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Computing Linearly Conjugate Weakly Reversible Kinetic Structures Using Optimization and Graph Theory

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Abstract

A graph-theory-based algorithm is given in this paper for computing dense weakly reversible linearly conjugate realizations of kinetic systems using a fixed set of complexes. The algorithm is also able to decide whether such a realization exists or not. To prove the correctness of the method, it is shown that weakly reversible linearly conjugate chemical reaction network realizations containing the maximum number of directed edges form a unique super-structure among all linearly conjugate weakly reversible realizations. An illustrative example taken from the literature is used to show the operation of the algorithm.

1 Introduction

Chemical reaction networks (CRNs, also called kinetic systems) obeying the mass action law originally come from the dynamical modelling of chemical and biochemical processes, but they can be used to describe a much wider range of nonlinear phenomena with possible

applications far away from chemistry [8, 22]. The simple algebraic structure of kinetic models makes it particularly appealing to develop computational model analysis methods for dynamical analysis, and even control, see e.g. [3, 4, 23].

Since the 1970's, the exploration of the relation between the reaction graph structure and the dynamics of the network without the precise knowledge of the reaction rate coefficients has become an important research area in chemical reaction network theory (CRNT), see e.g. [7, 12, 14]. From the numerous and continuously extending results in this field, we only mention a few with clear relevance to the topic of this paper. The Deficiency Zero Theorem [11,12] says that a weakly reversible CRN having zero deficiency has precisely one locally asymptotically equilibrium point in each positive stoichiometric compatibility class for any choice of positive rate constants. According to the Global Attractor Conjecture proved for one linkage class networks in [2], this stability is actually global (with respect to the the positive orthant) not just for deficiency zero weakly reversible CRNs, but for a wider class of systems called complex balanced networks that are weakly reversible, too (see, e.g. [10,13]). Moreover, according to the Boundedness Conjecture, the trajectories of weakly reversible CRNs are bounded. This conjecture was proved for one linkage class networks in [1]. The above mentioned results and conjectures emphasize the importance of the weak reversibility property of reaction graphs.

In the language of graph theory, weak reversibility means that the components of the directed reaction graph are strongly connected. It is also known, however, that the reaction graph corresponding to a given kinetic dynamics is generally non-unique. This phenomenon is called *macro-equivalence, confoundability* or *dynamical equivalence* [6, 14, 15]. An important extension of dynamical equivalence is linear conjugacy, where we allow a positive definite diagonal linear transformation between the solutions of linearly conjugate CRN dynamics [16]. Obviously, linear conjugacy preserves the main qualitative dynamical properties of CRNs like stability, multiplicities or the boundedness of solutions. Therefore, several computational methods have been suggested to find dynamically equivalent or linearly conjugate realizations for kinetic ordinary differential equations having preferred properties such as density/sparsity [25, 27], complex or detailed balance [26], or minimum deficiency [19]. The first solution for computing dynamically equivalent weakly reversible realizations using a graph-theoretic approach and mixed integer linear programming (MILP) was given in [28]. In [18] the computation of linearly conjugate weakly

reversible CRN realizations was described using a necessary and sufficient algebraic condition in the framework of MILP. Later, in [20] a purely linear programming (LP) based method was proposed for computing linearly conjugate weakly reversible CRN realizations. However, that algorithm has certain limitations: first, the applied transformation of the original MILP problem into LP form is only valid in a pre-defined interval in the space of decision variables. The second drawback is that the size of the optimization problem (i.e. the number of decision variables and constraints) grows quickly as the problem size (i.e. the number of complexes) increases. Moreover, no specific properties (such as having the maximal number of reactions) were proved for the CRN realization found by the method in [20].

In this paper, our aim is to give such a solution to the linearly conjugate weakly reversible realization problem that uses the minimum number of variables in each optimization step and does not use integer variables. This iterative approach is often advantageous over fewer but larger optimization steps even if the execution of the computation steps is sequential, especially when computational resources are limited [5]. Therefore, we will generalize the results of [28] to the linearly conjugate case. During the solution process, we also prove some new results on the structural properties of kinetic systems that are useful for showing the correctness of our algorithm.

2 Basic notions for dynamical and structural descriptions of kinetic systems

In this section, we briefly recall the basic notions and results for the algebraic and graph-based representations of CRNs.

The sets of natural numbers (including 0), real numbers and non-negative real numbers will be denoted by $\mathbb{N}$, $\mathbb{R}$ and $\mathbb{R}_+$, respectively. We denote the set of matrices with elements from any set H of numbers with n rows and m columns by $H^{n\times m}$, and the element in row i and column j of matrix M by $[M]_{i,j}$.

2.1 Algebraic characterization

Definition 2.1. *Chemical reaction networks can be defined by the following three sets* (see, e.g. [11, 12]).

1. *A set of* ***species:*** $\mathcal{S} = \{X_i \mid i \in \{1, \dots, n\}\}$

2. *A set of* ***complexes:*** $\mathcal{C} = \{C_j \mid j \in \{1, \ldots, m\}\}$, *where*
   $C_j = \sum_{i=1}^{n} \alpha_{j,i} X_i \qquad \forall j \in \{1, \ldots, m\}$
   $\alpha_{j,i} \in \mathbb{N} \qquad \forall j \in \{1, \ldots, m\},\ \forall i \in \{1, \ldots, n\}$

   That is, $\mathcal{C}$ *is a finite set of formal linear combinations of the species with non-negative integer coefficients, which are called* ***stoichiometric coefficients****.*

3. *A set of* ***reactions:*** $\mathcal{R} \subseteq \{(C_i, C_j) \mid C_i, C_j \in \mathcal{C}\}$,
   $\mathcal{R}$ *is a set of ordered pairs consisting of complexes. The ordered pair* (C_i, C_j) *corresponds to the reaction* $C_i \to C_j$.

To each reaction in $\mathcal{R}$ there belongs a positive real number $k_{i,j}$ called the **reaction rate coefficient**. According to our convention, $k_{i,j} = 0$ indicates that $(C_i, C_j) \notin \mathcal{R}$.

