A generalization of Birch’s theorem and vertex-balanced steady states for generalized mass-action systems

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Abstract

Mass-action kinetics and its generalizations appear in mathematical models of (bio-)chemical reaction networks, population dynamics, and epidemiology. Vertex-balanced steady states may contain information about the dynamical properties of these systems and have useful algebraic properties. The problem of existence and uniqueness of vertex-balanced steady states can be reformulated in two different ways, one of which is related to Birch’s theorem in statistics, and the other one to the bijectivity of generalized polynomial maps, similar to maps appearing in geometric modelling. We present a generalization of Birch’s theorem that provides a sufficient condition for the existence and uniqueness of vertex-balanced steady states for generalized mass-action systems.

1 Introduction

Reaction networks are used to represent the numerous interactions of chemical species in chemistry and biochemistry. An example is the following enzymatic reaction, where a substrate $S_0$ is converted into a product $S_1$ by an enzyme $E$ via an intermediate species $ES_0$:

$$E + S_0 \xrightleftharpoons[\kappa_2]{\kappa_1} ES_0 \xrightarrow[\kappa_3]{\quad} E + S_1$$

To model the dynamics of the concentrations of the chemical species involved in a network, one typically assumes that the reactions proceed according to some specified kinetic rate functions. A well-studied model is mass-action kinetics; it assumes that the reaction rate is proportional to the concentrations of its reactants. According to mass-action kinetics, the reaction $E + S_0 \rightarrow ES_0$ proceeds at rate $\kappa_1 [E][S_0]$, where $\kappa_1 > 0$ is a rate constant, and $[X]$ is the concentration of species $X$ as a function of time $t$. The rates of change of the concentrations of $E$, $S_0$ and $ES_0$ due to this single reaction are

$$-\frac{d[E]}{dt} = -\frac{d[S_0]}{dt} = \frac{d[ES_0]}{dt} = \kappa_1 [E][S_0].$$

The overall rate of change due to all reactions in the network is the sum over its individual reactions, e.g.

$$\frac{d[E]}{dt} = -\kappa_1 [E][S_0] + \kappa_2 [ES_0] + \kappa_3 [ES_0],$$

$$\frac{d[S_0]}{dt} = -\kappa_1 [E][S_0] + \kappa_2 [ES_0].$$

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\[
\frac{d[ES_0]}{dt} = \kappa_1[E][S_0] - \kappa_2[ES_0] - \kappa_3[ES_0],
\]
\[
\frac{d[S_1]}{dt} = \kappa_3[ES_0].
\]

Mass-action systems have been studied extensively. Reaction network theory, as initially developed by Horn, Jackson and Feinberg \[9, 11, 15\], tries to conclude dynamical properties from simple characteristics of the underlying reaction network. Moreover, as the reaction rate constant is usually obtained empirically and thus subjected to uncertainty, an ideal theoretical result should not depend on the precise values of the rate constants; indeed this is the case for many classical results in reaction network theory. Much of the early work on mass-action systems can be found in the lecture notes \[10, 14\].

Mass-action kinetics is the most common model for the dynamics of chemical concentrations when the reactions occur at dilute concentrations in a well-mixed fluid. That is not the typical environment in which biochemical reactions naturally take place. The cell is typically crowded and the intracellular matrix viscous; proteins might be embedded in membranes. Various models have been developed to account for this difference.

One proposed model is that of \textit{power-law kinetics}, where the exponents (or kinetic orders) in the reaction rate functions do not necessarily follow the stoichiometric coefficients. In the catalysis example above, we may want the concentration of \(E\) to be modelled by the equation

\[
\frac{d[E]}{dt} = -\kappa_1[E][S_0]^\alpha + \kappa_2[ES_0]^\gamma + \kappa_3[ES_0]^\delta,
\]

for some constants \(\alpha, \beta, \gamma, \delta > 0\). This is an example of power-law kinetics. Classical mass-action kinetics and power-law kinetics can be incorporated into the framework of \textit{generalized mass-action kinetics} introduced in \[20, 21\]. (See Section \[3\] for a precise definition of generalized mass-action systems.)

For classical mass-action systems, an important subset of positive steady states is the set of \textit{complex-balanced equilibria} \(Z_\kappa\). They have been introduced also for generalized mass-action systems and are called \textit{vertex-balanced steady states} in this work (Definition \[4, 11\]). Such a steady state is a concentration vector \(x^*\) (one coordinate for each chemical species) such that at every vertex of the graph, the sum of the incoming rate functions evaluated at \(x^*\) equals to the sum of the outgoing rate functions evaluated at \(x^*\).

The existence of a complex-balanced equilibrium of a classical mass-action system has major implications for its dynamical properties. For example, it implies that all positive steady states are complex-balanced, and that there is a unique positive steady state within every invariant affine subspace \[11\]; moreover, it also implies that there is a monomial parametrization for the set of complex-balanced equilibria \[6\]. Not surprisingly, the story for vertex-balanced steady states of a \textit{generalized} mass-action system is more complicated, and less is known about these steady states. Nonetheless, the existence of a vertex-balanced steady state also implies that the set of vertex-balanced steady states admits a monomial parametrization \[21\].

In this paper, we are interested in how many (if any) vertex-balanced steady states there are within each invariant affine subspace of a generalized mass-action system. This paper initially aims to understand which reaction networks admit vertex-balanced steady states, and if so, how many are there. Interestingly, this question can be reformulated in two different ways, one related to a generalization of Birch’s theorem in statistics \[22\], and the other to the bijectivity of generalized polynomial maps, similar to ones which appear in geometric modelling \[7, 20\]. Indeed, the following questions are essentially equivalent:
1. When does a generalized mass-action system have exactly one vertex-balanced steady state within each invariant affine subspace, for any choice of rate constants?

2. Given vector subspaces \( S, \tilde{S} \subseteq \mathbb{R}^n \), when does the intersection \((x_0 + S) \cap (x^* \circ \exp S^\perp)\) consist of exactly one point, for any \( x_0, x^* \in \mathbb{R}^n_{>0} \)?

3. Given vectors \( w^1, \ldots, w^n, \tilde{w}^1, \ldots, \tilde{w}^n \in \mathbb{R}^d \), when is the generalized polynomial map on \( \mathbb{R}^n_{>0} \) defined by
   \[
   f_{x^*}(\xi) = \sum_{i=1}^{n} x^*_i \xi \tilde{w}^i
   \]
   bijective onto the relative interior of the polyhedral cone generated by \( w^1, \ldots, w^n \), for any \( x^* \in \mathbb{R}^n_{>0} \)?

These questions will be expanded upon and explained in detail in Section 5.

Among the questions 1 to 3 above, we initially focus on question 2, which is strongly related to Birch’s theorem in statistics. One way to state Birch’s theorem is: given a vector subspace \( S \subseteq \mathbb{R}^n \), the intersection \((x_0 + S) \cap (x^* \circ \exp S^\perp)\) consists of exactly one point, for any \( x_0, x^* \in \mathbb{R}^n_{>0} \). In question 2, we have two vector subspaces \( S, \tilde{S} \), so it should not come as a surprise that an additional hypothesis is needed.

This hypothesis is given in terms of sign vectors. For a subset \( S \subseteq \mathbb{R}^n \), its set of sign vectors \( \sigma(S) \) is the image of vectors in \( S \) under the coordinate-wise sign function. Its closure \( \overline{\sigma(S)} \) contains \( \sigma(S) \) and all sign vectors where one or more coordinates may be replaced by zeros (see Definition 6.1).

We obtain the following generalization of Birch’s theorem:

**Theorem 6.7.** Let \( S, \tilde{S} \subseteq \mathbb{R}^n \) be vector subspaces of equal dimension with \( \sigma(S) \subseteq \overline{\sigma(S)} \). Then for any positive vectors \( x_0, x^* \in \mathbb{R}^n_{>0} \), the intersection \((x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp)\) consists of exactly one point.

As a consequence of this theorem, we provide a sufficient condition in Theorem 6.8 for question 1 above. More precisely, provided that certain conditions hold, we show that if a generalized mass-action system has at least one vertex-balanced steady state, then there is exactly one vertex-balanced steady state within every invariant affine subspace.

We introduce generalized mass-action systems and vertex-balanced steady states in Section 3 and 4 respectively. We prove Theorem 6.7 in Section 6 and conclude with an example in Section 7.

### 2 Notation

There are several component-wise operations on vectors and matrices that will appear frequently. In the list below, let \( x, z \in \mathbb{R}^n \) with \( x = (x_1, x_2, \ldots, x_n)^T \) and \( z = (z_1, z_2, \ldots, z_n)^T \). Let \( Y = (y_1, y_2, \ldots, y_m) \) be a \( n \times m \) matrix. The operations we will use are:

- \( x^x = \prod_{i=1}^{n} x_i^x \), with the convention \( 0^0 = 1 \);
- \( x^y = (x^y_1, x^y_2, \ldots, x^y_n)^T \);
- \( x \circ z = (x_1 z_1, x_2 z_2, \ldots, x_n z_n)^T \);
- \( x = \begin{pmatrix} x_1 & x_2 & \cdots & x_n \\ z_1 & z_2 & \cdots & z_n \end{pmatrix}^T \) whenever \( z_j \neq 0 \) for all \( j \);
- \( \exp x = (e^{x_1}, e^{x_2}, \ldots, e^{x_n})^T \);

\(^1\)Here, \( x^* \circ z \) denotes the component-wise product of the vectors \( x^* \) and \( z \); see Section 2 for detail.
\log \mathbf{x} = (\log x_1, \log x_2, \cdots, \log x_n)^T \text{ whenever } x_j > 0 \text{ for all } j.

