

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 $\{S, C, R, K\}$, a composition trajectory in \overline{IP}^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 particular set of rate constants. We will not, for example, ask whether the differential equations for a specified mass action system $\{S, C, R, k\}$ admit a periodic orbit. We will, however, ask if, for the network $\{S, C, R\}$, there exists some $k \in IP^R$ such that the differential equations induced by the mass action system $\{S, C, R, k\}$ admit a periodic orbit. That is, we shall ask whether the network 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 questions, 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., $A \rightarrow 2B$) 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.

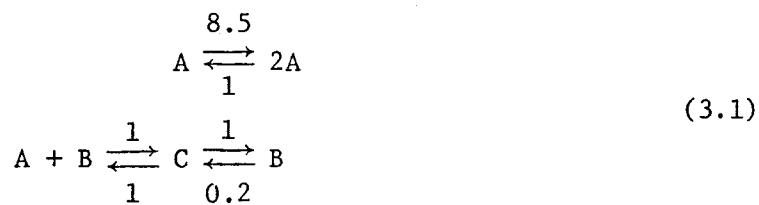
On the other hand, some networks (e.g., $A \rightleftharpoons 2B$) taken with mass action kinetics admit at least one equilibrium in each positive stoichiometric compatibility class, regardless of values that the rate constants take. (Recall Figure 2.1 in Example 2.D.1.)

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)



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.

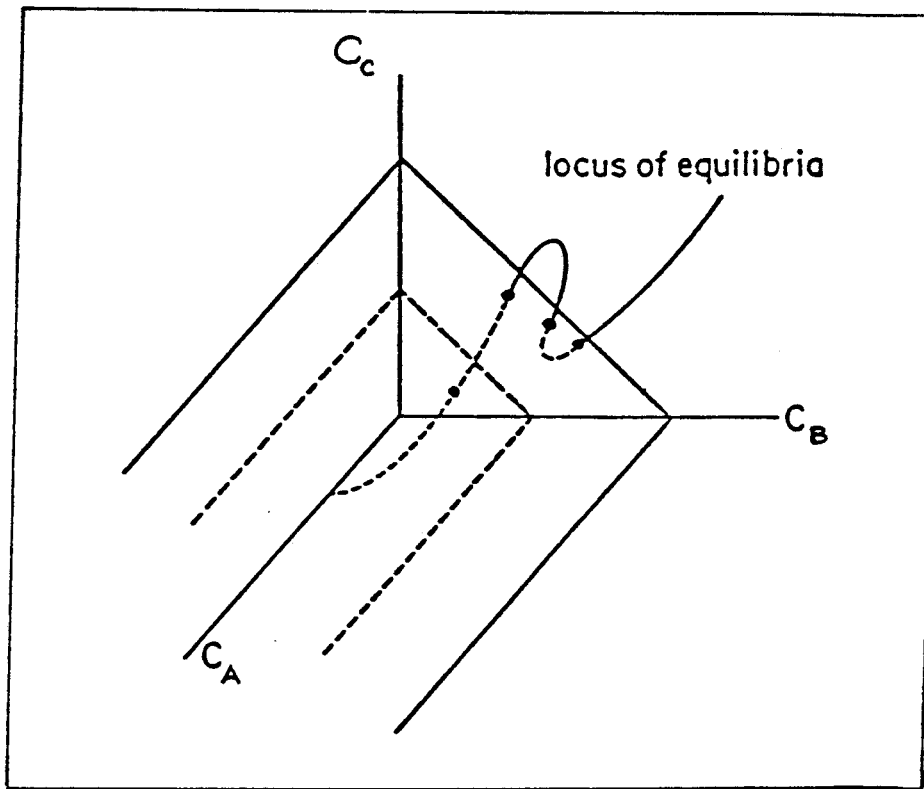
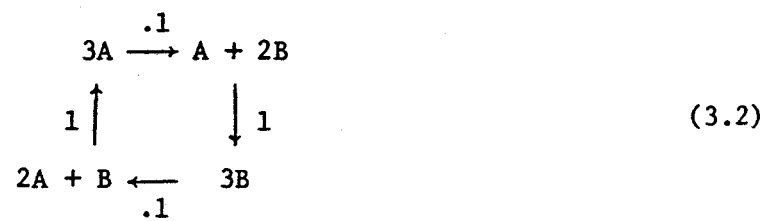


Figure 3.1

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):



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.

