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Stability and Instability in Isothermal CFSTRs with Complex Chemistry: Some Recent Results

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Although the classical 1955 paper by Bilous and Amundson was largely devoted to the study of nonisothermal systems, they also found it worthwhile to establish the stable behavior of a model isothermal multireaction continuous flow stirred tank reactor for all values of residence time, rate constants, and feed concentrations. Over a half century later, there remains a predisposition to the idea that isothermal reactors are prone to dull, stable behavior even when the underlying chemistry is complex. That idea is revisited in light of some recent findings in chemical reaction network theory. © 2013 American Institute of Chemical Engineers *AIChE J*, 59: 3403-3411, 2013
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Introduction

In a seminal 1955 article,[1] Bilous and Amundson devoted much of their attention to the stability characteristics of nonisothermal continuous flow stirred tank reactors (CFSTRs). In their examples, the chemistry was mostly simple, often first order, with instabilities resulting largely from an interplay of heating effects and the occurrence of chemical reactions.

Usually unnoticed, however, is that Bilous and Amundson also examined the behavior of an isothermal CFSTR driven by the somewhat more complicated three-reaction Network 1, taken with mass action kinetics. They found that regardless of the rate constants, feed composition, and residence time the steady state is asymptotically stable. Left implicit in their narrative was that the steady state is invariably unique. “Thus,” they wrote, “the isothermal system is always stable.”

$$\begin{array}{l} A + B \rightleftarrows C + F \\ C \rightarrow E \end{array} \tag{1}$$

That Bilous and Amundson saw fit to study the stability characteristics of an isothermal CFSTR was rare for its time. Even today, it is often taken for granted that isothermal CFSTRs—including ones with highly complex chemistry—admit just one steady state and, moreover, that all composition trajectories approach that steady state in the limit with increasing time. It is common, for example, to refer, without justification, to *the* steady state, as if there could not be more than one.

A little thought will indicate why this predisposition toward dull behavior is surprising. If the kinetics is, for example, mass action, then a positive steady state* is a solution of a (perhaps large) system of nonlinear polynomial equations in the species concentrations—a system in which many parameters (e.g., the residence time, rate constants, and feed concentrations) appear. Uniqueness of a positive steady state regardless of parameter values is mathematically surprising in itself. That this uniqueness should persist over very large families of distinct reaction networks is more surprising still.

Although it would have been extremely difficult at the time, had Bilous and Amundson undertaken the study of an isothermal CFSTR driven not by Network 1 but, rather, by the augmented Network 2, also taken with mass action

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[*] *By a positive steady state we mean one in which all species concentrations are strictly positive.*

kinetics, a very different lesson might have been learned. In particular, over a half-century ago we would have been made much more sensitive to the possibility that instabilities can indeed result from intricacies of the chemistry itself, divorced from the involvement of thermal phenomena.

$$\begin{aligned} &A + B \rightleftarrows C + F \\ &B \rightleftarrows C \rightleftarrows E \\ &A + E \rightleftarrows D \end{aligned} \tag{2}$$

In contrast to the findings of Bilous and Amundson for Network 1, there are for Network 2 values of the rate constants, feed concentrations, and residence time such that the resulting CFSTR differential equations admit multiple positive steady states, including one that is unstable. A phase portrait is shown in Figure 1 corresponding to parameter values given in the Appendix.

By now, it is well known that there are, in fact, both experimental and (mass action) theoretical counterexamples in which reaction networks give rise to multiple and unstable steady states in an isothermal CFSTR setting. Nevertheless, the belief remains strong that isothermal CFSTRs admit only dull behavior far more often than not. This belief seems to be based less on firm analysis than on broad experience accumulated over many years in the study of a wide variety of chemistries.

A problem, then, is to make sense of this, to understand why, despite examples such as Network 2, very many (if not most) reaction networks give rise to differential equations that admit only dull behavior, regardless of parameter values. Put differently, it is important to understand for which reaction networks experience acquired over many years might be seriously misleading. As we shall see, it is for biochemical systems, even very simple ones, that we are most likely to be led astray by our ingrained expectation of dull behavior in isothermal settings.

We should say in advance that there must be considerable subtlety in any theory that purports to distinguish between reaction networks that might engender multiple steady states in an isothermal CFSTR context and those that cannot. In Table 1, we show six reaction networks, all variants of the simpler Network 1 studied by Bilous and Amundson. When the second and fifth entries are taken with mass action kinetics, there are values for the rate constants, feed concentrations, and residence time such that the corresponding isothermal CFSTR differential equations admit multiple positive steady states (see the Appendix). For the remaining networks in Table 1, so similar to the second and fifth, we shall see that no such parameter values exist. In fact, for the remaining networks there is no possibility of multiple steady states even for very broad classes of kinetics (e.g., weakly monotonic) discussed in the next section.