When the above operations are applied to a subset of \( \mathbb{R}^n \), they are applied to elements of the set. For example, given a set \( S \subseteq \mathbb{R}^n \), we have \( \exp(S) = \{ \exp(\mathbf{x}) : \mathbf{x} \in S \} \), and \( \mathbf{x} \circ S = \{ \mathbf{x} \circ \mathbf{z} : \mathbf{z} \in S \} \).

When \( \mathbf{x} \) is a vector, we write \( \mathbf{x} \geq 0 \) to mean that every component of the vector is non-negative. Similarly, \( \mathbf{x} > 0 \) means that every component of the vector is positive. We let \( \mathbb{R}^n_\geq = \{ \mathbf{x} \in \mathbb{R}^n : \mathbf{x} \geq 0 \} \), and \( \mathbb{R}^n_> = \{ \mathbf{x} \in \mathbb{R}^n : \mathbf{x} > 0 \} \). We denote the cardinality of a set \( M \) as \( |M| \).

### 3 Generalized mass-action systems

Consider a simple directed graph \( G = (V, E) \) and the corresponding weighted graph \( G_\kappa = (V, E, \kappa) \) with \( \kappa \in \mathbb{R}^E_\geq \) providing a positive weight for each edge in \( E \). Let \( V = \{v_1, v_2, \ldots, v_m\} \) be the set of vertices. Given an edge \( e = v_i \rightarrow v_j \in E \), we call \( v_i \) the source of \( e \), and \( v_j \) its target. Let us denote by \( V_s \subseteq V \) the set of source vertices, that is, the set of vertices that are sources of some edges. The weight \( \kappa_e > 0 \) on the edge \( e = v_i \rightarrow v_j \) is called a rate constant, and we refer to the vector \( \kappa = (\kappa_e)_{e \in E} \) as the vector of rate constants, or more simply as the rate constants. Often, we use the indices of the source and target vertices as edge label, i.e., \( \kappa_{v_i \rightarrow v_j} = \kappa_{ij} \).

Let \( \Phi : V \rightarrow \mathbb{R}^n \) be a map assigning to each vertex \( v \in V \) a reaction complex \( \Phi(v) \in \mathbb{R}^n \), and let \( \widetilde{\Phi} : V_s \rightarrow \mathbb{R}^n \) be another map that assigns to each source vertex \( v \in V_s \) a kinetic-order complex \( \widetilde{\Phi}(v) \in \mathbb{R}^n \). An edge \( v_i \rightarrow v_j \) is called a reaction, and the vector \( \Phi(v_j) - \Phi(v_i) \) is the reaction vector associated to the edge \( v_i \rightarrow v_j \). For convenience, we often write \( \mathbf{y}_i \) instead of \( \Phi(v_i) \), and \( \mathbf{y}_i \) instead of \( \widetilde{\Phi}(v_i) \). The graph \( G \) and the two maps \( \Phi, \widetilde{\Phi} \) on \( G \) provide all the ingredients needed to define a generalized mass-action network, while the weighted graph \( G_\kappa \) and the maps \( \Phi, \widetilde{\Phi} \) are all that is needed to define a generalized mass-action system.

**Definition 3.1.** A **generalized mass-action network** is given by \((G, \Phi, \widetilde{\Phi})\), where \( G = (V, E) \) is a simple directed graph, and \( \Phi : V \rightarrow \mathbb{R}^n, \widetilde{\Phi} : V_s \rightarrow \mathbb{R}^n \) respectively assign to each vertex a reaction complex and to each source vertex a kinetic-order complex.

**Remark.** We follow the definition of a generalized mass-action network given by Müller and Regensburger in [21], rather than the one given in [20]. In particular, we do not assume the maps \( \Phi \) and \( \widetilde{\Phi} \) are one-to-one.

**Remark.** Throughout this paper, we are concerned with generalized mass-action networks where \( V_s = V \). In this case, the graphs \( \Phi(G) \) and \( \widetilde{\Phi}(G) \) are two Euclidean embedded graphs [25]. One of the equivalent definitions of a (classical) reaction network is a graph \( G = (V, \mathcal{E}) \), where the set \( V \) of vertices is a subset of \( \mathbb{R}^n \). Using the notation above, a reaction network is given by \((G, \Phi)\), where \( \Phi \) is one-to-one [21].

**Example 3.2.** To illustrate the terminology above, consider a directed graph \( G = (V, E) \), and its corresponding weighted graph \( G_\kappa = (V, E, \kappa) \):

![Diagram](image.png)

The set of vertices is \( V = \{v_1, v_2, v_3, v_4, v_5\} \), which coincides with the set of source vertices \( V_s \). The set of edges is \( E = \{v_1 \rightarrow v_2, v_2 \rightarrow v_1, v_3 \rightarrow v_4, v_4 \rightarrow v_3, v_4 \rightarrow v_5, v_5 \rightarrow v_3\} \). The maps \( \Phi, \widetilde{\Phi} \) are defined by their images in \( \mathbb{R}^2 \), as shown in Figure 1.
Figure 1: The (a) reaction complex map $\Phi(v_j) = y_j$ and (b) kinetic-order complex map $\tilde{\Phi}(v_j) = \tilde{y}_j$ as seen in $\mathbb{R}^2$. The vertex $v_3$ is mapped differently by $\Phi$ and $\tilde{\Phi}$, in such a way that the number of connected components and number of vertices are different in the graphs $\Phi(G)$ and $\tilde{\Phi}(G)$.

Note that the vertex $v_3$ is mapped differently by $\Phi$ and $\tilde{\Phi}$. Indeed, $v_3$ is mapped by $\Phi$ to the reaction complex $(1, 2)^T$ and by $\tilde{\Phi}$ to the kinetic-order complex $(3, 1)^T$. Moreover, the vertices $v_2$ and $v_3$ are mapped by $\Phi$ to the same reaction complex, and hence the number of connected components and the number of vertices are different in the graphs $\Phi(G)$ and $\tilde{\Phi}(G)$.

Now we are in a position to define generalized mass-action systems and the associated dynamical systems.

**Definition 3.3.** A **generalized mass-action system** is given by $(G_\kappa, \Phi, \tilde{\Phi})$, where $(G, \Phi, \tilde{\Phi})$ is a generalized mass-action network, with directed graph $G = (V, E)$, and $\kappa \in \mathbb{R}_{\geq 0}^E$ is a vector of rate constants.

**Definition 3.4.** For a generalized mass-action system $(G_\kappa, \Phi, \tilde{\Phi})$, the **associated dynamical system** on $\mathbb{R}_{>0}^n$ is given by

$$\frac{dx}{dt} = \sum_{v_i \rightarrow v_j \in E} \kappa_{ij} x \tilde{y}_i (y_j - y_i). \tag{1}$$

As the ODE system (1) is our main object of interest, we pause to make two observations. First, the rate of change $\frac{dx}{dt}$ is restricted to the stoichiometric subspace $S = \text{span}_{\mathbb{R}} \{y_j - y_i : v_i \rightarrow v_j \in E\}$. Consequently, every trajectory $x(t)$ of this dynamical system is restricted to a stoichiometric compatibility class $x(0) + S$. Second, if $v_i \rightarrow v_j$ is a reaction and $\Phi(v_i) = \Phi(v_j)$, then this particular reaction does not contribute to the dynamics.

It is sometimes more convenient to write the ODE system (1) in matrix form. Let $Y \in \mathbb{R}^{n \times m}$ be the reaction complex matrix, the $j$-th column of which is the reaction complex $y_j$. Let the kinetic-order complex matrix $\tilde{Y} \in \mathbb{R}^{n \times m}$ be defined analogously; in particular, its $j$-th column is the kinetic-order complex $\tilde{y}_j$ if $v_j \in V_s$ and $0$ if $v_j \not\in V_s$. Let $A_\kappa \in \mathbb{R}^{m \times m}$ be the negative transpose

\[ \text{of interest to us. In particular, they do not contribute to the right-hand side $Y A_\kappa x \tilde{Y}$ of the system of differential equations shown in (3), because they do not affect the vector $A_\kappa x \tilde{Y}$ [21].} \]
of the Laplacian of the weighted directed graph $G_{\kappa}$, i.e.,

$$[A_{\kappa}]_{ij} = \begin{cases} \kappa_{ji} & \text{if } v_j \to v_i \in E, \\ -\sum_{v_j \to v_k \in E} \kappa_{jk} & \text{if } i = j, \\ 0 & \text{otherwise}. \end{cases} \quad (2)$$

