Dynamical equivalence and linear conjugacy of biochemical reaction network models

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Abstract: The distinguishability and identifiability of biological network models are key properties influencing the reliability of structural and parametric identification of such models. Recently, several new results have been published about dynamically equivalent and linearly conjugate reaction networks. In this paper, the notion and importance of dynamical equivalence and linear conjugacy of biochemical network models obeying the mass action law is shown. For this, new concepts in the form of core complexes and core reactions for linearly conjugate networks are introduced. Two examples illustrate the developed computation methods.

Keywords: biological systems, chemical reaction networks, optimization

1. INTRODUCTION

An important subset of nonnegative nonlinear dynamical systems (and also of QP systems) is the class of chemical reaction network (CRN) models obeying the mass-action law (Horn and Jackson, 1972). Such networks can be used to describe pure chemical reactions, but they are also widely used to model the dynamics of intracellular processes, metabolic or cell signalling pathways (Haag et al., 2005). Thus, CRNs are able to describe key mechanisms both in industrial processes and living systems. Being able to produce all the important qualitative dynamical properties like stable and unstable equilibria, multiple equilibria, bifurcation phenomena, oscillatory and even chaotic behaviour (Epstein and Pojman, 1998), CRNs "have become a prototype of nonlinear science" (Érdi and Tóth, 1989).

Many of these phenomena have been actually observed in real chemical experiments where the practical constraints are much more severe than in the case of mathematical models (Noszticzius and Bódiss, 1980; Marlovits et al., 1995). This 'dynamical richness' of the model class explains that CRNs have attracted significant attention not only among chemists but in numerous other fields such as physics, or even pure and applied mathematics where non-linear dynamical systems are considered. The increasing interest towards reaction networks among mathematicians and engineers is also shown by recent tutorial and survey papers in the nonlinear control community (Sontag, 2001; Angeli, 2009; Chellaboina et al., 2009). From now on, only deterministic mass-action type models are meant by CRNs in this paper, although it is well-known that in many applications, reaction rates different from mass-action type and/or stochastic models are required.

Chemical reaction network theory (CRNT) is originated in the 1970's by the pioneering works of Horn, Jackson and Feinberg (Horn and Jackson, 1972; Feinberg, 1979). Since then, many strong results have been published on the relation between network structure and qualitative dynamical properties. One of the most significant results in the study of the dynamical properties of chemical reaction systems is described in (Feinberg, 1979, 1987), where (among other important results) the notion of 'deficiency' is introduced. The deficiency of a CRN is a nonnegative integer number that only depends on the stoichiometry and the graph structure of a CRN but not on the reaction rate coefficients. In the same paper, the stability of CRNs with zero deficiency is proved with a given Lyapunov function that is independent of the system parameters and therefore suggests a robust stability property with respect to parameter changes. These concepts were revisited, extended and put into a control theoretic framework in (Sontag, 2001). The relationship between the chemical network structure and the possibility of multiple equilibria is investigated in (Craciun and Feinberg, 2005) from and algebraic and in (Craciun and Feinberg, 2006; Craciun et al., 2006) from a graph-theoretic point of view.

It has been known for long that different reaction networks can produce exactly the same kinetic differential equations (Krambeck, 1970; Horn and Jackson, 1972). This phenomenon is also called macro-equivalence. We will call CRNs with different parametrization (that often implies structural difference as well) dynamically equivalent, if they give rise to the same ODEs. A possible CRN (with a certain structure and parametrization) having a given dynamical properties will be called a realization of that dynamics. Naturally, the phenomenon of dynamical equivalence has
an important impact on the identifiability of reaction rate constants: if a kinetic dynamics have different dynamically equivalent CRN realizations, then it is worth examining whether there exists a dynamically equivalent (or sufficiently ‘similar’) realization that guarantees certain properties of the corresponding dynamics that are not directly recognizable from the initial CRN or from the corresponding differential equations. Such an approach also gives us valuable help to set up meaningful constraints that guarantee the structural uniqueness and identifiability of the examined network structure (Szederkényi et al., 2011a). The notion of dynamical equivalence was extended in (Johnston and Siegel, 2011) by introducing linear conjugacy that allows a positive diagonal state transformation between the conjugate realizations.