Table 1. Six Highly Similar Networks and their Capacity for Isothermal CFSTR Multiple Steady States

1. $A+B \rightleftarrows C+F$ $C \rightleftarrows E$ $A+E \rightleftarrows D$ $B+C \rightleftarrows G$ ✗	2. $A+B \rightleftarrows C+F$ $B \rightleftarrows C \rightleftarrows E$ $A+E \rightleftarrows D$ ✓	3. $A+B \rightleftarrows F$ $B \rightleftarrows C \rightleftarrows E$ $A+E \rightleftarrows D$ $A+C \rightleftarrows G$ ✗
4. $A+B \rightleftarrows F$ $B \rightleftarrows C \rightleftarrows E$ $A+E \rightleftarrows D$ ✗	5. $A+B \rightleftarrows F$ $B \rightleftarrows C \rightleftarrows 2E$ $A+E \rightleftarrows D$ ✓	6. $A+F \rightleftarrows B$ $B \rightleftarrows C \rightleftarrows 2E$ $A+E \rightleftarrows D$ ✗

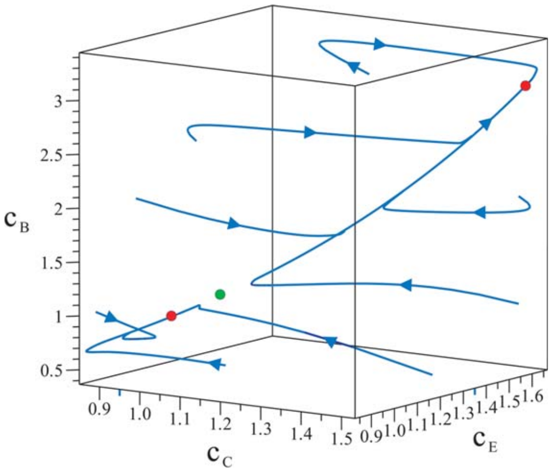

Figure 1. A CFSTR phase portrait deriving from Network 2.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

When the kinetics is mass action, there has already been substantial progress in describing large classes of reaction networks, including highly complex ones, in which multiple steady states are impossible within a classical isothermal CFSTR context (see, for example, Refs. 2–6). Beginning with surprising work by Banaji and Craciun, more recent research has extended some of the earlier mass action results on the impossibility of multiple steady states to far broader classes of kinetics and, in addition, has provided information related to the impossibility of at least certain kinds of instability.[7–11]

It is the purpose of this article to give a sense of these more recent results in a fairly simple (but not the most powerful) form. The central organizing result presented here is Theorem 1. Underlying that result is the theory of *concordant* chemical reaction networks, a class of networks for which a certain dullness of dynamical behavior is enforced even for very broad categories of kinetics. (Banaji and Craciun[7–9] arrived at aspects of Theorem 1 in a different way.) The theory of concordant reaction networks is developed in Refs. 10 and 11, which contain results that go far deeper than those discussed here. In particular, Ref. 11 contains a substantially more potent (but somewhat more complicated) variant of Theorem 1. Although the concordance idea does not appear explicitly in Theorem 1, we shall say more about it in a later section.

The remainder of this article is organized as follows: In the next section, we describe a class of kinetics, far broader than but including mass action kinetics, for which the main results of this article obtain. Then we introduce the Species-Reaction Graph for a network. This sets the stage for the central theorem of this article—a theorem that serves to distinguish, on the basis of a network's Species-Reaction Graph, between those chemistries that might give rise to isothermal CFSTR multiple steady states and those that cannot. In light of the theorem, we then revisit Table 1. This is followed by a discussion of reaction networks that arise naturally in biochemistry—in particular a discussion of why, with respect to the theorem, they are somewhat singular. In the next-to-last section, we provide a brief overview of the theory of concordant chemical reaction networks, a theory that provides a foundation for much of this article. Throughout the article, it will be understood that we have in mind perfectly mixed, constant density isothermal CFSTRs of the kind that give rise to the usual isothermal CFSTR differential equations.

The final section contains a concluding remark about Neal Amundson, to whom this volume is dedicated. Our aim in this article is to provide just a glimpse at some ongoing work motivated by questions Neal raised over a half century ago.

Monotonic Kinetics

We presume, as usual, that for every reaction operative within a particular (isothermal) CFSTR under study, there is a kinetic rate function that indicates how the instantaneous occurrence rate (per unit volume) of that reaction depends on the instantaneous mixture composition within the reactor. Thus, for reaction Network 1 we suppose that there are three non-negative-valued rate functions, $\mathscr{K}_{A+B\to C+F}(\cdot), \mathscr{K}_{C+F\to A+B}(\cdot)$, and $\mathscr{K}_{C\to E}(\cdot)$ such that, when the instantaneous mixture state within the reactor is given by the composition vector $c := [c_A, c_B, c_C, c_E, c_F]$,[†] the corresponding reaction rates are $\mathscr{K}_{A+B\to C+F}(c), \mathscr{K}_{C+F\to A+B}(c)$, and $\mathscr{K}_{C\to E}(c)$. Here, of course, c_A, c_B, c_C, c_E, and c_F are the instantaneous molar concentrations of the five species in Network 1. More generally, by a kinetics for a reaction network, we mean a specification of such a rate function for each reaction.

Once Network 1 is given a kinetics, the CFSTR differential equations take the form shown in Eqs. 3, where θ is the residence time and $c^f_A, c^f_B, \ldots c^f_E$ are the feed stream concentrations.

$$\begin{aligned}
\dot{c}_A &= \frac{1}{\theta}\left(c^f_A - c_A\right) - \mathscr{K}_{A+B\to C+F}(c) + \mathscr{K}_{C+F\to A+B}(c)\\
\dot{c}_B &= \frac{1}{\theta}\left(c^f_B - c_B\right) - \mathscr{K}_{A+B\to C+F}(c) + \mathscr{K}_{C+F\to A+B}(c)\\
\dot{c}_C &= \frac{1}{\theta}\left(c^f_C - c_C\right) + \mathscr{K}_{A+B\to C+F}(c) - \mathscr{K}_{C+F\to A+B}(c) - \mathscr{K}_{C\to E}(c)\\
\dot{c}_E &= \frac{1}{\theta}\left(c^f_E - c_E\right) + \mathscr{K}_{C\to E}(c)\\
\dot{c}_F &= \frac{1}{\theta}\left(c^f_F - c_F\right) + \mathscr{K}_{A+B\to C+F}(c) - \mathscr{K}_{C+F\to A+B}(c)
\end{aligned} \tag{3}$$

