Modeling and Analysis of Mass-Action Kinetics

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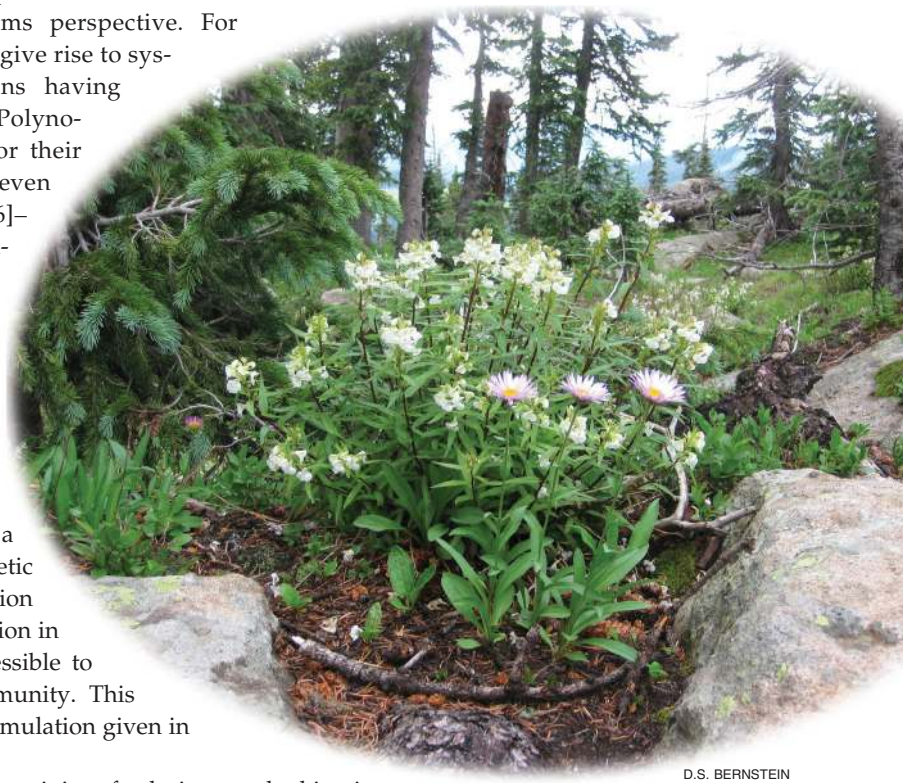
NONNEGATIVITY, REALIZABILITY, REDUCIBILITY, AND SEMISTABILITY

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].



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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

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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

$$2H_2 + O_2 \xrightarrow{k} 2H_2O. \tag{1}$$

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

$$\sum_{j=1}^{3} A_j X_j \xrightarrow{k} \sum_{j=1}^{3} B_j X_j, \tag{2}$$

where X_1, X_2, and X_3 denote the species H_2, O_2, and H_2O, 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

$$AX \xrightarrow{k} BX, \tag{3}$$

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

Next, consider the *reversible* reaction

$$Na_2CO_3 + CaCl_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} CaCO_3 + 2NaCl, \tag{4}$$

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

$$Na_2CO_3 + CaCl_2 \xrightarrow{k_1} CaCO_3 + 2NaCl, \tag{5}$$

$$CaCO_3 + 2NaCl \xrightarrow{k_2} Na_2CO_3 + CaCl_2, \tag{6}$$

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 Na_2CO_3, $CaCl_2$, $CaCO_3$, and NaCl, respectively, so that (4) can be written as

$$X_1 + X_2 \xrightarrow{k_1} X_3 + 2X_4, \tag{7}$$

$$X_3 + 2X_4 \xrightarrow{k_2} X_1 + X_2, \tag{8}$$

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

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

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*

$$\sum_{j=1}^{s} A_{ij} X_j \xrightarrow{k_i} \sum_{j=1}^{s} B_{ij} X_j, \quad i = 1, \ldots, r, \tag{9}$$

where, for $i = 1, \ldots, r$, $k_i > 0$ is the *reaction rate* of the ith reaction, $\sum_{j=1}^{s} A_{ij} X_j$ is the *reactant* of the ith reaction, and $\sum_{j=1}^{s} B_{ij} X_j$ is the *product* of the ith 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

$$AX \xrightarrow{k} BX, \tag{10}$$

where $X = [X_1 \cdots X_s]^{\mathrm{T}}$ is a column vector of species, $k = [k_1 \cdots k_r]^{\mathrm{T}} \in [0, \infty)^r$, 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 $\left[\begin{smallmatrix} A \\ B \end{smallmatrix}\right]$ is zero. Furthermore, in special cases and only when specifically mentioned, we allow $k_i = 0$, which effectively denotes the

fact that the ith reaction is absent. Finally, we assume that, for all $i = 1, \ldots, r$, $\mathrm{row}_i(A) \neq \mathrm{row}_i(B)$ 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 $\dot{x}_1(t) = 0$ and $\dot{x}_1(t) = 0$, $\dot{x}_2(t) = 0$, 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

$$X_1 + X_2 \xrightarrow{k} bX_3, \tag{11}$$

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

$$\dot{x}_i(t) = -kx_1(t)x_2(t), \quad x_i(0) = x_{i0}, \quad t \geq 0, \quad i = 1, 2, \tag{12}$$
$$\dot{x}_3(t) = bkx_1(t)x_2(t), \quad x_3(0) = x_{30}, \tag{13}$$

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

$$\mathrm{H_2} + \mathrm{H_2} + \mathrm{O_2} \xrightarrow{k} 2\mathrm{H_2O}, \tag{14}$$

Matrix Notation

A vector $x \in \mathbb{R}^p = \mathbb{R}^{p \times 1}$ 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 $x \geq\geq 0$ 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 $A \geq\geq 0$ 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 $x \geq\geq 0$ 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 $[1, 1, \ldots, 1]^{\mathrm{T}}$ is written as $\mathbf{e}$. 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 $A \in \mathbb{R}^{p \times q}$, $\mathrm{row}_i(A)$ and $\mathrm{col}_j(A)$ denote the ith row and jth 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 spec (A) denotes the spectrum of A.

the law of mass action implies that

$$\dot{x}_1(t) = -2kx_1^2(t)x_2(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{15}$$
$$\dot{x}_2(t) = -kx_1^2(t)x_2(t), \quad x_2(0) = x_{20}, \tag{16}$$
$$\dot{x}_3(t) = 2kx_1^2(t)x_2(t), \quad x_3(0) = x_{30}, \tag{17}$$

where $x_1(t)$, $x_2(t)$, and $x_3(t)$ denote the concentrations of $\mathrm{H_2}$, $\mathrm{O_2}$, and $\mathrm{H_2O}$, 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

$$\dot{x}_1(t) = -k_1x_1(t)x_2(t) + k_2x_3(t)x_4^2(t), \quad x_1(0) = x_{10}, \ t \geq 0, \tag{18}$$
$$\dot{x}_2(t) = -k_1x_1(t)x_2(t) + k_2x_3(t)x_4^2(t), \quad x_2(0) = x_{20}, \tag{19}$$
$$\dot{x}_3(t) = k_1x_1(t)x_2(t) - k_2x_3(t)x_4^2(t), \quad x_3(0) = x_{30}, \tag{20}$$
$$\dot{x}_4(t) = 2k_1x_1(t)x_2(t) - 2k_2x_3(t)x_4^2(t), \quad x_4(0) = x_{40}. \tag{21}$$

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*

$$\dot{x}(t) = (B - A)^{\mathrm{T}}[k \circ x^A(t)], \quad x(0) = x_0, \quad t \geq 0, \tag{22}$$

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

$$\dot{x}(t) = (B - A)^{\mathrm{T}}Kx^A(t), \quad x(0) = x_0, \quad t \geq 0. \tag{23}$$

In mass-action kinetics the *reaction order* $\sum_{j=1}^{s} A_{ij}$ of the ith reaction is the sum of the stoichiometric coefficients of the species appearing in the reactant of the ith 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

$$\dot{x}(t) = Mx(t), \quad x(0) = x_0, \quad t \geq 0, \tag{24}$$

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

$$M \triangleq (B - A)^{\mathrm{T}}KA. \tag{25}$$

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 $AX_1 \xrightarrow{k_1} BX_1$. The kinetic equations for the reactions $X_1 \xrightarrow{k_1} 0$ and $0 \xrightarrow{k_1} X_1$, which represent the removal and addition of mass, are $\dot{x}_1(t) = -k_1x_1(t)$ and $\dot{x}_1(t) = k_1$ with solutions $x_1(t) = x_1(0)e^{-k_1t}$ and $x_1(t) = k_1t + x_1(0)$, respectively. The reactions $X_1 \xrightarrow{k_1} 2X_1$ and $2X_1 \xrightarrow{k_1} 3X_1$, which also represent

the addition of mass, have the kinetics $\dot{x}_1(t) = k_1 x_1(t)$ and $\dot{x}_1(t) = k_1 x_1^2(t)$ with solutions $x_1(t) = x_1(0)e^{k_1 t}$ and $x_1(t) = x_1(0)/(1 - k_1 x_1(0)t)$, respectively. Note that the latter solution 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, $\dot{x}(t) = -kx(t)$, $\dot{y}(t) = kx(t)$ and $\dot{x}(t) = -kx^2(t)$, $\dot{y}(t) = kx^2(t)$, 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

$$X_1 \xrightarrow{k_1} X_2, \tag{26}$$

$$X_2 \xrightarrow{k_2} X_1, \tag{27}$$

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

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

The kinetic equations are thus given by

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

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

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

$$M = \begin{bmatrix} -k_1 & k_2 \\ k_1 & -k_2 \end{bmatrix}. \tag{31}$$

■

Example 2

Consider the reaction network

$$X_1 + X_2 \xrightarrow{k_1} 2X_1, \tag{32}$$

$$2X_1 \xrightarrow{k_2} X_1 + X_2, \tag{33}$$

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

$$A = \begin{bmatrix} 1 & 1 \\ 2 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 2 & 0 \\ 1 & 1 \end{bmatrix}. \tag{34}$$

The kinetic equations are thus given by

$$\dot{x}_1(t) = k_1 x_1(t) x_2(t) - k_2 x_1^2(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{35}$$

$$\dot{x}_2(t) = -k_1 x_1(t) x_2(t) + k_2 x_1^2(t), \quad x_2(0) = x_{20}. \tag{36}$$

■

Example 3

The Lotka-Volterra reaction is given by

$$X_1 \xrightarrow{k_1} 2X_1, \tag{37}$$

$$X_1 + X_2 \xrightarrow{k_2} 2X_2, \tag{38}$$

$$X_2 \xrightarrow{k_3} 0, \tag{39}$$

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

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

Consequently, the kinetic equations have the form

$$\dot{x}(t) = \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} k_1 x_1(t) \\ k_2 x_1(t) x_2(t) \\ k_3 x_2(t) \end{bmatrix},$$

$$x(0) = \begin{bmatrix} x_{10} \\ x_{20} \end{bmatrix}, \quad t \geq 0, \tag{41}$$

that is,

$$\dot{x}_1(t) = k_1 x_1(t) - k_2 x_1(t) x_2(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{42}$$

$$\dot{x}_2(t) = -k_3 x_2(t) + k_2 x_1(t) x_2(t), \quad x_2(0) = x_{20}. \tag{43}$$