The dynamical system (1) can be rewritten as

$$\frac{dx}{dt} = Y A_{\kappa} \tilde{Y}. \quad (3)$$

**Example 3.2.** Returning to Example 3.2, the dynamical system associated to $(G_{\kappa}, \Phi, \tilde{\Phi})$ is

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \end{bmatrix} = \begin{bmatrix} \kappa_{12} x_2 \left( \frac{1}{1} \right) + \kappa_{21} x_1 x_2^2 \left( -\frac{1}{2} \right) + \kappa_{34} x_1^3 x_2 \left( \frac{1}{2} \right) \\ + \kappa_{43} x_1^2 \left( -\frac{1}{2} \right) + \kappa_{45} x_1^2 x_2 \left( \frac{2}{2} \right) + \kappa_{53} x_1^4 x_2 \left( -\frac{3}{0} \right) \end{bmatrix},$$

where each term corresponds to an edge in the graph $G$. Expanding the equations, we recognize it to be a polynomial (more generally, a power-law) dynamical system:

$$\begin{align*}
\frac{dx_1}{dt} &= \kappa_{12} x_2 - \kappa_{21} x_1 x_2^2 + \kappa_{34} x_1^3 x_2 - \kappa_{43} x_1^2 - 2\kappa_{45} x_1^2 - 3\kappa_{53} x_1^4 x_2, \\
\frac{dx_2}{dt} &= \kappa_{12} x_2 - \kappa_{21} x_1 x_2^2 + 2\kappa_{34} x_1^3 x_2 - 2\kappa_{43} x_1^2 + 2\kappa_{45} x_1^2.
\end{align*} \quad (4)$$

Its stoichiometric subspace is $S = \mathbb{R}^2$. The reaction complex matrix and kinetic-order complex matrix are

$$Y = (y_1, y_2, y_3, y_4, y_5) = \begin{bmatrix} 0 & 1 & 1 & 2 & 4 \\ 1 & 2 & 2 & 0 & 2 \end{bmatrix} \quad \text{and} \quad \tilde{Y} = (\tilde{y}_1, \tilde{y}_2, \tilde{y}_3, \tilde{y}_4, \tilde{y}_5) = \begin{bmatrix} 0 & 1 & 3 & 2 & 4 \\ 1 & 2 & 1 & 0 & 2 \end{bmatrix}$$

respectively. The matrix

$$A_{\kappa} = \begin{bmatrix} -\kappa_{12} & \kappa_{21} \\ \kappa_{12} & -\kappa_{21} \\ -\kappa_{34} & \kappa_{43} & \kappa_{53} \\ \kappa_{34} & -\kappa_{43} - \kappa_{45} & 0 \\ 0 & \kappa_{45} & -\kappa_{53} \end{bmatrix}$$

is the negative transpose of the Laplacian of the weighted graph $G_{\kappa}$.

The definitions above and Example 3.2 are relatively abstract; one may wonder how generalized mass-action systems show up in applications. Suppose we are interested in modelling the following chemical system:

Let us assume that based on experimental data, the reaction rate functions are as shown below, with rate constants $\kappa_{ij} > 0$:
Reaction Rate Function
\[ \begin{align*}
X_2 & \rightarrow X_1 + 2X_2 & \kappa_{12}x_2 \\
X_1 + 2X_2 & \rightarrow X_3 & \kappa_{21}x_1x_2^2 \\
X_1 + 2X_2 & \rightarrow 2X_1 & \kappa_{34}x_1^2x_2 \\
2X_1 & \rightarrow X_1 + 2X_2 & \kappa_{43}x_1^2 \\
2X_1 & \rightarrow 4X_1 + 2X_2 & \kappa_{45}x_1^2 \\
4X_1 + 2X_2 & \rightarrow X_1 + 2X_2 & \kappa_{53}x_1^2x_2^2 \\
4X_1 + 2X_2 & \rightarrow 4X_1 + 2X_2 & \kappa_{54}x_1^2x_2^2
\end{align*} \]

Note that the third reaction follows power-law kinetics, and not classical mass-action kinetics. The system of ordinary differential equations modelling this system of reactions is precisely (4), the dynamical system associated to \((G_\kappa, \Phi, \tilde{\Phi})\) of Example 3.2.

Remark. We defined a generalized mass-action network as a triple \((G, \Phi, \tilde{\Phi})\). As pointed out in an earlier remark, if \(\Phi\) is one-to-one, then \((G, \Phi)\) is a (classical) reaction network. A classical mass-action system can be obtained as a special case of a generalized mass-action system \((G_\kappa, \Phi, \tilde{\Phi})\), where \(\Phi\) is one-to-one and \(\tilde{\Phi} = \Phi|_{V_s}[20]\). It is thus natural to extend some of the standard definitions for classical mass-action systems to generalized mass-action systems.

We say the underlying graph \(G\) is weakly reversible if every connected component of \(G\) is strongly connected, i.e., every edge is part of a directed cycle. We have already defined the stoichiometric subspace \(S\) as the span of reaction vectors. Whenever \(V_s = V\) (in particular, when \(G\) is weakly reversible), we define its kinetic analogue, the kinetic-order subspace \(\tilde{S} = \text{span}_\mathbb{R} \{\tilde{y}_j - \tilde{y}_i : v_i \rightarrow v_j \in E\}\).

The stoichiometric deficiency of the generalized mass-action network \((G, \Phi, \tilde{\Phi})\) is the non-negative integer
\[ \delta_G = |V| - \ell_G - \dim S, \] (5)
where \(|V| = m\) is the number of vertices in \(G\), \(\ell_G\) is the number of connected components of \(G\), and \(S\) is the stoichiometric subspace. From the equivalent definition \(\delta_G = \dim(\ker Y \cap \text{im} I_E)\), where \(I_E\) is the incidence matrix of \(G\), it follows that \(\delta_G\) is a non-negative integer [16]. In the case when \(G\) is weakly reversible, we also have the formula [14]
\[ \delta_G = \dim(\ker Y \cap \text{im} A_\kappa). \] (6)
Whenever \(V_s = V\), the kinetic-order deficiency is defined as the non-negative integer
\[ \tilde{\delta}_G = |V| - \ell_G - \dim \tilde{S}, \] (7)
where \(\tilde{S}\) is the kinetic-order subspace.

Remark. In the definitions above, \(|V|\) is the number of vertices in the underlying abstract graph \(G\), not necessarily the number of distinct reaction complexes or the number of kinetic-order complexes; \(\ell_G\) is the number of connected components of \(G\), not necessarily the number of connected components in \(\Phi(G)\) or \(\tilde{\Phi}(G)\).

In Example 3.2, we have a weakly reversible network with \(|V| = 5\) vertices and \(\ell_G = 2\) connected components. We already observed that the stoichiometric subspace \(S\) is all of \(\mathbb{R}^2\). However, the kinetic-order subspace is \(\tilde{S} = \text{span}_\mathbb{R} (1, 1)^T\). The stoichiometric deficiency in this example is \(\delta_G = 5 - 2 - 2 = 1\), but the kinetic-order deficiency is \(\tilde{\delta}_G = 5 - 2 - 1 = 2\).

Example 3.5. We have seen earlier that generalized mass-action systems arise naturally from power-law kinetics. This example illustrates how generalized mass-action systems also arise naturally in the
study of mass-action systems, via a process called network translation \[16,17\]. Network translation produces a generalized mass-action system that has the same dynamics as the original mass-action system. We look at the \(n\)-site distributive phosphorylation-dephosphorylation system under mass-action kinetics.

This example first appeared in \[16\]; below we consider a different translation of the same mass-action system. Under the original definition of generalized mass-action system in \[20\], which requires the reaction complex map \(\Phi\) and the kinetic-order complex map \(\tilde{\Phi}\) to be one-to-one, the translated network presented below would not have been a well-defined generalized mass-action network. However, the later definition in \[21\] removes the requirements that \(\Phi\) and \(\tilde{\Phi}\) are one-to-one. As a result, many more dynamical systems can be written as a generalized mass-action system, and for this example, a more natural translation exists for the \(n\)-site distributive phosphorylation-dephosphorylation system.

Let \(E, F\) be enzymes that catalyze the phosphorylation and dephosphorylation processes, by forming intermediates \(ES_j\) and \(FS_j\) respectively. The \(n\)-site distributive phosphorylation-dephosphorylation system consists of the following reactions:

\[
\begin{align*}
E + S_0 & \xrightarrow{\quad} ES_0 & \quad E + S_1 & \xrightarrow{\quad} ES_1 & \quad \cdots & \quad E + S_{n-1} & \xrightarrow{\quad} ES_{n-1} & \quad E + S_n \\
F + S_0 & \xleftarrow{\quad} FS_0 & \quad F + S_1 & \xleftarrow{\quad} FS_1 & \quad \cdots & \quad F + S_{n-1} & \xleftarrow{\quad} FS_{n-1} & \quad F + S_n
\end{align*}
\]

We assume that the reaction rates follow classical mass-action kinetics. There are \(3n + 3\) species involved, so the system of differential equations modeling their concentrations is defined on \(\mathbb{R}^{3n+3}\). By network translation, we create a generalized mass-action system with the same differential equations. The main step involves changing the reaction complexes: adding enzyme \(F\) to the series of reactions for phosphorylation by \(E\); and adding enzyme \(E\) to the series of reactions for dephosphorylation by \(F\). This process produces a weakly reversible network:

\[
\begin{align*}
F + ES_0 & \\
E + F + S_0 & \xrightarrow{\quad} E + F + S_1 & \quad \cdots & \quad E + F + S_{n-1} & \quad E + FS_1
\end{align*}
\]