Were the kinetics mass action, the rate functions would take the form

$$\mathscr{K}_{A+B\to C+F}(c) = \alpha c_A c_B \quad \mathscr{K}_{C+F\to A+B}(c) = \beta c_C c_F \quad \mathscr{K}_{C\to E}(c) = \gamma c_C \tag{4}$$

where α, β, and γ are rate constants for the corresponding reactions. In this case, Eqs. 3 become a coupled system of five polynomial differential equations in the five species concentrations, a system that contains as parameters the five feed concentrations, the residence time, and the three rate constants. Although reaction Network 1 is very simple, the corresponding mass action CFSTR equations already become somewhat difficult to analyze. In particular, it is not so trivial to determine whether, for at least some combination of parameter values, the mass action CFSTR equations might admit an unstable steady state[1] or multiple steady states.

Our aim is to state a theorem that will help decide such questions for a very large class of reaction networks, not only when the kinetics is mass action but, far more broadly, whenever the kinetics is weakly monotonic, a category that contains mass action kinetics as just one special case. A formal definition is given in Ref. 10. Here, we will proceed informally, using Network 1 as motivation.

By the reactant species of a particular reaction, we mean, of course, the species that appear on the reactant side of that reaction; the product species are those that appear on the product side. Thus, the reactant species of the reaction $A + B \to C + F$ are A and B; the product species are C and F. For the reaction $C \to E$, the only reactant species is C, and the only product species is E. For every kinetics considered hereafter, we presume that the rate function for each reaction takes a strictly positive (but perhaps very small) value precisely when all of the reactant species for that reaction have strictly positive concentrations. (In slightly less precise terms, we presume that a reaction proceeds if and only if all of its reactant species are present.)

We say that a kinetics for a reaction network is *weakly monotonic* if, for every reaction in the network, the following condition is satisfied: If c and $\bar{c}$ are any two compositions in which the reactant species of the reaction have nonzero concentrations, then

1. the rate of the reaction is greater at composition $\bar{c}$ than it is at composition c only if the concentration of at least one reactant species is greater in composition $\bar{c}$ than it is in composition c, and
2. the rate of the reaction at composition $\bar{c}$ is identical to its rate at composition c only if (a) the concentrations of all reactant species are identical in compositions $\bar{c}$ and c or (b) there are two reactant species, say S and S′, such that $\bar{c}_S > c_S$ and $\bar{c}_{S'} < c_{S'}$.

Example. Consider a kinetics for Network 1 that is weakly monotonic, and suppose that $\bar{c}$ and c are two compositions at which all species concentrations are strictly positive. Then $\mathscr{K}_{A+B\to C+F}(\bar{c}) > \mathscr{K}_{A+B\to C+F}(c)$ requires that $\bar{c}_A > c_A$ or $\bar{c}_B > c_B$ or both. On the other hand, if $\mathscr{K}_{A+B\to C+F}(\bar{c}) = \mathscr{K}_{A+B\to C+F}(c)$ then we must have that $\bar{c}_A = c_A$ and $\bar{c}_B = c_B$ or else that $\bar{c}_A - c_A$ and $\bar{c}_B - c_B$ are of opposite sign. Similarly, $\mathscr{K}_{C\to E}(\bar{c}) > \mathscr{K}_{C\to E}(c)$ requires that $\bar{c}_C > c_C$. If $\mathscr{K}_{C\to E}(\bar{c}) = \mathscr{K}_{C\to E}(c)$, we must have $\bar{c}_C = c_C$.

Clearly, the mass action rate functions given in Eqs. 4 satisfy the requirements for weak monotonicity. But so too do the rate functions

$$\begin{aligned}
\mathscr{K}_{A+B\to C+F}(c) &\equiv \frac{k_1 c_A c_B}{k_2 + k_3 c_A + k_4 c_B},\\
\mathscr{K}_{C+F\to A+B}(c) &\equiv k_5 c_C^3 c_F^2,
\end{aligned}$$

and

$$\mathscr{K}_{C\to E}(c) \equiv \frac{k_6 c_C}{k_7 + k_8 c_C},$$

where the k_i are positive numbers.

It should be evident that the class of weakly monotonic kinetics is far larger than the class of mass action kinetics. In fact, we do not even impose the requirement that, in a weakly monotonic kinetics, the individual reaction rate functions be differentiable with respect to the species concentrations. For

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[†] *Sometimes we will refer to "the composition* c*" rather than to "the composition vector* c*." An unsubscripted* c *will always be understood to be a vector of molar concentrations of the various species in the reaction network under consideration.*

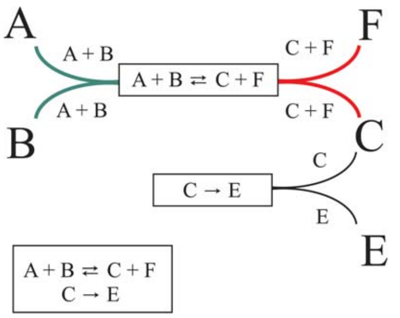

Figure 2. The Species-Reaction Graph for Network 1.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

use later, however, we say that a kinetics for a network is *differentiably monotonic* if, for each reaction in the network, the corresponding kinetic rate function has the following property: At every positive composition,[‡] the partial derivatives with respect to the various species concentrations exist, are positive for the reactant species, and are zero otherwise.

