Computing Weakly Reversible Linearly Conjugate Chemical Reaction Networks with Minimal Deficiency

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Abstract

Mass-action kinetics is frequently used in systems biology to model the behaviour of interacting chemical species. Many important dynamical properties are known to hold for such systems if their underlying networks are weakly reversible and have a low deficiency. In particular, the Deficiency Zero and Deficiency One Theorems guarantee strong regularity with regards to the number and stability of positive equilibrium states. It is also known that chemical reaction networks with distinct reaction structure can admit mass-action systems with the same qualitative dynamics. The theory of linear conjugacy encapsulates the cases where this relationship is captured by a linear transformation. In this paper, we propose a mixed-integer linear programming algorithm capable of determining the minimal deficiency weakly reversible reaction network capable of admitting a mass-action system which is linearly conjugate to a given reaction network.

Keywords: chemical kinetics; stability theory; weak reversibility; linear programming; dynamical equivalence

1. Introduction

A chemical reaction network is given by sets of chemical reactants reacting to form sets of chemical products. Under suitable assumptions, such as mass-action kinetics and spatial homogeneity, the time evolution of the concentrations of the chemical species can be modeled by a set of autonomous polynomial ordinary differential equations. Such mass-action systems are frequently used to model systems in systems biology and other areas of computational biology [27, 37, 38].

The systematic study of chemical reaction networks and their related mass-action systems was initiated in 1972 in the papers [6, 15, 17]. In [17], the authors presented a condition on the positive equilibrium concentrations, called *complex balancing*, which is sufficient to guarantee that within each linear invariant space of the mass-action system there exists a unique equilibrium concentration, and that this concentration is locally asymptotically stable relative to its invariant space. In [6]

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and [15], the authors related the capacity of a network to admit systems which exhibit complex balancing to a nonnegative network parameter called the *deficiency*. In particular, they showed that mass-action systems with the same underlying network are complex balanced for all sets of rate constant values if and only if the network is weakly reversible and has a deficiency of zero. This *deficiency*-oriented approach to analysing chemical reaction networks has since been applied to a wide variety of biochemical systems, including enzymatic models, signal transduction, and phosphorylation networks [30, 31, 23, 4, 25].

It is also known that many qualitative properties of the dynamics of mass-action systems can be shared by systems with distinct network structure. The most thorough study of *dynamical equivalence*, the property that two mass-action systems with distinct reaction network structure give rise to identical governing dynamics, was conducted in [2]. (This property of networks has been known since at least the 1970's and was termed *macro-equivalence* in [17], *non-uniqueness* of rate constants in [22], and *confoundability* in [2].) In [19], dynamical equivalence was extended to *linear conjugacy*, whereby the trajectories of two mass-action systems could be related by a non-trivial linear transformation. The problem of determining dynamically equivalent systems with the greatest and fewest number of reactions was placed in a mixed-integer linear programming (MILP) context in [33]. This methodology has since been extended to detailed and complex balanced systems [34, 35], weakly reversible networks [36, 21], and linear conjugate systems [21, 20].

Linear conjugacy effectively creates classes of mass-action systems which, despite distinct network structure and properties, have equivalent qualitative dynamics in terms of number and stability of equilibria, boundedness/persistence or trajectories, and dimension of invariant spaces. A long-standing problem in chemical reaction network theory, first stated in [14], is to "... look for a mechanism in a class of mechanisms with a given - chemically relevant - property. Such a property may be conservativity, (weak) reversibility, zero deficiency or just structural stability as well." In this paper, we use linear conjugacy and MILP methods to address this challenge for the class of weakly reversible networks where the structural property of interest is the deficiency.

In general, we will be interested in mass-action systems within the class of all linearly conjugate systems for which the underlying reaction network has the *minimal* deficiency. This is due to the observation that mass-action systems generally exhibit more regular dynamics (e.g. fewer steady states, lower capacity for oscillations, etc.) when the underlying networks have a lower deficiency than a higher deficiency [6, 15, 10, 8]. We therefore modify the existing MILP framework to compute linearly conjugate systems for which the underlying network is weakly reversible and has the minimal deficiency. The methodology is based on known properties of the kernel of the kinetics matrix of a mass-action system for which the underlying reaction network is weakly reversible.

2. Background

In this section we present terminology and notation relevant to the study of chemical reaction networks. We introduce the notion of the deficiency of a network and a few classical results which relate the deficiency of a network to the dynamics of the network's corresponding mass-action systems. We also introduce the notion of two mass-action systems being linearly conjugate.

2.1. Chemical Reaction Networks

The chemical *species* or *reactants* of a network will be given by the set $\mathcal{S} = \{X_1, X_2, \ldots, X_n\}$. The combined elements on the left- and right-hand side of a reaction are given by linear combinations

of these species. These combined terms are called *complexes* and will be denoted by the set $\mathcal{C} = \{C_1, C_2, \ldots, C_m\}$ where

$$C_i = \sum_{j=1}^{n} \alpha_{ij} X_j, \quad i = 1, \ldots, m$$

and the α_{ij} are nonnegative integers called the *stoichiometric coefficients*. The complex with all stoichiometric coefficients equal to zero will be called the *null complex* and denoted by $C_i = \emptyset$. We define the reaction set to be $\mathcal{R} = \{(C_i, C_j) \mid C_i \text{ reacts to form } C_j\}$. The property $(C_i, C_j) \in \mathcal{R}$ will commonly be denoted $C_i \to C_j$. The triplet $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ will be called the *chemical reaction network*.

The above formulation naturally gives rise to a directed graph $G(V, E)$ where the set of vertices is given by $V = \mathcal{C}$ and the set of directed edges is given by $E = \mathcal{R}$. That is to say, if we are given the set of *elementary reactions*

$$\begin{aligned} X_1 &\longrightarrow X_2 \\ X_2 &\longrightarrow X_3 + X_4 \\ X_3 + X_4 &\longrightarrow X_1 \end{aligned}$$

we will prefer to express the network with each stoichiometrically distinct complex appearing only once as

$$\begin{array}{ccc} X_1 & \longrightarrow & X_2 \\ & \nwarrow \quad \swarrow & \\ & X_3 + X_4. & \end{array} \tag{1}$$

In the literature this has been termed the *reaction graph* of the network [17]. In this setting, a *linkage class* is a maximally connected set of complexes, that is to say, two complexes are in the same linkage class if and only if there is a sequence of reactions in the reaction graph (of either direction) which connects them. We will denote by ℓ the number of linkage classes in a network. A reaction network is called *weakly reversible* if $C_i \to C_j$ for any $C_i, C_j \in \mathcal{C}$ implies there is some sequence of complexes such that $C_j = C_{\mu(1)} \to C_{\mu(2)} \to \cdots \to C_{\mu(l-1)} \to C_{\mu(l)} = C_i$. The network given in (1) is weakly reversible and has a single linkage class so that $\ell = 1$.

A directed graph is called *strongly connected* if there exists a directed path from each vertex to every other vertex. A *strongly connected component* of a directed graph is a maximal set of vertices for which paths exist from each vertex in the set to every other vertex in the set. A strongly connected component is called *terminal* if there is no reaction leading from a vertex in the strongly connected component to a vertex not in the component. For a weakly reversible network, all strongly connected components are terminal, and they correspond to the linkage classes of the reaction graph.

We would like to ascribe a kinetics to the chemical reaction network $\mathcal{N}$ which will control how the species concentrations evolve over time. A commonly used choice is mass-action kinetics, whereby the rate of each reaction is assumed to be proportional to the product of the reactant concentrations, e.g. the rate of the reaction $X_1 + X_2 \longrightarrow X_3$ is given by $[\text{rate}] = k[X_1][X_2]$ where $k > 0$ is a proportionality constant [13, 17]. Other common choices, especially in biochemistry, are Michaelis-Menten kinetics [24] and Hill kinetics [15]. In this paper, we will focus exclusively on mass-action kinetics.

