

MULTIPLE EQUILIBRIA IN COMPLEX CHEMICAL REACTION NETWORKS: I. THE INJECTIVITY PROPERTY*

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Abstract. The capacity for multiple equilibria in an isothermal homogeneous continuous flow stirred tank reactor is determined by the reaction network. Examples show that there is a very delicate relationship between reaction network structure and the possibility of multiple equilibria. We suggest a new method for discriminating between networks that have the capacity for multiple equilibria and those that do not. Our method can be implemented using standard computer algebra software and gives answers for many reaction networks for which previous methods give no information.

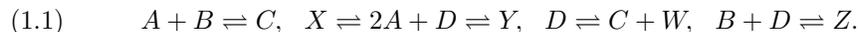
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1. Introduction. We are interested in studying the uniqueness of positive equilibrium points of a special but large class of systems of nonlinear ordinary differential equations (ODEs): those that derive from chemical reaction networks. In order to understand how these equations arise, we will first look informally at an example of a reaction network and see how it induces a system of ODEs.

Consider some chemical species A, B, C, D, W, X, Y, and Z, and suppose that the chemical reactions occurring among these species are



We will study a particular kind of reactor, called a continuous flow stirred tank reactor (CFSTR; see [3]) by chemical engineers. Think of a CFSTR as just some enclosed volume endowed with a feed stream and an outflow stream. Suppose that its contents are kept at constant temperature and are spatially uniform. Now imagine that a liquid mixture of species A, B, C, D, W, X, Y, and Z is continuously supplied to some CFSTR at a constant volumetric flow rate g (volume/time). Also, the contents of the CFSTR are continuously removed at the same volumetric flow rate g . Chemical reactions occur in the CFSTR, according to (1.1). We would like to investigate the temporal evolution of the composition of the mixture within the CFSTR. Let us denote by $c_A^f, c_B^f, \dots, c_Z^f$ the molar concentrations (moles/volume) in the feed stream and by $c_A(t), c_B(t), \dots, c_Z(t)$ the molar concentrations within the CFSTR (and effluent stream) at time t . We will denote the vector of all molar concentrations within the CFSTR by $c(t)$. We get the picture shown in Figure 1.1.

One source of change in composition is the occurrence of chemical reactions. It is generally assumed that the occurrence rate of each reaction at time t depends just

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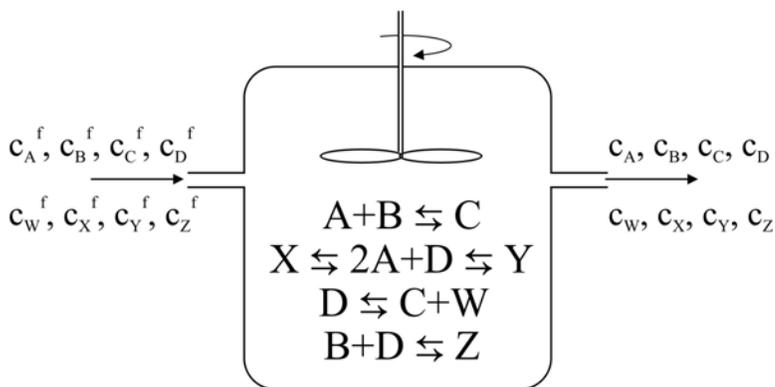


FIG. 1.1. The CFSTR of the reaction network (1.1).

on the mixture composition $c(t)$. For example, for the reaction $A + B \rightarrow C$ there exists a nonnegative real-valued *rate function* $K_{A+B \rightarrow C}$ such that $K_{A+B \rightarrow C}(c)$ is the occurrence rate of reaction $A + B \rightarrow C$ per unit volume of mixture when the mixture composition is given by the vector c . Let us now think about the instantaneous rate of change of c_A . Whenever the reaction $A + B \rightarrow C$ occurs we lose one molecule of A . Also, whenever the reaction $C \rightarrow A + B$ occurs we gain one molecule of A . Similarly, whenever the reaction $X \rightarrow 2A + C$ occurs we gain two molecules of A , and so on.

The other source of changes in composition is the difference between the composition c^f in the feed stream and the composition c in the effluent stream. (Note that the composition of the effluent stream is presumed to be identical to that of the homogeneous mixture within the vessel.) If V is the total volume of the mixture within the CFSTR,¹ we get

$$(1.2) \quad \begin{aligned} V\dot{c}_A = & g(c_A^f - c_A) - VK_{A+B \rightarrow C}(c) + VK_{C \rightarrow A+B}(c) \\ & - 2VK_{2A+D \rightarrow X}(c) + 2VK_{X \rightarrow 2A+D}(c) \\ & - 2VK_{2A+D \rightarrow Y}(c) + 2VK_{Y \rightarrow 2A+D}(c). \end{aligned}$$

We will now look more closely at the structure of the rate functions. In most cases chemists suppose the rate functions to be of *mass-action* type (see [26]). This means that, for example, for the reaction $A + B \rightarrow C$, the more A there is in the CFSTR, the more occurrences of the reaction there will be, and similarly for B . More precisely, we presume that the occurrence rate of the reaction $A + B \rightarrow C$ is proportional to the probability of A and B meeting in the CFSTR, which, in turn, is proportional to the value of $c_A c_B$. Thus, we write

$$K_{A+B \rightarrow C}(c) = k_{A+B \rightarrow C} c_A c_B,$$

where $k_{A+B \rightarrow C}$ is a positive *rate constant* for the reaction $A + B \rightarrow C$. For the reaction $2A + D \rightarrow X$ an occurrence requires two molecules of A and one molecule of D to meet in the CFSTR, and we consider the probability of this encounter to be proportional to $c_A^2 c_D$. Therefore we get

$$K_{2A+D \rightarrow X}(c) = k_{2A+D \rightarrow X} c_A^2 c_D,$$

¹We assume hereafter that the densities of the feed and the effluent streams are identical and time-invariant. This implies that V is constant in time. We also assume throughout that the temperature of the reacting mixture is held constant.

where $k_{2A+D \rightarrow X}$ is the rate constant for the reaction $2A + D \rightarrow X$. In the case of a reaction such as $D \rightarrow C + W$ it is presumed that the occurrence rate is simply proportional to the molar concentration of D , i.e.,

$$K_{D \rightarrow C+W}(c) = k_{D \rightarrow C+W}c_D.$$

The rate constants are usually either approximated on the basis of chemical principles or are deduced from experiments. If we assume mass-action kinetics for the network (1.1), then we get the following *associated system of differential equations*:

$$(1.3) \quad \begin{aligned} \dot{c}_A &= (g/V)(c_A^f - c_A) - k_{A+B \rightarrow C}c_Ac_B + k_{C \rightarrow A+B}c_C - 2k_{2A+D \rightarrow X}c_A^2c_D \\ &\quad + 2k_{X \rightarrow 2A+D}c_X - 2k_{2A+D \rightarrow Y}c_A^2c_D + 2k_{Y \rightarrow 2A+D}c_Y, \\ \dot{c}_B &= (g/V)(c_B^f - c_B) - k_{A+B \rightarrow C}c_Ac_B + k_{C \rightarrow A+B}c_C \\ &\quad + k_{Z \rightarrow B+D}c_Z - k_{B+D \rightarrow Z}c_Bc_D, \\ \dot{c}_C &= (g/V)(c_C^f - c_C) + k_{A+B \rightarrow C}c_Ac_B - k_{C \rightarrow A+B}c_C \\ &\quad + k_{D \rightarrow C+W}c_D - k_{C+W \rightarrow D}c_Cc_W, \\ \dot{c}_D &= (g/V)(c_D^f - c_D) + k_{X \rightarrow 2A+D}c_X - k_{2A+D \rightarrow X}c_A^2c_D \\ &\quad + k_{Y \rightarrow 2A+D}c_Y - k_{2A+D \rightarrow Y}c_A^2c_D - k_{D \rightarrow C+W}c_D + k_{C+W \rightarrow D}c_Cc_W \\ &\quad - k_{B+D \rightarrow Z}c_Bc_D + k_{Z \rightarrow B+D}c_Z, \\ \dot{c}_W &= (g/V)(c_W^f - c_W) + k_{D \rightarrow C+W}c_D - k_{C+W \rightarrow D}c_Cc_W, \\ \dot{c}_X &= (g/V)(c_X^f - c_X) - k_{X \rightarrow 2A+D}c_X + k_{2A+D \rightarrow X}c_A^2c_D, \\ \dot{c}_Y &= (g/V)(c_Y^f - c_Y) + k_{2A+D \rightarrow Y}c_A^2c_D - k_{Y \rightarrow 2A+D}c_Y, \\ \dot{c}_Z &= (g/V)(c_Z^f - c_Z) + k_{B+D \rightarrow Z}c_Bc_D - k_{Z \rightarrow B+D}c_Z. \end{aligned}$$

Therefore we obtain a system of ODEs where all equations are determined by the reaction network up to some constants: $c_A^f, c_B^f, \dots, c_Z^f, g/V$, and $k_{A+B \rightarrow C}, k_{C \rightarrow A+B}, \dots, k_{Z \rightarrow B+D}$. We are now going to ask the question: does this system of ODEs have no more than one positive equilibrium for all positive values of g/V , all positive values of the rate constants, and all nonnegative values of the feed concentrations $c_A^f, c_B^f, \dots, c_Z^f$?