Remark. For the sake of a simple exposition, our focus in this article is entirely on weakly monotonic kinetics. We should say, however, that the conclusions of the main theorem in this article, Theorem 1, obtain not only for any weakly monotonic kinetics (and, in particular, for any differentiably monotonic kinetics) but also for certain families of kinetics that embrace product inhibition: In *two-way weakly monotonic kinetics*,[10] the rate of a reaction such as $A + B \rightarrow C + F$ might be greater at composition $\bar{c}$ than it is at composition c when, for example, the product concentration $\bar{c}_F$ is less than c_F. That Theorem 1 obtains for two-way weakly monotonic kinetics (and, in particular, for two-way differentiably monotonic kinetics) follows from results in Refs. 10 and 11. See also Refs. 7–9.

The Species-Reaction Graph

The central result of this article will be stated in terms of a reaction network's Species-Reaction Graph (SR Graph), which amounts to a graphical depiction of the network of chemical reactions operative within the reactor under consideration.[§] The SR Graph for Network 1 is shown in Figure 2. With this as a motivating example, we can explain how, for a given network, the SR Graph is drawn.

The SR Graph for a reaction network has two types of nodes, species nodes and reaction nodes. There is precisely one species node for each species in the network. Thus, for Network 1 there are nodes in Figure 2 labeled A,B,C,E, and F. There is a reaction node for each reaction in the network, with the understanding that the two reactions of a reversible reaction pair are included in the same reaction node. Thus, in Figure 2 there are two reaction nodes, one labeled $A + B \rightleftarrows C + F$ and the other labeled $C \rightarrow E$. (The small box in the lower left of the figure is not part of the SR Graph. It is placed there simply to remind the reader of the network under consideration.)

By the *complexes*[12] of a reaction network, we mean the objects that appear before and after the reaction arrows. The complexes in Network 1 are $A + B, C + F, C$, and E.

We are now in a position to explain how arcs are drawn in the SR Graph. If a species appears within a complex in a given reaction, then an arc is drawn from the corresponding species node to the corresponding reaction node, and the arc is labeled by the complex in which that species appears. Thus, in Figure 2 species A appears in the complex $A + B$ within the reaction(s) $A + B \rightleftarrows C + F$, so an arc is drawn from the species node A to that reaction node; the arc carries the complex label $A + B$. Similarly, species C appears in the complex C of the reaction $C \rightarrow E$, so an arc is drawn from species node C to reaction node $C \rightarrow E$, and the arc is labeled with the complex C.

The SR Graph results when all such connecting arcs are drawn. In Figure 3, we provide another example, the SR Graph for Network 5, which, like Network 2, is an extension of Network 1.

$$\begin{aligned} &A + B \rightleftarrows C + F \\ &C \rightleftarrows E \\ &A + E \rightleftarrows D \\ &B + C \rightleftarrows G \end{aligned} \tag{5}$$

Note that, unlike the SR Graph in Figure 2, the SR Graph in Figure 3 contains cycles—that is, paths that begin at a certain species (or reaction) and end at that same species (or reaction). In fact, there are three cycles in Figure 3: cycle I (containing only species A, C, and E), cycle II (containing only species B and C), and also the unlabeled large outer cycle (containing species A, B, C, and E).

The central theorem of this article will draw on a classification of cycles that might appear within a network's SR Graph. There will be *odd cycles*, *even cycles*, and *1-cycles*. Also important will be consideration of how the various cycles meet. To describe these SR Graph attributes, we will need a little more vocabulary.

By a *c-pair* in an SR Graph, we mean a pair of arcs that are adjacent to the same reaction node and that carry the same complex label. Thus, in Figure 3 the two arcs connecting the species nodes A and B to reaction node $A + B \rightleftarrows C + F$ constitute a c-pair because they are adjacent to the same reaction node and carry the same complex label,

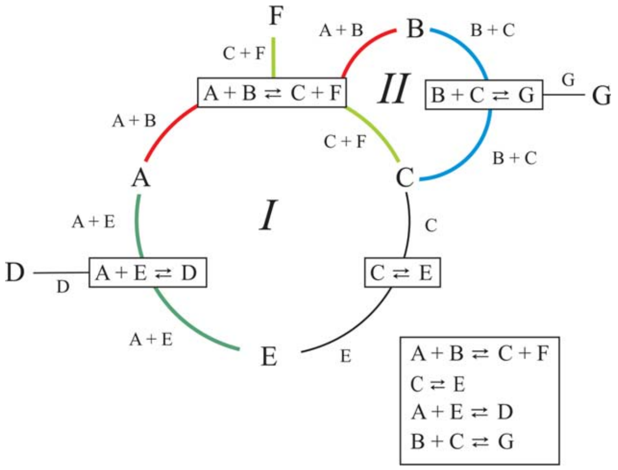

Figure 3. The Species-Reaction Graph for Network 5.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

[‡] *By a positive composition, we mean one in which all species concentrations are strictly positive.*

[§] *In some parts of chemical reaction network theory, the network of "true" chemical reactions is supplemented with pseudo-reactions such as $0 \rightarrow A$ or $A \rightarrow 0$ to model the effect of the inflow or outflow of species A to or from a reactor vessel. Here, when we refer to the Species-Reaction Graph for a reaction network, we have in mind the graph constructed as indicated for the network of "true" chemical reactions.*

$A + B$. Similarly, the pair of arcs labeled $A + E$ constitute a c-pair. The term c-pair is an abbreviation for *complex-pair*.[¶]

By an *odd-cycle* in a Species-Reaction Graph, we mean a cycle containing an odd number of c-pairs. Similarly, an *even-cycle* is one containing an even number of c-pairs. In Figure 3, cycle I is odd because it contains just one c-pair, the pair of arcs labeled by $A + E$. Cycle II is odd because the only c-pair it contains is the pair of arcs carrying the label $B + C$. The large outer cycle is also odd: it contains three c-pairs, carrying labels $A + E, A + B$, and $B + C$. We shall soon meet SR Graphs that have both odd and even cycles.

