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Realization of Linearly Conjugate and Uncertain Kinetic Systems with Time Delay

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Abstract

In this paper, the kinetic realization problem of nonnegative delayed polynomial systems with uncertainty is addressed. A polynomial delayed differential equation (DDE) is given, and the goal is to compute reaction graphs (i.e., chemical reaction networks) realizing its dynamics. Model uncertainty is considered through the assumption that the coefficients of the DDE belong to a convex polytope. Moreover, it is shown that linearly conjugate delayed realizations can also be analyzed in the same framework. We give an algorithm with correctness proof for the computation of all possible linearly conjugate chemical reaction networks corresponding to an uncertain delayed model. The developed theory and methods are illustrated on two examples.

1 Introduction

Nonnegative dynamical models have a wide range of applications from molecular (bio)chemistry through higher level compartmental systems to certain economical or even transportation processes [1]. A fairly general subset of nonnegative systems is the class of kinetic models (also called chemical reaction networks or simply, CRNs) [2]. A weighted directed graph called the reaction graph can be naturally associated to CRNs from which several key features of the qualitative dynamics can be deduced even in generalized cases [3, 4].

Explicit time delays are frequently present in various dynamical processes and it is known that they can fundamentally influence the qualitative dynamical properties of the models [5, 6]. A common engineering approach is to approximate delayed terms by a series of ordinary differential equations and thus to trace back the problem to a more easily tractable model class [7]. However, showing the uniform convergence of the solution of the approximation and that of the original delayed differential equation (DDE) is far from being trivial, especially for unbounded nonlinearities such as mass action reaction rates [8, 9].

Delayed reactions where the substrate consumption is immediate while the product formation is delayed, have been introduced to kinetic models to simplify reaction cascades by the omission of intermediate complexes [10]. Moreover, delayed reactions can also represent explicit transport delays in formally kinetic systems such as in compartmental models. The dynamical consequences of reaction delays were studied in [11]. The semistability of complex balanced CRNs was shown in [12] for arbitrary time delays, where a logarithmic Lyapunov-Krasovskii functional was also proposed.

It is known that the structure and the parametrization of the reaction graph corresponding to a given kinetic dynamics are generally non-unique [2, 13]. Therefore, theoretical results and computational algorithms have been developed to determine different reaction networks realizing a given dynamics [14], clearly showing that optimization is a useful tool in the analysis of reaction mechanisms (see, also [15]). It is even possible to compute all distinct reaction graphs corresponding to a set of kinetic ODEs [16]. The kinetic realization problem of delayed differential equations (DDEs) was first addressed in [18], where necessary and sufficient conditions of kinetic realizability were given, and an algorithm was proposed to compute a possible delayed CRN realizing a given DDE.

The purpose of this paper is to complete the work reported in [18] by extending the results to uncertain and linearly conjugate models. The structure of the paper is the following. The basic notations and known results from previous literature are summarized briefly in Section 2, while the new contributions can be found in Sections 3-5. In Section 3, we introduce uncertain delayed kinetic models and show their most important structural properties. Section 4 contains the developed computational methods for determining delayed reaction graphs from DDEs with correctness proofs. We show two examples in Section 5 to illustrate the proposed approach followed by a brief summary in Section 6.

2 Notations and background

In this section, we summarize the notations and definitions used throughout the paper following mainly [12] and [18]. We denote the sets of real numbers and nonnegative integers by $\mathbb{R}$ and $\mathbb{N}_0$, respectively. The kth basis vector of $\mathbb{R}^n$ is denoted by e_k^n. $\mathbf{0}_{n\times m}$ and $\mathbf{1}_{n\times m}$ denotes the $n\times m$ zero matrix and $n\times m$ unit matrix, respectively. The positive and nonnegative orthants in the n-dimensional Euclidean space $\mathbb{R}^n$ are denoted by $\mathbb{R}^n_{>0}$ and $\mathbb{R}^n_{\geq 0}$, respectively. For $\tau \geq 0$, let $\mathcal{C}([-\tau, 0], \mathbb{R}^n)$ denote the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^n$. Similarly, let $\mathcal{C}([-\tau, 0], \mathbb{R}^n_{>0})$ and $\mathcal{C}([-\tau, 0], \mathbb{R}^n_{\geq 0})$ denote the set of positive and nonnegative functions. For $x, y \in \mathbb{R}^n_{\geq 0}$, $x^y = \prod_{i=1}^n x_i^{y_i}$. For any matrix $P \in \mathbb{R}^{n\times m}$, $[P]_{i,j}$ denotes the entry in row i and column j. Further, $[P]_{i,\cdot}$ is the ith row, and $[P]_{\cdot,j}$ is the jth column of P. Finally, $[P]_{\neq j,j}$ is the column vector of size $m-1$ containing the off-diagonal elements of the jth column. We say that a square matrix is a Metzler matrix if its off-diagonal entries are nonnegative. A Metzler matrix is called a Kirchhoff matrix if all of its column-sums are zero. For any tensor $Q \in \mathbb{R}^{p\times n\times m}$, $[Q]_{i,j,k}$ denotes the entry in matrix i, row j and column k. Further, $[Q]_{i,:,:}$ is the ith matrix of Q. For any matrix $P \in \mathbb{R}^{l\times n}$, the results of the multiplication PQ is the tensor R with $[R]_{i,:,:} = P[Q]_{i,:,:}$. Similarly, for any matrix $P \in \mathbb{R}^{m\times l}$, the result of the multiplication QP is the tensor R with $[R]_{i,:,:} = [Q]_{i,:,:}P$. For $x \in \mathbb{R}^n_{\geq 0}$ and $Y \in \mathbb{R}^{n\times m}_{\geq 0}$, $x^Y = [f_1(x)\ \ldots\ f_m(x)]^T$, where $f_i(x) = x^{Y_{\cdot,i}}$ for $i = 1, \ldots, m$.

2.1 Nonlinear polynomial models with time delay

We consider general polynomial models with time delay in the following form

$$\dot{x}(t) = M_0\psi\big(x(t)\big) + \sum_{i=1}^{p} M_i\psi\big(x(t-\tau_i)\big) \tag{1}$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $M_i \in \mathbb{R}^{n\times m}$ for $i = 0, \ldots, p$ are coefficient matrices, $\psi(x) = x^Y$ with $Y \in \mathbb{N}_0^{n\times m}$, and $\tau_i > 0$ for $i = 1, \ldots, p$ are constant time delays such that $\tau_i \neq \tau_j$ for $i \neq j$. The initial function for the model (1) is $\theta \in \mathcal{C}([-\tau, 0], \mathbb{R}^n_{\geq 0})$, i.e., $x(t) = \theta(t)$ for $-\tau \leq t \leq 0$, where $\tau = \max_{1\leq i\leq p} \tau_i$ is the maximum delay. Note that the tuple $(Y, M_0, \ldots, M_p)$ uniquely characterizes the system (1).

2.2 Kinetic models with delayed reactions

In delayed kinetic models, we assume that the consumption of the reactants is immediate, while the product formation for any delayed reaction starts after a given constant time specific to the reaction [10]. Therefore, we can define *delayed chemical reaction networks* with three sets, analogously to the classical non-delayed case as follows:

- A set of *species*: $\mathcal{S} = \{X_i \mid i = 1, \ldots, n\}$.
- A set of *complexes*: $\mathcal{C} = \{C_j \mid j = 1, \ldots, m\}$, where

$$C_j = \sum_{i=1}^{n} \alpha_{i,j} X_i \qquad j = 1, \ldots, m \tag{2}$$

$$\alpha_{i,j} \in \mathbb{N}_0, \quad i = 1, \ldots, n, \ j = 1, \ldots, m. \tag{3}$$

  It is visible that the complexes are formal linear combinations of the species with the nonnegative integer *stoichiometric coefficients* α_{ij}. The *stoichiometric coefficient vector* of the complex C_j is $[\alpha_{1,j} \ \ldots \ \alpha_{n,j}]^T \in \mathbb{R}^n$ such that $C_i \neq C_j$ for $i \neq j$. For the representation of the environment, we will use the so-called *zero complex* with all stoichiometric coefficients equal to zero.

- A set of *reactions*: $\mathcal{R} = \{\mathcal{R}_1, \mathcal{R}_2, \ldots, \mathcal{R}_r\}$ of the form

$$\mathcal{R}_j : C_l \xrightarrow{\kappa_j, \tau_j} C_{l'}, \quad l, l' \in \{1, \ldots, m\}, \ j = 1, \ldots, r \tag{4}$$

  where C_l and $C_{l'}$ are the *reactant* (or *source*) and *product complexes*, respectively. The positive numbers κ_j are the *reaction rate coefficients*, and the nonnegative real numbers τ_j are the time delays associated to the reactions.