There are special matrices that will be necessary to define the dynamics of the system.

Definition 2.2. $Y \in \mathbb{N}^{n \times m}$ *is the* ***complex composition matrix*** *of the system if its entries are the stoichiometric coefficients as follows:*

$$[Y]_{i,j} = \alpha_{j,i} \qquad \forall i \in \{1, \ldots, n\},\ \forall j \in \{1, \ldots, m\} \tag{1}$$

Definition 2.3. $A_k \in \mathbb{R}^{m \times m}$ *is the* ***Kirchhoff matrix*** *belonging to the system if its off-diagonal entries are the reaction rate coefficients, and the following property is fulfilled:*

$$[A_k]_{i,j} = \begin{cases} k_{j,i} & \text{if } i \neq j \\ -\sum\limits_{l=1, l \neq i}^{m} k_{i,l} & \text{if } i = j \end{cases} \tag{2}$$

Since the sum of the elements in each column is zero, A_k *is also called a* ***column conservation matrix****.*

Assuming mass-action kinetics, the following dynamical equations can be used to describe the species' concentrations [11]:

$$\dot{x} = Y \cdot A_k \cdot \psi(x), \tag{3}$$

where $x : \mathbb{R} \to \mathbb{R}_+^n$ denotes the **concentrations of the species** depending on time, and $\psi : \mathbb{R}_+^n \to \mathbb{R}_+^m$ is a vector function defined by its coordinate functions as follows:

$$\psi_j(x) = \prod_{i=1}^{n} x_i^{\alpha_{j,i}} \quad j \in \{1, \ldots, m\} \tag{4}$$

Definition 2.4. *Let $x : \mathbb{R} \to \mathbb{R}^n_+$ be a function, $M \in \mathbb{R}^{n\times p}$ a matrix and $\varphi : \mathbb{R}^n_+ \to \mathbb{R}^p_+$ a monomial function. The polynomial system*

$$\dot{x} = M \cdot \varphi(x), \tag{5}$$

is called ***kinetic*** *if there exist a matrix $Y \in \mathbb{N}^{n\times m}$, a Kirchhoff matrix $A_k \in \mathbb{R}^{m\times m}$, so that*

$$M \cdot \varphi(x) = Y \cdot A_k \cdot \psi(x) \tag{6}$$

where $\psi : \mathbb{R}^n_+ \to \mathbb{R}^m_+$ is a monomial function determined by matrix Y, $\psi_j(x) = \prod_{i=1}^n x_i^{Y_{i,j}}$ for $j \in \{1, \ldots, m\}$. In this case the matrix pair (Y, A_k) is called a ***dynamically equivalent realization*** *of the kinetic system (5).*

We note that a necessary and sufficient condition for the kinetic property of polynomial vector fields based on the composition of monomials in φ and the sign-pattern of M was given in [15], where the constructive proof contains a procedure for obtaining suitable matrices Y and A_k as well.

It can be seen from Equations (3) and (4) that the matrices Y and A_k completely characterize the dynamics of the kinetic system, as well as a CRN and (as it will be shown in Section 2.2) the weighted directed graph belonging to it. But reaction networks with different species sets and structures may belong to exactly the same kinetic differential equations (i.e. the realizations of kinetic systems are generally non-unique), see e.g. [6, 14, 25]. By applying the method presented in [15], a suitable realization (Y, A_k) of the kinetic polynomial system (5) can be determined, called the **canonical structure**, which is very helpful to determine a possible set of complexes (i.e. matrix Y) and a Kirchhoff matrix, which together represent the given kinetic dynamics as a CRN.

Now we extend the notion of dynamical equivalence to the case where the kinetic model (5) is subject to a positive linear diagonal state transformation based on [16]. It is known from [9] that such a transformation preserves the kinetic property of the system.

Let us perform a state transformation defined by a positive definite diagonal matrix $T \in \mathbb{R}^{n\times n}$ on the kinetic model (5):

$$\bar{x} = T^{-1} \cdot x, \quad x = T \cdot \bar{x}. \tag{7}$$

Then, the differential equations of the transformed model are given by

$$\dot{\bar{x}} = T^{-1} \cdot \dot{x} = T^{-1} \cdot M \cdot \varphi(x) = T^{-1} \cdot M \cdot \varphi(T \cdot \bar{x}) = T^{-1} \cdot M \cdot \Phi_T \cdot \varphi(\bar{x}), \tag{8}$$

where $\Phi_T \in \mathbb{R}^{n\times n}$ is a positive definite diagonal matrix so that $[\Phi_T]_{i,i} = \varphi_i(T \cdot \mathbf{1})$ for $i \in \{1, \dots n\}$, φ_i is the ith coordinate function of φ, $\mathbf{1} \in \mathbb{R}^n$ is a vector with all coordinates equal to 1, and the product $T \cdot \mathbf{1}$ is also a vector that has the diagonal elements of matrix T as coordinates. Using the above notations and calculations, we can define the linearly conjugate realizations of a kinetic system.

Definition 2.5. *A CRN realization (Y, A'_k) is **linearly conjugate** to the kinetic system (5) if there exists a positive definite diagonal matrix $T \in \mathbb{R}^{n\times n}$ such that*

$$Y \cdot A'_k \cdot \psi(x) = T^{-1} \cdot M \cdot \Phi_T \cdot \varphi(x), \tag{9}$$

where $Y \in \mathbb{N}^{n\times m}$ so that $\psi_j(x) = \prod_{i=1}^{n} x_i^{Y_{i,j}}$ for $j \in \{1, \dots, m\}$, and $A'_k \in \mathbb{R}^{m\times m}$ is a Kirchhoff matrix.