To introduce the idea of a 1-cycle, we note first that we can associate a stoichiometric coefficient with each arc of an SR Graph. By the *stoichiometric coefficient of an arc*, we mean the stoichiometric coefficient in the arc's labeling complex of the species at the species-node end of the arc. Thus, in Figure 3 the arc connecting species node A to reaction node $A + B \rightleftarrows C + F$ has stoichiometric coefficient 1 because that is the stoichiometric coefficient of A in the labeling complex $A + B$. Similarly, the stoichiometric coefficient of the arc connecting species node C to reaction node $C \rightleftarrows E$ is also 1.

By a *1-cycle*, we mean a cycle in the SR Graph whose arcs all have stoichiometric coefficient 1. In Figure 3, all cycles are 1-cycles. Clearly, this will be the case more generally when every (nonzero) stoichiometric coefficient in the underlying network is 1.

By the intersection of two cycles in the SR Graph, we mean the subgraph consisting of vertices and arcs common to the two cycles. We say that two cycles have a *species-to-reaction intersection* if their intersection is nonempty and if the connected components of the intersection consist of one or more paths, each having a species node at one end and a reaction node at the other end.

Thus, in Figure 3 cycles I and II have a species-to-reaction intersection because they intersect in the one-arc path joining reaction(s) $A + B \rightleftarrows C + F$ and species C. Similarly, the large outer cycle intersects cycle II in a three-arc path joining reaction(s) $A + B \rightleftarrows C + F$ to species C, this time via species B and reaction(s) $B + C \rightleftarrows G$. (In the phrase "species-to-reaction" no directionality is implied.) As we shall see later (Figure 5), it is possible for two cycles to intersect without having a species-to-reaction intersection.

The Main Theorem

What follows is the main theorem of this article. Throughout the remainder of this article, it will be understood that the networks we consider satisfy the natural and relatively weak requirement that in no reaction does the same species appear as both a reactant and as a product. Thus, we permit inclusion of reactions such as $A + B \rightarrow C \rightarrow A + D$ but not $A + B \rightarrow A + D$. Although the theorem in its present form derives entirely from the theory of concordant reaction networks described in Refs.10 and 11, it also has strong connections to Refs. 3–9.

Theorem 1. *Consider a reaction network for which the Species-Reaction Graph satisfies both of the following conditions: Every even cycle is a 1-cycle, and no two even cycles have a species-to-reaction intersection.*

(A) If the kinetics is weakly monotonic then, regardless of the feed composition and regardless of the residence time, the corresponding CFSTR differential equations cannot admit multiple steady states, at least one of which is positive.

(B) If, in addition, the kinetics is differentiably monotonic and the feed composition and residence time are such that the corresponding CFSTR differential equations admit a positive steady state, then not only is that the only steady state but also all real eigenvalues associated with it are negative.

Remark. To a considerable extent, the theorem provides mathematical underpinning for the belief that isothermal CFSTRs behave in largely dull ways, across a wide part of the reaction network landscape and for very broad categories of kinetics. Note that the theorem invokes two conditions about the SR Graph, both commonly satisfied.

The first condition requires only that every even cycle in the SR graph be a 1-cycle. This will happen automatically in the highly common situation in which no stoichiometric coefficient is different from 1. Even when this is not the case, coefficients that are different from 1 are nevertheless permitted, so long as within the SR Graph they appear only in odd cycles. (This stricture too can be weakened while the conclusions of the theorem still hold.[11])

The second SR Graph condition is also somewhat difficult to violate. Violation requires not only that two cycles have a species-to-reaction intersection, but also that both cycles having such an intersection be even. (See Ref. 11 for an even weaker version of the second condition.)

Remark. Even when the conditions of the theorem are satisfied, it does not entirely preclude the possibility that a unique positive steady state is unstable, for the steady state might have associated with it complex eigenvalues with nonnegative real part. This situation is discussed in Ref. 10.

However, when all reactions are reversible, when the kinetics is mass action, and when there are no cycles at all in the SR Graph it follows from a restatement of older "knot-graph" theory[13] in SR Graph terms that all eigenvalues associated with a positive steady state are real (and negative). The same can be said in the not-so-likely event that every cycle in the SR graph is the union of c-pairs, even when the conditions of Theorem 1 are not satisfied.

Table 1 Revisited

In this section, we shall see that Theorem 1 is sufficiently delicate as to make fine distinctions between the highly similar reaction network entries displayed in Table 1.

The SR Graph for Entry 1 was already displayed as Figure 3. Note that there are no even cycles at all. Thus, the two SR Graph conditions of Theorem 1 are satisfied trivially. It follows that the corresponding isothermal CFSTR differential equations have the stability attributes ensured by the theorem, so long as the kinetics is weakly monotonic.