The stoichiometric coefficients are collected into the *complex composition matrix*: $[Y]_{i,j} = \alpha_{i,j}$ for $i = 1, \ldots, n$, $j = 1 \ldots, m$. That is, the jth column of Y is the stoichiometric coefficient vector of complex C_j. We assume mass action type reaction rates of the form $\rho_j(x) = \kappa_j x^{[Y]_{\cdot,l}}$ for $j = 1, \ldots, r$, where x denotes the concentration vector of the species (i.e., $x_i = [X_i]$), and $Y_{\cdot,l}$ is the stoichiometric coefficient vector of the source complex of reaction $\mathcal{R}_j$ (see, Eq. (4)).

We assign a weighted directed graph $D = \big(V, E\big) = \big(V, E^{\tau_0}, E^{\tau_1}, \ldots, E^{\tau_p}\big)$ where $\tau_0 = 0$, to a delayed reaction network as follows.

- The vertices correspond to the complexes, i.e., $V = \{C_1, \dots, C_m\}$.
- The directed edges represent reactions, i.e., $(C_l, C_l') \in E^{\tau_i}$, if C_l is transformed into C_l' in the network with time delay τ_i. The union of the E^{τ_i} sets of directed edges form the E set of edges.
- The reaction rate coefficients κ_j are assigned as positive weights to the edges.

It is important to remark that in contrast to non-delayed reaction networks, we allow delayed loop edges in delayed CRNs, since a non-zero term in the differential equations and also physical interpretation can be assigned to them. Furthermore, multiple identically directed edges can be present between the same pair of vertices if the corresponding reactions have different time delays.

The general dynamic equations of delayed kinetic systems are the following (see, [12])

$$\dot{x}(t) = \sum_{j=1}^{r} \kappa_j \left[\big(x(t-\tau_j)\big)^{y_j} \, y_j' - \big(x(t)\big)^{y_j} \, y_j \right], \tag{5}$$

where κ_j is the reaction rate coefficient of $\mathcal{R}_j$, and $y_j,\ y_j' \in \mathbb{N}_0^n$ are the stoichiometric coefficient vectors of the source and product complexes in $\mathcal{R}_j$, respectively. Moreover, $\tau_j \geq 0$ and the initial function is $\theta \in \mathcal{C}([-\tau, 0], \mathbb{R}^n_{\geq 0})$. It has been shown in [18] that in the special case when all $\tau_j = 0$, Eq. (5) gives the classical model of mass action kinetic systems known from the literature [2, 19].

Similarly to the non-delayed case, the model (5) can be written in an alternative form, where the complex composition and the structure of the reaction graph explicitly appear. For this, we introduce the following notation. Let $\bar{\kappa}_{j,k}^{\bar{\tau}_i}$ be the reaction rate of the reaction $C_k \xrightarrow{\bar{\tau}_i} C_j$, and let $\bar{\tau}_0 = 0$. If there is no reaction with source complex C_k, product complex C_j and delay $\bar{\tau}_i$ then $\bar{\kappa}_{j,k}^{\bar{\tau}_i} = 0$.

It was shown in [18] that the dynamics of a delayed CRN with reaction steps written in Eq. (4) can be described by a system of delay differential equations (DDEs) of the form

$$\dot{x}(t) = Y A_0 \psi\big(x(t)\big) + \sum_{i=1}^{p} Y A_i \psi\big(x(t-\bar{\tau}_i)\big), \tag{6}$$

where $A_i \in \mathbb{R}^{m \times m}$, $i = 0, \dots, p$ contain all information about the reaction graph D. The

structure of A_i is given by

$$[A_0]_{j,k} = \begin{cases} -\sum_{l=1}^{m} \bar{\kappa}_{j,l}^{\bar{\tau}_0} - \sum_{i=1}^{p}\sum_{l=1}^{m} \bar{\kappa}_{j,l}^{\bar{\tau}_i} = -\sum_{i=0}^{p}\sum_{l=1}^{m} \bar{\kappa}_{j,l}^{\bar{\tau}_i}, & j = k \\ \bar{\kappa}_{k,j}^{\bar{\tau}_0}, & j \neq k \end{cases} \tag{7}$$

$$[A_i]_{j,k} = \bar{\kappa}_{k,j}^{\bar{\tau}_i} \qquad i = 1, \ldots, p. \tag{8}$$

From now on, a delayed CRN given in Eq. (6) is denoted by $(Y, A_0, \ldots, A_p)$, where A_0 is a Metzler matrix, and each A_i has nonnegative entries for $i = 1, \ldots, p$.

Using the following definition we can formalize the relationship between delayed polynomial models and delayed kinetic systems.

Definition 2.1. *A delayed reaction network $(Y, A_0, \ldots, A_p)$ is said to be dynamically equivalent to a DDE $(\bar{Y}, M_0, \ldots, M_p)$ if*

$$\sum_{i=0}^{p} M_i \bar{\psi}\big(x(t-\tau_i)\big) = \sum_{i=0}^{p} Y A_i \psi\big(x(t-\tau_i)\big) \tag{9}$$

where $\bar{\psi}(x) = x^{\bar{Y}}$ and $\psi = x^{Y}$.

Note that the functions $\bar{\psi}$ and ψ on the two sides of Eq. (9) are not necessarily identical, since the monomials corresponding to purely product complexes generally do not appear in the differential equations of kinetic systems [3].

We can give necessary and sufficient conditions for kinetic realizability in the delayed case as follows (see, [18] for more details).

Theorem 2.2. *A delayed system $(\bar{Y}, M_0, \ldots, M_p)$ can be realized as a delayed CRN if and only if $M_0\bar{\psi}\big(x(t)\big)$ is kinetic (in other words, it does not contain negative cross-effects), i.e.,*

$$[M_0]_{j,k} < 0 \implies \big[\bar{Y}\big]_{j,k} > 0 \quad j = 1, \ldots, n, \ k = 1, \ldots, m \tag{10}$$

and M_i has only nonnegative elements for $i = 1, \ldots, p$.

To show the main idea behind the realization algorithm described later, let us consider the kinetic realization of a general delayed monomial in the jth equation of a set of kinetic DDEs:

$$\dot{x}_j(t) = \kappa \prod_{i=1}^{n} x_i^{\alpha_i}(t-\tau) \tag{11}$$

where $\kappa, \tau > 0$ and $\alpha_i \in \mathbb{N}$, for $i = 1, \ldots, n$. It can be checked that the following reactions realize (11)

$$R_0: \quad \sum_{i=1}^{n} \alpha_i X_i \xrightarrow{\kappa,\tau} X_j \tag{12}$$

$$R_l: \quad \sum_{i=1}^{n} \alpha_i X_i \xrightarrow{\operatorname{sign} \alpha_l \kappa} \sum_{i=1}^{n} \alpha_i X_i + \operatorname{sign} \kappa X_l \qquad l = 1, \ldots, n \tag{13}$$

where a zero reaction rate coefficient in the case of $\alpha_l = 0$ means that no reaction is added to the realization. To show the correctness of (12)-(13), let us write the corresponding delayed kinetic model (5) which is given by

$$\dot{x}_l(t) = \underbrace{-\operatorname{sign} \alpha_l \kappa \prod_{i=1}^{n} x_i^{\alpha_i}(t)}_{R_0} + \underbrace{\operatorname{sign} \alpha_l \kappa \prod_{i=1}^{n} x_i^{\alpha_i}(t)}_{R_l} \quad l = 1, \ldots, j-1, j+1, \ldots, n \tag{14}$$

$$\dot{x}_j(t) = \underbrace{\kappa \prod_{i=1}^{n} x_i^{\alpha_i}(t-\tau) - \operatorname{sign} \alpha_j \kappa \prod_{i=1}^{n} x_i^{\alpha_i}(t)}_{R_0} + \underbrace{\operatorname{sign} \alpha_j \kappa \prod_{i=1}^{n} x_i^{\alpha_i}(t)}_{R_j}. \tag{15}$$

As we can see from the above example we can realize a polynomial DDE by assigning delayed and non-delayed reactions to the monomials. This will allow us to generalize the concept of the so-called canonical realization described originally in [13].

