A Computational Approach to Steady State Correspondence of Regular and Generalized Mass Action Systems

Matthew D. Johnston

Abstract It has been recently observed that the dynamical properties of mass action systems arising from many models of biochemical reaction networks can be characterized by considering the corresponding properties of a related generalized mass action system. The correspondence process known as network translation in particular has been shown to be useful in characterizing a system’s steady states. In this paper, we further develop the theory of network translation with particular focus on a subclass of translations known as improper translations. For these translations, we derive conditions on the network topology of the translated network which are sufficient to guarantee the original and translated systems share the same steady states. We then present a mixed-integer linear programming algorithm capable of determining whether a mass action system can be corresponded to a generalized system through the process of network translation.

Keywords Chemical reaction network · Mass action system · Generalized network · Network translation · Mixed-integer Linear programming

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1 Introduction

Many biochemical and industrial processes can be represented graphically as networks of simultaneously occurring chemical reactions. Under simplifying assumptions such as spatially homogeneity and mass action kinetics, the dynamical behavior of these chemical reaction networks can be modeled mathematically by systems of autonomous polynomial ordinary differential equations known as mass action systems.

Motivated by the growth of systems biology, there has been significant recent interest in characterizing the long-term and steady state properties of such systems. A recent addition to this field has been the study of generalized chemical reaction networks introduced by Müller and Regensburger (2012). A generalized chemical reaction network is given by a chemical reaction network together with an additional set of vertices which are in one-to-one correspondence with the vertices of the original network. The dynamics of these generalized networks are then given by a generalized mass action system, where the first set of vertices controls the stoichiometry of the system (i.e., the reaction vectors), and the second set controls the kinetic rates (i.e., the reaction monomials).

For example, consider the generalized network

\[ X_1 \rightarrow \cdots \rightarrow X_1 \xrightleftharpoons[k_2]{k_1} X_2 \rightarrow \cdots \rightarrow 2X_2 \]  

(1)

where the dotted lines denote the correspondence between the stoichiometric vertices and the kinetic vertices. The dynamical formulation of the corresponding generalized mass action system is the same as for a regular one except that we substitute the monomial \( x_2^2 \) corresponding to \( 2X_2 \) in the place of the monomial \( x_2 \) corresponding to \( X_2 \). Although the theoretical study of generalized systems is in its early stages, several substantial results are known, including results sufficient to guarantee the existence of “complex-balanced-like” steady states and results guaranteeing the uniqueness of such states within stoichiometric compatibility classes (Müller and Regensburger 2012; Müller et al. 2013).

It was noted by Johnston (2014) that dynamical and steady state properties of classical mass action systems can often be determined by first making a suitable correspondence with a generalized mass action system. For example, consider the network

\[ X_1 \xrightarrow{k_1} X_2, \quad 2X_2 \xrightarrow{k_2} X_1 + X_2. \]  

(2)

Despite the difference in appearance and network structure between (1) and (2), it can be easily verified that they share the governing set of differential equations: \( \dot{x}_1 = -\dot{x}_2 = -k_1x_1 + k_2x_2^2 \).

Johnston subsequently introduced a correspondence process called network translation and was able to identify two subcategories: proper translations and improper translations. A translation is said to be proper if there is a one-to-one correspondence between the source vertices of the original network and those of the translated network; otherwise, it is said to be improper. For proper translations, the original and generalized systems are known to be dynamically equivalent (Lemma 2, Johnston 2014),
while for improper translations, supplemental conditions are known which allow rate constants to be selected so that the original and generalized systems share the same steady states (Lemma 4, Johnston 2014). Johnston also gave conditions which are sufficient to guarantee the existence of toric steady states as introduced by Pérez Millán et al. (2012) (Theorem 5, Johnston 2014). The method of network translation has since been applied to characterize the steady states of processive multisite phosphorylation networks by Conradi and Shiu (2014).

Two important questions were left open by Johnston (2014) which we address in the current work:

(Q1) Given an improper translation, are there sufficient conditions on the structure of the translated reaction graph alone which guarantee steady state equivalence of the original and translated systems?

While sufficient conditions were given by Johnston (2014) for guaranteeing steady state equivalence of the two systems, the conditions depended upon an algebraic combination of rate constants which may be difficult to compute in practice. In Sect. 3, we present structural conditions which are sufficient to guarantee such a correspondence can be made (Theorem 1 and Corollary 1). This is in keeping with the general flavor of so-called chemical reaction network theory (CRNT) which has placed considerable emphasis on dynamical results which follow from properties of the underlying network structure.

We then address the following equally fundamental question:

(Q2) Given an arbitrary mass action system or reaction network, can a suitable translated network be constructed algorithmically? In particular, is it possible to algorithmically construct a translation satisfying Theorem 1 and therefore guarantee steady state equivalence?

In practice, we do not have the structure of the translated network given to us; rather we must find it. An algorithm for constructing translations was presented by Johnston (2014); however, it was not directly amenable to computational implementation as it required a full enumeration of the network’s elementary flux modes. There was also no guarantee that the translation found by that algorithm would satisfy desirable network properties such as being weakly reversible or having a low deficiency.

In Sect. 4, we recast the question of whether a translation satisfying Theorem 1 exists as a mixed-integer linear programming (MILP) problem. This framework has been previously used within CRNT to determine dynamically equivalent and linearly conjugate network structures in the papers of Szederkényi and various collaborators (2010, 2011, 2011, 2012a, 2012b, 2012, 2013, 2014). The algorithm we present in this paper is capable of determining the structure of the translated chemical reaction network, ensuring steady state equivalence may be made in accordance with Theorem 1, and also guaranteeing weak reversibility and a minimal deficiency are attained according to the results of Johnston et al. (2012b, 2013). In Sect. 5, we apply this MILP procedure to a pair of models drawn from the mathematical biochemistry literature to determine a weakly reversible generalized mass action system with the same steady states (Shinar and Feinberg 2010; Karp et al. 2012; Dasgupta et al. 2014).
2 Background

In this section, we present the required background information on CRNT in both the classical and generalized setting.

2.1 Chemical Reaction Networks

The central object of study in this paper is the following.

Definition 1 A chemical reaction network is a triple \( N = (S, C, R) \) where:

1. The species set \( S = \{X_1, \ldots, X_n\} \) consists of the individual (chemical) species \( X_i \) capable of undergoing chemical change.
2. The complex set \( C = \{C_1, \ldots, C_m\} \) consists of linear combinations of the species, i.e., terms of the form \( C_j = \sum_{i=1}^{n} y_{ij} X_i, j = 1, \ldots, m \). The values \( y_{ij} \in \mathbb{Z}_{\geq 0} \) are called stoichiometric coefficients, and each complex \( C_j \) is associated with a stoichiometric vector \( y_j = (y_{1j}, y_{2j}, \ldots, y_{nj}) \).
3. The reaction set \( R \subseteq C \times C \) consists of ordered pairs \((C_i, C_j)\) where \( C_i, C_j \in C \).

It is also common to represent reactions in the form \( C_i \rightarrow C_j \).

Remark 1 It is typical in CRNT to assume that (i) every species appears in at least one complex, (ii) every complex appears in at least one reaction (as either a reactant or product), and (iii) there are no self-reactions (i.e., reactions of the form \( C_i \rightarrow C_i \)). To accommodate the computational process used in Sect. 4, it will be occasionally necessary to violate condition (ii). These exceptions will be noted in the text.

Remark 2 It will be convenient to allow the complex set \( C \) to correspond interchangeably to the underlying index set; i.e., we will let \( C = \{1, \ldots, m\} \) and allow \( i \in C \) to stand in for \( C_i \in C \). We will also allow the ordered index pair \((i, j)\) to represent the reaction \( C_i \rightarrow C_j \).

It is natural to interpret chemical reaction networks as directed graphs \( G(V, E) \) where the vertex set is given by the complexes (i.e., \( V = C \)) and the edge set is given by the reactions (i.e., \( E = R \)). Two complexes \( C_i \) and \( C_j \) are said to be connected if there is an ordering of complexes \( \{v(1), v(2), \ldots, v(l)\} \subseteq C \) such that \( C_i = C_{v(1)} \leftrightarrow C_{v(2)} \leftrightarrow \cdots \leftrightarrow C_{v(l)} = C_j \) where \( C \leftrightarrow C' \) if \( C \rightarrow C' \) or \( C' \rightarrow C \). If there is such a chain where all the reactions are of the form \( C \rightarrow C' \), we say there is a path from \( C_i \) to \( C_j \). The maximal sets of connected complexes are called linkage classes and are denoted \( \mathcal{L} = (L_1, \ldots, L_\ell) \) where \( \ell = |\mathcal{L}| \). Two complexes \( C_i \) and \( C_j \) are said to be strongly connected if, given a path from \( C_i \) to \( C_j \), there is a path from \( C_j \) to \( C_i \). The maximal sets of strongly connected complexes are called a strong linkage classes. A network is said to be weakly reversible if the linkage classes and strong linkage classes coincide.

To each reaction \( C_i \rightarrow C_j \), we associate a reaction vector \( y_j - y_i \in \mathbb{Z}^n \) which keeps track of the change in the number of each species as a result of the reaction. The span of the reaction vectors is called the stoichiometric subspace and is denoted \( S = \text{span}\{y_j - y_i \mid (i, j) \in \mathcal{R}\} \). The dimension of the stoichiometric subspace is denoted \( s = \text{dim}(S) \).
A network parameter which has been particularly well studied in the literature is the deficiency (Feinberg 1972, 1987, 1988, 1995; Horn 1972).

**Definition 2** The deficiency of a chemical reaction network $\mathcal{N} = (S, \mathcal{C}, \mathcal{R})$ is given by

$$
\delta = m - \ell - s
$$

where $m$ is the number of stoichiometrically distinct complexes (i.e., $m = |\mathcal{C}|$), $\ell$ is the number of linkage classes (i.e., $\ell = |\mathcal{L}|$), and $s$ is the dimension of the stoichiometric subspace (i.e., $s = \dim(S)$).

### 2.2 Weighted Networks and Mass Action Systems

A common kinetic assumption for chemical reaction networks is mass action kinetics, which states that the rate of a reaction is proportional to the product of the concentrations of the reacting species. For instance, if a reaction $C_i \rightarrow C_j$ has the form $X_1 + X_2 \rightarrow \cdots$, then the associated rate function would be $\text{rate} = k(i, j)[X_1][X_2]$ where $k(i, j) > 0$ is the rate constant (i.e., proportionality constant) of the reaction and $[X]$ denotes the concentration of the species $X$. Other kinetic assumptions are also frequently used, especially in the mathematical biochemistry literature, including Michaelis–Menten kinetics (Michaelis and Menten 1913) and Hill kinetics (Hill 1910).

It is therefore natural to associate with every reaction $(i, j) \in \mathcal{R}$ a weight $k(i, j) > 0$. We formally define the following.

**Definition 3** Suppose $\mathcal{N} = (S, \mathcal{C}, \mathcal{R})$ is a chemical reaction network. We will say that $K = \{k(i, j) \mid i, j \in \mathcal{C}\}$ is a weight set if $k(i, j) > 0$ if $(i, j) \in \mathcal{R}$ and $k(i, j) = 0$ if $(i, j) \notin \mathcal{R}$. We furthermore define the weighted chemical reaction network associated with $\mathcal{N}$ and $K$ to be $\mathcal{N}(K) = (S, \mathcal{C}, \mathcal{R}, K)$.

Note that $k(i, i) = 0$ for all $i \in \mathcal{C}$ since $(i, i) \notin \mathcal{R}$ for all $i \in \mathcal{C}$ by definition.

It is common to incorporate the weights $k(i, j)$ into the reaction graph as edge weights. This gives rise to an edge-weighted reaction graph $G(V, E(K))$. For instance, we write

$$
G(V, E) : \\
C_1 \xrightleftharpoons{k(1,2)} C_2 \rightarrow C_3 \xleftarrow{k(4,3)} C_4
$$

for the unweighted and weighted reaction graphs of $\mathcal{N}$, respectively.

Defining $x = (x_1, x_2, \ldots, x_n) \in \mathbb{R}_{\geq 0}^n$ to be the vector of species concentrations, the mass action system corresponding to a weighted chemical reaction network $\mathcal{N}(K) = (S, \mathcal{C}, \mathcal{R}, K)$ is given by the system of ordinary differential equations

$$
\frac{dx}{dr} = Y \cdot A(K) \cdot \Psi(x) \quad (3)
$$
where

1. The complex matrix \( Y \in \mathbb{Z}_{\geq 0}^{n \times m} \) is the matrix with columns \( Y_i = y_i \).
2. The kinetic or Kirchhoff matrix \( A(K) \in \mathbb{R}^{m \times m} \) is the matrix with entries
   \[
   [A(K)]_{i,j} = \begin{cases} 
   -\sum_{l=1}^{m} k(i, l), & \text{for } i = j, \\
   k(j, i), & \text{for } i \neq j,
   \end{cases}
   \]
   for \( i, j = 1, \ldots, m \).
3. The mass action vector \( \Psi(x) \in \mathbb{R}_0^m \) is the vector with entries
   \[
   [\Psi(x)]_i = x^{y_i} = \prod_{j=1}^{n} x_j^{y_{ij}}, \quad i = 1, \ldots, m.
   \]

It is known that positive trajectories of any mass action system are restricted to stoichiometric compatibility classes \( C_{x_0} = (x_0 + S) \cap \mathbb{R}_{>0}^n \) for all \( x_0 \in \mathbb{R}_{>0}^n \) (Vol’pert and Hudjaev 1985).

Remark 3 In the language of graph theory, \( A(K) \) is the transpose of the weighted Laplacian of the weighted reaction graph \( G(V, E(K)) \). Note that an off-diagonal element \( [A(K)]_{i,j} \) is nonzero if and only if there is a reaction in the network from \( C_j \) to \( C_i \).