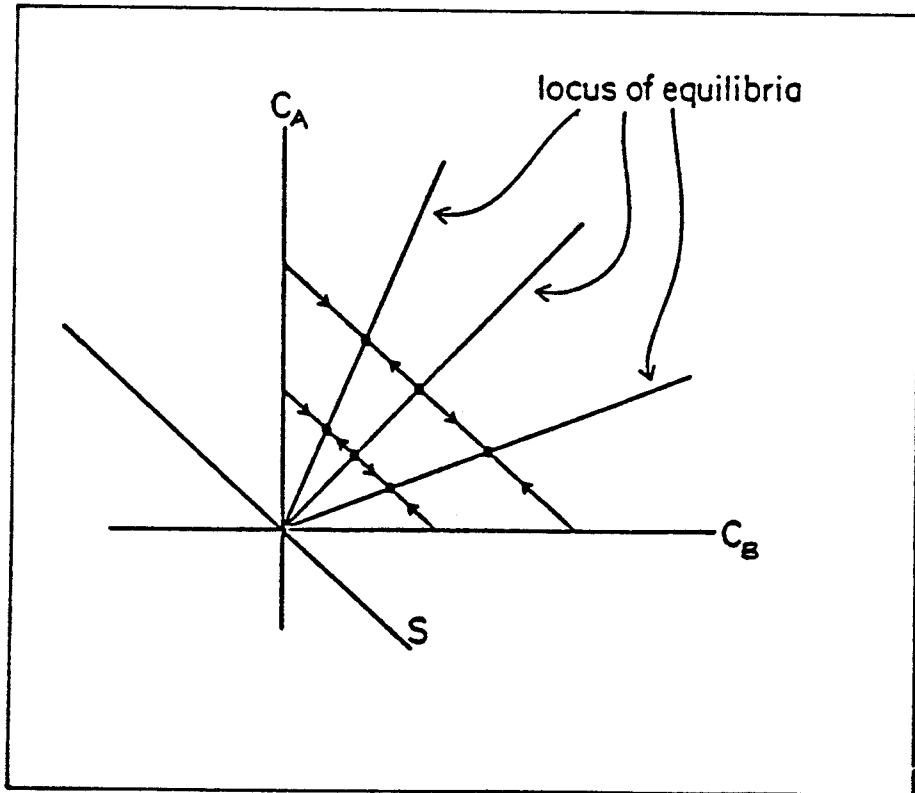
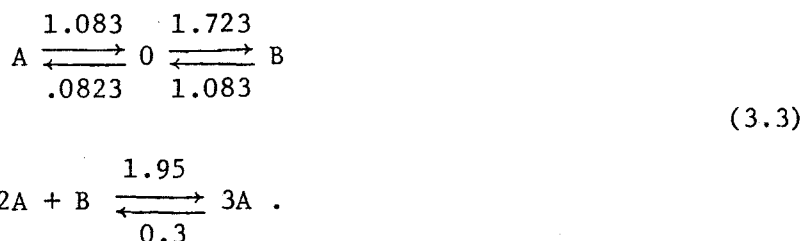


Figure 3.2

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 some values of the rate constants. Consider the mass action system*



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).