To define the generalized mass-action system, we take a more top-down approach, starting from a graph \(G\) with \(n\) components and \(4n\) vertices:

\[
\begin{align*}
z_0 & \quad v_0 & \quad w_1 \\
z_1 & \quad v_1 & \quad w_2 \\
z_{n-1} & \quad v_{n-1} & \quad w_n
\end{align*}
\]

Although \(\Phi\) and \(\tilde{\Phi}\) map vertices to vectors in \(\mathbb{R}^{3n+3}\), to make this example more readable, we will specify the images of \(\Phi\) and \(\tilde{\Phi}\) in terms of formal linear combination of species.
The reaction complexes are
\[ \Phi(v_j) = E + F + S_j, \quad \Phi(v'_j) = E + F + S_j, \quad \Phi(z_j) = F + ES_j, \quad \Phi(w_j) = E + FS_j, \]
and the kinetic-order complexes are
\[ \tilde{\Phi}(v_j) = E + S_j, \quad \tilde{\Phi}(v'_j) = F + S_j, \quad \tilde{\Phi}(z_j) = ES_j, \quad \tilde{\Phi}(w_j) = FS_j. \]

Note that the map \( \Phi \) is not one-to-one, as \( \Phi(v_j) = \Phi(v'_j) \) for \( 1 \leq j \leq n - 1 \). The image of the graph \( G \) under \( \Phi \) is connected:

One can check that \( \dim S = \dim \tilde{S} = 3n \); therefore, the stoichiometric deficiency and kinetic-order deficiency are \( \delta_G = \tilde{\delta}_G = (4n) - (n) - (3n) = 0. \)

### 4 Vertex-balanced steady states

Given the dynamical system associated to a generalized mass-action system \( (G_\kappa, \Phi, \tilde{\Phi}) \), written either as \( \frac{dx}{dt} = \sum_{v_i \rightarrow v_j \in E} \kappa_{ij} x_i (y_j - y_i) \) or in matrix form \( \frac{dx}{dt} = Y \kappa x \tilde{Y} \), it is natural to ask how many steady states there are. We define the set of positive steady states as

\[ E_\kappa = \{ x \in \mathbb{R}^n_+ : Y \kappa x \tilde{Y} = 0 \}. \]

For a classical mass-action system, an important subset of positive steady states is the set of complex-balanced equilibria \[ \text{(11)}, \] also known as complex-balancing equilibria or vertex-balanced equilibria \[ \text{[4]}. \] Horn and Jackson introduced the idea of complex balancing at equilibrium to generalize the common physical assumption of detailed balancing at thermodynamic equilibrium \[ \text{[11]}. \]

We illustrate the intuition behind the definition of such a steady state before introducing its analogue for a generalized mass-action system. Consider the graph \( G \) of the reaction network, and associate to each edge \( v_i \rightarrow v_j \) a reaction rate function \( \kappa_{ij} \). A concentration vector \( x^* \in \mathbb{R}^n_+ \) is a complex-balanced equilibrium of the classical mass-action system if at every vertex \( v_j \in V \) of the graph, the sum of incoming fluxes balances the sum of outgoing fluxes, i.e.,

\[ \sum_{v_i \rightarrow v_j \in E} \kappa_{ij} (x^*)^{Y_i} = \sum_{v_j \rightarrow v_k \in E} \kappa_{jk} (x^*)^{Y_j}. \]

This occurs if and only if \( A_\kappa (x^*)^Y = 0 \) \[ \text{(11)} \]. Clearly, a complex-balanced equilibrium is a positive solution to a system of polynomial equations. Surprisingly, it is also a positive solution to a system of binomial equations \[ \text{[6]}. \]

For a generalized mass-action system, one can define a vertex-balanced steady state analogously: it is a positive steady state at which the net flux is zero across every vertex of the graph, where the flux is given by generalized mass-action kinetics.

**Definition 4.1.** The set of **vertex-balanced steady states** for a generalized mass-action system \( (G_\kappa, \Phi, \tilde{\Phi}) \) is the set

\[ Z_\kappa = \{ x \in \mathbb{R}^n_+ : A_\kappa x \tilde{Y} = 0 \}. \]
Note that $x \in Z_κ$ if and only if
\[
\sum_{v_i \to v_j \in E} κ_{ij}(x^*)^{y_j} = \sum_{v_j \to v_i \in E} κ_{jk}(x^*)^{y_j}.
\] (11)

**Remark.** What we call vertex-balanced steady state here, is also called complex balancing equilibrium [20,21] or generalized complex-balanced steady state [16].

We call such a steady state vertex-balanced instead of complex-balanced to avoid a subtle point of confusion. In the case when $Φ$ is not one-to-one, the balancing of in-fluxes and out-fluxes occurs at each vertex $v ∈ V$ of the underlying abstract graph $G$. This in turn implies the balancing of fluxes at each reaction complex $Φ(v) ∈ Φ(V)$; however, the converse is generally false. For example, let $κ > 0$, and consider the generalized mass-action system given by the weighted graph $G_κ$

\[
\begin{array}{c}
v_1 \bullet \xrightarrow{κ} v_2 \\
v_3 \bullet \xleftarrow{κ} v_4
\end{array}
\]

and the maps $Φ(v_1) = Φ(v_3) = 0 ∈ ℝ^1$, $Φ(v_2) = Φ(v_4) = 1$, $Φ(ν_1) = 0$, and $Φ(ν_4) = 1$. The associated dynamical system $\frac{dx}{dt} = κ − κx$ is the same as that of the classical mass-action system given by the weighted graph $G_κ'$

\[
\begin{array}{c}
v_1 \bullet \xrightarrow{κ} v_2 \\
v_3 \bullet \xleftarrow{κ} v_4
\end{array}
\]

and the maps $Φ'(v_1) = 0 ∈ ℝ^1$ and $Φ'(v_2) = 1$. The concentration $x^* = 1$ is complex-balanced for the classical mass-action system given by $G_κ'$ but not vertex-balanced for the generalized mass-action system given by $G_κ$.

**Example 3.2.** To illustrate the connection between positive steady states and vertex-balanced steady states, consider Example 3.2 again. A vertex-balanced steady state is a point $x = (x_1, x_2)^T ∈ ℝ^2_{>0}$ satisfying five polynomial equations, one equation for each vertex of the graph $G$:

\[
\begin{align*}
v_1 : & \quad κ_{12}x_2 = κ_{21}x_1^2, \\
v_2 : & \quad κ_{21}x_1^2 = κ_{12}x_2, \\
v_3 : & \quad κ_{34}x_1^2x_2 = κ_{43}x_1^2 + κ_{53}x_1^4x_2^2, \\
v_4 : & \quad (κ_{43} + κ_{45})x_1^2 = κ_{34}x_1^3x_2, \\
v_5 : & \quad κ_{53}x_1^4x_2 = κ_{45}x_1^2.
\end{align*}
\] (12)

However, a positive steady state $x = (x_1, x_2)^T ∈ ℝ^2_{>0}$ has to satisfy only two polynomial equations:

\[
\begin{align*}
0 = \frac{dx_1}{dt} &= κ_{12}x_2 − κ_{21}x_1x_2^2 + κ_{34}x_1x_2^3 − κ_{43}x_1^2 + 2κ_{45}x_1^2 − 3κ_{53}x_1^4x_2^2, \\
0 = \frac{dx_2}{dt} &= κ_{12}x_2 − κ_{21}x_1x_2^2 + 2κ_{34}x_1^2x_2 − 2κ_{43}x_1^2 + 2κ_{45}x_2.
\end{align*}
\] (13)

The two polynomial equations (13) are linear combinations of the five polynomial equations (12); thus $Z_κ ⊆ E_κ$. This follows from the matrix expression of the associated dynamical system $\frac{dx}{dt} = Y(A_κx^Y)$.

Complex-balanced equilibria of classical mass-action systems have been studied extensively. Some of the classical results extend directly to the case of generalized mass-action systems, even when the maps $Φ$ and $Φ$, assigning reaction complexes and kinetic-order complexes, are not one-to-one. For example, it is known that [20,21].

\*\*Some of these results were first proved in [20], under the assumption that $Φ$ and $Φ$ are one-to-one, but the same proof goes through without these hypotheses.
i) If \( Z_\kappa \neq \emptyset \) for some \( \kappa > 0 \), then the underlying graph \( G \) is weakly reversible.

ii) If \( Z_\kappa \neq \emptyset \) and \( x^* \in Z_\kappa \), then \( Z_\kappa = \{ x \in \mathbb{R}_{>0}^n : \ln x - \ln x^* \in \overline{S^*} \} = x^* \circ \exp \overline{S^*} \).

iii) For a weakly reversible generalized mass-action network, \( \delta_G = 0 \) if and only if \( Z_\kappa \neq \emptyset \) for any choices of rate constants \( \kappa > 0 \).

iv) For a weakly reversible generalized mass-action network, if \( \delta_G = 0 \), then for any choice of rate constants \( \kappa > 0 \), any positive steady state is a vertex-balanced steady state, i.e., \( E_\kappa = Z_\kappa \).