Several optimization-based algorithms have been published for the computation of dynamically equivalent or linearly conjugate CRN structures with prescribed properties such as the minimal/maximal number of reactions or complexes, (weak) reversibility, detailed/complex balance (Szederkényi, 2010; Szederkényi and Hangos, 2011; Szederkényi et al., 2011b, 2012; Johnston et al., 2012). The aim of this paper is to extend these results by introducing and illustrating new notions and the corresponding optimization-based computation methods for the analysis of mass-action type biochemical network models.

2. BASIC NOTIONS AND TOOLS

In this section, the mathematical description of reaction networks and the notions of dynamical equivalence and linear conjugacy are summarized.

2.1 Mathematical modeling of reaction networks

Let us suppose \( X_i, \ i = 1, ..., n \) chemical species taking part in \( r \) chemical reactions. The concentrations \( x_i, \ i = 1, ..., n \) form the state vector of the elements which are naturally non-negative. The elementary reaction steps taking place between the chemical species are in the following form:

\[
\sum_{i=1}^{n} \alpha_{ij} X_i \rightarrow \sum_{i=1}^{n} \beta_{ij} X_i, \quad j = 1, ..., r
\]  

(1)

where \( \alpha_{ij} \) is the so-called stoichiometric coefficient of component \( X_j \) in the \( j \)th reaction, and \( \beta_{ij} \) is the stoichiometric coefficient of the product \( X_i \). The linear combinations of the species in eq. (1), namely \( \sum_{i=1}^{n} \alpha_{ij} X_i \) and \( \sum_{i=1}^{m} \beta_{ij} X_i \) for \( j = 1, ..., r \) are called the complexes and are denoted by \( C_1, C_2, ..., C_r \). The stoichiometric coefficients are all non-negative integers.

We say that the reaction network (1) obeys the mass action law (MAL), if the reaction rate of the above reactions can be described as

\[
\rho_j = k_j \prod_{i=1}^{n} [X_i]^{\alpha_{ij}} = k_j \prod_{i=1}^{n} x_i^{\alpha_{ij}}, \quad j = 1, ..., r
\]  

(2)

where \( [X_i] = x_i \) is the concentration of the component \( X_i \), and \( k_j > 0 \) is the reaction rate constant of the \( j \)th reaction, that is always positive.

We use the following dynamical description to describe the time-evolution of specie concentrations (Feinberg, 1979, 1987):

\[
\dot{x} = Y \cdot A_k \cdot \psi(x)
\]  

(3)

where \( Y \in \mathbb{R}^{n \times m} \) stores the stoichiometric composition of the complexes, \( A_k \in \mathbb{R}^{m \times m} \) contains the information corresponding to the weighted directed graph of the reaction network, and \( \psi : \mathbb{R}^n \rightarrow \mathbb{R}^m \) is a monomial-type vector mapping defined by

\[
\psi_j(x) = \prod_{i=1}^{n} x_i^{y_{ij}}, \quad j = 1, ..., m
\]  

(4)

where \( y_{ij} = [Y]_{ij} \). The explanation of the structures of \( Y \) and \( A_k \) is the following. The \( i \)th column of \( Y \) contains the composition of complex \( C_i \), i.e. \( Y_{ij} \) is the stoichiometric coefficient of \( C_i \) corresponding to the specie \( X_j \). \( A_k \) is a column conservation matrix (i.e. the sum of the elements in each column is zero) defined as

\[
[A_k]_{ij} = \begin{cases} -\sum_{l=1, l \neq i}^{m} k_{il}, & \text{if } i = j \\ k_{ij}, & \text{if } i \neq j \end{cases}
\]  

(5)

Based on the above, we will call a quadratic matrix a Kirchhoff matrix, if it is a column conservation matrix with non-positive diagonal and non-negative off-diagonal entries. Using \( Y \) and \( A_k \), it is possible to assign a weighted directed graph (often called ‘Feinberg-Horn-Jackson graph’) to a reaction network, where the vertices correspond to complexes, reactions are represented by directed edges between complexes, and the weights corresponding to directed edges are the appropriate reaction rate coefficients (Feinberg, 1987; Érdi and Tóth, 1989).