In Figure 4, we show the SR Graph for Table 1's Entry 2, which was also displayed earlier as Network 2. Cycle I is odd because it has just one c-pair, carrying the complex label $A + E$. On the other hand, cycle II has no c-pairs, so it is even. The large outer cycle is also even; it contains two c-pairs, carrying the complex labels $A + B$ and $A + E$. Note that the even cycle II and the (even) large outer cycle have a species-to-reaction intersection, the path through species node

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[¶] *For readers with access to color, arcs that constitute c-pairs will be colored identically.*

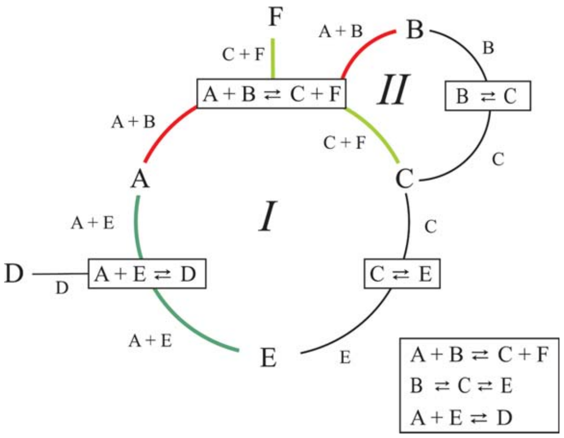

Figure 4. The Species-Reaction Graph for Entry 2 in Table 1.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

B that connects species node C with the reaction node $A + B \leftrightarrows C + F$. In this case, then, Theorem 1 is silent. In fact, it will be recalled—see Figure 1—that for Entry 2, taken with mass action kinetics, there are parameter values such that the corresponding isothermal CFSTR differential equations admit multiple positive steady states, one of which is unstable.

The SR Graph for Entry 3 is displayed as Figure 5. In this case, there are again three cycles, but now they are all even, each having two c-pairs. As every stoichiometric coefficient in the network is 1, all cycles are 1-cycles, so the first SR Graph condition is satisfied. Although each pair of (even) cycles has an intersection, no two cycles have a *species-to-reaction* intersection. (Each intersection is a path that begins and ends with a species node.) Thus, the second SR Graph condition is also satisfied. In contrast to the situation for Entry 2, then, the dull behavior ensured by Theorem 1 is to be expected for Entry 3, so long as the kinetics is weakly monotonic.

The same dull behavior is to be expected for Entry 4, the SR Graph for which is given in Figure 6. In this case, there is a single cycle, and it is even: there are two c-pairs in the cycle, carrying labels A + B and A + E. The cycle is a 1-cycle, so the first SR Graph condition of Theorem 1 is satisfied. Because there is only a single cycle, the second condition is satisfied trivially. Thus, the conclusions of the theorem follow.

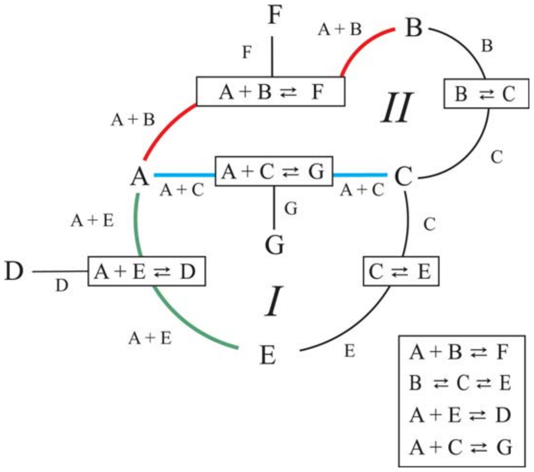

Figure 5. The Species-Reaction Graph for Entry 3 in Table 1.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

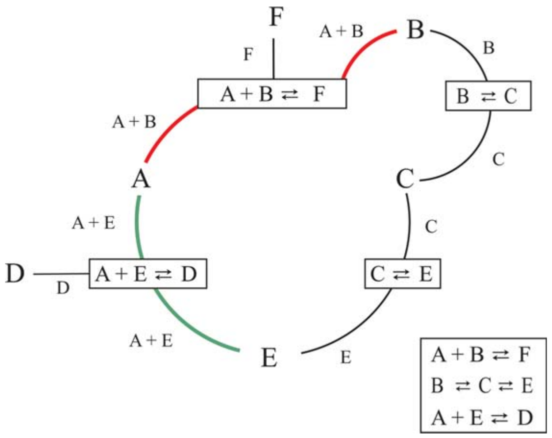

Figure 6. The Species-Reaction Graph for Entry 4 in Table 1.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The situation for the very similar Entry 5 is different. Its SR Graph is displayed as Figure 7. Again, there is just one cycle, and it is even. This time, however, there is a stoichiometric coefficient of 2 within the cycle, so it is not a 1-cycle. In this case, Theorem 1 says nothing. Recall that when Entry 5 is taken with mass action kinetics, there are values for the rate constants, feed concentrations, and residence time such that the resulting isothermal CFSTR differential equations admit multiple positive steady states.

In Figure 8, we display the SR Graph for Entry 6 of Table 1. As in the case of Entry 5, the lone cycle is once again not a 1-cycle. This time, however, the cycle is odd: it contains just one c-pair, labeled by complex A + E. Because there are no even cycles at all in the SR Graph, both SR Graph conditions of Theorem 1 obtain, and the conclusions of the theorem follow.