We now make the connection between a chemical reaction network $\mathcal{N}$ and mass-action kinetics. We start by assigning to each $(C_i, C_j) \in \mathcal{R}$ a positive *rate constant* $k(i, j) > 0$. For each $(C_i, C_j) \notin \mathcal{R}$

we will set $k(i,j) = 0$. We let $\mathbf{x} = [x_1\ x_2\ \cdots\ x_n]^T$ denote the vector of species concentrations and denote by $\Psi(\mathbf{x}) \in \mathbb{R}^m_{\geq 0}$ the vector given by

$$\Psi_j(\mathbf{x}) = \prod_{i=1}^{n} x_i^{[Y]_{ij}}, \quad j = 1, \ldots, m. \tag{2}$$

The entries of $\Psi(\mathbf{x})$ are the mass-action terms disjoint from their corresponding rate constants. The rate constants instead appear in the *Kirchoff/kinetics* matrix $A_k \in \mathbb{R}^{m\times m}$ given by

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1, l\neq i}^{m} k(i,l), & \text{if} \quad i = j \\ k(j,i) & \text{if} \quad i \neq j \end{cases} \qquad i,j = 1, \ldots, m. \tag{3}$$

Due to the correspondence between elementary reactions $(C_i, C_j) \in \mathcal{R}$ and the non-zero rate constants $k(i,j) > 0$, the *structure* of the network's reaction graph can be determined by considering the distribution of positive and zero entries in the off-diagonal elements of A_k. Finally, we define the *complex matrix* $Y \in \mathbb{Z}^{n\times m}_{\geq 0}$ to be the matrix with entries $[Y]_{ij} = \alpha_{ji}$. The complex matrix keeps track of how the species $X_1, \ldots, X_n$ are embedded in the complexes $C_1, \ldots, C_m$.

Following the derivation of equation (2-28) of [17], the system of differential equations governing the evolution of species concentrations over time under mass-action kinetics can be given by

$$\frac{d\mathbf{x}}{dt} = Y \cdot A_k \cdot \Psi(\mathbf{x}). \tag{4}$$

A chemical reaction network endowed with the mass-action kinetics (4) will be called a *mass-action system* and denoted by the quadruple $\mathcal{M} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$ where $\mathbf{k}$ is the set of specified rate constants.

Since mass-action kinetics is the only kinetics considered in this paper, we will consider a chemical reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ to be a *super-set* of the mass-action systems $\mathcal{M} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$. That is to say, we will think of chemical reaction networks as the set of all mass-action systems $\mathcal{M}$ with specified network structure. Since two mass-action systems $\mathcal{M} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$ and $\mathcal{M}' = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k}')$ can possess wildly disparate behaviour despite having the same underlying reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$, it will be important to distinguish between dynamical results which hold for all mass-action systems $\mathcal{M}$ with a particular network structure $\mathcal{N}$ and those which hold for only some.

The behaviour of solutions of (4) can be further understood by consideration of the *reaction vectors*

$$v_{ij} = \begin{cases} [Y]_{\cdot,j} - [Y]_{\cdot,i} & \text{for } (C_i, C_j) \in \mathcal{R} \\ 0 & \text{otherwise} \end{cases}$$

where $[Y]_{\cdot,i}$ denotes the ith column of Y. The span of the vectors is called the *stoichiometric subspace* and is denoted by $S = \text{span}\{v_{ij} \mid (C_i, C_j) \in \mathcal{R}\}$. We will denote the dimension of S by $s = \dim(S)$. It is clear that the right-hand side of (4) is contained in S so that the vector field always directs trajectories within an affine translation of S. It can be shown that trajectories are restricted to the *stoichiometric compatibility classes* $(\mathbf{x}_0 + S) \cap \mathbb{R}^n_{>0}$ [17, 39].

2.2. Complex Balanced Mass-Action Systems and Deficiency

The structure of the reaction graph of a chemical reaction network $\mathcal{N}$ plays an important role in determining the dynamical behaviour of the network's admissible mass-action systems $\mathcal{M}$.

A particularly important structural parameter of a chemical reaction network is the *deficiency*, which was introduced in [15, 6] and has been studied extensively since [7, 11, 8, 29].

Definition 2.1. *The **deficiency** of a chemical reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is given by*

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

where m is the number of stoichiometrically distinct complexes, ℓ is the number of linkage classes, and s is the dimension of the stoichiometric subspace.

The deficiency is strongly related to the capacity for a network $\mathcal{N}$ to admit mass-action systems $\mathcal{M}$ with *complex balanced equilibrium concentrations*. It may only take on nonnegative integer values [6].

Definition 2.2. *An equilibrium concentration $\mathbf{x}^* \in \mathbb{R}^n_{>0}$ of a mass-action system $\mathcal{M}$ is called a **complex balanced equilibrium concentration** if*

$$A_k \cdot \Psi(\mathbf{x}^*) = \mathbf{0}.$$

*A mass-action system is called **complex balanced** if every equilibrium concentration is a complex balanced equilibrium concentration.*

It is known that if a mass-action system is complex balanced at one equilibrium concentration then it is complex balanced at all of them (Theorem 6A, [17]). Consequently, a mass-action system for which any equilibrium concentration is complex balanced is a complex balanced system.

The following results relate the deficiency of a chemical reaction network to its capacity to admit complex balanced mass-action systems (see Theorem 4A of [15] and Theorem 4.1 of [6]). Theorem 2.1 is a special case of Theorem 2.2, taking the deficiency to be zero. We state it separately, however, due to its historical importance.

Theorem 2.1 (Deficiency Zero Theorem). *Every mass-action system admitted by a chemical reaction network is complex balanced if and only if the network is weakly reversible and has a deficiency of zero.*

Theorem 2.2. *If a chemical reaction network is weakly reversible, then the deficiency corresponds to the number of algebraically independent conditions on the rate constants which need to be satisfied in order for a corresponding mass-action system to be complex balanced.*

Predictable dynamical properties are known to follow from complex balancing; in particular, the following was proved in [17].

Theorem 2.3 (Theorem 6A and Lemma 4C, [17]). *If a mass-action system $\mathcal{M}$ is complex balanced then there exists within each positive stoichiometric compatibility class exactly one equilibrium concentration, and that equilibrium concentration is locally asymptotically stable relative to its compatibility class.*

The surprising implication of Theorem 2.1 and Theorem 2.3 is that we can know very strong properties about the equilibrium set of a mass-action system *based on structural properties of the underlying chemical reaction network alone*. In other words, the results hold regardless of the values of the rate constants. This is particularly important for biological examples, where the relevant rate constants are frequently difficult to obtain or measure. In cases where the deficiency is nonzero, supplemental conditions on the rate constants are required to bridge the gap from weak reversibility to complex balancing. Theorem 2.2 tells us that we are more likely to be interested

in mass-action systems where the underlying network has a *lower* deficiency, since networks with a lower deficiency permit more mass-action systems exhibiting complex balancing (and the regular dynamics guaranteed by Theorem 2.3) than networks with a higher deficiency.

A result which further relates the deficiency of a chemical reaction network to properties of the equilibrium set of the corresponding mass-action systems is the following, which can be found in [10]. It is worth noting, once again, that a lower deficiency generally guarantees more predictable behaviour than a higher deficiency. (Further work investigating the capacity of deficiency one networks to admit mass-action systems which exhibit multistability was presented in [8].)