This question is motivated by experiments. For homogeneous liquid phase CFSTRs, there are very few reports of reaction networks with more than one positive equilibrium, despite hundreds of reaction networks being studied (see [9] for one such report). We are asking this question for *all* positive rate constants since in practice there is poor knowledge of the rate constants of reactions.

This question is not easy to answer, in general. Even if, for the simple example above, we could decide one way or the other by some ad-hoc method, there will be thousands of other reaction networks for which we will still not know the answer. There are important reaction networks with hundreds of reactions. Ideally, there will be a simple way to decide on the uniqueness of equilibria.

We say that a mass-action network *has the capacity for multiple positive equilibria* (in an isothermal homogeneous CFSTR context) if there are positive values of the flow rate, the volume, the rate constants, and nonnegative values of the feed concentrations such that the resulting differential equations admit two or more distinct positive equilibria.

According to [30], there are examples of very similar reaction networks with very different capacities for multiple positive equilibria (see Table 1.1). Networks (i) and

TABLE 1.1

Some examples of reaction networks and their capacity for multiple positive equilibria [30].

Reaction network	Has the capacity for multiple equilibria?
(i) $A + B \rightleftharpoons P$ $B + C \rightleftharpoons Q$ $C \rightleftharpoons 2A$	Yes
(ii) $A + B \rightleftharpoons P$ $B + C \rightleftharpoons Q$ $C + D \rightleftharpoons R$ $D \rightleftharpoons 2A$	No
(iii) $A + B \rightleftharpoons P$ $B + C \rightleftharpoons Q$ $C + D \rightleftharpoons R$ $D + E \rightleftharpoons S$ $E \rightleftharpoons 2A$	Yes
(iv) $A + B \rightleftharpoons P$ $B + C \rightleftharpoons Q$ $C \rightleftharpoons A$	No
(v) $A + B \rightleftharpoons F$ $A + C \rightleftharpoons G$ $C + D \rightleftharpoons B$ $C + E \rightleftharpoons D$	Yes
(vi) $A + B \rightleftharpoons 2A$	No
(vii) $2A + B \rightleftharpoons 3A$	Yes
(viii) $A + 2B \rightleftharpoons 3A$	No

(iii) in Table 1.1 have the capacity for multiple positive equilibria, but the “middle case” network (ii) does not. Similarly, network (iv) is almost identical to (i), but does not have the capacity for multiple positive equilibria. Moreover, network (v) is an example that shows that we don’t need two or more copies of the same species to appear in the same reaction for the network to admit multiple positive equilibria. Also, changing (vi) to (vii) does bring in multiple positive equilibria, but changing (vi) to (viii) does not. Therefore, a good theory of multiple positive equilibria in CFSTRs should be able to differentiate between these subtle differences.

Let us look again at the system of ODEs in (1.3). If we are just interested in equilibria, we set all the left-hand side terms equal to zero, and we get a system of polynomial (algebraic) equations. Let us also move the feed terms c_A^f, \dots, c_Z^f to the other side of the equations. We choose units such that $g/V = 1$. If we now change signs in both sides and rearrange terms, then we get the following system of eight polynomial equations:

$$\begin{aligned}
 (1.4) \quad c_A^f &= c_A + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C + 2k_{2A+D \rightarrow X} c_A^2 c_D \\
 &\quad - 2k_{X \rightarrow 2A+D} c_X + 2k_{2A+D \rightarrow Y} c_A^2 c_D - 2k_{Y \rightarrow 2A+D} c_Y, \\
 c_B^f &= c_B + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C - k_{Z \rightarrow B+D} c_Z \\
 &\quad + k_{B+D \rightarrow Z} c_B c_D, \\
 c_C^f &= c_C - k_{A+B \rightarrow C} c_A c_B + k_{C \rightarrow A+B} c_C - k_{D \rightarrow C+W} c_D \\
 &\quad + k_{C+W \rightarrow D} c_C c_W,
 \end{aligned}$$

$$\begin{aligned}
c_D^f &= c_D - k_{X \rightarrow 2A+D} c_X + k_{2A+D \rightarrow X} c_A^2 c_D - k_{Y \rightarrow 2A+D} c_Y \\
&\quad + k_{2A+D \rightarrow Y} c_A^2 c_D + k_{D \rightarrow C+W} c_D - k_{C+W \rightarrow D} c_C c_W \\
&\quad + k_{B+D \rightarrow Z} c_B c_D - k_{Z \rightarrow B+D} c_Z, \\
c_W^f &= c_W - k_{D \rightarrow C+W} c_D + k_{C+W \rightarrow D} c_C c_W, \\
c_X^f &= c_X + k_{X \rightarrow 2A+D} c_X - k_{2A+D \rightarrow X} c_A^2 c_D, \\
c_Y^f &= c_Y - k_{2A+D \rightarrow Y} c_A^2 c_D + k_{Y \rightarrow 2A+D} c_Y, \\
c_Z^f &= c_Z - k_{B+D \rightarrow Z} c_B c_D + k_{Z \rightarrow B+D} c_Z.
\end{aligned}$$

Let us denote by k the vector formed by the parameters $k_{A+B \rightarrow C}$, $k_{C \rightarrow A+B}, \dots$, $k_{Z \rightarrow B+D}$. Now we denote by $p(c, k)$ the vector of right-hand sides of the system of polynomial equations (1.4), and we call it *the polynomial function associated to the reaction network* (1.1). We regard $p(c, k)$ as a vector-valued function of a (positive) composition vector c and depending on a (positive) vector of rate constants k .

We say that the reaction network (1.1) is an *injective reaction network* if the function $c \rightarrow p(c, k)$ is injective for all positive k .

The following simple fact is a key observation: *If a reaction network has the capacity for multiple positive equilibria, then there exists some choice of positive vector k_0 such that the function $c \rightarrow p(c, k_0)$ is not injective.* In particular, $p(c^*, k_0) = p(c^\#, k_0) = c^f$ for some feed composition c^f and some distinct compositions c^* , $c^\#$. In other words, an injective reaction network does not have the capacity for multiple positive equilibria; i.e., injectivity is a sufficient condition for the absence of multiple positive equilibria.

Remark 1.1. Injectivity is *not* a necessary condition for the absence of multiple positive equilibria. The reason is that, for a network to admit multiple positive equilibria, there must be a k_0 such that $p(\cdot, k_0)$ maps two distinct compositions not only into the same vector, but, in fact, also into a *nonnegative* feed composition c^f (see (1.4), (3.10)). Were it not for this nonnegativity condition, injectivity would be equivalent to uniqueness of equilibria.

Nevertheless, the class of injective reaction networks subsumes the largest class of reaction networks for which the answer was previously found in [20, 30, 31]. *The main purpose of this paper is to describe a method that allows us to decide whether a given reaction network is injective or not.*

Remark 1.2. In general, it is of course very difficult to check whether a given multidimensional polynomial function is injective or not. Moreover, the function $c \rightarrow p(c, k)$ involves several unknown parameters. Our method derives, first, from a theoretical observation about the function $p(\cdot, \cdot)$ and, second, from a rather remarkable empirical observation.

The theoretical observation, discussed in section 3, is that a reaction network is injective whenever its associated polynomial function has the property that $\frac{\partial p(c, k)}{\partial c}$ is nonsingular for all positive c and all positive k . (There is no claim here that any such assertion is true for polynomial functions in general; rather, the assertion is made specifically for polynomial functions that derive, in the manner indicated, from chemical reaction networks.)