Remarks about Biochemistry

We argued earlier that the two SR Graph conditions stated in the hypothesis of Theorem 1 will often be satisfied,

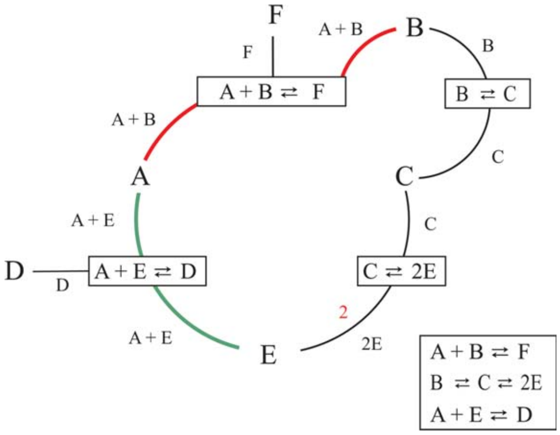

Figure 7. The Species-Reaction Graph for Entry 5 in Table 1.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

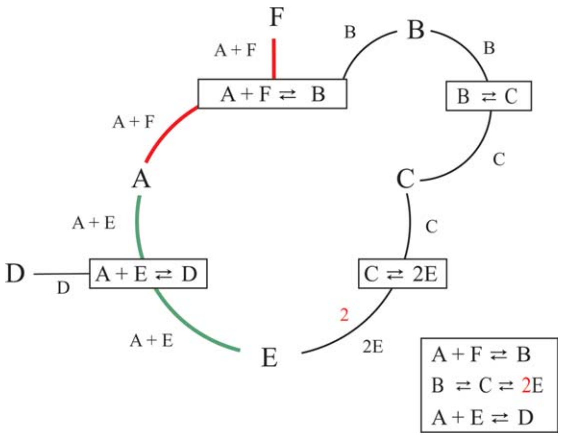

Figure 8. The Species-Reaction Graph for Entry 6 in Table 1.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

perhaps more often than not, across the entire reaction network landscape. This is not to say, however, that there cannot be crucially important regions in that landscape in which one or another of the two conditions is not satisfied. Indeed, we have made the point elsewhere[6] that biochemical reaction networks, written at the fine mechanistic level of enzyme catalysis, will often give rise to multiple cycles in the corresponding SR Graph.

Suppose, for example, that an enzyme E serves as a catalyst for the overall reaction $S1 + S2 \rightarrow P$, whereby substrates S1 and S2 are converted to product P. Just so that we might remain within our classical CFSTR framework, suppose that the conversion is (impractically) carried out in a CFSTR in which substrates and enzyme are in the feed stream, while product, unreacted substrates, enzyme, and enzyme-catalysis intermediates are withdrawn in the effluent stream.

If the mechanism for enzyme catalysis is the classical "ordered binding" one shown in Eq. 6, whereby one substrate must bind to the enzyme before the other,[14] then the corresponding SR Graph is a fairly simple one, having just one cycle. The cycle contains no c-pairs, so it is even, but it is also a 1-cycle. The first SR Graph condition of Theorem 1 is thereby satisfied. Because there is only one cycle, the second condition is satisfied trivially. Thus, the consequences of the theorem follow, not only for mass action kinetics but also for any weakly monotonic kinetics.

$$\begin{array}{l} S1 + E \rightleftarrows ES1 \\ S2 + ES1 \rightleftarrows ES1S2 \rightarrow P + E \end{array} \tag{6}$$

If, on the other hand, the mechanism for enzyme catalysis is the classical "random binding"[14] one shown in Eq. 7, the situation is very different. In this case, the SR Graph is quite complicated. It has several interwoven cycles, and, in particular, there are two even cycles that have a species-to-reaction intersection. In this case, Theorem 1 remains silent. In fact, when the mechanism shown in Eq. 7 is taken with mass action kinetics, there are values of the rate constants, feed concentrations, and residence time such that the resulting isothermal CFSTR differential equations admit multiple positive steady states. (A phase portrait is given in Ref. 6 for a slightly different reactor, in which the enzyme is entrapped within the reactor chamber by means of membranes at the inlet and outlet ports.)

$$\begin{array}{c} S1 + E \rightleftarrows ES1 \quad S2 + E \rightleftarrows ES2 \\ S2 + ES1 \rightleftarrows ES1S2 \leftrightarrows S1 + ES2 \\ \downarrow \\ P + E \end{array} \tag{7}$$

Because, at the mechanistic level, enzyme catalysis (and catalysis generally) can give rise to multiple cycles within the SR Graph, compliance with the hypothesis of Theorem 1 becomes less likely in such contexts. There is, then, a lesson to be learned from the fact that the classical biochemical mechanism in Eq. 7 for a *single* overall reaction can give rise to multiple steady states in a simple isothermal CFSTR setting: when catalysis is at work, we should be cautious about our traditional expectation that isothermal systems behave in dynamically dull ways.

Remarks about the Underlying Theory: Concordant Chemical Reaction Networks

It should be kept in mind that our focus here has been on classical homogeneous CFSTRs. These are reactors in which, of course, every species is in the effluent. In chemical reaction network theory terms—see, for example, Ref. 15—such "fully open" reactors are sometimes modeled by reaction networks that incorporate not only the true chemical reactions but also an "effluent reaction" of the form $s \rightarrow 0$ for each species s in the network. (There is also a reaction of the form $0 \rightarrow s$ for each species s in the feed stream.) In some ways, "fully open reaction networks" of this kind are simpler to study than those that do not contain an effluent (or "degradation") reaction for each species. In particular, for fully open reactors stoichiometric considerations play a less substantial role.