Remark 4 It is tempting to automatically correspond weighted networks \( (S, C, R, K) \) with mass action systems (3). The theory developed in Sect. 3, however, will necessitate the construction of weighted chemical reaction networks which do not have meaningful interpretations as mass action systems. We will use the notation \( B \) to denote weight sets which do not necessarily correspond to the kinetic rate constants in a corresponding mass action system.

2.3 Generalized Chemical Reaction Networks

An alternative to mass action kinetics is power-law formalism, where the powers of the kinetic terms in the governing equations (3) are allowed to take (potentially non-integer) powers which are not necessarily implied by the stoichiometry of the network (Savageau 1969). A recent graph-based extension of this is the concept of a generalized chemical reaction network (Müller and Regensburger 2012).

Definition 4 A generalized chemical reaction network \( N = (S, C, C_K, R) \) is a chemical reaction network \( (S, C, R) \) together with a set of kinetic complexes \( C_K \) which are in one-to-one correspondence with the elements of \( C \).

When permitted by space, we denote the correspondence between the stoichiometric and kinetic complexes with dotted lines. For example, we write
\[
7X_1 + X_2 \cdots X_1 \iff X_2 + X_3 \cdots X_3
\]
to imply that the stoichiometric complex \( C_1 = X_1 \) is associated with the kinetic complex \( (C_K)_1 = 7X_1 + X_2 \) and that the stoichiometric complex \( C_2 = X_2 + X_3 \) is
associated with the kinetic complex $(C_K)_2 = X_3$. We define properties of the reaction graph $(S, C, R)$ as we do for a standard reaction network. For example, this network has the stoichiometric subspace $S = \text{span}\{(-1, 1, 1)\}$ and $\delta = 0$.

A reaction graph for $(S, C_K, R)$ can also be defined. We do this by substituting the kinetic complexes for the stoichiometric complexes. For example, network (5), $(S, C_K, R)$ is given by

$$7X_1 + X_2 \xrightleftharpoons{} X_3.$$ 

We define the kinetic-order subspace $S_K$ and the kinetic-order deficiency $\delta_K$ as the corresponding quantities for the reaction graph of $(S, C_K, R)$. For this example, we have $S_K = \text{span}\{(-7, -1, 1)\}$ and $\delta_K = 0$.

Given a weight set $K$, we define the generalized weighted chemical reaction network associated with $N$ and $K$ to be $N(K) = (S, C, C_K, R, K)$. The generalized mass action system corresponding to $N(K)$ is given by

$$\frac{dx}{dt} = Y \cdot A(K) \cdot \Psi_K(x) \tag{6}$$

where $\Psi_K(x)$ has entries $[\Psi_K(x)]_i = x^{(y_K)_i}$, $i = 1, \ldots, m$. In other words, a generalized mass action system is the mass action system (3) with the monomials $x^{y_i}$ replaced by the monomials $x^{(y_K)_i}$. For example, given the weight set $K = \{k(1, 2), k(2, 1)\}$, the generalized mass action system corresponding to the network (5) is

$$\frac{dx_1}{dt} = -\frac{dx_2}{dt} = -\frac{dx_3}{dt} = -k(1, 2)x_1^7x_2 + k(2, 1)x_3.$$ 

Notice that the stoichiometry of the network comes from the stoichiometric complexes $C$, but the monomials come from the kinetic complexes $C_K$. Results regarding the existence and location of steady states of generalized mass action systems have been considered by Müller and Regensburger (2012) and Müller et al. (2013) but will not be summarized here.

### 2.4 Source Complexes

It is clear that a complex is only associated with a monomial in (3) if it is at the tail end of a reaction edge. In exceptional cases, however, it is possible for such a complex to be omitted from (3) due to cancelation. For example, consider the network

$$2X_1 \xrightleftharpoons[k(1,2)]{k(2,1)} X_1 + X_2 \xrightleftharpoons[k(2,3)]{k(3,2)} 2X_2. \tag{7}$$

For $k(1, 2) = k(2, 1) = k(2, 3) = k(3, 2) = 1$, we have $(k(2, 1) - k(2, 3))x_1x_2 = 0$ so that $x_1x_2$ does not appear in the expanded form of (3).
For the theory developed in Sect. 3, we will be interested only in those complexes for which the coefficients of the corresponding monomials $x^y$ or $x^{(yk)^y}$ do not vanish after expanding (3) or (6). We introduce the following.

**Definition 5** Consider a regular or generalized weighted chemical reaction network $(N(K) = (S, C, \mathcal{R}, K)$ or $\tilde{N}(K) = (\tilde{S}, \tilde{C}, \tilde{\mathcal{R}}, K)$, respectively). We say that $C_i \in C$ is a **source complex** of $N(K)$ if

$$\sum_{j=1}^{m} k(i, j) (y_j - y_i) \neq 0.$$  \hfill (8)

The set of all source complexes in $N(K)$ will be denoted $\mathcal{C}(K)$.

Notice that the left-hand side of (8) is the coefficient vector in the expanded form of $Y \cdot A(K)$ in (3) [or (6)] for the $i^{th}$ entry of $\Psi(x)$ [respectively, $\Psi_K(x)$].

Definition 5 captures both (i) the notion of being the source of a reaction in the network, since $k(i, j) \neq 0$ only if $(i, j) \in \mathcal{R}$ and (ii) the requirement that the aggregate effect of all reactions from this complex be nontrivial. This terminology for source complex is more restrictive than typically considered in CRNT, which only requires (i).

Note also that $\mathcal{C}(K)$ may depend upon both the structure of $N(K)$ and the weight set $K$. For example, if we set $C_1 = 2X_1$, $C_2 = X_1 + X_2$, and $C_3 = 2X_2$ in (7), we have $\mathcal{C}(K) = \{1, 3\}$ for $k(1, 2) = k(2, 1) = k(2, 3) = k(3, 2) = 1$; however, we have $\mathcal{C}(K) = \{1, 2, 3\}$ for $k(1, 2) = k(2, 1) = k(3, 2) = 1$ and $k(2, 3) = 2$.

### 3 Weighted Translations

It was observed by Johnston (2014) that many mass action systems (3) have dynamically equivalent representations as generalized mass action systems (6). In cases where the network underlying the generalized mass action system is better structured (e.g., weakly reversible, lower deficiency), it may be beneficial to analyze the generalized system rather than the classical one. Consider the following example.

**Example 1** Consider the weighted chemical reaction network $N(K) = (S, C, \mathcal{R}, K)$ and the weighted generalized chemical reaction network $\tilde{N}(\tilde{K}) = (\tilde{S}, \tilde{C}, \tilde{\mathcal{R}}, \tilde{K})$ given, respectively, by:

$$N(K) = (S, C, \mathcal{R}, K)$$

\[
\begin{array}{c}
X_1 \xrightarrow{k_1} 2X_1 \\
X_1 + X_2 \xrightarrow{k_2} 2X_2 \\
X_2 \xrightarrow{k_3} \emptyset
\end{array}
\]  \hfill (9)

$$\tilde{N}(\tilde{K}) = (\tilde{S}, \tilde{C}, \tilde{\mathcal{R}}, \tilde{K})$$

\[
\begin{array}{c}
X_1 \cdots \emptyset \xrightarrow{\tilde{k}_1} X_1 \cdots X_1 + X_2 \\
\tilde{x}_3 \leftarrow \tilde{k}_2 \\
X_2 \cdots X_2
\end{array}
\]

It can be easily verified by expanding (3) or (6), respectively, that if we take $k_1 = \tilde{k}_1$, $k_2 = \tilde{k}_2$, and $k_3 = \tilde{k}_3$, then the mass action system corresponding to $N(K)$ and the generalized mass action system corresponding to $\tilde{N}(\tilde{K})$ are identical.
Johnston (2014) noted that the process of corresponding $\mathcal{N}(\mathcal{K})$ to $\tilde{\mathcal{N}}(\tilde{\mathcal{K}})$ could be visualized by “translating” the complexes of each reaction. For this example, we have

$$
\begin{align*}
X_1 &\rightarrow 2X_1 \ (\ -X_1 \ ) & \emptyset &\rightarrow X_1 \\
X_1 + X_2 &\rightarrow 2X_2 \ (\ -X_2 \ ) & \implies X_1 &\rightarrow X_2 \\
X_2 &\rightarrow \emptyset \ (\ +\emptyset \ ) & X_2 &\rightarrow \emptyset.
\end{align*}
$$

Notice that this process does not change the reaction vectors and that we may preserve the monomials in (3) by associating the source complexes of the original reactions as the kinetic complexes of the new ones [e.g., associate $X_1$ (left) as the kinetic complex of $\emptyset$ (right)]. If we transfer the weights with the reactions, we arrive at the generalized network in (9). Notice that $\tilde{\mathcal{N}}(\tilde{\mathcal{K}})$ is weakly reversible, while $\mathcal{N}(\mathcal{K})$ is not. This will be the primary network property identified when understanding “better” versus “poorer” structure.

Johnston (2014) also identified a class of systems for which (3) and (6) do not coincide but for which the steady states are identical (see Example 2 in Sect. 3.2). We introduce the following.

**Definition 6** Let $\mathcal{N}(\mathcal{K}) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$ denote a weighted chemical reaction network with corresponding mass action system (3), and $\tilde{\mathcal{N}}(\tilde{\mathcal{K}}) = (\tilde{\mathcal{S}}, \tilde{\mathcal{C}}, \tilde{\mathcal{K}}, \tilde{\mathcal{R}}, \tilde{\mathcal{K}})$ denote a generalized weighted chemical reaction network with corresponding generalized mass action system (6). We will say that $\mathcal{N}(\mathcal{K})$ and $\tilde{\mathcal{N}}(\tilde{\mathcal{K}})$ are

1. **dynamically equivalent** if (3) and (6) coincide, and
2. **steady state equivalent** if (3) and (6) have the same steady states.

We can see that the weighted networks in (9) of Example 1 are dynamically equivalent. Johnston (2014) called the process outlined in (10) network translation. In this paper, we adopt a modified definition of network translation which explicitly takes weight sets into account.

**Definition 7** Consider a weighted chemical reaction network $\mathcal{N}(\mathcal{K}) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$ with weight set $\mathcal{K} = \{k(i, j) \mid i, j = 1, \ldots, m\}$ and source complex set $\mathcal{C}(\mathcal{K})$, and a weighted generalized chemical reaction network $\tilde{\mathcal{N}}(\tilde{\mathcal{K}}) = (\tilde{\mathcal{S}}, \tilde{\mathcal{C}}, \tilde{\mathcal{K}}, \tilde{\mathcal{R}}, \tilde{\mathcal{K}})$ with weight set $\tilde{\mathcal{B}} = \{\tilde{b}(i', j') \mid i', j' = 1, \ldots, \tilde{m}\}$ and source complex set $\tilde{\mathcal{C}}(\tilde{\mathcal{B}})$.

We say $\tilde{\mathcal{N}}(\tilde{\mathcal{B}})$ is a **weighted translation** of $\mathcal{N}(\mathcal{K})$ if:

1. There is a surjection $h : \mathcal{C}(\mathcal{K}) \mapsto \tilde{\mathcal{C}}(\tilde{\mathcal{B}})$ such that the following two conditions hold:
   (a) For every $i' \in \tilde{\mathcal{C}}(\tilde{\mathcal{B}})$,

   $$
   \sum_{i \mid h(i) = i'} \sum_{j=1}^{m} k(i, j)(y_j - y_i) = \sum_{j'=1}^{\tilde{m}} \tilde{b}(i', j')(\tilde{y}_{j'} - \tilde{y}_{i'}). \tag{11}
   $$

   (b) For every $(i, j) \in \mathcal{R}$, we have

   $$
   y_j - y_i \in \text{cone}\left\{ y_{j'} - y_{i'} \mid h(i) = i' \text{ and } (i', j') \in \text{\tilde{R}} \right\}
   $$

\[\square\]
where \( \text{cone}\{v_1, \ldots, v_p\} \subseteq \mathbb{R}^n \) is the closed convex cone generated by \( \{v_1, \ldots, v_p\} \).

2. There is an injection \( h_K : \hat{\mathcal{C}}(\hat{\mathcal{B}}) \mapsto \mathcal{C}(\mathcal{K}) \) so that \( h(h_K(i')) = i' \) and \( (\hat{C}_K)i' = C_{h_K(i') \mathcal{K}} \) for all \( i' \in \hat{\mathcal{C}}(\hat{\mathcal{B}}) \).

The process of finding a generalized network \( \tilde{N} \) which is a weighted translation of \( N \) is called **weighted network translation**.

We interpret the conditions of Definition 7 as follows:

- **Condition 1.(a):** The mapping \( h \) assigns every source complex in the original network to a source complex in the translated network. Condition (11) guarantees that the “push” (aggregate weight and direction) out of each source complex in the translated network corresponds to the net push of all reactions out of all source complexes which are mapped to it through \( h \). That is, there is a conservation in pushes between the two networks.

- **Condition 1.(b):** The reaction vector \( y_j - y_i \in \mathbb{Z}^n \) of every reaction in the original network must be representable as a weighted sum of reaction vectors from the corresponding source complex in the translated network. This technical condition does not follow from 1.(a) alone and is only important if the weights need to be rescaled as a result of the translation being improper (see Definition 8).

- **Condition 2:** The mapping \( h_K \) assigns a kinetic complex to each source complex in the translated network. This kinetic complex is assigned from the pool of source complexes which are mapped to the complex by \( h \). Notice that, if multiple complexes in the original network are mapped to a single complex in the translated network, we may pick only one as the corresponding kinetic complex.