In the example of the \( n \)-site phosphorylation-dephosphorylation system (Example 3.5), we noted that \( \delta_G = \overline{\delta_G} = 0 \). By statements (iii) and (iv) above, we conclude for any rate constants \( \kappa \), the set of vertex-balanced steady states \( Z_\kappa \) is non-empty, and all positive steady states are vertex-balanced. Moreover, the set of positive steady states is given by \( E_\kappa = Z_\kappa = x^* \circ \exp \overline{S^*} \), where \( x^* \) is any positive steady state and \( \overline{S} \) is the kinetic-order subspace, i.e., the vector space spanned by the differences of kinetic-order complexes according to the edges in the graph. It should be noted that the \( n \)-site phosphorylation-dephosphorylation system is multistationary when \( n \geq 2 \) [13], i.e., the system admits multiple steady states within the same stoichiometric compatibility class. In other words, for some choices of rate constants, there are multiple vertex-balanced steady states within some stoichiometric compatibility class. This contrasts with any classical complex-balanced mass-action system, where \( Z_\kappa \) meets every stoichiometric compatibility class at most once.

In applications, the vector of rate constants \( \kappa \in \mathbb{R}^E_{>0} \) is often not known precisely. Surprisingly, some important results for complex-balanced equilibria in classical mass-action systems hold irrespective of the precise values of the rate constants. We are interested in results for vertex-balanced equilibria of generalized mass-action systems that are in this sense independent of the choice of rate constants. We have observed that the solution trajectories are confined to a stoichiometric compatibility class \( x_0 + S \), where \( x_0 \in \mathbb{R}^n_{>0} \) is an initial state and \( S \) is the stoichiometric subspace. Therefore, our object of study is the intersection \( (x_0 + S) \cap Z_\kappa \) for any \( x_0 \in \mathbb{R}^n_{>0} \) and any \( \kappa \in \mathbb{R}^E_{>0} \).

5 Problem reformulations

In the introduction, we have mentioned that the following questions are essentially equivalent:

1. When does a generalized mass-action system have exactly one vertex-balanced steady state within each stoichiometric compatibility class, for any choice of rate constants?

2. Given vector subspaces \( S, \overline{S} \subseteq \mathbb{R}^n \), when does the intersection \( (x_0 + S) \cap (x^* \circ \exp \overline{S^*}) \) consist of exactly one point, for any \( x_0, x^* \in \mathbb{R}^n_{>0} \)?

3. Given vectors \( w^1, \ldots, w^n, \overline{w}^1, \ldots, \overline{w}^n \in \mathbb{R}^d \), when is the generalized polynomial map on \( \mathbb{R}^d_{>0} \) defined by

\[
f_{x^*}(\xi) = \sum_{i=1}^n x_i^* \xi i \overline{w}^i w^i
\]

bijection onto the relative interior of the polyhedral cone generated by \( w^1, \ldots, w^n \), for any \( x^* \in \mathbb{R}^n_{>0} \)?

Before we discuss the relationship between these problems in detail, let us first make a historical note. When speaking of a weakly reversible classical mass-action system, Horn and Jackson [11] proved that if the system has at least one complex-balanced equilibrium, then every stoichiometric compatibility class has exactly one complex-balanced equilibrium. Indeed, they showed that every positive steady
state of such a system is complex-balanced and locally asymptotically stable within its stoichiometric compatibility class. A complex-balanced equilibrium is globally stable within its stoichiometric compatibility class when the network has a single connected component \[1\], or is strongly endotactic \[12\], or when the system is in \(\mathbb{R}^3\) \[23\]. A general proof of global stability of complex-balanced equilibrium within its stoichiometric compatibility class was proposed for all complex-balanced systems in \[4\].

The first of the three questions above is phrased in the context of reaction networks. We start with a generalized mass-action network and suppose that for some rate constants \(\kappa\), there is a vertex-balanced steady state \(x^* \in Z_\kappa\). What is a condition (E) on the network \((G, \Phi, \tilde{\Phi})\) for the existence of a vertex-balanced steady state within every stoichiometric compatibility class? What is a condition (U) on \((G, \Phi, \tilde{\Phi})\) so that a vertex-balanced steady state is unique within its stoichiometric compatibility class? We would like to obtain conditions for these to hold or fail that are independent of the rate constants \(\kappa\). More precisely:

**Problem 1.** Let \((G_\kappa, \Phi, \tilde{\Phi})\) be a generalized mass-action system. Suppose that \(Z_\kappa \neq \emptyset\). What are conditions (E) and (U) on \((G, \Phi, \tilde{\Phi})\), so that the following statements are true?

1. If \((G, \Phi, \tilde{\Phi})\) satisfies condition (E), then there is at least one vertex-balanced steady state in every stoichiometric compatibility class, i.e., \((x_0 + S) \cap Z_\kappa\) contains at least one point for any \(x_0 \in \mathbb{R}_>^n\).
2. If \((G, \Phi, \tilde{\Phi})\) satisfies condition (U), then there is at most one vertex-balanced steady state in every stoichiometric compatibility class, i.e., \((x_0 + S) \cap Z_\kappa\) contains at most one point for any \(x_0 \in \mathbb{R}_>^n\).

Recall that \(Z_\kappa = x^* \circ \exp \tilde{S}^\perp\) for any \(x^* \in Z_\kappa\). Thus, the vertex-balanced steady states within any stoichiometric compatibility class \(x_0 + S\) belong to the intersection \((x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp)\). This leads us to the following reformulation of Problem 1:

**Problem 2.** Let \(S, \tilde{S} \subseteq \mathbb{R}^n\) be vector subspaces. What are conditions (E) and (U) on \(S, \tilde{S}\), so that the following statements are true?

1. If \(S, \tilde{S}\) satisfy condition (E), then \((x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp)\) contains at least one point, for any \(x_0, x^* \in \mathbb{R}_>^n\).
2. If \(S, \tilde{S}\) satisfy condition (U), then \((x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp)\) contains at most one point, for any \(x_0, x^* \in \mathbb{R}_>^n\).

If a generalized mass-action system happens to be a classical mass-action system, then its stoichiometric subspace \(S\) is also the kinetic-order subspace \(\tilde{S}\). The existence and uniqueness of a point in the intersection \((x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp)\) for any \(x_0, x^* \in \mathbb{R}_>^n\) is the content of Birch’s theorem in algebraic statistics \[22\].

Another reformulation of the above problems was introduced by Müller and Regensburger \[20\], in terms of injectivity/surjectivity of an exponential map or a generalized polynomial map onto a polyhedral cone. Such polynomial maps appear in other applications; for example, a renormalized version of the generalized polynomial appears in computer graphics and geometric modelling, where the map being one-to-one implies that the curve or surface does not self-intersect \[7\].

Let \(x^* \in \mathbb{R}_>^n\) be an arbitrary vector, and \(S, \tilde{S} \subseteq \mathbb{R}^n\) be vector subspaces, with \(d = \text{codim } S, d = \text{codim } \tilde{S}\). Choose a basis for \(S^\perp\) and let the basis vectors be the rows of the matrix \(W \in \mathbb{R}^{d \times n}\).
Similarly, choose a basis for $\tilde{S}^\perp$ and let the basis vectors be the rows of $\tilde{W} \in \mathbb{R}^{d \times n}$. Write the two matrices in terms of their columns: $W = (w^1, w^2, \ldots, w^n)$ and $\tilde{W} = (\tilde{w}^1, \tilde{w}^2, \ldots, \tilde{w}^n)$. In this manner, $S^\perp = \text{im}(W^T)$, $S = \text{ker} W$, and $\tilde{S}^\perp = \text{im}(\tilde{W}^T)$, $\tilde{S} = \text{ker} \tilde{W}$. Finally, write $C^0(W)$ for the relative interior of the polyhedral cone $C(W)$, i.e., $C^0(W)$ is the set of all positive combinations of $\{w^i\}_{i=1}^n$. For any $x^* \in \mathbb{R}^n_{>0}$, define the maps

$$f_{x^*} : \mathbb{R}^d_{>0} \to C^0(W) \subseteq \mathbb{R}^d,$$

$$\xi \mapsto W(x^* \circ \xi^W) = \sum_{i=1}^n x_i^* \xi^W w^i,$$

and

$$F_{x^*} : \mathbb{R}^d \to C^0(W) \subseteq \mathbb{R}^d,$$

$$\lambda \mapsto W(x^* \circ e^{W^T \lambda}) = \sum_{i=1}^n x_i^* e^{(\tilde{w}^i, \lambda)} w^i.$$  

Problem 2 is equivalent to the following (see [20][21] for details):

**Problem 3.** Let $S, \tilde{S} \subseteq \mathbb{R}^n$ be vector subspaces. What are conditions (E) and (U) on $S, \tilde{S}$, so that the following statements are true?

1. If $S, \tilde{S}$ satisfy condition (E), then the map $f_{x^*}$ (respectively $F_{x^*}$) is surjective onto $C^0(W)$, for any $x^* \in \mathbb{R}^n_{>0}$.

2. If $S, \tilde{S}$ satisfy condition (U), then the map $f_{x^*}$ (respectively $F_{x^*}$) is one-to-one, for any $x^* \in \mathbb{R}^n_{>0}$.