For this reason, it should not be presumed that the central result presented here about classical CFSTRs remains true for reactors that are not fully open. (Especially in reaction network models of biological systems, it is rare that there be a "degradation reaction" $s \rightarrow 0$ for every species.) On the other hand, Theorem 1 in this article is, to a large extent, a special case of theorems in Refs. 10 and 11 that obtain for reactors that are not necessarily fully open.

In fact, results in Refs. 10 and 11 are far broader than those presented here, and they address a wider variety of questions. These articles are devoted to study of the behavioral consequences of a reaction network property called *concordance*. Some reaction networks are "concordant," while others are not. The definition of concordance, which is contained in Ref. 10, is mathematical and does not lend itself to intuitive explanation. Nevertheless, it is important to know that whether or not a particular network is concordant can be easily ascertained by means of freely available easy-to-use software.[16]

What we can say here is that concordance seems to be a fundamental means by which reaction network structure alone enforces a degree of stable behavior against *all* assignments of kinetics within the weakly monotonic class: If a (not necessarily fully open) reaction network is concordant then, for *any* weakly monotonic kinetics, there is no possibility of multiple stoichiometrically compatible steady states, at least one of which is positive. If a reversible[**] reaction network is *not* concordant, then there will invariably exist for it a weakly monotonic kinetics for which the resulting differential equations admit a positive *unstable* steady state. Again,

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[**] *The reversibility requirement here can be weakened considerably.[10] For example, weak reversibility[15] will do.*

whether or not a network is concordant can be determined easily by means of software provided in Ref. 16.

Underlying Theorem 1 is the following idea: The central result in Ref. 11 implies that, if a reaction network's SR Graph satisfies the two conditions of Theorem 1, then one has concordance of the reaction network obtained by adding to the original network an "effluent reaction" s → 0 for every species s in the network and a "feed reaction" of the form 0 → s for each species s in the feed.[††] In this case, the properties of concordant networks impart to the CFSTR differential equations the stability characteristics described in Theorem 1.

We note in closing that, while attributes of a network's SR Graph will often *suffice* to ensure concordance, a network might *still* be concordant even when, for example, the SR Graph conditions stated in Theorem 1 are not satisfied. In such instances, the inherent stability properties of concordant networks still accrue to the resulting differential equations, so long as the kinetics is weakly monotonic.

For this reason, it should be kept in mind that easy-to-use computational tools such as those provided in Ref. 16 give an alternate and more decisive way to ascertain concordance of a particular network at hand. It should also be kept in mind that consequences of concordance provided in Refs. 10 and 11 reach much further than the special "fully open" CFSTR setting considered here.

Discussion: Neal Amundson

In an article dedicated to Neal Amundson, it is worth stating explicitly something that all contributors to this memorial volume know with certainty but which some current students might not know at all: During the last half of the 20th century Neal changed chemical engineering. He was a mathematician by training, so he helped elevate the theoretical side of the subject to new heights. But Neal was also the leader much more broadly. His example changed our culture profoundly for the better in all its aspects. MF is grateful for his presence over so many years.

Acknowledgment

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Appendix

Here we provide parameter values for which two networks, shown as the second and fifth entries of Table 1, give multiple steady states in an isothermal CFSTR context. The units are presumed self-consistent, with the CFSTR residence time in each case taken to be 1. Recall that Entry 2 is identical to Network 2 in the text. The phase portrait in Figure 1 is for the parameter values given below.

Parameter values for Entry 2 in Table 1

Feed composition:

$$c_{\mathrm{A}}^{f} = 60.694,\, c_{\mathrm{B}}^{f} = 15.133,\, c_{\mathrm{C}}^{f} = c_{\mathrm{D}}^{f} = c_{\mathrm{E}}^{f} = c_{\mathrm{F}}^{f} = 0$$

Mass action rate constants:

$$\mathrm{A} + \mathrm{B} \underset{0.272}{\overset{4.997}{\rightleftharpoons}} \mathrm{C} + \mathrm{F}$$

$$\mathrm{B} \underset{25.575}{\overset{1.000}{\rightleftharpoons}} \mathrm{C} \underset{57.077}{\overset{70.211}{\rightleftharpoons}} \mathrm{E}$$

$$\mathrm{A} + \mathrm{E} \underset{0.082}{\overset{1.333}{\rightleftharpoons}} \mathrm{D}$$

Two distinct steady states:

Steady State 1	Species	Steady State 2
10.020	A	4.438
0.976	B	2.994
0.990	C	1.490
12.181	D	9.002
0.987	E	1.646
38.493	F	47.254

Parameter values for Entry 5 in Table 1

Feed composition:

$$c_{\mathrm{A}}^{f} = 52.484,\, c_{\mathrm{B}}^{f} = 41.771,\, c_{\mathrm{C}}^{f} = c_{\mathrm{D}}^{f} = c_{\mathrm{E}}^{f} = c_{\mathrm{F}}^{f} = 0$$

[††] *From the viewpoint of reaction network theory, it is this augmented network that serves to model the classical CFSTR.*[15]

Mass action rate constants:

$$A + B \underset{0.037}{\overset{28.058}{\rightleftharpoons}} F$$

$$B \underset{26.760}{\overset{40.473}{\rightleftharpoons}} C \underset{1.660}{\overset{14.373}{\rightleftharpoons}} 2E$$

$$A + E \underset{0.041}{\overset{25.426}{\rightleftharpoons}} D$$

Two distinct steady states:

Steady State 1	Species	Steady State 2
8.782	A	0.497
0.165	B	1.649
0.158	C	1.822
4.530	D	29.834
0.021	E	2.460
39.172	F	22.154

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