**Example 1** We make the assignments \( C_1 = X_1, C_2 = X_1 + X_2, C_3 = X_2, C_4 = 2X_1, C_5 = 2X_2, C_6 = \emptyset, \hat{C}_1 = \emptyset, \hat{C}_2 = X_1, \) and \( \hat{C}_3 = X_2 \). We can satisfy the requirements on \( h \) and \( h_K \) given in Definition 7 by taking \( h(1) = 1, h(2) = 2, h(3) = 3, h_K(1) = 1, h_K(2) = 2, \) and \( h_K(3) = 3 \) so that \( (\hat{C}_K)_1 = C_1 = X_1, (\hat{C}_K)_2 = C_2 = X_1 + X_2, \) and \( (\hat{C}_K)_3 = C_3 = X_2 \) (condition 2). Conditions 1.(a) and (b) are satisfied by taking \( \hat{b}(1, 2) = k_1, \hat{b}(2, 3) = k_2, \) and \( \hat{b}(3, 1) = k_3 \), and we are done.

**Remark 5** Following the conventions of Johnston (2014), we distinguish objects and sets related to translations with the tilde notation (\( \tilde{\cdot} \)), e.g., \( \tilde{L} \in \tilde{\mathcal{L}} \) for linkage classes, \( \tilde{m} = |\tilde{\mathcal{C}}| \) for the number of complexes. In particular, we will denote the structural and kinetic deficiencies of translations by \( \delta \) and \( \delta_K \), respectively, and denote the kinetic-order subspace by \( \tilde{SK} \). Wherever possible, we will distinguish the indices of the translated complexes by primes, e.g., \( i', j' = 1, \ldots, \tilde{m}, (i', j') \in \tilde{R} \). We note that this notation differs from that used by Müller and Regensburger (2012).

**Remark 6** In general, the weight set \( \hat{\mathcal{B}} \) in Definition 7 consists of computational constructs which encode the structure of the translation but do not necessarily correspond to the weights for any meaningful generalized mass action system. We will reserve the symbol \( \hat{\mathcal{K}} \) for weight sets for which the weighted generalized network \( \hat{N} (\hat{\mathcal{K}}) \) is either dynamically or steady state equivalent to the original weighted network \( N(\mathcal{K}) \).
The stoichiometric and kinetic-order subspaces $\tilde{S}$ and $\tilde{S}_K$ of translated chemical reaction networks are characterized by the following result.

**Lemma 1** (Lemma 1, Johnston 2014) Suppose $\tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$ is a weighted translation of a weighted chemical reaction network $N(K) = (S, C, R, K)$. Then, if $\tilde{N}$ is weakly reversible, the stoichiometric subspaces $S$ of $N$ and $\tilde{S}$ of $\tilde{N}$ coincide and the kinetic-order subspace $\tilde{S}_K$ of $\tilde{N}$ is given by

$$\tilde{S}_K = \text{span} \left\{ (\tilde{y}_K)_{i'} - (\tilde{y}_K)_{j'} \mid i', j' \in \tilde{L}_\theta, \theta = 1, \ldots, \tilde{\ell} \right\}$$

where $\tilde{L}_\theta, \theta = 1, \ldots, \tilde{\ell}$, are the linkage classes of $\tilde{N}$.

**Proof** The result follows from the proof of Lemma 1 of Johnston (2014) and the fact that, since the network is weakly reversible, the kinetic and stoichiometric subspaces of $\tilde{N}$ coincide by Corollary 1 of Feinberg and Horn (1977). (Note here that we define the kinetic subspace as in Feinberg and Horn (1977) and that this is not the same object as the kinetic-order subspace $\tilde{S}_K$.) \qed

### 3.1 Proper Weighted Translations

An important subset of weighted translations is the following, which is modified from Definition 7 in Johnston (2014) to accommodate weights.

**Definition 8** Consider a weighted chemical reaction network $N(K) = (S, C, R, K)$ and a weighted translation $\tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$. We will say $\tilde{N}(\tilde{B})$ is a **proper weighted translation** of $N(K)$ if $h : C(K) \mapsto \tilde{C}(\tilde{B})$ is injective as well as surjective. A weighted translation $\tilde{N}(\tilde{B})$ will be called **improper** if it is not proper.

That is, a weighted translation is proper if every source complex in $N(K)$ corresponds to exactly one source complex in $\tilde{N}(\tilde{B})$. Notice that, if $\tilde{N}$ is proper, condition 1.(a) implies condition 1.(b) in Definition 7. For proper translations, we also have $h_K = h^{-1}$.

**Lemma 2** (Lemma 2, Johnston 2014) Suppose $\tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$ is a proper weighted translation of the weighted chemical reaction network $N(K) = (S, C, R, K)$. Then the weighted network $\tilde{N}(\tilde{K}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{K})$ with $\tilde{K} = \tilde{B}$ is dynamically equivalent to $N(K)$.

**Proof** The result follows immediately from the proof of Lemma 2 in Johnston (2014) and Definition 6. \qed

**Example 1** Since there is a one-to-one correspondence between the source complexes of $N(K)$ and $\tilde{N}(\tilde{K})$, the translation scheme (10) in Example 1 results in a proper translation (9). It was previously noted that the two weighted networks have the same dynamics. This is consistent with the application of Lemma 2. \qed
3.2 Improper Weighted Translations

It was noted by Johnston (2014) that any generalized mass action system (6) corresponding to an improper translation $\tilde{N}(\tilde{\mathcal{B}}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$ must necessarily differ from the mass action system (3) corresponding to the original network $N(K) = (S, C, R, K)$. A result analogous to Lemma 2 is therefore not possible. Nevertheless, Johnston (2014) gave conditions under which a rescaled weight set $\tilde{K}$ could be constructed so that $N(K)$ and $\tilde{N}(\tilde{K})$ shared the same steady state set. Consider the following example.

**Example 2** Consider the weighted chemical reaction network $N(K)$ with weight set $K = \{k_i > 0 \mid i = 1, \ldots, 14\}$ corresponding to the reactions as labeled:

\[
\begin{align*}
X_1 & \overset{1}{\rightleftharpoons} X_2 \overset{3}{\rightarrow} X_3 \rightarrow X_4 \\
X_4 + X_5 & \overset{6}{\rightarrow} X_6 \overset{8}{\rightarrow} X_2 + X_7 \\
X_3 + X_7 & \overset{9}{\rightarrow} X_8 \overset{11}{\rightarrow} X_3 + X_5 \\
X_1 + X_7 & \overset{12}{\rightarrow} X_9 \overset{14}{\rightarrow} X_1 + X_5.
\end{align*}
\]

This network was introduced as a model of the EnvZ/OmpR signaling pathway in *Escherichia coli* by Shinar and Feinberg (2010) and was subsequently studied by Pérez Millán et al. (2012). (Further details are contained in the Supplemental Material.) It was noted by Johnston (2014) that the translation scheme

\[
\begin{align*}
X_1 & \overset{1}{\rightleftharpoons} X_2 \overset{3}{\rightarrow} X_3 \rightarrow X_4 \\
X_4 + X_5 & \overset{6}{\rightarrow} X_6 \overset{8}{\rightarrow} X_2 + X_7 \\
X_3 + X_7 & \overset{9}{\rightarrow} X_8 \overset{11}{\rightarrow} X_3 + X_5 \\
X_1 + X_7 & \overset{12}{\rightarrow} X_9 \overset{14}{\rightarrow} X_1 + X_5
\end{align*}
\]

yields the following translation $\tilde{N}(\tilde{B})$, where $\tilde{b}_i = k_i$, $i = 1, \ldots, 14$, in Definition 7

\[
\begin{align*}
2X_1 + X_3 + X_5 & \overset{1}{\rightleftharpoons} X_1 + X_2 + X_3 + X_5 \overset{3}{\rightarrow} X_1 + 2X_3 + X_5 \\
X_2 + X_3 + X_9 & \overset{13}{\downarrow} X_1 + X_2 + X_8 \overset{11}{\uparrow} X_1 + X_3 + X_4 + X_5 \overset{5}{\rightarrow} X_1 + X_2 + X_3 + X_7 \overset{8}{\leftarrow} X_1 + X_3 + X_6.
\end{align*}
\]
and the kinetic complexes may be chosen according to (13). The translated network \( \tilde{N}(\tilde{B}) \) is improper since the source complexes \( X_3 + X_7 \) and \( X_1 + X_7 \) are both translated to \( X_1 + X_2 + X_3 + X_7 \). We may only assign one as the corresponding kinetic complex. Regardless of the choice of kinetic complex corresponding to \( X_1 + X_2 + X_3 + X_7 \), the generalized system (6) corresponding to (14) is not dynamically equivalent to the system (3) corresponding to (12).

It was shown by Johnston (2014), however, that if we choose \( X_3 + X_7 \) as the kinetic complex of the stoichiometric complex \( X_1 + X_2 + X_3 + X_7 \), then the weighted networks \( N(K) \) and \( \tilde{N}(\tilde{B}) \) given in (12) and (14), respectively, are steady state equivalent for \( \tilde{k}_i = k_i, i = 1, \ldots, 14, i \neq 12, \) and

\[
\tilde{k}_{12} = \left( \frac{k_2 (k_4 + k_5)}{k_1 k_3} \right) k_{12}.
\]

In other words, the systems (3) and (6) coincide at steady state after a rescaling of the rate parameter \( k_{12} \). Notice importantly that the set \( \tilde{K} \) does not satisfy (11) and that substituting the set \( \tilde{B} \) in (6) does not produce a system which is steady state equivalent with (3). That is, while corresponding to the same network structure, the weight sets \( \tilde{K} \) and \( \tilde{B} \) serve distinct and non-interchangeable functions.

3.3 Sufficient Conditions for Steady State Resolvability

In this section, we consider the following problem: Given a chemical reaction network \( N(K) \) and an improper translation \( \tilde{N}(\tilde{B}) \), are there sufficient conditions on the reaction graph of the translation alone which guarantee that \( \tilde{N}(\tilde{B}) \) is steady state resolvable with \( N(K) \)? This approach differs from that taken by Johnston (2014) where the resolvability conditions were algebraic in nature. We will answer the question affirmatively with Theorem 1. We use Example 2 introduced in Sect. 3.2 as a running example.

We begin by introducing the following definitions.
**Definition 10** Suppose $\tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$ is a weighted improper translation of a weighted chemical reaction network $N(\kappa) = (S, C, R, K)$. Then:

1. The **improper complex set** $\tilde{C}_I \subseteq \tilde{C}(\tilde{B})$ is given by
   \[
   \tilde{C}_I = \{ k' \in \tilde{C}(\tilde{B}) \mid h(i) = h(j) = k' \text{ for some } i, j \in C(\kappa), i \neq j \}. \tag{15}
   \]

2. The $k'$-**unresolved complex set** $h^{-1}(k') \subseteq C(\kappa)$ is given by
   \[
   h^{-1}(k') = \{ i \in C(\kappa) \mid h(i) = k' \text{ where } k' \in \tilde{C}_I \}. \tag{16}
   \]

3. The **improper subspace** $\tilde{S}_I$ of $\tilde{N}(\tilde{B})$ is given by
   \[
   \tilde{S}_I = \text{span} \left\{ y_j - y_i \mid i, j \in h^{-1}(k') \text{ where } k' \in \tilde{C}_I \right\}. \tag{17}
   \]

Note that the improper subspace $\tilde{S}_I$ has been introduced previously (Definition 9, Johnston 2014) but differs notationally here. It can easily be checked that the two definitions are equivalent.

**Example 2** Consider the weighted network $N(\kappa)$ given by (12) and the generalized weighted network given by $\tilde{N}(\tilde{B})$. We index the complexes of $N(\kappa)$ according to:

\[
\begin{align*}
C_1 &= X_1, \quad C_2 = X_2, \quad C_3 = X_3, \quad C_4 = X_4 + X_5, \quad C_5 = X_6, \\
C_6 &= X_3 + X_7, \quad C_7 = X_8, \quad C_8 = X_1 + X_7, \quad C_9 = X_9, \\
C_{10} &= X_4, \quad C_{11} = X_2 + X_7, \quad C_{12} = X_3 + X_5, \quad C_{13} = X_1 + X_5.
\end{align*}
\]

and the complexes of $\tilde{N}(\tilde{B})$ according to:

\[
\begin{align*}
\tilde{C}_1 &= 2X_1 + X_3 + X_5, \quad \tilde{C}_2 = X_1 + X_2 + X_3 + X_5, \quad \tilde{C}_3 = X_1 + 2X_3 + X_5, \\
\tilde{C}_4 &= X_1 + X_3 + X_4 + X_5, \quad \tilde{C}_5 = X_1 + X_3 + X_6, \quad \tilde{C}_6 = X_1 + X_2 + X_3 + X_7, \\
\tilde{C}_7 &= X_1 + X_2 + X_8, \quad \tilde{C}_8 = X_2 + X_3 + X_9.
\end{align*}
\]

We furthermore index the kinetic complex set $\tilde{C}_K$ according to:

\[
\begin{align*}
(\tilde{C}_K)_1 &= X_1, \quad (\tilde{C}_K)_2 = X_2, \quad (\tilde{C}_K)_3 = X_3, \quad (\tilde{C}_K)_4 = X_4 + X_5, \\
(\tilde{C}_K)_5 &= X_6, \quad (\tilde{C}_K)_6 = X_3 + X_7, \quad (\tilde{C}_K)_7 = X_8, \quad (\tilde{C}_K)_8 = X_9.
\end{align*}
\tag{18}
\]

Notice that we have chosen $(\tilde{C}_K)_6 = C_6 = X_3 + X_7$ but could have chosen $(\tilde{C}_K)_6 = C_8 = X_1 + X_7$ by condition 2. of Definition 7. Since we have $h(6) = 6$ and $h(8) = 6$, it follows by (15), (16), and (17), that $\tilde{C}_I = \{6\}$, $h^{-1}(6) = \{6, 8\}$, and $\tilde{S}_I = \text{span}\{y_8 - y_6\} = \text{span}\{(1, 0, -1, 0, 0, 0, 0, 0)\}$. □

The relationship between the kinetic-order subspace $\tilde{S}_K$ and the improper subspace $\tilde{S}_I$ is known to be crucial in obtaining steady state resolvability of $\tilde{N}(\tilde{B})$ (Johnston 2014). We therefore introduce the following.
**Definition 11** Let $\tilde{N} (\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$ be an improper weighted translation of a weighted chemical reaction network $N (K) = (S, C, R, K)$. Suppose furthermore that $\tilde{N}$ is weakly reversible and that $\tilde{S}_I \subseteq \tilde{S}_K$. Then we say $\tilde{C}_R \subseteq \tilde{C} (\tilde{B})$ is a **resolving complex set** of $\tilde{N} (\tilde{B})$ if, for every $i, j \in h^{-1}(k')$ where $k' \in \tilde{C}_I$, there is a set of constants $c(i', j'), i', j' = 1, \ldots, \tilde{m}, i' < j'$, such that:

1. $y_j - y_i = \sum_{i':j'=1}^{\tilde{m}} c(i', j') (\tilde{y}_K (j') - \tilde{y}_K (i'))$;
2. $c(i', j') \neq 0$ implies $i', j' \in \tilde{L}_\theta$ for some linkage class $\tilde{L}_\theta$ of $\tilde{N} (\tilde{B})$; and
3. $c(i', j') \neq 0$ implies $i', j' \in \tilde{C}_R$.