A set of complexes \( \{C_1, C_2, ..., C_k\} \) is a linkage class of a reaction network if the complexes of the set are linked to each other in the reaction graph but not to any other complex (Feinberg, 1987) (i.e. the individual linkage classes form the connected components of the directed graph of the reaction network). Two different complexes are said to be strongly linked if there exists a directed path from one complex to the other, and a directed path from the second complex back to the first. Moreover, each complex is defined to be strongly linked to itself. A strong linkage class is a set of complexes with the following properties: each pair of complexes in the set is strongly linked, and no complex in the set is strongly linked to a complex that is not in the set. A terminal strong linkage class is a strong linkage class that contains no complex that reacts to a complex in a different strong linkage class (i.e. there is no “exit” from a terminal strong linkage class through a directed edge).

For the reaction \( C_i \rightarrow C_j \), the corresponding reaction vector \( v_{ij} \) is defined as

\[
v_{ij} = [Y]_{j} - [Y]_{i}
\]  

(6)

where \( [Y]_{j} \) denotes the \( j \)th column of \( Y \). The rank of a reaction network denoted by \( s \) is defined as the rank of the vector set \( H = \{v_{ij} \mid C_i \rightarrow C_j \text{ exists}\} \). We use
the classical definition for the deficiency $\delta$ of a reaction network (Feinberg, 1987):
\[
\delta = m - l - s
\] (7)
where $m$ is the number of complexes in the network, $l$ is the number of linkage classes (graph components) and $s$ is the rank of the reaction network.

2.2 Dynamically equivalent and linearly conjugate reaction networks

As it is known even from the early literature (Horn and Jackson, 1972), CRNs with different structures and/or parametrization can give rise to the same kinetic differential equations. Therefore, we will call two CRNs given by the matrix pairs $(Y^{(1)}, A^{(1)})$ and $(Y^{(2)}, A^{(2)})$ dynamically equivalent, if
\[
Y^{(1)} A^{(1)}_k \psi^{(1)}(x) = Y^{(2)} A^{(2)}_k \psi^{(2)}(x) = f(x), \quad \forall x \in \mathbb{R}^n.
\] (8)
where for $i = 1, 2$, $Y^{(i)} \in \mathbb{R}^{n \times m_i}$ have nonnegative integer entries, $A^{(i)}_k$ are valid Kirchhoff matrices, and
\[
\psi^{(i)}_j(x) = \prod_{k=1}^n x^{(1)}_{k,j}, \quad i = 1, 2, j = 1, \ldots, m_i.
\] (9)
In this case, $(Y^{(i)} A^{(i)}_k)$ for $i = 1, 2$ are called realizations of a kinetic vector field $f$ (see, e.g. Hars and Töth (1981) for more details). It is also appropriate to call $(Y^{(1)}, A^{(1)}_k)$ a realization of $(Y^{(2)}, A^{(2)}_k)$ and vice versa.

We will assume throughout the paper that the set of complexes (i.e. the stoichiometric matrix $Y$) is fixed and known before the computations. In this case, the condition (8) for dynamical equivalence can be written as
\[
Y \cdot A^{(1)}_k = Y \cdot A^{(2)}_k =: M,
\] (10)
where $A^{(1)}_k$ and $A^{(2)}_k$ are valid Kirchhoff matrices and $M$ is the invariant matrix containing the coefficients of the monomials.

The concept of linear conjugacy originally introduced in (Johnston and Siegel, 2011) extends the notion of dynamical equivalence by allowing a positive diagonal state transformation between the realizations. Thus, dynamical equivalence becomes a special case of linear conjugacy by taking the identity transformation. Importantl, linearly conjugate networks share the same qualitative dynamics (e.g. number and stability of equilibria, persistence/extinction of species, dimensions of invariant spaces, etc.). Similarly to different realizations of the same kinetics (3), if a network with unknown kinetics is linearly conjugate to a network with known dynamics, then the qualitative properties of the second network are naturally transferred to the first. Using the results of (Johnston and Siegel, 2011), the notion of linear conjugacy can be briefly summarized as follows. Two mass-action systems $(Y, A^{(1)}_k)$ and $(Y, A^{(2)}_k)$ are linearly conjugate, if $x^{(2)}(t) = T^{-1} \cdot x^{(1)}(t), \forall t \geq 0$, where $x^{(i)}$ is the solution of (3) for $(Y, A^{(i)}_k), i = 1, 2$ and $T \in \mathbb{R}^{n \times n}$ is a positive definite diagonal matrix. The following condition for linear conjugacy was proved in (Johnston and Siegel, 2011): Suppose that there is a Kirchhoff matrix $A_b$ with the same structure as $A^{(2)}_k$ (i.e. the positions of zero and non-zero elements in the two matrices are identical) and a vector $c \in \mathbb{R}^n_{>0}$ such that
\[
Y \cdot A^{(1)}_k = T \cdot Y \cdot A_b
\] (11)
where $T = \text{diag}\{c\}$. Then $(Y, A^{(1)}_k)$ is linearly conjugate to $(Y, A^{(2)}_k)$ with kinetics matrix
\[
A^{(2)}_k = A_b \cdot \text{diag}\{\psi(c)\}.
\] (12)