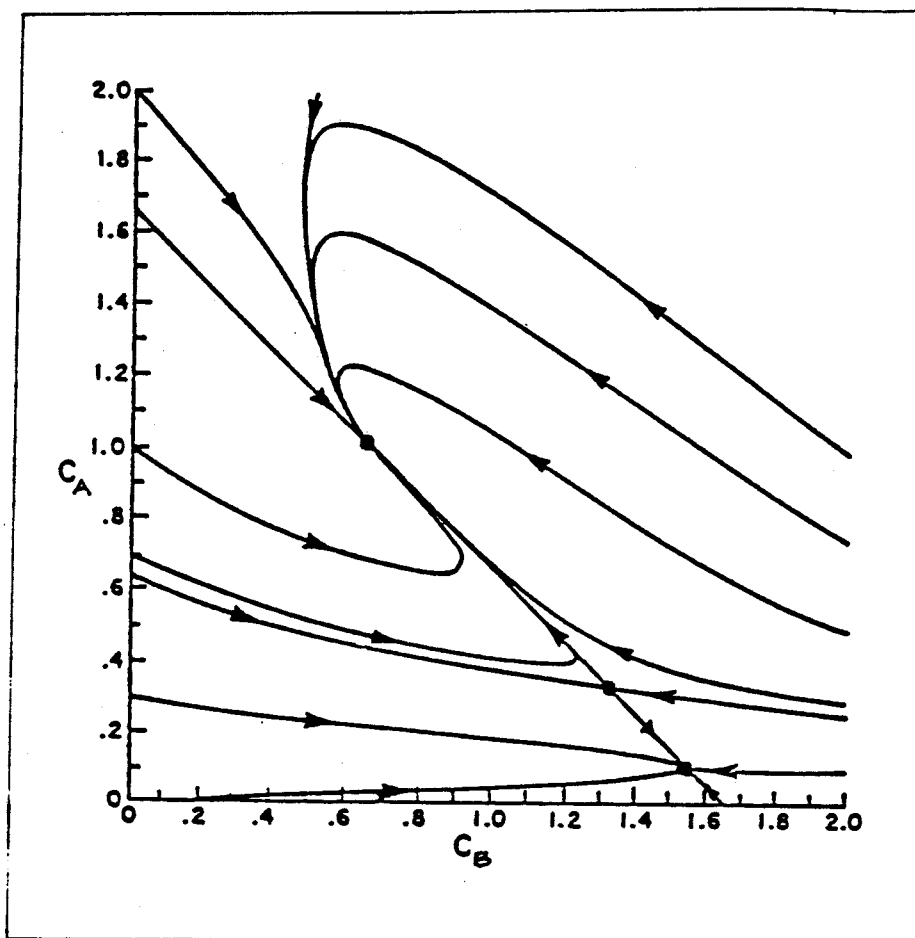


Figure 3.3

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)*:



For this two-species network, the stoichiometric subspace is two dimensional and therefore coincides with \mathbb{R}^2 . There is but one positive stoichiometric compatibility class; it coincides with \mathbb{P}^1 . 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.

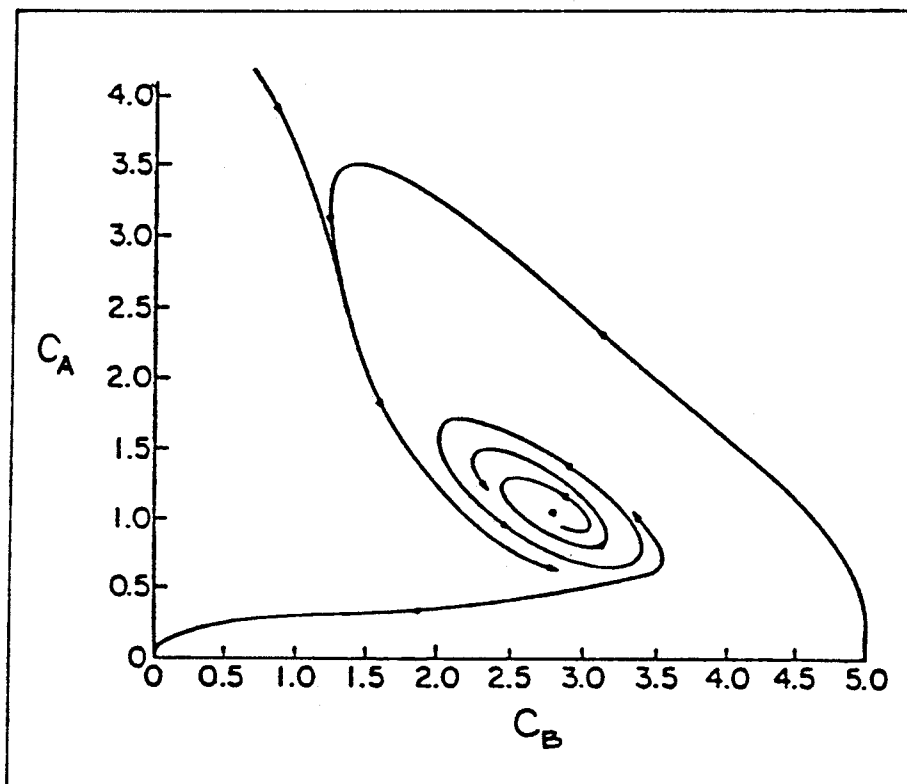


Figure 3.4

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.