■

Vector-Matrix Exponentiation

For $x = [x_1 \ldots x_q]^{\mathrm{T}} \in \mathbb{R}^q$ and nonnegative $A = [A_{ij}] \in \mathbb{R}^{p \times q}$, x^A denotes the element of $\mathbb{R}^p$ whose ith component for $i = 1, \ldots, p$ is the product $x_1^{A_{i1}} \cdots x_q^{A_{iq}}$. For example, if

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

then

$$x^A = \begin{bmatrix} x_1 x_2^2 \\ x_1^3 x_2^4 \end{bmatrix}.$$

We define $0^0 \triangleq 1$. The matrix exponentiation operation has many convenient properties [21], [S1]. For example, if $A, B \in \mathbb{R}^{p \times q}$ then $x^{(A+B)} = x^A x^B$. If $B \in \mathbb{R}^{n \times p}$, then $(x^A)^B = x^{BA}$. Furthermore, $(x \circ y)^A = (x^A) \circ (y^A) = x^A y^A$. Note that $x^{I_p} = x$ and $x^{-A} \circ (x^A) = \mathrm{e}$. Alternatively, if $A \in \mathbb{R}^{p \times p}$ then $x^{-I_p} \circ x^A = x^{A - I_p}$. Furthermore, if $\det A \neq 0$, $x >> 0$, and $y >> 0$, then $x^A = y$ implies that $x = y^{A^{-1}}$. In addition, $\log x^A = A \log x$ and $e^{A \log x} = x^A$, while $x^A = y$ implies $A \log x = \log y$, where, for $x = [x_1, \ldots, x_s]^{\mathrm{T}} \in (0, \infty)^p$, $\log x$ denotes the vector in $\mathbb{R}^p$ whose ith component is $\log x_i$. Finally, if $f(x) = x^A$ then $f'(x) = \mathrm{diag}(x^A) A [\mathrm{diag}(x)]^{-1}$, where

$$\mathrm{diag}(x_1, x_2, \ldots, x_n) \triangleq \begin{bmatrix} x_1 & & \\ & \ddots & \\ & & x_n \end{bmatrix}.$$

For $x = [x_1, \ldots, x_s]^{\mathrm{T}} \in \mathbb{R}^p$, e^x denotes the vector in $\mathbb{R}^p$ whose ith component is e^{x_i}. Throughout the article "log" denotes natural logarithm.

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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

$$\mathrm{S} + \mathrm{E} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{k_3} \mathrm{P} + \mathrm{E} \tag{44}$$

so that $s = 4$ and $r = 3$. Letting $X_1 = \mathrm{S}$, $X_2 = \mathrm{C}$, $X_3 = \mathrm{E}$, and $X_4 = \mathrm{P}$, the corresponding reaction network can be written as

$$X_1 + X_3 \xrightarrow{k_1} X_2, \tag{45}$$

$$X_2 \xrightarrow{k_2} X_1 + X_3, \tag{46}$$

$$X_2 \xrightarrow{k_3} X_3 + X_4. \tag{47}$$

It thus follows that A and B are given by

$$A = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}. \tag{48}$$

Consequently, the kinetic equations have the form

$$\dot{x}(t) = \begin{bmatrix} -1 & 1 & 0 \\ 1 & -1 & -1 \\ -1 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} k_1 x_1(t) x_3(t) \\ k_2 x_2(t) \\ k_3 x_2(t) \end{bmatrix},$$

$$x(0) = \begin{bmatrix} x_{10} \\ x_{20} \\ x_{30} \\ x_{40} \end{bmatrix}, \quad t \geq 0, \tag{49}$$

that is,

$$\dot{x}_1(t) = k_2 x_2(t) - k_1 x_1(t) x_3(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{50}$$

$$\dot{x}_2(t) = -(k_2 + k_3) x_2(t) + k_1 x_1(t) x_3(t), \quad x_2(0) = x_{20}, \tag{51}$$

$$\dot{x}_3(t) = (k_2 + k_3) x_2(t) - k_1 x_1(t) x_3(t), \quad x_3(0) = x_{30}, \tag{52}$$

$$\dot{x}_4(t) = k_3 x_2(t), \quad x_4(0) = x_{40}. \tag{53}$$

■

NONNEGATIVITY OF SOLUTIONS

Since the states of the kinetic equations (22) represent concentrations, it is natural to expect that, for nonnegative initial concentrations, the concentrations remain nonnegative for as long as the solution exists. In this section, we show that this property holds for the class of essentially nonnegative systems, and then we show that the kinetic equations (22) are in fact essentially nonnegative.

Definition 1

Let $f = [f_1 \cdots f_n]^{\mathrm{T}} : [0, \infty)^n \to \mathbb{R}^n$. Then f is *essentially nonnegative* if, for all $i = 1, \ldots, n$, $f_i(x) \geq 0$ for all $x \in [0, \infty)^n$ such that $x_i = 0$, where x_i denotes the ith component of x.

It is easy to see that the linear function $f(x) = Mx$, where $M \in \mathbb{R}^{n \times n}$, is essentially nonnegative if and only if all of the off-diagonal entries of M are nonnegative. In this case, we say that M is *essentially nonnegative*. In the terminology of [22] it follows that M is essentially nonnegative if and only if $-M$ is a Z-matrix.

For the following definitions and results, we consider the system

$$\dot{x}(t) = f(x(t)), \quad x(0) = x_0, \quad t \in [0, T_{x_0}), \tag{54}$$

where $f : \mathcal{D} \to \mathbb{R}^n$ is locally Lipschitz, $\mathcal{D}$ is an open subset of $\mathbb{R}^n$, $x_0 \in \mathcal{D}$, 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 $\mathcal{U} \subseteq \mathcal{D}$ is *invariant* with respect to (54) if $x_0 \in \mathcal{U}$ implies that $x(t) \in \mathcal{U}$ for all $t \in [0, T_{x_0})$. The following technical result is needed. For this result, $\mathcal{B}_\varepsilon(x)$ denotes the *open ball centered* at $x \in \mathbb{R}^n$ with *radius* $\varepsilon > 0$.

Lemma 1

Consider the dynamical system (54), and let $\mathcal{U} \subset \mathcal{D}$ be closed relative to $\mathcal{D}$. Then the following statements are equivalent:

i) For all $x \in \mathcal{U}$, $\lim_{h \to 0^+} \inf_{y \in \mathcal{U}} \|x + hf(x) - y\|/h = 0$, where $\|\cdot\|$ denotes the Euclidean vector norm on $\mathbb{R}^n$.

ii) $\mathcal{U}$ is an invariant set with respect to (54).

Proof

Assume that i) holds. To show ii), let $x_0 \in \mathcal{U}$. Since $f(\cdot)$ is Lipschitz continuous it follows that there exist $\varepsilon > 0$ and $L > 0$ such that, for all $x, y \in \mathcal{B}_{2\varepsilon}(x_0)$,

$$\|f(x) - f(y)\| \leq L \|x - y\|. \tag{55}$$

Let $T \in [0, T_{x_0})$ be such that $s(t, x), s(t, y) \in \mathcal{B}_{2\varepsilon}(x_0)$ for all $t \in [0, T)$ and $x, y \in \mathcal{B}_\varepsilon(x_0)$ where $s(t, x) \in \mathcal{D}$ denotes the solution to (54) at time t and initial condition x. Now, it follows from Gronwall's lemma [23, p. 81] that, for all $x, y \in \mathcal{B}_\varepsilon(x_0)$ and $t \in [0, T)$,

$$\|s(t, x) - s(t, y)\| \leq e^{Lt} \|x - y\|. \tag{56}$$

Next, let $t_1 \in [0, T)$ be such that $\|s(t, x_0) - x_0\| < \varepsilon/3$ for all $t \in (0, t_1)$, and define $\varphi(t) \triangleq \operatorname{dist}(s(t, x_0), \mathcal{U}) \triangleq \inf_{y \in \mathcal{U}} \|s(t, x_0) - y\|$. Note that since $x_0 \in \mathcal{U}$, it follows that $\varphi(0) = 0$ and $\varphi(t) \leq \|s(t, x_0) - x_0\| < \varepsilon/3$ for all $t \in (0, t_1)$. Now, let $t \in (0, t_1)$ and $y_t \in \mathcal{U}$ be such that $\|s(t, x_0) - y_t\| - \varphi(t) \leq \varepsilon/3$. Hence,

$$\begin{aligned} \|y_t - x_0\| &= \|y_t - s(t, x_0) + s(t, x_0) - x_0\| \\ &\leq \|s(t, x_0) - x_0\| + \|s(t, x_0) - y_t\| \\ &\leq \|s(t, x_0) - x_0\| + \varphi(t) + \varepsilon/3 \\ &< \varepsilon. \end{aligned}$$

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

$$\begin{aligned} \varphi(t + h) &= \inf_{z \in \mathcal{U}} \|s(t + h, x_0) - z\| \\ &\leq \inf_{z \in \mathcal{U}} \{\|s(t + h, x_0) - s(h, y_t)\| + \|s(h, y_t) - y_t - hf(y_t)\| \\ &\quad + \|y_t + hf(y_t) - z\|\} \\ &= \|s(t + h, x_0) - s(h, y_t)\| + \|s(h, y_t) - y_t - hf(y_t)\| \\ &\quad + \operatorname{dist}(y_t + hf(y_t), \mathcal{U}) \\ &\leq e^{Lh} \|s(t, x_0) - y_t\| + \|s(h, y_t) - y_t - hf(y_t)\| \\ &\quad + \operatorname{dist}(y_t + hf(y_t), \mathcal{U}), \end{aligned} \tag{57}$$

which implies that

$$\frac{\varphi(t+h)-\varphi(t)}{h} \leq \left(\frac{e^{Lh}-1}{h}\right)\varphi(t) + \left\|\frac{s(h,y_t)-y_t}{h} - f(y_t)\right\| + \frac{\operatorname{dist}(y_t + hf(y_t), \mathcal{U})}{h}.$$

Now, letting $h \longrightarrow 0^+$ and using i) yields

$$\limsup_{h \longrightarrow 0^+} \frac{\varphi(t+h)-\varphi(t)}{h} \leq L\varphi(t). \tag{58}$$

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 $x_0 \in \mathcal{U}$ is arbitrary, it follows that, for every $\tau_1 > 0$ such that $\varphi(\tau_1) = 0$, there exists $h > 0$ such that $\varphi(t) = 0$ for all $t \in [\tau_1, \tau_1 + h)$. Next, let $\tau \triangleq \inf\{t > 0 : \varphi(t) > 0\}$ and suppose, *ad absurdum*, that $\tau < T_{x_0}$. Since $\varphi(t) = 0$ for all $t \in [0, t_1)$, it follows that $\tau \geq t_1 > 0$ and, by the definition of τ, $\varphi(t) = 0$ for all $t \in [0, \tau)$ or, equivalently, $s(t, x_0) \in \mathcal{U}$ for all $t \in [0, \tau)$. Hence, since $s(\tau, x_0) = \lim_{t \to \tau^-} s(t, x)$ and $\mathcal{U}$ is relatively closed with respect to $\mathcal{D}$, it follows that $s(\tau, x_0) \in \mathcal{U}$. Therefore, $\varphi(\tau) = 0$, which implies that there exists $h > 0$ such that $\varphi(t) = 0$ for all $t \in [\tau, \tau + h)$, contradicting the definition of τ. Thus, $\varphi(t) = 0$ for all $t \in [0, T_{x_0})$, establishing the result.