3 Uncertain kinetic models with time delay

In this section we will consider constrained delayed uncertain systems. We will introduce parametric uncertainty and additional linear constraints to delayed kinetic models. It is assumed that the monomial coefficients are uncertain and they belong to a convex polytope in the parameter space. The basic idea behind this approach is that these coefficients are often determined (estimated) from imperfect (typically noisy) measurement data, which results in uncertain estimates. Thus, the used uncertainty polytope can be computed from, e.g. the covariance matrix of the estimates. We will also consider linear conjugacy, which is a generalization of dynamical equivalence [20].

3.1 Delayed uncertain kinetic systems

The M_i matrices in Eq. (9) can be arranged in the tensor

$$\mathcal{M}^p = [M_0 \ \ldots \ M_p] \in \mathbb{R}^{(p+1)\times n \times m}. \tag{16}$$

From the entries of $\mathcal{M}^p$, we construct the column vector

$$vec(\mathcal{M}^p) = \left[[M_0]_{.,1}^{\mathrm{T}} \ \dots \ [M_0]_{.,m}^{\mathrm{T}} \ \dots \ [M_p]_{.,1}^{\mathrm{T}} \ \dots \ [M_p]_{.,m}^{\mathrm{T}}\right]^{\mathrm{T}} \tag{17}$$

which defines a point in the Euclidean space $\mathbb{R}^{(p+1)nm}$. Similarly, with the A_i matrices in Eq. (9) we can construct the tensor

$$\mathcal{A}^p = [A_0 \ \dots \ A_p] \in \mathbb{R}^{(p+1)\times m\times m}. \tag{18}$$

From the entries of $\mathcal{A}^p$, we define the vector

$$vec(\mathcal{A}^p) = \left[[A_0]_{.\neq 1,1}^{\mathrm{T}} \ \dots \ [A_0]_{.\neq m,m}^{\mathrm{T}} \ \dots \ [A_1]_{.,1}^{\mathrm{T}} \ \dots \ [A_1]_{.,m}^{\mathrm{T}} \ \dots \ [A_p]_{.,1}^{\mathrm{T}} \ \dots \ [A_p]_{.,m}^{\mathrm{T}}\right]^{\mathrm{T}} \tag{19}$$

i.e., $vec(\mathcal{A}^p)$ contains the off-diagonal entries of A_0 and all of the entries of $A_1, \dots, A_p$ taken columnwise as coordinates, which defines a point in the Euclidian space $\mathbb{R}^{(p+1)m^2-m}$. Using (16) and (18) we can write Eq. (9) as

$$\sum_{i=0}^{p} [\mathcal{M}^p]_{i,.,.} \bar{\psi}\big(x(t-\tau_i)\big) = \sum_{i=0}^{p} Y[\mathcal{A}^p]_{i,.,.} \psi\big(x(t-\tau_i)\big). \tag{20}$$

The parametric uncertainty will be modelled by assuming that the $\mathcal{M}^p$ tensor is constant but not precisely known, and it is represented by a point of a $(p+1)nm$ dimensional polytope, which is defined as the intersection of l halfspaces with normal vectors $n_1, \dots, n_l \in \mathbb{R}^{(p+1)nm}$ and constants $b_1, \dots, b_l \in \mathbb{R}$. Thus, the polytope can be described by the linear inequality system

$$\mathcal{P} = \left\{q \in \mathbb{R}^{(p+1)nm} \middle| n_i^{\mathrm{T}} q \leq b_i, \ i = 1, \dots, l\right\}. \tag{21}$$

The task of generating an appropriate complex set for the kinetic representation of a DDE can be handled as follows. For delayed kinetic systems without uncertainties, we can generate complexes using Algorithm 1 of [18]. We know that each $\mathcal{M}^p \in \mathcal{P}$ can be expressed as the convex combination of the corner points of $\mathcal{P}$, thus for each nonzero entry of $\mathcal{M}^p$ there exists at least one corner point of $\mathcal{P}$ with the same entry being a nonzero number with the same sign. Also the complex generation procedure of Algorithm 1 in [18] creates complexes for each monomial in the DDE sequentially. Therefore we can run Algorithm 1 in [18] for each corner point of $\mathcal{P}$, and then take the union of the obtained complexes. The corner points of $\mathcal{P}$ can be algorithmically determined from the inequalities in Eq. (21) (see e.g., [21]). This is particularly simple if we assume that the

model coefficients are the points of a cuboid (i.e., we have minimum and maximum values for the coefficients). Thus from now on we will consider the complex composition matrix Y to be given.

We should also consider the kinetic property characterized by Theorem 2.2, i.e., a polynomial system $(Y, \mathcal{M}^p)$ with $vec(\mathcal{M}^p) \in \mathcal{P}$ should be a kinetic system. This can be ensured by additional linear inequalities

$$[Y]_{j,k} = 0 \implies \left[\mathcal{M}^p\right]_{0,j,k} \geq 0 \qquad j = 1, \ldots, n,\ k = 1, \ldots, m \tag{22}$$

$$\left[\mathcal{M}^p\right]_{i,j,k} \geq 0 \qquad i = 1, \ldots, p,\ j = 1 \ldots, n,\ k = 1 \ldots, m \tag{23}$$

These kinetic constraints can be expressed in the same form as the inequalities in Eq. (21) using unit vectors as the n_i normal vectors and zero as the b_i constant

$$[Y]_{j,k} = 0 \implies -e^{(p+1)nm}_{(j-1)n+k} vec(\mathcal{M}^p) \leq 0 \quad j = 1, \ldots, n,\ k = 1, \ldots, m \tag{24}$$

$$-e^{(p+1)nm}_{inm+(j-1)n+k} vec(\mathcal{M}^p) \leq 0 \qquad i = 1, \ldots, p,\ j = 1, \ldots, n,\ k = 1, \ldots, m \tag{25}$$

Therefore, we can characterize a delayed uncertain kinetic system by the pair $[\mathcal{P}, Y]$.

3.2 Realization types

We can generalize the dynamical equivalence of delayed uncertain systems as follows.

Definition 3.1. *A delayed reaction network $(Y, \mathcal{A}^p)$ is called a dynamically equivalent realization of the delayed uncertain kinetic system $[\mathcal{P}, Y]$ if there exists a coefficient tensor $\mathcal{M}^p \in \mathbb{R}^{(p+1)\times n\times m}$ such that $Y\mathcal{A}^p = \mathcal{M}^p$ holds and $vec(\mathcal{M}^p) \in \mathcal{P}$.*

Consider a delayed uncertain system $[\mathcal{P}, Y]$ and a dynamically equivalent realization $\big(Y, \mathcal{A}^p\big)$. It is easy to see from Theorem 2.2 that the kinetic property of a DDE is not changed by a positive diagonal transformation of the states. By performing a state transformation defined by a positive definite diagonal matrix $T \in \mathbb{R}^{n\times n}$ we get

$$x = T\bar{x}, \qquad \bar{x} = T^{-1}x \tag{26}$$

and

$$\dot{\bar{x}}(t) = T^{-1}\dot{x}(t) = \sum_{i=0}^{p} T^{-1}[\mathcal{M}^p]_{i,:,:}\psi\big(x(t-\tau_i)\big) = \sum_{i=0}^{p} T^{-1}[\mathcal{M}^p]_{i,:,:}\psi\big(T\bar{x}(t-\tau_i)\big) =$$

$$= \sum_{i=0}^{p} T^{-1}[\mathcal{M}^p_{i,:,:}]\underbrace{\operatorname{diag}\left(\psi(T\cdot\mathbf{1}_{n\times 1})\right)}_{\Psi_T}\psi\big(\bar{x}(t-\tau_i)\big) = \sum_{i=0}^{p} T^{-1}[\mathcal{M}^p]_{i,:,:}\Psi_T\psi\big(\bar{x}(t-\tau_i)\big). \tag{27}$$

We can see from the result of (27) that a kinetic realization is given as $Y\left[\mathcal{A}^p\right]_{i,\cdot,\cdot} = T^{-1}[\mathcal{M}^p]_{i,\cdot,\cdot}\Psi_T$ for each $i \in \{0,\ldots,p\}$, i.e., the following equality should hold:

$$Y\mathcal{A}^p\Psi_T^{-1} = T^{-1}\mathcal{M}^p. \tag{28}$$

Using the above, we can formalize linear conjugacy for delayed CRNs as follows.

