Mass-action kinetics are used in chemistry and chemical engineering to describe the dynamics of systems of chemical reactions, that is, reaction networks [1], [2]. These models are a special form of compartmental systems, which involve mass- and energy-balance relations [3]–[5]. Aside from their role in chemical engineering applications, mass-action kinetics have numerous analytical properties that are of inherent interest from a dynamical systems perspective. For example, mass-action kinetics give rise to systems of differential equations having polynomial nonlinearities. Polynomial systems are notorious for their intricate analytical properties even in low-dimensional cases [6]–[10]. Because of physical considerations, however, mass-action kinetics have special properties, such as nonnegative solutions, that are useful for analyzing their behavior [11]–[14].

With this motivation in mind, this article has several objectives. First, we provide a general construction of the kinetic equations based on the reaction laws. We present this construction in a state-space form that is accessible to the systems and control community. This presentation is based on the formulation given in [11] and [15].

Next, we consider the nonnegativity of solutions to the kinetic equations. Since the kinetic equations govern the concentrations of the species in the reaction network, it is obvious from physical arguments that nonnegative initial conditions must give rise to trajectories that remain in the nonnegative orthant. To demonstrate this fact, we show that the kinetic equations are essentially nonnegative, and we prove that, for all nonnegative initial conditions, the resulting concentrations...
are nonnegative. A related result is mentioned in [11] and [16]. In addition, we consider the realizability problem, which is concerned with the inverse problem of constructing a reaction network having specified essentially nonnegative dynamics. In particular, we provide an explicit construction of a reaction network for essentially nonnegative polynomial dynamics involving a scalar state.

Next, we consider the reducibility of the kinetic equations. In certain cases, such as in enzyme kinetics, kinetic equations can be reduced in dimensionality by using constants involving initial concentrations. We provide a general statement of this procedure. We then consider the stability of the equilibria of the kinetic equations. To do this, we apply Lyapunov methods to the kinetic equations, and we obtain results that guarantee semistability, that is, convergence to a Lyapunov-stable equilibrium that depends on the initial concentrations. Semistability is the appropriate notion of stability for compartmental systems in general, and reaction networks in particular, where the limiting concentration may be nonzero and may depend on the initial concentrations. Semistability theory is developed in [17], which extends the linear semistability results of [18] to nonlinear systems. Finally, we revisit the zero deficiency result of [19] and [20], which provides rate-independent conditions that guarantee convergence of the species concentrations. In this regard we have two objectives. First, we present the zero deficiency result for mass-action kinetics in standard matrix terminology, and, second, we prove semistability using the techniques of [17].

**REACTION NETWORKS**

We begin by reviewing the general formulation of the kinetic equations that describe chemical reactions with mass-action kinetics. First, consider the familiar reaction

\[
2\text{H}_2 + \text{O}_2 \overset{k_1}{\rightarrow} 2\text{H}_2\text{O}. \tag{1}
\]

The quantities on the left-hand side of reaction (1) are the *reactants*, the quantities on the right-hand side are the *products*, and \(k\) denotes the *reaction rate*. The reactants and products are collectively referred to as the *species* of the reaction. Equation (1) can be rewritten as

\[
\sum_{j=1}^{3} A_jX_j \overset{k}{\rightarrow} \sum_{j=1}^{3} B_jX_j, \tag{2}
\]

where \(X_1, X_2,\) and \(X_3\) denote the species \(\text{H}_2, \text{O}_2,\) and \(\text{H}_2\text{O},\) respectively; \(A_1 = 2, A_2 = 1, A_3 = 0, B_1 = 0, B_2 = 0,\) and \(B_3 = 2\) are the *stoichiometric coefficients*; and \(k\) denotes the *reaction rate*. Note that (2) can be written compactly using the matrix-vector notation

\[
AX \overset{k}{\rightarrow} BX, \tag{3}
\]

where \(X = [X_1 X_2 X_3]^T, A = [A_1 A_2 A_3] = [2 1 0]^T,\) and \(B = [B_1 B_2 B_3] = [0 0 2].\)

Next, consider the *reversible* reaction

\[
\text{Na}_2\text{CO}_3 + \text{CaCl}_2 \overset{k_1}{\rightleftharpoons} \text{CaCO}_3 + 2\text{NaCl}, \tag{4}
\]

which is a concise notation for the *forward* and *backward* reactions

\[
\text{Na}_2\text{CO}_3 + \text{CaCl}_2 \overset{k_1}{\rightarrow} \text{CaCO}_3 + 2\text{NaCl}, \tag{5}
\]

\[
\text{CaCO}_3 + 2\text{NaCl} \overset{k_2}{\rightarrow} \text{Na}_2\text{CO}_3 + \text{CaCl}_2, \tag{6}
\]

where \(k_1\) and \(k_2\) are the reaction rates for the forward and backward reactions, respectively. Now, let \(X_1, X_2, X_3,\) and \(X_4\) denote the species \(\text{Na}_2\text{CO}_3, \text{CaCl}_2, \text{CaCO}_3,\) and \(\text{NaCl},\) respectively, so that (4) can be written as

\[
X_1 + X_2 \overset{k_1}{\rightarrow} X_3 + 2X_4, \tag{7}
\]

\[
X_3 + 2X_4 \overset{k_2}{\rightarrow} X_1 + X_2, \tag{8}
\]

or, equivalently, as (3), where \(X = [X_1 X_2 X_3 X_4]^T, k = [k_1 k_2],\) and

\[
A = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 2 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 0 & 1 & 2 \\ 1 & 1 & 0 & 0 \end{bmatrix}. \tag{9}
\]

Next, we formulate the kinetic equations for multiple chemical reactions such as (7) and (8). Specifically, consider \(s\) species \(X_1, \ldots, X_s,\) where \(s \geq 1,\) whose interactions are governed by \(r\) reactions, where \(r \geq 1,\) comprising the reaction network

\[
\sum_{j=1}^{s} A_{ij}X_i \overset{k_i}{\rightarrow} \sum_{j=1}^{s} B_{ij}X_j, \quad i = 1, \ldots, r, \tag{9}
\]

where, for \(i = 1, \ldots, r, k_i > 0\) is the *reaction rate* of the \(i\)th reaction, \(\sum_{j=1}^{s} A_{ij}X_j\) is the *reactant* of the \(i\)th reaction, and \(\sum_{j=1}^{s} B_{ij}X_j\) is the *product* of the \(i\)th reaction. Note that each reaction in the reaction network (9) is represented as being irreversible. However, reversible reactions can be modeled by including the reverse reaction as a separate reaction, as in the case of reaction (4). Each *stoichiometric coefficient* \(A_{ij}\) and \(B_{ij}\) is assumed to be a nonnegative integer. The reaction network (9) can be written compactly in matrix-vector form as

\[
AX \overset{k}{\rightarrow} BX, \tag{10}
\]

where \(X = [X_1 \cdots X_s]^T\) is a column vector of species, \(k = [k_1 \cdots k_r]^T \in [0, \infty)^r,\) and \(A\) and \(B\) denote the *\(r \times s\) nonnegative matrices* \(A = [A_{ij}]\) and \(B = [B_{ij}].\)

To avoid vacuous cases, we assume that each species \(X_1, \ldots, X_s\) appears in the reaction network (10) with at least one nonzero coefficient \(A_{ij}\) or \(B_{ij}\). This assumption is equivalent to assuming that none of the columns of \([a_b]\) is zero. Furthermore, in special cases and only when specifically mentioned, we allow \(k_i = 0,\) which effectively denotes the
fact that the $i$th reaction is absent. Finally, we assume that, for all $i = 1, \ldots, r$, $row_i(A) \neq row_i(B)$ to avoid trivial reactions of the form $X_1 \xrightarrow{k} X_1$ or $X_1 + X_2 \xrightarrow{k} X_1 + X_2$, whose kinetics equations are $x_1(t) = 0$ and $x_1(t) = 0$, $x_2(t) = 0$, respectively.

THE LAW OF MASS ACTION AND THE KINETIC EQUATIONS

To derive the dynamics of the reaction network, we invoke the law of mass action [1], which states that, for an elementary reaction, that is, a reaction in which all of the stoichiometric coefficients of the reactants are one, the rate of reaction is proportional to the product of the concentrations of the reactants. In particular, consider the reaction

$$X_1 + X_2 \xrightarrow{k} bX_3,$$

where $X_1$, $X_2$, $X_3$ are the species and $b$ is a positive integer. Then

$$\dot{x}_i(t) = -kx_i(t)x_2(t), \quad x_i(0) = x_{i0}, \quad t \geq 0, \quad i = 1, 2,$$

$$\dot{x}_3(t) = bkx_1(t)x_2(t), \quad x_3(0) = x_{30},$$

where $x_i(t), i = 1, 2, 3$, denotes the concentration of the species $X_i$. Now, writing (1) as the elementary reaction

$$H_2 + H_2 + O_2 \xrightarrow{k} 2H_2O,$$

the law of mass action implies that

$$\dot{x}_1(t) = -2kx_1^2(t)x_2(t), \quad x_1(0) = x_{10}, \quad t \geq 0,$$

$$\dot{x}_2(t) = -kx_1^2(t)x_2(t), \quad x_2(0) = x_{20},$$

$$\dot{x}_3(t) = 2kx_1^2(t)x_2(t), \quad x_3(0) = x_{30},$$

where $x_1(t)$, $x_2(t)$, and $x_3(t)$ denote the concentrations of $H_2$, $O_2$, and $H_2O$, respectively, at time $t$.

Similarly, let $x_i(t)$ denote the concentration of $X_i$, $i = 1, \ldots, 4$, in (7) and (8), or, equivalently, the reversible reaction (4). In this case, it follows from the law of mass action that

$$\dot{x}_1(t) = -k_1x_1(t)x_3(t) + k_2x_3(t)x_4(t), \quad x_1(0) = x_{10}, \quad t \geq 0,$$

$$\dot{x}_2(t) = -k_1x_1(t)x_2(t) + k_3x_2(t)x_4(t), \quad x_2(0) = x_{20},$$

$$\dot{x}_3(t) = k_1x_1(t)x_2(t) - k_2x_3(t)x_4(t), \quad x_3(0) = x_{30},$$

$$\dot{x}_4(t) = 2k_1x_1(t)x_2(t) - 2k_2x_3(t)x_4(t), \quad x_4(0) = x_{40}.$$

More generally, consider reaction (10) and, for $j = 1, \ldots, s$, let $x_j(t)$ denote the concentration of the species $X_j$ at time $t$. Then, by applying the law of mass action, the dynamics of the reaction network (10) are given by the kinetic equations

$$\dot{x}(t) = (B - A)^T[k \circ x^A(t)], \quad x(0) = x_0, \quad t \geq 0,$$

where the notation $k \circ x^A$ is defined in “Matrix Notation” and the notation $x^A$ is defined in “Vector-Matrix Exponentiation.” Defining $K \triangleq \text{diag}(k_1, \ldots, k_s)$, (22) can be written as

$$\dot{x}(t) = (B - A)^TKx^A(t), \quad x(0) = x_0, \quad t \geq 0.$$

In mass-action kinetics the reaction order $\sum_{j=1}^s A_{ij}$ of the $i$th reaction is the sum of the stoichiometric coefficients of the species appearing in the reactant of the $i$th reaction. Equation (22), which is equivalent to [11, (4.7)], is a matrix-vector formulation of mass-action kinetics. It can be seen that the kinetic equations (22) are linear if and only if each row of $A$ contains exactly one 1 with the remaining entries equal to zero, that is, if and only if each reaction is unimolecular. In this case, it can be seen that $x^A = Ax$, and thus (22) becomes

$$\dot{x}(t) = Mx(t), \quad x(0) = x_0, \quad t \geq 0,$$

where $M \in \mathbb{R}^{r \times s}$ is defined by

$$M \triangleq (B - A)^TKA.$$

The reaction network (10) is not limited to closed systems for which conservation of mass holds. In fact, (10) can also be used to represent open systems in which mass removal and mass addition are allowed. For example, either $A = 0$ or $B = 0$ (but not both) is allowed in the reaction $AX_1 \xrightarrow{k_1} BX_1$, which represents the removal and addition of mass, respectively.

\[x_1(t) = k_1x_1(0)e^{-k_1t} \quad \text{and} \quad x_1(t) = k_1t + x_1(0), \quad \text{respectively.}\]

The reactions $X_1 \xrightarrow{k_1} 2X_1$ and $2X_1 \xrightarrow{k_1} 3X_1$, which also represent

**Matrix Notation**

A vector $x \in \mathbb{R}^p \triangleq \mathbb{R}^{p \times 1}$ is a $p \times 1$ column vector, while the set of $p \times q$ real matrices is denoted by $\mathbb{R}^{p \times q}$. For $x \in \mathbb{R}^p$ we write $x \geq 0$ to indicate that every component of $x$ is nonnegative and $x > 0$ to indicate that every component of $x$ is positive. In this case, we say that $x$ is nonnegative or positive, respectively. Likewise, $A \in \mathbb{R}^{p \times q}$ is nonnegative or positive if every entry of $A$ is nonnegative or positive, respectively, which is written as $A \geq 0$ or $A > 0$, respectively. Let $[0, \infty)^n$ and $(0, \infty)^n$ denote the nonnegative and positive orthants of $\mathbb{R}^n$, respectively; that is, if $x \in \mathbb{R}^n$, then $x \in [0, \infty)^n$ and $x \in (0, \infty)^n$ are equivalent, respectively, to $x \geq 0$ and $x > 0$.

For vectors $x, y \in \mathbb{R}^p$ and matrices $A, B \in \mathbb{R}^{p \times q}$ we use $x \circ y$ and $A \circ B$ to denote component-by-component and entry-by-entry multiplication, respectively. The $p \times p$ identity matrix is written as $I_p$. The vector $[1, \ldots, 1]^T$ is written as $e$. The transposes of $x \in \mathbb{R}^p$ and $A \in \mathbb{R}^{p \times q}$ are denoted by $x^T$ and $A^T$, respectively. For a matrix $A \in \mathbb{R}^{p \times q}$, $row_i(A)$ and $col_j(A)$ denote the $i$th row and $j$th column of $A$, respectively. Finally, $\mathcal{R}(A)$ and $\mathcal{N}(A)$ denote the range and null spaces of $A \in \mathbb{R}^{p \times q}$, respectively, $\rho(A)$ denotes the spectral radius of $A$, and $\text{spec}(A)$ denotes the spectrum of $A$. 