Müller and Regensburger characterized when the maps $f_{x^*}, F_{x^*}$ are one-to-one, namely, if and only if $\sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0\}$. Recall that, for a subset $S \subseteq \mathbb{R}^n$, its set of **sign vectors** $\sigma(S)$ is the image of vectors in $S$ under the coordinate-wise sign function (Definition 6.1). They also provided a sufficient condition for bijectivity: if $\sigma(S) = \sigma(\tilde{S})$ and $(+, +, \ldots, +)^T \in \sigma(\tilde{S}^\perp)$, then $f_{x^*}, F_{x^*}$ are bijective (and indeed, real analytic isomorphisms). Our main result (Theorem 6.8) can be regarded as a generalization of this result. Recently, Müller, Hofbauer, and Regensburger have used a different approach to characterize when $f_{x^*}, F_{x^*}$ are bijective maps for arbitrary $x^* \in \mathbb{R}^n_{>0}$.

### 6 Main result

In previous work as well as in ours, the conditions (E) and (U) are stated in terms of sign vectors. For a brief introduction to sign vectors of linear subspaces, we refer the reader to the appendix in [20].

**Definition 6.1.** Given a vector $x \in \mathbb{R}^n$, we define its **sign vector** to be

$$\sigma(x) = (\text{sgn}(x_1), \text{sgn}(x_2), \ldots, \text{sgn}(x_n))^T \in \{0,+,-\}^n.$$  

The set of **sign vectors** for a subset $S \subseteq \mathbb{R}^n$ is the collection $\sigma(S) = \{\sigma(x) : x \in S\}$. A partial order on the set $\{0, +, -\}^n$ is given by $\tau \geq \tau'$ if and only if $\tau_j \geq \tau'_j$ for all $j$, with the convention $+ > 0$ and $- < 0$. The **closure** of a set $\Lambda$ of sign vectors is the set

$$\overline{\Lambda} = \{\tau \in \{0, +, -\}^n : \text{there exists } \tau' \in \Lambda \text{ such that } \tau \leq \tau'\}.$$  

We define an **orthant** $\mathcal{O}_x$ of $\mathbb{R}^n$ to be a maximal subset of $\mathbb{R}^n$ on which $\sigma$ is constant. Geometrically, the sign vector $\sigma(x)$ tells us which orthant $\mathcal{O}_x$ the vector $x$ lies in, while the closure $\overline{\sigma(x)}$ refers to the union of $\mathcal{O}_x$ and the boundary of $\mathcal{O}_x$. Finally, we define an orthogonality relation on $\{0, +, -\}^n$; we say that two sign vectors $\tau$ and $\tau'$ are **orthogonal** (denoted $\tau \perp \tau'$) if

---

*This differs from the typical definition of an orthant of $\mathbb{R}^n$, which is full dimensional.*
Lemma 6.2

We show in this section that if \( \sigma(S) \subseteq \sigma(S) \) and \( \dim S = \dim \tilde{S} \), then for any \( x_0, x^* \in \mathbb{R}_{>0}^n \), the intersection \( (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \) contains exactly one point. The intuitive idea behind our result is that the sign condition \( \sigma(S) \subseteq \sigma(S) \) is related to a transversal intersection of the two manifolds \( (x_0 + S) \) and \( (x^* \circ \exp \tilde{S}^\perp) \). If we have one intersection point, say \( x^* \in (x^* + S) \cap (x^* \circ \exp \tilde{S}^\perp) \), we cannot lose the intersection point as we translate the affine plane from \( (x^* + S) \) to \( (x_0 + S) \).

We first show in Lemma 6.2 that our sign condition \( \sigma(S) \subseteq \sigma(S) \) implies the uniqueness condition \( \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0 \} \) in \( \mathbb{R}_0^n \). In Lemma 6.3 we establish transversality of the manifolds \( (x + S) \) and \( (x^* \circ \exp \tilde{S}^\perp) \). Lemma 6.3 prevents our desired intersection point from escaping to the boundary of \( \mathbb{R}_0^n \) or to infinity. Finally, these results lead to Theorem 6.4 concluding the existence and uniqueness of a point in the intersection \( (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \). In Theorem 6.5 and Corollary 6.6 we apply this result to generalized mass-action systems.

Lemma 6.2 (Uniqueness). Let \( S, \tilde{S} \subseteq \mathbb{R}^n \) be vector subspaces. If \( \sigma(S) \subseteq \sigma(\tilde{S}) \), then \( \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0 \} \). In particular, for any \( x_0, x^* \in \mathbb{R}_{>0}^n \) the intersection \( (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \) contains at most one point.

**Proof.** By assumption, \( \sigma(S) \cap \sigma(\tilde{S}^\perp) \subseteq \sigma(S) \cap \sigma(\tilde{S}^\perp) \). We show that \( \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0 \} \). Let \( \tau \in \sigma(S) \cap \sigma(\tilde{S}^\perp) \) be a sign vector. There exist vectors \( x \in \tilde{S} \) and \( y \in \tilde{S}^\perp \) such that \( \tau \leq \sigma(x) \) and \( \tau = \sigma(y) \). It is easy to see that if \( \tau \leq \sigma(x) \), and \( \tau \perp \sigma(x) \), then \( \tau = 0 \).

By [20], \( \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0 \} \) is necessary and sufficient for the intersection \( (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \) to contain at most one point for any \( x_0, x^* \in \mathbb{R}_{>0}^n \). \( \square \)

Lemma 6.3 (Compactness). Let \( S, \tilde{S} \subseteq \mathbb{R}^n \) be vector subspaces, and let \( K \subseteq \mathbb{R}_{>0}^n \) be a compact subset, and \( x^* \in \mathbb{R}_{>0}^n \). Suppose \( \sigma(S) \subseteq \sigma(\tilde{S}) \). Then \( (K + S) \cap (x^* \circ \exp \tilde{S}^\perp) \) is a compact subset of \( \mathbb{R}_0^n \).

**Proof.** Let \( \Gamma = (K + S) \cap (x^* \circ \exp \tilde{S}^\perp) \). Since \( x^* \circ \exp \tilde{S}^\perp \subseteq \mathbb{R}_{>0}^n \), the intersection \( \Gamma \) also lies in the positive orthant. We first show that \( \Gamma \) is bounded away from infinity and from the boundary of \( \mathbb{R}_{>0}^n \).

Suppose that is not the case. Let \( x^k \in \Gamma \) be a sequence such that either \( \lim \sup_{k \to \infty} x^k_i = \infty \) or \( \lim \inf_{k \to \infty} x^k_i = 0 \) for some index \( 1 \leq i \leq n \). Passing to a subsequence, we may assume that

\[
\lim_{k \to \infty} x^k_i = \infty \quad \text{for } i \in I_1,
\lim_{k \to \infty} x^k_i = 0 \quad \text{for } i \in I_2,
\lim_{k \to \infty} x^k_i \in (0, \infty) \quad \text{for } i \in I_3,
\]

where \( I_1, I_2, I_3 \) partition the index set \( \{1, 2, \ldots, n\} \), and \( I_1 \cup I_2 \neq \emptyset \).

On one hand, \( x^k \in K + S \), so decompose it as \( x^k = v^k + s^k \), where \( v^k \in K \) and \( s^k \in S \). Since \( K \subseteq \mathbb{R}_{>0}^n \) is compact, each component of \( v^k \) is uniformly bounded from above and below from zero. Thus for \( i \in I_1 \), we have \( s^k_i \to \infty \); in particular, \( s^k_i > 0 \) for sufficiently large \( k \). Similarly, if \( i \in I_2 \), then
For any intersection point \( p \) of two closed sets, and thus it is closed in \( \mathbb{R}^n \). This is the content of the follow lemma.

Next, we want to show that \( \Gamma \subseteq \mathbb{R}^n \) is a closed subset. Let us fix \( \varepsilon > 0 \) such that \( \Gamma \) lies inside the hypercube \( Q = [\varepsilon, \varepsilon^{-1}]^n \subseteq \mathbb{R}^n \). Being the intersection of two closed sets, \( Q \cap (K + S) \) is closed.

The set \( Q \cap (x^* \circ \exp \tilde{S}^\perp) \) is diffeomorphic to \([\log \varepsilon, \log \varepsilon^{-1}]^n \cap (\ln x^* + \tilde{S}^\perp)\), which is again a closed set. Therefore, the set \((K + S) \cap (x^* \circ \exp \tilde{S}^\perp) = \{Q \cap (K + S)\} \cap \{Q \cap (x^* \circ \exp \tilde{S}^\perp)\}\) is the intersection of two closed sets, and thus it is closed in \( \mathbb{R}^n \).

We say two manifolds \( X \) and \( Y \) of \( \mathbb{R}^n \) intersect transversally if at each point \( p \in X \cap Y \), their tangent spaces span the entire Euclidean space, i.e., \( T_p(X) + T_p(Y) = \mathbb{R}^n \). We refer the reader to [13][24] for the theory of transversality and intersection.