To describe the empirical observation, we first note that the nonsingularity property is, of course, equivalent to the requirement that $\det(\frac{\partial p(c, k)}{\partial c})$ be nonzero for all positive c and all positive k . For moderately large networks, the calculation of $\det(\frac{\partial p(c, k)}{\partial c})$ will result in hundreds or thousands of terms, even after combining all similar monomials. Each resulting nonzero term will be a monomial in the (positive)

species concentrations and the (positive) rate constants, with each term containing an integer coefficient. Thus the sign of each term is carried by the sign of its integer coefficient. The empirical observation is this: *For very large and robust classes of networks it is the case that, despite the huge number of terms, the integer coefficient in every term is positive!* In this case, $\det(\frac{\partial p(c,k)}{\partial c})$ cannot vanish, and injectivity of the network is ensured (as is the impossibility of multiple positive equilibria). In fact, we will show that positivity of all nonzero coefficients is *both necessary and sufficient* for injectivity of the network.

In a subsequent article we intend to characterize, in graph-theoretical terms, large classes of networks for which all coefficients are positive. In the meantime, we observe that, for a given network of interest, checking for positivity of the coefficients is a matter that can be resolved by presently available computer algebra systems.

By way of example, we show in (1.5) the first few terms of the expansion of $\det(\frac{\partial p(c,k)}{\partial c})$ for network (1.1):

$$\begin{aligned}
 (1.5) \quad & \det\left(\frac{\partial p(c,k)}{\partial c}\right) \\
 &= 10k_{C \rightarrow A+B}k_{D \rightarrow C+W}k_{2A+D \rightarrow X}c_Ac_D^2k_{W \rightarrow 0}k_{B+D \rightarrow Z}k_{X \rightarrow 0}k_{Y \rightarrow 0}k_{Z \rightarrow 0} \\
 &+ 4k_{C \rightarrow A+B}k_{D \rightarrow 0}k_{2A+D \rightarrow X}c_Ac_D^2k_{W \rightarrow 0}k_{B+D \rightarrow Z}k_{X \rightarrow 0}k_{Y \rightarrow 2A+D}k_{Z \rightarrow 0} \\
 &+ 4k_{C \rightarrow A+B}k_{D \rightarrow 0}k_{2A+D \rightarrow Y}c_Ac_Dk_{W \rightarrow 0}k_{B \rightarrow 0}k_{X \rightarrow 0}k_{Y \rightarrow 0}k_{Z \rightarrow 0} \\
 &+ k_{C \rightarrow A+B}k_{2A+D \rightarrow X}c_A^2k_{A \rightarrow 0}k_{W \rightarrow 0}k_{B+D \rightarrow Z}c_Dk_{X \rightarrow 0}k_{Y \rightarrow 2A+D}k_{Z \rightarrow 0} \\
 &+ 4k_{C \rightarrow A+B}k_{D \rightarrow 0}k_{2A+D \rightarrow Y}c_Ac_Dk_{W \rightarrow 0}k_{B \rightarrow 0}k_{X \rightarrow 2A+D}k_{Y \rightarrow 0}k_{Z \rightarrow 0} \\
 &+ 6k_{C \rightarrow A+B}k_{D \rightarrow C+W}k_{2A+D \rightarrow Y}c_Ac_Dk_{W \rightarrow 0}k_{B \rightarrow 0}k_{X \rightarrow 2A+D}k_{Y \rightarrow 0}k_{Z \rightarrow B+D} \\
 &+ 9k_{C \rightarrow 0}k_{2A+D \rightarrow Y}c_A^2c_Dk_{A+B \rightarrow C}k_{C+W \rightarrow D}c_Ck_{B+D \rightarrow Z}c_Bk_{Z \rightarrow 0}k_{X \rightarrow 0}k_{Y \rightarrow 0} \\
 &+ 9k_{C \rightarrow 0}k_{2A+D \rightarrow Y}c_A^2c_Dk_{A+B \rightarrow C}k_{C+W \rightarrow D}c_Ck_{B+D \rightarrow Z}c_Bk_{Z \rightarrow 0}k_{X \rightarrow 2A+D}k_{Y \rightarrow 0} \\
 &+ \dots
 \end{aligned}$$

In Table 1.2 we exhibit the (computer-generated) set of all coefficients that would have resulted had the expansion been completed. Note that all the entries are positive. Thus, we conclude that network (1.1) does not have the capacity for multiple positive equilibria in an isothermal CFSTR context.

Our claim that, across wide varieties of reaction networks, it is common for all coefficients to be positive is consistent with the paucity of experimental observations of multiple equilibria in isothermal homogeneous CFSTRs.

In section 3 we provide elaboration on the remarks made here.

Before we describe our results we would like to specify their place in the general landscape of chemical reaction network theory.

Stability results are discussed in [6, 7, 8, 11, 12, 13, 14, 15, 16, 18, 20, 24].

In [12, 13, 14, 15, 16, 17, 18, 19, 20, 25] reaction networks are classified by means of a nonnegative integer index called the *deficiency*. It is then shown how, for reaction networks of *small* deficiency, one can decide whether they have the capacity for multiple positive equilibria (see also the software package [21]).

On the other hand, it is also shown (see [27]) that the deficiency-oriented theory is not likely to give information for a large class of isothermal homogeneous CFSTRs. Work that is *complementary* to the deficiency-oriented theory, and aimed specifically at CFSTRs, was originated in [29] and then substantially broadened in [30, 31].

In [30, 31] Schlosser and Feinberg associate to any reaction network a graph called the *Species-Complex-Linkage (SCL) graph* of the reaction network. Then they describe

2. Definitions and notation. We denote by \mathbb{R}_+ the set of strictly positive real numbers, and by $\bar{\mathbb{R}}_+$ the set of nonnegative real numbers. For an arbitrary finite set I we denote by \mathbb{R}^I the real vector space of all formal sums $\sum_{i \in I} \alpha_i i$ for all $\alpha_i \in \mathbb{R}$. Note that I becomes a basis of \mathbb{R}^I . By \mathbb{R}_+^I we mean the set of sums $\sum_{i \in I} \alpha_i i$ in which all α_i are strictly positive. By $\bar{\mathbb{R}}_+^I$ we mean the set of sums $\sum_{i \in I} \alpha_i i$ in which all α_i are nonnegative.

In the following definition the *complexes* of a reaction network are to be understood as the objects (such as $A + B$) at the heads and tails of the reaction arrows.

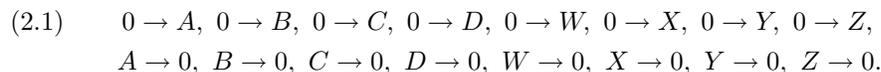
DEFINITION 2.1 (see [14, 18]). A chemical reaction network consists of three finite sets:

- (i) a set \mathcal{S} of species of the network;
- (ii) a set $\mathcal{C} \subset \bar{\mathbb{R}}_+^{\mathcal{S}}$ of complexes of the network;
- (iii) a set $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$ of reactions, with the following properties:
 - (a) $(y, y) \notin \mathcal{R}$ for any $y \in \mathcal{C}$;
 - (b) for each $y \in \mathcal{C}$ there exists $y' \in \mathcal{C}$ such that $(y, y') \in \mathcal{R}$ or such that $(y', y) \in \mathcal{R}$.

When $(y, y') \in \mathcal{R}$ we say that the complex y reacts to complex y' . When this is the case we will write $y \rightarrow y'$, since it is the usual notation in chemistry.

If we look at the differential equations in (1.3), it is clear that, for CFSTRs in general, there will be not only terms that derive from the occurrence of chemical reactions but also linear terms (such as $-(g/V)c_A$) that derive from the presence of the outflow stream, and constant terms (such as $(g/V)c_A^f$) that derive from the presence of the feed stream. So that all such terms can be brought into a common reaction network theory framework, it will be useful to regard such “flow” terms as having derived from formal chemical “reactions” such as $A \rightarrow 0$ (corresponding to the outflow of A) and $0 \rightarrow A$ (corresponding to the feed of A); see [12, 25]. Here we view “0” as the zero vector of $\mathbb{R}^{\mathcal{S}}$. If we imagine $A \rightarrow 0$ to be governed by mass-action kinetics with rate constant $k_{A \rightarrow 0} = g/V$, then the contribution to \dot{c}_A in (1.3) will be precisely $-(g/V)c_A$. We adopt the convention that the mass-action rate of a reaction of the form $0 \rightarrow A$ is constant (and equal to the associated rate constant $k_{0 \rightarrow A}$). Thus, if we choose $k_{0 \rightarrow A} = (g/V)c_A^f$, then the contribution of the reaction $0 \rightarrow A$ to \dot{c}_A is just $(g/V)c_A^f$. In this way, the formal “flow reactions” $A \rightarrow 0$ and $0 \rightarrow A$ account for the flow terms that appear in the equation for \dot{c}_A . More generally, there are advantages to viewing CFSTR mass-action differential equations as having derived from a mass-action system in which the set of “true” reactions is augmented with the set of “flow reactions,” with appropriately chosen rate constants. (Recall that we have chosen units such that $g/V = 1$ so that, for us, $k_{s \rightarrow 0} = 1$ for all $s \in \mathcal{S}$.)