Definition 3.2. *A delayed reaction network $(Y,\mathcal{A}^p)$ is called a linearly conjugate realization of the delayed uncertain kinetic system $[\mathcal{P},Y]$ if there exists $\mathcal{M}^p \in \mathbb{R}^{(p+1)\times n\times m}$ and $T \in \mathbb{R}^{n\times n}$ positive definite diagonal matrix, such that $Y\mathcal{A}^p\Psi_T^{-1} = T^{-1}\mathcal{M}^p$ holds and $vec(T^{-1}\mathcal{M}^p) \in \mathcal{P}$. We will refer to this realization as the triple $(T^{-1},\mathcal{M}^p,\mathcal{A}^p\Psi_T^{-1})$.*

Let us arrange the diagonal entries of T^{-1} in the n-dimensional column vector

$$vec\big(T^{-1}\big) = \left[\left[T^{-1}\right]_{1,1}\ \ldots\ \left[T^{-1}\right]_{n,n}\right]^T \tag{29}$$

We will also consider a set L of finitely many additional linear constraints guaranteeing a prescribed property of the computed realizations such as zeroing given reaction rates, or even weak reversibility which means that each component of the reaction graph is strongly connected (see, Section 4.3). These constraints can affect the entries of the transformation matrix T (or T^{-1} for convenience) and the entries of $\mathcal{A}^p\Psi_T^{-1}$. Thus the inequalities in L can be written in the form

$$\alpha_i^{\mathrm{T}}vec\big(T^{-1}\big) + \beta_i^{\mathrm{T}}vec\big(\mathcal{A}^p\Psi_T^{-1}\big) \le d_i \tag{30}$$

where $\alpha_i \in \mathbb{R}^n,\ \beta_i \in \mathbb{R}^{(p+1)m^2-m},\ d_i \in \mathbb{R}$ hold for $i = 1,\ldots,r$, where r is the number of constraints in L. Thus, we can characterize a constrained delayed uncertain kinetic system by $[\mathcal{P},Y,L]$.

Definition 3.3. *A delayed reaction network $(Y,\mathcal{A}^p)$ is called a linearly conjugate realization of the constrained delayed uncertain kinetic system $[\mathcal{P},L,Y]$ if there exists a coefficient tensor $\mathcal{M}^p \in \mathbb{R}^{n\times m\times(p+1)}$ and a positive definite diagonal matrix $T \in \mathbb{R}^{n\times n}$ such that the equation $Y\mathcal{A}^p\Psi_T^{-1} = T^{-1}\mathcal{M}^p$ holds, $vec(T^{-1}\mathcal{M}^p) \in \mathcal{P}$ and the entries of the matrix T^{-1} and tensor $\mathcal{A}^p\Psi_T^{-1}$ fulfil the set L of constraints. We will refer to this realization as the triple $(T^{-1},\mathcal{M}^p,\mathcal{A}^p\Psi_T^{-1})$.*

3.3 Structural analysis

The following definitions and propositions generalizing the notions in [16] and [17] will help us understand the structure of the linearly conjugate realizations of a constrained delayed uncertain kinetic system.

Proposition 3.4. *Let us consider a constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$ *and two linearly conjugate realizations* $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p\Psi_T^{-1})$, $\left(\bar{T}^{-1}, \bar{\mathcal{M}}^p, \bar{\mathcal{A}}^p\Psi_{\bar{T}}^{-1}\right)$. *Then for each* $c \in [0,1]$ *the realization* $(T_c^{-1}, \mathcal{M}_c^p, \mathcal{A}_c^p)$ *with*

$$T_c^{-1} = cT^{-1} + (1-c)\bar{T}^{-1} \tag{31}$$

$$\mathcal{M}_c^p = \left(cT^{-1} + (1-c)\bar{T}^{-1}\right)^{-1}\left(cT^{-1}\mathcal{M}^p + (1-c)\bar{T}^{-1}\bar{\mathcal{M}}^p\right) \tag{32}$$

$$\mathcal{A}_c^p\Psi_{T_c}^{-1} = c\mathcal{A}^p\Psi_T^{-1} + (1-c)\bar{\mathcal{A}}^p\Psi_{\bar{T}}^{-1} \tag{33}$$

is also a linearly conjugate realization of $[\mathcal{P}, L, Y]$.

Proof.

Since both

$$\mathcal{A} = \sum_{i=0}^{p}\left[\mathcal{A}^p\Psi_T^{-1}\right]_{i,\cdot,\cdot} \tag{34}$$

$$\bar{\mathcal{A}} = \sum_{i=0}^{p}\left[\bar{\mathcal{A}}^p\Psi_{\bar{T}}^{-1}\right]_{i,\cdot,\cdot} \tag{35}$$

are Kirchhoff matrices

$$\mathcal{A}_c = \sum_{i=0}^{p}[\mathcal{A}_c^p]_{i,\cdot,\cdot} = \sum_{i=0}^{p}\left(c\left[\mathcal{A}^p\Psi_T^{-1}\right]_{i,\cdot,\cdot} + (1-c)\left[\bar{\mathcal{A}}^p\Psi_{\bar{T}}^{-1}\right]_{i,\cdot,\cdot}\right) = c\mathcal{A} + (1-c)\bar{\mathcal{A}} \tag{36}$$

is also a Kirchhoff matrix. Moreover, since both T^{-1} and $\bar{T}^{-1}$ are positive definite diagonal matrices, T_c^{-1} is also a positive definite diagonal matrix. Furthermore we have that

$$Y\mathcal{A}^p\Psi_T^{-1} = T^{-1}\mathcal{M}^p \tag{37}$$

$$Y\bar{\mathcal{A}}^p\Psi_{\bar{T}}^{-1} = \bar{T}^{-1}\bar{\mathcal{M}}^p \tag{38}$$

hold, thus

$$Y\mathcal{A}_c^p\Psi_{T_c}^{-1} = cY\mathcal{A}^p\Psi_T^{-1} + (1-c)Y\bar{\mathcal{A}}^p\Psi_{\bar{T}}^{-1} = cT^{-1}\mathcal{M}^p + (1-c)\bar{T}^{-1}\bar{\mathcal{M}}^p = T_c^{-1}\mathcal{M}_c^p. \tag{39}$$

We know that $vec(T_c^{-1}\mathcal{M}_c^p) \in \mathcal{P}$, since $\mathcal{P}$ is a polytope, which is of course convex. For the matrix T_c^{-1} and tensor $\mathcal{A}_c^p\Psi_{T_c}^{-1}$ the following holds

$$\begin{aligned}\alpha_i^{\mathrm{T}} vec\big(T_c^{-1}\big) + \beta_i^{\mathrm{T}} vec\big(\mathcal{A}_c^p\Psi_{T_c}^{-1}\big) \leq \alpha_i^{\mathrm{T}}\big(cT^{-1} + (1-c)\bar{T}^{-1}\big) + \beta_i^{\mathrm{T}}\big(c\mathcal{A}^p\Psi_T^{-1} + (1-c)\bar{\mathcal{A}}_c^p\Psi_{\bar{T}}^{-1}\big) = \\ = c\alpha_i^{\mathrm{T}} vec\big(T^{-1}\big) + c\beta_i^{\mathrm{T}} vec\big(\mathcal{A}^p\Psi_T^{-1}\big) + \\ + (1-c)\alpha_i^{\mathrm{T}} vec\big(\bar{T}^{-1}\big) + (1-c)\beta_i^{\mathrm{T}} vec\big(\bar{\mathcal{A}}_c^p\Psi_{\bar{T}}^{-1}\big) \leq \\ \leq cd_i + (1-c)d_i = d_i\end{aligned} \tag{40}$$

for $i = 1, \ldots, r$, i.e., the realization $(T_c^{-1}, \mathcal{M}_c^p, \mathcal{A}_c^p\Psi_{T_c}^{-1})$ also fulfills the set L of constraints. ■

Definition 3.5. *Let us consider a constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$ *and a linearly conjugate realization* $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p\Psi_T^{-1})$. *It is said that the realization is*

1. *a sparse realization, if it contains the minimum number of reactions,*
2. *a dense realization, if it contains the maximum number of reactions.*

Definition 3.6. *Let us consider a constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$ *and a linearly conjugate realization* $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p\Psi_T^{-1})$. *It is said that the realization has a superstructure property if its reaction graph contains the reaction graphs of all other linearly conjugate realizations of the delayed uncertain kinetic system as subgraphs.*

Using the above definitions we can now state the following key result.