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the addition of mass, have the kinetics $\dot{x}_1(t) = k_1 x_1(t)$ and $\dot{x}_2(t) = k_2 x_2(t)$ with solutions $x_1(t) = x_1(0) e^{k_1 t}$ and $x_1(t) = x_1(0)/(1 - k_1 x_1(0))$, respectively. Note that the latter reaction has finite escape time since it exists only on the interval $[0, 1/(k_1 x_1(0))]$. Finally, the reactions $X \xrightarrow{k} Y$ and $2X \xrightarrow{k} 2Y$, although stoichiometrically equivalent, have different kinetic equations, namely, $\dot{x}(t) = -k x(t)$ and $\dot{x}(t) = -k x^2(t)$, respectively. We adopt the convention that the law of mass action applies to the reaction involving the minimum number of molecules necessary for the reaction to occur.

Example 1
Consider the reaction network

$$X_1 \xrightarrow{k_1} X_2,$$

$$X_2 \xrightarrow{k_2} X_1,$$

so that $s = 2$, $r = 2$, and $A$ and $B$ are given by

$$A = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}. \quad (28)$$

The kinetic equations are thus given by

$$\dot{x}_1(t) = -k_1 x_1(t) + k_2 x_2(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \quad (29)$$

$$\dot{x}_2(t) = k_1 x_1(t) - k_2 x_2(t), \quad x_2(0) = x_{20}. \quad (30)$$

that is, in linear system form (24), where

$$M = \begin{bmatrix} -k_1 & k_2 \\ k_1 & -k_2 \end{bmatrix}. \quad (31)$$

Example 2
Consider the reaction network

$$X_1 + X_2 \xrightarrow{k_1} 2X_1,$$

$$2X_1 \xrightarrow{k_2} X_1 + X_2,$$

so that $s = 2$, $r = 2$,

$$A = \begin{bmatrix} 1 & 1 \\ 2 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 1 \\ 1 & 1 \end{bmatrix}. \quad (32)$$

The kinetic equations are thus given by

$$\dot{x}_1(t) = k_1 x_1(t) x_2(t) - k_2 x_1^2(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \quad (33)$$

$$\dot{x}_2(t) = -k_1 x_1(t) x_2(t) + k_2 x_1^2(t), \quad x_2(0) = x_{20}. \quad (34)$$

Example 3
The Lotka-Volterra reaction is given by

$$X_1 \xrightarrow{k_1} 2X_2,$$

$$X_1 + X_2 \xrightarrow{k_2} 2X_2,$$

$$X_2 \xrightarrow{k_1} 0,$$

where $x_1$ and $x_2$ denote prey and predator species, respectively, so that $s = 2$ and $r = 3$. Furthermore, $A$ and $B$ are given by

$$A = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \quad B = \begin{bmatrix} 2 & 0 \\ 0 & 2 \end{bmatrix}. \quad (40)$$

Consequently, the kinetic equations have the form

$$\dot{x}(t) = \begin{bmatrix} k_1 x_1(t) \\ -k_2 x_1(t) x_2(t) \\ k_3 x_2(t) \end{bmatrix}, \quad x(0) = \begin{bmatrix} x_{10} \\ x_{20} \end{bmatrix}, \quad t \geq 0, \quad (41)$$

that is,

$$x_1(t) = k_1 x_1(t) - k_2 x_1(t) x_2(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \quad (42)$$

$$x_2(t) = -k_3 x_2(t) + k_2 x_1(t) x_2(t), \quad x_2(0) = x_{20}. \quad (43)$$

Vector-Matrix Exponentiation

For $x = [x_1 \ldots x_q]^T \in \mathbb{R}^q$ and nonnegative $A = [A_{ij}] \in \mathbb{R}^{q \times q}$, $x^A$ denotes the element of $\mathbb{R}^q$ whose $i$th component for $i = 1, \ldots, q$ is the product $x_1 x_2^2 \cdots x_q^a_i$. For example, if

$$A = \begin{bmatrix} 1 & 2 \\ 3 & 4 \end{bmatrix},$$

then

$$x^A = \begin{bmatrix} x_1 x_2^2 \\ x_2^3 x_2 \end{bmatrix}.$$ We define $0^0 = 1$. The matrix exponentiation operation has many convenient properties [21], [31]. For example, if $A, B \in \mathbb{R}^{q \times q}$ then $(A + B)^x = x^A x^B$. If $B \in \mathbb{R}^{n \times p}$, then $(x^A)^B = x^{A B}$. Furthermore, $(x \circ y)^A = (x^A) \circ (y^A) = x^A y^A$. Note that $x^b = x$ and $x^{-a} = (x^A)^{-1}$. Alternatively, if $A \in \mathbb{R}^{p \times q}$ then $x^{A \circ p} = x^A$. Furthermore, if det $A \neq 0$, $x > 0$, and $y > 0$, then $x^y = y^x$ implies that $x = y^{a^{1/A}}$. In addition, $\log x^A = A \log x$ and $e^{\log x} = x^A$, while $x^A = y^A$ implies $\log x = \log y$, where, for $x = [x_1, \ldots, x_q]^T \in (0, \infty)^q$, $\log x$ denotes the vector in $\mathbb{R}^q$ whose $i$th component is $\log x_i$. Finally, if $f(x) = x^A$ then $f'(x) = \text{diag}(x^A) A \text{diag}(x)^{-1}$, where

$$\text{diag}(x_1, x_2, \ldots, x_q) = \Delta \begin{bmatrix} x_1 & \cdots & x_q \end{bmatrix}.$$

For $x = [x_1, \ldots, x_q]^T \in \mathbb{R}^p$, $e^x$ denotes the vector in $\mathbb{R}^p$ whose $i$th component is $e^{x_i}$. Throughout the article “log” denotes natural logarithm.

REFERENCE

Example 4
A widely studied reaction network [21] involves the interaction of a substrate S and an enzyme E to produce a product P by means of an intermediate species C. The reactions are given by
\[ S + E \xrightarrow{k_1} \frac{k_1}{k_2} \xrightarrow{k_3} P + E \]  
so that \( s = 4 \) and \( r = 3 \). Letting \( X_1 = S, X_2 = C, X_3 = E, \) and \( X_4 = P, \) the corresponding reaction network can be written as
\[ X_1 + X_3 \xrightarrow{k_1} X_2, \]
\[ X_2 \xrightarrow{k_2} X_1 + X_3, \]
\[ X_3 \xrightarrow{k_3} X_3 + X_4. \]
It thus follows that \( A \) and \( B \) are given by
\[ A = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}. \]
(48)

Consequently, the kinetic equations have the form
\[ \dot{x}(t) = \begin{bmatrix} -1 & 1 & 0 \\ 1 & -1 & 1 \\ 0 & -1 & 0 \end{bmatrix} \begin{bmatrix} k_1 x_1(t) x_3(t) \\ k_2 x_2(t) \\ k_3 x_2(t) \end{bmatrix}, \]
\[ x(0) = \begin{bmatrix} x_{10} \\ x_{20} \\ x_{40} \end{bmatrix}, \quad t \geq 0, \]
(49)
that is,
\[ \dot{x}_1(t) = k_2 x_2(t) - k_1 x_1(t) x_3(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \]
\[ \dot{x}_2(t) = -(k_2 + k_3) x_2(t) + k_1 x_1(t) x_3(t), \quad x_2(0) = x_{20}, \]
\[ \dot{x}_3(t) = (k_2 + k_3) x_2(t) - k_1 x_1(t) x_3(t), \quad x_3(0) = x_{30}, \]
\[ \dot{x}_4(t) = k_3 x_2(t), \quad x_4(0) = x_{40}. \]
(52)

For the following definitions and results, we consider the system
\[ \dot{x}(t) = f(x(t)), \quad x(0) = x_0, \quad t \in [0, T_{x_0}), \]
(54)
where \( f : D \to \mathbb{R}^n \) is locally Lipschitz, \( D \) is an open subset of \( \mathbb{R}^n, x_0 \in D, \) and \([0, T_{x_0}),\) where \( 0 < T_{x_0} \leq \infty, \) is the maximal interval of existence for the solution \( x(\cdot) \) of (54). A subset \( U \subseteq D \) is invariant with respect to (54) if \( x_0 \in U \) implies that \( x(t) \in U \) for all \( t \in [0, T_{x_0}). \) The following technical result is needed. For this result, \( B_r(x_0) \) denotes the open ball centered at \( x \in \mathbb{R}^n \) with radius \( r > 0. \)

Lemma 1
Consider the dynamical system (54), and let \( U \subseteq D \) be closed relative to \( D. \) Then the following statements are equivalent:

i) For all \( x \in U, \) \( \lim_{t \to 0^+} \inf_{y \in U} \|x + hf(x) - y\| = 0, \)

ii) \( U \) is an invariant set with respect to (54).

Proof
Assume that i) holds. To show ii), let \( x_0 \in U. \) Since \( f(\cdot) \) is Lipschitz continuous it follows that there exist \( \varepsilon > 0 \) and \( L > 0 \) such that, for all \( x, y \in B_{Lx_0}(x_0), \)
\[ \|f(x) - f(y)\| \leq L \|x - y\|. \]
(55)

Next, let \( t \in (0, T) \) be such that \( \|s(t, x_0) - x_0\| \leq \varepsilon/3 \) for all \( t \in (0, t_1), \) and define \( \phi(t) \triangleq \inf_{y \in U} \|s(t, x_0) - y\|. \) Note that since \( x_0 \in U, \) it follows that \( \phi(0) = 0 \) and \( \phi(t) \leq \|s(t, x_0) - x_0\| \leq \varepsilon/3 \) for all \( t \in (0, t_1). \) Now, let \( t \in (0, t_1) \) and \( y_t \in U \) be such that \( \|s(t, x_0) - y_t\| - \phi(t) \leq \varepsilon/4. \) Hence,
\[ \|y_t - x_0\| = \|y_t - s(t, x_0) + s(t, x_0) - x_0\| \leq \|s(t, x_0) - x_0\| + \|s(t, x_0) - y_t\| \leq \|s(t, x_0) - x_0\| + \phi(t) + \varepsilon/4 \leq \varepsilon. \]
(56)

Now, for all \( h > 0 \) such that \( t + h \leq t_1, \) since \( \|s(t, x_0) - x_0\| < \varepsilon/3 < \varepsilon \) and \( \|y_t - x_0\| < \varepsilon, \) it follows from (56) that
\[ \phi(t + h) = \inf_{z \in D} \|s(t + h, x_0) - z\| \leq \inf_{z \in D} \|s(t + h, x_0) - s(h, y_t)\| + \|s(h, y_t) - y_t - hf(t)\| + \|y_t + hf(t) - z\| \leq \|s(t + h, x_0) - s(h, y_t)\| + \|s(h, y_t) - y_t - hf(t)\| + \|y_t + hf(t) - y_t - hf(t)\| \leq e^{Lh} \|s(t, x_0) - y_t\| + \|s(h, y_t) - y_t - hf(t)\| + \|y_t + hf(t) - y_t - hf(t)\|. \]
(57)
which implies that
\[
\frac{\varphi(t + h) - \varphi(t)}{h} - \varphi(t) \leq \left( \frac{1}{h^2} - \frac{1}{h^2} \right) \varphi(t) + \frac{\left\| s(h, y_t) - y_t \right\|}{h} + \frac{\text{dist}(y_t, hf(y_t), U)}{h}.
\]

Now, letting \( h \to 0^+ \) and using i) yields
\[
\limsup_{h \to 0^+} \frac{\varphi(t + h) - \varphi(t)}{h} \leq L \varphi(t).
\]

(58)

Next, by Gronwall's lemma [23, p. 81], it follows from (58) that, for all \( t \in (0, t_1) \), \( 0 \leq \varphi(t) \leq e^{Lt} \varphi(0) \), and hence, since \( \varphi(0) = 0 \), it follows that \( \varphi(t) = 0 \) for all \( t \in (0, t_1) \). Now, since \( x_0 \in U \) is arbitrary, it follows that, for every \( t_1 > 0 \) such that \( \varphi(t_1) = 0 \), there exists \( h > 0 \) such that \( \varphi(h) = 0 \) for all \( t \in [t_1, t_1 + h) \). Next, let \( r \inf \{ t > 0 : \varphi(t) = 0 \} > 0 \) and suppose, \textit{ad absurdum}, that \( r > T_{x_0} \). Since \( \varphi(t) = 0 \) for all \( t \in [0, t_1) \), it follows that \( r \geq t_1 > 0 \) and, by the definition of \( r \), \( \varphi(t) = 0 \) for all \( t \in [0, r) \) or, equivalently, \( s(t, x_0) \in U \) for all \( t \in [0, r) \). Hence, since \( s(t, x_0) = \lim_{s \to 0} s(t, x) \) and \( U \) is relatively closed with respect to \( D \), it follows that \( s(r, x_0) \in U \). Therefore, \( \varphi(t) = 0 \), which implies that there exists \( h > 0 \) such that \( \varphi(t) = 0 \) for all \( t \in [r, r + h) \), contradicting the definition of \( r \). Thus, \( \varphi(t) = 0 \) for all \( t \in [0, T_{x_0}) \), establishing the result.

Conversely, assume \( U \) is an invariant set with respect to (54) so that, for all \( x_0 \in U \) and \( h \neq 0 \),
\[
\text{dist}(x_0 + h \varphi(x_0), U) \leq \left\| s(h, x_0) - x_0 - hf(x_0) \right\| = \left\| s(h, x_0) - x_0 \right\|.
\]

Now, the result follows by letting \( h \to 0^+ \).

The flow-invariant set result given by Lemma 1, which is proved in [24], uses the fact that the vector field \( f \) in (54) is Lipschitz continuous on \( D \). This result is generalized in [25] to the case where \( f \) is continuous on \( D \) and (54) has a unique right maximally defined solution.

Theorem 1
Suppose that \( [0, \infty)^n \subset D \). Then \( [0, \infty)^n \) is an invariant set with respect to (54) if and only if \( f : D \to \mathbb{R}^n \) is essentially nonnegative.