Hereafter, we shall regard the operative reaction network under discussion to be the augmented one. If, for example, all species are present in the feed stream, then we augment the set of reactions in (1.1) by adding the following flow reactions:



If a certain species, say W , is deemed absent from the feed stream (i.e., if $c_W^f = 0$), then the reaction $0 \rightarrow W$ would be omitted. (With respect to injectivity considerations, the presence or absence of certain species in the feed is of no consequence.) Flow reactions of type $0 \rightarrow A$ are called *feed reactions*, and flow reactions of type $A \rightarrow 0$ are called *outflow reactions*. As Figure 1.1 indicates, all species are deemed present

in the effluent stream, so there is an outflow reaction for each species. (In a future paper we will discuss the implications of relaxing this assumption.)

So, the augmented network corresponding to the reaction network (1.1) has the set of species $\mathcal{S} = \{A, B, C, D, W, X, Y, Z\}$ and the set of complexes $\mathcal{C} = \{A, B, C, D, W, X, Y, Z, 0, A + B, 2A + D, C + W, B + D\}$. It contains the ten true reactions in (1.1) and, when all species are deemed to be in the feed, the sixteen flow reactions in (2.1).

In general, we denote by \mathcal{R}_t the set of true reactions, by \mathcal{R}_f the set of feed reactions, and by \mathcal{R}_o the set of outflow reactions.

DEFINITION 2.2. *A mass-action system is a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ taken together with an element $k \in \mathbb{R}_+^{\mathcal{R}}$. The number $k_{y \rightarrow y'}$ is the rate constant of the reaction $y \rightarrow y' \in \mathcal{R}$.*

For two vectors in $\bar{\mathbb{R}}_+^{\mathcal{S}}$, say $u = \sum_{s \in \mathcal{S}} u_s s$ and $v = \sum_{s \in \mathcal{S}} v_s s$, we denote $u^v = \prod_{s \in \mathcal{S}} (u_s)^{v_s}$. Here we use the convention that $0^0 = 1$.

We will now show how, by using the notation above, we can express the system of ODEs associated to a reaction network as a very compact formula. For example, note that the term $k_{A+B \rightarrow C} c_A c_B$ on the first line in (1.3) can be written as $k_{y \rightarrow y'} c^y$; here $y = A + B$ and $y' = C$ are regarded as vectors in $\mathbb{R}^{\mathcal{S}}$, where \mathcal{S} is the set of species. Also, the term $-2k_{2A+D \rightarrow Y} c_A^2 c_D$ on the second line in (1.3) can be written as $-2k_{y \rightarrow y'} c^y$, where $y = 2A + D, y' = Y$.

If we look for *all* appearances of $k_{2A+D \rightarrow Y} c_A^2 c_D$ in (1.3), we notice that they take place in equations corresponding to species A, D, Y , i.e., exactly the species that appear in the complexes y, y' . Moreover, the coefficient of each species in the reaction $2A + D \rightarrow Y$ is equal (up to sign) to the coefficient of the monomial $k_{2A+D \rightarrow Y} c_A^2 c_D$ in the equation corresponding to that species. The sign is minus for species in y and plus for species in y' . Therefore the factor $k_{2A+D \rightarrow Y} c_A^2 c_D$ contributes to the right side of the (vector) ODE precisely as the term $k_{y \rightarrow y'} c^y (y' - y)$, where $y = 2A + D, y' = Y$.

Then we get the following two definitions (see [14, 19]).

DEFINITION 2.3. *The species-formation-rate function (or simply the rate function) for a mass-action system $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ is the function $r(\cdot, k) : \bar{\mathbb{R}}_+^{\mathcal{S}} \rightarrow \mathbb{R}^{\mathcal{S}}$, defined by*

$$r(c, k) = \sum_{y \rightarrow y' \in \mathcal{R}} k_{y \rightarrow y'} c^y (y' - y).$$

DEFINITION 2.4. *The system of differential equations associated to a mass-action system $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ is given by*

$$\dot{c} = r(c, k).$$

We see here again that the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and the vector k uniquely determine the system of differential equations associated to a mass-action system.

DEFINITION 2.5. *A positive equilibrium of a mass-action system $(\mathcal{S}, \mathcal{C}, \mathcal{R}, k)$ is an element $c \in \mathbb{R}_+^{\mathcal{S}}$ such that $r(c, k) = 0$.*

DEFINITION 2.6. *We say that a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ has the capacity for multiple positive equilibria if there exist $k \in \mathbb{R}_+^{\mathcal{R}}$, $a \in \mathbb{R}_+^{\mathcal{S}}$, $b \in \mathbb{R}_+^{\mathcal{S}}$, $a \neq b$, such that $r(a, k) = r(b, k) = 0$.*

To formulate the following definition recall that we have $\mathcal{R} = \mathcal{R}_f \cup \mathcal{R}_o \cup \mathcal{R}_t$, where $\mathcal{R}_f \cup \mathcal{R}_o$ is the set of flow reactions (\mathcal{R}_f is the set of feed reactions, \mathcal{R}_o is the set of outflow reactions), and \mathcal{R}_t is the set of true reactions.

DEFINITION 2.7. Given a chemical reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$, its associated polynomial function $p_{\mathcal{N}}(\cdot, \cdot) : \mathbb{R}_+^{\mathcal{S}} \times \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \rightarrow \mathbb{R}^{\mathcal{S}}$ is

$$p_{\mathcal{N}}(c, k) = \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} k_{y \rightarrow y'} c^y (y - y').$$

Note that

$$r(c, k) = -p_{\mathcal{N}}(c, k) + \sum_{y \rightarrow y' \in \mathcal{R}_f} k_{y \rightarrow y'} c^y (y' - y).$$

With \mathcal{S}_f denoting the set of species in the feed stream, note also that

$$\sum_{y \rightarrow y' \in \mathcal{R}_f} k_{y \rightarrow y'} c^y (y' - y) = \sum_{s \in \mathcal{S}_f} k_{0 \rightarrow s} s.$$

The last equation results from the fact that $\mathcal{R}_f = \{0 \rightarrow s : s \in \mathcal{S}_f\}$ and, for $y = 0$, $c^y = 1$. Finally, note that the equilibrium equation $r(c, k) = 0$ is equivalent to

$$(2.2) \quad p_{\mathcal{N}}(c, k) = \sum_{s \in \mathcal{S}_f} k_{0 \rightarrow s} s,$$

and the sum on the right side of (2.2) is constant. Therefore, if the polynomial function $c \rightarrow p_{\mathcal{N}}(c, k)$ is injective for every value of the parameter $k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$, then there cannot exist multiple positive equilibria.

DEFINITION 2.8. We say that a chemical reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is injective if the polynomial function $c \rightarrow p_{\mathcal{N}}(c, k)$ is injective for all $k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$.

Remark 2.9. Our consideration of CFSTRs suggests that, for the outflow reactions (i.e., those of the form $s \rightarrow 0$), we should require the rate constants to be identical for all $s \in \mathcal{S}$. Recall that these rate constants were identified with g/V , which we set to 1. It would appear then that our requirement of injectivity of $p_{\mathcal{N}}(\cdot, k)$ for all $k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ is stronger than it need be for the application we have in mind. However, it is not hard to show that if $p_{\mathcal{N}}(\cdot, k)$ is injective for all $k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ satisfying the restriction $k_{s \rightarrow 0} = 1$ for every $s \in \mathcal{S}$, then $p_{\mathcal{N}}(\cdot, k)$ is injective for all $k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$.