Conversely, assume $\mathcal{U}$ is an invariant set with respect to (54) so that, for all $x_0 \in \mathcal{U}$ and $h \neq 0$,

$$\operatorname{dist}(x_0 + hf(x_0), \mathcal{U}) \leq \|s(h, x_0) - x_0 - hf(x_0)\| = |h|\left\|\frac{s(h,x_0)-x_0}{h} - f(x_0)\right\|.$$

Now, the result follows by letting $h \longrightarrow 0^+$. □

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 $\mathcal{D}$. This result is generalized in [25] to the case where f is continuous on $\mathcal{D}$ and (54) has a unique right maximally defined solution.

Theorem 1

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

Proof

Suppose f is essentially nonnegative, and let $x \in [0, \infty)^n$. If $x_i = 0$, then $x_i + hf_i(x) = hf_i(x) \geq 0$ for all $h \geq 0$, whereas, if $x_i > 0$, then $x_i + hf_i(x) > 0$ for all $|h|$ sufficiently small. Thus, $x + hf(x) \in [0, \infty)^n$ for all $h > 0$ sufficiently small, and hence, $\lim_{h \to 0^+} \inf_{y \in [0,\infty)^n} \|x + hf(x) - y\|/h = 0$. It now 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 $x(0) \in [0, \infty)^n$, let $x(t)$, $t \in [0, T_{x_0})$, denote the solution to (54), and suppose there exists $i \in \{1, \ldots, n\}$ such that $x_i(0) = 0$ and $f_i(x(0)) < 0$. 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, $x_i(t)$ is decreasing on $[0, h)$ and therefore $x(t) \notin [0, \infty)^n$ for all $t \in [0, h)$, which is a contradiction. □

Proposition 1

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

Proof

Since f is continuously differentiable it follows that f is locally Lipschitz. Next, let $x \in [0, \infty)^s$. For $j \in \{1, \ldots, s\}$ we have

$$f_j(x) = [\operatorname{col}_j(B) - \operatorname{col}_j(A)]^{\mathrm{T}} \begin{bmatrix} k_1 x^{\operatorname{row}_1(A)} \\ \vdots \\ k_r x^{\operatorname{row}_r(A)} \end{bmatrix} = \sum_{i=1}^{r} B_{ij} k_i x^{\operatorname{row}_i(A)} - \sum_{i=1}^{r} A_{ij} k_i x^{\operatorname{row}_i(A)}.$$

Note that the first summation is nonnegative since x is nonnegative. Next, note that $A_{ij}k_i x^{\operatorname{row}_i(A)}$ contains the factor $A_{ij}x_j^{A_{ij}}$. Now, to verify Definition 1, let $x_j = 0$. If $A_{ij} > 0$, then $A_{ij}x_j^{A_{ij}} = A_{ij}(0^{A_{ij}}) = 0$, while, if $A_{ij} = 0$, then $A_{ij}x_j^{A_{ij}} = \lim_{x_j \to 0} 0(x_j^0) = \lim_{x_j \to 0} 0(1) = 0$. Consequently, the second summation is zero for all nonnegative $A_{1j}, \ldots, A_{rj}$ whenever $x_j = 0$. Thus, f is essentially nonnegative. □

Theorem 2

$[0, \infty)^s$ 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 $M = (B - A)^{\mathrm{T}}KA$ and A has exactly one nonzero entry in each row. Then $f(x) = Mx$ is essentially nonnegative, and $[0, \infty)^s$ 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 $A^{\mathrm{T}}KA$ is diagonal. Now, since $B^{\mathrm{T}}KA$ is nonnegative it follows that M is essentially nonnegative, and hence $f(x) = Mx$ is essentially nonnegative. The invariance of $[0, \infty)^s$ is a direct consequence of Theorem 2. □

In the linear case $f(x) = Mx$, where $M \in \mathbb{R}^{n \times n}$ is essentially nonnegative, Theorem 1 implies the following result [3], [26]. For this special case we provide a separate, self-contained proof.

Proposition 2

Let $M \in \mathbb{R}^{n \times n}$. Then M is essentially nonnegative if and only if $e^{Mt} \geq\geq 0$ for all $t \geq 0$.

Proof

To prove necessity, note that, since M is essentially nonnegative it follows that $M_\alpha \triangleq M + \alpha I_n$ is nonnegative, where

$\alpha \triangleq -\min\{M_{11}, \ldots, M_{nn}\}$. Hence, $e^{M_\alpha t} \geq\geq 0$ for all $t \geq 0$, and thus $e^{Mt} = e^{-\alpha t} e^{M_\alpha t} \geq\geq 0$ for all $t \geq 0$. Conversely, suppose $e^{Mt} \geq\geq 0$ 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

$$[e^{Mt}]_{ij} = (I_n)_{ij} + tM_{ij} + o(t),$$

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. □

Example 1, Continued

For the kinetic equations (24) with M given by (31) it can be seen that $M = \left[\begin{smallmatrix} -k_1 & k_2 \\ k_1 & -k_2 \end{smallmatrix}\right]$ 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 $x(\cdot)$ 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

$$f(x) = \sum_{i=0}^{v} a_i x^i \tag{59}$$

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 $f(x) = (B - A)^{\mathrm{T}}(k \circ x^A)$.

Proof

For $i = 1, \ldots, v$, define A, B, and $k \in [0, \infty)^{v+1}$ as

$$A_i \triangleq i, \quad B_i \triangleq (i + \operatorname{sign} a_i), \quad k_i \triangleq |a_i|, \tag{60}$$

where $\operatorname{sign} 0 \triangleq 0$. Note that $A \geq\geq 0$ and, since $a_0 \geq 0$, it follows that $B \geq\geq 0$. Then the dynamics of the reaction network (10) are given by the kinetic equation

$$\begin{aligned} \dot{x}(t) &= (B - A)^{\mathrm{T}}(k \circ x^A(t)) \\ &= \sum_{i=0}^{v} (B_i - A_i) k_i x^{A_i}(t) \\ &= \sum_{i=0}^{v} (\operatorname{sign} a_i)|a_i| x^i(t) \\ &= \sum_{i=0}^{v} a_i x^i(t) \\ &= f(x(t)). \end{aligned}$$

Hence, (10) is a realization of (22), where f is given by (59). □

To demonstrate Theorem 3, let $v = 3$. Then a realization of $\dot{x}_1(t) = a_3 x_1^3(t) + a_2 x_1^2(t) + a_1 x_1(t) + a_0$ is given by the reaction network

$$0 \xrightarrow{a_0} X_1, \tag{61}$$

$$X_1 \xrightarrow{|a_1|} (1 + \operatorname{sign} a_1) X_1, \tag{62}$$

$$2X_1 \xrightarrow{|a_2|} (2 + \operatorname{sign} a_2) X_1, \tag{63}$$

$$3X_1 \xrightarrow{|a_3|} (3 + \operatorname{sign} a_3) X_1, \tag{64}$$

where we follow the convention that any reaction with rate constant zero is removed from the network to avoid trivial reactions of the form $aX_1 \xrightarrow{0} bX_1$.

If $n \geq 2$ and f is an essentially nonnegative multivariate polynomial in $x_1, \ldots, x_n$, then there does not necessarily exist a reaction network such that $f(x) = (B - A)^{\mathrm{T}}(k \circ x^A)$. For example, consider the case $n = 2$ and the dynamic equations

$$\dot{x}_1(t) = x_2^2(t) - 2x_2^3(t) + x_2^4(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{65}$$

$$\dot{x}_2(t) = 0, \quad x_2(0) = x_{20}. \tag{66}$$

Then

$$f(x_1, x_2) = \begin{bmatrix} x_2^2 - 2x_2^3 + x_2^4 \\ 0 \end{bmatrix}$$

is essentially nonnegative. However, (65), (66) cannot be realized as a reaction network. To see this, suppose that (65), (66) are the kinetic equations for a reaction network of r reactions involving the species X_1 and X_2. Since $f(\cdot, \cdot)$ is independent of x_1, it follows that the reaction network must have the form

$$a_i X_2 \xrightarrow{k_i} b_i X_1 + c_i X_2, \tag{67}$$

where a_i, b_i, and c_i 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

$$\dot{x}_1(t) = \sum_{i=1}^{r} b_i k_i x_2^{a_i}(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{68}$$

$$\dot{x}_2(t) = \sum_{i=1}^{r} (c_i - a_i) k_i x_2^{a_i}(t), \quad x_2(0) = x_{20}. \tag{69}$$

Comparing (65) with (68), it follows that $a_i \in \{2, 3, 4\}$ for all $i = 1, \ldots, r$. Furthermore, $\sum_{i \in \mathcal{R}} b_i k_i = -2$, where

$\mathcal{R} \triangleq \{i \in \{1,\dots,r\} : a_i = 3\}$, which is a contradiction since $b_i \geq 0$ and $k_i \geq 0$ for all $i = 1,\dots,r$.

Next, we present a necessary and sufficient condition that guarantees a reaction network realization such that $f(x) = (B - A)^{\mathrm{T}}(k \circ x^A)$.

Theorem 4

Consider the system (54), where $n > 1$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a multivariate polynomial. Then there exists a reaction network of the form (10) with $s = n$ such that $f(x) = (B - A)^{\mathrm{T}}(k \circ x^A)$, where the stoichiometric coefficient matrices A and B have nonnegative integer entries, if and only if for each $j \in \{1,\dots,n\}$, $f_j(x_1, x_2, \dots, x_{j-1}, 0, x_{j+1}, \dots, x_n)$ is a multivariate polynomial with nonnegative coefficients.