Proof
Suppose \( f \) is essentially nonnegative, and let \( x \in [0, \infty)^n \). If \( x(0) = 0 \), then \( x(t) = 0 \) for all \( t \geq 0 \), whereas if \( x(0) > 0 \), then \( x(t) > 0 \) for all \( t \) sufficiently small. Thus, \( x + hf(x) \in [0, \infty)^n \) for all \( h \) sufficiently small, and hence,\[ \lim_{h \to 0^+} \inf_{x \in [0, \infty)^n} \left\| x + hf(x) - y \right\| = 0. \]
Now it follows from Lemma 1 that, with \( x(0) = x, x(t) \in [0, \infty)^n \) for all \( t \in [0, T_{x_0}) \).

Conversely, suppose that \( [0, \infty)^n \) is invariant with respect to (54). Let \( x(0) = [0, \infty)^n \), let \( x(t) \), \( t \in [0, T_{x_0}) \), denote the solution to (54), and suppose there exists \( t \in [1, \ldots, n] \) such that \( x(t) = 0 \) and \( f_i(x(t)) < 0 \). Then, since \( f \) is continuous, there exists \( h > 0 \) sufficiently small such that \( f_i(x(t)) < 0 \) for all \( t \in [0, h] \). Hence, \( x(t) \) is decreasing on \( [0, h] \) and therefore \( x(t) \not\in [0, \infty)^n \) for all \( t \in [0, h] \), which is a contradiction. 

Proposition 1
Define \( f : \mathbb{R}^n \to \mathbb{R}^n \) by \( f(x) = (B - A)^T (k \circ x)^t \). Then \( f \) is locally Lipschitz and essentially nonnegative.

Proof
Since \( f \) is continuously differentiable it follows that \( f \) is locally Lipschitz. Next, let \( x \in [0, \infty)^n \). For \( j \in \{1, \ldots, s\} \) we have
\[
f_j(x) = \left[ \text{col}_j(B) - \text{col}_j(A) \right]^T \begin{bmatrix} k_1 x^{\text{row}_1(A)} \\ \vdots \\ k_s x^{\text{row}_s(A)} \end{bmatrix} = \sum_{j=1}^r B_j k_j x^{\text{row}_j(A)}.
\]
Note that the first summation is nonnegative since \( x \) is nonnegative. Next, note that \( A_j \circ x^{\text{row}_j(A)} \) contains the factor \( x^{\text{row}_j(A)} \). Now, to verify Definition 1, let \( x_j = 0 \). If \( A_j \circ x_j = A_j(0^a) = 0 \), while, if \( A_j \circ x_j = \lim_{x_j \to 0} 0(x_j) = \lim_{x_j \to 0} 0(1) = 0 \). Consequently, the second summation is zero for all nonnegative \( A_j \) whenever \( x_j = 0 \). Thus, \( f \) is essentially nonnegative.

Theorem 2
\([0, \infty)^n \) is an invariant set with respect to (22).

Proof
The result is an immediate consequence of Theorem 1 and Proposition 1.

Corollary 1
Consider the linear kinetic reaction (24), where \( M = (B - A)^T KA \) and \( A \) has exactly one nonzero entry in each row. Then \( f(x) = Mx \) is essentially nonnegative, and \([0, \infty)^n \) is an invariant set with respect to (24).

Proof
Since \( A \) is nonnegative, \( K \) is nonnegative and diagonal, and \( A \) has exactly one nonzero entry in each row, it follows that \( A^T KA \) is diagonal. Now, since \( B^T KA \) is nonnegative it follows that \( M \) is essentially nonnegative, and hence \( f(x) = Mx \) is essentially nonnegative. The invariance of \([0, \infty)^n \) is a direct consequence of Theorem 2.

In the linear case \( f(x) = Mx, \) where \( M \in \mathbb{R}^{m \times n} \) is essentially nonnegative, Theorem 1 implies the following result. For this special case we provide a separate, self-contained proof.

Proposition 2
Let \( M \in \mathbb{R}^{m \times n} \). Then \( M \) is essentially nonnegative if and only if \( e^{Mh} \geq 0 \) for all \( t \geq 0 \).

Proof
To prove necessity, note that, since \( M \) is essentially nonnegative it follows that \( M \circ x \) is nonnegative, where
\( x \triangleq -\min\{ M_{11}, \ldots, M_{mm} \} \). Hence, \( e^{Mt} \geq 0 \) for all \( t \geq 0 \), and thus \( e^{Mt} = e^{-\Delta t} e^{kM} \geq 0 \) for all \( t \geq 0 \). Conversely, suppose \( e^{Mt} \geq 0 \) for all \( t \geq 0 \), and suppose \( M \) is not essentially nonnegative, that is, there exist distinct \( i, j \) such that \( M_{ij} < 0 \). Now, since \( e^{Mt} = \sum_{k=0}^{\infty} (k!)^{-1} t^k M^k \), it follows that
\[
[e^{Mt}]_{ij} = (I_n)_{ij} + t M_{ij} + o(t),
\]
where \( o(t)/t \to 0 \) as \( t \to 0 \). Thus, for \( i \neq j \), it follows that \( [e^{Mt}]_{ij} < 0 \) for all \( t \) sufficiently small, which is a contradiction. Hence, \( M \) is essentially nonnegative. \( \square \)

**Example 1, Continued**
For the kinetic equations (24) with \( M \) given by (31) it can be seen that \( M = [-k_1 \; k_2] \) is essentially nonnegative. The exponential of \( M \) is given by
\[
e^{Mt} = I_2 + \frac{1 - e^{-(k_1+k_2)t}}{k_1+k_2} M,
\]
which is nonnegative for all \( t \geq 0 \). Consequently, if \( x(0) \) is nonnegative, then the solution \( x(t) \) of (24) given by \( x(t) = e^{Mt} x(0) \) is nonnegative for all \( t \geq 0 \).

**Examples 2, 3, 4, Continued**
It can be seen that the function \( f \) for each of these examples is essentially nonnegative.

### REALIZATION OF MASS-ACTION KINETICS

In this section, we consider the realization problem, which is concerned with the construction of a reaction network whose dynamics are given by specified kinetic equations. In this case, the reaction network is a realization of the kinetic equations. Note that the polynomial
\[ f(x) = \sum_{i=0}^{v} a_i x^i \]  

(59)
in the real scalar \( x \) is essentially nonnegative if and only if \( a_0 \geq 0 \).

**Theorem 3**
Consider the system (54), where \( n = 1 \) and \( f : \mathbb{R} \to \mathbb{R} \) is an essentially nonnegative polynomial of degree \( v \) of the form (59). Then there exists a reaction network of the form (10) with \( s = 1 \) and \( r \leq v + 1 \), and with stoichiometric coefficient matrices \( A \) and \( B \) having nonnegative integer entries such that \( f(x) = (B - A)^T (k \circ x^4) \).

**Proof**
For \( i = 1, \ldots, v \), define \( A_i, B_i \) and \( k_i \) as \( i + \text{sign}(a_i) \), \( |a_i| \), respectively, and let \( s = 1 \). Then the dynamics of the reaction network (10) are given by the kinetic equation
\[ \chi(t) = (B - A)^T (k \circ x^4) 
\]

(60)

where \( x(t) \) is the state vector, \( f(x) \) is the polynomial, and \( A, B, k \) are the stoichiometric matrices. The system is then given by
\[ \dot{x}_i(t) = f(x_1(t), \ldots, x_r(t), t), \]  

(61)
\[ \dot{x}_i(t) = f(x_1(t), \ldots, x_r(t), t), \]  

(62)
\[ \dot{x}_i(t) = f(x_1(t), \ldots, x_r(t), t), \]  

(63)
\[ \dot{x}_i(t) = f(x_1(t), \ldots, x_r(t), t), \]  

(64)

where \( f(x) \) is the polynomial. Hence, (10) is a realization of (22), where \( f \) is given by (59). \( \square \)

To demonstrate Theorem 3, let \( v = 3 \). Then a realization of \( \dot{x}_1(t) = a_0 x_1^2(t) + a_2 x_2(t) + a_3 x_3(t) + a_4 x_4(t) \) is given by the reaction network

\[ 0 \rightarrow a_0 X_1, \]  

(65)
\[ X_1 \xrightarrow{a_1} (1 + \text{sign} a_1) X_1, \]  

(66)
\[ 2X_1 \xrightarrow{a_2} (2 + \text{sign} a_2) X_1, \]  

(67)
\[ 3X_1 \xrightarrow{a_3} (3 + \text{sign} a_3) X_1, \]  

(68)

where the reaction network is a realization of the kinetic equations (22), where \( f(x) \) is given by (59). To demonstrate Theorem 3, let \( v = 3 \). Then a realization of \( \dot{x}_1(t) = a_0 x_1^2(t) + a_2 x_2(t) + a_3 x_3(t) + a_4 x_4(t) \) is given by the reaction network

\[ 0 \rightarrow a_0 X_1, \]  

(69)
\[ X_1 \xrightarrow{a_1} (1 + \text{sign} a_1) X_1, \]  

(70)
\[ 2X_1 \xrightarrow{a_2} (2 + \text{sign} a_2) X_1, \]  

(71)
\[ 3X_1 \xrightarrow{a_3} (3 + \text{sign} a_3) X_1, \]  

(72)

where \( a_0, a_1, a_2, \) and \( a_3 \) are nonnegative integers and \( k_i \geq 0 \) for all \( i = 1, \ldots, r \). Now, it follows from the law of mass action that the kinetic equations for (67) are given by
\[ \dot{x}_1(t) = \sum_{i=1}^{r} b_i k_i x_i^2(t), \]  

(73)
\[ \dot{x}_2(t) = \sum_{i=1}^{r} (c_i - a_i) k_i x_i^2(t), \]  

(74)

Comparing (65) with (67), it follows that \( a_i \in \{2, 3, 4\} \) for all \( i = 1, \ldots, r \). Furthermore, \( \sum_{i=1}^{r} b_i k_i = -2 \), where
Consider the system (54), where \( n > 1 \) and \( f: \mathbb{R}^n \rightarrow \mathbb{R}^n \) is a multivariate polynomial. Then there exists a reaction network of the form (10) with \( s = n \) such that \( f(x) = (B - A)\overline{x} (k \odot x^4) \), where the stoichiometric coefficient matrices \( A \) and \( B \) have nonnegative integer entries, if and only if for each \( j \in \{1, \ldots, n\}, f_j(x_1, x_2, \ldots, x_{j-1}, 0, x_{j+1}, \ldots, x_n) \) is a multivariate polynomial with nonnegative coefficients.

**Proof**

To prove sufficiency, let \( j \in \{1, \ldots, n\} \). By assumption, \( f_j(x) \) is a sum of terms either of the form

\[
a_i x_1^{p_{1i}} x_2^{p_{2i}} \cdots x_n^{p_{ni}},
\]

(70)

where \( p_i \geq 0 \) for all \( i = 1, \ldots, n \) and \( p_j > 0 \), or of the form

\[
b_j x_1^{p_{1j}} \cdots x_{j-1}^{p_{j-1}} x_{j+1}^{p_{j+1}} \cdots x_n^{p_{nj}},
\]

(71)

with \( b_j > 0 \). Next, note that the reaction

\[
\sum_{i=1}^n p_i x_i \rightarrow (p_i + \text{sign } a_i) x_i + \sum_{i=1, i \neq j}^n p_i x_i
\]

contributes the term (70) to \( \dot{x}_i \) and no terms to \( \dot{x}_j \) for all \( i = 1, \ldots, n \) such that \( i \neq j \). Similarly, the reaction

\[
\sum_{i=1}^n q_i x_i \rightarrow (q_i + \text{sign } a_i) x_i + \sum_{i=1, i \neq j}^n q_i x_i
\]

(73)

contributes the term (71) to the rate of \( \dot{x}_j \) and zero terms to \( \dot{x}_i \) for all \( i = 1, \ldots, n \), \( i \neq j \). Hence, for all \( j = 1, \ldots, n \), each term of \( f_j(x) \) can be realized as a valid reaction which establishes sufficiency.

To prove necessity, let \( x \in [0, \infty)^s \) and let \( j \in \{1, \ldots, s\} \). Then

\[
f_j(x) = \sum_{i=1}^r (B_j - A_j) k_i x_{\text{row},i}(A).
\]

(74)

Let \( A_j \geq 0 \). If \( A_j \geq 0 \), then \( x^\text{row}(A) \) and hence \( (B_j - A_j) x_{\text{row},i}(A) \geq 0 \), whereas, if \( A_j = 0 \), then

\[
(B_j - A_j) x_{\text{row},i}(A) = \lim_{x_i \rightarrow 0^+} B_j k_i x_{A_i} x_{j-1} A_{j-1} x_{j+1} A_{j+1} \cdots x_n.
\]

Hence,

\[
f_j(x) = \sum_{i \in I_j} B_j k_i x_{A_i} x_{j-1} A_{j-1} x_{j+1} A_{j+1} \cdots x_n,
\]

where \( I_j = \{i \in \{1, \ldots, r\} : A_{ij} = 0\} \), establishing the result.

---

**REDUCIBILITY OF THE KINETIC EQUATIONS**

In this section, we provide a technique for reducing the number of kinetic equations needed to model the dynamics of the reaction network (10). The reduced-order kinetic equations model a subset of the species appearing in the original reaction network. This technique is based on the fact that, while \( x(t) \), \( t \geq 0 \), is confined to the nonnegative orthant for nonnegative initial conditions, the structure of the kinetic equations (22) imposes an additional constraint on the allowable trajectories.

To state this result we define the stoichiometric subspace \( S \) by \( S \triangleq \mathcal{R}(B - A)^T \), which is a subspace of \( \mathbb{R}^n \). The dimension of this subspace is given by \( q \triangleq \text{rank}(B - A)^T = \text{rank}(B - A) \), which is the rank of the reaction network. Note that \( q \leq \min\{r, s\} \). The following result shows that the solution of the kinetic equations (22) is confined to an affine subspace that is parallel to the stoichiometric subspace. For convenience, we let \( P \in \mathbb{R}^{s \times q} \) denote the unique orthogonal projector whose range is \( S \) and define \( P_z = P \cdot I_z \). In terms of the generalized inverse \( (\cdot)^+ \), \( P \) is given by \( P = (B - A)^T (B - A)^T + (B - A)^{-1} \). Note, that if \( z \in \mathbb{R}^r \), then \( P_z = z \) if and only if \( z \in S \) and therefore \( P_z \cdot z = 0 \) if and only if \( z \in S \).