In fact, suppose that, for some $k^* \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$, there are distinct $a^* \in \mathbb{R}_+^{\mathcal{S}}$, $b^* \in \mathbb{R}_+^{\mathcal{S}}$ such that $p_{\mathcal{N}}(a^*, k^*) = p_{\mathcal{N}}(b^*, k^*)$. Now choose $k^\#, a^\#, b^\#$ as follows:

$$\begin{aligned} a_s^\# &= a_s^* k_{s \rightarrow 0}^* \quad \forall s \in \mathcal{S}, \\ b_s^\# &= b_s^* k_{s \rightarrow 0}^* \quad \forall s \in \mathcal{S}, \\ k_{y \rightarrow y'}^\# &= k_{y \rightarrow y'}^* / \prod_{s \in \mathcal{S}} k_{s \rightarrow 0}^{* y_s} \quad \forall y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o. \end{aligned}$$

Then $k_{s \rightarrow 0}^\# = 1$ for all $s \in \mathcal{S}$, and $p_{\mathcal{N}}(a^\#, k^\#) = p_{\mathcal{N}}(b^\#, k^\#)$. This is to say that if $p_{\mathcal{N}}(\cdot, k^*)$ is not injective for some unrestricted k^* , then there is a restricted $k^\#$ such that $p_{\mathcal{N}}(\cdot, k^\#)$ also fails to be injective.

3. Characterizations of the injectivity property. In this section we prove some equivalent characterizations of the injectivity property that make it possible to check whether a given reaction network is injective by using standard computer algebra software.

Recall that for each reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ we defined its associated polynomial function $p_{\mathcal{N}}(\cdot, \cdot) : \mathbb{R}_+^{\mathcal{S}} \times \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \rightarrow \mathbb{R}^{\mathcal{S}}$.

THEOREM 3.1. *A reaction network \mathcal{N} is injective if and only if we have*

$$(3.1) \quad \det \left(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k) \right) \neq 0 \quad \forall c \in \mathbb{R}_+^{\mathcal{S}} \text{ and } \forall k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}.$$

Remark 3.1. Note that there is some similarity between this theorem and the Jacobian conjecture² over the field of real numbers, since we are concluding injectivity from the nonsingularity of the Jacobian of a polynomial function. Of course, there are also important differences, e.g., the fact that the domain of the function $p(\cdot, k)$ is restricted to $\mathbb{R}_+^{\mathcal{S}}$, and (3.1) holds for all positive values of the parameter k .

Proof. We will show a chain of equivalences from the negation of (3.1) to the noninjectivity of $p_{\mathcal{N}}(\cdot, k)$. The derivative of $p_{\mathcal{N}}(\cdot, k)$ at some point $c \in \mathbb{R}_+^{\mathcal{S}}$ is a linear transformation from $\mathbb{R}^{\mathcal{S}}$ to $\mathbb{R}^{\mathcal{S}}$. According to [18], the result of applying the derivative of $p_{\mathcal{N}}(\cdot, k)$ to an arbitrary vector $\gamma \in \mathbb{R}^{\mathcal{S}}$ can be written as

$$\left(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k) \right) (\gamma) = \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} k_{y \rightarrow y'} c^y (y * \gamma)(y - y'),$$

where “ $*$ ” is a special scalar product in $\mathbb{R}^{\mathcal{S}}$, defined by

$$v * w = \sum_{s \in \mathcal{S}} (v_s w_s / c_s).$$

(Here we use the fact that all the components of c are strictly positive.) Note that to say that (3.1) is *not true* is equivalent to

$$(3.2) \quad \left(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k) \right) (\gamma) = 0 \text{ for some } c \in \mathbb{R}_+^{\mathcal{S}}, k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}, \gamma \in \mathbb{R}^{\mathcal{S}}, \gamma \neq 0,$$

which is also equivalent to

$$(3.3) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} k_{y \rightarrow y'} c^y (y * \gamma)(y - y') = 0 \text{ for some } c \in \mathbb{R}_+^{\mathcal{S}}, k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \text{ and} \\ \text{some } \gamma \in \mathbb{R}^{\mathcal{S}}, \gamma \neq 0.$$

Using the change of variables $\eta_{y \rightarrow y'} = k_{y \rightarrow y'} c^y$ and $\delta_s = \gamma_s / c_s$ we notice that condition (3.3) is equivalent to

$$(3.4) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} (y \cdot \delta)(y - y') = 0 \text{ for some } \eta \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \text{ and} \\ \text{some } \delta \in \mathbb{R}^{\mathcal{S}}, \delta \neq 0,$$

where “ \cdot ” is the usual scalar product in $\mathbb{R}^{\mathcal{S}}$. The condition (3.4) in turn is equivalent to

$$(3.5) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} K_{y \rightarrow y'} (e^{y \cdot \delta} - 1)(y - y') = 0 \text{ for some } K \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \text{ and} \\ \text{some } \delta \in \mathbb{R}^{\mathcal{S}}, \delta \neq 0,$$

²The Jacobian conjecture over the field of real numbers says that if a polynomial function $f : \mathbb{R}^m \rightarrow \mathbb{R}^m$ has nonsingular Jacobian everywhere, then f is injective. This conjecture was proved to be false in [28].

since the signs of $y \cdot \delta$ and $e^{y \cdot \delta} - 1$ are the same, regardless of the value of $y \cdot \delta$. Then the condition (3.5) is equivalent to

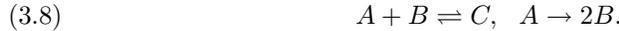
$$(3.6) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} K_{y \rightarrow y'} \left(\frac{b^y}{a^y} - 1 \right) (y - y') = 0 \text{ for some } K \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \text{ and} \\ \text{some } a \neq b \in \mathbb{R}_+^{\mathcal{S}}$$

via another change of variables, such that $\frac{b_s}{a_s} = e^{\delta_s}$ for all $s \in \mathcal{S}$. Note that $a \neq b$ if and only if $\delta \neq 0$. Condition (3.6) is equivalent to

$$(3.7) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} (b^y - a^y) (y - y') = 0 \text{ for some } \kappa \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \text{ and} \\ \text{some } a \neq b \in \mathbb{R}_+^{\mathcal{S}},$$

where $\kappa_{y \rightarrow y'} = \frac{K_{y \rightarrow y'}}{a^y}$. Now, note that this is equivalent to saying that for some value of $\kappa \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ the function $p_{\mathcal{N}}(\cdot, \kappa)$ is not injective on $\mathbb{R}_+^{\mathcal{S}}$. Therefore, we showed that the reaction network \mathcal{N} is injective if and only if (3.1) is true. \square

It is perhaps worthwhile to consider a small example, which is easily worked by hand. Consider network (3.8):



The system of CFSTR differential equations associated to (3.8) is

$$(3.9) \quad \begin{aligned} \dot{c}_A &= c_A^f - c_A - k_{A+B \rightarrow C} c_A c_B + k_{C \rightarrow A+B} c_C - k_{A \rightarrow 2B} c_A, \\ \dot{c}_B &= c_B^f - c_B - k_{A+B \rightarrow C} c_A c_B + k_{C \rightarrow A+B} c_C + 2k_{A \rightarrow 2B} c_A, \\ \dot{c}_C &= c_C^f - c_C + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C, \end{aligned}$$

where we supposed that $g/V = 1$. If we now again look for equilibria and rearrange terms, we get

$$(3.10) \quad \begin{aligned} c_A^f &= c_A + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C + k_{A \rightarrow 2B} c_A, \\ c_B^f &= c_B + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C - 2k_{A \rightarrow 2B} c_A, \\ c_C^f &= c_C - k_{A+B \rightarrow C} c_A c_B + k_{C \rightarrow A+B} c_C. \end{aligned}$$

Therefore the associated polynomial function for the reaction network (3.8) is

$$(3.11) \quad \begin{aligned} p(c, k) &= (c_A + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C + k_{A \rightarrow 2B} c_A, \\ &\quad c_B + k_{A+B \rightarrow C} c_A c_B - k_{C \rightarrow A+B} c_C - 2k_{A \rightarrow 2B} c_A, \\ &\quad c_C - k_{A+B \rightarrow C} c_A c_B + k_{C \rightarrow A+B} c_C). \end{aligned}$$

Then, for the reaction network (3.8), we have

$$(3.12) \quad \det \left(\frac{\partial p}{\partial c}(c, k) \right) \\ = \det \begin{bmatrix} 1 + k_{A+B \rightarrow C} c_B + k_{A \rightarrow 2B} & k_{A+B \rightarrow C} c_A & -k_{C \rightarrow A+B} \\ k_{A+B \rightarrow C} c_B - 2k_{A \rightarrow 2B} & 1 + k_{A+B \rightarrow C} c_A & -k_{C \rightarrow A+B} \\ -k_{A+B \rightarrow C} c_B & -k_{A+B \rightarrow C} c_A & 1 + k_{C \rightarrow A+B} \end{bmatrix} \\ = 1 + k_{C \rightarrow A+B} + k_{A+B \rightarrow C} c_A + k_{A+B \rightarrow C} c_B \\ + 3k_{A \rightarrow 2B} k_{A+B \rightarrow C} c_A + k_{A \rightarrow 2B} k_{C \rightarrow A+B}.$$

Notice that in (3.12) all coefficients³ of the monomials in the expansion of the determinant are 1, except the coefficient of $k_{A \rightarrow 2B} k_{A+B \rightarrow C} c_A$, which is 3. In particular, they are all positive numbers. Therefore, in this case, $\det(\frac{\partial f}{\partial c}(c, k)) > 0$ for all $c \in \mathbb{R}_+^n$ and for all $k \in \mathbb{R}_+^m$, so the reaction network (3.8) is injective as well.