Proof

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

$$a_j x_1^{p_1} x_2^{p_2} \cdots x_j^{p_j} \cdots x_n^{p_n}, \tag{70}$$

where $p_i \geq 0$ for all $i = 1,\dots,n$ and $p_j > 0$, or of the form

$$b_j x_1^{q_1} \cdots x_{j-1}^{q_{j-1}} x_{j+1}^{q_{j+1}} \cdots x_n^{q_n}, \tag{71}$$

with $b_j > 0$. Next, note that the reaction

$$\sum_{i=1}^{n} p_i X_i \xrightarrow{|a_j|} (p_j + \operatorname{sign} a_j) X_j + \sum_{i=1,\, i\neq j}^{n} p_i X_i, \tag{72}$$

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

$$\sum_{i=1}^{n} q_i X_i \xrightarrow{b_j} X_j + \sum_{i=1,\, i\neq j}^{n} q_i X_i, \tag{73}$$

contributes the term (71) to the rate of $\dot{x}_j$ and zero terms to $\dot{x}_i$ for all $i = 1,\dots,n$, $i \neq j$. Hence, for all $j = 1,\dots,n$, 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 $j \in \{1,\dots,s\}$. Then

$$f_j(x) = \sum_{i=1}^{r} (B_{ij} - A_{ij}) k_i x^{\mathrm{row}_i(A)}.$$

Let $x_j = 0$. If $A_{ij} > 0$, then $x^{\mathrm{row}_i(A)}$ and hence $(B_{ij} - A_{ij}) k_i x^{\mathrm{row}_i(A)} = 0$, whereas, if $A_{ij} = 0$, then

$$(B_{ij} - A_{ij}) k_i x^{\mathrm{row}_i(A)} = \lim_{x_j \to 0^+} B_{ij} k_i x_1^{A_{i1}} \cdots x_{j-1}^{A_{i(j-1)}} x_j^0 x_{j+1}^{A_{i(j+1)}} \cdots x_n^{A_{in}}.$$

Hence,

$$f_j(x) = \sum_{i \in \mathcal{I}_j} B_{ij} k_i x_1^{A_{i1}} \cdots x_{j-1}^{A_{i(j-1)}} x_{j+1}^{A_{i(j+1)}} \cdots x_n^{A_{in}},$$

where $\mathcal{I}_j \triangleq \{i \in \{1,\dots,r\} : A_{ij} = 0\}$, 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) impose an additional constraint on the allowable trajectories. To state this result we define the *stoichiometric subspace* $\mathcal{S}$ by $\mathcal{S} \triangleq \mathcal{R}((B - A)^{\mathrm{T}})$, which is a subspace of $\mathbb{R}^s$. The dimension of this subspace is given by $q \triangleq \operatorname{rank}((B - A)^{\mathrm{T}}) = \operatorname{rank}(B - A)$, 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 $P \in \mathbb{R}^{s \times s}$ denote the unique orthogonal projector whose range is $\mathcal{S}$, and define $P_\perp \triangleq I_s - P$. In terms of the generalized inverse $(\cdot)^+$, P is given by $P = (B - A)^{\mathrm{T}}[(B - A)^{\mathrm{T}}]^+ = (B - A)^+(B - A)$. Note that, if $z \in \mathbb{R}^s$, then $Pz = z$ if and only if $z \in \mathcal{S}$, and therefore $P_\perp z = 0$ if and only if $z \in \mathcal{S}$.

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

$$x(t) \in (x(0) + \mathcal{S}) \cap [0,\infty)^s. \tag{74}$$

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 $x(t) \in x(0) + \mathcal{S}$ for all $t \in [0, T_{x(0)})$, note that $\dot{x}(t) \in \mathcal{S}$ for all $t \in [0, T_{x(0)})$, which implies that $\mathrm{d}/\mathrm{d}t P_\perp [x(t) - x(0)] = P_\perp \dot{x}(t) = 0$ for all $t \in [0, T_{x(0)})$. Hence, $P_\perp [x(t) - x(0)]$ is constant for all $t \in [0, T_{x(0)})$. Thus, for all $t \in [0, T_{x(0)})$, it follows that $P_\perp [x(t) - x(0)] = P_\perp [x(0) - x(0)] = 0$, and hence, $x(t) - x(0) \in \mathcal{S}$, as required. □

Corollary 2

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

Proof

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

$$\begin{aligned} \hat{x}(t) &\in (\hat{x}(0) + \mathcal{S}) \cap [0,\infty)^s \\ &= (x(0) + w + \mathcal{S}) \cap [0,\infty)^s \\ &= (x(0) + \mathcal{S}) \cap [0,\infty)^s, \end{aligned}$$

establishing the invariance. □

Proposition 3 shows that the solution $x(\cdot)$ of the kinetic equations (22) is confined to the *stoichiometric compatibility class* $(x(0) + \mathcal{S}) \cap [0,\infty)^s$, which is a q-dimensional manifold

with boundary. (The set $(x(0)+\mathcal{S})\cap(0,\infty)^s$ 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 $x_1,\ldots,x_s$ 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 $\operatorname{rank}(B_1-A_1)=q$. In addition, let $F\in\mathbb{R}^{q\times(s-q)}$ satisfy $A_2-B_2=(A_1-B_1)F$. Finally, partition $x=[\hat{x}_1^{\mathrm{T}}\ \ \hat{x}_2^{\mathrm{T}}]^{\mathrm{T}}$, where $\hat{x}_1\stackrel{\Delta}{=}[x_1\cdots x_q]^{\mathrm{T}}$ and $\hat{x}_2\stackrel{\Delta}{=}[x_{q+1}\cdots x_s]^{\mathrm{T}}$. Then

$$\hat{x}_2(t)=F^{\mathrm{T}}\hat{x}_1(t)+\gamma,\quad \hat{x}_2(0)=\hat{x}_{20},\quad t\geq 0, \tag{75}$$

where $\gamma\stackrel{\Delta}{=}\hat{x}_2(0)-F^{\mathrm{T}}\hat{x}_1(0)\in\mathbb{R}^{s-q}$, and $\hat{x}_1(\cdot)$ satisfies

$$\begin{aligned}&\dot{\hat{x}}_1(t)=(B_1-A_1)^{\mathrm{T}}[k\circ\hat{x}_1^{A_1}(t)\circ(F^{\mathrm{T}}\hat{x}_1(t)+\gamma)^{A_2}],\\&\hat{x}_1(0)=\hat{x}_{10},\quad t\geq 0.\end{aligned} \tag{76}$$

Proof

Left multiplying (22) by $[F^{\mathrm{T}}\ \ -I_{s-q}]$ yields $\dot{\hat{x}}_2(t)=F^{\mathrm{T}}\dot{\hat{x}}_1(t)$, which implies (75). Next, note that $\dot{\hat{x}}_1(t)=(B_1-A_1)^{\mathrm{T}}[k\circ x^A(t)]=(B_1-A_1)^{\mathrm{T}}[k\circ\hat{x}_1^{A_1}(t)\circ\hat{x}_2^{A_2}(t)]$, which, with (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 $x_2(t)=-x_1(t)+\gamma$ for all $t\geq 0$, where $\gamma\stackrel{\Delta}{=}x_1(0)+x_2(0)$. Applying Proposition 4 with $\hat{x}_1=x_1$ and $\hat{x}_2=x_2$, (76) yields the scalar kinetic equation

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

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

$$0\xrightarrow{k_2\gamma}X_1, \tag{78}$$

$$X_1\xrightarrow{k_1+k_2}0, \tag{79}$$

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 $x_2(t)=-x_1(t)+\gamma$ for all $t\geq 0$, where $\gamma\stackrel{\Delta}{=}x_1(0)+x_2(0)$. Applying Proposition 4 with $\hat{x}_1=x_1$ and $\hat{x}_2=x_2$, (76) yields the scalar kinetic equation

$$\dot{x}_1(t)=-(k_1+k_2)x_1^2(t)+k_1\gamma x_1(t),\quad x_1(0)=x_{10},\quad t\geq 0, \tag{80}$$

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

$$X_1\xrightarrow{k_1\gamma}2X_1, \tag{81}$$

$$2X_1\xrightarrow{k_1+k_2}X_1, \tag{82}$$

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 $F=\left[\begin{smallmatrix}0&-1\\-1&-1\end{smallmatrix}\right]$. It thus follows that $x_3(t)=-x_2(t)+\gamma_1$ and $x_4(t)=-x_1(t)-x_2(t)+\gamma_2$ for all $t\geq 0$, where $\gamma_1\stackrel{\Delta}{=}x_2(0)+x_3(0)$ and $\gamma_2\stackrel{\Delta}{=}x_1(0)+x_2(0)+x_4(0)$. Applying Proposition 4 with $\hat{x}_1=[x_1\ x_2]^{\mathrm{T}}$ and $\hat{x}_2=[x_3\ x_4]^{\mathrm{T}}$, (76) yields

$$\dot{x}_1(t)=-k_1\gamma_1x_1(t)+k_2x_2(t)+k_1x_1(t)x_2(t),\ x_1(0)=x_{10},\ t\geq 0, \tag{83}$$

$$\dot{x}_2(t)=k_1\gamma_1x_1(t)-(k_2+k_3)x_2(t)-k_1x_1(t)x_2(t),\quad x_2(0)=x_{20}, \tag{84}$$

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

$$X_1\xrightarrow{k_1\gamma_1}X_2, \tag{85}$$

$$X_2\xrightarrow{k_2}X_1, \tag{86}$$

$$X_2\xrightarrow{k_3}0, \tag{87}$$

$$X_1+X_2\xrightarrow{k_1}2X_1, \tag{88}$$

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 $X_1=\mathrm{S}$, $X_2=\mathrm{P}$, $X_3=\mathrm{C}$, and $X_4=\mathrm{E}$. The reaction network (45)–(46) can now be written as

$$X_1+X_4\xrightarrow{k_1}X_3, \tag{89}$$

$$X_3\xrightarrow{k_2}X_1+X_4, \tag{90}$$

$$X_3\xrightarrow{k_3}X_4+X_2, \tag{91}$$

whose kinetic equations are

$$\dot{x}_1(t)=-k_1x_1(t)x_4(t)+k_2x_3(t),\quad x_1(0)=x_{10},\quad t\geq 0, \tag{92}$$

$$\dot{x}_2(t)=k_3x_3(t),\quad x_2(0)=x_{20}, \tag{93}$$

$$\dot{x}_3(t)=k_1x_1(t)x_4(t)-(k_2+k_2)x_3(t),\quad x_3(0)=x_{30}, \tag{94}$$

$$\dot{x}_4(t)=-k_1x_1(t)x_4(t)+(k_2+k_2)x_3(t),\quad x_4(0)=x_{40}. \tag{95}$$

Since $s=4$, $r=3$, and $q=2<s$, Proposition 4 can be applied with $\hat{x}_1=[x_1\ x_2]^{\mathrm{T}}$, $\hat{x}_2=[x_3\ x_4]^{\mathrm{T}}$, and $F=\left[\begin{smallmatrix}-1&1\\-1&1\end{smallmatrix}\right]$. It thus follows that $x_3(t)=-x_1(t)-x_2(t)+\gamma_1$ and $x_4(t)=x_1(t)+x_2(t)+\gamma_2$ for all $t\geq 0$, where $\gamma_1\stackrel{\Delta}{=}x_1(0)+x_2(0)+x_3(0)$

and $\gamma_2 \stackrel{\Delta}{=} x_4(0) - x_1(0) - x_2(0)$. By applying Proposition 4, it follows from (76) that

$$\dot{x}_1(t) = -k_1 x_1^2(t) - k_1 x_1(t) x_2(t) - (k_1\gamma_2 + k_2) x_1(t) - k_2 x_2(t) + k_2\gamma_1, \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{96}$$

$$\dot{x}_2(t) = -k_3 x_1(t) - k_3 x_2(t) + k_3\gamma_1, \quad x_2(0) = x_{20}, \tag{97}$$

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 $A_1, B_1 \in \mathbb{R}^{r\times q}$, and assume that $\operatorname{rank}(B_1 - A_1) = q$. In addition, let $F \in \mathbb{R}^{q\times(s-q)}$ satisfy $A_2 - B_2 = (A_1 - B_1)F$. Finally, partition $x = [\hat{x}_1^{\mathrm{T}} \; \hat{x}_2^{\mathrm{T}}]^{\mathrm{T}}$, where $\hat{x}_1 \stackrel{\Delta}{=} [x_1 \cdots x_q]^{\mathrm{T}}$ and $\hat{x}_2 \stackrel{\Delta}{=} [x_{q+1} \cdots x_s]^{\mathrm{T}}$. Then, for all $\hat{x}_1(0) \in [0,\infty)^q$ and $\gamma \in \mathbb{R}^{s-q}$ such that $\gamma + F^{\mathrm{T}}\hat{x}_1(0) \in [0,\infty)^{s-q}$, the solution $\hat{x}_1(t)$ to (76) is nonnegative for all $t \geq 0$.