Theorem 2.4 (Deficiency One Theorem). *Consider a chemical reaction network $\mathcal{N}$ with deficiency δ and linkage classes $\mathcal{L}_1, \ldots, \mathcal{L}_\ell$. Let δ_i, $i = 1, \ldots, \ell$, be the deficiency of the linkage class $\mathcal{L}_i$ considered as its own subnetwork. Suppose that*

1. $\delta_i \leq 1$, *for* $i = 1, \ldots, \ell$;
2. $\sum_{i=1}^{\ell} \delta_i = \delta$; *and*
3. *each linkage class contains only one terminal strongly connected component.*

Then, if a mass-action system $\mathcal{M}$ admitted by $\mathcal{N}$ has a positive equilibrium concentration, there is exactly one equilibrium concentration in each positive stoichiometric compatibility class of the system. Furthermore, if $\mathcal{N}$ is weakly reversible, then every mass-action system admitted by the network has a positive equilibrium concentration.

2.3. Linearly Conjugate Networks

It is possible for two mass-action systems to give rise to the same governing kinetics (4); interestingly, this can occur even when the underlying network structures are different. For example, the mass-action systems

$$\mathcal{M}: \qquad 2X_1 \underset{1}{\overset{1}{\rightleftarrows}} 2X_2 \tag{5}$$

and

$$\mathcal{M}': \qquad 2X_1 \xrightarrow{1} 2X_2 \xrightarrow{2} X_1 + X_2 \tag{6}$$

both generate the dynamics $\dot{x}_1 = -2x_1 + 2x_2$, $\dot{x}_2 = 2x_1 - 2x_2$ under (4). We can see that, while the networks $\mathcal{N}$ and $\mathcal{N}'$ underlying $\mathcal{M}$ and $\mathcal{M}'$ share several qualitative features, they also have many fundamental differences, e.g. $\mathcal{N}$ is weakly reversible while $\mathcal{N}'$ is not; $\mathcal{N}'$ contains the complex $X_1 + X_2$ while does not, etc. In spite of these structural differences, however, it nevertheless follows that $\mathcal{M}$ and $\mathcal{M}'$ exhibit *identical* dynamical behaviour as a result of sharing the same governing kinetics.

Two mass-action systems which give rise to the same mass-action kinetics (4) are said to be *dynamically equivalent*. Two dynamically equivalent mass-action systems $\mathcal{M}$ and $\mathcal{M}'$ are alternatively said to be *realizations* of the kinetics (4), although it is sometimes preferable to say that $\mathcal{M}$ is an alternative realization of $\mathcal{M}'$ or vice-versa [34]. (This phenomenon has long been known and has also been called *macro-equivalence* in [17], *non-uniqueness* of rate constants in [22], and *confoundability* in [2].) The most complete analysis of dynamical equivalence to date was conducted in [2], where the authors considered the question of whether a network structure could be uniquely determined based on information about the mass-action kinetics. The authors give necessary and sufficient conditions under which two chemical reaction networks $\mathcal{N}$ and $\mathcal{N}'$ can admit mass-action systems $\mathcal{M}$ and $\mathcal{M}'$, respectively, which are dynamically equivalent. (A technical correction to the main result of [2] was made in [32].)

In [19], the notion of dynamical equivalence was extended to *linear conjugacy*, whereby the trajectories of two mass-action systems could be related by a non-trivial linear transformation. For completeness, we include the formal definition of linear conjugacy as presented in [19]. We will let $\Phi(\mathbf{x}_0, t)$ denote the flow of (4) associated with $\mathcal{M}$ and $\Psi(\mathbf{x}_0, t)$ denote the flow of (4) associated with $\mathcal{M}'$.

Definition 2.3. *Two mass-action systems $\mathcal{M}$ and $\mathcal{M}'$ are said to be **linearly conjugate** if there exists a bijective linear mapping $\mathbf{h} : \mathbb{R}^n_{>0} \mapsto \mathbb{R}^n_{>0}$ such that $\mathbf{h}(\Phi(\mathbf{x}_0, t)) = \Psi(\mathbf{h}(\mathbf{x}_0), t)$ for all $\mathbf{x}_0 \in \mathbb{R}^n_{>0}$.*

It is known that a bijective linear transformation $\mathbf{h} : \mathbb{R}^n_{>0} \mapsto \mathbb{R}^n_{>0}$ can consist of at most positive scaling and reindexing of coordinates (Lemma 3.1, [19]). Consequently, when consideringly linearly conjugate systems, it will be sufficient to consider transformations of the form $\mathbf{h}(\mathbf{x}) = T\mathbf{x}$ where $T = \text{diag}\{\mathbf{c}\}$ for $\mathbf{c} = [c_1\ c_2\ \cdots\ c_m]^T \in \mathbb{R}^m_{>0}$. The components of $\mathbf{c}$ will be called the *conjugacy constants*.

Conditions which guarantee linear conjugacy are known. We now state the main result of [19]; to accommodate the notation used in this paper, however, we state the result as it appears in a later paper [21].

Theorem 2.5 (Theorem 3.2 of [19]; Theorem 2 of [21]). *Consider a mass-action system $\mathcal{M} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$ and a chemical reaction network $\mathcal{N}' = (\mathcal{S}, \mathcal{C}', \mathcal{R}')$. Let Y be the complex matrix consisting of the union of the complexes contained in either $\mathcal{C}$ or $\mathcal{C}'$ and let A_k denote the kinetics matrix corresponding to $\mathcal{M}$. Suppose that there is a kinetics matrix A_b corresponding to a mass-action system admitted by $\mathcal{N}'$ and a vector $\mathbf{c} \in \mathbb{R}^n_{>0}$ such that*

$$Y \cdot A_k = T \cdot Y \cdot A_b \tag{7}$$

where $T = diag\{\mathbf{c}\}$. Then $\mathcal{M}$ is linearly conjugate to the mass-action system $\mathcal{M}'$ admitted by $\mathcal{N}'$ which has the kinetics matrix given by

$$A'_k = A_b \cdot diag\{\Psi(\mathbf{c})\}. \tag{8}$$

Theorem 2.5 gives conditions under which a mass-action system $\mathcal{M}$ can be shown to be linearly conjugate to a mass-action system $\mathcal{M}'$ within a specified network structure $\mathcal{N}'$. If the conditions can be satisfied (i.e. a $\mathbf{c} \in \mathbb{R}^n_{>0}$ and kinetics matrix A_b satisfying (7) can be found) then Theorem 2.5 tells us a linearly conjugate network $\mathcal{M}' = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k}')$ exists and the rate constant set $\mathbf{k}'$ can be determined according to (12).

An important property of linear conjugacy is that, if a mass-action system $\mathcal{M}$ is linearly conjugate to another mass-action system $\mathcal{M}'$ which has known dynamics, properties such as number and stability of equilibria, persistence/boundedness of trajectories, and dimension of invariant spaces are easily transferred to $\mathcal{M}$ (Lemma 3.2, [19]). In particular, if the dynamics of $\mathcal{M}'$ can be determined by the underlying network structure $\mathcal{N}'$, as in Theorem 2.1 and Theorem 2.4, then this behaviour is transferred to $\mathcal{M}$ *even if* the underlying network structure $\mathcal{N}$ is not sufficient to guarantee such behaviour by itself. For example, consider the networks

$$\mathcal{N}: \qquad \begin{array}{rcl} X_1 & \xrightarrow{k_1} & X_2 \\ 2X_2 & \xrightarrow{k_2} & 2X_1 \end{array}$$

and

$$\mathcal{N}': \quad X_1 \underset{k_2'}{\overset{k_1'}{\rightleftarrows}} 2X_2.$$

These networks give rise to the dynamics $\dot{x}_1 = -k_1 x_1 + 2k_2 x_2^2$, $\dot{x}_2 = k_1 x_1 - 2k_2 x_2^2$ and $\dot{y}_1 = -k_1' x_1 + k_2' x_2^2$, $\dot{y}_2 = 2k_1' x_1 - 2k_2' x_2^2$, respectively. These systems are not dynamically equivalent for any rate constant choices; however, it can be easily checked that every mass-action system $\mathcal{M}$ admitted by $\mathcal{N}$ is linearly conjugate to a mass-action system $\mathcal{M}'$ admitted by $\mathcal{N}'$ under the transformation $y_1(t) = x_1(t)$, $y_2(t) = 2x_2(t)$ (that is to say, taking conjugacy constants $c_1 = 1$ and $c_2 = 2$). Since $\mathcal{N}'$ is weakly reversible and has a deficiency of zero, it follows by Theorem 2.1 that every mass-action system admitted by $\mathcal{N}$ satisfies the restrictive dynamics guaranteed by Theorem 2.3. It follows that every mass-action system $\mathcal{M}$ admitted by $\mathcal{N}$ exhibits the same restrictive dynamics even though the network is neither weakly reversible nor deficiency zero.