**Proposition 3**

Suppose \( x(0) \in [0, \infty)^s \). Then, for all \( t \in [0, T_{x(0)}) \), the solution \( x(\cdot) \) of (22) satisfies

\[
x(t) \in (x(0) + S) \cap [0, \infty)^s.
\]

**Proof**

It follows from Proposition 1 that, for all \( t \in [0, T_{x(0)}) \), \( x(t) \) is confined to the nonnegative orthant. To show that \( x(t) \in (x(0) + S) \) for all \( t \in [0, T_{x(0)}) \), note that \( \dot{x}(t) \in S \) for all \( t \in [0, T_{x(0)}) \), which implies that \( \frac{d}{dt} \text{P}_z x(t) = \text{P}_z \dot{x}(t) = 0 \) for all \( t \in [0, T_{x(0)}) \). Hence, \( \text{P}_z [x(t) - x(0)] \) is constant for all \( t \in [0, T_{x(0)}) \). Thus, for all \( t \in [0, T_{x(0)}) \), it follows that \( \text{P}_z [x(t) - x(0)] = \text{P}_z [x(0) - x(0)] = 0 \), and hence, \( x(t) - x(0) \in S \), as required.

---

**Corollary 2**

Suppose \( x(0) \in [0, \infty)^s \). Then \( (x(0) + S) \cap [0, \infty)^s \) is an invariant set with respect to (22).

**Proof**

Let \( \dot{x}(0) \in (x(0) + S) \cap [0, \infty)^s \) so that \( \dot{x}(0) = x(0) + w \), where \( w \in S \), and let \( \dot{x}(\cdot) \) denote the corresponding solution to (22). Then, since \( x(0) \in [0, \infty)^s \), it follows from Proposition 3 that, for all \( t \in [0, T_{x(0)}) \),

\[
\dot{x}(t) = (x(0) + S) \cap [0, \infty)^s
\]

establishing the invariance.

Proposition 3 shows that the solution \( x(\cdot) \) of the kinetic equations (22) is confined to the stoichiometric compatibility class \( (x(0) + S) \cap [0, \infty)^s \), which is a \( q \)-dimensional manifold.
with boundary. (The set \((x(0)+S)\cap (0,\infty)^s\) is a positive stoichiometric compatibility class.) This fact suggests that the dynamics of the reaction network can be represented by a set of \(q\) species. In fact, the following result shows that, if \(q<s\), then the number of species can be reduced from \(s\) to \(q\). Since \(q \leq \min(r,s)\), this reduction is always possible when \(r<s\). For convenience, the following result assumes that the species \(x_1, \ldots, x_r\) are labeled such that the first \(q\) columns of \(B-A\) are linearly independent.

**Proposition 4**

Assume that \(q<s\). Furthermore, partition \(A = [A_1 \ A_2]\) and \(B = [B_1 \ B_2]\), where \(A_1, B_1 \in \mathbb{R}^{r \times q}\), and assume that \(\text{rank}(B_1 - A_1) = q\). In addition, let \(F \in \mathbb{R}^{r \times (s-q)}\) satisfy \(A_2 - B_2 = (A_1 - B_1)F\). Finally, partition \(x = [x_1^T \ x_2^T]^T\), where \(x_1 = [x_1 \cdots x_q]^T\) and \(x_2 = [x_{r+1} \cdots x_r]^T\). Then

\[
\dot{x}_1(t) = F^T \dot{x}_1(t) + \gamma, \quad x_2(0) = x_{20}, \quad t \geq 0, \tag{75}
\]

where \(\gamma = \dot{x}_2(0) - F^T \dot{x}_1(0) \in \mathbb{R}^{r \times s-q}\), and \(x_1(t)\) satisfies

\[
\dot{x}_1(t) = (B_1 - A_1)^T [k \circ x_1^2(t) \circ (F^T \dot{x}_1(t) + \gamma)],
\]

\[
x_1(0) = x_{10}, \quad t \geq 0. \tag{76}
\]

**Proof**

Left multiplying (22) by \([F^T - L_{s-q}]\) yields \(\dot{x}_2(t) = F^T \dot{x}_1(t)\), which implies (75). Next, note that \(\dot{x}_1(t) = (B_1 - A_1)^T [k \circ x_1^2(t) \circ (F^T \dot{x}_1(t) + \gamma)]\), and (75) yields (76).

**Example 1, Continued**

Note that \(s = 2, r = 2\), and \(q = 1 < s\), and thus Proposition 4 can be applied with \(F = -1\). It thus follows that \(\dot{x}_2(t) = -x_2(t) + \gamma\) for all \(t \geq 0\), where \(\gamma \triangleq x_1(0) + x_2(0)\). Applying Proposition 4 with \(\dot{x}_1 = x_1\) and \(\dot{x}_2 = x_2\), (76) yields the scalar kinetic equation

\[
\dot{x}_1(t) = -(k_1 + k_2)x_1(t) + k_2, \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{77}
\]

which is essentially nonnegative. A reduced reaction network realization for this kinetic equation is given by

\[
\begin{align*}
0 & \xrightarrow{k_2} X_1, \tag{78} \\
x_1 & \xrightarrow{k_1 + k_2} 0, \tag{79}
\end{align*}
\]

for which \(q = s = 1\) and \(r = 2\).

**Example 2, Continued**

Note that \(s = 2, r = 2\), and \(q = 1 < s\), and thus Proposition 4 can be applied with \(F = -1\). It thus follows that \(\dot{x}_2(t) = -x_2(t) + \gamma\) for all \(t \geq 0\), where \(\gamma \triangleq x_1(0) + x_2(0)\). Applying Proposition 4 with \(\dot{x}_1 = x_1\) and \(\dot{x}_2 = x_2\), (76) yields the scalar kinetic equation

\[
\dot{x}_1(t) = -(k_1 + k_2)x_1(t) + k_1, \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{80}
\]

which is essentially nonnegative. A reaction network realization for this reduced-order kinetic equation is given by

\[
\begin{align*}
X_1 & \xrightarrow{k_{10}} 2X_1, \tag{81} \\
2X_1 & \xrightarrow{k_{12}} X_1, \tag{82}
\end{align*}
\]

for which \(q = s = 1\) and \(r = 2\).

**Example 3, Continued**

Note that \(s = 2, r = 3,\) and \(q = 2 < s\), and thus reduction is not possible.

**Example 4, Continued**

Note that \(s = 4, r = 3,\) and \(q = 2 < s\), and thus Proposition 4 can be applied with \(F = \begin{bmatrix} 0 & 1 \end{bmatrix}^T\). It thus follows that \(\dot{x}_3(t) = -x_3(t) + \gamma_1\) and \(\dot{x}_4(t) = -x_4(t) - x_2(t) + \gamma_2\) for all \(t \geq 0\), where \(\gamma_1 \triangleq x_2(0) + x_3(0)\) and \(\gamma_2 \triangleq x_1(0) + x_2(0) + x_4(0)\). Applying Proposition 4 with \(\dot{x}_1 = [x_1 x_2]^T\) and \(\dot{x}_2 = [x_3 x_4]^T\), (76) yields

\[
\begin{align*}
\dot{x}_1(t) = -k_1 x_1(t) + k_2 x_2(t) + k_1 x_1(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{83} \\
\dot{x}_2(t) = k_2 x_2(t) - k_1 x_1(t) x_2(t) - k_1 x_1(t), \quad x_2(0) = x_{20}, \tag{84}
\end{align*}
\]

which is essentially nonnegative. The dynamics of the system (83) and (84) are discussed in [21] and the references given therein. A reaction network realization for these reduced-order kinetic equations are given by

\[
\begin{align*}
X_1 & \xrightarrow{k_{12}} X_2, \tag{85} \\
X_2 & \xrightarrow{k_{21}} X_1, \tag{86} \\
X_1 & \xrightarrow{k_3} 0, \tag{87} \\
X_1 + X_2 & \xrightarrow{k_4} 2X_1, \tag{88}
\end{align*}
\]

for which \(q = s = 2\) and \(r = 4\).

**Example 4, Continued**

We now show that not every reduced-order kinetic equation can be realized as a reaction network. For convenience, we relabel the species of Example 4 as \(X_1 = S, X_2 = P, X_3 = C,\) and \(X_4 = E\). The reaction network (45)–(46) can now be written as

\[
\begin{align*}
X_1 + X_4 & \xrightarrow{k_1} X_3, \tag{89} \\
X_3 & \xrightarrow{k_2} X_1 + X_4, \tag{90} \\
X_3 & \xrightarrow{k_3} X_4 + X_2, \tag{91}
\end{align*}
\]

whose kinetic equations are

\[
\begin{align*}
\dot{x}_1(t) = -k_1 x_1(t) x_4(t) + k_1 x_3(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{92} \\
\dot{x}_2(t) = k_3 x_2(t), \quad x_2(0) = x_{20}, \tag{93} \\
\dot{x}_3(t) = k_1 x_1(t) x_4(t) - (k_2 + k_3) x_3(t), \quad x_3(0) = x_{30}, \tag{94} \\
\dot{x}_4(t) = -k_1 x_1(t) x_4(t) + (k_2 + k_2) x_3(t), \quad x_4(0) = x_{40}. \tag{95}
\end{align*}
\]

Since \(s = 4, r = 3,\) and \(q = 2 < s\), Proposition 4 can be applied with \(\dot{x}_1 = [x_1 x_2]^T, \dot{x}_2 = [x_3 x_4]^T,\) and \(F = \begin{bmatrix} 0 & 1 \end{bmatrix}^T\). It thus follows that \(\dot{x}_3(t) = -x_3(t) + \gamma_1\) and \(\dot{x}_4(t) = -x_4(t) + x_1(t) + x_2(t) + \gamma_2\) for all \(t \geq 0\), where \(\gamma_1 \triangleq x_2(0) + x_3(0)\) and \(\gamma_2 \triangleq x_1(0) + x_2(0) + x_3(0)\).
and $y_2 = x_4(0) - x_1(0) - x_2(0)$. By applying Proposition 4, it follows from (76) that

$$
\begin{align*}
\dot{x}_1(t) &= -k_1x_1^2(t) - k_1x_1(t)x_2(t) - (k_1\gamma_2 + k_2)x_1(t) \\
&\quad - k_2x_2(t) + k_2\gamma_1, \quad x_1(0) = x_{10}, \quad t \geq 0, \\
\dot{x}_2(t) &= -k_3x_1(t) - k_3x_2(t) + k_3\gamma_1, \quad x_2(0) = x_{20},
\end{align*}
$$

which have nonnegative solutions as long as the initial conditions coincide with the initial conditions of the original kinetic equations (92)–(95). However, due to the terms $-k_2x_2$ and $-k_3x_1$, (96), (97) are not essentially nonnegative, and hence, there exist initial conditions such that solutions become negative. Therefore, (96), (97) are not realizable by a reaction network.

The following result presents conditions that guarantee nonnegativity of the solutions to the reduced-order kinetic equations (76).

**Proposition 5**
Assume that $q < s$. Furthermore, partition $A = [A_1 \ A_2]$ and $B = [B_1 \ B_2]$, where $A_1, B_1 \in \mathbb{R}^{r \times r}$, and assume that rank$(B_1 - A_1) = q$. In addition, let $F \in \mathbb{R}^{r \times (s-q)}$ satisfy $A_2 - B_2 = (A_1 - B_1)F$. Finally, partition $x = [x_1^T \ x_2^T]^T$, where $x_1 = [x_1 \cdots x_r]^T$ and $x_2 = [x_{r+1} \cdots x_s]^T$. Then, for all $x_1(0) \in [0, \infty)^q$ and $\gamma \in \mathbb{R}^{r-s}$ such that $y + F^T x_1(0) \in [0, \infty)^{q-s}$, the solution $x_1(t)$ to (76) is nonnegative for all $t \geq 0$.

**Proof**
With $\dot{x}_2(0) = \gamma + F^T \dot{x}_1(0)$, it follows from Proposition 4 that the solution to (22) is given by $[x_1^T(t) \ x_2^T(t)]^T$ for all $t \geq 0$, where $x_2(t)$ is given by (75). Hence, since $x_1(0) \geq 0$ and $\dot{x}_2(0) \geq 0$, it follows that $\dot{x}_1(t) \geq 0$ for all $t \geq 0$.

**STABILITY ANALYSIS**
We now consider the stability of equilibria of the kinetic equations (22). First, we define several notions of stability for the system (54), where $f : \mathcal{D} \to \mathbb{R}^n$ is locally Lipschitz continuous on $\mathcal{D}$ and $\mathcal{D} \subseteq \mathbb{R}^n$ is open. Note that, since $f(\cdot)$ is Lipschitz continuous, it follows that, for all $x_0 \in \mathcal{D}$, (54) has a unique solution on the maximum interval of existence $(0, T_{x_0})$. If $x_e \in \mathcal{D}$ satisfies $f(x_e) = 0$, then $x_e$ is an equilibrium of (54).

**Definition 2**
Let $\mathcal{U} \subseteq \mathcal{D}$ be invariant with respect to (54), and let $x_e \in \mathcal{U}$ be an equilibrium of (54). Then $x_e$ is Lyapunov stable with respect to $\mathcal{U}$ if, for every relatively open subset $\mathcal{U}_e$ of $\mathcal{U}$ containing $x_e$, there exists a relatively open subset $\mathcal{U}_e$ of $\mathcal{U}$ containing $x_e$ such that, if $x(0) \in \mathcal{U}_e$, then the solution $x(\cdot) \in (54)$ satisfies $x(t) \in \mathcal{U}$ for all $t \in [0, \infty)$. Furthermore, $x_e$ is semistable with respect to $\mathcal{U}$ if $x_e$ is Lyapunov stable with respect to $\mathcal{U}$ and there exists a relatively open neighborhood $\mathcal{U}_e \subseteq \mathcal{U}$ of $x_e$ such that, for every $x(0) \in \mathcal{U}_e$, $\lim_{t \to \infty} x(t)$ is a Lyapunov stable equilibrium with respect to $\mathcal{U}$. In addition, $x_e$ is asymptotically stable with respect to $\mathcal{U}$ if $x_e$ is Lyapunov stable with respect to $\mathcal{U}$ and there exists a relatively open subset $\mathcal{U}_e$ of $\mathcal{U}$ containing $x_e$ such that, if $x(0) \in \mathcal{U}_e$, then $\lim_{t \to \infty} x(t) = x_e$. Finally, $x_e$ is globally asymptotically stable with respect to $\mathcal{U}$ if the previous statement holds with $\mathcal{U}_e = \mathcal{U}$.