Proof

With $\hat{x}_2(0) = \gamma + F^{\mathrm{T}}\hat{x}_1(0)$, it follows from Proposition 4 that the solution to (22) is given by $[\hat{x}_1^{\mathrm{T}}(t) \; \hat{x}_2^{\mathrm{T}}(t)]^{\mathrm{T}}$ for all $t \geq 0$, where $\hat{x}_2(t)$ is given by (75). Hence, since $\hat{x}_1(0) \geq\geq 0$ and $\hat{x}_2(0) \geq\geq 0$, it follows that $\hat{x}_1(t) \geq\geq 0$ 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 $x_{\mathrm{e}} \in \mathcal{D}$ satisfies $f(x_{\mathrm{e}}) = 0$, then x_{e} is an *equilibrium* of (54).

Definition 2

Let $\mathcal{U} \subseteq \mathcal{D}$ be invariant with respect to (54), and let $x_{\mathrm{e}} \in \mathcal{U}$ be an equilibrium of (54). Then x_{e} is *Lyapunov stable* with respect to $\mathcal{U}$ if, for every relatively open subset $\mathcal{U}_\varepsilon$ of $\mathcal{U}$ containing x_{e} there exists a relatively open subset $\mathcal{U}_\delta$ of $\mathcal{U}$ containing x_{e} such that, if $x(0) \in \mathcal{U}_\delta$, then the solution $x(\cdot)$ of (54) satisfies $x(t) \in \mathcal{U}_\varepsilon$ 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 $\mathcal{U}_\varepsilon \subseteq \mathcal{U}$ of x_{e} such that, for every $x(0) \in \mathcal{U}_\varepsilon$, $\lim_{t\to\infty} x(t)$ is a Lypunov 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 $\mathcal{U}_\delta$ of $\mathcal{U}$ containing x_{e} such that, if $x(0) \in \mathcal{U}_\delta$, then $\lim_{t\to\infty} x(t) = x_{\mathrm{e}}$. Finally, x_{e} is *globally asymptotically stable* with respect to $\mathcal{U}$ if the previous statement holds with $\mathcal{U}_\delta = \mathcal{U}$.

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

Definition 3

A vector $x_{\mathrm{e}} \in [0,\infty)^s$ satisfying

$$(B - A)^{\mathrm{T}}(k \circ x_{\mathrm{e}}^A) = 0 \tag{98}$$

is an *equilibrium* of (22). If, in addition, $x_{\mathrm{e}} \in (0,\infty)^s$, 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 $x_{\mathrm{e}} \in \mathcal{E}$, then $\lambda^z \circ x_{\mathrm{e}} \in \mathcal{E}$. Furthermore, if $x_{\mathrm{e}} \in \mathcal{E}_+$, then $\lambda^z \circ x_{\mathrm{e}} \in \mathcal{E}_+$.

Proof

Note that

$$\begin{aligned}(B - A)^{\mathrm{T}}K(\lambda^z \circ x_{\mathrm{e}})^A &= (B - A)^{\mathrm{T}}K((\lambda^z)^A \circ x_{\mathrm{e}}^A)\\ &= (B - A)^{\mathrm{T}}K(\lambda^{Az} \circ x_{\mathrm{e}}^A)\\ &= (B - A)^{\mathrm{T}}Kx_{\mathrm{e}}^A.\end{aligned}$$

The proof for the case $x_{\mathrm{e}} \in \mathcal{E}_+$ 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 $x_{\mathrm{e}} = 0$ is an equilibrium of (22) if and only if (22) has no reaction of the form $0 \stackrel{k}{\longrightarrow} C$, 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) $\mathcal{E} = \{0, k_1\gamma/(k_1 + k_2)\}$. ■

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 $\gamma_1 = x_2(0) + x_3(0) > 0$, then $\mathcal{E} = \{(0,0)\}$, whereas, if $\gamma_1 = x_2(0) + x_3(0) = 0$, 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 $x_{\mathrm{e}} \in \mathcal{U}$ satisfy $f(x_{\mathrm{e}}) = 0$. 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 $V(x_e) = 0$, $V(x) > 0$ for all $x \in \mathcal{U}\backslash\{x_e\}$, and $\dot{V}(x) \stackrel{\Delta}{=} V'(x)f(x) \leq 0$ for all $x \in \mathcal{U}$. Then x_e is Lyapunov stable with respect to $\mathcal{U}$. If, in addition, $\dot{V}(x) < 0$ for all $x \in \mathcal{U}\backslash\{x_e\}$, then x_e is asymptotically stable with respect to $\mathcal{U}$. Finally, if V is proper, that is, $V^{-1}(\mathcal{K})$ is relatively compact with respect to $\mathcal{D}$ for all compact subsets $\mathcal{K}$ of $\mathbb{R}$, and $\dot{V}(x) < 0$ for all $x \in \mathcal{U}\backslash\{x_e\}$, then x_e is globally asymptotically stable with respect to $\mathcal{U}$.

Note that if $\mathcal{U} = [0, \infty)^s$, 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 $\mathcal{M}$ denote the largest invariant subset of $\{x \in \mathcal{U} : \dot{V}(x) = 0\}$. If every element of $\mathcal{M}$ 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

$$\dot{x}(t) = Mx(t), \qquad x(0) = x_0, \qquad t \geq 0, \tag{99}$$

where $M \in \mathbb{R}^{n \times n}$. In this case, the following results hold. An equilibrium x_e 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 $x_e = 0$. Thus, all three types of stability can be characterized independently of the equilibrium. Specifically, the equilibrium $x_e = 0$ 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 negative real part or is zero and, if M is singular, the zero eigenvalue is semisimple; and an equilibrium x_e 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 ith species, and define $\mu \stackrel{\Delta}{=} [\mu_1 \cdots \mu_s]^{\mathrm{T}}$. Then the function $V(x) = \mu^{\mathrm{T}}x$ 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 $M^{\mathrm{T}}\mu \leq\leq 0$.
ii) M is Lyapunov stable.
iii) M is semistable.
iv) There exists $\mu \geq\geq 0$ such that $\mu \neq 0$ and $M^{\mathrm{T}}\mu \leq\leq 0$.

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 $M^{\mathrm{T}}\mu << 0$
vii) There exists $\mu \geq\geq 0$ such that $M^{\mathrm{T}}\mu << 0$.

Proof

Define $V(x) \stackrel{\Delta}{=} \mu^{\mathrm{T}}x$ so that $V(0) = 0$ and $V(x) > 0$ for all $x \in [0, \infty)^s\backslash\{0\}$. Furthermore, $\dot{V}(x) = \mu^{\mathrm{T}}Mx \leq 0$ for all $x \in [0, \infty)^s$, 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 $-M^{\mathrm{T}}$ is an M-matrix. Hence, it follows from [29, p. 119] that there exist a scalar $\alpha > 0$ and a nonnegative matrix $Q \geq\geq 0$ such that $\alpha \geq \rho(Q)$ and $M^{\mathrm{T}} = Q - \alpha I_s$. Now, since $Q \geq\geq 0$, it follows from [22, Thrm. 1.1] that $\rho(Q) \in \mathrm{spec}(Q)$, and hence, there exists $\mu \geq\geq 0$ such that $\mu \neq 0$ and $Q\mu = \rho(Q)\mu$. Thus, $M^{\mathrm{T}}\mu = Q\mu - \alpha\mu = (\rho(Q) - \alpha)\mu \leq\leq 0$, which proves that there exists $\mu \geq\geq 0$ such that $\mu \neq 0$ and $M^{\mathrm{T}}\mu \leq\leq 0$.

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

$[0,\infty)^s\backslash\{0\}$, and hence it follows that M is asymptotically stable. Thus, vi) implies v). Next, suppose that M is asymptotically stable. Hence, $-M^{-\mathrm{T}} \geq\geq 0$, and thus, for every $r \in (0,\infty)^s$, it follows that $\mu \stackrel{\Delta}{=} -M^{-\mathrm{T}} r \geq\geq 0$ satisfies $M^{\mathrm{T}}\mu << 0$, which proves that v) implies vii). □

Example 1, Continued

Choosing $\mu = [1/k_1\ 1/k_2\,]^{\mathrm{T}} >> 0$, it follows that $M\mu = 0$. Hence, M is semistable. ■

STABILITY OF NONLINEAR KINETICS

The following result uses the Lyapunov function $V(x) = \mu^{\mathrm{T}}x$ to analyze the stability of the zero solution of (22). Recall that $x_{\mathrm{e}} = 0$ 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 $x_{\mathrm{e}} = 0$ is an equilibrium of (22) and suppose there exists $\mu >> 0$ such that $B\mu \leq\leq A\mu$. Then x_{e} is Lyapunov stable with respect to $[0,\infty)^s$. If, in addition, $B\mu << A\mu$, then x_{e} is globally asymptotically stable with respect to $[0,\infty)^s$.

Proof

Define $V(x) \stackrel{\Delta}{=} \mu^{\mathrm{T}}x$ so that $V(0) = 0$ and $V(x) > 0$ for all $x \in [0,\infty)^s\backslash\{0\}$. Since $(B-A)\mu \leq\leq 0$, it follows that $\dot{V}(x) = \mu^{\mathrm{T}}(B-A)^{\mathrm{T}}(k \circ x^A) \leq 0$ for all $x \in [0,\infty)^s$. Hence, Theorem 5 implies that $x_{\mathrm{e}} = 0$ is Lyapunov stable with respect to $[0,\infty)^s$. Now suppose that $B\mu << A\mu$. Then $\dot{V}(x) < 0$ for all $x \in [0,\infty)^s\backslash\{0\}$. Since V is proper, it follows from Theorem 5 that $x_{\mathrm{e}} = 0$ is globally asymptotically stable with respect to $[0,\infty)^s$. □

Example 1, Continued

Let $\mu = [1/k_1\ 1/k_2\,]^{\mathrm{T}}$ so that $(A-B)\mu = 0$. It thus follows from Proposition 8 that $x_{\mathrm{e}} = 0$ 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_{e} of the form $(0,\varepsilon)$, where $\varepsilon > 0$. 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 $\mathcal{U}$ be the closed set $\mathcal{U} \stackrel{\Delta}{=} \{(x_1,x_2) \in [0,\infty)^2 : x_2 - ax_1 \leq 0\}$, where $a > k_2/k_1$. Note that $\mathcal{U}$ is invariant since $(\mathrm{d}/\mathrm{d}t)(x_2 - ax_1)$ 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 $\mathcal{U}$ are of the form $(\delta, k_2\delta/k_1)$.