In general, we are not given a network structure $\mathcal{N}$ within which to search for linearly conjugate mass-action systems. This raises the question of how to *find* the network structure $\mathcal{N}$ underlying the linearly conjugate mass-action system $\mathcal{M}'$ when only the original system $\mathcal{M}$ is given. This question was first addressed for dynamically equivalent systems in [33]. In that paper, the authors presented a mixed-integer linear programming (MILP) procedure capable of determining, within the class of mass-action systems with a fixed complex set, a dynamically equivalent system with the greatest and fewest reactions (terms the *sparse* and *dense* realization, respectively). This MILP framework was extended to search for complex balanced and detailed balanced realizations in [35] and realizations for which the underlying network structure is weakly reversible in [36].

This methodology was extended to linearly conjugate networks in [21] and [20]. Given a mass-action network $\mathcal{M}$ and a fixed complex set $\mathcal{C}$ (and the associated kinetics matrix $A_k \in \mathbb{R}^{m\times m}$ and complex matrix $Y \in \mathbb{Z}_{\geq 0}^{n\times m}$), we can restrict our feasible region to the space of mass-action systems $\mathcal{M}'$ which are linearly conjugate to $\mathcal{M}$ and have complex set $\mathcal{C}$ with the linear constraint set

$$\textbf{(LC)} \quad \begin{cases} Y \cdot A_b = T^{-1} \cdot M \\ \sum_{i=1}^{m} [A_b]_{ij} = 0, \quad j = 1, \ldots, m \\ 0 \leq [A_b]_{ij} \leq 1/\epsilon, \quad i, j = 1, \ldots, m, \; i \neq j \\ [A_b]_{ii} \leq 0, \quad i = 1, \ldots, m \\ \epsilon \leq c_j \leq 1/\epsilon, \quad j = 1, \ldots, n \end{cases} \tag{9}$$

where $0 < \epsilon \ll 1$, and the matrices $M \in \mathbb{R}^{n\times m}$ and $T \in \mathbb{R}^{n\times n}$ are given by:

$$M = Y \cdot A_k, \text{ and} \tag{10}$$

$$T = \operatorname{diag}\{\mathbf{c}\}. \tag{11}$$

The kinetics matrix for the linearly conjugate mass-action system $\mathcal{M}'$ can then be constructed from $A_b \in \mathbb{R}^{m\times m}$ and $\mathbf{c} \in \mathbb{R}^n_{>0}$ by the relation

$$A_k' = A_b \cdot \operatorname{diag}\{\Psi(\mathbf{c})\}. \tag{12}$$

Finding a network satisfying (9) and then solving (12) is sufficient to determine a mass-action system $\mathcal{M}'$ which is linearly conjugate to $\mathcal{M}$ via the transformation $\mathbf{h}(\mathbf{x}) = T^{-1}\mathbf{x}$.

There are several important observations to make about the constraint set (9):

1. The given mass-action system $\mathcal{M}$ and underlying network $\mathcal{N}$ will be called the *original system* and the *original network*, respectively. The linearly conjugate system $\mathcal{M}'$ and its underlying network $\mathcal{N}'$ will be called the *target system* and *target network*, respectively.
2. The complex set $\mathcal{C}$, and consequently the complex matrix $Y \in \mathbb{Z}_{\geq 0}^{n\times m}$, must be specified before any optimization procedure may begin, but it is not immediately obvious how this specification should be done. It is common in the literature to initialize the complexes set $\mathcal{C}$ as the union of the reactant and product complexes from the original network $\mathcal{N}$ [33, 34, 36, 21]. This choice is not the only or necessarily the best which could be made, and for some systems it is beneficial to add additional complexes [20]. At any rate, it is possible for different initiations with different complex sets to give mass-action systems with different underlying network structures. Consequently, it is important to recognize that the constraint set (9) is over the space of systems $\mathcal{M}'$ which are linearly conjugate to $\mathcal{M}$ *for a fixed complex set only.*
3. While the matrix A_b does not exactly correspond to the kinetics matrix A'_k of $\mathcal{M}'$, the matrix has the same *structure* as A'_k. Consequently, the chemical reaction network $\mathcal{N}'$ can be determined from consideration of the structure of A_b. It is sufficient, therefore, to impose on A_b network properties of $\mathcal{N}'$ such as weak reversibility, minimal deficiency, etc.
4. There is no guarantee *a priori* that all the complexes assigned to Y will be present in the network $\mathcal{N}'$ underlying $\mathcal{M}'$. Without further clarification, therefore, the value m may be different in the linear conjugacy constraints (9) than that in Definition 2.1. We will avoid this notational difficulty by expanding the definition of the network $\mathcal{N}'$ to include all of the complexes initialized in Y; that is to say, we will allow complexes to be in $\mathcal{N}'$ *even if they are not the reactant or product complex for any reaction in* $\mathcal{N}'$. We will see in Section 3.1 that expanding the definition of a chemical reaction network does not pose a problems when determining the deficiency of the network $\mathcal{N}'$.

3. Minimal Deficiency Networks

We saw in Section 2.2 that many properties of the equilibrium set of a mass-action system $\mathcal{M} = \mathcal{S}, \mathcal{C}, \mathcal{R}, \mathbf{k})$ can be related to the value of the deficiency of the underlying chemical reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. Theorem 2.1 and Theorem 2.2 show that weakly reversible networks with lower deficiency permit more complex balanced mass-action systems (which have the restrictive dynamics guaranteed by Theorem 2.3) than ones with higher deficiency. Theorem 2.4 gives conditions under which a reaction network with a nonzero deficiency can still be guaranteed to permit only mass-action systems with a unique positive equilibrium concentration in each compatibility class.

In both of these cases, we find that for mass-action systems with underlying network structures which are weakly reversible, a *lower* deficiency is more likely to be indicative of predictable dynamics than a *higher* deficiency. In cases where a mass-action system is linearly conjugate to multiple mass-action systems with underlying network structures which are weakly reversible, we are likely to be most interested in the system corresponding to the underlying network with the minimal deficiency. In this section, we develop a mixed-integer linear programming procedure capable of determining linearly conjugate mass-action systems whose underlying reaction network is weakly reversible and has the minimal deficiency.

3.1. Parameters of Interest

We recall that, according to Definition 2.1, the deficiency of a chemical reaction network depends on three structural parameters of the reaction network: the number of stoichiometrically distinct complexes m, the number of linkage classes ℓ, and the dimension of the stoichiometric space s.