Among the dynamically equivalent and linearly conjugate realizations, it is important to recall the following characteristic ones described in (Szederkényi, 2010; Szederkényi et al., 2011b). A sparse realization contains the minimal number of reactions that is needed for the exact description of the corresponding dynamics (3). A dense realization contains the maximal number of reactions among dynamically equivalent realizations with a fixed complex set given by $Y$. While sparse realizations are generally structurally non-unique (as it will be illustrated for the constrained case, too, in Example 1), the structure of dense realizations with a given complex set is unique, and it contains every possible dynamically equivalent structure as a proper subgraph (i.e. a dense realization is a kind of super-structure) (Szederkényi et al., 2011b).

2.3 Mixed integer linear programming

A special subset of optimization problems is the class of Mixed Integer Linear Programs (MILPs) where the objective function and the constraints are linear functions of the decision variables. A mixed integer linear program with $k$ variables (denoted by $w \in \mathbb{R}^k$) and $p$ constraints can be written as (Nemhauser and Wolsey, 1999):
\[
\text{minimize } c^T w
\]
subject to:
\[
A_1 w = b_1
A_2 w \leq b_2
l_i \leq w_i \leq u_i \quad \text{for } i = 1, \ldots, k
w_j \text{ is integer for } j \in I, \quad I \subseteq \{1, \ldots, k\}
\] (13)
where $c \in \mathbb{R}^k$, $A_1 \in \mathbb{R}^{p_1 \times k}$, $A_2 \in \mathbb{R}^{p_2 \times k}$, and $p_1 + p_2 = p$.

If all the variables can be real, then (13) is a simple linear programming problem that can be solved in polynomial time. However, if any of the variables is integer, then the problem becomes NP-hard. In spite of this, there exist a number of free (e.g. YALMIP or the GNU Linear Programming Kit) and commercial (such as CPLEX or TOMLAB) solvers that can efficiently handle many practical problems.

A propositional logic problem, where a statement denoted by $S$ must be proved to be true given a set of compound statements containing so-called literals $S_1, \ldots, S_n$, can be solved by means of a linear integer program. For this, logical variables denoted by $\delta_i$ ($\delta_i \in \{0, 1\}$) must be associated with the literals $S_i$. Then the original compound statements can be translated to linear inequalities involving the logical variables $\delta_i$ (Raman and Grossmann, 1994; Bemporad and Morari, 1999). This theoretical background allows us the translation of certain structural network properties (e.g. density/sparsity) to MILP or LP problems.
3. CORE COMPLEXES AND REACTIONS IN LINEARLY CONJUGATE REALIZATIONS

In (Szederkényi et al., 2011a), the so-called core reactions for dynamically equivalent CRNs were defined. These are such reactions that must be present in any dynamically equivalent realizations of a CRN, and can be computed by using linear programming. In this section, this notion will be extended to the case of linear conjugacy, together with the introduction of the analogous concept of core complexes.

For this, we first give the optimization constraints corresponding to linear conjugacy. Using the definition given at the end of subsection 2.2, the linear constraints for two CRN realizations \((Y, A_k^{(1)})\) and \((Y, A_k^{(2)})\) to be linearly conjugate can be given as follows (see also (Johnston et al., 2012)). Given \(Y\) and \(A_k^{(1)}\), find the matrices \(A_b\) and \(T^{-1}\) such that

\[
Y \cdot A_b = T^{-1} \cdot M
\]

(14)

\[
\sum_{i=1}^{m} [A_b]_{ij} = 0, \quad j = 1, \ldots, m
\]

(15)

\[
[A_b]_{ij} \geq 0, \quad i, j = 1, \ldots, m, \quad i \neq j
\]