Next, define the Lyapunov candidate $V : \mathcal{U} \longrightarrow \mathbb{R}$ by

$$V_\delta(x) = \frac{1}{2}(x_1 - \delta + x_2 - k_2\delta/k_1)^2 + \frac{1}{2}(k_1x_2 - k_2x_1)^2. \quad (100)$$

Then, for all $\delta \geq 0$, it follows that $V_\delta(\delta, k_2\delta/k_1) = 0$ and $V_\delta(x) > 0$ for all $x \in \mathcal{U}\backslash\{(\delta, k_2\delta/k_1)\}$. Since $\dot{V}_\delta(x) = -(k_1+k_2)\,x_1(k_1x_2 - k_2x_1)^2 \leq 0$ for all $x \in \mathcal{U}$, it follows that the equilibrium $(\delta, k_2\delta/k_1)$ is Lyapunov stable with respect to $\mathcal{U}$ for all $\delta \geq 0$. Finally, to show semistability, define $U(x) = x_1 + x_2$, which satisfies $U(0) = 0$, $U(x) > 0$ for all $x \in \mathcal{U}\backslash\{0\}$, and $\dot{U}(x) = 0$ for all $x \in \mathcal{U}$. Hence, every trajectory in $\mathcal{U}$ is bounded. Next, note that $\dot{V}_\delta^{-1}(0) = f^{-1}(0)$, which shows that $\dot{V}_\delta^{-1}(0)$ is an invariant set. Thus, the largest invariant set $\mathcal{M}$ contained in $\dot{V}_\delta^{-1}(0) \cap \mathcal{U}$ is the set of equilibria $\{(\delta, k_2\delta/k_1) : \delta \geq 0\}$, all of which are Lyapunov stable. Hence, by Theorem 6, the kinetic equations are semistable with respect to $\mathcal{U}$. ■

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 $x_{\mathrm{e}} = (k_3/k_2, k_1/k_2)$, consider, as in [30, p. 115], the function $U : (0,\infty)^2 \to \mathbb{R}$ defined by $U(x) = k_2(x_1 + x_2) - k_3 \ln x_1 - k_1 \ln x_2$, which satisfies $\dot{U}(x) = 0$ for all $x \in (0,\infty)^2$. It can be seen from the form of the gradient and the Hessian of U that $x = x_{\mathrm{e}}$ is an isolated local minimizer of U. Hence $V(x) = U(x) - U(x_{\mathrm{e}})$ satisfies $V(x_{\mathrm{e}}) = 0$ and $V(x) > 0$ for all $x \in \mathcal{D}\backslash\{x_{\mathrm{e}}\}$, where $\mathcal{D}$ is an open neighborhood of x_{e}. Hence, the equilibrium $x_{\mathrm{e}} = (k_3/k_2, k_1/k_2)$ 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 $\mu = [1\ 2\ 1\ 1]^{\mathrm{T}} >> 0$ so that $(A-B)\mu = 0$. It thus follows from Proposition 8 that $x_{\mathrm{e}} = 0$ is Lyapunov stable with respect to $[0,\infty)^4$. For the reduced kinetic equations (83), (84), with $x_2(0) + x_3(0) > 0$, it follows that $x_1 = x_2 = 0$ is the only equilibrium. Now, consider the radially unbounded Lyapunov function $V(x_1,x_2) = (1/2)k_3x_2^2 + (1/2)\,k_1\gamma_1(x_1+x_2)^2$. Since $\dot{V}(x_1,x_2) \leq 0$ 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 $m \geq 1$ 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 $c_1, \ldots, c_m$ of stoichiometric

coefficients. Obviously, $m \leq 2r$. We can identify each complex with a row of A or B so that $c_i \in \mathbb{R}^{1\times s}$. Thus, m is the number of distinct rows of $\left[\begin{smallmatrix}A\\B\end{smallmatrix}\right]$. In examples 1, 2, 3, 4 the number of complexes is 2, 2, 6, and 3, respectively. In particular, Example 4 involves the complexes $c_1 = [1\ 0\ 1\ 0]$, $c_2 = [0\ 1\ 0\ 0]$, and $c_3 = [0\ 0\ 1\ 1]$ corresponding to S + E, C, and P + E, respectively. For the following definition, "$c_i \to c_j$" denotes the reaction $c_i X \xrightarrow{k_l} c_j X$, where we assume $k_l > 0$. Recall that reactions of the form $c \to c$ are not allowed.

It is useful to represent the reaction network by a directed graph. Consider a directed graph $\mathfrak{C}$ having m vertices and r edges such that the ith 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 $c_i \to c_j$. Each edge of $\mathfrak{C}$ 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 $c_i \to c_j$ or $c_j \to c_i$. Furthermore, c_i and c_j are *indirectly linked* if there exist complexes $c_{i_1}, \ldots, c_{i_p}$ such that c_i is directly linked to c_{i_1}, c_{i_1} is directly linked to $c_{i_2}, \ldots,$ c_{i_p} is directly linked to c_j. Finally, c_i and c_j are *linked* if either c_i and c_j are directly linked or c_i and c_j are indirectly 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 $\mathfrak{C}$. Let ℓ denote the number of linkage classes of $\mathfrak{C}$, 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 $\mathfrak{C}$ 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_1 rows of $[A\ \ B]$ include the complexes in $\mathcal{C}_1$, rows $r_1 + 1, \ldots, r_1 + r_2$ 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 $q \leq \sum_{i=1}^{\ell} q_i$. 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 jth reaction is either $c_j \to c_{j+1}$ or $c_{j+1} \to c_j$. 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 $[0, \infty)^s$ [31, pp. 7, 12]. □

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

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* δ of the reaction network (10) is

$$\delta \stackrel{\Delta}{=} m - \ell - q. \tag{101}$$

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 $\hat{A}, \hat{B} \in \mathbb{R}^{r\times m}$ be the matrices whose rows are unit coordinate vectors in $\mathbb{R}^m$ and that satisfy

$$A = \hat{A}C, \quad B = \hat{B}C. \tag{102}$$

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

It follows that

$$B - A = (\hat{B} - \hat{A})C. \tag{103}$$

Note that

$$\mathcal{N}\left((\hat{B} - \hat{A})^{\mathrm{T}}\right) \subseteq \mathcal{N}\left((B - A)^{\mathrm{T}}\right). \tag{104}$$

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

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

Proposition 10

The following statements hold:

i) $\operatorname{rank}(\hat{B} - \hat{A}) = m - \ell$.

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

iii) If $\mu \in \mathbb{R}^s$, then $e^{A\mu} = \hat{A}e^{C\mu}$ and $e^{B\mu} = \hat{B}e^{C\mu}$.

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

Proof

Statement i) follows from the fact that the rank of the incidence matrix of a directed graph $\mathfrak{C}$ is equal to the difference between the number of vertices and the number of connected components of $\mathfrak{C}$ [32, Proposition 4.3]. Here, we provide a self-contained proof. Consider the rows of $\hat{B} - \hat{A}$ corresponding to $\mathcal{C}_1$. 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 jth reaction is either $c_j \to c_{j+1}$ or $c_{j+1} \to c_j$. Therefore, for $j = 1, \ldots, m_1 - 1$, the jth row of $\hat{B} - \hat{A}$ is either $e_j - e_{j+1}$ or $e_{j+1} - e_j$, where e_j denotes the jth unit coordinate vector in $\mathbb{R}^m$. Thus, the first r_1 rows of $\hat{B} - \hat{A}$ have rank $m_1 - 1$. Using a similar argument for each linkage class and noting that rows of $\hat{B} - \hat{A}$ corresponding to different linkage classes are linearly independent, it follows that $\operatorname{rank}(\hat{B} - \hat{A}) = \sum_{i=1}^{\ell}(m_i - 1) = m - \ell$.

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

$$\begin{aligned} q &= \operatorname{rank}(B - A) \\ &= \operatorname{rank}\left(C^{\mathrm{T}}(\hat{B} - \hat{A})^{\mathrm{T}}\right) \\ &= \operatorname{rank}\left((\hat{B} - \hat{A})^{\mathrm{T}}\right) - \dim\left(\mathcal{R}\left((\hat{B} - \hat{A})^{\mathrm{T}}\right) \cap \mathcal{N}(C^{\mathrm{T}})\right) \\ &= m - \ell - \dim\left(\mathcal{R}\left((\hat{B} - \hat{A})^{\mathrm{T}}\right) \cap \mathcal{N}(C^{\mathrm{T}})\right). \end{aligned}$$

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

$$e^{B_j\mu} = e^{\hat{B}_j C\mu} = \hat{B}_j e^{C\mu}.$$

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

$$\operatorname{rank}\left((B - A)^{\mathrm{T}}\right) + \dim\left(\mathcal{N}((B - A)^{\mathrm{T}})\right) = r$$

and

$$\operatorname{rank}\left((\hat{B} - \hat{A})^{\mathrm{T}}\right) + \dim\left(\mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}})\right) = r.$$

Since $\delta = 0$, it follows from i) that $\operatorname{rank}((B - A)^{\mathrm{T}}) = q = m - \ell = \operatorname{rank}(\hat{B} - \hat{A})$, and thus $\dim(\mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}})) = \dim(N((B - A)^{\mathrm{T}}))$. Since $\mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}}) \subseteq \mathcal{N}((B - A)^{\mathrm{T}})$ it follows that $\mathcal{N}((B - A)^{\mathrm{T}}) = \mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}})$. 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 $c_i \to c_j$. Furthermore, there exists an *indirect path* from c_i to c_j if there exist complexes $c_{i_1}, \ldots, c_{i_p}$ such that $c_i \to c_{i_1} \to c_{i_2} \to \cdots \to c_{i_p} \to c_j$. 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 $\mathfrak{C}$. Consequently, weak reversibility is equivalent to the requirement that every vertex or, equivalently, every edge of $\mathfrak{C}$ must be part of a directed cycle of $\mathcal{C}_1$ [32, p. 25]. In the terminology of [33, pp. 357–358] and [34], weak reversibility of (10) is equivalent to strong connectedness of each connected component of $\mathfrak{C}$.

The following lemmas are needed. Furthermore, for $l = 1, \ldots, \ell$, let $\mathrm{v}_l \in \mathbb{R}^m$ (respectively, $\mathrm{e}_l \in \mathbb{R}^r$) be such that the jth component of v_l (respectively, e_l) is one if the jth

vertex (respectively, jth edge) of $\mathfrak{C}$ belongs to the lth connected component of $\mathfrak{C}$ and zero otherwise. It is easy to see that $\hat{A}\mathrm{v}_l = \hat{B}\mathrm{v}_l = \mathrm{e}_l$ for all $l = 1, \ldots, \ell$, which implies that $\mathrm{v}_l \in \mathcal{N}(\hat{B} - \hat{A})$ for all $l = 1, \ldots, \ell$. Next, note that, since each vertex of $\mathcal{C}_1$ belongs to exactly one connected component of $\mathfrak{C}$, $\{\mathrm{v}_1, \ldots, \mathrm{v}_\ell\}$ are linearly independent and hence, since $\operatorname{rank}(\hat{B} - \hat{A}) = m - \ell$, it follows that $\mathcal{N}(\hat{B} - \hat{A})$ is the span of $\{\mathrm{v}_1, \ldots, \mathrm{v}_\ell\}$. Finally, note that

$$e^{\sum_{l=1}^{\ell} \theta_l \mathrm{v}_l} = \sum_{l=1}^{\ell} e^{\theta_l} \mathrm{v}_l, \tag{105}$$

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

Lemma 3

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

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

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

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

Proof

To prove i), note that it follows from [32, Thrms. 4.5, 5.2] that $\mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}})$ is the span of $\{\eta_1, \ldots, \eta_{n_c}\}$, where n_c is the number of directed cycles of the graph $\mathfrak{C}$ and η_i is such that the jth component of η_i is one if the jth edge is part of ith directed cycle of $\mathfrak{C}$ and zero otherwise. Hence, if the reaction network is weakly reversible, then every edge of $\mathfrak{C}$ is part of at least one directed cycle of $\mathfrak{C}$. Now, a positive linear combination of all the cycles of $\mathfrak{C}$ yields $p \in (0, \infty)^r$ such that $(\hat{B} - \hat{A})^{\mathrm{T}} p = 0$. To prove the converse, assume that the reaction network is not weakly reversible or, equivalently, there exists an edge (say the Jth edge) that does not belong to any cycle of $\mathcal{C}_1$. Hence, it follows that the Jth component of all vectors in $\mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}})$ is zero, which implies that there does not exist $p \in (0, \infty)^r$ such $(\hat{B} - \hat{A})^{\mathrm{T}} p = 0$.