Compare this to $\det(\frac{\partial p}{\partial c}(c, k))$ for the polynomial function associated to the reaction network (vii) in Table 1.1, which is

$$(3.13) \quad \det\left(\frac{\partial p}{\partial c}(c, k)\right) = 1 + k_{2A+B \rightarrow 3A} c_A^2 - 2k_{2A+B \rightarrow 3A} c_A c_B + 3k_{3A \rightarrow 2A+B} c_A^2.$$

The reaction network (vii) in Table 1.1 does admit multiple positive equilibria, and, as we have seen above, the determinant of the Jacobian of its associated polynomial function has a monomial with a negative coefficient.

Now we are in a position to review and elaborate further on what was said in Remark 1.2. It is worth repeating here that $\det(\frac{\partial p}{\partial c}(c, k))$ can be calculated using currently available computer algebra software and that the result of such a computation will sometimes have hundreds or even thousands of terms, each a monomial in the (positive) species concentrations and the (positive) rate constants. It is remarkable that, more often than not, *all* such monomials will have positive coefficients, so that $\det(\frac{\partial p}{\partial c}(c, k))$ is positive for all positive c and all positive k (recall Table 1.2). Indeed, for large networks the positivity of the monomial coefficients can also be checked with computer algebra software. In this way, Theorem 3.1 provides a (surprisingly robust) way to ensure that a given network is injective and, therefore, incapable of multiple positive equilibria.

In fact, Theorem 3.1 provides the information that networks (ii) and (iv) in Table 1.1 cannot give rise to multiple positive equilibria. On the other hand, Theorem 3.1 by itself stands silent on the capacity for multiple positive equilibria of the very similar networks (i) and (iii). In section 4 we will discuss extensions of Theorem 3.1 that do give information about networks (i) and (iii).

For polynomials in general, it is not necessary that each coefficient be positive in order for the polynomial to take strictly positive values for all positive values of the variables. (The polynomial $x^2 - xy + y^2$ is, of course, an elementary counterexample.) On the other hand, we will show that, for the class of polynomials considered here, positivity of the numerical coefficients is also necessary if positive values of the polynomial are to result for all positive values of the variables (i.e., the species concentrations and rate constants). In turn, this will imply that positivity of all (nonzero) coefficients is not only sufficient but also necessary for a network's injectivity (see Theorem 3.3).

In the following theorem we draw a relationship between the underlying network of chemical reactions and the numerical coefficients in the expansion of $\det(\frac{\partial p}{\partial c}(c, k))$. This relationship will have some importance not only here but also in a subsequent paper, in which we describe large classes of networks for which all (nonzero) coefficients are positive.

THEOREM 3.2. *Consider some reaction network \mathcal{N} with n species. Then for each coefficient in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ there is a set of n reactions $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$ (taken from the true and outflow reactions) such that the coefficient is equal to*

$$(3.14) \quad \det([y_1, \dots, y_n]) \det([y_1 - y'_1, \dots, y_n - y'_n]).$$

³We are looking at coefficients of monomials with respect to the coordinates of c and k .

Moreover, for each choice of n reactions such that (3.14) is not zero, there is a corresponding coefficient in the expansion of $\det(\frac{\partial p_N}{\partial c}(c, k))$.

Proof. Recall that, with the notation from the proof of Theorem 3.1, we have

$$\left(\frac{\partial p_N}{\partial c}(c, k)\right)(\gamma) = \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y * \gamma)(y - y'),$$

where $\eta_{y \rightarrow y'} = k_{y \rightarrow y'} c^y$. With $\{e_1, \dots, e_n\}$ denoting the canonical basis of $\mathbb{R}^{\mathcal{S}}$, we have

$$\begin{aligned} & \det\left(\frac{\partial p_N}{\partial c}(c, k)\right) \\ &= \det\left[\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y * e_1)(y - y'), \dots, \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y * e_n)(y - y')\right], \end{aligned}$$

and, according to the definition of “*”, it follows that

$$\begin{aligned} & \left(\prod_{i=1}^n c_i\right) \det\left(\frac{\partial p_N}{\partial c}(c, k)\right) \\ &= \det\left[\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y \cdot e_1)(y - y'), \dots, \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y \cdot e_n)(y - y')\right]. \end{aligned}$$

Therefore the coefficients in the expansion of $\det(\frac{\partial p_N}{\partial c}(c, k))$ are exactly the coefficients in the expansion of

$$\det\left[\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y \cdot e_1)(y - y'), \dots, \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}(y \cdot e_n)(y - y')\right].$$

Note now that each term in the expansion of the determinant above is a scalar multiple of a product of the form $\prod_{i=1}^n \eta_{y_i \rightarrow y'_i}$, where $y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n$ are some reactions in $\mathcal{R}_t \cup \mathcal{R}_o$.

Let us look at some fixed set $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\} \subset \mathcal{R}_t \cup \mathcal{R}_o$. With S_n denoting the set of all permutations of $\{1, \dots, n\}$, the coefficient of $\prod_{i=1}^n \eta_{y_i \rightarrow y'_i}$ in the expansion of the determinant above is

$$\begin{aligned} & \sum_{\sigma \in S_n} \det[(y_{\sigma(1)} \cdot e_1)(y_{\sigma(1)} - y'_{\sigma(1)}), \dots, (y_{\sigma(n)} \cdot e_n)(y_{\sigma(n)} - y'_{\sigma(n)})] \\ &= \sum_{\sigma \in S_n} \det[y_{\sigma(1)}^1 (y_{\sigma(1)} - y'_{\sigma(1)}), \dots, y_{\sigma(n)}^n (y_{\sigma(n)} - y'_{\sigma(n)})] \\ &= \sum_{\sigma \in S_n} y_{\sigma(1)}^1 y_{\sigma(2)}^2 \dots y_{\sigma(n)}^n \det[(y_{\sigma(1)} - y'_{\sigma(1)}), \dots, (y_{\sigma(n)} - y'_{\sigma(n)})] \\ &= \sum_{\sigma \in S_n} y_{\sigma(1)}^1 y_{\sigma(2)}^2 \dots y_{\sigma(n)}^n \operatorname{sgn}(\sigma) \det[(y_1 - y'_1), \dots, (y_n - y'_n)] \\ &= \left(\sum_{\sigma \in S_n} y_{\sigma(1)}^1 y_{\sigma(2)}^2 \dots y_{\sigma(n)}^n \operatorname{sgn}(\sigma)\right) \det[(y_1 - y'_1), \dots, (y_n - y'_n)] \\ &= \det[y_1, \dots, y_n] \det[(y_1 - y'_1), \dots, (y_n - y'_n)]. \end{aligned}$$

Therefore all coefficients in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ are of the form

$$\det[y_1, \dots, y_n] \det[y_1 - y'_1, \dots, y_n - y'_n]$$

for some set $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\} \subset \mathcal{R}_t \cup \mathcal{R}_o$. \square

Remark 3.2. In a future paper we will use the result of Theorem 3.2 to explain why, for large classes of reaction networks, all coefficients of the monomials in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ are nonnegative (i.e., our empirical observation).

Note that Theorem 3.2 gives us a way of computing the coefficients of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ one by one. In particular, it suggests a simple parallel computation algorithm for checking injectivity.

We prove now that the injectivity of a reaction network \mathcal{N} is completely characterized by the signs of the coefficients of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$.

THEOREM 3.3. *A reaction network \mathcal{N} is injective if and only if all the coefficients in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ are nonnegative.*

Proof. Suppose that all the coefficients in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ are nonnegative. We want to show that \mathcal{N} is injective.