In order to avoid ambiguity with the value m used to represent the number of *potential* complexes in the linear constraints (9) and the value in Definition 2.1, we allow the network $\mathcal{N}'$ underlying the target system $\mathcal{M}'$ to contain complexes which do not correspond to the reactant or product complex of a reaction in $\mathcal{N}'$. These unused complexes will appear in the reaction graph as isolated nodes. For example, if we initialize the complex set $\{2X_1, 2X_2, X_1 + X_2\}$ and find the desired network $\mathcal{N}'$ only contains the complexes $\{2X_1, 2X_2\}$ as in (5), we will represent the underlying network as

$$\mathcal{N}': \qquad \begin{array}{c} 2X_1 \rightleftarrows 2X_2 \\ X_1 + X_2 \end{array}$$

We can see that each unused complex in this setting corresponds to a linkage class in itself and this linkage class is trivially strongly connected. Consequently, including these unused complexes in $\mathcal{N}'$ will not change the value of the deficiency of $\mathcal{N}'$, since the increase to m will be offset by a corresponding increase in ℓ in Definition 2.1. (In other words, the deficiency of the network above is zero whether we include $\{X_1 + X_2\}$ as its own trivial linkage class or exclude it from the network entirely.) Including these unused complexes will also not alter properties related to the reversibility of the network.

In order to minimize the deficiency within a linear programming framework, we need to find a way to quantify the parameters m, ℓ, and s. Since we will restrict the target system $\mathcal{M}'$ to have an underlying network $\mathcal{N}'$ which is weakly reversible, the largest invariant linear space of $\mathcal{M}'$ will correspond to the dimension of the stoichiometric space s of the underlying network $\mathcal{N}'$ (see Corollary 1 of [16]). Furthermore, since linear conjugacy preserves the dimension of invariant linear spaces of mass-action systems, it follows that *s is given by the dimension of the largest invariant linear space of the original system $\mathcal{M}$.* (It is worth noting that this many not, and need not, correspond to the dimension of the stoichiometric space of the original network $\mathcal{N}$ underlying $\mathcal{M}$ (see Example 2 of [19]).) We also notice that the value of *m corresponds to the number of potential complexes* and is consequently determined prior the optimization procedure.

It follows that, in order to minimize the deficiency of the network $\mathcal{N}'$ underlying a linearly conjugate target system $\mathcal{M}'$, it is sufficient to maximize ℓ. In other words, we need to maximize the number of linkage classes of $\mathcal{N}'$, where we allow that each unused complex will correspond trivially to its own linkage class.

3.2. Counting Linkage Classes

We need to keep track of the number of linkage classes ℓ of the target network $\mathcal{N}'$. In general, this is a difficult task; however, we are aided by the following result.

Theorem 3.1 (Appendix of [16]). *Let A_k be the kinetics matrix of a mass-action network $\mathcal{M}$ and let Λ_i, $i = 1, \ldots, \ell$, denote the support of the i^{th} linkage class of the underlying network $\mathcal{N}$. Then the reaction graph corresponding to A_k is weakly reversible if and only if there is a basis of ker(A_k), $\left\{\mathbf{b}^{(1)}, \ldots, \mathbf{b}^{(\ell)}\right\}$, such that, for $i = 1, \ldots, \ell$,*

$$\mathbf{b}^{(i)} = \begin{cases} b_j^{(i)} > 0, & j \in \Lambda_i \\ b_j^{(i)} = 0, & j \notin \Lambda_i. \end{cases} \tag{13}$$

It is easy to see that, for a mass-action system with an underlying network which is weakly reversible, the dimension of $\ker(A_k)$ given by Theorem 3.1 corresponds to the number of linkage classes. Consequently, the parameter ℓ here coincides with the earlier usage.

When applying Theorem 3.1, it is typical to assume that the kinetics matrix A_k corresponds to a network where every complex appears on either the reactant or product side of at least one reaction. It is easy to extend this to the case where complexes are not used by the reaction network by noting that any unused complexes will contribute an element to $\ker(A_k)$ satisfying (13) corresponding to a single positive value in the coordinate corresponding to the unused complex and zeroes elsewhere. In other words, for weakly reversible networks with unused complexes, we can extend the basis of $\ker(A_k)$ by considering unused complexes *as their own linkage classes*. Throughout this section, we will allow ℓ to correspond to both traditional linkage classes containing several complexes *and* unused complexes.

Theorem 3.1 implies that for a weakly reversible network, the supports of the basis elements of $\ker(A_k)$ represent a complete partition of the set $\{1, \ldots, m\}$, that is to say, we require

$$\begin{aligned} \Lambda_{k_1} \cap \Lambda_{k_2} = \emptyset, \quad & \text{for all } k_1, k_2 = 1, \ldots, \ell, k_1 \neq k_2 \\ \bigcup_{k=1}^{\ell} \Lambda_k = \{1, \ldots, m\}. & \end{aligned} \tag{14}$$

The value of ℓ, however, is not known; in fact, it is what is to be determined through the procedure. In order to implement this into a computational framework, therefore, we need to determine an upper limit for the number of possible supports Λ_k. We recall that the deficiency is a nonnegative parameter, so that we have $\delta = m - \ell - s \geq 0$ [6, 15]. Consequently, we have $\ell \leq m - s$ and therefore may use $m - s$ as an upper bound for ℓ. It is also clear that the deficiency will be zero if and only if this upper bound is attained.

We now introduce the binary variables $\gamma_{ik} \in \{0, 1\}$, for $i = 1, \ldots, m$, $k = 1, \ldots, m - s$, defined according to

$$\gamma_{ik} = \begin{cases} 1, & \text{if } i \in \Lambda_k \\ 0, & \text{if } i \notin \Lambda_k. \end{cases} \tag{15}$$

The variables γ_{ik} keep track of how the supports of the basis vectors in $\ker(A_k)$ according to (13) partition the set $\{1, \ldots, m\}$. For weakly reversible networks, this corresponds to an assignment between the complexes and the linkage classes by Theorem 3.1. In other words, $\gamma_{ik} = 1$ if and only if $C_i \in \mathcal{L}_k$.

We also introduce variables $\theta_k \in [0, 1]$, $k = 1, \ldots, m - s$, defined according to

$$\theta_k = \begin{cases} 1, & \text{if } \operatorname{supp}(\Lambda_k) \neq \emptyset \\ 0, & \text{if } \operatorname{supp}(\Lambda_k) = \emptyset. \end{cases} \tag{16}$$

The variables θ_k keep track of whether the kth partition of $\{1, \ldots, m\}$ is empty or nonempty. It should be noted that, while we would like the θ_k's to count the number of non-empty supports, and are therefore interested in only the values $\theta_k = 0$ and $\theta_k = 1$, it will be possible to relax the integrality of the θ_k's to vary continuously within the range $[0, 1]$. This will be justified in Section 3.5.

In order to accommodate the *complete partition* requirements (14) as linear constraints, and to accommodate (16), we impose

$$\textbf{(CP)} \quad \begin{cases} \sum_{k=1}^{m-s} \gamma_{ik} = 1, \quad i = 1, \ldots, m \\ \sum_{i=1}^{m} \gamma_{ik} - \epsilon\theta_k \geq 0, \quad k = 1, \ldots, m-s \\ -\sum_{k=1}^{m} \gamma_{ik} + \frac{1}{\epsilon}\theta_k \geq 0, \quad k = 1, \ldots, m-s \\ \gamma_{ik} \in \{0, 1\}, \quad i = 1, \ldots, m, k = 1, \ldots, m-s \\ \theta_k \in [0, 1], \quad k = 1, \ldots, m-s. \end{cases} \tag{17}$$

where $0 < \epsilon \ll 1$ is sufficiently small and can be chosen to be the same as in (9).

The first constraint set guarantees that each complex appears in exactly one partition. The second two constraint sets of (17) correspond to the constraint

$$0 \leq \epsilon\theta_k \leq \sum_{i=1}^{m} \gamma_{ik} \leq \frac{1}{\epsilon}\theta_k$$

which keeps track of whether the kth partition is empty or nonempty. If no element is in the kth partition, then the sum is zero, which forces θ_k to be zero (first inequality). If there is an element in the kth partition, then the sum is nonzero, which forces θ_k to be nonzero (second inequality). An argument in Section 3.5 will allow us to conclude that any nonzero θ_k must be one, so that this fulfills the requirements of (16).