Proposition 3.7. *Let us consider a constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$. *Then a dense linearly conjugate realization* $(T_d^{-1}, \mathcal{M}_c^p, \mathcal{A}_c^p\Psi_{T_d}^{-1})$ *has superstructure property.*

Proof. Let us assume that there is a reaction R that does not appear in the dense realization but appear in another linearly conjugate realization $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p\Psi_T^{-1})$. From Proposition 3.4 we know that the convex combination of $(T_d^{-1}, \mathcal{M}_d^p, \mathcal{A}_d^p\Psi_{T_d}^{-1})$ and $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p\Psi_T^{-1})$ is also a linearly conjugate realization of the delayed uncertain kinetic system. The reaction graph of the convex combination contains all the reactions of the dense realization and R, which means it strictly contains the reaction graph of the dense realization, i.e., we obtain a contradiction. ■

The following corollary allows us to compute all of the structurally different linearly conjugate realizations of a delayed uncertain kinetic system (see, Algorithm 4).

Corollary 3.8. *Let us consider a constrained delayed uncertain kinetic system. Then the structure of the unweighted directed reaction graph of the dense linearly conjugate realization is unique.*

Proof.

This follows directly from Proposition 3.7. ■

Note that these general results enable us to compute a wide variety of structures as special cases. Namely, dynamical equivalence is the special case of linear conjugacy, when $T, T^{-1}, \Psi_T, \Psi_T^{-1}$ are identity matrices, non-delayed systems are special cases with each delay equal to zero and finally, no uncertainty is a special case when the polytope $\mathcal{P}$ is in fact a single point in the parameter space.

3.4 Example

As an elementary illustrative example, let us consider the kinetic realization of the following delayed uncertain monomial

$$\dot{x}(t) = \lambda x(t-\tau) \tag{41}$$

where $\tau > 0$ and $\lambda \in [1, 3]$. The complex matrix generated by Algorithm 1 of [18] and the coefficient tensor is

$$Y = [1\ 2] \qquad [\mathcal{M}^p]_{0,..} = [0\ 0] \qquad [\mathcal{M}^p]_{1,..} = [\lambda\ 0]. \tag{42}$$

The uncertainty can be expressed in accordance to Eq. (21) by the following inequalities (omitting the inequalities ensuring that a particular entry is zero)

$$[0\ 0\ 1\ 0]^{\mathrm{T}} q \leq 3 \qquad [0\ 0\ -1\ 0]^{\mathrm{T}} q \leq -1. \tag{43}$$

According to Eqs. (22) and (23) the kinetic property of the system can be ensured by the additional inequality

$$[0\ 0\ 0\ -1]^{\mathrm{T}} q \leq 0. \tag{44}$$

Note that since $[\mathcal{M}^p]_{0,1,2} = 0$ the above inequality is not necessary. By Eqs. (12) and (13) it is easy to see that the following reaction network is a linearly conjugate realization of the system

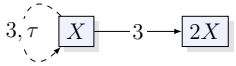


Figure 1. A realization of (41)

$$T^{-1} = [10] \quad [\mathcal{M}^p]_{0,..} = [0\ \ 0] \quad [\mathcal{M}^p]_{1,..} = [0.3\ \ 0]$$
$$[\mathcal{A}^p]_{0,..} = \begin{bmatrix} -6 & 0 \\ 3 & 0 \end{bmatrix} \quad [\mathcal{A}^p]_{1,..} = \begin{bmatrix} 3 & 0 \\ 0 & 0 \end{bmatrix}. \tag{45}$$

The dense linearly conjugate realization of the model is the following (the reactions of the realization shown in Figure 1 are highlighted in blue colour):

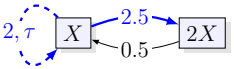


Figure 2. Dense realization of (41)

$$T^{-1} = [10] \quad [\mathcal{M}^p]_{0,..,.} = [0 \;\; 0] \quad [\mathcal{M}^p]_{1,..,.} = [0.3 \;\; 0]$$
$$[\mathcal{A}^p]_{0,..,.} = \begin{bmatrix} -5 & 0 \\ 2.5 & 0 \end{bmatrix} \quad [\mathcal{A}^p]_{1,..,.} = \begin{bmatrix} 2 & 0 \\ 0.5 & 0 \end{bmatrix}. \tag{46}$$

4 Computational approach

In this section, we present the computational framework for the structural analysis of delayed uncertain kinetic models. The algorithms and results are mainly generalized from [30] and [17].

Let us consider a constrained delayed uncertain kinetic system $[\mathcal{P}, L, Y]$ and a linearly conjugate realization $(T^{-1}, \bar{\mathcal{M}}^p, \bar{\mathcal{A}}^p \Psi_T^{-1})$. Eq. (28) tells us that linearly conjugate realizations are characterized by

$$Y \bar{\mathcal{A}}^p \Psi_T^{-1} - T^{-1} \bar{\mathcal{M}}^p = \mathbf{0} \in \mathbb{R}^{(p+1)\times n \times m} \tag{47}$$

where the known parameter is Y and the decision variables to be computed are T^{-1}, $\bar{\mathcal{M}}^p$, and $\bar{\mathcal{A}}^p$. We aim to develop an optimization framework based on linear programming, but Eq. (47) is bilinear in the variable pairs $\bar{\mathcal{A}}^p$, Ψ_T^{-1} and T^{-1}, $\bar{\mathcal{M}}^p$, respectively. We can solve this problem by introducing the auxiliary variables

$$\mathcal{A}^p = \bar{\mathcal{A}}^p \Psi_T^{-1} \tag{48}$$
$$\mathcal{M}^p = T^{-1} \bar{\mathcal{M}}^p. \tag{49}$$

Since both Ψ_T^{-1} and T^{-1} are diagonal matrices the tensors $\bar{\mathcal{A}}^p$ and $\bar{\mathcal{M}}^p$ can be simply computed from $\mathcal{A}^p$ and $\mathcal{M}^p$ (as it will be shown by Eqs. (60) – (61) later). Using the new variables we can rewrite the constraints necessary for the kinetic realization as

$$n_i^{\mathrm{T}} vec(\mathcal{M}^p) \le b_i \qquad i = 1, \ldots, l \tag{50}$$
$$\alpha_i^{\mathrm{T}} vec\big(T^{-1}\big) + \beta_i vec(\mathcal{A}^p) \le d_i \qquad i = 1, \ldots, r \tag{51}$$
$$Y[\mathcal{A}^p]_{i,..,.} - [\mathcal{M}^p]_{i,..,.} = \mathbf{0} \qquad i = 0, \ldots, p \tag{52}$$

$$[T^{-1}]_{j,j} > 0 \qquad j = 1, \ldots, n \tag{53}$$

$$[\mathcal{A}^p]_{0,j,k} \geq 0 \qquad j, k = 1, \ldots, m,\ j \neq k \tag{54}$$

$$[\mathcal{A}^p]_{i,j,k} \geq 0 \qquad i = 1, \ldots, p,\ j, k = 1, \ldots, m \tag{55}$$

$$\sum_{i=0}^{p} \sum_{j=1}^{m} [\mathcal{A}^p]_{i,k,j} = 0 \qquad k = 1, \ldots, m. \tag{56}$$

Considering the number of decision variables, namely the elements of $vec(T^{-1}) \in \mathbb{R}^n$, the elements of $vec(\mathcal{M}^p) \in \mathbb{R}^{(p+1)nm}$ and the elements of $vec(\mathcal{A}^p) \in \mathbb{R}^{(p+1)m^2-m}$, the above constraints define a polyhedron $\mathcal{Q} \in \mathbb{R}^{n+(p+1)nm+(p+1)m^2-m}$. Thus a point $Q \in \mathcal{Q}$ corresponds to the realization $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p)$ in the following way

$$Q = [\underbrace{q_1 \ \ldots \ q_n}_{vec(T^{-1})} \ \underbrace{q_{n+1} \ \ldots \ q_{n+(p+1)nm}}_{vec(\mathcal{M}^p)} \ \underbrace{q_{n+(p+1)nm+1} \ \ldots \ q_{n+(p+1)nm+(p+1)m^2-m}}_{vec(\mathcal{A}^p)}]. \tag{57}$$

Moreover, each inequality in L defined in Eq. (30) is stored as the triple (α_i, β_i, d_i).