Next, we define equilibria for the kinetic equations (22).

**Definition 3**
A vector $x_e \in [0, \infty)^n$ satisfying

$$
(b - A)^T (k \circ x_e^3) = 0
$$

is an equilibrium of (22). If, in addition, $x_e \in (0, \infty)^n$, then $x_e$ is a positive equilibrium of (22).

Let $\mathcal{E}$ denote the set of equilibria of (22), and let $\mathcal{E}_+ \subseteq \mathcal{E}$ denote the set of positive equilibria of (22). The following result can be used to obtain additional equilibria from known equilibria.

**Proposition 6**
Let $z \in \mathcal{N}(A)$ and let $\lambda \in (0, \infty)$. If $x_e \in \mathcal{E}$, then $\lambda \circ x_e \in \mathcal{E}_+$. Furthermore, if $x_e \in \mathcal{E}_+$, then $\lambda \circ x_e \in \mathcal{E}_+$.

**Proof**
Note that

$$
(b - A)^T K(\lambda \circ x_e^3) = (b - A)^T K(\lambda \circ x_e^3) = (b - A)^T K(\lambda \circ x_e^3) = (b - A)^T Kx_e^3.
$$

The proof for the case $x_e \in \mathcal{E}_+$ is identical.

Note that if $x_e$ is an equilibrium but not a positive equilibrium, then at least one of the species has zero concentration for this solution. Furthermore, it can be seen that $x_e = 0$ is an equilibrium of (22) if and only if (22) has no reaction of the form $0 \to C$, where $C$ is a nonzero product and $k > 0$.

**Example 1, Continued**
For this example $\mathcal{E} = \{(x_1, x_2) \in [0, \infty)^2 : x_2 = (k_1/k_2)x_1\}$. 

**Example 2, Continued**
For this example $\mathcal{E} = \{(x_1, x_2) \in [0, \infty)^2 : x_1 = 0 \text{ or } x_2 = (k_2/k_1)x_1\}$. For the reduced system (80) $\mathcal{E} = \{(0, k_1/k_1)\}$.

**Example 3, Continued**
For this example $\mathcal{E} = \{(0, 0), (k_3/k_2, k_1/k_2)\}$.

**Example 4, Continued**
For this example $\mathcal{E} = \{(x_1, x_2, x_3, x_4) \in [0, \infty)^4 : x_2 = 0 \text{ and } x_1x_3 = 0\}$. For the reduced system (83), (84), if $\gamma_1 = x_2(0) > 0$, then $\mathcal{E} = \{(0, 0)\}$, whereas, if $\gamma_1 = x_2(0) = 0$, then $\mathcal{E} = \{(x_1, 0) : x_1 \geq 0\}$.

Next we analyze the stability of equilibria of the kinetic equations (22) by means of Lyapunov methods. The following standard result [23, p. 193] concerns Lyapunov and asymptotic stability.

**Theorem 5**
Let $\mathcal{U} \subseteq \mathcal{D}$ be invariant with respect to (54), and let $x_e \in \mathcal{U}$ satisfy $f(x_e) = 0$. Let $V : \mathcal{U} \to \mathbb{R}$ be a continuously...
Because of physical considerations, mass-action kinetics have special properties, such as nonnegative solutions, that are useful for analyzing their behavior.

differentiable function and assume that \( V(x_c) = 0, V(x) > 0 \) for all \( x \in \mathcal{U} \setminus \{x_c\} \), and \( V(x) \equiv V'(x) f(x) \leq 0 \) for all \( x \in \mathcal{U} \).

Then \( x_c \) is Lyapunov stable with respect to \( \mathcal{U} \). If, in addition, \( V(x) < 0 \) for all \( x \in \mathcal{U} \setminus \{x_c\} \), then \( x_c \) is asymptotically stable with respect to \( \mathcal{U} \). Finally, if \( V \) is proper, that is, \( V^{-1}(K) \) is relatively compact with respect to \( \mathcal{D} \) for all compact subsets \( K \) of \( \mathbb{R} \), and \( V(x) < 0 \) for all \( x \in \mathcal{U} \setminus \{x_c\} \), then \( x_c \) is globally asymptotically stable with respect to \( \mathcal{U} \).

Note that if \( \mathcal{U} = [0, \infty)^n \), then \( V \) is proper if and only if \( V \) is radially unbounded. The following result given in [17] provides a sufficient condition for semistability.

**Theorem 6**
Assume that \( \mathcal{U} \subseteq \mathcal{D} \) is closed and invariant with respect to (54), and suppose that every trajectory with \( x(0) \in \mathcal{U} \) of (54) is bounded. Furthermore, let \( V : \mathcal{U} \to \mathbb{R} \) be a continuously differentiable function such that \( \dot{V}(x) \leq 0 \) for all \( x \in \mathcal{U} \). Finally, let \( M \) denote the largest invariant subset of \( \{ x \in \mathcal{U} : V(x) = 0 \} \). If every element of \( M \) is a Lyapunov stable equilibrium with respect to \( \mathcal{U} \), then every solution to (54) with \( x(0) \in \mathcal{U} \) converges to an equilibrium that is semistable with respect to \( \mathcal{U} \).

**STABILITY OF LINEAR KINETICS**
First we consider the linear case, that is, the case in which (54) is of the form

\[
\dot{x}(t) = Mx(t), \quad x(0) = x_0, \quad t \geq 0,
\]

where \( M \in \mathbb{R}^{n \times n} \). In this case, the following results hold. An equilibrium \( x_0 \) of (99) is Lyapunov stable (respectively, semistable) if and only if every equilibrium \( x_e \) of (99) is Lyapunov stable (respectively, semistable). Furthermore, if an equilibrium of (99) is asymptotically stable, then \( x_0 = 0 \). Thus, all three types of stability can be characterized independently of the equilibrium. Specifically, the equilibrium \( x_0 = 0 \) of (99) is asymptotically stable if and only if every eigenvalue of \( M \) has negative real part; an equilibrium \( x_e \) of (99) is semistable if and only if every eigenvalue of \( M \) has nonpositive real part and is zero and, if \( M \) is singular, the zero eigenvalue is semisimple; and an equilibrium \( x_0 \) of (99) is Lyapunov stable if and only if every eigenvalue of \( M \) has nonpositive real part and every eigenvalue with zero real part is semisimple [27, pp. 437, 438].

Now, we specialize the above results to (24) with \( M \) given by (25). The following result follows from results given in [22, pp. 135, 136, 153–155]. However, we provide proofs based on Theorem 5 and Theorem 6. For these proofs we construct a linear Lyapunov function that can be interpreted as the mass of the system. To do this, let \( \mu_i > 0, i = 1, \ldots, s \), denote the molecular mass of the \( i \)th species, and define \( \mu = [\mu_1 \ldots \mu_s]^T \). Then the function \( V(x) = \mu^T x \) represents the total mass of the system. Note that arbitrary constants \( \mu_i > 0 \) can be used, and thus “mass” need not be interpreted literally. Note that \( V \) is a positive-definite function with respect to \([0, \infty)^s \). We note that the following result makes no use of the structure of \( M \) except that it is essentially nonnegative. For the proof of this result, recall that \( -M \) is an M-matrix if and only if \(-M \) is a Z-matrix and every eigenvalue of \( M \) has nonnegative real part [5, Definition 2.10].

**Proposition 7**
Consider the following statements:

i) There exists \( \mu >> 0 \) such that \( M^T \mu \leq 0 \).

ii) \( M \) is Lyapunov stable.

iii) \( M \) is semistable.

iv) There exists \( \mu \geq 0 \) such that \( \mu \neq 0 \) and \( M^T \mu \leq 0 \).

Then i) implies ii), ii) is equivalent to iii), and iii) implies iv).

Furthermore, the following statements are equivalent:

v) \( M \) is asymptotically stable.

vi) There exists \( \mu >> 0 \) such that \( M^T \mu << 0 \).

vii) There exists \( \mu \geq 0 \) such that \( M^T \mu \leq 0 \).

**Proof**
Define \( V(x) = \Delta x^T \mu \) so that \( V(0) = 0 \) and \( V(x) > 0 \) for all \( x \in [0, \infty)^n \setminus \{0\} \). Furthermore, \( V(x) = \mu^T Mx \leq 0 \) for all \( x \in [0, \infty)^n \), which proves that i) implies ii). The equivalence of ii) and iii) follows from [28, Thrm. 3.2]. To show that iii) implies iv), note that since \( M \) is semistable it follows that \( -M^T \) is an M-matrix. Hence, it follows from [29, p. 119] that there exist a scalar \( z > 0 \) and a nonnegative matrix \( Q \geq 0 \) such that \( x \geq \rho(Q) \) and \( M^T = Q - zI \). Now, since \( Q \geq 0 \), it follows from [22, Thrm. 1.1] that \( \rho(Q) \in \text{spec}(Q) \), and hence, there exists \( \mu \geq 0 \) such that \( \mu \neq 0 \) and \( \rho(Q) \mu \). Thus, \( M^T \mu = Q \mu - z \mu = (\rho(Q) - z) \mu \leq 0 \), which proves that there exists \( \mu \geq 0 \) such that \( \mu \neq 0 \) and \( M^T \mu \leq 0 \).

To show the equivalence of v)–vii), first suppose there exists \( \mu \geq 0 \) such that \( M^T \mu << 0 \). Now, there exists sufficiently small \( \varepsilon > 0 \) such that \( M^T (\mu + \varepsilon) << 0 \) and \( \mu + \varepsilon >> 0 \), where \( \varepsilon \equiv [1, 1, \ldots, 1]^T \), which proves that vii) implies vi). Since vii) implies vii) follows that vii) and vii) are equivalent. Now, suppose vii) holds, that is, there exists \( \mu >> 0 \) such that \( M^T \mu << 0 \), and consider the Lyapunov candidate \( V(x) = \mu^T x \), where \( x \in [0, \infty)^n \). Computing the Lyapunov derivative yields \( \dot{V}(x) = \mu^T Mx < 0 \) for all \( x \in
Example 1, Continued
Choosing $\mu = [1/k_1\ 1/k_2]^T > 0$, it follows that $M\mu = 0$. Hence, $M$ is semistable.

STABILITY OF NONLINEAR KINETICS
The following result uses the Lyapunov function $V(x) = x^T M x$ to analyze the stability of the zero solution of (22). Recall that $x_e = 0$ is an equilibrium of (22) if and only if $A$ has no zero rows, that is, if and only if 0 is not a reactant of the reaction network (10).

Proposition 8
Assume that $x_e = 0$ is an equilibrium of (22) and suppose there exists $\mu > 0$ such that $B\mu \leq A\mu$. Then $x_e$ is Lyapunov stable with respect to $[0, \infty)^n$. If, in addition, $B\mu < A\mu$, then $x_e$ is globally asymptotically stable with respect to $[0, \infty)^n$.

Proof
Define $V(x) = x^T M x$ so that $V(0) = 0$ and $V(x) > 0$ for all $x \in [0, \infty)^n \setminus \{0\}$. Since $(B-A)\mu \leq 0$, it follows that $\dot{V}(x) = x^T (B-A)^T (k \circ x^3) \leq 0$ for all $x \in [0, \infty)^n$. Hence, Theorem 5 implies that $x_e = 0$ is Lyapunov stable with respect to $[0, \infty)^n$. Now suppose that $B\mu < A\mu$. Then $\dot{V}(x) < 0$ for all $x \in [0, \infty)^n \setminus \{0\}$. Since $V$ is proper, it follows from Theorem 5 that $x_e = 0$ is globally asymptotically stable with respect to $[0, \infty)^n$.

Example 1, Continued
Let $\mu = [1/k_1\ 1/k_2]^T$ so that $(A-B)\mu = 0$. It thus follows from Proposition 8 that $x_e = 0$ is Lyapunov stable. Since the kinetic equations are linear it follows from Proposition 7 that $M$ is both Lyapunov stable and semistable.

Example 2, Continued
First note that, because of the structure of the set of equilibria, none of the equilibria are asymptotically stable. Next, we consider an equilibrium $x_0$ of the form $(0, e)$, where $e > 0$. By linearizing the system about this equilibrium, it can be seen that this equilibrium is not Lyapunov stable. Hence, it remains to determine the stability of an equilibrium of the form $(\delta, k_2 \delta/k_1)$, where $\delta \geq 0$. To do this, let $U$ be the closed set $U = \{(x_1, x_2) \in [0, \infty)^2 : x_2 - ax_1 \leq 0\}$, where $a > k_2/k_1$. Note that $U$ is invariant since $(d/dt)(x_2 - ax_1)$ is negative on the set $\{(x_1, x_2) : x_2 = ax_1, x_2 \geq 0\}$, while the point $(0, 0)$ is an equilibrium. Note that all of the equilibria contained in $U$ are of the form $(\delta, k_2 \delta/k_1)$.

Example 3, Continued
By linearizing the kinetic equations about the origin, it can be seen that the origin is not Lyapunov stable. To analyze the stability of the equilibrium $x_e = (k_3/k_2, k_1/k_2)$, consider, as in [30, p. 115], the function $U : (0, \infty)^2 \rightarrow \mathbb{R}$ defined by $U(x) = k_3 (x_1 + x_2) - k_3 \ln x_1 - k_1 \ln x_2$, which satisfies $U(0) = 0$, $U(x) > 0$ for all $x \in \mathcal{D}(x_e)$, where $\mathcal{D}$ is an open neighborhood of $x_e$. Hence, the equilibrium $x_e = (k_3/k_2, k_1/k_2)$ is Lyapunov stable with respect to $(0, \infty)^2$. Since the solutions consist of closed orbits [30], this equilibrium is not semistable.