3.3. Constructing the Kernel

We still need to guarantee that the sets Λ_k considered in Section 3.2 correspond to the supports of vectors in $\ker(A_b)$ which satisfy (13). In other words, we need to restrict ourselves to sets Λ_i, $i = 1, \ldots, \ell$, where there exists a $\mathbf{b}^{(i)}$ satisfing (13) and

$$A_b \cdot \mathbf{b}^{(i)} = \mathbf{0}, \quad i = 1, \ldots, \ell. \tag{18}$$

We follow the technique outlined in the paper [21] for determining weakly reversible networks. We define a matrix $\Phi \in \mathbb{R}^{m \times m}$ with entries

$$\Phi_{ij} = [A_b]_{ij} \cdot \mathbf{b}_j \tag{19}$$

where $\mathbf{b} = \sum_{k=1}^{\ell} \mathbf{b}^{(k)}$ and $\left\{\mathbf{b}^{(1)}, \ldots, \mathbf{b}^{(\ell)}\right\}$ is any set of vectors satisfying (13) and forming a basis of $\ker(A_b)$. We can see that the system of non-linear equations (18) is satisfied if and only if the system of linear equations

$$\sum_{j \in \Lambda_k} \Phi_{ij} = 0, \quad \text{for all } i = 1, \ldots, m, k = 1, \ldots, \ell, \tag{20}$$

is satisfied.

We know that Φ is a kinetics matrix since A_b is and (19) preserves this property. That is to say, we have

$$\sum_{j=1}^{m} \Phi_{ji} = 0, \quad \text{for all } i = 1, \ldots, m \tag{21}$$

and

$$\Phi_{ij} \geq 0, \quad \text{for all } i, j = 1, \ldots, m, i \neq j.$$

Consequently, we can solve the diagonal elements of Φ in (21) and substitute them into (20) to get the simplified constraint set

$$\sum_{\substack{j \in \Lambda_k \\ j \neq i}} \Phi_{ij} = \sum_{\substack{j=1 \\ j \neq i}}^{m} \Phi_{ji}, \quad \text{for } i = 1, \ldots, m, k = 1, \ldots, \ell. \tag{22}$$

We need to derive linear constraints capable of constructing a matrix Φ according to (19) which satisfies (22) and has the same structure as A_b. This is made more challenging than the case considered in [21] by the requirement that the kernel vector $\mathbf{b}$ in (19) decompose according to the partitions Λ_k, $k = 1, \ldots, \ell$.

We notice first of all that we do not know how many partitions Λ_k we will need, so we will take the upper bound $m - s$ on the number of partitions (see Section 3.2). We also notice that the construction (19) requires that $\Phi_{ij} = 0$ for any i and j such that $i \in \Lambda_k$ and $j \notin \Lambda_k$ for some $k = 1, \ldots, m-s$. That is to say, we do not permit reactions to occur between complexes in different linkage classes. This can be accommodated by noticing that, if two indices i and j are on the same support Λ_k, then we will have $\gamma_{ik} - \gamma_{jk} = 0$ *for all* $k = 1, \ldots, m - s$, where as if i and j are not on the same support Λ_k, we will have $\gamma_{ik} - \gamma_{jk} \in \{-1, 0, 1\}$ and attain the value -1 for at least one k. Consequently, we can accommodate this requirement with the linear constraints

$$\begin{gathered} \Phi_{ij} \leq 1/\epsilon(\gamma_{ik} - \gamma_{jk} + 1), \\ \text{for } i, j = 1, \ldots, m, i \neq j, k = 1, \ldots, m - s. \end{gathered} \tag{23}$$

We can accommodate (22), (23), and the requirement that Φ have the same structure as A_b, with the linear constraint set

$$\textbf{(Ker)} \quad \begin{cases} \displaystyle\sum_{\substack{l=1 \\ l \neq i}}^{m} \Phi_{il} = \sum_{\substack{l=1 \\ l \neq i}}^{m} \Phi_{li} \\ \Phi_{ij} \leq \dfrac{1}{\epsilon}(\gamma_{ik} - \gamma_{jk} + 1) \\ \Phi_{ij} \geq \epsilon [A_b]_{ij} \\ \Phi_{ij} \leq \dfrac{1}{\epsilon}[A_b]_{ij} \\ i, j = 1, \ldots, m, i \neq j, \;\; k = 1, \ldots, m - s. \end{cases} \tag{24}$$

Notice that (22) can be generalized to the first constraint in (24) because of the imposition that $\Phi_{il} = 0$ for any $l \notin \Lambda_k$ in the left sum. This is guaranteed by (23).

3.4. Uniqueness of Solution

The constraint sets (9), (17), and (24), form the basis of a mixed-integer linear programming (MILP) problem. The problem is mixed-integer due to the non-continuous binary variables γ_{ik}, $i = 1, \ldots, m$, $j = 1, \ldots, m-s$, which keep track of how the complexes are assigned to the partitions.

MILP problems are known to NP-hard and are generally approached by a branch-and-bound method (for an accessible introduction to branch-and-bound methodology, see [12, 26]). One well-known complicating factor for branch-and-bound methods is non-uniqueness of the integer portion of the problem. There is nothing in the constraint sets (17) which guarantee a unique assignment of the complexes to partitions. That is to say, a linkage class could be assigned to the first partition as easily as the second or third. Consequently, we would like to introduce further constraints which guarantee a unique partitioning structure for the optimal solution.

An intuitive way to structure the partitioning variables γ_{ik} is to always assign the first complex to the first partition, and then to assign each subsequent free complex to the next available partition. That is to say, if the second complex is not in the same partition as the first complex, it will be assigned to the second partition. If it is in the same partition as the first complexes, but the third is not, then the third complex will be assigned to the second partition.

This *unique* partition structure can be guaranteed by the linear constraint set

$$\textbf{(U)} \quad \begin{cases} \displaystyle\sum_{j=1}^{i-1} \gamma_{jk} \geq \sum_{l=k+1}^{m-s} \gamma_{il}, \\ i = 1, \ldots, m, k = 1, \ldots, m-s, k \leq i. \end{cases} \tag{25}$$

This constraint set guarantees that, in ascending order, each complex which is assigned to a new partition is assigned to the unused partition with the lowest index. It does so in the following way:

1. For the case $i = k = 1$, the left sum in (25) is empty and therefore returns a value of zero. This forces $\gamma_{1l} = 0$ for $l = 2, \ldots, m-s$, which forces $\gamma_{11} = 1$ by the first condition of (17). In other words, the first complex is always assigned to the first partition.
2. The left sum in (25) is zero for $i = k = 2$, which forces $\gamma_{2j} = 0$ for $j = 3, \ldots, m-s$. This forces the second complex to be assigned to either the first partition or the second partition by (17), depending on whether it is grouped with the first complex or not.
3. Following an induction on the complexes as $i = 3, \ldots, m$, we can see that the constraint (25) corresponding to the ith complex and the first unused partition will always guarantee this complex may not be assigned to a partition of a higher index than the first unused partition. Consequently, if it not grouped with an earlier complex, it must be assigned the index of the next available partition.
4. It is easy to see that the conditions (25) are satisfied for all of the entries not corresponding to leading ones, so that we are done.

3.5. Minimizing the Deficiency

We know that minimizing the deficiency δ is equivalent to maximizing the number of linkage classes ℓ, where we include the unused complexes as linkage classes unto themselves.