4.1 Computing dense linearly conjugate realizations

Firstly, we describe some simple procedures (subroutines) used later in our algorithms. The procedure FindPositive$\big([\mathcal{P}, L, Y], H\big)$ computes a point $Q \in \mathcal{Q}$ that fulfils Eqs. (50) – (56), such that considering a set H of indices the value of the objective function $\sum_{j \in H} q_j$ is maximal. The procedure also returns the set $B = \{j | j \in H,\ q_j > 0\}$ of indices and can be computed in polynomial time in the number of complexes, since it requires the solution of an LP with $n + (p+1)nm + (p+1)m^2 - m$ decision variables and $l + r + n + (p+1)nm + (p+1)m^2 - m$ constraints (see the Appendix for the formalized linear program). The procedure ConvComb($Results$) computes the convex combination of the elements of the input vector based on Eqs. (31) – (33), i.e., if

$$Results = \Big[\big[vec(T_1^{-1})\ vec(\mathcal{M}_1^p)\ vec(\mathcal{A}_1^p)\big]\ \ldots\ \big[vec(T_k^{-1})\ vec(\mathcal{M}_k^p)\ vec(\mathcal{A}_k^p)\big]\Big] \tag{58}$$

then ConvComb($Results$) returns $\big[vec(T^{-1})\ vec(\mathcal{M}^p)\ vec(\mathcal{A}^p)\big]$, where

$$T^{-1} = \frac{1}{k} \sum_{i=1}^{k} T_i^{-1} \qquad \mathcal{M}^p = \frac{1}{k} \sum_{i=1}^{k} \mathcal{M}_i^p \qquad \mathcal{A}^p = \frac{1}{k} \sum_{i=1}^{k} \mathcal{A}_i^p. \tag{59}$$

This computation can also be done in polynomial time.

The procedure Decomp($Result$) decomposes the original variables based on Eq. (48) – (49) and returns $(T^{-1}, \bar{\mathcal{M}}^p, \bar{\mathcal{A}}^p)$, where

$$\bar{\mathcal{M}}^p = T\left(\frac{1}{k} \sum_{i=1}^{k} \mathcal{M}_i^p\right) \tag{60}$$

$$\bar{\mathcal{A}}^p = \left(\frac{1}{k}\sum_{i=1}^{k}\mathcal{A}_i^p\right)\Psi_T. \tag{61}$$

The decomposition of the variables corresponding to $\mathcal{A}^p$ is not necessary, since it doesn't contain structural information, but the decomposition of the variables corresponding to $\mathcal{M}^p$ enables us to use tensors such that $\bar{\mathcal{M}}^p \notin \mathcal{P}$.

Using the above procedures we can formalize the algorithm for computing the dense linearly conjugate realization for a given uncertain kinetic system as follows.

Algorithm 1 Construct a dense linearly conjugate realization of a given constrained delayed uncertain kinetic system $[\mathcal{P}, L, Y]$.

1: **procedure** $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p) = \textsc{DenseRealization}(\mathcal{P}, L, Y)$
2: $H := \{1, \ldots, n, n+(p+1)nm+1, \ldots, n+(p+1)nm+(p+1)m^2-m\}$
3: $B := H$
4: **while** $B\backslash\{1,\ldots,n\} \neq \emptyset$ **and** $\{1,\ldots,n\} \subset B$ **do**
5: $H := H \cup \{1,\ldots,n\}$
6: $(Q, B) :=$ FindPositive$\big([\mathcal{P}, L, Y], H\big)$
7: $H := H\backslash B$
8: push Q into *Results*
9: **end while**
10: **if** $H \cap \{1,\ldots,n\} \neq \emptyset$ **then**
11: There is no linearly conjugate realization of $[\mathcal{P}, L, Y]$.
12: **else**
13: *Result* :=ConvComb(*Results*)
14: Decomp(*Result*) determines a dense linearly conjugate realization of $[\mathcal{P}, L, Y]$.
15: **end if**
16: **end procedure**

Proposition 4.1. *Algorithm* 1 *returns a dense linearly conjugate realization of the constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$. *The computation runs in polynomial time.*

Proof.

In the while loop (lines 4-9) we maximize the sum of all variables corresponding to $vec(T^{-1})$ and $vec(\mathcal{A}^p)$. After each loop we do not consider those variables, which had positive value and we try to find another point of $\mathcal{Q}$ where the remaining variables have positive value. We repeat this step until no points of $\mathcal{Q}$ have positive values among the remaining variables, which is equivalent to the value of the objective function being zero, or until the realization corresponding to the computed point have a diagonal transformation

matrix T^{-1} which is only positive semi-definite (since all variables of interest in the loop have nonnegative value, a positive semi-definite T^{-1} can only be optimal if there are no points left with positive definite T^{-1}). This loop will end in finitely many steps, since $|H|$ is finite and it gets smaller in each step, in fact the loop ends after at most $(p+1)m^2-m$ steps. Let us denote the computed points of $\mathcal{Q}$ as $Q^1,\ldots,Q^k$.

If for an index $i \in \{1,\ldots,n,n+(p+1)nm+1,\ldots,n+(p+1)nm+(p+1)m^2-m\}$ there is a point $Q \in \mathcal{Q}$ such that $q_i > 0$, then there must be a step in the while loop when the procedure FindPositive$\big([\mathcal{P},L,Y],H\big)$ returns a points $Q^j \in \mathcal{Q}$ where $q_i^j > 0$. Otherwise $j \in H$ after exiting the while loop but in this case the value of the objective function is not zero, which is a contradiction.

A point $D \in \mathcal{Q}$ represents a dense linearly conjugate realization if it has the maximum number of positive elements among the variables $q_{n+(p+1)nm+1},\ldots,q_{n+(p+1)nm+(p+1)m^2-m}$, which are representing $vec(\mathcal{A}^p)$. Obviously only those such coordinates of D can be positive, which are positive in some of the computed points $Q^1,\ldots,Q^k$, and these coordinates will be positive in the point *Result*. Therefore the point *Result* has the maximum number of positive coordinates among the coordinates of interest.

The point *Result* it the arithmetic mean of the points $Q^1,\ldots,Q^k$, which is a convex combination of these points, therefore, according to Proposition 3.4, $Result \in \mathcal{Q}$ holds.

Considering the running time, in the while loop we have to solve at most $(p+1)m^2-m$ LPs with $n+(p+1)nm+(p+1)m^2-m$ decision variables and $l+r+n+(p+1)nm+(p+1)m^2-m$ constraints. Therefore, the algorithm runs in polynomial time. ■

4.2 Computing all linearly conjugate realizations

Generally, linearly conjugate realizations are not unique either structurally or parametrically. Our aim is to compute all structurally distinct linearly conjugate realizations of a constrained delayed uncertain kinetic system, thus from now on we will consider the reaction graph structures to be unweighted directed graphs. According to Proposition 3.7 if G_D is the reaction graph of the dense linearly conjugate realization and G_R is the reaction graph of another linearly conjugate realization, then $E(G_R) \subseteq E(G_D)$ holds, i.e., G_R is the subgraph of G_D. According to Corollary 3.8 and Proposition 4.1 G_D is unique and can be computed in polynomial time which is essential for this method.

Our main idea is to try to find a linearly conjugate realization for each subgraph of G_D

(we don't actually need to check each subgraph, see the complexity analysis of Proposition 4). Our first observation is that some reactions (i.e., edges in the reaction graph) are present in each realization. These are called core reactions, and the edges representing them are called core edges. We will denote the set of core edges by E_c and non-core edges by E_{nc}. To find out if an edge is core or not we simply need to check the feasibility of the FindPositive($[\mathcal{P}, L, Y], H$) (with H containing each index corresponding to the elements of T^{-1} and $\mathcal{A}^p$) LP with an additional linear constraint in L, which ensures that a particular reaction should not be present.

The procedure ZeroEdge(i, j, k) computes the necessary coefficient vectors of the new constraint.

Algorithm 2 Compute coefficient vectors (α, β, d) of a constraint expressing that $[\mathcal{A}^p]_{i,j,k} = 0$.

procedure $(\alpha, \beta, d) :=$ ZeroEdge(i, j, k)
  $\alpha := \mathbf{0} \in \mathbb{R}^n$
  $d := 0$
  if $i = 0$ **then**
    if $j > k$ **then**
      $\beta = e^{(p+1)m^2-m}_{(k-1)(m-1)+j-1}$
    else
      $\beta = e^{(p+1)m^2-m}_{(k-1)(m-1)+j}$
    end if
  else
    $\beta = e^{(p+1)m^2-m}_{im^2+(k-2)m+j}$
  end if
end procedure

Using this procedure we can now easily express the additional constraints in the following algorithm, which computes the core reactions.

Proposition 4.2. *Algorithm* 3 *returns the core reactions of the constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$. *The computation runs in polynomial time.*

Proof.

Let us assume by contradiction that the algorithm does not return the correct set of core reactions. The following cases can arise:

- There is a core edge that was not returned by the algorithm. This means that the corresponding LP was feasible, i.e., there is a realization where the edge is not present. This is a contradiction.