Example 4, Continued
For this example let $\mu = [1\ 2\ 1\ 1]^T > 0$ so that $(A-B)\mu = 0$. It thus follows from Proposition 8 that $x_e = 0$ is Lyapunov stable with respect to $(0, \infty)^3$. For the reduced kinetic equations (83), (84), with $x_0(0) + x_3(0) > 0$, it follows that $x_1 = x_2 = 0$ is the only equilibrium. Now, consider the radially unbounded Lyapunov function $V(x_1, x_2) = (1/2)k_3 x_1^2 + (1/2) k_1 x_1 x_2$. Since $V(x_1, x_2) \leq 0$ for all $x_1, x_2 \geq 0$, global asymptotic stability follows from the invariant set theorem.

THE ZERO DEFICIENCY THEOREM
In this section, we analyze the stability of positive equilibria of the kinetic equations (22) using the zero deficiency theorem [19], [20]. This result provides a sufficient condition for Lyapunov stability and semistability based on the structure of the reaction network and independent of the value of the rate constants. The following definitions are required. A complex is either a reactant or a product. For example, in Example 3, the complexes include the reactants $X_1$, $X_1 + X_2$, and $X_2$ as well as the products $2X_1$, $2X_2$, and 0. Let $m_i \geq 1$ denote the number of distinct complexes of the reaction network (including the reactant or product zero if present), and denote the complexes by their corresponding vectors $e_1, \ldots, e_m$ of stoichiometric
coefficients. Obviously, $m \leq 2r$. We can identify each complex with a row of $A$ or $B$ so that $c_i \in \mathbb{R}^{r \times s}$. Thus, $m$ is the number of distinct rows of $[B]$. In examples 1, 2, 3, 4 the number of complexes is 2, 2, 6, and 3, respectively. In particular, Example 4 involves the complexes $c_1 = [1 \ 0 \ 1 \ 0 \ 0]$, $c_2 = [0 \ 1 \ 0 \ 0 \ 0]$, and $c_3 = [0 \ 0 \ 1 \ 1]$ corresponding to $S + E$, $C$, and $P + E$, respectively. For the following definition, $"c_i \rightarrow c_j"$ denotes the reaction $c_iX \rightarrow c_jX$, where we assume $k_i > 0$. Recall that reactions of the form $c \rightarrow c$ are not allowed.

It is useful to represent the reaction network by a directed graph. Consider a directed graph $\mathcal{C}$ having $m$ vertices and $r$ edges such that the $i$th vertex represents the complex $c_i$, and there exists a directed edge from vertex $i$ to vertex $j$ if and only if the reaction network contains the reaction $c_i \rightarrow c_j$. Each edge of $\mathcal{C}$ is numbered according to the reaction that it represents.

**Definition 4**
Let $c_i$ and $c_j$ be complexes of the reaction network (10). Then $c_i$ and $c_j$ are directly linked if either $c_i \rightarrow c_j$ or $c_j \rightarrow c_i$. Furthermore, $c_i$ and $c_j$ are indirectly linked if there exist complexes $c_{i_1}, \ldots, c_{i_l}$ such that $c_i$ is directly linked to $c_{i_1}, c_{i_l}$ is directly linked to $c_{i_{l-1}}, \ldots, c_{i_1}$ is directly linked to $c_j$. Finally, $c_i$ and $c_j$ are linked if either $c_i$ and $c_j$ are indirectly linked or $c_i$ and $c_j$ are directly linked.

The statement that complexes $c_i$ and $c_j$ are linked is an equivalence relation on the set of complexes. This relation induces a partitioning of the set of complexes into disjoint linkage classes. These linkage classes are the connected components of $\mathcal{C}$. Let $\ell$ denote the number of linkage classes of $\mathcal{C}$, and denote these linkage classes by $\mathcal{C}_1, \ldots, \mathcal{C}_\ell$. Since the reactant and product in each reaction belong to the same linkage class, it follows that $\ell \leq r$. Furthermore, since each linkage class of $\mathcal{C}$ contains at least two complexes it follows that $\ell \leq m/2$.

As noted in the section “Reducibility of the Kinetic Equations,” the rank $q = \text{rank}(B - A)$ of the reaction network (22) satisfies $q \leq \min\{r, s\}$. The following result provides a bound for $q$ that is sometimes better. Some additional notation is needed. For $i = 1, \ldots, \ell$, let $m_i$ denote the number of complexes in $\mathcal{C}_i$ so that $\sum_{i=1}^\ell m_i = m$. Furthermore, for convenience we order the complexes $c_1, \ldots, c_m$ so that $\mathcal{C}_1 = \{c_1, \ldots, c_{m_1}\}, \mathcal{C}_2 = \{c_{m_1+1}, \ldots, c_{m_2}\}$, and so forth. Next, we reorder the reactions so that the first $r_i$ rows of $[A \ B]$ include the complexes in $\mathcal{C}_i$, rows $r_1 + 1, \ldots, r_i$ of $[A \ B]$ include the complexes in $\mathcal{C}_2$, and so forth. Hence, $\sum_{i=1}^\ell r_i = r$. For $i = 1, \ldots, \ell$, define the rank $q_i$ of the linkage class $\mathcal{C}_i$ to be the number of linearly independent rows in the submatrix of $B - A$ comprised of the rows of $[A \ B]$ corresponding to the complexes in $\mathcal{C}_i$. Note that $q_i \leq \sum_{i=1}^\ell q_i$. For $i = 1, \ldots, \ell$, it can be seen that $m_i \leq r_i + 1$, and thus $m \leq r + \ell$. If $q_i = m_i - 1$, then the linkage class $\mathcal{C}_i$ has full rank.

**Lemma 2**
Let $i \in \{1, \ldots, \ell\}$. Then $q_i \leq m_i - 1$. Furthermore, $q_i = m_i - 1$ if and only if the complexes in $\mathcal{C}_i$ are the vertices of an $(m_i - 1)$-dimensional simplex in $[0, \infty)^s$.

**Proof**
For notational convenience, let $i = 1$ and order the first $m_1 - 1$ reactions so that, for $j = 1, \ldots, m_1 - 1$, the $j$th reaction is either $c_i \rightarrow c_{i+1}$ or $c_{i+1} \rightarrow c_i$. The span of the first $m_1$ rows of $B - A$ is thus equal to the span of $\{c_2 - c_1, \ldots, c_{m_1} - c_{m_1-1}\}$. Furthermore, since $\mathcal{C}_1$ is a linkage class, it follows that rows $m_1 + 1, \ldots, r_1$ of $B - A$ are contained in the span of the first $m_1$ rows of $B - A$. Thus, $q_1 \leq m_1 - 1$.

Next, note that the span of $\{c_2 - c_1, \ldots, c_{m_1} - c_{m_1-1}\}$ is equal to the span of $\{c_2 - c_1, c_3 - c_1, \ldots, c_{m_1} - c_1\}$, which has dimension $m_1 - 1$ if and only if the complexes in $\mathcal{C}_1$ are the vertices of an $(m_1 - 1)$-dimensional simplex in $[0, \infty)^s$.

In the terminology of [31], an affine subspace is the translate of a subspace. Furthermore, the affine hull of a set $S$ is the smallest affine subspace that contains $S$. It can be seen that $\mathcal{C}_1$ has full rank if and only if the subspace parallel to the affine hull of $\mathcal{C}_1$ has dimension $m_1 - 1$.

**Proposition 9**
$q \leq m - \ell$.

**Proof**
As noted above, $q \leq \sum_{i=1}^\ell q_i$, while Lemma 2 implies that $q_i \leq m_i - 1$. Therefore, $q \leq \sum_{i=1}^\ell q_i \leq \sum_{i=1}^\ell (m_i - 1) = m - \ell$.

**Definition 5**
The deficiency $\delta$ of the reaction network (10) is
\[ \delta = m - \ell - q. \quad (101) \]

It follows from Proposition 9 that the deficiency of a reaction network is a nonnegative integer. If the deficiency of a reaction network is zero, then the reaction network has zero deficiency. It can be seen that a reaction network has deficiency zero if and only if i) every linkage class has full rank, and ii) for every pair $\mathcal{C}_i, \mathcal{C}_j$ of distinct linkage classes, the subspaces parallel to the affine hulls of the linkage classes $\mathcal{C}_i, \mathcal{C}_j$ have trivial intersection.

**Example 1, Continued**
For this reaction network, $m = 2, \ell = 1, q = 1$, and thus $\delta = 0$.

**Example 2, Continued**
For this reaction network, $m = 2, \ell = 1, q = 1$, and thus $\delta = 0$.

**Example 3, Continued**
For this reaction network, $m = 6, \ell = 3, q = 2$, and thus $\delta = 1$.

**Example 4, Continued**
For this reaction network, $m = 3, \ell = 1, q = 2$, and thus $\delta = 0$.

Now define the matrix $C \in \mathbb{R}^{m \times s}$ whose rows are $c_1, \ldots, c_m$. Furthermore, let $A, B \in \mathbb{R}^{r \times m}$ be the matrices whose rows are unit coordinate vectors in $\mathbb{R}^m$ and that satisfy
\[ A = \tilde{A}C, \quad B = \tilde{B}C. \]  

(102)
To derive the dynamics of the reaction network, we invoke the law of mass action.

It follows that

$$B - A = (\bar{B} - \bar{A})C.$$  \hspace{1cm} (103)

Note that

$$\mathcal{N}((\bar{B} - \bar{A})^T) \subseteq \mathcal{N}((B - A)^T).$$  \hspace{1cm} (104)

Next, observe that \( \bar{A}_{ij} = 1 \) if and only if the complex \( c_j \) is the reactant of the \( i \)th reaction, that is, if and only if the \( i \)th edge of \( \mathcal{C} \) originates from vertex \( j \). Similarly, \( \bar{B}_{ij} = 1 \) if and only if the \( i \)th edge of \( \mathcal{C} \) terminates at vertex \( j \). Consequently, the matrix \((\bar{B} - \bar{A})^T\) is the incidence matrix of the directed graph \( \mathcal{C} \) (see [32, p. 24]).

The following result gives some properties of \( \bar{B} - \bar{A} \) and shows that the reverse inclusion of (104) holds if \( \delta = 0 \).

**Proposition 10**

The following statements hold:

i) \( \text{rank}(\bar{B} - \bar{A}) = m - \ell \).

ii) \( \delta = \text{dim} [\mathcal{R}((\bar{B} - \bar{A})^T) \cap \mathcal{N}(C^T)] \).

iii) If \( \mu \in \mathbb{R}^\ell \), then \( e^{\bar{A} \mu} = \bar{A} e^{C \mu} \) and \( e^{\bar{B} \mu} = \bar{B} e^{C \mu} \).

iv) \( \delta = 0 \) if and only if \( \mathcal{N}((\bar{B} - \bar{A})^T) = \mathcal{N}((B - A)^T) \).

**Proof**

Statement i) follows from the fact that the rank of the incidence matrix of a directed graph \( \mathcal{C} \) is equal to the difference between the number of vertices and the number of connected components of \( \mathcal{C} \) [32, Proposition 4.3]. Here, we provide a self-contained proof. Consider the rows of \( \bar{B} - \bar{A} \) corresponding to \( C \). As in the proof of Lemma 2 we order the first \( m_1 - 1 \) reactions so that, for \( j = 1, \ldots, m_1 - 1 \), the \( j \)th reaction is either \( c_j \rightarrow c_{j+1} \) or \( c_{j+1} \rightarrow c_j \). Therefore, for \( j = 1, \ldots, m_1 - 1 \), the \( j \)th row of \( \bar{B} - \bar{A} \) is either \( c_j - c_{j+1} \) or \( c_{j+1} - c_j \), where \( c_j \) denotes the \( j \)th unit coordinate vector in \( \mathbb{R}^m \). Thus, the first \( m_1 \) rows of \( \bar{B} - \bar{A} \) have rank \( m_1 - 1 \). Using a similar argument for each linkage class and noting that rows of \( \bar{B} - \bar{A} \) corresponding to different linkage classes are linearly independent, it follows that

\[
\text{rank}(\bar{B} - \bar{A}) = \sum_{j=1}^{m_1}(m_1 - 1) = m - \ell.
\]

Next, to prove ii) it follows from Sylvester’s theorem (see [27, Fact 2.10.13]) that

\[
q = \text{rank}(\bar{B} - \bar{A}) = \text{rank}(\bar{B} - \bar{A})^T = \text{rank}((\bar{B} - \bar{A})^T) = \dim(\mathcal{R}((\bar{B} - \bar{A})^T) \cap \mathcal{N}(C^T)) = m - \ell - \dim(\mathcal{R}((\bar{B} - \bar{A})^T) \cap \mathcal{N}(C^T)).
\]

To prove iii), let \( j \in \{1, \ldots, r\}, A_j = \text{row}_j(A), B_j = \text{row}_j(B), \bar{A}_j = \text{row}_j(\bar{A}), \) and \( \bar{B}_j = \text{row}_j(\bar{A}) \). Now, since each row of \( B \) corresponds to a unique row of \( C \), it follows that \( B_j = \text{row}_k(\bar{C}) \) for some \( k_j \in \{1, \ldots, m\} \). Hence, \( B_j = \bar{B}_j C \), where \( \bar{B}_j k_j = 1 \), \( k = k_j \), and \( \bar{B}_j k = 0, k \neq k_j \). Thus,

\[
e^{\bar{B}_j \mu} = e^{B_j C \mu} = \hat{B}_j e^{C \mu}.
\]

Similarly, we can show that \( \hat{A}_j e^{C \mu} = e^{A_j \mu} \).

To prove iv), assume that \( \delta = 0 \) and note that

\[
\text{rank}((\bar{B} - \bar{A})^T) + \text{dim}(\mathcal{N}((\bar{B} - \bar{A})^T)) = r
\]

and

\[
\text{rank}((\bar{B} - \bar{A})^T) + \text{dim}(\mathcal{N}((\bar{B} - \bar{A})^T)) = r.
\]

Since \( \delta = 0 \), it follows from i) that \( \text{rank}(\bar{B} - \bar{A})^T = q = m - \ell = \text{rank}(\bar{B} - \bar{A}) \), and thus \( \text{dim}(\mathcal{N}((\bar{B} - \bar{A})^T)) = \text{dim}(\mathcal{N}((\bar{B} - \bar{A})^T)) \). Since \( \mathcal{N}((\bar{B} - \bar{A})^T) \subseteq \mathcal{N}((\bar{B} - \bar{A})^T) \) it follows that \( \mathcal{N}((\bar{B} - \bar{A})^T) = \mathcal{N}((\bar{B} - \bar{A})^T) \). The converse follows by reversing the steps.