It can be seen that in Equation (6) and in Definition 2.5 the set of complexes is not fixed. As it was mentioned before, by applying the method described in [15] a suitable set of complexes can be determined from the function φ in Equation (5), but arbitrary further complexes might be involved as well, which appear in the original kinetic equations with zero coefficients. These additional complexes change the dimension of the possible matrices Y and A'_k as well, therefore if we want to find realizations with a set of complexes different from the set in the canonical realization, we have to modify the matrices M and Φ_T in order to get the following equation:

$$Y \cdot A'_k \cdot \psi(x) = T^{-1} \cdot M' \cdot \Phi'_T \cdot \psi(x) \tag{10}$$

where the matrices $M' \in \mathbb{R}^{n\times m}$ and $\Phi'_T \in \mathbb{R}^{m\times m}$ have the same columns and diagonal entries as M and Φ_T belonging to the complexes determined by φ, and zero columns and 1 diagonal entries belonging to all additional complexes, respectively.

Since the function ψ is a monomial-type vector mapping, by using the notation $A_k = A'_k \cdot {\Phi'_T}^{-1}$, Equation (9) is fulfilled for all $x \in \mathbb{R}^n_+$ if and only if

$$Y \cdot A_k = T^{-1} \cdot M, \tag{11}$$

where A_k is a Kirchhoff matrix, too, obtained by scaling the columns of A'_k by positive scalars. It will be shown in Section 2.2 that this operation preserves the structure of the reaction graph encoded by A'_k.

It can be seen that dynamical equivalence is a special case of linear conjugacy, when the matrix T, and therefore the matrices T^{-1}, Φ_T, Φ'_T and ${\Phi'_T}^{-1}$ as well, are identity matrices.

From now on we will consider only linearly conjugate realizations on a given set of complexes. Consequently, matrix Y is fixed, and a Kirchhoff matrix A_k and a positive definite transformation matrix T has to be determined. According to Equation (11) these matrices uniquely determine a linearly conjugate realization, therefore such a realization will be denoted by the matrix pair (T, A_k). In Section 3 we describe a method for computing possible realizations.

2.2 Graph representation

A reaction network can also be described by a weighted directed graph.

Definition 2.6. *The graph $G(V, E)$ belonging to the CRN is called* ***Feinberg-Horn-Jackson graph****, or* ***reaction graph*** *for short. The sets and properties of the reaction network are represented as follows:*

1. *the vertices correspond to the complexes, $V(G) = \mathcal{C}$;*
2. *the directed edges describe the reactions, $E(G) = \mathcal{R}$,*
   there is a directed edge from the vertex C_i to C_j if and only if the reaction $C_i \to C_j$ takes place;
3. *the weights of the edges are the reaction rate coefficients, $w((C_i, C_j)) = k_{i,j}$ for $(C_i, C_j) \in \mathcal{R}$.*

In the reaction graph loops and multiple edges are not allowed.

There are several properties of the CRN that are easier to define using the reaction graph.

Definition 2.7. *A reaction network is called* ***weakly reversible*** *if for all $C_i, C_j \in \mathcal{C}$ it holds that if complex C_j is reachable from complex C_i, then C_i is reachable from C_j as well.*

If in the reaction graph complexes C_i and C_j are represented by vertices v_i and v_j, then Definition 2.7 means that if there is a directed path from vertex v_i to vertex v_j, then there is one from v_j to v_i as well.

Definition 2.8. *A directed graph is called* ***strongly connected*** *if all the vertices are reachable on a directed path from all other vertices. If a subgraph of a directed graph is a maximal strongly connected subgraph, then it is called a* ***strong component*** *of the directed graph. If a strong component contains only one vertex, then it is called a* ***trivial strong component****.*

We note that the vertex set of every directed graph can be partitioned into strong components in a unique way, since mutual reachability defines an equivalence relation on the set of vertices, where the equivalence classes are the strong components.

The following lemma gives a necessary and sufficient condition for weak reversibility, which is easy to prove.

Lemma 2.9. *A reaction network is weakly reversible if and only if there are no edges between different strong components of the reaction graph belonging to it.*

Paths between strong components need not be mentioned, because all the vertices are in some strong component, even the interior points of the paths. If in the reaction graph of a weakly reversible realization there is a trivial strong component, then it must be an isolated vertex.

It turns out that CRN realizations are special in a sense, since among them the 'biggest' one (the dense, according to Definition 2.10) is also maximal.

Definition 2.10. *A realization of a kinetic system is called a* ***dense realization*** *if the maximum number of reactions take place. This type of realization can be defined in the set of linearly conjugate, dynamically equivalent or any other kind of realizations.*

This means that there are the maximum number of edges in the reaction graph.

It was proven in [17] that the dense realizations determine a **super-structures** among dynamically equivalent and linearly conjugate realizations. It means that the reaction graphs of all the possible dynamically equivalent/linearly conjugate realizations on the same vertex set – not considering the weights of the edges – are subgraphs of the reaction graph of the corresponding dense realization.

It is clear that in both cases the reaction graph belonging to the dense realization is unique, because there cannot be two different graphs that are subgraphs of each other.

3 Optimization model

We are going to compute linearly conjugate realizations by using a linear optimization model. As described in Section 2.1, the equation which must be fulfilled by all linearly conjugate realizations of the kinetic system (3) can be written as

$$T^{-1} \cdot M - Y \cdot A_k = \mathbf{0} \tag{12}$$

where $\mathbf{0} \in \mathbb{R}^{n \times m}$ represents a zero matrix. The matrix Y (that describes the set of complexes) and the matrix M (that determines the dynamics of the system) are constant. The **variables** are represented by the matrices T and A_k, specifically by the off-diagonal entries of the matrix A_k and the diagonal entries of the matrix T^{-1} (because all others are zero).