To prove ii), note that $-\Gamma^{\mathrm{T}}$ is the Laplacian of the weighted directed graph [34] obtained by assigning the weight α_i to the ith edge of $\mathfrak{C}$. There exists a permutation matrix $\Pi \in \mathbb{R}^{m \times m}$ such that $\hat{\Gamma} \stackrel{\Delta}{=} \Pi^{\mathrm{T}} \Gamma \Pi$ and $\hat{\Gamma} = \operatorname{blockdiag}(\hat{\Gamma}_1, \ldots, \hat{\Gamma}_\ell)$, where $\hat{\Gamma}_l \in \mathbb{R}^{m_l \times m_l}$, $l = 1, \ldots, \ell$, are such that $\sum_{l=1}^{\ell} m_l = m$ and $-\hat{\Gamma}_l^{\mathrm{T}}$ is the Laplacian of $\mathcal{C}_l$. Weak reversibility implies that each connected component of $\mathfrak{C}$ is strongly connected. [Note that $-\hat{\Gamma}^{\mathrm{T}}$ is the Laplacian of $\mathfrak{C}$ in the case where the vertices are reordered such that the lth connected component (linkage class) of $\mathfrak{C}$ contains the vertices (complexes) numbered as $m_{l-1} + 1, \ldots, m_l$, $l = 1, \ldots, \ell$, where $m_0 \stackrel{\Delta}{=} 0$.] Hence, it follows from [34, Thrm. 1] that $\operatorname{rank} \hat{\Gamma}_l = m_l - 1$ for all $l = 1, \ldots, \ell$, which implies that $\operatorname{rank} \Gamma = \operatorname{rank} \hat{\Gamma} = m - \ell$.

To prove the second assertion of ii), let $l \in \{1, \ldots, \ell\}$, let $c_l \stackrel{\Delta}{=} -\min_{i=1,\ldots,m_l} \gamma_i$, and let $X_l \stackrel{\Delta}{=} \Gamma_l + c_l I_{m_l}$, where γ_i denotes the (i,i)th entry of Γ_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 $\hat{p}_l \in (0, \infty)^m$ such that $X_l \hat{p}_l = \rho(X_l) \hat{p}_l$ (see [33, Thrm. 8.4.4]). Consequently, $\hat{\Gamma}_l \hat{p}_l = (X_l - c_l I_{m_l}) \hat{p}_l = (\rho(X_l) - c_l) \hat{p}_l$ and, since $0 = \mathbf{e}^{\mathrm{T}} \hat{\Gamma}_l \hat{p}_l = (\rho(X_l) - c_l) \mathbf{e}^{\mathrm{T}} \hat{p}_l$ and $\mathbf{e}^{\mathrm{T}} \hat{p}_l > 0$, it follows that $c_l = \rho(X_l)$. Thus, there exists a positive vector $\hat{p}_l \in \mathbb{R}^m$ satisfying $\hat{\Gamma}_l \hat{p}_l = 0$ for all $l = 1, \ldots, \ell$. Now, letting $\hat{p} = [\hat{p}_1^{\mathrm{T}} \cdots \hat{p}_\ell^{\mathrm{T}}]^{\mathrm{T}}$ it can be shown that $\hat{p} \circ (\Pi^{\mathrm{T}} \mathrm{v}_l) = [0 \cdots \hat{p}_l^{\mathrm{T}} \cdots 0]^{\mathrm{T}}$ so that $\hat{\Gamma}(\hat{p} \circ (\Pi^{\mathrm{T}} \mathrm{v}_l)) = 0$. Finally, taking $p = \Pi \hat{p}$ implies that $\Gamma(p \circ \mathrm{v}_l) = \Pi \hat{\Gamma} \Pi^{\mathrm{T}} (p \circ \mathrm{v}_l) = \Pi \hat{\Gamma}(\hat{p} \circ (\Pi^{\mathrm{T}} \mathrm{v}_l)) = 0$, establishing the result.

To prove iii), let $x \in \mathbb{R}^m$ be such that $x^{\mathrm{T}}[C \ \mathrm{v}_1 \cdots \mathrm{v}_\ell] = 0$ or, equivalently, $x \in \mathcal{N}(C^{\mathrm{T}})$ and $x^{\mathrm{T}} \mathrm{v}_l = 0$ for all $l = 1, \ldots, \ell$. Next, since $\mathcal{N}(\hat{B} - \hat{A})$ is the span of $\{\mathrm{v}_1, \ldots, \mathrm{v}_\ell\}$, it follows that $x \in [\mathcal{N}(\hat{B} - \hat{A})]^{\perp} = \mathcal{R}((\hat{B} - \hat{A})^{\mathrm{T}})$. Hence, $x \in \mathcal{R}((\hat{B} - \hat{A})^{\mathrm{T}}) \cap \mathcal{N}(C^{\mathrm{T}})$, and, since the reaction network has zero deficiency, it follows from ii) of Proposition 10 that $x = 0$, which proves that $\operatorname{rank}[C \ \mathrm{v}_1 \cdots \mathrm{v}_\ell] = m$. □

Lemma 4

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

Proof

Since the reaction network (22) has zero deficiency, it follows from iv) of Proposition 10 that $\mathcal{N}((B - A)^{\mathrm{T}}) = \mathcal{N}((\hat{B} - \hat{A})^{\mathrm{T}})$, and hence, $\mathcal{N}((B - A)^{\mathrm{T}})$ is the span of $\{\eta_1, \ldots, \eta_{n_c}\}$ defined in the proof of i) of Lemma 3. Furthermore, since $\alpha \in \mathcal{N}((B - A)^{\mathrm{T}})$ it follows that $\alpha = \sum_{i=1}^{n_c} \beta_i \eta_i$ for some $\beta_i \in \mathbb{R}$, $i = 1, \ldots, n_c$. Now, note that $\eta_i \circ \mathrm{e}_l = \eta_i$ if the ith cycle of $\mathfrak{C}$ belongs to the lth linkage class of $\mathfrak{C}$ and zero otherwise. In both cases, $(B - A)^{\mathrm{T}}(\eta_i \circ \mathrm{e}_l) = (\hat{B} - \hat{A})^{\mathrm{T}}(\eta_i \circ \mathrm{e}_l) = 0$ for all $i = 1, \ldots, n_c$ and $l = 1, \ldots, \ell$.

To prove necessity, let $\mu \in \mathcal{N}(B - A)$. Hence, $(\hat{B} - \hat{A}) C\mu = 0$, which, since $\mathcal{N}(\hat{B} - \hat{A})$ is the span of $\{\mathrm{v}_1, \ldots, \mathrm{v}_\ell\}$, implies that $C\mu = \sum_{l=1}^{\ell} \theta_l \mathrm{v}_l$ for some $\theta_1, \ldots, \theta_\ell \in \mathbb{R}$. Hence, it follows that

$$\begin{aligned}
(B - A)^{\mathrm{T}}(\alpha \circ e^{A\mu}) &= (B - A)^{\mathrm{T}}(\alpha \circ \hat{A} e^{C\mu}) \\
&= (B - A)^{\mathrm{T}} \left(\alpha \circ \hat{A} \sum_{l=1}^{\ell} e^{\theta_l} \mathrm{v}_l \right) \\
&= \sum_{l=1}^{\ell} (B - A)^{\mathrm{T}}(\alpha \circ e^{\theta_l} \mathrm{e}_l) \\
&= \sum_{l=1}^{\ell} \sum_{i=1}^{n_c} (B - A)^{\mathrm{T}}(\beta_i e^{\theta_l} (\eta_i \circ \mathrm{e}_l)) \\
&= 0,
\end{aligned}$$

where iii) of Proposition 10 is used to obtain the first equality, (105) is used to obtain the second equality, and the fact that $\hat{A}\mathrm{v}_l = \mathrm{e}_l$ for all $l = 1, \ldots, \ell$, is used to obtain the third equality.

Conversely, assume that $(B-A)^{\mathrm{T}}(\alpha \circ e^{A\mu}) = 0$, which implies that $(\hat{B}-\hat{A})^{\mathrm{T}}(\alpha \circ e^{A\mu}) = 0$. Hence,

$$0 = (\hat{B}-\hat{A})^{\mathrm{T}}(\alpha \circ \hat{A}e^{C\mu}) = (\hat{B}-\hat{A})^{\mathrm{T}}(\alpha \mathbf{e}^{\mathrm{T}} \circ \hat{A})e^{C\mu} = \Gamma e^{C\mu}, \tag{106}$$

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

$$\begin{aligned}\Gamma \mathrm{v}_l &= (\hat{B}-\hat{A})^{\mathrm{T}}(\alpha \mathbf{e}^{\mathrm{T}} \circ \hat{A})\mathrm{v}_l \\ &= (\hat{B}-\hat{A})^{\mathrm{T}}(\alpha \circ \hat{A}\mathrm{v}_l) \\ &= (\hat{B}-\hat{A})^{\mathrm{T}}(\alpha \circ \mathrm{e}_l) \\ &= \sum_{i=1}^{n_c} \beta_i (\hat{B}-\hat{A})^{\mathrm{T}}(\eta_i \circ \mathrm{e}_l) \\ &= 0.\end{aligned}$$

Furthermore, it follows from ii) of Lemma 3 that $\operatorname{rank}\Gamma = m - \ell$, which implies that $\mathcal{N}(\Gamma)$ is the span of $\{\mathrm{v}_1, \ldots, \mathrm{v}_\ell\}$. Hence, it follows from (106) that $e^{C\mu} = \sum_{l=1}^{\ell} e^{\theta_l}\mathrm{v}_l$ for some $\theta_1, \ldots, \theta_\ell \in \mathbb{R}$, which implies that $C\mu = \sum_{l=1}^{\ell} \theta_l \mathrm{v}_l$. Now, the result follows by noting that $(B-A)\mu = (\hat{B}-\hat{A})C\mu = \sum_{l=1}^{\ell} \theta_l(\hat{B}-\hat{A})\mathrm{v}_l = 0$. □

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_{e} be a positive equilibrium of (22). Hence, it follows from iv) of Proposition 10 that $(\hat{B}-\hat{A})^{\mathrm{T}}p = 0$, where $p = Kx_{\mathrm{e}}^A \in (0,\infty)^r$. Now, it follows from i) of Lemma 3 that the reaction network is weakly reversible.