Again, let \( x_0, \ x^* \in \mathbb{R}^n_\geq 0 \) be two arbitrary vectors in what follows. In Lemma 6.2, we showed that our sign condition \( \sigma(S) \subseteq \sigma(\tilde{S}) \) implies \( \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0\} \), which is equivalent to the intersection \((x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp)\) containing at most one point. Indeed, this weaker sign condition together with \( \dim S = \dim \tilde{S} \) is enough to conclude that the two manifolds \( x_0 + S \) and \( x^* \circ \exp \tilde{S}^\perp \) intersect transversally. This is the content of the follow lemma.

**Lemma 6.4** (Transversality). Let \( S, \tilde{S} \subseteq \mathbb{R}^n \) be vector subspaces. Assume \( \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0\} \). Let \( x_0, \ x^* \in \mathbb{R}^n_\geq 0 \) be any two positive vectors. Then the tangent spaces of \( x_0 + S \) and \( x^* \circ \exp \tilde{S}^\perp \) satisfy

\[
T_p(x_0 + S) \cap T_p(x^* \circ \exp \tilde{S}^\perp) = \{0\}
\]

for any point \( p \in (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \).

If we further assume that \( \dim S = \dim \tilde{S} \), then \( T_p(x_0 + S) + T_p(x^* \circ \exp \tilde{S}^\perp) = \mathbb{R}^n \) for any intersection point \( p \in (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \), i.e., \( x_0 + S \) and \( x^* \circ \exp \tilde{S}^\perp \) intersect transversally.

**Proof.** For any intersection point \( p \in (x_0 + S) \cap (x^* \circ \exp \tilde{S}^\perp) \), we note that \( T_p(x_0 + S) = S \) and \( T_p(x^* \circ \exp \tilde{S}^\perp) = p \circ \tilde{S}^\perp \) and hence \( \sigma(T_p(x^* \circ \exp \tilde{S}^\perp)) = \sigma(\tilde{S}^\perp) \).

Now consider \( x \in T_p(x_0 + S) \cap T_p(x^* \circ \exp \tilde{S}^\perp) \). Then \( \sigma(x) \in \sigma(S) \cap \sigma(\tilde{S}^\perp) = \{0\} \), which implies \( x = 0 \). Consequently, \( T_p(x_0 + S) \cap T_p(x^* \circ \exp \tilde{S}^\perp) = \{0\} \).

If we further assume that \( \dim S = \dim \tilde{S} \), we note that \( T_p(x_0 + S) + T_p(x^* \circ \exp \tilde{S}^\perp) \) is of dimension \( n \). In other words, the manifolds \( x_0 + S \) and \( x^* \circ \exp \tilde{S}^\perp \) intersect transversally.

Now we are ready to state and prove our main result. The proof starts with a known intersection point, \( x^* \in (x_0^* + S) \cap (x^* \circ \exp \tilde{S}^\perp) \). Next, we translate the affine space \((x_0^* + S) \cap (x^* + S)\) creating a \((d + 1)\)-dimensional strip of the form \( K + S \), where \( d = \dim S \) and \( K \) is a compact subset of \( \mathbb{R}^n_\geq 0 \). This strip intersects \( x^* \circ \exp \tilde{S}^\perp \) transversally, and we use Corollary 6.6 below to conclude that
the intersection \((K + S) \cap (x^* \circ \exp \bar{S}^\perp)\) is a one-dimensional manifold, whose boundary lies on the boundary of the affine strip \(K + S\). Finally, we conclude the existence of a boundary point on \(x_0 + S\) by the uniqueness condition.

Consider the following differential topology result:

**Theorem 6.5** ([24] Theorem 3.5.1). Let \(X\) and \(Y\) be manifolds and \(Z \subseteq Y\) a submanifold, where \(Z\) and \(Y\) are boundaryless. Let \(f : X \to Y\) be a smooth map. Suppose \(f\) intersects \(Z\) transversally and \(f|_{\partial X}\) also intersects \(Z\) transversally. Then \(f^{-1}(Z)\) is a submanifold of \(X\) with boundary \(\partial(f^{-1}(Z)) = \partial X \cap f^{-1}(Z)\) and \(\text{codim}_X(f^{-1}(Z)) = \text{codim}_Y(Z)\).

Consider the setting where the ambient manifold is \(Y = \mathbb{R}^n_{>0}\). If \(f\) is the inclusion map of a submanifold \(X\) into \(\mathbb{R}^n_{>0}\), to say that the maps \(f\) and \(f|_{\partial X}\) intersect the manifold \(Z\) transversally is equivalent to the manifolds \(X\) and \(\partial X\) intersect \(Z\) transversally. The preimage \(f^{-1}(Z)\) is the submanifold \(X \cap Z\). Moreover, dimension of the the intersection \(X \cap Z\) is given by the equation

\[
\dim X - \dim(X \cap Z) = \text{codim}_X(X \cap Z) = \text{codim}_{\mathbb{R}^n_{>0}}(Z) = n - \dim Z.
\]

In other words, \(\dim(X \cap Z) = \dim X + \dim Z - n\). We arrive at the following corollary:

**Corollary 6.6.** Let \(X, Z \subseteq \mathbb{R}^n_{>0}\) be submanifolds, where \(Z\) is boundaryless. Suppose \(X\) intersects \(Z\) transversally and \(\partial X\) also intersects \(Z\) transversally. Then \(X \cap Z\) is a manifold with boundary \(\partial(X \cap Z) = \partial X \cap Z\) and of dimension \(\dim(X \cap Z) = \dim X + \dim Z - n\).

Our main result is:

**Theorem 6.7.** Let \(S, \bar{S} \subseteq \mathbb{R}^n\) be vector subspaces of equal dimension with \(\sigma(S) \subseteq \overline{\sigma(S)}\). Then for any positive vectors \(x_0, x^* \in \mathbb{R}^n_{>0}\), the intersection \((x_0 + S) \cap (x^* \circ \exp \bar{S}^\perp)\) consists of exactly one point.

**Proof.** Let \(x_0, x^* \in \mathbb{R}^n_{>0}\) be arbitrary positive vectors. Lemma 6.2 implies that the intersection \((x_0 + S) \cap (x^* \circ \exp \bar{S}^\perp)\) contains at most one point. Consider first \(x^* \in x_0 + S\). Clearly, \((x_0 + S) \cap (x^* \circ \exp \bar{S}^\perp) = \{x^*\}\).

Now consider the case when \(x^* \not\in x_0 + S\). Let \(d = \dim S\). We define a \((d + 1)\)-dimensional affine strip, which we will intersect with \((x^* \circ \exp \bar{S}^\perp)\). To define this affine strip, we consider the interpolation function

\[
K : [0, 1] \to \mathbb{R}^n_{>0}, \quad \delta \mapsto \delta x_0 + (1 - \delta)x^*.
\]

Since the line segment \(K([0, 1]) \subseteq \mathbb{R}^n_{>0}\) is compact, the intersection \((K([0, 1]) + S) \cap (x^* \circ \exp \bar{S}^\perp)\) is compact by Lemma 6.3. Moreover, the manifolds \(K([0, 1]) + S\) and \(x^* \circ \exp \bar{S}^\perp\) intersect transversally, as a consequence of Lemma 6.4, i.e.,

\[
T_p(K([0, 1]) + S) + T_p(x^* \circ \exp \bar{S}^\perp) \supseteq T_p(x^* + S) + T_p(x^* \circ \exp \bar{S}^\perp) = \mathbb{R}^n.
\]

By Corollary 6.6, the intersection \(\Gamma = (K([0, 1]) + S) \cap (x^* \circ \exp \bar{S}^\perp)\) is a manifold with boundary \(\partial \Gamma \subseteq \partial(K([0, 1]) + S) = (x^* + S) \cup (x_0 + S)\). In addition, \(\Gamma\) is 1-dimensional because

\[
\dim(\Gamma) = \dim(K([0, 1]) + S) + \dim(x^* \circ \exp \bar{S}^\perp) - n = 1 + \dim S + \dim \bar{S}^\perp - n = 1.
\]

Consider the connected component \(\Gamma^* \subseteq \Gamma\) containing the point \(x^*\). The point \(x^*\) must be an endpoint of \(\Gamma^*\); otherwise uniqueness fails at \(K(\delta_0) + S\) for some small \(\delta_0 > 0\). Since \(\Gamma^*\) is compact, it
is a curve with two endpoints. As \( \partial \Gamma^* \subseteq \partial \Gamma = (x^* + S) \cup (x_0 + S) \), by uniqueness the other endpoint of \( \Gamma^* \) must be in \( x_0 + S \). Thus, a point exists in \( (x_0 + S) \cap (\exp S) \).

We apply Theorem 6.7 to show the existence and uniqueness of vertex-balanced steady state for a generalized mass-action system.

**Theorem 6.8** (Vertex-balanced steady states of a generalized mass-action system). Let \((G, \Phi, \Phi)\) be a generalized mass-action network, with stoichiometric subspace \( S \), and suppose that every vertex of \( G \) is the source of some edge, so that the kinetic-order subspace \( S \) is well-defined. Assume that \( \dim S = \dim \overline{S} \) and \( \sigma(S) \subseteq \overline{\sigma(S)} \). Then the following statements hold:

i) Suppose for some rate constants \( \kappa \), the generalized mass-action system \((G_\kappa, \Phi, \Phi)\) admits a vertex-balanced steady state \( x^* \). Then every stoichiometric compatibility class contains exactly one vertex-balanced steady state.

ii) Suppose \( G \) is weakly reversible and \( \delta_G = 0 \). Then for all rate constants \( \kappa \), the generalized mass-action system \((G_\kappa, \Phi, \Phi)\) admits a vertex-balanced steady state \( x^* \). Moreover, every stoichiometric compatibility class contains exactly one vertex-balanced steady state.

iii) Under the premises of i), additionally suppose \( \delta_G = 0 \). Then every stoichiometric compatibility class contains exactly one positive steady state, which is vertex-balanced.