Equation (12) guarantees the linear conjugacy of the system if the matrices T^{-1} and A'_k meet the definitions. To ensure this, Equations (13), (14) and (15) should hold as well:

$$[A_k]_{i,j} \geq 0 \qquad \forall i, j \in \{1, 2, \dots m\},\ i \neq j \tag{13}$$

$$\sum_{i=1}^{m} [A_k]_{i,j} = 0 \qquad \forall j \in \{1, 2, \dots m\} \tag{14}$$

$$[T^{-1}]_{i,i} > 0 \qquad \forall i \in \{1, 2, \dots m\} \tag{15}$$

When computing weakly reversible realizations, it will be necessary to exclude some set $\mathcal{H} \subseteq \mathcal{R}$ of reactions. This requirement can be arranged by adding a set of linear equations as follows:

$$[A_k]_{j,i} = 0 \qquad \forall (C_i, C_j) \in \mathcal{H} \tag{16}$$

An LP problem can be solved by a computer program if all variables are bounded. All the diagonal entries of T^{-1} and all the off-diagonal entries of A_k must be positive, but there is no upper bound for these. (If the off-diagonal entries of A_k are bounded, then the diagonal entries will also be bounded because of Equation (14). Also for this reason we will not consider these diagonal entries as variables.) The following proposition ensures that we can add such upper bounds without changing the existence of solutions.

Proposition 3.1. *For any linearly conjugate realization (T, A_k) of a kinetic system there is another linearly conjugate realization (T', A'_k) with all variables smaller than the given upper bound(s) so that the two realizations belong to the same graph structure, but the weights are different.*

Proof. If (T, A_k) is a linearly conjugate realization of the kinetic system, then Equation (12) must hold. By multiplying the equation with some positive constant $c \in \mathbb{R}_+ \setminus \{0\}$, we get another linearly conjugate realization

$$c \cdot T^{-1} \cdot M - c \cdot Y \cdot A_k = c \cdot \mathbf{0}, \tag{17}$$

that can be written as

$$(c \cdot T^{-1}) \cdot M - Y \cdot (c \cdot A_k) = \mathbf{0} \tag{18}$$

It is easy to see that the multiplication of the matrices by a constant does not change their essential properties. The matrix $c \cdot T^{-1} = T'^{-1}$ is a positive definite diagonal matrix, $c \cdot A_k = A'_k$ is a column conservation matrix and $[A'_k]_{i,j} = 0$ if and only if $[A_k]_{i,j} = 0$ for $i, j \in \{1, \ldots, m\}$. Therefore (T', A'_k) represents a linearly conjugate realization of the kinetic system that has the same reaction graph structure as the realization (T, A_k) does.

The value of the positive constant c can be determined so that all variables are below the given upper bound(s). The matrix equation can be considered as nm linear equations. It is easy to determine possible c values for each equation, and clearly all smaller values are also suitable. Therefore we can get an appropriate global constant c by taking the minimum of all the constants computed for the individual equations. □

Remark 3.2. *The method demonstrated in Proposition 3.1 cannot be used in the case of dynamically equivalent realizations, since the equation $M = Y \cdot A_k$ determining the connection to the dynamics is not homogeneous.*

4 A new method for determining dense realizations

In this section, we give a new efficient method that can be used for computing constrained dense linearly conjugate realizations. There exist several alternative solutions for this problem in the literature. In [24] an iterative method was proposed that consists of $m(m-1)+1$ linear programming steps. In [17], binary variables are assigned to the reaction rate coefficients to track the presence of reactions and their sum is maximized to obtain a dense realization. In [21], the binary variables are relaxed to the [0,1] interval and the problem is traced back to linear programming in the dynamically equivalent case (which is straightforward to extend to handle linear conjugacy). Our design principle here is to use the minimal number of decision variables in each computation step. Therefore, we propose an iterative method that is similar to the one presented in [24], but contains

less optimization steps. As we will see, the solution also ensures Eq. (15) even if linear programming itself handles only non-strict inequalities.

All the possible solutions of an LP problem are points of a convex (closed) polyhedron P, which is the intersection of the closed halfplanes determined by the constraints. The halfplanes are closed since all the constraints are non-strict inequalities.

In our model the off-diagonal entries of the matrix A_k and the diagonal entries of T^{-1} are the variables, which are the coordinates of the solution vector in a given order. The problem is that in our model there are also strict inequalities, which determine open halfplanes, therefore some of the boundary points of P are not valid solutions, these do not describe linearly conjugate realizations.

The idea for avoiding integer variables is to modify the model by changing all strict inequalities to be non- strict ones, compute some suitable boundary points of P (as an optimal solution is always a vertex or a point of a facet of the set of possible solutions) and determine a solution of the original problem as a convex combination of the computed vertices. For computing suitable points of P, we will manipulate the objective function of the modified model.

We may add some further constraints that are non-strict linear inequalities, but these do not require special handling.

According to the number of variables the polyhedron P is in $\mathbb{R}^{m^2-m+n}$. Let the point describing the linearly conjugate realization (T^i, A_k^i) be $P^i = (p_1^i, \ldots, p_n^i, \ldots, p_{m^2-m+n}^i) \in P$ so that the first n coordinates represent the diagonal entries of matrix T^{-1} and the rest are the off-diagonal entries of matrix A_k according to columns.

In the algorithm we use the following procedure repeatedly:

- **FindPositive**(M, Y, L, H) returns a point $Q \in P$ that fulfils the modified model determined by matrices M and Y and a finite set L of non-strict linear inequalities, so that considering a set H of indices the value of the objective function $\sum_{j \in H} q_j$ is maximal.

  This procedure also returns the set B of indices where $k \in B$ if and only if $q_k > 0$.

  The computation can be performed in polynomial time since it requires the solution of an LP problem and the checking of the elements in a set of size $m^2 - m + n$.

Remark 4.1. *The set L of linear non-strict inequalities is added to the procedure to extend our method to a wider class of problems. These inequalities are of the form*

$$\alpha_1 \cdot [T^{-1}]_{1,1} + \ldots + \alpha_n \cdot [T^{-1}]_{n,n} + \alpha_{n+1} \cdot [A_k]_{2,1} + \ldots + \alpha_{m^2-m+n} \cdot [A_k]_{n-1,n} \leq \beta \quad (19)$$

In Algorithm 2 we use these kinds of constraints to define the property that the reaction graph determined by the computed dense linearly conjugate realization is a subgraph of a given graph G, i.e. in the reaction network a given set of reactions can not take place, the reaction rate coefficients describing them are zero.