Algorithm 3 Compute the core reactions of the constrained delayed uncertain kinetic system $[\mathcal{P}, L, Y]$.

procedure $E_c = \textsc{CoreReactions}(\mathcal{P}, L, Y)$
  $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p) :=$ DenseRealization$(\mathcal{P}, L, Y)$
  $n :=$ size$(Y, 1)$
  $m :=$ size$(Y, 2)$
  $H := \{1, \ldots, n, n + (p+1)nm + 1, \ldots, n + (p+1)nm + (p+1)m^2 - m\}$
  for $i := 0, \ldots, p$ **do**
    for $j := 1, \ldots, m$ **do**
      for $k := 1, \ldots, m$ **do**
        if $[\mathcal{A}^p]_{i,j,k} > 0$ **then**
          $L_c := L$
          push ZeroEdge(i, j, k) into L_c
          if FindPositive$([\mathcal{P}, L_c, Y], H)$ is infeasible **then**
            push (i, j, k) into E_c.
          end if
        end if
      end for
    end for
  end for
end procedure

- There is a non-core edge that was returned by the algorithm. This means that the corresponding LP was infeasible, i.e., there are no realizations where the edge is not present. This is a contradiction.

Considering the running time, we need to solve at most $(p+1)m^2 - m$ LPs with $n + (p+1)nm + (p+1)m^2 - m$ decision variables and $l + r + n + (p+1)nm + (p+1)m^2 - m + 1$ constraints. Therefore, the algorithm runs in polynomial time. ■

Based on the above, each reaction graph can be uniquely described by their non-core edges. Thus, we will represent reaction graphs by a binary sequence of length $N = \left|E(G_D) \backslash E_c\right|$, where each value represents an edge. If R is a binary squence, then let $R[r]$ denote the rth element of the sequence, with $R[r] = 1$ meaning that the rth edge is present in the G_R reaction graph corresponding to R.

For the efficient computation of all realizations we need appropriate data structures. Since a binary sequence of length N uniquely describes a reaction graph, each graph can be labeled by the decimal value of the binary sequence, which is in the interval $\left[0, 2^N - 1\right]$. We will denote this mapping as $\text{dec}(R)$. We could store the computed realizations in an array of length 2^N, but our experience shows that the resulting array would be sparse and allocating memory for a sparse array of this size is not optimal considering memory use.

Thus, we will store the realizations in an associative array called *Realizations*. We also need $N+1$ stacks, indexed from 0 to N. The kth stack is denoted as $S[k]$. During the algorithm we will temporarily store the computed realizations in these stacks. The stack $S[k]$ can contain realizations with exactly k reactions, i.e., with exactly k elements equal to 1 of the corresponding binary sequence. We will compute the number of coordanates equal to 1 in the sequence R as $\mathrm{sum}(R)$.

During the algorithm we will first compute the dense realizations with reaction graph G_D. Then we will compute the core reactions to finally select the non-core realizations. Then we will try to find dense realizations with one particular non-core edge missing compared to G_D. We do this by adding an additional linear constraint. Then we will repeat this step by leaving out one particular non-core edge from the computed realizations. We do this, until all stacks are empty. This way we prune the search tree and don't have to check all subgraphs of G_D.

The procedure binarize($\mathcal{A}^p$) computes the binary sequence representing the reaction graph described by $\mathcal{A}^p$.

Proposition 4.3. *Algorithm* 4 *returns all linearly conjugate realizations of the constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$.

Proof.

Let us assume there is a sequence W which is not returned by the algorithm, but it describes a linearly conjugate realization of the constrained delayed uncertain kinetic system. Let R be another realization, which was computed by the algorithm and $G_W \subsetneq G_R$, i.e., $W[i] = 1 \implies R[i] = 1$ for $i = 1, \ldots, N$. If there are multiple realizations fulfiling this property, let R be the one with minimal $\mathrm{sum}(R)$. It follows from the definition of the sequences W and R that there must be an index j such that $W[j] = 0$ and $R[j] = 1$.

During the algorithm we compute the sequence U, which is returned by the procedure call DenseRealization($\mathcal{P}, L_{R,j}, Y$), which is a dense realization with the property $U[j] = 0$. It is clear that such U sequence always exists, since W satisfies these constraints. We also know that $W \neq U$, since it is not returned by the algorithm. Thus, $G_W \subsetneq G_U$ holds, which is a contradiction, since R is minimal.

Considering the running time, we know that the procedure DenseRealization runs in polynomial time but it is theoretically possible that each subgraph of G_D corresponds to a linearly conjugate realization, i.e., in the worst case scenario, we need to compute each

subpgrah of G_D, thus, we need to call the procedure DenseRealization 2^N times. This means that the algorithm might require exponential time. ■

Algorithm 4 Compute all of the linearly conjugate realizations of a constrained delayed uncertain kinetic system $[\mathcal{P}, L, Y]$.

procedure $Realizations$ = AllRealizations$(\mathcal{P}, L, Y)$
  $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p)$:= DenseRealization$(\mathcal{P}, L, Y)$
  E_c :=CoreReactions$(\mathcal{P}, L, Y)$
  for $i := 0, \ldots, p$ **do**
    for $j := 1, \ldots, m$ **do**
      for $k := 1, \ldots, m$ **do**
        if $(i \neq 0$ **or** $j \neq k)$ **and** $[\mathcal{A}^p]_{i,j,k} > 0$ **and** $(i, j, k) \notin E_c$ **then**
          push (i, j, k) into E_{nc}
        end if
      end for
    end for
  end for
  $N :=$ size$(E_{nc}, 1)$
  $D :=$ binarize$(\mathcal{A}^p)$
  $Realizations[D] := (T^{-1}, \mathcal{M}^p, \mathcal{A}^p)$
  push D into $S[N]$
  for $k := N, \ldots, 0$ **do**
    while size$\big(S[k]\big) > 0$ **do**
      $R :=$ pop $S[k]$
      $L_R := L$
      for $r := 1, \ldots, N$ **do**
        if $R[r] = 0$ **then**
          push ZeroEdge$\big(E_{nc}[r][1], E_{nc}[r][2], E_{nc}[r][3]\big)$ into L_R
        end if
      end for
      for $r := 1, \ldots, N$ **do**
        if $R[r] = 1$ **then**
          $L_{R,r} := L_R$
          push ZeroEdge$\big(E_{nc}[r][1], E_{nc}[r][2], E_{nc}[r][3]\big)$ into $L_{R,r}$
          $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p)$:= DenseRealization$(\mathcal{P}, L_{R,r}, Y)$
          $U :=$binarize$(\mathcal{A}^p)$
          if dec$(U) \geq 0$ **and** dec(U) **not in** $Realizations$ **then**
            $Realizations[\text{dec}(U)] := (T^{-1}, \mathcal{M}^p, \mathcal{A}^p)$
            push U into $S\big[\text{sum}(U)\big]$
          end if
        end if
      end for
    end while
  end for
end procedure

4.3 Computing weakly reversible linearly conjugate realizations

In this section we will demonstrate further the applicability of the general results and algorithms. We can find realizations with special structural or parametrical properties as long as we can express the property through additional linear constraints. Weak reversibility is such a property and finding these realizations is also motivated by strong theoretical results [22, 23].
First we define a strong notion of connectedness, which is reversibility.

Definition 4.4. *Let us consider a reaction network with complexes $\mathcal{C}$. It is said that the reaction network is reversible if each reaction has a reverse pair, i.e., if $C_i, C_j \in \mathcal{C}$ and there is a reaction with C_i as source complex and C_j as product complex, then there is also a reaction with C_j as source complex and C_i as product complex.*

We can see that this is a particularly rigorous condition, therefore we want to introduce a weaker condition, namely weak reversibility.

Definition 4.5. *Let us consider a reaction network with complexes $\mathcal{C}$. It is said that a complex set $\bar{\mathcal{C}} \subset \mathcal{C}$ is a strongly connected component, if $C_i, C_j \in \bar{\mathcal{C}}$ implies that there is a directed path from C_i to C_j and $\bar{C}$ is maximal.*

Definition 4.6. *Let us consider a reaction network with complexes $\mathcal{C}$. It is said that the reaction network is weakly reversible if $C_i, C_j \in \mathcal{C}$ and there is a directed path of reaction between C_i and C_j, then there is also a directed path of reactions between C_j and C_i.*

It is not trivial from this definition that this property can be expressed in the form of linear constraints, but there exists necessary and sufficient conditions for weak reversibility, namely a reaction network is weakly reversible if and only if there are no edges between its strongly connected components.