**Remark 7** Resolving complex sets $\tilde{C}_R$ are not unique. In particular, any superset of a resolving complex set is also a resolving complex set. This will not be a concern for the computational procedure presented in Sect. 4 since, if required, we will be able to determine a minimal resolving complex set.

**Remark 8** A resolving complex set $\tilde{C}_R$ corresponds to a choice of kinetic complexes which relate the vectors in $\tilde{S}_I$ to those in $\tilde{S}_K$. Note that $\tilde{S}_I \subseteq \tilde{S}_K$ gives a sufficient condition for $\tilde{C}_R \neq \emptyset$. Condition 2 follows from (Lemma 3, Johnston 2014) and Lemma 2 here.

**Example 2** By (18) we have that

$$y_8 - y_6 = (1, 0, -1, 0, 0, 0, 0, 0) = (\tilde{y}_K)_1 - (\tilde{y}_K)_3. \tag{19}$$

It follows that we may satisfy condition 1. of Definition 11 by choosing $c(1, 3) = 1$ and $c(i', j') = 0$ for all other $i', j' = 1, \ldots, 8$. We may therefore take $\tilde{C}_R = \{1, 3\}$ as our resolving constant set.

Intuitively, at steady state we may “resolve” the competition between the two complexes translated to $\tilde{C}_6$ by appealing to the resolving kinetic complexes $(\tilde{C}_K)_1 = X_1$ and $(\tilde{C}_K)_3 = X_3$. Rearranging condition (19) gives

$$x^{38} = \left(\frac{x^{\tilde{y}_K}_1}{x^{\tilde{y}_K}_3}\right) x^{36} \implies x_1 x_7 = \left(\frac{x_1}{x_3}\right) x_3 x_7.$$ 

The key insight is that the monomials $x_1, x_3$, and $x_3 x_7$ correspond to kinetic complexes in (18), while the monomial $x_1 x_7$ does not. This is the monomial which needs to be “resolved” since it appears in the original equations (3) but not in the generalized equations (6). \hfill $\Box$

We now state the main technical result of the paper (Theorem 1). We also present an alternative statement which is more amenable to the computational procedures of Sect. 4 (Corollary 1). Proofs of Theorem 1, and its equivalence to Corollary 1, can be found in “Appendix 2”.
**Theorem 1** Let \( \tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B}) \) denote an improper weighted translation of a weighted chemical reaction network \( \tilde{N}(\tilde{K}) = (\tilde{S}, \tilde{C}, \tilde{R}, \tilde{K}) \). Suppose that \( \tilde{N} \) is weakly reversible, \( \delta = 0 \), \( \tilde{S}_I \subseteq \tilde{S}_K \) and that there is a resolving complex set \( \tilde{C}_R \) satisfying \( \tilde{C}_I \cap \tilde{C}_R = \emptyset \), where \( \tilde{C}_I \) is the improper complex set of \( \tilde{N}(\tilde{B}) \). Suppose furthermore that \( \tilde{C}_I \) and \( \tilde{C}_R \) satisfy the following property:

\(*(\star)\ For every \( C' \in \tilde{C}_I \), there is a \( C' \in \tilde{C}(\tilde{B}) \), \( k' \neq p' \), such that, if \( P \) is a path from \( \tilde{C}_P \) to \( \tilde{C}_I' \) where \( C_i' \in \tilde{C}_R \), then \( P \) goes through \( \tilde{C}_R' \).

Then \( \tilde{N}(\tilde{K}) \) and \( \tilde{N}(\tilde{B}) \) are steady state resolvable.

This result says that, given the other technical requirements, a translation is resolvable if, for any given improper complex, every path to a resolving complex goes through a common complex. It is worth noting similarities in condition \(*(\star)\) and those of conditions (14–16) of Boros (2013), although no deeper connection is known to the author at present.

The following result is equivalent to Theorem 1.

**Corollary 1** Let \( \tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B}) \) denote an improper weighted translation of a weighted chemical reaction network \( \tilde{N}(\tilde{K}) = (\tilde{S}, \tilde{C}, \tilde{R}, \tilde{K}) \). Suppose that \( \tilde{N} \) is weakly reversible, \( \delta = 0 \), and \( \tilde{S}_I \subseteq \tilde{S}_K \). Suppose furthermore that there are complex sets \( \tilde{C}^* \), \( \tilde{C}^{**} \subseteq \tilde{C} \), and reaction sets \( \tilde{R}^* \subseteq \tilde{R} \) and \( \tilde{R}^{**} \subseteq \tilde{C}^{**} \times \tilde{C}^* \) such that:

1. \( \tilde{C}_I \subseteq \tilde{C}^* \) and \( \tilde{C}_R \cap \tilde{C}^* = \emptyset \);
2. \( (i', j') \in \tilde{R}^* \) if and only if \( i' \in \tilde{C}^* \) and \( (i', j') \in \tilde{R}^* \);
3. \( |\tilde{C}^{**}| = |\tilde{C}^*| \) where \( \tilde{C}^* \) is the set of linkage classes of the network \( (\tilde{S}, \tilde{C}^* \cup \tilde{C}^{**}, \tilde{R}^* \cup \tilde{R}^{**}) \); and
4. The network \( (\tilde{S}, \tilde{C}^* \cup \tilde{C}^{**}, \tilde{R}^* \cup \tilde{R}^{**}) \) is weakly reversible.

Then \( \tilde{N}(\tilde{K}) \) and \( \tilde{N}(\tilde{B}) \) are steady state resolvable.

The conditions of Corollary 1 may be understood in the following way. After determining \( \tilde{C}_I \) and \( \tilde{C}_R \), we construct subcomponents by following paths beginning at the complexes in \( \tilde{C}_I \) (conditions 1.–2.). If these paths coalesce before reaching \( \tilde{C}_R \), the component may be made weakly reversible by adding reactions from these sinks back to their source(s) (conditions 3.–4.). The proof of the equivalence between Theorem 1 and Corollary 1 is contained in “Appendix 2”.

**Example 2** We have that \( \tilde{C}_I = \{6\} \) and \( \tilde{C}_R = \{1, 3\} \). It is clear that \( \tilde{C}_I \cap \tilde{C}_R = \emptyset \) and it can be computed from (14) that \( \delta = 0 \). The translation therefore satisfies the technical conditions of both Theorem 1 and Corollary 1.

To verify \(*(\star)\) of Theorem 1, we note that every path from \( \tilde{C}_6 \) to either \( \tilde{C}_1 \) or \( \tilde{C}_3 \) goes through \( \tilde{C}_2 \) (see Fig. 1b). It follows that \( k' = 2 \) in condition \(*(\star)\), so that we may apply Theorem 1 to guarantee that \( N(\tilde{K}) \) and \( N(\tilde{B}) \) are steady state resolvable.

To verify the conditions 1.–4. of Corollary 1, we note that we may construct the network \( (\tilde{S}, \tilde{C}^* \cup \tilde{C}^{**}, \tilde{R}^* \cup \tilde{R}^{**}) \) as given in Fig. 1c. We identify \( \tilde{C}^* = \{6, 7, 8\} \) (pink), \( \tilde{C}^{**} = \{2\} \) (green), \( \tilde{R}^* = \{(6, 7), (6, 8), (7, 2), (7, 6), (8, 2), (8, 6)\} \) (solid red arrows), and \( \tilde{R}^{**} = \{(2, 6)\} \) (dotted red arrow). It is clear that \( |\tilde{C}^{**}| = |\tilde{C}^*| \) and \( (\tilde{S}, \tilde{C}^* \cup \tilde{C}^{**}, \tilde{R}^* \cup \tilde{R}^{**}) \) are weakly reversible. Notice that \( \tilde{C}^* \) does not contain any
In Fig. 1, we show the improper weighted network $\tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{C}_K, \tilde{R}, \tilde{B})$ corresponding to Example 2. In (b), we show that every path from $\tilde{C}_6$ to either $\tilde{C}_1$ or $\tilde{C}_3$ goes through $\tilde{C}_2$ so that condition $(\ast)$ of Theorem 1 is satisfied. In (c), we show the weakly reversible network $(\tilde{S}, \tilde{C}_* \cup \tilde{C}_**, \tilde{R}_* \cup \tilde{R}_**) \text{ consistent with the application of Corollary 1}$ (Color figure online)
4.1 Initialization of MILP procedure

Suppose we have a weighted chemical reaction network $\mathcal{N}(\mathcal{K}) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$ and wish to determine a weighted translation $\mathcal{N}(\hat{\mathcal{B}}) = (\hat{\mathcal{S}}, \hat{\mathcal{C}}, \hat{\mathcal{K}}, \hat{\mathcal{R}}, \hat{\mathcal{B}})$. We first reorder the complexes of $\mathcal{C}$ so that the first $q = |\mathcal{C}(\mathcal{K})|$ complexes correspond to be source complexes. We let $\hat{m}$ denote the number of potential source complexes $\hat{\mathcal{C}}(\hat{\mathcal{B}})$. We initialize the following matrices:

1. The matrix $Y \in \mathbb{Z}_{\geq 0}^{q \times n}$ with entries $[Y]_{i, j} = y_{i, j}$ where $y_{i, j} \geq 0$, are the stoichiometric vectors of the source complexes $\mathcal{C}(\mathcal{K})$.
2. The matrix $\hat{Y} \in \mathbb{Z}_{\geq 0}^{\hat{m} \times n}$ with entries $[\hat{Y}]_{i, j} = \hat{y}_{i, j}$ where $\hat{y}_{i, j} \geq 0$, are the stoichiometric vectors of the potential set of source complexes $\hat{\mathcal{C}}(\hat{\mathcal{B}})$.
3. The matrix $M \in \mathbb{R}^{q \times n}$ with entries $[M]_{i, j} = [Y \cdot A(\mathcal{K})]_{i, j}$, where $A(\mathcal{K})$ is the Kirchhoff matrix of $\mathcal{N}(\mathcal{K})$. That is, it is the restriction of $Y \cdot A(\mathcal{K})$ to the source complex set $\mathcal{C}(\mathcal{K})$.

We note the following:

- The source complexes $\hat{\mathcal{C}}(\hat{\mathcal{B}})$ which compose $\hat{Y}$ need not overlap with the source complexes $\mathcal{C}(\mathcal{K})$ which compose $Y$ as they did in Szederkényi et al. (2010, 2011, 2012a, 2012b, 2012, 2013, 2014). We leave the selection of the candidate stoichiometric complexes as an avenue for future work.
- The complexes in $\hat{Y}$ may not appear in any reaction selected by the computational algorithm and therefore may not appear in $\mathcal{N}(\hat{\mathcal{B}})$. This is a slight abuse of convention within CRNT literature but will be allowed in the present context. It was shown by Johnston et al. Johnston et al. (2013) that this abuse of convention does not alter the deficiency of the network or the property of weak reversibility.
- In contrast to the results of Johnston (2014), the method presented here determines a translation for a specific set of weights only. In particular, the weights of $\mathcal{N}(\mathcal{K})$ must be numeric rather than symbolic. The numerical procedure presented here, however, may inform subsequent symbolic analysis.

4.2 Implementing Proper and Improper Translations

In this section, we derive the necessary logical relations to guarantee that the conditions of Definition 7 are satisfied. We introduce decision variables $H[i, j'] \in \{0, 1\}$, so that

\[ \begin{cases} H[i, j'] = 1, & \text{if and only if } h(i) = j', \\ \hat{b}[i', j'] > 0, & \text{if and only if } (i', j') \in \hat{R} \end{cases} \tag{20} \]

We can accommodate (20) and (11) with the constraint set (Trl1) where $\hat{A}(\hat{\mathcal{B}})$ is the matrix with off-diagonal entries $[\hat{A}(\hat{\mathcal{B}})]_{i', j} = \hat{b}[j', i']$, $i' \neq j'$, and $H \in \mathbb{R}^{\hat{m} \times q}$ is the matrix with entries $H_{i,j'} = H[i, j']$. We can further restrict to proper translations by imposing the constraint set (Trl2).

In order to satisfy condition 1\,(b) of Definition 7, we introduce variables $\lambda[i, j'] \geq 0$, so that $\lambda[i, j'] > 0$, $i = 1, \ldots, q$, $j' = 1, \ldots, \hat{m}$, and the constraint set (Trl3) where $\Lambda \in \mathbb{R}^{\hat{m} \times q}$ is the
matrix with entries $\Lambda_{j',i} = \lambda[i, j']$. Notice that this constraint set is only distinct from (Trl1) if we are allowing improper translations. Consequently, if we are interested only in proper translations, we use (Trl1) and (Trl2), and if we are interested in improper translations (or do not care which is attained), we use (Trl1) and (Trl3).