Algorithm 1

procedure DENSE_ALGORITHM(M, Y, L)
  $H := \{1, 2, \ldots, m^2 - m + n\}$
  $B := H$
  $Result := \mathbf{0} \in \mathbb{R}^{m^2-m+n}$
  $loops := 0$
  while $B \neq \emptyset$ **do**
    $(Q, B) :=$ FindPositive(Y, M, L, H)
    $Result := Result + Q$
    $H := H \setminus B$
    $loops := loops + 1$
  end while
  $Result := Result/loops$
  if $\exists i \in \{1, \ldots, n\} \cap H$ **then**
    There is no linearly conjugate realization of the kinetic system (M, Y)
    fulfilling the set L of constraints.
  else
    Result determines a dense linearly conjugate realization of the kinetic
    system (M, Y) fulfilling the L of constraints.
  end if
end procedure

Proposition 4.2. Algorithm 1 *returns a dense linearly conjugate realization of the kinetic system determined by the matrix M on a given set of complexes described by matrix Y, and fulfilling finitely many additional linear constraints in set L, if it exists. The computation runs in polynomial time.*

Proof. In the algorithm in case of each variable we try to find at least one point of the polyhedron P, where it has a positive value, if it is possible.

In the first step of the while loop we maximize the sum of all variables, then in the next step we do not consider those variables that had positive value before, and try to

find another point of P where the remaining variables have positive value. We repeat this step until no point in P can have a positive value among the remaining variables, or equivalently the value of the objective function is zero. This procedure will end in finitely many steps since the size of set H is finite and it gets smaller in each step. Let us denote the computed points of P by $P^1, P^2, \ldots, P^k$.

If for an index $j \in \{1, 2, \ldots, m^2 - m + n\}$ there is a point $Q \in P$ so that $q_j > 0$, then there must be a step in the while loop when the procedure FindPositive(M,Y,B,H) returns a point $P_i \in P$ where $p_j^i > 0$. Otherwise $i \in H$ after exiting the while loop but it would be a contradiction since in case of this set H the value of the objective function must be zero, but the point Q shows that it can be positive.

For any variable belonging to diagonal entries of matrix T^{-1} there must be a point of P where it has a positive value. If there exists $j \in \{1, \ldots, n\}$ so that for each point $Q \in P$ the coordinate q_j is zero, then there cannot be any linearly conjugate realization, since in case of a linearly conjugate realization T^{-1} must be a positive definite diagonal matrix.

The point $D \in P$ represents a dense linearly conjugate realization if it has the maximum number of positive off-diagonal entries in the matrix A_k (i.e. the maximum number of reactions take place). Since all other coordinates must be positive if D represents a linearly conjugate realization, this condition is equivalent to the point D having the maximum number of positive coordinates. Obviously only those coordinates of D can be positive which are positive in some of the computed points of P because of the computation method, and these will be positive in the variable *Result*.

The variable *Result* is computed as the arithmetic mean of points $P^1, P^2, \ldots, P^k \in P$, which is a convex combination of these points, therefore $Result \in P$ holds.

For $j \in \{1, \ldots, m^2 - m + n\}$ we have $Result_j > 0$ if and only if there is an index $i \in \{1, \ldots k\}$ so that $P_j^i > 0$ holds. Consequently the variable *Result* has the maximum number of positive coordinates.

It still needs to be proven that the point *Result* determines a valid solution of the problem. Since $Result \in P$, it would be an invalid solution only if it was on one of the hyperplanes defined by a strict inequality. But in this case there would be an index $j \in \{1, \ldots, n\}$ so that $Result_j = 0$, consequently for each index $i \in \{1, \ldots, k\}$ we would have $P_j^i = 0$, which according to the computation of these points means that there is no linearly conjugate realization of the kinetic system.

Considering the running time, in the while loop there are boundedly many steps (at most $|H|$), in each step an LP problem is solved besides some additional easy computation, therefore each step can be performed in polynomial time, and thus the algorithm runs in polynomial time. □

Remark 4.3. *During the actual computations we consider a reaction $C_i \to C_j$ to be present in the reaction network if and only if $[A_k]_{j,i} > \varepsilon$, where ε is a sufficiently small positive threshold value for distinguishing between practically zero and non-zero reaction rate coefficients. In our computations, we set ε to 10^{-6}.*
It is important to remark as well that all variables of the dense realization have value greater than ε, since the computed realizations were determined so that this property holds for them. The dense realization has coordinates which are the arithmetic means of the corresponding coordinates of the computed realizations, and it is true that the mean is greater than the smallest number in the set (if there are at least two different numbers in the set).

5 Algorithm for finding linearly conjugate weakly reversible realizations

The motivation for the algorithm presented in this section was published by Szederkényi et al. in [28]. It computes the dense dynamically equivalent weakly reversible realization for given dynamics on a fixed set of complexes. This solution can be extended to find linearly conjugate weakly reversible realizations. The main difference is that we have to look for dense linearly conjugate instead of dense dynamically equivalent realizations in each iteration step. However, the applicability of this approach is not trivial at all. Therefore, the main result of this section is the proof of the correctness of the extended algorithm.

The basic idea of the method is that edges between different strong components cannot occur in any subgraph which is the reaction graph of a weakly reversible realization.

There are two procedures applied repeatedly during the algorithm:

- **FindLinConjDense**(M, Y, G) returns the dense linearly conjugate realization of the dynamical system determined by the matrices M and Y with some subgraph of G as reaction graph. As it turned out from the first paragraph of Section 4 and

Proposition 4.2, there are several alternatives to solve this problem in polynomial time. Any of these can be used as the procedure **FindLinConjDense**. In the numerical computations of this paper, we used the newly proposed **Algorithm 1** for this purpose.