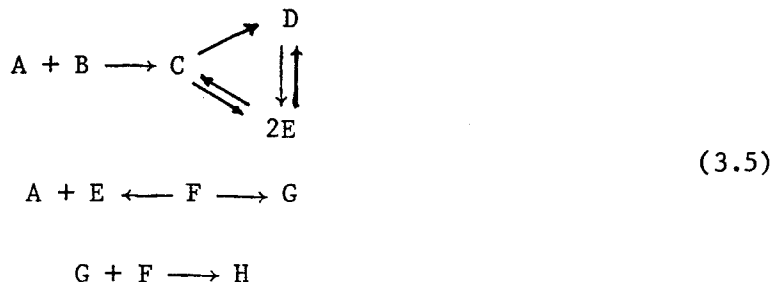
We pose the following problem: Describe the class of networks which, when endowed with mass action kinetics, induce differential equations that admit no (nonconstant) periodic composition cycles regardless of values the rate constants might take.

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



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 $y \rightarrow y'$ is a reaction in a reversible network then so is $y' \rightarrow y$. Thus, the network (3.6) is reversible:



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



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:



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 $B + E \rightarrow D$ is not contained in any directed arrow cycle.

Similarly, network (3.9) is not weakly reversible:



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

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

(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 $\{S, C, R\}$ be any reaction network of deficiency zero.

- (i) If the network is not weakly reversible then, for arbitrary kinetics K , the differential equations for the reaction system $\{S, C, R, K\}$ cannot admit a positive equilibrium (i.e., an equilibrium in \mathbb{P}^S).
- (ii) If the network is not weakly reversible then, for arbitrary kinetics K , the differential equations for the reaction system $\{S, C, R, K\}$ cannot admit a cyclic composition trajectory containing a positive composition (i.e., a point in \mathbb{P}^S).
- (iii) If the network is weakly reversible (in particular, if the network is reversible) then, for any mass action kinetics $k \in \mathbb{P}^R$, the differential equations for the mass action system $\{S, C, R, k\}$ 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}^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.

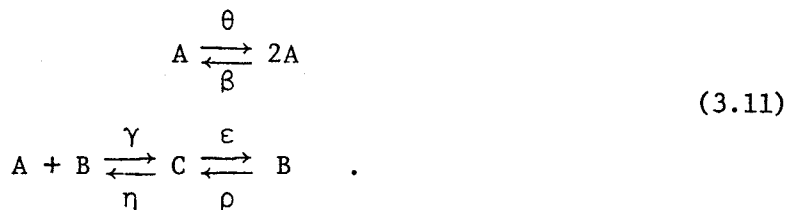
Example 3.C.1. I'll begin by recalling the very first network we discussed, (1.1) in Lecture 1. Remember that we gave the network mass action kinetics (with rate constants indicated by Greek letters in (1.6)), we wrote out the corresponding system (1.7) of differential equations, and we posed some questions 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:

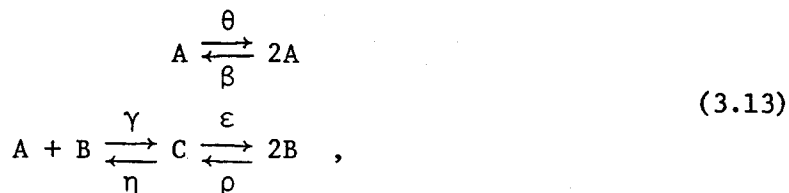


The induced differential equations are

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

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



for which the induced differential equations are

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

In very rough terms the system (3.14) is "more nonlinear" than the system (3.12): While the rate of reaction $B \rightarrow C$ in network (3.11) is proportional to c_B , the rate of reaction $2B \rightarrow C$ 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 $\delta_1, \delta_2, \dots, \delta_\ell$, 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 :

$$s := \text{rank} \{y' - y \in \mathbb{R}^{\mathcal{S}} : y \rightarrow y' \in \mathcal{R}\}. \quad (3.15)$$