4.3 Implementing Weak Reversibility

In this section, we reiterate the results of Johnston et al. for guaranteeing that the translation is weak reversibility (2012b) and that it has the minimal structural deficiency (2013).

In order to guarantee $\tilde{N}(\tilde{B})$ is weakly reversible, we introduce decision variables $\tilde{w}[i', j'] \geq 0, i', j' = 1, \ldots, \tilde{m}, i' \neq j'$, so that

$$
\begin{align*}
\tilde{w}[i', j'] &> 0, \quad \text{if and only if } (i', j') \in \tilde{R} \\
1 \cdot \tilde{A}(\tilde{V}) &\equiv 0, \quad \text{for } 1 = (1, \ldots, 1), \quad 0 = (0, \ldots, 0) \quad (21)
\end{align*}
$$

where $\tilde{A}(\tilde{V})$ is the matrix with off-diagonal entries $[\tilde{A}(\tilde{V})]_{i', j'} = \tilde{w}[j', i'], i' \neq j'$. The matrix $\tilde{A}(\tilde{V})$ has the same structure as $\tilde{A}(\tilde{B})$ but has been scaled along its columns (Johnston et al. 2012b). The logical requirements (21) can be accommodated by the constraint set (WR).

We now introduce decision variables capable of calculating the deficiency of a chemical reaction network. It was observed by Johnston et al. (2013) that $m$ and $s$ are fixed prior to the optimization begin, so that to determine the deficiency, it suffices to calculate the number of linkage classes. It also follows by the well-known property $\delta = m - s - \ell \geq 0$ that $\ell \leq m - s$. Since we have $\tilde{s} = s$ for weakly reversible network translations by Lemma 1, it is sufficient to allow at most $\tilde{\ell} = \tilde{m} - s$ linkage classes. We introduce decision variables $\gamma[i', \theta] \in \{0, 1\}, i' = 1, \ldots, \tilde{m}, \theta = 1, \ldots, \tilde{m} - s$, and $\tilde{L}[\theta] \in \{0, 1\}, \theta = 1, \ldots, \tilde{m} - s$, so that

$$
\begin{align*}
\gamma[i', \theta] & = 1, \quad \text{if and only if } i' \in \tilde{L}[\theta] \\
\tilde{L}[\theta] & = 1, \quad \text{if and only if } \tilde{L}[\theta] \neq \emptyset \\
\tilde{w}[i', j'] & > 0, \quad \text{for } i' \neq j' \text{ implies } i', j' \in \tilde{L}[\theta] \text{ for some } \theta \in \{1, \ldots, \tilde{m} - s\} \quad (22)
\end{align*}
$$

where $\tilde{L}[\theta], \theta = 1, \ldots, \tilde{m} - s$, are the (potential) linkage classes of $\tilde{N}(\tilde{B})$.

The variables $\gamma[i', \theta]$ keep track of which complexes are assigned to which linkage class, while the variables $\tilde{L}[\theta]$ keep track of whether a particular linkage classes has complexes in it. It is worth noting that unused complexes in the potential complex set are assigned to their own isolated linkage classes. This is a slight abuse of chemical reaction network convention but will be allowed in the present context. It was noted by Johnston et al. (2013) that allowing isolated linkage classes does not alter the network property of weak reversibility or the value of the deficiency. The final requirement of (22) guarantees that no reaction may proceed between complexes on different linkage classes.
It was also noted by Johnston et al. (2013) that the assignment of complexes to linkage classes is not unique since any permutation of the assignment of linkage classes corresponds to the same network. This can be a significant problem for the efficiency of mixed-integer programming methods. We therefore require that partition structure, if it can be found, is unique. This uniqueness requirement and (22) can be accommodated with the constraint set (Def).

We may now find the weakly reversible weighted translated chemical reaction network with the underlying reaction network with the minimal deficiency by optimizing (MinDef) over the constraint (Trl1), (Trl3), (WR), and (Def). If we are only interested in proper weighted translations, we may substitute the constraint set (Trl2) in place of (Trl3).

4.4 Implementing Steady State Resolvability

In this section, we develop constraint sets which guarantee that the conditions of Corollary 1 are satisfied for improper translations. We will divide this into the three steps.

Step 1: Determine constants $c(i', j')$ consistent with Definitions 10 and 11: It will not be necessary to assign decision variables to track $\tilde{C}_I$ and $\tilde{C}_R$ specifically. We will instead build conditions which will accurately determine the constants $c(i', j')$ in Definition 11. Note first of all, however, that the complex vectors relevant to condition 1. of Definition 11 are found in the matrix $\tilde{Y}$ rather than $\tilde{Y}$. We therefore define the variables $c[i, j] ≥ 0$, $i, j = 1, \ldots, q$, $i \neq j$, and require that $c[i, j] > 0$ if and only if $h(i) = i'$, $h(j) = j'$, and either $c(i', j') \neq 0$ or $c(j', i') \neq 0$.

To track the improper and resolving complex sets, $\tilde{C}_I$ and $\tilde{C}_R$, we introduce the variables

$$
\begin{align*}
\delta_I[i, j] \in \{0, 1\}, & \quad i, j = 1, \ldots, q, i < j \\
\delta_K[i, j] \in \{0, 1\}, & \quad i, j = 1, \ldots, q, i < j \\
\gamma_K[i, \theta] \in \{0, 1\}, & \quad i = 1, \ldots, q, \theta = 1, \ldots, \tilde{m} - s.
\end{align*}
$$

The variables $\delta_I[i, j]$ track the supports of the complexes in $Y$ which are mapped through $h$ to $\tilde{C}_I$ (left-hand sides of condition 1. of Definition 11), while variables $\delta_R[i, j]$ track the supports of the complexes in $Y$ which are mapped through $h$ to $\tilde{C}_R$ (right-hand sides of condition 1. of Definition 11). The variables $\gamma_K[i, \theta]$ correspond to the linkage classes in $\tilde{N}(\tilde{B})$ to the supports of the complexes in $Y$ so that condition 2. of Definition 11 may be imposed.

In order to limit the number of variables in the system, we attempt to satisfy condition 1. of Definition 11 simultaneously over all pairs $i, j \in h^{-1}(k')$ where $k' \in \tilde{C}_I$. We introduce a stochastic parameter $v[i, j] \in [\sqrt{\epsilon}, 1/\sqrt{\epsilon}], i, j = 1, \ldots, q, i < j$, and consider the $v[i, j]$-weighted sum of the conditions in condition 1. of Definition 11. The introduction of the parameter stochastic parameter $v[i, j]$ makes it almost
certain that linear dependence does not become an issue when summing over the left-hand sides of condition 1 of Definition 11. The parameters are chosen over the range $[\sqrt{\varepsilon}, 1/\sqrt{\varepsilon}]$ rather than $[\varepsilon, 1/\varepsilon]$ for numerical stability.

In order to satisfy the requirements of Definition 10 and 11, we require the following logical relations:

$$
\begin{align*}
\delta_I[i, j] &= 1, & \text{if and only if } h(i) = k' \text{ and } h(j) = k' \text{ for some } k' \in \tilde{C}_I \\
\delta_K[i, j] &= 1, & \text{if and only if } c(i, j) > 0 \text{ or } c(j, i) > 0 \\
\gamma_K[i, \theta] &= 1, & \text{if and only if } h(i) = k' \text{ and } k' \in \tilde{L}_\theta
\end{align*}
$$

We can accommodate the requirements of (23) with the constraint set (Rsl1).

Step 2: (conditions 1,–2. of Corollary 1): We introduce the decision variables $\tilde{C}*[i'] \in \{0, 1\}, i' = 1, \ldots, \tilde{m}$, and $\tilde{b}*[i', j'] \geq 0, i', j' = 1, \ldots, \tilde{m}, i' \neq j'$, and impose

$$
\begin{align*}
\tilde{C}*[i'] &= 1, & \text{if and only if } i' \in \tilde{C}^* \\
\tilde{b}*[i', j'] &> 0, & \text{if and only if } (i', j') \in \tilde{R}^*.
\end{align*}
$$

We want $\tilde{C}^*$ to restrict the supports of $\tilde{C}_I$ and $\tilde{C}_R$ according to condition 1. of Corollary 1. We also want $\tilde{C}^*$ and the reaction network $\tilde{R}$ to restrict $\tilde{R}^*$ according to condition 2. of Corollary 1. We can accomplish this with the constraint set (Rsl2).

Step 3: (conditions 3. – 4. of Corollary 1): We introduce the decision variables

$$
\begin{align*}
\tilde{C}**[i'] &\in \{0, 1\}, & i' = 1, \ldots, \tilde{m} \\
\tilde{b}**[i', j'] &\geq 0, & i', j' = 1, \ldots, \tilde{m}, i' \neq j' \\
\gamma^*[i', \theta] &\geq 0, & i' = 1, \ldots, \tilde{m}, \theta = 1, \ldots, \tilde{\ell}^* \\
\tilde{L}^*[\theta] &\in \{0, 1\}, & \theta = 1, \ldots, \tilde{\ell}^*
\end{align*}
$$

where $\tilde{\ell}^*$ is a predetermined upper limit on the number of linkage classes of $(\tilde{S}, \tilde{C}^* \cup \tilde{C}**, \tilde{R}^* \cup \tilde{R}**)$. Note that this may be strictly larger than $\tilde{m} - s$. We impose that

$$
\begin{align*}
\tilde{C}**[i'] &= 1, & \text{if and only if } i' \in \tilde{C}** \\
\tilde{b}**[i', j'] &> 0, & \text{if and only if } (i', j') \in \tilde{R}** \\
\gamma^*[i', \theta] &= 1, & \text{if and only if } i' \in \tilde{L}_\theta^* \\
\tilde{L}^*[\theta] &= 1, & \text{if and only if } \tilde{L}_\theta^* \neq \emptyset
\end{align*}
$$

where $\tilde{L}_\theta^*$ is a linkage class of $(\tilde{S}, \tilde{C}^* \cup \tilde{C}**, \tilde{R}^* \cup \tilde{R}**)$. That is, the variables $\tilde{C}**[i']$ keep track of the complexes in $\tilde{C}**$, while the variables $\tilde{b}**[i', j']$ keep track of the structure of $\tilde{R}**$. The variables $\gamma^*[i', \theta]$ and $\tilde{L}^*[\theta]$ keep track of the linkage classes of $(\tilde{S}, \tilde{C}^* \cup \tilde{C}**, \tilde{R}^* \cup \tilde{R}**)$ (see Sect. 4.3). We can accommodate the requirements of conditions 3.,– 4. of Corollary 1 with the constraint set (Rsl3). In order to limit the size of the components in $(\tilde{S}, \tilde{C}^* \cup \tilde{C}**, \tilde{R}^* \cup \tilde{R}**)$, we can additionally optimize over (MinC).
5 Applications

In this section, we apply the MILP procedure introduced in Sect. 4 to two examples drawn from the mathematical biology literature.

The first network was considered earlier as Example 2 in Sect. 3.2. The model was originally introduced as a candidate EnvZ/OmpR signaling pathway in *Escherichia coli* in the Supporting Online Material of Shinar and Feinberg (2010). The model was previously shown to be steady state equivalent to a generalized reaction network by Johnston (2014). The second network is modified from a model of the PFK-2/FBPase-2 mechanism in mammals originally presented by Karp et al. (2012) and Dasgupta et al. (2014). The application of network translation to this model is novel. All computations were performed with the GNU Linear Programming Kit (GLPK) on the author’s personal use Toshiba Satellite laptop (AMD Quad-Core A6-Series APU, 6GB RAM). Full details of the computations are contained in the Supplemental Material.

5.1 Application I: EnvZ/OmpR Mechanism

Reconsider the mechanism given in Example 2 in Sect. 3.2. We now apply the computational process presented in Sect. 4. The details of the initialization are contained in the Supplementary Material. We note here, however, that we have initialized the rate constants stochastically within the range $k_i \in [\sqrt{\epsilon}, 1/\sqrt{\epsilon}]$, $i = 1, \ldots, 14$, rather than choosing them to be fixed constants. The code was run 25 times, with an average time to completion of 2.788 s and a standard deviation of 1.4898 s. In each case, the algorithm successfully found the weakly reversible network translation given in Fig. 1.

This is consistent with the translated network obtained by Johnston (2014). To further check the consistency of the code, we observe that it returned the sets $\tilde{C} = \{6\}$, $\tilde{C}_R = \{1, 3\}$, $\tilde{C}(6) = \{6, 7, 8\}$, $\tilde{R}^* = \{(6, 7), (6, 8), (7, 2), (7, 6), (8, 2), (8, 6)\}$, $\tilde{C}^* = \{2\}$, and $\tilde{R}^{**} = \{(2, 6)\}$. This is consistent with the application of Corollary 1 to the weighted translation $\tilde{\mathcal{N}}(\tilde{\mathcal{B}})$ (see Fig. 1b). Since the network has $\tilde{\delta} = 0$, it follows by Corollary 1 that the network is steady state resolvable. [Further methodology for characterizing the steady state set is contained in the Supplemental Material and in Johnston (2014)].

5.2 Application II: PFK-2/FBPase-2 Mechanism

Consider the following hypothetical PFK-2/FBPase-2 mechanism contained in Fig. 2. This model is based on one proposed by Karp et al. (2012) and Dasgupta et al. (2014). Our model, however, introduced a reversible reaction pair $C_3 \rightleftharpoons C_4$ corresponding to $\emptyset \rightleftharpoons X_3$; that is, we introduce inflow and outflow of Fructose 6-phosphate ($F6P$). We defer biochemical justification and analysis of this mechanism to Karp et al. (2012), Dasgupta et al. (2014).