- **FindCrossedges**(G) returns the set of edges between the strong components of graph G. The strong components of a graph can be determined by the Kosaraju-Sharir algorithm in polynomial time.

In the algorithm $G(T, A_k)$ represents the reaction graph belonging to the realization (T, A_k), $E(G)$ is the edge set of graph G, and K_n denotes the complete directed graph on n vertices with edges directed in both directions, for each pair of vertices.

Algorithm 2

```
1:  procedure WR_ALGORITHM(M, Y)
2:      (T, A_k) :=FindLinConjDense(M, Y, K_n)
3:      G := G(T, A_k)
4:      while FindCrossedges(G) ≠ ∅ do
5:          E(G) := E(G)\ FindCrossedges(G)
6:          (T, A_k) := FindLinConjDense(M, Y, G)
7:          G := G(T, A_k)
8:      end while
9:      if E(G) = ∅ then
10:         There is no weakly reversible linearly conjugate realization.
11:     else
12:         (T, A_k) is a weakly reversible linearly conjugate realization.
13:     end if
14: end procedure
```

In the first step of the algorithm a dense linearly conjugate realization is found, and it is known from [17] that all other realizations are subgraphs of its reaction graph. If it is not weakly reversible, then it has edges between its strong components. These edges cannot be contained by any subgraph of it, which describes a weakly reversible realization. Therefore, we search for a dense linearly conjugate realization without these edges. If the result is again not weakly reversible, then we have to repeat these steps.

The question is: is it enough to examine only the subgraphs of the actual dense realization? Since deleting edges is a linear constraint in the optimization model, according to Proposition 5.1 the answer is yes.

Proposition 5.1. *Among all the realizations linearly conjugate to a given CRN and fulfilling a finite set of linear constraints there is a realization determining a super-structure.*

Proof. According to the optimization model, every realization can be represented as a point in $\mathbb{R}^{m^2-m+n}$ (since the diagonal entries of the matrix A_k are not considered as variables). All constraints are linear, therefore the possible solutions are in a convex polyhedron P. If the point $Q = (q_1, \ldots, q_n, \ldots, q_{m^2-m+n}) \in P$ represents the realization (T, A_k), then let the first n coordinates be the diagonal entries of matrix T^{-1} and the others the off-diagonal entries of matrix A_k according to columns.

Let us assume that the point Q has the maximum number of positive coordinates. Since it represents a linearly conjugate realization, the variables $q_1, \ldots, q_n$ are all positive, and maximality is equivalent to having the maximum number of positive coordinates belonging to off-diagonal entries of matrix A_k, or shortly it represents a dense linearly conjugate realization.

Let R represent another realization. Let us assume that there exists an index $i \in \{n+1, \ldots m^2-m+n\}$ so that $Q_i = 0$ but $R_i > 0$ (it must represent an off-diagonal entry of A_k). Then consider an interior point S of the interval (Q, R), where

$$(Q, R) = \{S \in \mathbb{R}^{m^2-m+n} \mid S = c \cdot Q + (1-c) \cdot R,\ c \in (0,1)\} \tag{20}$$

All the coordinates that are positive (not zero) in Q or R have to be positive in the point $S \in (Q, R) \subset P$ as well. Therefore S has more positive coordinates than Q, which is a contradiction.

Consequently there cannot be a suitable point $R \in P$, so points in the polyhedron P can have positive coordinates only where the point Q does, and the reaction graphs are subgraphs of the one describing Q. □

Corollary 5.2. *For any kinetic system, the dense weakly reversible linearly conjugate realization determines a super-structure among weakly reversible linearly conjugate realizations, and this realization can be computed by the algorithm above in polynomial time.*

Proof. Let G be the reaction graph of a weakly reversible linearly conjugate realization of the kinetic system. The graph G must be a subgraph of the reaction graph describing the dense linearly conjugate realization, which we shall denote by G_0. Since there cannot be any edge between the strong components of G, and each strong component of G is

a subgraph of a strong component of G_0, the cross-component edges of G_0 cannot be in $E(G)$. The realization described by graph G is a linearly conjugate realization, hence according to Proposition 5.1 G must be a subgraph of the dense realization without these edges. Let graph G_1 be its reaction graph.

If there are cross-component edges in graph G_1, then these cannot be in $E(G)$ either. Therefore another realization is computed, without the cross-component edges of G_1, described by some graph G_2 as reaction graph. According to its properties, G must be a subgraph of G_2. The computation goes on until such a realization is found that there are no cross-component edges, or no edges at all, as written in **Algorithm 2**. If there is any weakly reversible realization, then the first case must occur, and G must be a subgraph of the graph computed by the algorithm, therefore this result determines a super-structure among weakly reversible linearly conjugate realizations, and it must be the dense one. □

6 Example

In this section we examine the operation of our algorithm on a kinetic system with a given set of complexes. This kinetic system has a linearly conjugate weakly reversible realization but no dynamically equivalent weakly reversible realization.

Let us consider the kinetic system studied previously in Example 3 of [18] given by the differential equations

$$\begin{aligned}\dot{x}_1 &= x_1x_2^2 - 2x_1^2 + x_1x_3^2\\ \dot{x}_2 &= -x_1^2x_2^2 + x_1x_3^2\\ \dot{x}_3 &= x_1^2 - 3x_1x_3^2\end{aligned}$$

which can be originated from the matrix equation $\dot{x} = M' \cdot \varphi(x)$, where

$$M' = \begin{bmatrix} 1 & 0 & -2 & 1 \\ 0 & -1 & 0 & 1 \\ 0 & 0 & 1 & -3 \end{bmatrix}, \qquad \varphi(x) = \begin{bmatrix} x_1x_2^2 & x_1^2x_2^2 & x_1^2 & x_1x_3^2 \end{bmatrix}^\top$$

The polynomial system is kinetic if there are suitable matrices Y and A_k so that $Y \cdot A_k \cdot \psi(x) = M' \cdot \varphi(x)$, where the function ψ is determined by the matrix Y according to its coordinate functions

$$\psi_i(x) = \prod_{i=1}^{n} x_i^{Y_{i,j}} \quad i \in \{1, \ldots, n\},\ j \in \{1, \ldots, m\}$$