Consider the function $f : \mathbb{R}_+^{\mathcal{S}} \times \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o} \rightarrow \mathbb{R}$ defined by

$$f(c, k) = \left(\prod_{s \in \mathcal{S}} c_s \right) \det \left(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k) \right).$$

Note that f vanishes if and only if $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ vanishes. As in the proof of Theorem 3.2, the terms in the expansion of $f(c, k)$ are of the form

$$(3.15) \quad \det[y_1, \dots, y_n] \det[y_1 - y'_1, \dots, y_n - y'_n] \left(\prod_{i=1}^n \eta_{y_i \rightarrow y'_i} \right),$$

where $\eta_{y \rightarrow y'} = k_{y \rightarrow y'} c^y$, and with each term corresponding to some choice of n reactions from the set $\mathcal{R}_t \cup \mathcal{R}_o$. Note that $\prod_{s \in \mathcal{S}} c_s$ and $\prod_{i=1}^n \eta_{y_i \rightarrow y'_i}$ are strictly positive, since c and k are regarded to have strictly positive coordinates. Then, to show injectivity, it is enough to show that there exists some set $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\} \subset \mathcal{R}_t \cup \mathcal{R}_o$ such that $\det[y_1, \dots, y_n] \det[y_1 - y'_1, \dots, y_n - y'_n] \neq 0$. But if we just choose the set $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$ to be \mathcal{R}_o , we have

$$\det[y_1, \dots, y_n] \det[y_1 - y'_1, \dots, y_n - y'_n] = 1,$$

because, up to a permutation, $y_i = e_i$ and $y'_i = 0$ for $i = 1, \dots, n$. Therefore (3.1) is true, and, according to Theorem 3.1, \mathcal{N} is injective.

Suppose now that \mathcal{N} is injective. We want to show that all the coefficients in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ are nonnegative. Of course, the coefficients in the expansion of $\det(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k))$ are the same as the coefficients in the expansion of $f(c, k)$. We will show that all the coefficients in the expansion of $f(c, k)$ are nonnegative. Note that $f(c, k)$ equals a homogeneous polynomial of degree n of the coordinates of η . Note also that, since we can write the terms in the expansion of $f(c, k)$ as in (3.15), it follows that each monomial in this expansion contains a product $\prod_{i=1}^n \eta_{y_i \rightarrow y'_i}$ for some set of n distinct reactions $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$, and there is no other monomial with the same set of n reactions. Suppose now that there is some monomial with a negative coefficient in the expansion of $f(c, k)$. Then, by choosing some $\eta \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ such that the coordinates of η that appear in the negative monomial are very large, and

all other coordinates of η are very small (i.e., very close to zero), we conclude that f takes a negative value somewhere in its domain. Similarly, by using a monomial with a positive coefficient (for example, the monomial with the coefficient “1” that we mentioned above) we conclude that f takes a positive value somewhere in its domain. Since the domain of f is connected, it follows that f is zero somewhere in its domain. According to Theorem 3.1, this contradicts the hypothesis that \mathcal{N} is injective. Therefore there cannot exist any monomial with a negative coefficient in the expansion of $f(c, k)$, so there cannot exist any monomial with a negative coefficient in the expansion of $\det\left(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k)\right)$. \square

Remark 3.3. Theorem 3.3 allows us to show that, although injectivity is *sufficient* to conclude that a reaction network does not admit multiple positive equilibria, *it is not a necessary condition*. One such example is the reaction network (vi) in Table 1.1. Indeed, that reaction network does not admit multiple positive equilibria but has

$$\det\left(\frac{\partial p}{\partial c}(c, k)\right) = 1 + k_{A+B \rightarrow 2AC} - k_{A+B \rightarrow 2AC} + 2k_{2A \rightarrow A+BC},$$

which does have one negative coefficient, so the network is not injective.

Remark 3.4. Theorems 3.2 and 3.3 imply that, given a reaction network with n species and m reactions, it is only the structure of its subnetworks of exactly n reactions (some of which could be outflow reactions) that dictates whether the reaction network is injective or not. Also, given some reaction network that *does* admit multiple positive equilibria, Theorems 3.2 and 3.3 allow us to pinpoint the subnetwork or subnetworks that create the capacity for multiple positive equilibria as exactly the ones for which the product of determinants $\det[y_1, \dots, y_n] \det[y_1 - y'_1, \dots, y_n - y'_n]$ is negative. Or, consider some finite family of reaction networks, each containing exactly n species. According to Theorem 3.2, we can enumerate all possible “bad” subnetworks in that family (i.e., subnetworks that have exactly n reactions, and for which the product of determinants above is negative). Then, in that family, only the reaction networks that contain a copy of some “bad” subnetwork can have the capacity for multiple positive equilibria.

Remark 3.5. Up to now we have considered only reaction networks where all species are in the outflow. If \mathcal{N} is a reaction network such that not all species are in the outflow, but there are n reactions $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$ in \mathcal{N} (some of which could be outflow reactions) such that $\det[y_1, \dots, y_n] \det[y_1 - y'_1, \dots, y_n - y'_n] > 0$, then Theorem 3.3 remains valid.

4. Sufficient conditions for existence of multiple positive equilibria. Recall that, as we mentioned in section 1, the injectivity property is not a necessary condition for the absence of multiple positive equilibria (see also Remark 3.3). In other words, if a network \mathcal{N} is not injective, this does not imply that \mathcal{N} has the capacity for multiple positive equilibria. Theorems 4.1 and 4.2 below say that if \mathcal{N} is not injective and satisfies an additional condition, then \mathcal{N} does have the capacity for multiple positive equilibria. We begin with a lemma.

LEMMA 4.1. *Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be some reaction network (augmented to include the flow reactions). Suppose that there is some $c \in \mathbb{R}_+^{\mathcal{S}}$ and some $k \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ such that*

$$\det\left(\frac{\partial p_{\mathcal{N}}}{\partial c}(c, k)\right) = 0$$

and

$$\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} k_{y \rightarrow y'} c^y (y - y') \in \mathbb{R}_+^{\mathcal{S}}.$$

Then \mathcal{N} does have the capacity for multiple positive equilibria.

Proof. The reaction network \mathcal{N} admits multiple positive equilibria if and only if there is some $\kappa \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ and some $a \neq b \in \mathbb{R}_+^{\mathcal{S}}$ such that

$$\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} a^y (y - y') = \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} b^y (y - y') = c^f$$

for some $c^f \in \bar{\mathbb{R}}_+^{\mathcal{S}}$ (recall Remark 1.1). Consider $\eta \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ such that $\eta_{y \rightarrow y'} = k_{y \rightarrow y'} c^y$ for each reaction $y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o$, where c and k are as in the theorem statement. Then, as in the proof of Theorem 3.1, there exists some $\delta \in \mathbb{R}^{\mathcal{S}}$, $\delta \neq 0$, such that

$$\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} (y \cdot \delta) (y - y') = 0.$$

Consider $a \in \mathbb{R}_+^{\mathcal{S}}$ given by $a_s = 1$ for every $s \in \mathcal{S}$, and consider $b \in \mathbb{R}_+^{\mathcal{S}}$ given by $b_s = e^{\delta_s}$ for every $s \in \mathcal{S}$. Note that $\delta \neq 0$ implies $a \neq b$. Denote by $\kappa \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ the vector given by $\kappa_{y \rightarrow y'} = \frac{y \cdot \delta}{e^{y \cdot \delta} - 1} \eta_{y \rightarrow y'}$ for all $y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o$ with $y \cdot \delta \neq 0$, and $\kappa_{y \rightarrow y'} = \eta_{y \rightarrow y'}$ for all $y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o$ with $y \cdot \delta = 0$.

Then we have

$$\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} (b^y - a^y) (y - y') = \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} (y \cdot \delta) (y - y') = 0.$$

Note that, without loss of generality, we can suppose that the norm of δ is very small. On the other hand we have

$$\begin{aligned} & \lim_{\delta \rightarrow 0} \left(\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} a^y (y - y') \right) \\ &= \lim_{\delta \rightarrow 0} \left(\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} (y - y') \right) \\ &= \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} (y - y') \\ &= \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} k_{y \rightarrow y'} c^y (y - y') \in \mathbb{R}_+^{\mathcal{S}}. \end{aligned}$$

Then, for small enough δ , it follows that $\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \kappa_{y \rightarrow y'} a^y (y - y') \in \mathbb{R}_+^{\mathcal{S}}$. \square

THEOREM 4.1. Consider some reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ (augmented to include the flow reactions). For $\eta \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ let $T_\eta : \mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}^{\mathcal{S}}$ be defined by

$$(4.1) \quad T_\eta(\delta) = \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} (y \cdot \delta) (y - y'),$$

and let

$$(4.2) \quad f(\eta) = \det(T_\eta).$$

Suppose that for some $\eta^* \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ we have

$$(4.3) \quad f(\eta^*) < 0,$$

$$(4.4) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'}^* (y - y') \in \mathbb{R}_+^{\mathcal{S}}.$$

Then \mathcal{N} has the capacity for multiple positive equilibria.