(16)

\[
[A_b]_{ii} \leq 0, \quad i = 1, \ldots, m
\]

(17)

\[
\epsilon \leq \frac{i}{j} \leq \frac{t_{\max}^{me}, j = 1, \ldots, n,}{t_{\max}^{me}, i = 1, \ldots, n,}
\]

(18)

where \(M = Y \cdot A_k^{(1)}, T = \text{diag}(\frac{1}{t_{ij}^{lower}}, \ldots, \frac{1}{t_{ij}^{upper}}), 0 \leq \epsilon \leq 1\), and \(t_{\max}^{me}\) is an appropriate upper bound for the reciprocals of the elements in \(T\). In this case, the decision variables are the off-diagonal elements of \(A_b\), and \(t_{\max}^{me}, i = 1, \ldots, n\). Moreover, the Kirchhoff matrix of the computed linearly conjugate realization is given by

\[
A_k^{(2)} = A_b \cdot \text{diag}(\psi(c))\]

where \(c\) is the vector composed of the diagonal elements of \(T\).

To keep track of which reaction rate coefficients in the conjugate realization are zero/nonzero, we introduce the binary variables \(\delta_{ij}\) for \(i, j = 1, \ldots, m, i \neq j\). The corresponding linear inequalities are

\[
0 \geq [A_b]_{ij} - \epsilon \delta_{ij}, \quad i, j = 1, \ldots, m, \quad i \neq j
\]

\[
0 \leq [A_b]_{ij} + u \delta_{ij}, \quad i, j = 1, \ldots, m, \quad i \neq j
\]

(19)

\[
\delta_{ij} \in [0, 1], \quad i, j = 1, \ldots, m, i \neq j
\]

where \(u\) is a parameter that is chosen such that \(0 < \delta_{ij} < 1\) is an upper bound for the off-diagonal elements of \(A_b\) (defining them as a necessary technical requirement for the stable solution of the corresponding MILP problem). Then, sparse or dense linearly conjugate realizations can be computed by minimizing or maximizing the following objective function, respectively:

\[
C(\delta) = \sum_{i,j=1}^{m} \delta_{ij}
\]

(20)

3.1 Core complexes

We define core complexes as the ones that cannot be omitted from any linearly conjugate CRN realizations. To define the corresponding computation method, we have to observe that a complex becomes isolated in the reaction graph (i.e. it has neither incoming nor outgoing adjacent edges) if and only if the corresponding row and column of the Kirchhoff matrix contains only zeros. Therefore, the complex \(C_k\) is a core complex, if the constraint

\[
\sum_{i=1}^{m} [A_b]_{ki} + \sum_{j=1}^{m} [A_b]_{kj} = 0
\]

(21)

together with (14)-(18) is infeasible. This can be safely checked, since the above constraints do not contain integer variables, therefore the identification of core complexes can be traced back to simple linear programming.

3.2 Core reactions

Similarly, a reaction \(C_i \rightarrow C_j\) is present in any linearly conjugate CRN realization with a fixed complex set given by \(Y\) (where the allowable diagonal transformations are defined by eq. (18)) if the constraints (14)-(18) and

\[
[A_b]_{ij} = 0
\]

(22)

are infeasible, which is again an LP feasibility problem.

The simple tests described in the above two subsections can be run for each complex of the network and for each reaction of a sparse realization to identify core complexes and core reactions, respectively.

4. EXAMPLES

We will illustrate the previously described concepts and computation methods in this section.

4.1 A simple system modeling DNA damage

The following mass-action model published in (Karschau et al., 2011) predicts the death rate of microorganisms during the repair of DNA damage caused by harmful chemical agents. The kinetic equations of the continuous approximation of the process are the following:

\[
x_1 = k_3 x_3 - k_1 x_1
\]

\[
x_2 = k_1 x_1 - k_2 x_2 x_4
\]

\[
x_3 = k_2 x_2 x_4 - k_3 x_3
\]

\[
x_4 = k_3 x_3 - k_2 x_2 x_1
\]