(assuming that the number of species and complexes are n and m, respectively). It may occur that considering only those complexes the monomials of which appear in the function φ no corresponding Kirchhoff matrix can be found, but by applying the method described in [15] we can get a suitable set of complexes:

$$\begin{array}{llll} C_1 = X_1 + 2X_2 & C_2 = 2X_1 + 2X_2 & C_3 = 2X_1 + X_2 & C_4 = 2X_1 \\ C_5 = X_1 & C_6 = 2X_1 + X_3 & C_7 = X_1 + 2X_3 & C_8 = 2X_1 + 2X_3 \\ & C_9 = X_1 + X_2 + 2X_3 & C_{10} = X_1 + X_3 & \end{array}$$

This determines the matrix Y and the vector function ψ:

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

$$\psi(x) = \begin{bmatrix} x_1x_2^2 & x_1^2x_2^2 & x_1^2x_2 & x_1^2 & x_1 & x_1^2x_3 & x_1x_3^2 & x_1^2x_3^2 & x_1x_2x_3^2 & x_1x_3 \end{bmatrix}^\top$$

Knowing the set of complexes, the polynomial system $\dot{x} = M' \cdot \varphi(x) = M \cdot \psi(x)$ defines the matrix M as well, since its coordinates are the coefficients of the corresponding monomials. The matrix is as follows:

$$M = \begin{bmatrix} 1 & 0 & 0 & -2 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & -3 & 0 & 0 & 0 \end{bmatrix}$$

By using the method described in [15] a Kirchhoff matrix A_k can also be determined, that fulfils the equation $Y \cdot A_k \cdot \psi(x) = M \cdot \psi(x)$, or equivalently the equation $Y \cdot A_k = M$, therefore the matrix pair (Y, A_k) describes a dynamically equivalent realization of the kinetic system. The matrix A_k defines the reaction graph of the canonical structure as it can be seen in Figure 1.

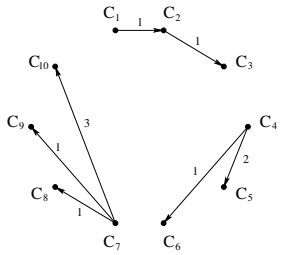

Figure 1: Canonical structure

$$A_k = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 3 & 0 & 0 & 0 \end{bmatrix}$$

It is possible to add further elements to the set of complexes, but this time the matrices Y and M should be modified accordingly by adding columns containing the coefficients of the species and zeros respectively.

Our algorithm works only if the set of complexes is fixed. We will take the set described by the matrix Y above.

The algorithm starts with computing a dense realization, then the strong components are determined and the edges between different ones get deleted. In each step a dense realization is computed where the reactions which belong to edges that were deleted at some step of the algorithm do not take place. This procedure is repeated until a weakly reversible realization is found or there is no realization fulfilling the constraints.

In the following figures we show the reaction graphs of the realizations computed during the running of the algorithm, where the edges between strong components are drawn dashed, and the weights of the edges are not indicated.
First we examine the case of dynamically equivalent realizations.

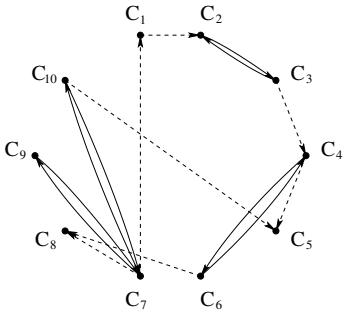

Figure 2: Reaction graph describing the dense dynamically equivalent realization

Figure 2 shows the reaction graph of the dense dynamically equivalent realization, and below it there is the corresponding Kirchhoff matrix A_{k1}. This realization determines a super-structure among dynamically equivalent realizations, and this is why the reaction graph in Figure 1 describing the canonical structure is a subgraph of it.

$$A_{k1} = \begin{bmatrix}
-1 & 0 & 0 & 0 & 0 & 0 & 0.5 & 0 & 0 & 0 \\
1 & -1 & 10000000 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & -20000000 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 10000000 & -3 & 0 & 10000000 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 2 & 0 & 0 & 0 & 0 & 0 & 10000000 \\
0 & 0 & 0 & 1 & 0 & -20000000 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -10000003.5 & 0 & 10000000 & 10000000 \\
0 & 0 & 0 & 0 & 0 & 10000000 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 10000000 & 0 & -10000000 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 2 & 0 & 0 & -20000000
\end{bmatrix}$$

As it is visible from Fig. 2, in the second step we have to compute a constrained realization not containing the reactions $C_7 \to C_8$, $C_6 \to C_8$, $C_7 \to C_1$, $C_{10} \to C_5$, $C_4 \to C_5$, $C_3 \to C_4$, and $C_1 \to C_2$. However, we find that this constrained problem is infeasible, therefore there is no weakly reversible dynamically equivalent realization of the kinetic system.

Now we examine the linearly conjugate realizations.

