lies in $S^{\perp}$ while $f(\cdot)$ takes values in S. Interpreting M as we have, we can regard (2.45) as ensuring that the total mass of the reactor contents is time-invariant.

One of the pleasant features of conservative networks is given by Horn and Jackson. They show that a network is conservative if and only if all its stoichiometric compatibility classes are compact. (What we call stoichiometric compatibility classes are called <u>reaction simplices</u> in [HJ].) Because our interest will not be limited to conservative networks, we shall not in general have compactness of the stoichiometric compatibility classes.

Partial Bibliography for "Lectures on Chemical Reaction Networks"

[A] Aris, R., Introduction to the Analysis of Chemical Reactors, Prentice-Hall, Inc., Englewood Cliffs, New Jersey (1965).

[E] Edelstein, B. A biochemical model with multiple steady states and hysteresis, J. Theor. Biol., **29**, 57 (1970).

[F1] Feinberg, M. On chemical kinetics of a certain class, Arch. Rational Mech. Anal., **46**, 1, (1972).

[F2] Feinberg, M. Complex balancing in general kinetic systems, Arch. Rational Mech. Anal., **49**, 187 (1972).

[F3] Feinberg, M., Mathematical Aspects of Mass Action Kinetics, Chapter 1 in Chemical Reactor Theory: A Review (eds. N. Amundson and L. Lapidus) Prentice-Hall (1977).

[F5] Fife, Paul, Mathematical Aspects of Reacting and Diffusing Systems, Lecture Notes in Biomathematics No. 28, Springer-Verlag, Berlin-Heidelberg-New York (1979).

[FH1] Feinberg, M. and F. Horn, Dynamics of open chemical systems and the algebraic structure of the underlying reaction network, Chem. Eng. Sci., **29**, 775 (1974).

[FH2] Feinberg, M. and F.J.M. Horn, Chemical mechanism structure and the coincidence of the stoichiometric and kinetic subspaces, Arch. Rational Mech. Anal., **66**, 83 (1977) [Corrigendum appended to this bibliography]

[G] Gantmacher, F., Matrix Theory, Chelsea Press, New York (1959).

[GP] Glansdorff, P. and I. Prigogine, Thermodynamic Theory of Structure, Stability and Fluctuations, J. Wiley & Sons, New York (1971).

[H] Harary, F., Graph Theory, Addison-Wesley, Reading, Massachusetts (1972).

[H3] Horn, F., Necessary and sufficient conditions for complex balancing in chemical kinetics, Arch. Rational Mech. Anal., **49**, 172 (1972)

[H4-H6] On a connexion between stability and graphs in chemical kinetics, Proc. Roy. Soc. London A, **334** 299 (1973).

[HJ] Horn, F. and R. Jackson, General mass action kinetics, Arch. Rational Mech. Anal., **47**, 81 (1972).

[HS] Hirsch, M.W. and S. Smale, Differential Equations, Dynamical Systems and Linear Algebra, Academic Press, New York (1974).

[K] Krambeck, F. J., The mathematical structure of chemical kinetics in homogeneous single phase systems, Arch. Rational Mech. Anal., **38**, 317 (1970).

[L1] Lorenz, E.N., Deterministic nonperiodic flow, J. Athmosph. Sc. **20**, 130-141 (1963).

[NSS] Nickerson, H.K. D. C. Spencer and N.E. Steenrod, Advanced Calculus, Van Nostrand, Princeton, N.J. (1959).

[S] Shapiro, Arnold, The Statics and Dynamics of Multicell Reaction Systems, Ph.D. thesis, University of Rochester (1975).

[SH] Shapiro, A. and F. Horn, On the possibility of sustained oscillations, multiple steady states, and asymmetric steady states in multicell reaction systems, Math. Biosciences, **44**, 19 (1979). NOTE: There are several errors in this. A corrigendum appeared in a later issue of the same journal, but I don't have the citation.]

[SW] Stoer and Witzgal, Convexity and Optimization in Finite Dimensions, Springer-Verlag, Berlin-Heidelberg-New York (1970).

Corrigendum: Chemical mechanism structure and the coincidence of the stoichiometric and kinetic subspaces, Arch. Rational Mech. Anal., **66,** 83 (1977)

Definition 8 should read as follows: Two complexes $y \in \mathscr{C}$ and $y' \in \mathscr{C}$ are directly linked if $y \to y'$ or if $y' \to y$; if y and y′ are directly linked we write $y \leftrightarrow y'$. Two complexes $y \in \mathscr{C}$ and $y' \in \mathscr{C}$ are linked if any of the following conditions are satisfied:

1. $y = y'$
2. $y \leftrightarrow y'$
3. $\mathscr{C}$ contains a subset $\{y_1, y_2, \ldots, y_k\}$ such that

$$y \leftrightarrow y_1 \leftrightarrow y_2 \leftrightarrow \ldots \leftrightarrow y_k \leftrightarrow y'.$$

If y and y′ are linked we write $y \Leftrightarrow y'$. The equivalence relation $\Leftrightarrow$ induces a partition of $\mathscr{C}$ into a family $\{\mathscr{L}_\theta\}$ of equivalence classes called the linkage classes of the mechanism. The number of linkage classes of a mechanism will be denoted by the symbol ℓ.