In Section 3.2 we introduced variables $\theta_k \in [0, 1], k = 1, \ldots, m-s$, according to (16) to keep track of the number of partitions Λ_k of $\{1, \ldots, m\}$ which corresponded to vectors in $\ker(A_b)$ satisfying (13). We have no guarantee, however, that these sets correspond to a complete basis of $\ker(A_b)$

since any two vectors in $\ker(A_b)$ satisfying (13) can be added to one another to produce another vector in $\ker(A_b)$ also satisfying (13). (This corresponds to multiple linkage classes being placed on the same support Λ_k.) We also have no guarantee that the θ_k's will properly enumerate the *number* of basis elements of $\ker(A_b)$ since any θ_k corresponding to a nonempty support may attain a value anywhere between zero and one, and not just the value of one.

We need to guarantee that the sum of the θ_k's corresponds to the maximal partition of $\{1,\ldots,m\}$ and that each θ_k attains a value of one when it corresponds to a nonempty support. Consider the objective function corresponding to maximizing the number of linkage classes, which corresponds to minimizing the deficiency. We have

$$\textbf{(Min Def)} \quad \left\{ \qquad \text{minimize} \quad \sum_{k=1}^{m-1} -\theta_k \right. \tag{26}$$

over the constraint sets (9), (17), and (24). We notice that this objective function guarantees that, if a θ_k is in between zero and one, it will attain the value one and that a maximal partition of $\{1,\ldots,m\}$ will be chosen, because in both cases such a situation is more optimal than the alternative. In other words, the θ_k's count the number of linkage classes when (26) is imposed.

If the off-diagonal elements are solved for in (9), the algorithm presented here for finding a weakly reversible network with minimal deficiency which is linearly conjugate to a given network contains $m(2m-1)+n-s$ continuous decision variables and $m(m-s)$ binary decision variables.

It should be noted that a linearly conjugate system whose underlying reaction network has a maximal deficiency *cannot* be obtained in the same fashion as outlined here. This is due to having to maximize the sum in (26) in order to make the correspondence between the sum of the θ_k's and the value of ℓ. Without this step, we could not rule out linkage classes clumping together onto the same support in $\ker(A_k)$.

4. Examples

We now introduce a few examples which illustrate the methods presented in this paper. All computations are performed on the primary author's personal-use Acer laptop (AMD Athlon II Neo K125 Processor 1.70 GHz, 4 GB RAM).

Example 1: We propose the following network. Consider a substrate which can bind to an enzyme T at one of three binding sites and let T_{100}, T_{010}, and T_{001} denote the enzyme with the substrate bound at the first, second, and third binding site, respectively. Suppose that binary collisions between the substrates can cause a spontaneous shift in the substrate from one binding site to another, but no transfer of substrate from one bound enzyme to another. This web of interactions can be visualized by the network in Figure 1.

This network is weakly reversible and has a deficiency of three ($m=6, \ell=1, s=2$, $\delta = m-\ell-s=3$). Due to the high deficiency, we may not apply Theorem 2.1 or Theorem 2.4; however, since the network is weakly reversible, we may apply Theorem 2.2. This tells us that there are three algebraically independent conditions on the rate constants which must be satisfied in order for a mass-action system admitted by the network to be complex balanced and therefore fall within the scope of dynamics guaranteed by Theorem 2.3. If we set $C_1 = 2T_{100}$, $C_2 = 2T_{010}$, $C_3 = 2T_{001}$, $C_4 = T_{100}+T_{010}$, $C_5 = T_{100}+T_{001}$, and $C_6 = T_{010}+T_{001}$, then the required conditions

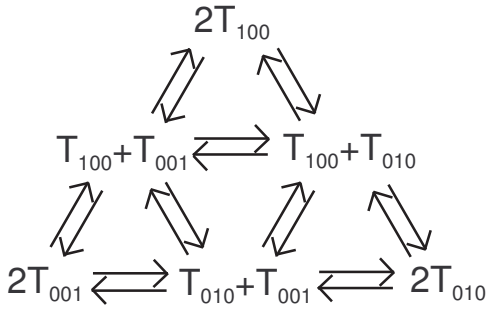

Figure 1: Network of singularly bound enzymes with three binding sites. Interactions between the enzymes allow transfer of substrates from one binding site to another.

are $K_1K_2 = K_4^2$, $K_1K_3 = K_5^2$, and $K_2K_3 = K_6^2$, where K_i is the absolute value of the (i,i) minor of A_k. (For details, see [1].)

We might wonder what additional behaviour is permitted by mass-action systems with the underlying reaction network given in Figure 1. A general analysis can be conducted by the CRN toolbox made freely available online [18]. This is a powerful computational toolbox capable of determining whether a chemical reaction network admits mass-action systems with the capacity for zero eigenvalues, injectivity, or multistability [9, 7, 5]. It is also capable of determining the deficiency of a chemical reaction network and determining whether it is concordant [28]. The toolbox's *Higher Deficiency Report* reveals that multiple positive steady states are permitted for the mass-action system corresponding to the rate constant choices

$$\begin{array}{lll} k(1,4) = 7.389056 & k(4,1) = 2.7182818 & k(5,4) = 4.3002585 \\ k(1,5) = 7.389056 & k(4,2) = 2.7182818 & k(5,6) = 4.3002585 \\ k(2,4) = 1 & k(4,5) = 55.125832 & k(6,2) = 32.08195 \\ k(2,6) = 1 & k(4,6) = 29.019118 & k(6,3) = 1.5819767 \\ k(3,5) = 2.5026503 & k(5,1) = 45.90757 & k(6,4) = 1.5819767 \\ k(3,6) = 2.5026503 & k(5,3) = 4.3002585 & k(6,5) = 1.5819767. \end{array} \tag{27}$$

Optimizing (26) over the constraint sets (9), (17), (24), and (25), using GLPK and the rate constant set (27) gives a mass-action system whose underlying reaction network has a deficiency of three. We conclude that there is no mass-action system which is linearly conjugate to the system given by the network in Figure 1 and the rate constant set (27) for which the underlying network has a lower deficiency than the original network. This is not necessarily surprising, since multistability is less common in mass-action systems for which the underlying reaction network has a low deficiency.

We now consider applying the deficiency-reducing methodology introduced in this paper on mass-action systems with the underlying network structure given by Figure 1 over different rate constant choices. Consider the mass-action systems with rate constants given by

$$k(i,j) = j, \quad i,j = 1,\dots 6, \quad (i,j) \in \mathcal{R} \tag{28}$$

and

$$k(i,j) = i, \quad i,j = 1,\dots,6, \quad (i,j) \in \mathcal{R}. \tag{29}$$

In other words, consider setting the rate constant for each reaction which produces C_j to be the same (28) and consider setting the rate constant for each reaction catalyzed by C_i to be the same (29). For simplicity, we have taken the differences between complexes to scale according to the index of the complex itself.

We optimize (26) over the contraint sets (9), (17), (24), and (25), in GLPK. The algorithm runs in under a second for both rate constant sets.

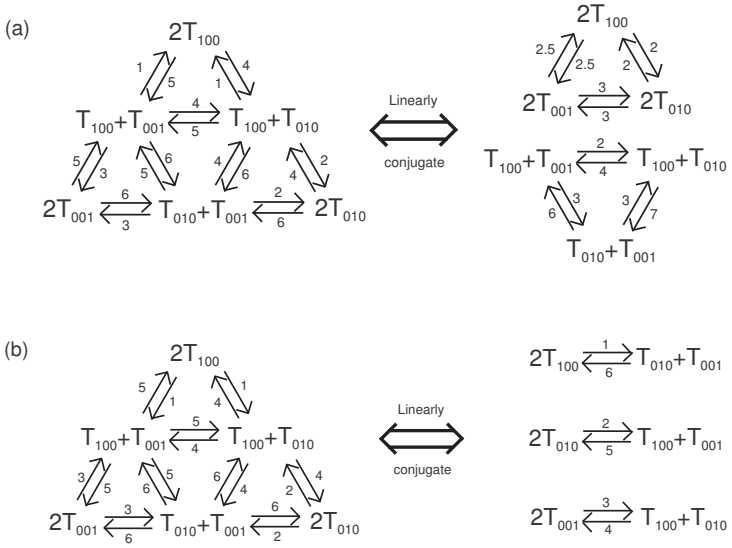

Figure 2: Weakly reversible networks which are dynamically equivalent to the one contained in Figure 1. The network in (a) is dynamically equivalent for the rate constant choices (28) and has a deficiency of two. The network in (b) is dynamically equivalent for the rate constant choices (29) and has a deficiency of one.