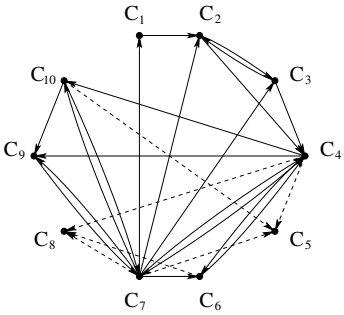

Figure 3: Reaction graph describing the dense linearly conjugate realization

The dense linearly conjugate realization defines a super-structure among linearly conjugate realizations, and since dynamically equivalent realizations form a subset of linearly conjugate realizations, the graph in Figure 2 is a subgraph of the reaction graph in Figure 3. The dense linearly conjugate realization is defined by the matrices A_{k2} and T_2^{-1}, which are presented below.

$$A_{k2} = \begin{bmatrix} -5714.29 & 0 & 0 & 0 & 0 & 0 & 714.29 & 0 & 0 & 0 \\ 5714.29 & -2857.14 & 7142857.14 & 0 & 0 & 0 & 714.29 & 0 & 0 & 0 \\ 0 & 1428.57 & -14285714.28 & 0 & 0 & 0 & 1428.57 & 0 & 0 & 0 \\ 0 & 1428.57 & 7142857.14 & -13571.44 & 0 & 7142857.14 & 1428.57 & 0 & 0 & 0 \\ 0 & 0 & 0 & 8571.43 & 0 & 0 & 4642.86 & 0 & 0 & 14285714.29 \\ 0 & 0 & 0 & 1428.57 & 0 & -14285714.28 & 714.29 & 0 & 0 & 0 \\ 0 & 0 & 0 & 714.29 & 0 & 0 & -14294642.86 & 0 & 14285714.29 & 7142857.14 \\ 0 & 0 & 0 & 714.29 & 0 & 7142857.14 & 1428.57 & 0 & 0 & 0 \\ 0 & 0 & 0 & 714.29 & 0 & 0 & 14280714.29 & 0 & -14285714.29 & 7142857.14 \\ 0 & 0 & 0 & 1428.57 & 0 & 0 & 2857.14 & 0 & 0 & -285714428.57 \end{bmatrix}$$

$$T_2^{-1} = \begin{bmatrix} 5714.2857 & 0 & 0 \\ 0 & 4285.7143 & 0 \\ 0 & 0 & 7142.8571 \end{bmatrix}$$

After the second step we get the reaction graph in Figure 4. According to Proposition 5.1 it is a subgraph of the reaction graph computed in the previous step.

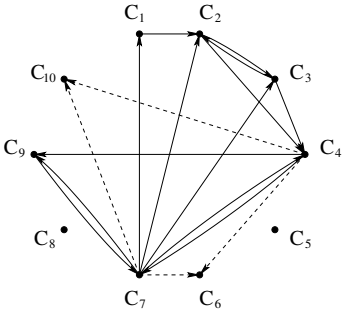

Figure 4: Reaction graph describing the realization computed in the second step of the algorithm

The realization is determined by the matrices A_{k3} and T_3^{-1} below.

$$A_{k3} = \begin{bmatrix} -2142.8571 & 0 & 0 & 0 & 0 & 0 & 1964.2857 & 0 & 0 & 0 \\ 2142.8571 & -3571.4286 & 7142857.1429 & 0 & 0 & 0 & 714.2857 & 0 & 0 & 0 \\ 0 & 1428.5714 & -14285714.2857 & 0 & 0 & 0 & 357.1429 & 0 & 0 & 0 \\ 0 & 2142.8571 & 7142857.1429 & -5714.2857 & 0 & 0 & 714.2857 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1428.5714 & 0 & 0 & 357.1429 & 0 & 0 & 0 \\ 0 & 0 & 0 & 714.2857 & 0 & 0 & -14300535.7143 & 0 & 14285714.2857 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 714.2857 & 0 & 0 & 14282857.1429 & 0 & -14285714.2857 & 0 \\ 0 & 0 & 0 & 2857.1429 & 0 & 0 & 13571.4286 & 0 & 0 & 0 \end{bmatrix}$$

$$T_3^{-1} = \begin{bmatrix} 2142.8571 & 0 & 0 \\ 0 & 5714.2857 & 0 \\ 0 & 0 & 7142.8571 \end{bmatrix}$$

Then again the cross-component edges get removed and only one non-trivial strong component remains. In the next step the algorithm returns that it is the reaction graph of a linearly conjugate realization. Consequently, it is a weakly reversible linearly conjugate realization. The realization is given by the matrices A_{k4} and T_4^{-1} below.

$$A_{k4} = \begin{bmatrix} -548.4848 & 0 & 0 & 0 & 0 & 0 & 2742.4242 & 0 & 0 & 0 \\ 548.4848 & -4000 & 10000000 & 0 & 0 & 0 & 166.6667 & 0 & 0 & 0 \\ 0 & 2000 & -20000000 & 0 & 0 & 0 & 181.8182 & 0 & 0 & 0 \\ 0 & 2000 & 10000000 & -1096.9697 & 0 & 0 & 200 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 733.3333 & 0 & 0 & -20002090.9091 & 0 & 20000000 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 363.6364 & 0 & 0 & 19998800 & 0 & -20000000 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$T_4^{-1} = \begin{bmatrix} 548.4848 & 0 & 0 \\ 0 & 6000 & 0 \\ 0 & 0 & 2193.9394 \end{bmatrix}$$

It can be clearly seen from the example that linear conjugacy may significantly increase the number and extend certain important properties of reaction graph structures corresponding to a given kinetic dynamics compared to dynamical equivalence.

7 Conclusion

A polynomial-time algorithm based on graph theory and linear programming was proposed in this paper to compute weakly reversible linearly conjugate realizations of kinetic systems. The algorithm is also capable to decide the existence of such realizations. It was shown that the algorithm returns the dense linearly conjugate weakly reversible realization, if it exists. For showing the correctness of the method, it was proved that dense, linearly conjugate realizations satisfying a finite set of linear constraints form a super-structure assuming a fixed set of complexes. Unlike the results in [18] and [20], the proposed approach does not use any auxiliary variables, only those that are essential for the solution of the problem i.e., the reaction rate coefficients and the parameters of the diagonal state transformation, although the solution is obtained in several iteration steps. At the same time, the proposed iterative graph theory based solution allows us to identify those unremovable edges in the reaction graph that prevent the existence of weakly reversible linearly conjugate realizations. This gives us additional insight into the causes of infeasibility compared to previous solutions that are based on the existence of a positive vector in the kernel of A_k. The operation and the steps of the algorithm were illustrated on an example taken from the literature. Additionally, a new iterative method was introduced for determining constrained linearly conjugate dense realizations that uses the minimal number of decision variables, too, and that is computationally more efficient than the one reported in [24].

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