**Definition 6**

Let \( c_i \) and \( c_j \) be complexes. Then there exists a direct path from \( c_i \) to \( c_j \) if \( c_i \rightarrow c_j \). Furthermore, there exists an indirect path from \( c_i \) to \( c_j \) if there exist complexes \( c_i, \ldots, c_k \) such that \( c_i \rightarrow c_j \rightarrow \cdots \rightarrow c_k \rightarrow c_j \). Finally, there exists a path from \( c_i \) to \( c_j \) if there exists either a direct path or an indirect path from \( c_i \) to \( c_j \).

Note that the existence of a path from \( c_i \) to \( c_j \) is stronger than the statement that \( c_i \) and \( c_j \) are linked since the former condition accounts for the directionality of the reactions.

**Definition 7**

The reaction network (10) is weakly reversible if, for all pairs of complexes \( c_i, c_j \), the existence of a path from \( c_i \) to \( c_j \) implies the existence of a path from \( c_j \) to \( c_i \).

Note that the existence of a path from \( c_i \) to \( c_j \) is equivalent to the existence of a directed path from vertex \( i \) to vertex \( j \) on the graph \( \mathcal{C} \). Consequently, weak reversibility is equivalent to the requirement that every vertex or, equivalently, every edge of \( \mathcal{C} \) must be part of a directed cycle. In the terminology of [33, pp. 357–358] and [34], weak reversibility of (10) is equivalent to strong connectedness of each connected component of \( \mathcal{C} \).

The following lemmas are needed. Furthermore, for \( l = 1, \ldots, \ell \), let \( v_l \in \mathbb{R}^m \) (respectively, \( e_l \in \mathbb{R}^m \)) be such that the \( j \)th component of \( v_l \) (respectively, \( e_l \)) is one if the \( j \)th
vertex (respectively, jth edge) of $\mathcal{C}$ belongs to the ith connected component of $\mathcal{C}$ and zero otherwise. It is easy to see that $A\mathbf{v}_i = B\mathbf{v}_i = e_i$ for all $l = 1, \ldots, \ell$, which implies that $\mathbf{v}_i \in \mathcal{N}(B - A)$ for all $l = 1, \ldots, \ell$. Next, note that, since each vertex of $C_l$ belongs to exactly one connected component of $\mathcal{C}$, $\{v_1, \ldots, v_l\}$ are linearly independent and hence, since $\text{rank}(B - A) = m - \ell$, it follows that $\mathcal{N}(B - A)$ is the span of $\{v_1, \ldots, v_l\}$. Finally, note that

$$\sum_{i=1}^{\ell} \theta_i \mathbf{v}_i = \sum_{i=1}^{\ell} e_i^{\theta_i} \mathbf{v}_i,$$

(105)

where $\theta_1, \ldots, \theta_\ell \in \mathbb{R}$.

**Lemma 3**

Let $x \in (0, \infty)^N$ and define $\Gamma = (B - A)^T (\alpha \mathbf{e}^T \circ \hat{A}) \in \mathbb{R}^{m \times m}$. Then the following statements hold:

i) The reaction network (22) is weakly reversible if and only if there exists $p \in (0, \infty)^N$ such that $(B - A)^T p = 0$.

ii) Assume that the reaction network (22) is weakly reversible. Then rank $\Gamma = m - \ell$ and there exists $p \in (0, \infty)^N$ such that $\Gamma(p \circ \mathbf{v}_i) = 0$ for all $l = 1, \ldots, \ell$.

iii) If the reaction network (22) has zero deficiency, then rank $[C \mathbf{v}_1 \cdots \mathbf{v}_l] = m$.

**Proof**

To prove i), note that it follows from [32, Thrm. 4.5.5.2] that $\mathcal{N}((B - A)^T)$ is the span of $\{n_1, \ldots, n_n\}$, where $n_j$ is the number of directed cycles of the graph $G$ and $n_1$ is such that the $j$th component of $n_j$ is 1 if the $j$th edge is part of $i$th directed cycle of $\mathcal{C}$ and zero otherwise. Hence, if the reaction network is weakly reversible, then every edge of $\mathcal{C}$ is part of at least one directed cycle of $\mathcal{C}$. Now, a positive linear combination of all the cycles of $\mathcal{C}$ yields $x \in (0, \infty)^N$ such that $(B - A)^T p = 0$. To prove the converse, assume that the reaction network is not weakly reversible or, equivalently, there exists an edge (say the $l$th edge) that does not belong to any cycle of $C_l$. Hence, it follows that the $l$th component of all vectors in $\mathcal{N}((B - A)^T)$ is zero, which implies that there does not exist $p \in (0, \infty)^N$ such $(B - A)^T p = 0$.

To prove ii), note that $-\Gamma^T$ is the Laplacian of the weighted directed graph $[34]$ obtained by assigning the weight $x_l$ to the $l$th edge of $\mathcal{C}$. There exists a permutation matrix $P \in \mathbb{R}^{m \times m}$ such that $\Gamma = -\Gamma^T P \Gamma P^T$ and $\Gamma = \text{block-diag}(\Gamma_1, \ldots, \Gamma_l)$, where $\Gamma_l \in \mathbb{R}^{m_l \times m_l}$ with $l = 1, \ldots, \ell$, are such that $\sum_{l=1}^{\ell} m_l = m$ and $-\Gamma^T_l$ is the Laplacian of $C_l$. Weak reversibility implies that each connected component of $\mathcal{C}$ is strongly connected. [Note that $-\Gamma^T$ is the Laplacian of $\mathcal{C}$ in the case where the vertices are reordered such that the $i$th connected component (linkage class) of $\mathcal{C}$ contains the vertices (complexes) numbered as $m_l + 1, \ldots, m_{l+1}$, $l = 1, \ldots, \ell$, where $m_0 = 0$.] Hence, it follows from [34, Thrm. 1] that rank $\Gamma_l = m_l - 1$ for all $l = 1, \ldots, \ell$, which implies that rank $\Gamma = \text{rank} \Gamma_l = m - \ell$.

To prove the second assertion of ii), let $l \in \{1, \ldots, \ell\}$, let $c_l = \min_{i=1, \ldots, m_l} \gamma_i$, and let $X_l = \Gamma_l + \gamma l$, where $\gamma_i$ denotes the $(i, j)$th entry of $\Gamma_l$. Now, note that $X_l$ is a nonnegative matrix and, for $i \neq j$, the $(i, j)$th entry of $X_l$ is positive if and only if there exists an edge from vertex $j$ to vertex $i$ of the linkage class $l$. Hence, since the reaction network is weakly reversible, it follows from [33, Thrm. 6.2.24] that $X_l$ is an irreducible matrix [33, p. 361], which further implies that there exists $\hat{p}_l \in (0, \infty)^N$ such that $X_l p_l = \rho(X_l) \hat{p}_l$ (see [33, Thrm. 8.4.4]). Consequently, $\Gamma p_l = (X_l - c L_m) \hat{p}_l = (\rho(X_l) - c_e \hat{p}_l)$ and, since $0 = e l \Gamma p_l = (\rho(X_l) - c_e \hat{p}_l)$ and $e l \hat{p}_l > 0$, it follows that $c_l = \rho(X_l)$. Thus, there exists a positive vector $p_l \in (0, \infty)^N$ satisfying $\Gamma p_l = 0$ for all $l = 1, \ldots, \ell$. Now, letting $p = [p_1 \cdots p_{\ell}]^T$ it can be shown that $\rho(\Gamma p_l) = 0$ so that $\rho(\Gamma p_l) = 0$. Finally, taking $p = \Pi p$ implies that $\rho(\Pi p_l) = \Pi \rho(p l) = \Pi \rho(\Pi p_l) = 0$, establishing the result.

To prove iii), let $x \in \mathbb{R}^{m_l}$ be such that $x \in \mathcal{N}(C_l)$ and $x^T v_i = 0$ for all $l = 1, \ldots, \ell$. Next, since $\mathcal{N}(B - A)$ is the span of $\{v_1, \ldots, v_l\}$, it follows that $x \in \mathcal{N}((B - A)^T) = \mathcal{R}(B - A)^T$. Hence, $x \in \mathcal{R}((B - A)^T) \cap \mathcal{N}(C_l)$, and since the reaction network has zero deficiency, it follows from ii) of Proposition 10 that $x = 0$, which proves that rank$[C v_1 \cdots v_l] = m$. \hfill \Box

**Lemma 4**

Assume that the reaction network (22) has zero deficiency, and assume that there exists $x \in (0, \infty)^N$ such that $(B - A)^T x = 0$. Then $\mu \in \mathbb{R}$ satisfies $(B - A)^T (\alpha \circ e^T \mu) = 0$ if and only if $\mu \in S^N$.

**Proof**

Since the reaction network (22) has zero deficiency, it follows from iv) of Proposition 10 that $\mathcal{N}((B - A)^T) = \mathcal{N}((B - A)^T)$, and hence, $\mathcal{N}((B - A)^T)$ is the span of $\{n_1, \ldots, n_n\}$ defined in the proof of ii) of Lemma 3. Furthermore, since $x \in \mathcal{N}((B - A)^T)$ it follows that $x = \sum_{l=1}^{m_l} \beta_l n_l$ for some $\beta_l \in \mathbb{R}$, $l = 1, \ldots, n$. Now, note that $n_l \circ \alpha = n_l$ if the $l$th cycle of $\mathcal{C}$ belongs to the $l$th linkage class of $\mathcal{C}$ and zero otherwise. In both cases, $(B - A)^T (n_l \circ \alpha) = (B - A)^T n_l = 0$ for all $l = 1, \ldots, n$. To prove necessity, let $\mu \in \mathcal{N}(B - A)$. Then, $(B - A)^T (\alpha \circ e^T \mu) = 0$, which, since $\mathcal{N}(B - A)$ is the span of $\{v_1, \ldots, v_l\}$, implies that $C \mu = \sum_{l=1}^{\ell} \theta_l v_l$ for some $\theta_1, \ldots, \theta_\ell \in \mathbb{R}$. Hence, it follows that

$$(B - A)^T (\alpha \circ e^T \mu) = (B - A)^T (\alpha \circ A e^T \mu)$$

$$= (B - A)^T (\alpha \circ A (\sum_{l=1}^{\ell} \theta_l \mathbf{v}_l))$$

$$= (B - A)^T (\alpha \circ \hat{A}^T (\sum_{l=1}^{\ell} \theta_l \mathbf{v}_l))$$

$$= (B - A)^T (\alpha \circ \hat{A}^T (\sum_{l=1}^{\ell} \theta_l \mathbf{v}_l))$$

$$= \sum_{l=1}^{\ell} (B - A)^T (\beta_l \mathbf{v}_l (\theta_l \circ \alpha))$$

$$= 0,$$

where iii) of Proposition 10 is used to obtain the first equality, (105) is used to obtain the second equality, and the fact that $\hat{A}^T v_l = e_l$ for all $l = 1, \ldots, \ell$, is used to obtain the third equality.
Conversely, assume that $(B - A)^T(\alpha \circ e^{t\mu}) = 0$, which implies that $(B - A)^T(\alpha \circ e^{t\mu}) = 0$. Hence,

$$0 = (B - A)^T(\alpha \circ Ae^\delta) = (B - A)^T(\alpha e^T \circ A)e^\delta = \Gamma e^\mu,$$

(106)

where $\Gamma$ is defined in Lemma 3. Next, note that, for all $l = 1, \ldots, \ell$,

$$\Gamma v_l = (B - A)^T(\alpha e^T \circ A)v_l = (B - A)^T(\alpha \circ Av_l) = (B - A)^T(\alpha \circ e_l) = \sum_{i=1}^{m} \beta_i (B - A)^T(\eta_i \circ e_i) = 0.$$

Furthermore, it follows from ii) of Lemma 3 that rank $\Gamma = m - \ell$, which implies that $N^\parallel(\Gamma)$ is the span of $\{v_1, \ldots, v_\ell\}$. Hence, it follows from (106) that $e^\mu = \sum_{i=1}^{m} \theta_i v_i$ for some $\theta_1, \ldots, \theta_\ell \in \mathbb{R}$, which implies that $C \mu = \sum_{i=1}^{m} \theta_i v_i$. Now, the result follows by noting that $(B - A)\mu = (B - A)C \mu = \sum_{i=1}^{m} \theta_i (B - A)v_i = 0$.

The following result shows that weak reversibility is a necessary and sufficient condition for a reaction network with zero deficiency to have at least one positive equilibrium.

**Proposition 11**

Assume that the reaction network (22) has zero deficiency. Then the reaction network (22) is weakly reversible if and only if it has a positive equilibrium.

**Proof**

To prove necessity, let $x_c$ be a positive equilibrium of (22). Hence, it follows from iv) of Proposition 10 that $(B - A)^T \sigma_p = 0$, where $p = Kx_c \in (0, \infty)^S$. Now, it follows from i) of Lemma 3 that the reaction network is weakly reversible.

To prove sufficiency, note that

$$(B - A)^T(k \circ x^C) = (B - A)^T(k \circ \dot{A}x^C) = (B - A)^T(k e^T \circ A)x^C = \Gamma x^C,$$

where $\Gamma := (B - A)^T(k e^T \circ A)$. Now, it follows from ii) of Lemma 3 that there exists a positive vector $p \in \mathbb{R}^m$ such that $\Gamma(p \circ v_i) = 0$ for all $l = 1, \ldots, \ell$. Next, we show that there exists a positive vector $x^C \in \mathbb{R}^S$ and scalars $\theta_1, \ldots, \theta_\ell$ such that $x^C = p \circ e^T + \sum_{i=1}^{m} \theta_i v_i$, such that $x^C = p \circ e^{T \circ A}$. To see this, note that the existence of a positive vector $x$ and scalars $\theta_1, \ldots, \theta_\ell$ satisfying $x^C = p \circ e^{T \circ A}$ is equivalent to the existence of a solution $x$ to the equation $C x = \log p + \sum_{i=1}^{m} \theta_i v_i$ or, equivalently,

$$\begin{bmatrix} C v_1 & \cdots & C v_\ell \end{bmatrix} \begin{bmatrix} \log x \\ -\theta_1 \\ \vdots \\ -\theta_\ell \end{bmatrix} = \log p.$$  

(107)

Now, since the reaction network has zero deficiency, it follows from iii) of Lemma 3 that rank$\{C v_1, \ldots, v_\ell\} = m$, and hence, (107) has a solution, which implies that there exists a positive vector $x$ and scalars $\theta_1, \ldots, \theta_\ell$ such that $x^C = p \circ e^{T \circ A}$.