We now apply the computational algorithm of Sect. 4. We first simplify the model by assuming that $k_{19} = k_{20}$ and initializing the remaining weights stochastically from the range $k_i \in [\sqrt{\epsilon}, 1/\sqrt{\epsilon}]$, $i = 1, \ldots, 20$. The code was run successfully.
Fig. 2 Candidate PFK-2/FBPase-2 mechanism in mammalian cells

Table 1 Weights for steady state equivalence of $N(K)$ and $\tilde{N}(\tilde{K})$

|  | $\tilde{k}_1 = k_1$ | $\tilde{k}_6 = k_6$ | $\tilde{k}_{11} = k_{11}$ | $\tilde{k}_{16} = k_{16}$ |
|---|---|---|---|---|
| $C_1 - X_1$ | $k_1$ | $k_6$ | $k_{11}$ | $k_{16}$ |
| $C_2 - X_2$ | $k_2$ | $k_7$ | $k_{12}$ | $k_{17} = k_{17} + k_{20}$ |
| $C_3 - 0$ | $k_3$ | $k_8$ | $k_{13}$ | $k_{18} = k_4 k_{18}$ |
| $C_4 - X_3$ | $k_4$ | $k_9$ | $k_{14}$ | $k_{19} = k_{19}$ |
| $C_5 - X_2 + X_3$ | $k_5$ | $k_{10} = k_{10}$ | $k_{15} = k_{15}$ | $k_{20} = k_{20}$ |

25 times with an average completion time of 6.604 s and a standard deviation of 2.6871 s.

A recurring network structure for the translation was the one contained in Fig. 3a. Note that both $C_2 = X_2$ and $C_5 = X_2 + X_3$ are translated to $\tilde{C}_4 = X_2 + 2X_3$, and both $C_9 = X_7$ and $C_{13} = X_3 + X_7$ are translated to $\tilde{C}_8 = X_3 + X_7$. The weighted translation is therefore improper. The algorithm returned the sets $\tilde{C}_I = \{4, 8\}$, $\tilde{C}_R = \{1, 2\}$, $\tilde{C}^* = \{3, 4, 5, 6, 7, 8, 9\}$, $\tilde{R}^* = \{(3, 4), (4, 3), (4, 5), (5, 4), (5, 6), (6, 7), (8, 4), (8, 7), (8, 9), (8, 11), (9, 8)\}$, $\tilde{C}** = \{11\}$, and $\tilde{R}** = \{(11, 9)\}$. Notice that, even though the technical conditions of Corollary 1 are satisfied trivially (see Fig. 3b), the algorithm still constructs a weakly reversible component containing $\tilde{C}_I$. Details of the computation are contained in the Supplementary Material.

Notice that we may not apply Corollary 1 directly since the network has $\tilde{\delta} = 2$. Nevertheless, it can shown that $\ker(\tilde{Y} \cdot A(\tilde{K}))$ decomposes in such a way steady state equivalence may be guaranteed (see Supplementary Material). The generalized mass action system with the rate constants given in Table 1 has the same steady states as the original system. Note that, although the computational process requires numerical values for the weights, the insight gained from the process was able to guide a correspondence which can be shown to work for all weights.
6 Conclusions and Future Work

In this paper, we have extended the theory of network translation presented by Johnston (2014) in two important ways:

(Q1) We have presented conditions which suffice to guarantee steady state equivalence of a weighted network $\mathcal{N}(\mathcal{K})$ and a generalized weighted network $\tilde{\mathcal{N}}(\tilde{\mathcal{K}})$ (Theorem 1). Importantly, these conditions are graph theoretical in nature and do not require an enumeration over all cycles on the support of the elementary flux modes as was previously required by Johnston (2014).

(Q2) We have presented an algorithm for determining whether a weighted translation of a given chemical reaction network exists. This algorithm is implementable within the well-known MILP framework and is capable of imposing the technical conditions of Corollary 1. The code is contained in “Appendix 3”.

Fig. 3 In (a), we have the computationally determined weighted translation $\tilde{\mathcal{N}}(\tilde{\mathcal{K}})$ for the PFK-2/FBPase-2 mechanism contained in Fig. 2. In (b), we identify $\tilde{\mathcal{C}}^* = \{3, 4, 5, 6, 7, 8, 9\}$ (pink), $\tilde{\mathcal{C}}^{**} = \{11\}$ (green), and the reaction sets $\tilde{\mathcal{R}}^* =$ (solid red arrows) and $\tilde{\mathcal{R}}^{**} =$ (dashed red arrow). The network $(\tilde{\mathcal{S}}, \tilde{\mathcal{C}}^* \cup \tilde{\mathcal{C}}^{**}, \tilde{\mathcal{R}}^* \cup \tilde{\mathcal{R}}^{**})$ is weakly reversible (Color figure online)
There are numerous avenues open for future work in the study of network translations, and generalized mass action systems in general. The avenues specifically related to the work contained in this paper include:

1. **Algorithmic determination of optimal \( \tilde{Y} \):** The MILP algorithm presented in Sect. 4 requires initialization of the matrix \( \tilde{Y} \) consisting of potential stoichiometric complexes in the network \( \tilde{N} \). Without prior intuition, a suitable choice of these complexes may not be obvious. Nevertheless, this choice set should be kept small to maintain computation efficiency. Algorithmically determining a suitable set of potential stoichiometric complexes is therefore a primary concern moving forward.

2. **Rate constant independence:** For the algorithm presented in Sect. 4, the rate constants of the original network \( \mathcal{N}(\mathcal{K}) \) may be specified by the user or determined stochastically. It is often desirable, however, to be able to leave these rates unspecified in order to determine an optimal network translation from within the entire class of mass action systems with the underlying structure \( \mathcal{N} \). Similar procedures have been studied by Johnston et al. (2012a) but are not at presently applicable to the algorithm presented in this paper due to nonlinearities in the decision variables.

3. **Expansion of underlying theory:** The main result of this paper (Theorem 1) depends implicitly on the results regarding translations given by Johnston (2014) and those regarding generalized mass action systems given by Müller and Regensburger (2012). It is anticipated that, as these nascent theories are further developed, the applications of computational approaches such as those contained in this paper will become necessary. We present in the Supplemental Material an example which illustrates one further avenue of research regarding the theory of network translation.

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**Appendix 1: Resolvability**

In order to make the connection between the results of Johnston (2014), Definition 9, and Theorem 1, we briefly introduce here some background on resolvability. We begin by defining the following concept, which was introduced informally in Sect. 2.

**Definition 12** Suppose \( \mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}) \) is a chemical reaction network. We say a subgraph \( P = (\mathcal{C}_P, \mathcal{R}_P) \) where \( \mathcal{C}_P \subseteq \mathcal{C} \) and \( \mathcal{R}_P \subseteq \mathcal{R} \) is a path from \( C_i \) to \( C_j \) if:

1. there is an ordering \( \{v(1), v(2), \ldots, v(l)\} \subseteq \mathcal{C} \) with all \( v(k), k = 1, \ldots, l \), distinct such that \( C_i = C_{v(1)} \rightarrow C_{v(2)} \rightarrow \cdots \rightarrow C_{v(l)} = C_j \);
2. \( \mathcal{C}_P = \{v(1), v(2), \ldots, v(l)\} \subseteq \mathcal{C} \); and
3. \( \mathcal{R}_P = \{\langle v(1), v(2)\rangle, \ldots, \langle v(l - 1), v(l)\rangle\} \subseteq \mathcal{R} \).

We will let \( \mathcal{P}(i, j) \) denote the set of all paths from \( C_i \) to \( C_j \).
Now consider the following.

**Definition 13** Suppose \( \mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}) \) is a chemical reaction network. We say a subgraph \( T = (\mathcal{C}_T, \mathcal{R}_T) \) where \( \mathcal{C}_T \subseteq \mathcal{C} \) and \( \mathcal{R}_T \subseteq \mathcal{R} \) is a **spanning i-tree** on \( \mathcal{C}_T \) if:

1. \( \mathcal{R}_T \) spans \( \mathcal{C}_T \);
2. \( T \) contains no directed or undirected cycles; and
3. \( T \) has a unique sink at \( C_i \).

We will let \( T(i) \) denote the set of all spanning \( i \)-trees on \( \mathcal{C}_T \).

In general, an arbitrary subset \( \mathcal{C}_T \subseteq \mathcal{C} \) may not permit any spanning \( i \)-trees; however, if the network is weakly reversible, there is at least one spanning \( i \)-tree on the set \( \mathcal{C}_T = L_\emptyset \) where \( L_\emptyset \) is the linkage class which contains \( C_i \). These are the components to which we will be interested in restricting. We may define the following for weakly reversible networks.

**Definition 14** Consider a weighted chemical reaction network \( \mathcal{N}(\mathcal{K}) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}) \) which is weakly reversible. Then the **tree constant** for \( i \in \mathcal{C} \) is given by

\[
K_i = \sum_{T \in T(i)} \prod_{(i^*, j^*) \in T} k(i^*, j^*)
\]  

(24)

where \( T(i) \) is the set of spanning \( i \)-trees on the component \( \mathcal{C}_T = L_\emptyset \) where \( C_i \in L_\emptyset \).

For example, for the network

\[
\begin{align*}
C_1 & \xrightarrow{k_1} C_2 \\
& \xleftarrow{k_2} \\
& \uparrow_k \downarrow k_3 \\
C_4 & \leftarrow C_3
\end{align*}
\]

we have

\[
K_1 = k_2 k_4 k_5 + k_3 k_4 k_5
\]

corresponding to the two spanning trees with unique sinks at \( C_1 \):

\[
\begin{align*}
C_1 & \xrightarrow{k_1} C_2 & \text{and} & & C_1 & \xrightarrow{k_1} C_2 \\
& \xleftarrow{k_2} \downarrow_k \downarrow k_3 & & & \uparrow_k \downarrow k_3 \\
C_4 & \leftarrow C_3 & & & C_4 & \leftarrow C_3.
\end{align*}
\]

**Remark 9** An immediate consequence of Definition 13 is that, given any \( i \)-tree which spans \( \mathcal{C}_T \) and any \( C_j \in \mathcal{C}_T \), there is a unique path from \( C_j \) to \( C_i \). We will make use of this fact in the proofs contained in “Appendix 2”.

**Remark 10** We will denote the tree constants of the translated weighted networks \( \mathcal{N}(\tilde{\mathcal{B}}) = (\tilde{\mathcal{S}}, \tilde{\mathcal{C}}, \tilde{\mathcal{C}}_K, \tilde{\mathcal{R}}, \tilde{\mathcal{B}}) \) as \( \tilde{B}_{i'} \), \( i' = 1, \ldots, \tilde{m} \). Note also that the convention of referring to these algebraic constructs as “tree constants” is original to Johnston (2014).
Appendix 2: Proof of Theorem 1 and Corollary 1

In this section, we prove Theorem 1 and the equivalence of Theorem 1 and Corollary 1. We first motivate the proof for Theorem 1 through Example 2 from Sect. 3.2.

Example 2: We have that $\tilde{C}_I = \{6\}$ and $h^{-1}(6) = \{6, 8\}$. That is, the complexes $C_6 = X_3 + X_7$ and $C_8 = X_1 + X_7$ are both mapped to the translated complex $\tilde{C}_6 = X_1 + X_2 + X_3 + X_7$. Following (18), we choose $(\tilde{C}_6)_K = C_6 = X_3 + X_7$ and note that $y_8 - y_6 = (1, 0, -1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$ so that $\tilde{C}_R = \{1, 3\}$. After manipulation, this yields the identity

$$x_8 = \left(x_1 \cdot \frac{\tilde{y}_K_1}{\tilde{y}_K_3}\right) x_6 \implies x_1 x_7 = \left(\frac{x_1}{x_3}\right) x_3 x_7.$$  \hspace{1cm} (25)

Equation (25) suggests that the monomial $x_8 = x_1 x_7$, which appears in (3) but not in (6), may be incorporated in (6) by relating it to the monomial $x_6 = x_3 x_7$. In particular, we can write the rate for reaction 12 in (12) as

$$k_{12} x_1 x_7 = \left[k_{12} \left(\frac{x_1}{x_3}\right)\right] x_3 x_7.$$  \hspace{1cm} (26)

That is, we reimagine reaction 12 as occurring from the complex $C_6 = X_3 + X_7$ with the state-dependent weight $k_{12} \cdot x_1/x_3$. We obtain dynamical equivalence between (12) and (14) by choosing the kinetic complexes (18) and the weights $\tilde{b}_i = k_i$ for $i = 1, \ldots, 14$, $i \neq 12$, and $\tilde{b}_{12} = k_{12} \cdot x_1/x_3$. In order to remove the dependence on the ratio $x_1/x_3$, we make the following observations:

1. **Network structure simplifies steady state representation:** Since $\tilde{\delta} = 0$ for the network (14), it follows that all steady states $x \in \mathbb{R}_{>0}^n$ of the corresponding generalized system (6) satisfy

$$\tilde{A}(\tilde{B}) \cdot \Psi(x) = 0$$

where $\tilde{A}(\tilde{B})$ is the Kirchhoff matrix (4) corresponding to (14). Since (14) consists of a single linkage class, it follows by Corollary 4 of Craciun et al. (2009) that

$$\Psi(x) \in \text{span}\{\tilde{B}_1, \ldots, \tilde{B}_8\}. \hspace{1cm} (26)$$

where $\tilde{B}_1, \ldots, \tilde{B}_8$ are the tree constants given in “Appendix 1” derived from the network (14) with rate constants given above. It follows from (18) and (26) that, at every steady state of (6), we have

$$\frac{x_1}{x_3} = \frac{x_1 \tilde{y}_K_1}{x_3 \tilde{y}_K_3} = \tilde{B}_1 \tilde{B}_3.$$  \hspace{1cm} (27)