To prove sufficiency, note that

$$\begin{aligned}(\hat{B}-\hat{A})^{\mathrm{T}}(k \circ x^A) &= (\hat{B}-\hat{A})^{\mathrm{T}}(k \circ \hat{A}x^C) \\ &= (\hat{B}-\hat{A})^{\mathrm{T}}(k\mathbf{e}^{\mathrm{T}} \circ \hat{A})x^C \\ &= \Gamma x^C,\end{aligned}$$

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

$$[C\ \mathrm{v}_1 \cdots \mathrm{v}_\ell] \begin{bmatrix} \log x \\ -\theta_1 \\ \vdots \\ -\theta_\ell \end{bmatrix} = \log p. \tag{107}$$

Now, since the reaction network has zero deficiency, it follows from iii) of Lemma 3 that $\operatorname{rank}[C\ \mathrm{v}_1 \cdots \mathrm{v}_\ell] = m$, and hence, (107) has a solution, which implies that there exists a positive vector x and scalars θ_l such that $x^C = p \circ e^{\sum_{l=1}^{\ell} \theta_l \mathrm{v}_l}$. Next, it follows from (105) that

$$\begin{aligned}(B-A)^{\mathrm{T}}(k \circ x^A) = C^{\mathrm{T}}\Gamma x^C &= C^{\mathrm{T}}\Gamma\left(p \circ e^{\sum_{l=1}^{\ell} \theta_l \mathrm{v}_l}\right) \\ &= \sum_{l=1}^{\ell} e^{\theta_l} C^{\mathrm{T}}\Gamma(p \circ \mathrm{v}_l) = 0,\end{aligned}$$

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 reversibile reaction network with zero deficiency. The following lemma is needed for this result.

Lemma 5

Let $p, \hat{p} \in (0,\infty)^s$, let $\mathcal{X}$ be a subspace of $\mathbb{R}^s$, and define $\mathcal{X}^{\perp} \stackrel{\Delta}{=} \{x \in \mathbb{R}^s : x^{\mathrm{T}}y = 0 \text{ for all } y \in \mathcal{X}\}$. Then there exists a unique $\mu \in \mathcal{X}^{\perp}$ such that $(p \circ e^{\mu} - \hat{p}) \in \mathcal{X}$.

Proof

Define $\varphi : \mathbb{R}^s \to \mathbb{R}$ by $\varphi(x) \stackrel{\Delta}{=} p^{\mathrm{T}}e^x - \hat{p}^{\mathrm{T}}x$. It can be shown that $\lim_{\|x\| \to \infty} \varphi(x) = \infty$. Now, let $r > 0$ and, since $\lim_{\|x\| \to \infty} \varphi(x) = \infty$, it follows that $\mathcal{C}_r \stackrel{\Delta}{=} \{x \in \mathbb{R}^s : \varphi(x) \le r\}$ is a compact set. Hence, $\hat{\mathcal{C}}_r \stackrel{\Delta}{=} \{x \in \mathcal{X}^{\perp} : \varphi(x) \le r\}$ is also a compact set, which implies that there exists $\mu \in \mathcal{X}^{\perp}$ such that $\varphi(\mu) \le \varphi(x)$ for all $x \in \hat{\mathcal{C}}_r$. Now, since $\mathcal{X}^{\perp} = \hat{\mathcal{C}}_r \cup \{x \in \mathcal{X}^{\perp} : \varphi(x) > r\}$ it follows that $\varphi(\mu) \le \varphi(x)$ for all $x \in \mathcal{X}^{\perp}$. Specifically, $\varphi(\mu) \le \varphi(\mu + \theta\gamma)$ for all $\theta \in \mathbb{R}$ and $\gamma \in \mathcal{X}^{\perp}$. Thus, $f(\theta) \stackrel{\Delta}{=} \varphi(\mu + \theta\gamma)$ has a minimum at $\theta = 0$, which implies that

$$0 = \left.\frac{\mathrm{d}f}{\mathrm{d}\theta}\right|_{\theta=0} = \left.\frac{\partial \varphi}{\partial x}\right|_{x=\mu} \gamma.$$

Hence, since $\gamma \in \mathcal{X}^{\perp}$ is arbitrary, $(\partial\varphi/\partial x)|_{x=\mu} = (p \circ e^{\mu} - \hat{p}) \in \mathcal{X}$, which establishes existence.

To prove uniqueness, let $\hat{\mu} \in \mathcal{X}^{\perp}$ be such that $(p \circ e^{\hat{\mu}} - \hat{p}) \in \mathcal{X}$. Since $\mu, \hat{\mu} \in \mathcal{X}^{\perp}$ and $(p \circ e^{\mu} - \hat{p})$, $(p \circ e^{\hat{\mu}} - \hat{p}) \in \mathcal{X}$ it follows that $(\mu - \hat{\mu}) \in \mathcal{X}^{\perp}$ and $[p \circ (e^{\mu} - e^{\hat{\mu}})] \in \mathcal{X}$, and hence,

$$0 = (\mu - \hat{\mu})^{\mathrm{T}}[p \circ (e^{\mu} - e^{\hat{\mu}})] = \sum_{i=1}^{s} p_i(\mu_i - \hat{\mu}_i)(e^{\mu_i} - e^{\hat{\mu}_i}). \tag{108}$$

Next, since the exponential function is an increasing function, it follows that $(\mu_i - \hat{\mu}_i)(e^{\mu_i} - e^{\hat{\mu}_i}) \ge 0$ for all $i = 1, \ldots, s$, and, since $p \in (0,\infty)^s$, it follows from (108) that $(\mu_i - \hat{\mu}_i)\ (e^{\mu_i} - e^{\hat{\mu}_i}) = 0$ for all $i = 1, \ldots, s$, or, equivalently, $\mu = \hat{\mu}$. □

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_{e} be a positive equilibrium. Then

$$\mathcal{E}_+ = \{x \in (0,\infty)^s : \log x - \log x_{\mathrm{e}} \in \mathcal{S}^{\perp}\}. \tag{109}$$

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 $x \in (0,\infty)^s$, and define $\mu \stackrel{\Delta}{=} \log x - \log x_e$. Then

$$\begin{aligned}(k \circ x^A) &= (k \circ x^A \circ x_e^{-A} \circ x_e^A)\\ &= (k \circ e^{A\log x} \circ e^{-A\log x_e} \circ x_e^A)\\ &= (k \circ e^{A\mu} \circ x_e^A)\\ &= (k \circ x_e^A \circ e^{A\mu}).\end{aligned}$$

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

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

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 $(0,\infty)^s$.

Proof

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

$$V(x) \stackrel{\Delta}{=} \sum_{i=1}^{s} [x_i(\log x_i - \log x_{ei}) - (x_i - x_{ei})],$$

where x_i and x_{ei} are the ith components of x and x_e, respectively. It follows from the inequality $\log a \le a - 1$ for all $a > 0$, with $a = x_{ei}/x_i$, that $V(x) \ge 0$ for all $x \in (0,\infty)^s$. 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 $x \in (0,\infty)^s$, define $\mu \stackrel{\Delta}{=} \log x - \log x_e$, and note that it follows from $\log a \le a - 1$, $a > 0$, with $a = e^{\mathrm{row}_i(B\mu)}/e^{\mathrm{row}_i(A\mu)}$, that

$$e^{A\mu} \circ [(B-A)\mu] \le\le e^{B\mu} - e^{A\mu}, \tag{110}$$

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

$$\begin{aligned}\dot{V}(x) &= \mu^{\mathrm{T}}(B-A)^{\mathrm{T}}Kx^A\\ &= \mu^{\mathrm{T}}(B-A)^{\mathrm{T}}Ke^{A\log x}\\ &= \mu^{\mathrm{T}}(B-A)^{\mathrm{T}}K(e^{A\log x_e} \circ e^{A\mu})\\ &= \left(\left[\mu^{\mathrm{T}}(B-A)^{\mathrm{T}}\right] \circ (e^{A\mu})^{\mathrm{T}}\right)Kx_e^A\\ &= (Kx_e^A)^{\mathrm{T}}\left(e^{A\mu} \circ [(B-A)\mu]\right)\\ &\le (Kx_e^A)^{\mathrm{T}}(e^{B\mu} - e^{A\mu})\\ &= (Kx_e^A)^{\mathrm{T}}(\hat{B} - \hat{A})e^{C\mu}\\ &= \left[(\hat{B} - \hat{A})^{\mathrm{T}}Kx_e^A\right]^{\mathrm{T}}e^{C\mu}\\ &= 0,\end{aligned} \tag{111}$$

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

Next, assume that the reaction network (22) has zero deficiency. If $x \in (0,\infty)^s$ satisfies $\dot{V}(x) = 0$, then it follows from (111) that $(Kx_e^A)^{\mathrm{T}}(e^{A\mu} \circ [(B-A)\mu]) = (Kx_e^A)^{\mathrm{T}}(e^{B\mu} - e^{A\mu})$. Now, since $Kx_e^A >> 0$, it follows from (110) that that $e^{A\mu} \circ [(B-A)\mu] = e^{B\mu} - e^{A\mu}$, which implies that $(B-A)\mu = 0$, and hence, $(\log x - \log x_e) \in \mathcal{S}^\perp$. 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 $\{x \in (0,\infty)^s : \dot{V}(x) = 0\}$ is a Lyapunov-stable equilibrium. Furthermore, for $\eta > 0$, let $\mathcal{U}_\eta$ denote the closure of the connected component of $\{x \in (0,\infty)^s : V(x) \le \eta\}$ containing x_e. Since $V(\cdot)$ is continuous in $(0,\infty)^s$ and $V(x_e) = 0$, it follows that there exists $\beta > 0$ such that $\mathcal{U}_\beta \subset (0,\infty)^s$ and is compact. Now, with $\mathcal{U} = \mathcal{U}_\beta$, Theorem 6 implies every solution to (22) with $x(0) \in \mathcal{U}_\beta$ converges to an equilibrium that is semistable with respect to $\mathcal{U}_\beta$. Finally, the result follows from the definition of semistability with respect to $(0,\infty)^s$ and the fact that $\mathcal{U}_\beta$ 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 assertation 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 $V(x) = \alpha x_1 + x_2$, where $\alpha \in (1, 1 + k_3/k_2)$, can be used to conclude semistability of every equilibrium in $\hat{\mathcal{E}} = \{x \in [0,\infty)^4 : x_1 = 0,\ x_2 = 0,\ x_3 > 0\}$. 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,

$$\mathrm{S} + \mathrm{E} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{C} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \mathrm{P} + \mathrm{E} \tag{112}$$

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

$$A = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 \end{bmatrix}, \tag{113}$$

and the kinetic equations have the form

$$\dot{x}_1(t) = k_2 x_2(t) - k_1 x_1(t) x_3(t), \quad x_1(0) = x_{10}, \quad t \geq 0, \tag{114}$$

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

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

$$\dot{x}_4(t) = k_3 x_2(t) - k_4 x_3(t) x_4(t), \quad x_4(0) = x_{40}. \tag{117}$$

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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