Next, it follows from (105) that

$$(B - A)^T(k \circ x^A) = C^T \Gamma x^C = C^T \Gamma \left( p \circ e^{T \circ A} + \sum_{i=1}^{m} \theta_i v_i \right) = 0,$$

which implies that $x$ is a positive equilibrium of the reaction network (22).

Next, we show that every positive stoichiometric compatibility class contains exactly one equilibrium for a weakly reversible reaction network with zero deficiency. The following lemma is needed for this result.

**Lemma 5**

Let $\rho, \bar{\rho} \in (0, \infty)^S$, let $\mathcal{X}$ be a subspace of $\mathbb{R}^m$, and define $\mathcal{X}^= \{x \in \mathbb{R}^m : x \in \mathcal{X}, \text{ } x \geq 0\}$. Then there exists a unique $\rho \in \mathcal{X}^+$ such that $(p \circ e^{\rho} - \bar{\rho})$.

**Proof**

Define $\phi : \mathbb{R}^m \to \mathbb{R}$ by $\phi(x) = \rho x - \bar{\rho}$. It can be shown that $\lim_{x \to \infty} \phi(x) = \infty$. Now, let $x>0$ and, since $\lim_{x \to \infty} \phi(x) = \infty$, it follows that $C_r \{x \in \mathbb{R}^m : \phi(x) \leq r\}$ is also a compact set, which implies that there exists a positive equilibrium of $(p \circ \mu(x) \leq \bar{\rho})$ for all $x \in \mathcal{X}$. Now, since $\mathcal{X}^= \mathcal{X} \cap \mathbb{R}^m$, it follows that $\phi(x) \leq r$ for all $x \in \mathcal{X}$. Specifically, $\phi(x) \leq \rho(x)$ for all $x \in \mathcal{X}^+$ and $\rho(x) \leq \bar{\rho}(x)$ for all $x \in \mathcal{X}$. Thus, $\phi(x) \leq \rho(x)$ has a minimum at $x = 0$, which implies that

$$0 = \frac{d \phi}{dx} \bigg|_{x=0} = \frac{\rho(x) - \bar{\rho}(x)}{x}.$$  

(108)

Hence, since $\gamma > 0$, it follows that $(p \circ e^{\rho} - \bar{\rho}) \in \mathcal{X}$, which establishes existence.

To prove uniqueness, let $\mu \in \mathcal{X}^+$ be such that $(p \circ e^{\rho} - \bar{\rho}) \in \mathcal{X}$. Then, since $\mu \in \mathcal{X}^+$ and $p \circ e^{\rho} \leq \bar{\rho} \in \mathcal{X}$ it follows that $(\rho - \bar{\rho}) \in \mathcal{X}$ and $(p \circ e^{\rho} - \bar{\rho}) \in \mathcal{X}$, and hence,

$$0 = (\mu - \bar{\rho})\frac{d \phi}{dx} \bigg|_{x=0} = \sum_{i=1}^{S} \rho_i (\mu_i - \bar{\rho}_i) (e^{\rho_i} - e^{\bar{\rho}_i}).$$  

(109)

Next, since the exponential function is an increasing function, it follows that $(\mu_i - \bar{\rho}_i) (e^{\rho_i} - e^{\bar{\rho}_i}) \geq 0$ for all $i = 1, \ldots, S$, and, since $p \in (0, \infty)^S$, it follows from (108) that $(\mu_i - \bar{\rho}_i) (e^{\rho_i} - e^{\bar{\rho}_i}) = 0$ for all $i = 1, \ldots, S$, or, equivalently, $\mu = \bar{\rho}$. The next result characterizes all positive equilibria of zero-deficiency, weakly reversible reaction networks.

**Proposition 12**

Assume that the reaction network (22) has zero deficiency and is weakly reversible, and let $x_c$ be a positive equilibrium. Then

$$\mathcal{E}_+ = \{x \in (0, \infty)^S : \log x - \log x_c \in \mathcal{S}^\bot \}.$$  

(109)

Furthermore, every positive stoichiometric compatibility class contains exactly one equilibrium.
We consider the realizability problem, which is concerned with the inverse problem of constructing a reaction network having specified essentially nonnegative dynamics.

Proof
To prove that $\mathcal{E}_+$ has the form (109), let $x_e$ be a positive equilibrium, let $x \in (0, \infty)^r$, and define $\mu \triangleq \log x - \log x_e$. Then

$$
(k \circ x^A) = (k \circ x^A \circ x^{-A} \circ x^A)
= (k \circ e^{A \log x} \circ e^{-A \log x_e} \circ x^A)
= (k \circ e^{\mu} \circ e^{\mu})
= (k \circ x^A_e \circ e^{\mu}).
$$

Now, assume that $x$ is also a positive equilibrium so that $(B - A)^T(k \circ x^A \circ e^{\mu}) = (B - A)^T(k \circ x^A) = 0$. Since $x_e$ is an equilibrium, we have $(B - A)^T(k \circ x^A_e) = 0$. It thus follows from Lemma 4, with $x = k \circ x^A_e$, that $\mu \in S^\perp$. Conversely, assume that $\mu \in S^\perp$. Since $(B - A)^T(k \circ x^A) = 0$, it follows from Lemma 4 that $0 = (B - A)^T(k \circ x^A_e \circ e^{\mu}) = (B - A)^T(k \circ x^A)$, which shows that $x$ is an equilibrium.

To prove the second assertion, let $S_p \triangleq \{p + x : x \in S\}$ denote a stoichiometric compatibility class, where $p \in (0, \infty)^r$. Now, with $X = S$, it follows from Lemma 5 that there exists a unique $\mu \in S^\perp$ such that $(x_o \circ e^\mu - p) \in S$ or, equivalently, $(x_o \circ e^\mu) \in S_p$. Now, the result follows by noting that $\mathcal{E}_+ = \{x \circ e^\mu : \mu \in S^\perp\} \subset (0, \infty)^r$.

We now have the main result of this section.

**Theorem 7**
If the reaction network (22) has zero deficiency, then every positive equilibrium of (22) is semistable with respect to $(0, \infty)^r$.

**Proof**
Let $x_e$ be a positive equilibrium of (22) and define the Lyapunov candidate $V : (0, \infty)^r \to \mathbb{R}$ by

$$
V(x) \triangleq \sum_{i=1}^{s} [x_i(\log x_i - \log x_e_i) - (x_i - x_e_i)],
$$

where $x_i$ and $x_e_i$ are the $i$th components of $x$ and $x_e$, respectively. It follows from the inequality $\log a \leq a - 1$ for all $a > 0$, with $a = x_e_i/x_i$, that $V(x) \geq 0$ for all $x \in (0, \infty)^r$. Since $\log a = a - 1$ if and only if $a = 1$, it follows that $V(x) = 0$ if and only if $x = x_e$.

Next, for $x \in (0, \infty)^r$, define $\mu \triangleq \log x - \log x_e$, and note that it follows from $\log a \leq a - 1$, $a > 0$, with $a = e^{\mu}/e^{\mu_i}$, that

$$
\mu \leq e^{\mu_i} - e^{\mu},
$$

with equality holding in (110) if and only if $(B - A)|\mu = 0$. Using (110), along with iii) and iv) of Proposition 10, yields

$$
\dot{V}(x) = \mu^T(B - A)^T K x^A
= \mu^T(B - A)^T K e^{A \log x} - e^{A \mu}
= ([\mu^T(B - A)^T] \circ (e^A \mu))
= (K x^A)^T (e^A \mu) \circ (B - A)\mu
\leq (K x^A)^T (e^A \mu) - e^A \mu
= (K x^A)^T (\dot{B} - \dot{A}) e^\mu
= [\dot{B} - \dot{A}] K x^A e^\mu
= 0,
$$

(111)

which proves that every positive equilibrium of (22) is Lyapunov stable.

Next, assume that the reaction network (22) has zero deficiency. If $x \in (0, \infty)^r$ satisfies $V(x) = 0$, then it follows from (111) that $(K x^A)^T (e^A \mu) = (K x^A)^T (e^A \mu)$. Now, since $K x^A > 0$, it follows from (110) that $e^A \mu \circ (B - A)\mu = e^A \mu - e^A \mu$, which implies that $(B - A)\mu = 0$, and hence, $(\log x - \log x_e) \in S^\perp$. It now follows from Proposition 12 that $x$ is a positive equilibrium of (22) and, as shown above, $x$ is Lyapunov stable. Thus, every element of the largest invariant set of $\{x \in (0, \infty)^r : V(x) = 0\}$ is a Lyapunov-stable equilibrium. Furthermore, for $\eta > 0$, let $\mathcal{U}_\eta$ denote the closure of the connected component of $\{x \in (0, \infty)^r : V(x) \leq \eta\}$ containing $x_e$. Since $V(\cdot)$ is continuous in $(0, \infty)^r$ and $V(x_e) = 0$, it follows that there exists $\beta > 0$ such that $\mathcal{U}_\beta \subset (0, \infty)^r$ and is compact. Now, with $\mathcal{U} = \mathcal{U}_\beta$, Theorem 6 implies every solution to (22) with $x(0) \in \mathcal{U}_\eta$ converges to an equilibrium that is semistable with respect to $\mathcal{U}_\eta$. Finally, the result follows from the definition of semistability with respect to $(0, \infty)^r$ and the fact that $\mathcal{U}_\eta$ has a nonempty interior.

The following version of Theorem 7 is proved in [19] and [20].

**Theorem 8**
Assume that the reaction network (22) has zero deficiency and is weakly reversible. Then every positive stoichiometric compatibility class contains exactly one equilibrium. This equilibrium is asymptotically stable with respect to the positive
stoichiometric compatibility class that it is contained in, and there exist no nontrivial periodic orbits in \((0, \infty)^s\).

Proof
The first assertion is a consequence of Propositions 11 and 12. The second assertion follows from Theorem 7 and using the facts that every positive stoichiometric compatibility class is invariant, contains exactly one positive equilibrium, and \(V(x(t))\) is a (strictly) decreasing function on every nontrivial solution to (22) in \((0, \infty)^s\), where \(V(\cdot)\) is the Lyapunov function defined in the proof of Theorem 7.

Note that the conclusions of Theorems 7 and 8 can be strengthened without any additional assumptions. Specifically, [14] shows that, for every initial condition in the nonnegative orthant, the positive limit set is a subset of the set of nonnegative equilibria. Furthermore, if every positive stoichiometric compatibility class has no equilibria on its boundary, then every equilibrium is globally asymptotically stable relative to its positive stoichiometric compatibility class.

Example 1, Continued
This reaction network has zero deficiency and is weakly reversible. Theorem 8 thus implies that every positive stoichiometric compatibility class contains exactly one equilibrium, and this equilibrium is semistable with respect to \([0, \infty)^s\).

Example 2, Continued
This reaction network has zero deficiency and is weakly reversible. Theorem 8 thus implies that every positive stoichiometric compatibility class contains exactly one equilibrium, and this equilibrium is semistable with respect to \([0, \infty)^s\).

Example 3, Continued
This reaction network has deficiency 1 and is not weakly reversible. Hence, Theorem 8 does not apply.

Example 4, Continued
Although this reaction network has zero deficiency, it is not weakly reversible. Accordingly, Theorem 7 cannot be used to conclude semistability. However, Lyapunov methods, based on nontangency between the vector field and invariant subsets of the level sets of the Lyapunov function \(V(x) = 2x_1 + x_2\), where \(x \in (1, 1 + k_3/k_2)\), can be used to conclude semistability of every equilibrium in \(\mathcal{E} = \{x \in [0, \infty)^s\} : x_1 = 0, x_2 = 0, x_3 > 0\}\). For details, see [17].

The following example is a modification of Example 4 to include weak reversibility.

Example 5
Consider a modification of Example 4 in which all reactions are reversible, that is,

\[
S + E \xrightleftharpoons[k_3]{k_2} C \xrightleftharpoons[k_4]{k_1} P + E
\]

so that \(s = 4\) and \(r = 4\). It thus follows that \(A\) and \(B\) are given by

\[
A = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 \end{bmatrix},
\]

(113)

and the kinetic equations have the form

\[
\dot{x}_1(t) = k_2 x_3(t) - k_1 x_1(t) x_3(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \quad (114)
\]

\[
\dot{x}_2(t) = -(k_2 + k_3) x_2(t) + k_1 x_1(t) x_3(t) + k_4 x_4(t) x_4(t), \quad x_2(0) = x_{20}, \quad (115)
\]

\[
\dot{x}_3(t) = (k_2 + k_3) x_2(t) - k_1 x_1(t) x_3(t) - k_4 x_4(t) x_4(t), \quad x_3(0) = x_{30}, \quad (116)
\]

\[
\dot{x}_4(t) = k_2 x_2(t) - k_4 x_3(t) x_4(t), \quad x_4(0) = x_{40}. \quad (117)
\]

Since this network has zero deficiency and is weakly reversible, Theorem 8 implies that every positive stoichiometric compatibility class contains exactly one equilibrium, and this equilibrium is semistable with respect to \([0, \infty)^s\).

CONCLUSIONS
In this article we presented a matrix-vector form of the kinetic equations for the mass-action kinetics of arbitrary reaction networks. We proved that these equations have nonnegative solutions for all nonnegative initial conditions, and we presented a procedure for reducing the order of these equations for reaction networks with low-rank dynamics. Next, we considered the stability of these equations, including asymptotic stability, semistability, and Lyapunov stability. In particular, the notion of semistability was shown to pertain to the kinetic equations for cases in which the equilibrium to which the network converges depends on the initial concentrations. We proved the sufficient condition for semistability given by Theorem 7 and due to [19] and [20], and we stated and applied Lyapunov conditions for each type of stability to four examples. Finally, we analyzed the stability of positive equilibria of the kinetic equations using the zero deficiency theorem of [19] and [20] and proved semistability using the techniques of [17].

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