Notice that, since $\tilde{A}(\tilde{B})$ depends upon the state-dependent ratio $x_1/x_3$, we must allow that $\tilde{B}_1, \ldots, \tilde{B}_8$ do as well.
Fig. 4 Four possible configurations for a spanning 1-tree for the network (14). Highlighted are the improper complex \( \tilde{C}_6 \) (pink), bottleneck complex \( \tilde{C}_2 \) (green), and resolving complex \( \tilde{C}_1 \) (blue). The four constructions (28) are realized with \( \tilde{T}^* \) (red arrows), \( \tilde{T}^{**} \) (blue arrow), and \( \tilde{X}^* \) (green arrows). Notice that \( \tilde{T}^*, \tilde{T}^{**}, \) and \( \tilde{X}^* \) may be chosen independently (Color figure online)

2. Construction of \( \tilde{B}_1 \): We now use the observation that every path from \( \tilde{C}_6 \) to \( \tilde{C}_1 \) in (14) goes through \( \tilde{C}_2 \) to construct the tree constant \( \tilde{B}_1 \). Our first step is to identify subcomponents \( \tilde{C}(6, 2) \) and \( \tilde{C}(2, 1) \) consisting of all complexes which lie on any path from \( \tilde{C}_6 \) to \( \tilde{C}_2 \) or \( \tilde{C}_2 \) to \( \tilde{C}_1 \), respectively. This gives \( \tilde{C}(6, 2) = \{2, 6, 7, 8\} \) and \( \tilde{C}(2, 1) = \{1, 2\} \). Our second step is to identify the set of all 2-trees which span \( \tilde{C}(6, 2) \) and all 1-trees which span \( \tilde{C}(2, 1) \). We denote these by \( \tilde{T}(6, 2) \) and \( \tilde{T}(2, 1) \), respectively. Our third step is to identify a set of configurations of edges on the remaining complexes, denoted \( \tilde{X}(6, 1) \), which connect each complex by a unique path to either \( \tilde{C}(6, 2) \) or \( \tilde{C}(2, 1) \). We may now construct a spanning 1-tree \( \tilde{T} \in \mathcal{T}(1) \) by considering

\[
\tilde{T} = \tilde{T}^* \cup \tilde{T}^{**} \cup \tilde{X}^*
\]  

where \( \tilde{T}^* \in \tilde{T}(6, 2), \tilde{T}^{**} \in \tilde{T}(2, 1), \) and \( \tilde{X}^* \in \tilde{X}(6, 1) \). The property that every path from \( \tilde{C}_6 \) to \( \tilde{C}_1 \) goes through \( \tilde{C}_2 \) guarantees that every spanning 1-tree may be constructed in this way. The four possible configurations are contained in Fig. 4. (Construction of \( \tilde{T} \) (3) follows similarly.) We have

\[
\tilde{B}_1 = \tilde{b}_2(\tilde{b}_4 + \tilde{b}_5)\tilde{b}_6\tilde{b}_8(\tilde{b}_9 + \tilde{b}_{12})\tilde{b}_{11}\tilde{b}_{14}
\]

\[
\tilde{B}_3 = \tilde{b}_1\tilde{b}_3\tilde{b}_6\tilde{b}_8(\tilde{b}_9 + \tilde{b}_{12})\tilde{b}_{11}\tilde{b}_{14}.
\]  

3. Ratio \( x_1/x_3 \) is constant at every steady state: From (27) and (29), we have

\[
\frac{x_1}{x_3} = \frac{\tilde{B}_1}{\tilde{B}_3} = \frac{\tilde{b}_2(\tilde{b}_4 + \tilde{b}_5)[\tilde{b}_6\tilde{b}_8(\tilde{b}_9 + \tilde{b}_{12})\tilde{b}_{11}\tilde{b}_{14}]}{\tilde{b}_1\tilde{b}_3[\tilde{b}_6\tilde{b}_8(\tilde{b}_9 + \tilde{b}_{12})\tilde{b}_{11}\tilde{b}_{14}]} = \frac{\tilde{b}_2(\tilde{b}_4 + \tilde{b}_5)}{\tilde{b}_1\tilde{b}_3}.
\]  

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Since (30) does not depend upon \( \tilde{b}_{12} \), it follows that the ratio \( x_1/x_3 \) is constant at any steady state of (6). We may therefore incorporate reaction 12 into the network (14) by using the rescaled weight

\[
k_{12}x_1x_7 = \left[ k_{12} \left( \frac{x_1}{x_3} \right) \right] x_3x_7 = k_{12} \left( \frac{k_2(k_4 + k_5)}{k_1k_3} \right) x_3x_7.
\]

That is, we obtain steady state equivalence between (12) and (14) with kinetic complex set (18) by setting \( \tilde{k}_i = k_i \) for \( i = 1, \ldots, 14, i \neq 12 \), and

\[
\tilde{k}_{12} = \left( \frac{k_2(k_4 + k_5)}{k_1k_3} \right).
\]

The key feature in obtaining steady state equivalence is that the state-dependent weight \( \tilde{b}_{12} \) does not appear in the ratio \( \tilde{B}_1/\tilde{B}_3 \). Since every path from \( \tilde{C}_6 \) to either \( \tilde{C}_1 \) or \( \tilde{C}_3 \) passes through \( \tilde{C}_2 \), it follows that set of configurations \( \tilde{T}(6, 2) \) in (28), which contains \( \tilde{b}_{12} \), is common to both the construction of the trees in \( \tilde{T}(1) \) and \( \tilde{T}(3) \) and may be chosen independently of the remaining edges. It follows that the corresponding algebraic combination of rates must factor in (24) and therefore cancel in the ratio \( \tilde{B}_1/\tilde{B}_3 \).

We now generalize the argument given above to prove Theorem 1. In particular, we will use the three-part construction (28) of spanning \( i \)-trees \( \tilde{T}(i) \).

Proof of Theorem 1 Suppose that \( \tilde{N}(\tilde{B}) = (\tilde{S}, \tilde{C}, \tilde{K}, \tilde{R}, \tilde{B}) \) is an improper weighted translation of a weighted chemical reaction network \( N(K) = (S, \mathcal{C}, \mathcal{R}, K) \) according to Definition 7. Suppose furthermore that \( \tilde{N}(\tilde{B}) \) is weakly reversible, \( \tilde{\delta} = 0 \), and \( \tilde{S}_I \subseteq \tilde{S}_K \).

Since \( \tilde{S}_I \subseteq \tilde{S}_K \), by Definition 11 there is a non-empty resolving complex set \( \tilde{C}_R \). Let \( \tilde{B}_{i'}, i' = 1, \ldots, \tilde{m}_i \), denote the tree constants (24) corresponding to the weighted reaction graph of \( \tilde{N}(\tilde{B}) \).

Consider any pair \( i, j \in h^{-1}(k') \) where \( k' \in \tilde{C}_I \) and define the ratios

\[
\tilde{B}_{i, j} = \prod_{i', j' = 1}^{m} \left( \frac{\tilde{B}_{j'}}{\tilde{B}_{i'}} \right)^{c(i', j')} = \prod_{\theta = 1}^{\tilde{\ell}} \prod_{i', j' \in \tilde{L}_{\theta}}^{\tilde{L}_{i', j'}} \left( \frac{\tilde{B}_{j'}}{\tilde{B}_{i'}} \right)^{c(i', j')}
\]

where the final decomposition into linkage classes can be made by condition 1.(b) of Definition 11. We will show that (31) does not depend on any rate constant from any complex in the set \( \tilde{C}_I \), which are the rates which may depend upon the state \( x \in \mathbb{R}_{>0}^n \).

Fix a \( \theta \in \{1, \ldots, \tilde{\ell}\} \) such that \( \tilde{C}_R \cap \tilde{L}_{\theta} \neq \emptyset \). Notice that condition 1.(b) of Definition 11 implies that there are at least two \( i', j' \in \tilde{C}_R \cap \tilde{L}_{\theta} \) such that \( j' \neq i' \). We consider two cases.
Case 1: Suppose \( \bar{C}_I \cap \bar{L}_\theta = \emptyset \). Since the spanning \( i \)-trees only span \( \bar{L}_\theta \), it follows that for any \( p' \in \bar{C}_I \), we have that

\[
\prod_{i', j' \in \bar{L}_\theta} \left( \frac{\bar{B}_{i'}^{(j')}}{\bar{B}_{i'}} \right)^{c(i', j')}
\]

(32)
does not depend on any reaction from any \( p' \in \bar{C}_I \). This completes consideration of Case 1.

Case 2: Suppose there is an \( p' \in \bar{C}_I \cap \bar{L}_\theta \). By assumption 2. of Theorem 1, there is a \( k' \in \bar{L}_\theta \) such that for every path \( \bar{P} = [\bar{C}_{p'}, \bar{R}_{p}] \) from \( \bar{C}_{p'} \) to \( \bar{C}_{i'} \), we have \( k' \in \bar{C}_{p'} \). Let \( \bar{P}(p', k') \) and \( \bar{P}(k', i') \) denote the set of all paths from \( \bar{C}_{p'} \) to \( \bar{C}_{k'} \) and from \( \bar{C}_{k'} \) to \( \bar{C}_{i'} \), respectively. Now define

\[
\bar{C}(p', k') = \bigcup_{\bar{P} \in \bar{P}(p', k')} \bar{C}_{p'} \quad \text{and} \quad \bar{R}(p', k') = \bigcup_{\bar{P} \in \bar{P}(p', k')} \bar{R}_{p'} ,
\]

\[
\bar{C}(k', i') = \bigcup_{\bar{P} \in \bar{P}(k', i')} \bar{C}_{p'} \quad \text{and} \quad \bar{R}(k', i') = \bigcup_{\bar{P} \in \bar{P}(k', i')} \bar{R}_{p'} .
\]

Let \( \bar{T}(p', k') \) denote the set of all \( k' \)-trees which span \( \bar{C}(p', k') \), and \( \bar{T}(k', i') \) denote the set of all \( i' \)-trees which span \( \bar{C}(k', i') \). Note that every path from a complex in \( \bar{C}(p', k') \) to \( \bar{C}_{i'} \) goes through \( \bar{C}_{k'} \) and that no path from a complex in \( \bar{C}(k', i') \) passes through \( \bar{C}(p', k') \) (since it would return to \( \bar{C}_{k'} \)).

We may write any \( \bar{T} \in \bar{T}(i') \) as

\[
\bar{T} = \bar{T}^* \cup \bar{T}^{**} \cup \bar{X}^*
\]

(33)
where \( \bar{T}^* \in \bar{T}(p', k') \), \( \bar{T}^{**} \in \bar{T}(k', i') \), and \( \bar{X}^* \in \bar{X}(p', i') \), where \( \bar{X}(p', i') \) is the set of configuration of reactions which connect the remaining complexes in \( \bar{L}_\theta \) along a unique path to \( \bar{C}(p', k') \cup \bar{C}(k', i') \).

We now construct \( \bar{B}_{j'} \) by considering all possible trees \( \bar{T} \in \bar{T}(i') \) constructed by (33). By the independence of \( T^* \), \( T^{**} \), and \( X^* \) in (33), we have that

\[
\bar{B}_{j'} = \left( \sum_{\bar{T}^* \in \bar{T}(p', k')} \prod_{(i^*, j^*) \in \bar{T}^*} \bar{b}(i^*, j^*) \right) \left( \sum_{\bar{T}^{**} \in \bar{T}(k', i')} \prod_{(i^*, j^*) \in \bar{T}^{**}} \bar{b}(i^*, j^*) \right) \left( \sum_{\bar{X}^* \in \bar{X}(p', i')} \prod_{(i^*, j^*) \in \bar{X}^*} \bar{b}(i^*, j^*) \right)
\]

(34)

Now consider any \( j' \in \bar{C}_R \cap \bar{L}_\theta \), \( j' \neq i' \). By assumption (*), we have that every path from \( C_{j'} \) to \( C_{j'} \) also goes through \( C_{k'} \), so that \( B_{j'} \) has the same form as (34). In
particular, $\tilde{T}(p', k')$ is common to both $\tilde{T}(i')$ and $\tilde{T}(j')$ in (33). After simplifying, it follows that
\[
\frac{\tilde{B}_{i'}}{\tilde{B}_{j'}} = \left( \sum_{\tilde{T}^{**} \in \tilde{T}(k', j')} \prod_{(i^*, j^*) \in \tilde{T}^{**}} \tilde{b}(i^*, j^*) \right) \left( \sum_{\tilde{T}^{**} \in \tilde{T}(k', i')} \prod_{(i^*, j^*) \in \tilde{T}^{**}} \tilde{b}(i^*, j^*) \right) \left( \sum_{\tilde{T}^{**} \in \tilde{X}(p', i')} \prod_{(i^*, j^*) \in \tilde{T}^{**}} \tilde{b}(i^*, j^*) \right) \left( \sum_{\tilde{T}^{**} \in \tilde{X}(p', j')} \prod_{(i^*, j^*) \in \tilde{T}^{**}} \tilde{b}(i^*, j^*) \right). \tag{35}
\]

The equation (35) does not depend on any reaction from any complex in $\tilde{C}(p', k')$. Since $p' \in \tilde{C}_I \cap \tilde{L}_0$ was chosen arbitrarily, it follows that (32) does not depend on any reaction from a complex in $\tilde{C}_I$. Now consider an arbitrary pair $i, j \in h^{-1}(k')$ where $k' \in \tilde{C}_I$. Applying the result of either case 1 of case 2 to (32), we have that $\tilde{B}_{i,j}$ given in (31) does not depend on any reaction from any complex in $\tilde{C}_I$. This completes consideration of Case 2.