(23)

where \(x_1\) denotes the number of undamaged guanine bases, \(x_2\) is the number of damaged guanine bases, \(x_3\) is the number of guanine bases under repair, and \(x_4\) is the number of free initiating repair enzymes. The constant parameters \(k_1, \ldots, k_4\) are appropriate kinetic constants that are described in detail in (Karschau et al., 2011). Using the algorithm described in (Härs and Tóth, 1981), we can generate the following feasible complex set suitable for realizing the dynamics (23) corresponding to the so-called "canonical" realization:

\[
C_1 = X_3, \quad C_2 = X_1 + X_3, \quad C_3 = X_1, \quad C_4 = 0
\]

\[
C_5 = X_1 + X_2, \quad C_6 = X_2 + X_4, \quad C_7 = X_4
\]

\[
C_8 = X_2 + X_3 + X_4, \quad C_9 = X_3 + X_4, \quad C_{10} = X_2
\]

(24)

The structure of the dense linearly conjugate realization (containing 14 reactions and all possible structures with the complex set (24)) is shown in Fig. 1, where the numbering of graph nodes is the same as the numbering of complexes in eq. (24). The structure of the dense
dynamically equivalent realization is the same, therefore linear conjugacy does not extend the ‘super-structure’ of the system in this case.

There are three core complexes in the model, namely $C_1 = X_3$, $C_3 = X_1$ and $C_6 = X_2 + X_4$. If we compute the core reactions of the system, we find the interesting result, that the set of core reactions is empty which means that individually, any reaction can be substituted by the others while maintaining dynamical equivalence or linear conjugacy. In other words, there is no indispensable reaction in the system with the complex set (24).

Using the tools and results described in section 3, it is possible to find all dynamically equivalent sparse realizations of the system. (i.e. now we fix $T$ to be the identity matrix. This is so because we would like to give symbolic solutions for the sparse realizations that is generally not possible in the linearly conjugate case.) The two solutions containing 4 reactions can be seen in Fig. 2. It is easy to see that both sparse realizations contain the core complexes, and their structures are indeed the proper subgraphs of the dense structure shown in Fig. 2. It turns out clearly even from this simple example that besides the sparsity condition, generally more constraints are needed for the correct dynamic model-based determination of CRN structures.

4.2 A computational example

The purpose of this purely computational example is to highlight the difference between dynamically equivalent and linearly conjugate realizations. Consider the following kinetic equations taken from (Johnston et al., 2012):

$$\begin{align*}
\dot{x}_1 &= x_1 x_2^2 - 2x_1^2 + x_1 x_3^2 \\
\dot{x}_2 &= -2x_1^2 x_2 + x_1 x_3^2 \\
\dot{x}_3 &= x_1^2 - 3x_1 x_3^2.
\end{align*}$$  (25)

It can be computed (see (Hárs and Tóth, 1981; Johnston et al., 2012)) that the above dynamics can be realized with a CRN using the following complex set:

$$\begin{align*}
C_1 &= X_1 + 2X_2, \\
C_2 &= 2X_1 + 2X_2, \\
C_3 &= 2X_1, \\
C_4 &= X_1, \\
C_5 &= X_1 + 2X_3, \\
C_6 &= 2X_1 + 2X_3, \\
C_7 &= X_1 + X_2 + 2X_3, \\
C_8 &= 2X_1 + X_2, \\
C_9 &= 2X_1 + X_3, \\
C_{10} &= X_1 + X_3.
\end{align*}$$  (26)

In this case, the core complexes in the case of dynamical equivalence are $C_1, C_2, C_3, C_4, C_5$. However, the core complexes in the linearly conjugate realizations are $C_1, C_2, C_3, C_5$ which is a notable difference. This can explain the difference between the sparse realizations of dynamical equivalent and linearly conjugate realizations that are shown in Figs. 3 and 4, respectively (complexes $C_6, \ldots, C_{10}$ not taking part in any reactions in the sparse realizations are not drawn in the figures). Observe that the CRN shown in Fig. 4 is weakly reversible, while it can be shown that there is no weakly reversible dynamically equivalent realization of the system (25) with the complex set in (26).
5. CONCLUSIONS

The different realizations of mass-action type biochemical network models have been studied in this paper. It was shown that the core reactions and core complexes present in any linearly conjugate realization (assuming a fixed complex set) can be determined using linear programming. The main motivation behind the application of optimization tools is that algebraically complex problems can often be successfully handled by putting them into an appropriate optimization framework. The results can hopefully contribute to two further research directions: firstly, to the distinguishability and identifiability analysis of kinetic models, and secondly, to the algorithmic building of reaction network structures realizing or approximating a given dynamics.

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