Suppose also that, in the sense of §3.B.1, I partition \mathcal{C} into linkage classes L^1, L^2, \dots, L^ℓ . For $\theta = 1, 2, \dots, \ell$ 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.

$$s_{\theta} := \text{rank} \{y' - y \in \mathbb{R}^{\mathcal{L}} : y \rightarrow y' \in \mathcal{R}, y \in L^{\theta}\} . \quad (3.16)$$

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 deficiency of linkage class L^{θ} as follows:

$$\delta_{\theta} := n_{\theta} - 1 - s_{\theta} . \quad (3.17)$$

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

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

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

$$\sum_{\theta=1}^{\ell} s_{\theta} \geq s . \quad (3.19)$$

*It is not difficult to see that s_{θ} is also given by

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

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

$$\delta \geq \sum_{\theta=1}^{\ell} \delta_{\theta} \quad (3.20)$$

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 $\theta = 1, 2, \dots, \ell$, 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) $\delta_{\theta} = 0$, $\theta = 1, 2, \dots, \ell$.
- (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 $\{S, C, R\}$ 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, $\theta = 1, 2, \dots, \ell$; and suppose that both of the following conditions are satisfied:

- (i) $\delta_\theta \leq 1$, $\theta = 1, 2, \dots, \ell$
- (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 $k \in \mathbb{P}^R$, the differential equations for the mass action system $\{S, C, R, k\}$ 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.

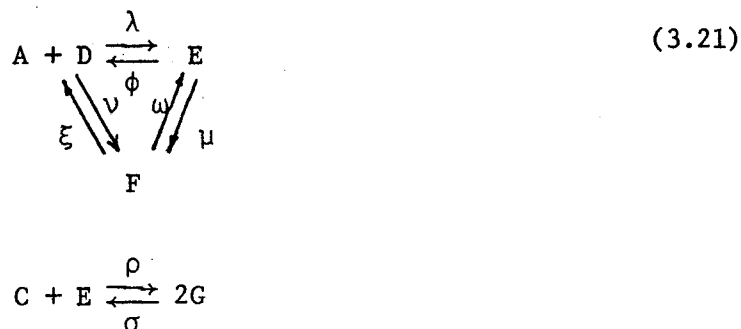
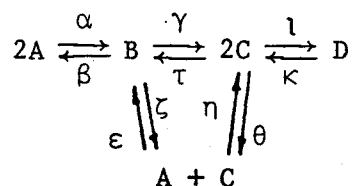
It should be clear, however, that not all (weakly reversible) deficiency one networks satisfy the hypothesis of Theorem 3.2. In particular the (weakly reversible) deficiency one networks which fail to satisfy its hypothesis are precisely those for which the deficiency of each linkage class is zero. On 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:

Corollary 3.3. 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.

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

Example 3.D.1. Consider the mass action system (3.21):



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

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

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 Edelman mass action system:



for which the differential equations are

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

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 Edelman system obtained by adding two reactions:



The corresponding differential equations are:

$$\begin{aligned}\dot{c}_A &= (\theta - \tau)c_A - \beta c_A^2 - \gamma c_A c_B + (\eta + \sigma)c_C \\ \dot{c}_B &= (\epsilon + \eta)c_C - \gamma c_A c_B - \rho c_B \\ \dot{c}_C &= \gamma c_A c_B - (\epsilon + \eta + \sigma)c_C + \rho c_B + \tau c_A.\end{aligned}\tag{3.26}$$

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 not the case. The deficiency of network (3.25) is one ($n=5$, $\ell=1$, $s=3$) and it contains but one linkage class. Thus, regardless of values of the rate constants there is precisely one 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 .)

Remark 3.5. It is natural to conjecture that networks which satisfy the conditions of Theorem 3.2 might have all 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}^3 . Thus, \mathbb{P}^3 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



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 $\text{span}(B-A)$ which lie in \mathbb{P}^2 . 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

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

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) invariably give rise to multiple positive equilibria for some assignment of rate constants. Consider, for example, the reversible Brusselator:



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.