It remains to construct a weight set $\tilde{K}$ such that $\tilde{N}(\tilde{K})$ is steady state equivalent to $\tilde{N}(\tilde{K})$. We follow the technique of the proof of Lemma 4 in Johnston (2014). For every reaction in $\tilde{N}(\tilde{K})$ corresponding to a source complex which is not a kinetic complex in $\tilde{N}(\tilde{B})$, we must rescale the weight. Supposing that $i, j \in h^{-1}(k')$ for some $k' \in \tilde{C}_I$, at steady state we have
\[
x^{y_j} = \left[ \prod_{i', j'=1}^{\tilde{m}} \left( \frac{\tilde{x}(\tilde{K})_{i', j'}}{\tilde{x}(\tilde{K})_{i,j'}} \right)^{c(i', j')} \right] x^{y_i} = \left[ \prod_{i', j'=1}^{\tilde{m}} \left( \frac{\tilde{B}_{i', j'}}{\tilde{B}_{i,j'}} \right)^{c(i', j')} \right] x^{y_i}, \tag{36}
\]
where the first equality follows from condition 1. of Definition 11, and the second equality follows from the fact that $\delta = 0$ and (35). By the argument so far, the coefficient in (36) does not depend upon the state $x \in \mathbb{R}^2_0$. We may now take any complex from the set $h^{-1}(k')$ as the kinetic complex $(\tilde{C}_K)_{k'}$ and use (36) to rescale the reactions from the remaining complexes which are mapped to $\tilde{C}_K$. This process forms our weight set $\tilde{B}$. Note that condition 1.(b) of Definition 7 guarantees that we may not rescale any reaction in such a way that the resulting net push is not representable as a weighted sum of reaction vectors from the corresponding source complex in $\tilde{N}(\tilde{B})$.

Since $\tilde{B}$ and $\tilde{K}$ correspond to the same network structure, it follows that $\tilde{N}(\tilde{K})$ and $\tilde{N}(\tilde{B})$ are steady state resolvable, which completes the proof. \hfill \square

**Proof of Corollary 1** It is sufficient to prove the equivalence of the technical condition (*) of Theorem 1 and the four technical conditions of Corollary 1.

**Theorem 1 $\implies$ Corollary 1:** Suppose condition (*) of Theorem 1 holds. That is, for every $p' \in \tilde{C}_I$, there is a $k' \in \tilde{C}$ such that every path from $\tilde{C}_{p'}$ to $\tilde{C}_{i'}$ where $i' \in \tilde{C}_R$ goes through $\tilde{C}_{k'}$. For a given $p' \in \tilde{C}_I$, define $k'(p')$ to be the corresponding $k'$ in condition (*) and define $\tilde{C}^*(p')$ to be the set of all complexes in $\tilde{C}$ which can be reached from $p'$ without passing through $k'(p')$. Note that, by assumption, $\tilde{C}^*(p') \cap \tilde{C}_R = \emptyset$ and $\tilde{C}^*(p') \cap k'(p') = \emptyset$. We define
\[
\tilde{C}^* = \bigcup_{p' \in \tilde{C}_I} \tilde{C}^*(p') \quad \text{and} \quad \tilde{R}^* = \bigcup_{(i', j') \in \tilde{R}} \{ (i', j') \in \tilde{C}^* \}.
\]
By construction, these sets satisfy conditions 1. and 2. of Corollary 1.

We now construct the supplemental sets \( \tilde{C}^{\ast*} \) and \( \tilde{R}^{\ast*} \). Notice that \( \tilde{C}^{\ast*} \) may contain complexes \( k' \) selected earlier but that there must be a path from such a complex to another \( k' \). We therefore define

\[
\tilde{C}^{\ast*} = \left[ \bigcup_{p' \in \tilde{C}_I} k'(p') \right] \setminus \tilde{C}^{\ast*}.
\]

We also define \( \tilde{R}^{\ast*} \) to be the set of all pairs \((k', p')\) where (1) \( k' \in \tilde{C}^{\ast*} \), and (2) for a given \( k' \), \( p' \in \tilde{C}_I \) such that there is a path from \( \tilde{C}_{p'} \) to \( \tilde{C}_{k'} \) in the network \((\tilde{S}, \tilde{C}^{\ast} \cup \tilde{C}^{\ast*}, \tilde{R}^{\ast*})\). Notice that these pairs need not be in the network \( \tilde{N}(\tilde{B}) \).

By construction, each linkage class of \((\tilde{S}, \tilde{C}^{\ast} \cup \tilde{C}^{\ast*}, \tilde{R}^{\ast*})\) has a unique sink. (Otherwise, we would contradict condition 2. of Corollary 1.) The addition of the reaction set \( \tilde{R}^{\ast*} \) clearly makes this network weakly reversible so that we have satisfied condition 3. of Corollary 1. Condition 4. follows from the uniqueness of the sinks in each linkage class prior to adding \( \tilde{R}^{\ast*} \), since these sinks correspond to complexes in \( \tilde{C}^{\ast*} \), and we are done.

**Corollary 1 \( \implies \) Theorem 1:** Suppose that there are sets \( \tilde{C}^{\ast}, \tilde{R}^{\ast}, \tilde{C}^{\ast*}, \) and \( \tilde{R}^{\ast*} \) which satisfy conditions 1 – 4. of Corollary 1. Take an arbitrary \( p' \in \tilde{C}_I \). By condition 1., we have that \( p' \in \tilde{C}^{\ast} \). By condition 3. and 4., we have that the each linkage class of the network \((\tilde{S}, \tilde{C}^{\ast} \cup \tilde{C}^{\ast*}, \tilde{R}^{\ast*})\) has a unique sink at some complex in \( \tilde{C}^{\ast*} \). From condition 2., however, we have that every path from \( p' \) to this complex in \( \tilde{N}(\tilde{B}) \) is contained in \((\tilde{S}, \tilde{C}^{\ast} \cup \tilde{C}^{\ast*}, \tilde{R}^{\ast*})\). Since \( \tilde{C}^{\ast} \cup \tilde{C}_R = \emptyset \) by condition 1., we have that for every \( p' \in \tilde{C}_I \) there is a \( k' \in \tilde{C}^{\ast} \) (the identified element in \( \tilde{C}^{\ast*} \)) such that every path from \( \tilde{C}_{p'} \) to \( \tilde{C}_{k'} \) where \( i' \in \tilde{C}_R \) goes through \( \tilde{C}_{k'} \). It follows that condition (*) of Theorem 1 is satisfied, and we are done.

**Appendix 3: Code for Sect. 4**

The following code corresponds to that derived in Sect. 4. We divide the code into four sections: parameters, decision variables, objective functions, and constraint sets.

**Parameters:**

\[
\begin{align*}
\begin{array}{ll}
\text{n} & \text{Number of chemical species} \\
\text{q} & \text{Number of source complexes in } \tilde{N}(\tilde{K}) \\
\text{m} & \text{Number of hypothetical stoichiometric complexes in } \tilde{N}(\tilde{B}) \\
\text{s} & \text{Dimension of stoichiometric subspace of } \tilde{N}(\tilde{K}) \\
\text{m} - s & \text{Upper bound on number of linkage classes in } \tilde{N}(\tilde{B}) \\
\hat{C} & \text{Upper bound on number of linkage classes in } (\tilde{S}, \tilde{C}^{\ast} \cup \tilde{C}^{\ast*}, \tilde{R}^{\ast} \cup \tilde{R}^{\ast*}) \\
V & \text{Matrix of uniform random variables, } V_{i,j} \in [\sqrt{\pi}, 1/\sqrt{\pi}] \\
Y & \text{Complex matrix of } \tilde{N}(\tilde{K}) \\
\hat{Y} & \text{Complex matrix of } \tilde{N}(\tilde{B}) \\
M & \text{Weighted stoichiometric matrix of } \tilde{N}(\tilde{K})
\end{array}
\end{align*}
\]

(Par)
Decision variables:

\[
\begin{align*}
    H[i, j'] &\in [0, 1], \\
    \lambda[i, j'] &\geq 0, \\
    q[i', j'] &\geq 0, \\
    b[i', j'] &\geq 0, \\
    C^k[i'] &\in [0, 1], \\
    C^{k*}[i'] &\in [0, 1], \\
    \delta_k[i, j] &\in [0, 1], \\
    \delta_k[i, j] &\in [0, 1], \\
    \gamma[i, j] &\geq 0, \\
    \gamma[i, j] &\geq 0, \\
    L[0] &\in [0, 1], \\
    L[0] &\in [0, 1], \\
    \theta[0] &\in [0, 1], \\
    \theta[0] &\in [0, 1], \\
    \theta &\in [0, 1], \\
    \theta &\in [0, 1], \\
    \tilde{\theta} &\in [0, 1], \\
    \tilde{\theta} &\in [0, 1], \\
    \tilde{\theta} &\in [0, 1].
\end{align*}
\]

Objective functions:

\[
\begin{align*}
    \text{minimize} & \quad \sum_{\theta=1}^{\tilde{m}-s} L[i, j'] \quad \text{(MinDef)} \\
    \text{minimize} & \quad \epsilon \sum_{j'=1}^{\tilde{m}} (C^k[i'] + C^{k*}[i']) \quad \text{(MinC)}
\end{align*}
\]

Constraint Sets:

\[
\begin{align*}
    \sum_{j'=1}^{\tilde{m}} b[i', j'] (\tilde{Y}_i, j' - \tilde{Y}_i) &\leq \sum_{i=1}^{q} M_k[i] \cdot H[i, j'], \\
    j' &\neq i, \\
    k &\in \{1, \ldots, n, i' = 1, \ldots, \tilde{m}\}, \\
    i &\in \{1, \ldots, q\}.
\end{align*}
\]

\[
\begin{align*}
    \sum_{i=1}^{q} H[i, j'] &\leq 1, \\
    j' &\in \{1, \ldots, \tilde{m}\}.
\end{align*}
\]

\[
\begin{align*}
    \lambda[i, j'] &\leq (1/e) (1 - H[i, j']), \\
    -\lambda[i, j'] &\leq (1/e) H[i, j'], \\
    \sum_{j'=1}^{\tilde{m}} \lambda[i, j'] &\leq 0, \\
    \sum_{j'=1}^{\tilde{m}} \lambda[i, j'] \tilde{Y}_i &\leq M_k[i, i], \\
    k &\in \{1, \ldots, n, i = 1, \ldots, q\}.
\end{align*}
\]
\[\sum_{l' = 1}^{\tilde{m}} \gamma(l', 0) \leq 1,\]
\[\sum_{l' = 1}^{\tilde{m}} \gamma(l', 0) \leq (1/\epsilon) L[0],\]
\[-\delta(l', 0) \leq -\epsilon L[0],\]
\[\delta[l', i] = (1/\epsilon) \gamma(l', 0) - \gamma[l', 0] + 1,\]
\[\sum_{l' = 1}^{\tilde{m}} \gamma[l', i] \leq \sum_{l' = 1}^{\tilde{m}} \gamma[l', 0].\]

\[\sum_{l = \theta + 1}^{\tilde{m}} \gamma[l', 0] \leq (1/\epsilon) \gamma[l', 0] - \gamma[l', 0] \leq 1 - H[l, k'],\]
\[\gamma[l, 0] - \gamma[l, k] \leq 1 - H[l, k'],\]
\[\sum_{i,j = 1}^{q} e(i, j) b[i, j] (Y_{k,i} - Y_{k,j}) = \sum_{i,j = 1}^{q} e(i, j) (Y_{k,i} - Y_{k,j}).\]

\[\sum_{l = \theta + 1}^{\tilde{m}} \gamma[l', 0] \leq (1/\epsilon) \gamma[l', 0] - \gamma[l', 0] \leq 1 - H[l, k'],\]
\[\gamma[l, 0] - \gamma[l, k] \leq 1 - H[l, k'],\]
\[\sum_{i,j = 1}^{q} e(i, j) b[i, j] (Y_{k,i} - Y_{k,j}) = \sum_{i,j = 1}^{q} e(i, j) (Y_{k,i} - Y_{k,j}).\]
\[
\begin{aligned}
\tilde{C}^*[v'_i] + \tilde{C}^{***}[v'_i] & \leq 1, \\
\tilde{b}^*[v'_i, j'_i] & \leq (1/\epsilon)\tilde{C}^{***}[v'_i], \\
\sum_{\theta=1}^{\tilde{m}} y^*[v'_i, \theta] & = \tilde{C}^*[v'_i] + \tilde{C}^{***}[v'_i], \\
\tilde{b}^{**}[v'_i, j'_i] + \tilde{b}^{***}[v'_i, j'_i] & \leq (1/\epsilon)\tilde{y}^*[v'_i, \theta] - y^*[v'_i, \theta] + 1, \\
\sum_{i'=1}^{\tilde{m}} y^*[v'_i, \theta] & \leq (1/\epsilon)L^*[\theta], \\
- \sum_{i'=1}^{\tilde{m}} y^*[v'_i, \theta] & \leq -\epsilon L^*[\theta], \\
\sum_{i'=1}^{\tilde{m}} \tilde{C}^{**}[v'_i] & = \sum_{\theta=1}^{\tilde{m}} \tilde{L}^*[\theta], \\
\sum_{j'=1}^{\tilde{m}} (\tilde{b}^*[v'_i, j'_i] + \tilde{b}^{**}[v'_i, j'_i]) & = \sum_{j'=1}^{\tilde{m}} (\tilde{b}^*[v'_i, j'_i] + \tilde{b}^{**}[v'_i, j'_i]), \\
\sum_{l=0+1}^{\tilde{m}} y[v'_i, l] & \leq \sum_{j'=1}^{\tilde{m}} y[v'_i, j'], \quad i' = 1, \ldots, \tilde{m}, \theta = 1, \ldots, \tilde{\epsilon}, \theta \leq i'.
\end{aligned}
\]

(Rsl3)

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