The results of the optimization for (28) and (29) together with their rate constants are contained in Figure 2. In both cases, the conjugacy constants are $c_1 = c_2 = c_3 = 1$, which implies the systems presented are dynamically equivalent. The network underlying the system in Figure 2(a) is deficiency two while the network underlying the system in Figure 2(b) is deficiency one. Neither network is amenable to application of Theorem 2.1 or Theorem 2.4. The CRN toolbox can, however, be used to verify (by the algorithm presented in [8]) that the mass-action system contained in Figure 2(b) admits at most one equilibrium concentration in each positive compatibility class. (Since weakly reversible networks contain at least one equilibrium concentration in each compatibility class, this is sufficient to guarantee that the network has exactly one equilibrium concentration in each compatibility class [3].)

Example 2: We are often only given information about the dynamics of a system and asked to infer a plausible network structure based on this kinetic information. For example, consider the

kinetic system given by

$$\begin{aligned}\frac{dx_1}{dt} &= 1 - x_1^2 - x_1 + x_2x_3\\ \frac{dx_2}{dt} &= 2x_1 - 2x_2x_3 - 2x_2^2 + 2x_3^2\\ \frac{dx_3}{dt} &= x_1 - x_2x_3 + x_2^2 - x_3^2.\end{aligned} \tag{30}$$

Using the algorithm presented in [14] and reproduced in [34] we can determine that the mass-action system given in Figure 3 generates the kinetics (30).

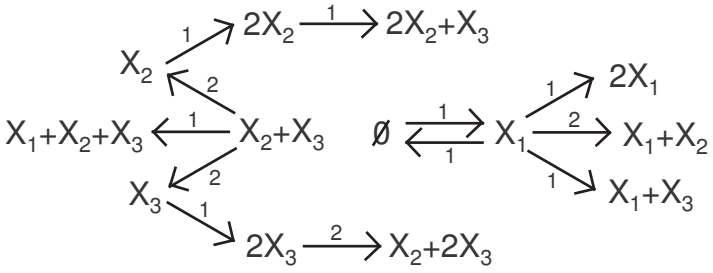

Figure 3: A mass-action system capable of generating the kinetics (30).

The underlying network of the mass-action system given in Figure 3 is not weakly reversible and has a deficiency of eight. It is therefore not amenable to Theorem 2.2 or Theorem 2.4. In order to apply these results, therefore, we would like to find a linearly conjugate mass-action system for which the underlying network is weakly reversible and which has a minimal deficiency. We construct the matrices

$$Y = \begin{bmatrix} 0 & 1 & 2 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0\\ 0 & 0 & 0 & 1 & 1 & 1 & 0 & 2 & 1 & 0 & 1 & 0 & 2\\ 0 & 0 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & 2 & 2 & 1 & 1 \end{bmatrix}$$

and

$$M = \begin{bmatrix} 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 2 & 0 & -2 & 0 & 0 & 0 & -2 & 0 & 2 & 0 & 0 & 0\\ 0 & 1 & 0 & -1 & 0 & 0 & 0 & 1 & 0 & -1 & 0 & 0 & 0 \end{bmatrix}$$

and optimize (26) over the contraint sets (9), (17), (24), and (25). The upper limit for the number of partitions, $m - s$, can be easily determined to be 10.

A quick computation in GLPK produces the network given in Figure 4(a). The underlying reaction network is a weakly reversible zero deficiency network and therefore falls within the scope of the networks considered by Theorem 2.1 and Theorem 2.3. Consequently, we know that (30) has exactly one positive equilibrium concentration and that this equilibrium concentration is locally asymptotically stable.

It is interesting to note that the network underlying the system contained in Figure 4(a) is not the only weakly reversible network which admits mass-action systems which are linearly conjugate to the network in Figure 3. If we do not insist on maximizing the number of linkage classes, other

networks can be selected with a sub-optimal deficiency value. For instance, the mass-action system in Figure 4(b) is also linearly conjugate to the system given in Figure 3 and has the same conjugacy constants as that of Figure 4(a). The underlying network is weakly reversible but has a deficiency of two and is therefore not amenable to either Theorem 2.1 or Theorem 2.4.

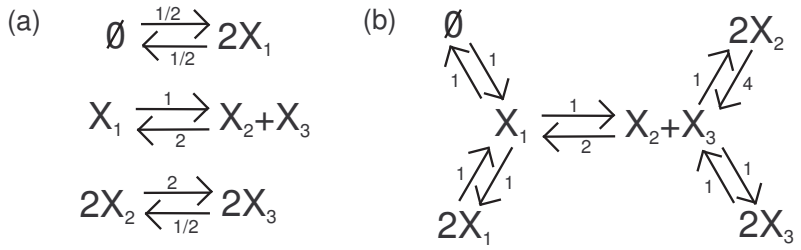

Figure 4: Two mass-action systems which are linearly conjugate to the mass-action system given by Figure 3. The conjugacy constants are $c_1 = c_3 = 1$ and $c_2 = 2$. The network underlying part (a) has a deficiency of zero while the network underlying part (b) has a deficiency of two. (Isolated complexes have been excluded from the reaction graph.)

5. Conclusions

In this paper, we have presented a computational method for determining mass-action systems which are linearly conjugate to a given mass-action system or kinetic system for which the underlying network is weakly reversible networks and has the minimal deficiency.

It was shown that, for this purpose, it is sufficient to maximize the number of the linkage classes of the underlying network, where linkage classes are defined to include isolated complexes as well as traditional linkage classes with multiple complexes. The proposed algorithm is based on mixed integer linear programming where the binary variables are used to keep track of the assignment of the complexes within the linkage classes, and the continuous variables keep track of the reaction rate coefficients, the conjugacy constants, the structure of the underlying network, and the emptiness/non-emptiness of complex partitions. An additional linear constraint on the binary variables ensures the uniqueness of the complex partitioning, which dramatically improves the computational efficiency of the algorithm. We then applied the algorithm to several examples and were able to use the Deficiency Zero Theorem (Theorem 2.1) and Deficiency One Theorem (Theorem 2.4) to determine properties of the equilibrium set of the original mass-action system or kinetic system.

Future work in this area includes:

1. In order to apply the algorithm outlined in this paper, it is necessary for the original network's rate constants be specified. Two mass-action systems, even with the same underlying reaction network, must be tested separately and can give different results. (Example 1 provides a good example of a network which permits different optimal deficiencies for different rate constant choices. If we were, for instance, only given the rate constant values specified by (27) or (28), we would not realize that the mechanism permitted a linearly conjugate network for which the underlying network had a deficiency of one.) Consequently, we may be overlooking linearly conjugate systems for which the underlying network has a lower deficiency due to poor rate

constant selection. (Research on these 'structurally-fixed' networks was initiated in [20] but can so far limited to dynamically equivalent systems.)

2. Many deficiency results do not require the networks in consideration be weak reversibility. For instance, the Deficiency One Theorem (Theorem 2.4) and the algorithm presented in [8] only require the networks have a single terminal strongly linked component within each linkage class. It would be useful, therefore, to adapt the presented algorithm to systems for which the underlying networks are not necessarily weakly reversible but rather have a single terminal strongly linked component in each linkage class.

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