Proof. Consider some $\eta^\# \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ such that for all $y \rightarrow y' \in \mathcal{R}_o$ the number $\eta_{y \rightarrow y'}^\#$ is very large, and for all $y \rightarrow y' \in \mathcal{R}_t$ the number $\eta_{y \rightarrow y'}^\#$ is very small. Then condition (4.4) holds for $\eta^\#$, and, for reasons similar to those in the proof of Theorem 3.3, $f(\eta^\#) > 0$.

Suppose now that there is some $\eta^* \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ such that both (4.3) and (4.4) are true. Because the set of vectors η that satisfy (4.4) is convex, and because the function f is continuous, it follows that on the line segment that connects $\eta^\#$ and η^* there will be some $\tilde{\eta}$ such that condition (4.4) holds for $\tilde{\eta}$, and $f(\tilde{\eta}) = 0$.

Now, for some fixed $\tilde{c} \in \mathbb{R}_+^{\mathcal{S}}$, choose $\tilde{k} \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ such that $\tilde{\eta}_{y \rightarrow y'} = \tilde{k}_{y \rightarrow y'} \tilde{c}^y$ for all $y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o$. According to the chain of equivalences in the proof of Theorem 3.1 (from (3.1) to (3.4)) we have

$$\det \left(\frac{\partial p_{\mathcal{N}}}{\partial c}(\tilde{c}, \tilde{k}) \right) = 0.$$

Also, note that

$$\sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \tilde{k}_{y \rightarrow y'} \tilde{c}^y (y - y') \in \mathbb{R}_+^{\mathcal{S}}.$$

Then the hypothesis of Lemma 4.1 is satisfied, so its conclusion is also true. \square

Remark 4.1. Note that if some vector $\eta^* \in \mathbb{R}_+^{\mathcal{R}_t \cup \mathcal{R}_o}$ satisfies (4.3) and (4.4), then $\lambda \eta^*$ also satisfies (4.3) and (4.4) for any positive number λ . Therefore, if there is some η^* that satisfies (4.3) and (4.4) and has all coordinates positive, then there is some η^{**} that satisfies (4.3) and (4.4) and has all coordinates positive *and of total sum 1*. Then Theorem 4.1 can be implemented by considering the polynomial optimization problem (4.5)–(4.8), with linear constraints on a compact domain:

$$(4.5) \quad \text{minimize } f(\eta)$$

subject to the constraints

$$(4.6) \quad \eta_{y \rightarrow y'} \geq \varepsilon \quad \forall y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o,$$

$$(4.7) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} = 1,$$

$$(4.8) \quad \sum_{y \rightarrow y' \in \mathcal{R}_t \cup \mathcal{R}_o} \eta_{y \rightarrow y'} (y_s - y'_s) \geq \varepsilon \quad \forall s \in \mathcal{S},$$

where ε is some very small positive number. Note that, from the point of view of applying Theorem 4.1, it is enough to find *some* vector η^* satisfying (4.6)–(4.8) and such that $f(\eta^*) < 0$ (i.e., we don't need to find the global minimum, as we are just interested in knowing if the minimum is negative).

THEOREM 4.2. Consider some reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ (augmented to include the flow reactions). Suppose that there is a set of n reactions $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$ (where n is the number of species) such that

$$(4.9) \quad \det(y_1, \dots, y_n) \det(y_1 - y'_1, \dots, y_n - y'_n) < 0$$

and

$$(4.10) \quad \sum_{i=1}^n \eta_i (y_i - y'_i) \in \mathbb{R}_+^{\mathcal{S}} \text{ for some positive numbers } \eta_1, \dots, \eta_n.$$

Then \mathcal{N} does have the capacity for multiple positive equilibria.

Proof. Consider some $\eta^* \in \mathbb{R}_+^{\mathcal{R}_i \cup \mathcal{R}_o}$ such that for all $y \rightarrow y' \in \{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$ the number $\eta_{y \rightarrow y'}^*$ is very large, and for all other $y \rightarrow y'$ the number $\eta_{y \rightarrow y'}^*$ is very small. Then, as in the proof of Theorem 3.3, it follows that $f(\eta^*) < 0$, because in the expansion of $\det(T_{\eta^*})$ the negative term corresponding to the subnetwork $\{y_1 \rightarrow y'_1, \dots, y_n \rightarrow y'_n\}$ dominates all other terms.

Suppose in particular that $\eta_{y_i \rightarrow y'_i}^* = \lambda \eta_i$ for some (very large) number λ . Then (4.4) holds for this η^* , since $\sum_{i=1}^n \eta_i (y_i - y'_i) \in \mathbb{R}_+^{\mathcal{S}}$, and $\sum_{y \rightarrow y' \in \mathcal{R}_i \cup \mathcal{R}_o} \eta_{y \rightarrow y'}^* (y - y')$ is very close to $\lambda \sum_{i=1}^n \eta_i (y_i - y'_i)$. Therefore we can apply Theorem 4.1. \square

Remark 4.2. Note that if some numbers η_1, \dots, η_n satisfy $\sum_{i=1}^n \eta_i (y_i - y'_i) \in \mathbb{R}_+^{\mathcal{S}}$, then the numbers $\lambda \eta_1, \dots, \lambda \eta_n$ satisfy $\sum_{i=1}^n \lambda \eta_i (y_i - y'_i) \in \mathbb{R}_+^{\mathcal{S}}$ for any positive number λ . Then, when implementing Theorem 4.2, we can replace condition (4.10) with the systems of inequalities

$$(4.11) \quad \eta_i \geq 1 \quad \text{for } i = 1, \dots, n,$$

$$(4.12) \quad \sum_{i=1}^n \eta_i (y_{is} - y'_{is}) \geq 1 \quad \forall s \in \mathcal{S}.$$

Remark 4.3. For networks (i), (iii), (v) in Table 1.1 the less powerful but easily applied Theorem 4.2 already affirms the capacity for multiple positive equilibria. For network (vii) Theorem 4.1 affirms the capacity for multiple positive equilibria, while Theorem 4.2 stands silent.

Remark 4.4. Suppose that we are given a reaction network \mathcal{N} having n species, and we would like to know if \mathcal{N} has the capacity for multiple positive equilibria (in the isothermal homogeneous CFSTR context). An algorithm that investigates this problem proceeds as follows: First, check⁴ if there is any subnetwork of n reactions such that (4.9) holds. If (4.9) is false for all such subnetworks, then, according to Theorems 3.2 and 3.3, \mathcal{N} does not have the capacity for multiple positive equilibria. If one or more subnetworks of \mathcal{N} satisfy (4.9), then check⁵ if Theorem 4.2 applies for any such subnetwork. If Theorem 4.2 remains indecisive, then try to apply the more computationally intensive method given by Theorem 4.1 and described in Remark 4.1.

⁴For example, this can be done by computing $\det(\frac{\partial p_{\mathcal{N}}(c,k)}{\partial c})$ in order to recover the coefficients for the various subnetworks (recall Theorem 3.2).

⁵This will be very easy, since we only have to check the feasibility of the system of linear inequalities (4.11) and (4.12).

5. Concluding remarks. We believe that the theorems presented here have broad utility in deciding the capacity of a complex mass-action system to engender multiple positive steady states in a homogeneous isothermal CFSTR context. That these techniques should be robust relies heavily on our assertion that, despite the presence of hundreds or even thousands of terms in the expansion of $\det\left(\frac{\partial p_N(c,k)}{\partial c}\right)$ for a complex reaction network, it will typically be the case that all (nonzero) coefficients are positive. (When there are negative coefficients for a given network, they will typically be very few in number.) Although we have given examples to support this assertion, we have not, in this paper, tried to explain why positivity of the coefficients is to be expected broadly. Nor have we tried to identify those aspects of reaction network structure that give rise to negative coefficients. We intend to take up these questions in a future paper. There we will show how certain representations of reaction networks in graph-theoretical terms give surprisingly rapid and incisive information.

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