**Proof.** As \( x^* \) is a vertex-balanced steady state for \((G_\kappa, \Phi, \Phi)\), the set of vertex-balanced steady state is \( Z_\kappa = x^* \cap \exp \overline{S} \). By Theorem 6.7, \( Z_\kappa \) intersects the stoichiometric compatibility class \( x_0 + S \) exactly once for any \( x_0 \in \mathbb{R}^n_{>0} \). This proves the statement i).

If \( G \) is weakly reversible and \( \delta_G = 0 \), then the set of vertex-balanced steady states \( Z_\kappa \neq \emptyset \) for any \( \kappa > 0 \). By statement i), we conclude that every stoichiometric compatibility class contains exactly one vertex-balanced steady state.

If in addition, \( \delta_G = 0 \), then \( E_\kappa = Z_\kappa \), i.e., there are no positive steady states that are not vertex-balanced. Consequently, there exists a unique steady state within each stoichiometric compatibility class, which is vertex-balanced.

We state a simpler version of iii) in the theorem above.

**Corollary 6.9.** Let \((G, \Phi, \Phi)\) be a weakly reversible generalized mass-action network, with stoichiometric subspace \( S \) and kinetic-order subspace \( \overline{S} \). Suppose that \( \dim S = \dim \overline{S} \), \( \sigma(S) \subseteq \overline{\sigma(S)} \), and \( \delta_G = 0 \). Then for any choice of rate constants, every stoichiometric compatibility class contains exactly one positive steady state, which is vertex-balanced.

We have focused almost exclusively on the existence and uniqueness of vertex-balanced steady states for generalized mass-action systems. For complex-balanced equilibria of classical mass-action systems, much more is known. For example, complex-balanced equilibria are locally asymptotically stable within their stoichiometric compatibility classes. They are conjectured to be globally stable in their stoichiometric compatibility classes; this is known as the **global attractor conjecture** \cite{1}. In particular, it has been shown that a complex-balanced equilibrium of a mass-action system is globally stable within its stoichiometric compatibility class if the network has a single connected component \cite{1}, or is strongly endotactic \cite{3,23}, or if the system is in \( \mathbb{R}^3 \) \cite{3,23}. A proof of the global attractor conjecture in full generality has been proposed in \cite{3}.

Not much is known about the local stability of vertex-balanced steady states of generalized mass-action systems. It is, however, not true that a vertex-balanced steady state is always globally stable.
within its stoichiometric compatibility class, since it is possible for a generalized mass-action system to have multiple vertex-balanced steady states within the same stoichiometric compatibility class. Consider, for example, the following generalized mass-action system:

\[
\begin{array}{c|cc|c}
0 & \kappa & X_1 + X_2 \\
(2X_1) & \kappa & (X_1 + 2X_2)
\end{array}
\]

where each box is a vertex of the graph; the top entry in each box is the reaction complex of that vertex (0 and \(X_1 + X_2\)), and the bottom entry in the parentheses is the kinetic-order complex \((2X_1\) and \(X_1 + 2X_2\)). The associated dynamical system of this generalized mass-action system is given by

\[
\begin{align*}
\frac{dx_1}{dt} &= \kappa x_1^2 - \kappa x_1 x_2^2, \\
\frac{dx_2}{dt} &= \kappa x_1^2 - \kappa x_1 x_2^2.
\end{align*}
\]

One can check that the set of vertex-balanced steady states is \(Z_\kappa = \{(t^2, t) : t > 0\}\). If \(x_0 = (0, \varepsilon)^T\) where \(0 < \varepsilon < \frac{1}{4}\), then there are two vertex-balanced steady states in \(x_0 + S = \{(r, \varepsilon + r) : r \in \mathbb{R}\}\).

Moreover, it is also possible for a unique vertex-balanced steady state (within its stoichiometric compatibility class) to be unstable. Consider the generalized mass-action system:

\[
\begin{array}{c|cc|c}
X_1 & \kappa & 2X_2 \\
(2X_1) & \kappa & (X_2)
\end{array}
\]

\[
\begin{array}{c|cc|c}
2X_1 & \kappa & X_2 \\
(X_1) & \kappa & (2X_2)
\end{array}
\]

Its associated dynamical system is

\[
\begin{align*}
\frac{dx_1}{dt} &= -\kappa x_1^2 + \kappa x_2 - 2\kappa x_1 + 2\kappa x_2^2, \\
\frac{dx_2}{dt} &= 2\kappa x_1^2 - 2\kappa x_2 + \kappa x_1 - \kappa x_2^2.
\end{align*}
\]

This is an example of a reversible generalized mass-action system with \(\delta_G = \tilde{\delta}_G = 0\), and its stoichiometric subspace \(S\) and its kinetic-order subspace \(\tilde{S}\) are \(\mathbb{R}^2\). There is a unique positive steady state, which is vertex-balanced; nonetheless, it can be shown that this steady state is unstable. Moreover, the system is neither permanent nor persistent because any non-constant solution either converges to the origin or escapes to infinity.

### 7 An illustrative example

We conclude by applying Theorem 6.8 to the following example of a family of generalized mass-action systems. Let \(a, b, \kappa_i > 0\). Consider the generalized mass-action system \((G_\kappa, \Phi, \tilde{\Phi})\)
At each vertex (box), a reaction complex (top entry) and a kinetic-order complex (second entry in parentheses) are assigned. Let $x_i$ be the concentration of species $X_i$, for $1 \leq i \leq 4$, and $x = (x_1, x_2, x_3, x_4)^T$. The reaction complexes and kinetic-order complexes are

\[
\begin{align*}
y_1 &= (0, 0, 0, 0)^T, & y_2 &= (1, 1, 0, 0)^T, & y_3 &= (0, 0, 1, 1)^T, \\
\tilde{y}_1 &= (0, 0, 0, 0)^T, & \tilde{y}_2 &= (1, a, 0, 0)^T, & \tilde{y}_3 &= (b, 0, 1, 1)^T.
\end{align*}
\]

The associated dynamical system is

\[
\begin{align*}
dx_1 &= \kappa_1 x_1 \tilde{y}_1 - \kappa_2 x_1 x_2 x_3 x_4, \\
dx_2 &= \kappa_1 x_1 \tilde{y}_2 - \kappa_2 x_1 x_2 x_3 x_4, \\
dx_3 &= \kappa_1 x_1 \tilde{y}_3 - \kappa_2 x_1 x_2 x_3 x_4, \\
dx_4 &= \kappa_1 x_3 \tilde{y}_3 - \kappa_2 x_1 x_2 x_3 x_4.
\end{align*}
\]

Another way to write the system of differential equations is

\[
\begin{align*}
dx_1 &= \kappa_1 x_1 (y_2 - y_1) + \kappa_2 x_1 x_3 x_4, \\
dx_2 &= \kappa_1 x_1 x_2 - \kappa_2 x_1 x_2 x_3 x_4, \\
dx_3 &= \kappa_1 x_1 x_3 - \kappa_2 x_1 x_2 x_3 x_4, \\
dx_4 &= \kappa_1 x_1 x_4 - \kappa_2 x_1 x_2 x_3 x_4.
\end{align*}
\]

The stoichiometric subspace and the kinetic-order subspace are

\[
S = \text{span}_\mathbb{R} \left\{ \begin{pmatrix} 1 \\ 1 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ 0 \\ 1 \end{pmatrix} \right\}, \quad \text{and} \quad \tilde{S} = \text{span}_\mathbb{R} \left\{ \begin{pmatrix} 1 \\ a \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} b \\ 0 \\ 1 \\ 0 \end{pmatrix} \right\}
\]

respectively. Their sign vectors are

\[
\sigma(S) = \left\{ \begin{pmatrix} 0 \\ + \\ + \\ + \\ + \\ - \\ - \\ - \end{pmatrix}, \begin{pmatrix} + \\ 0 \\ + \\ 0 \\ - \\ - \\ - \\ - \end{pmatrix}, \cdots \right\},
\]

and

\[
\sigma(\tilde{S}) = \left\{ \begin{pmatrix} 0 \\ + \\ + \\ + \\ + \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} + \\ + \\ + \\ + \\ + \\ 0 \\ 0 \\ 0 \end{pmatrix}, \cdots \right\}.
\]
where the dots indicate the negatives of the listed sign vectors. By visual inspection, we find that \(\sigma(S) \subseteq \sigma(\tilde{S})\). Moreover, one can check that the deficiency \(\delta_G\) and the kinetic-order deficiency \(\tilde{\delta}_G\) are zero. Therefore, Corollary 6.9 applies and we conclude that, for any choice of rate constants, every stoichiometric compatibility class contains exactly one positive steady state, which is vertex-balanced.

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