This condition enables us to use linear constraints, since we simply need to compute the dense realization, then identify the edges between the strong components and add linear constraints ensuring that these particular edges will no longer be present. Then we need to repeat this step until either we find a weakly reversible structure, or we reach an infeasible problem, which means that there are no such structures.
The procedure FindCrossEdges($\mathcal{A}^p$) returns the edges between the strongly connected

components of the unweighted and undelayed reacion graph described ba $\mathcal{A}^p$. The returned set of cross-component edges will be denoted E_{cr}. This is done by the Kosaraju-Sharir algorithm, which is a linear time algorithm for finding strongly connected components.

Algorithm 5 Compute the dense weakly reversible linearly conjugate realizations of a constrained delayed uncertain kinetic system $[\mathcal{P}, L, Y]$.

procedure $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p) = \text{WRREALIZATION}(\mathcal{P}, L, Y)$
  $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p) := \text{DenseRealization}(\mathcal{P}, L, Y)$
  $E_{cr} := \text{FindCrossEdges}(\mathcal{A}^p)$
  while $E_{cr} \neq \emptyset$ **do**
    for $r := \text{size}(E_{cr}, 1)$ **do**
      for $i := 0, \ldots, p$ **do**
        push $\text{ZeroEdge}\big(i, E_{cr}[r][2], E_{cr}[r][1]\big)$ into L
      end for
    end for
    $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p) = \text{DenseRealization}(\mathcal{P}, L, Y)$
    $E_{cr} := \text{FindCrossEdges}(\mathcal{A}^p)$
  end while
  if $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p)$ is an invalid realization **then**
    There is no weakly reversible linearly conjugate realization of $[\mathcal{P}, L, Y]$.
  else
    $(T^{-1}, \mathcal{M}^p, \mathcal{A}^p$ is a dense linearly conjugate realization of $[\mathcal{P}, L, Y]$.
  end if
end procedure

Proposition 4.7. *Algorithm* 5 *returns the dense weakly reversible linearly conjugate realization of the constrained delayed uncertain kinetic system* $[\mathcal{P}, L, Y]$*. The computation runs in polynomial time.*

Proof.

Let G be the reaction graph of a weakly reversible linearly conjugate realization. According to Proposition 3.7 G must be the subgraph of the dense linearly conjugate realization, which is denoted by $G_0 = G_D$. Since G cannot have edges between its strongly connected components and each strongly connected component in G is a subgraph of a strongly connencted component in G_0, the cross-component edges of G_0 cannot be in G. Since we can express this as linear constraints, there must be a dense linearly conjugate realization without these edges, and its reaction graph is denoted by G_1.

Similarly, the cross-component edges of G_1 cannot be in G, i.e., there exists a dense linearly conjugate realization without these edges, and its reaction graph is denoted by G_2. Repeating the same step we arrive at a reaction graph G_k, with no cross-component edges

or no edges at all. In the second case there is no weakly reversible linearly conjugate realization of $[\mathcal{P}, L, Y]$. In the first case $G \subset G_k$ and according to Proposition 3.7 G_k must be the dense weakly reversible linearly conjugate realization of $[\mathcal{P}, L, Y]$.

Considering the running time, the Kosaraju-Sharir algorithm is a linear time algorithm in the number of vertices and edges. If there are N edges in the unweighted and undelayed reaction graph, then the while loop runs at most N times, i.e., we have to call the DenseRealization procedure at most $N+1$ times, which is a polynomial algorithm. Thus, the algorithm runs in polynomial time. ■

5 Examples

The algorithms presented were implemented in Python 3.6.8 using the Gurobi Optimization 8.1 solver [24]. The computations were tested on a workstation with 2.7 GHz Intel Core i7-7500U processor and 8 Gb RAM (DDR4 2133 MHz, 0.5 ns).

5.1 Oregonator

The Oregonator is the simplest realistic model of the chemical dynamics of the Belousov-Zhabotinsky reaction [25]. The dimensionless form of the delayed Oregonator model is (see the Appendix for the derivation)

$$\dot{x}(\theta) = \alpha\big(f\beta y(\theta) - f\alpha x(\theta)y(\theta) + \alpha x(\theta) - 2\beta x^2(\theta)\big) \tag{62}$$

$$\dot{y}(\theta) = -y(\theta) - \frac{\alpha}{\beta}x(\theta)y(\theta) + \frac{\alpha}{\beta}x(\theta-\epsilon) \tag{63}$$

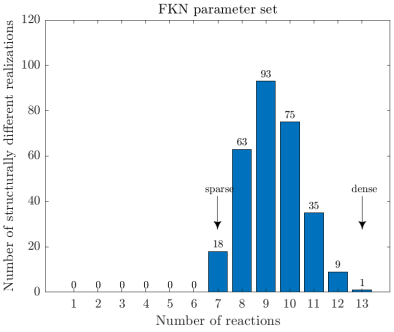
where θ is the rescaled time variable and $\alpha,\ \beta,\ f,\ \epsilon \in \mathbb{R}_{>0}$.

The matrices describing the system are

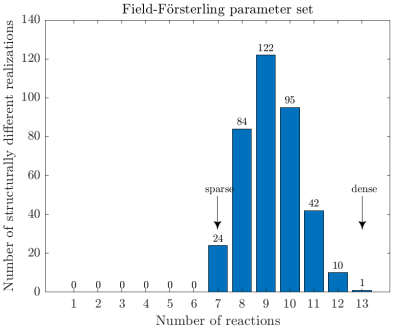
$$Y = \begin{bmatrix} 0 & 1 & 1 & 2 & 0 \\ 1 & 1 & 0 & 0 & 0 \end{bmatrix} \quad M_0 = \begin{bmatrix} \alpha f\beta & -f\alpha^2 & \alpha^2 & -2\alpha\beta & 0 \\ -1 & -\frac{\alpha}{\beta} & 0 & 0 & 0 \end{bmatrix} \quad M_1 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\alpha}{\beta} & 0 & 0 \end{bmatrix} \tag{64}$$

Regarding the $\alpha,\ \beta,\ f$ and ϵ parameters, there are two classical parametrizations of the model, namely the Field-Kőrös-Noyes (FKN) parameter set [26] (see, Figure 3(a)) and the Field-Försterling parameter set [27] (see, Figure 3(b)). Figure 3 shows the distribution of the number of structurally different linearly conjugate realizations depending on the number of reactions. Note that the different parametrizations yield different distributions,

and although we removed the Z intermediate species the sparse realizations still have 7 reactions.



(a) $\alpha = 77$ $\beta = 0.16$ $f = 1$



(b) $\alpha = 5.1$ $\beta = 0.035$ $f = 0.57$

Figure 3. Distributions of structurally different realizations

We will model the uncertainty of the Oregonator model by assuming that the α, β and f parameters are in the cuboid defined by the FKN and Field-Försterling parameter sets (we will not consider the ϵ parameter, since the exact value of the delay does not affect the structure of realizations):

$$0.10 \leq [\mathcal{M}^p]_{0,1,1} \leq 12.32 \qquad -5929.00 \leq [\mathcal{M}^p]_{0,1,2} \leq -14.83 \qquad 26.01 \leq [\mathcal{M}^p]_{0,1,3} \leq 5929.00 \quad (65)$$

$$-24.64 \leq [\mathcal{M}^p]_{0,1,4} \leq -0.36 \qquad -2200.00 \leq [\mathcal{M}^p]_{0,2,2} \leq -31.87 \qquad 31.87 \leq [\mathcal{M}^p]_{1,2,3} \leq 2200.00 \quad (66)$$

Figure 4 shows the distribution of the number of structurally different linearly conjugate realizations of the uncertain delayed system depending on the number of reactions.

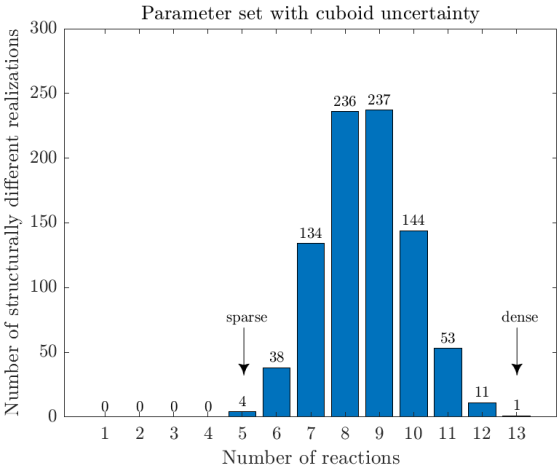


Figure 4. Distributions of structurally different realizations

Note that the introduction of uncertainty resulted in much more structurally different realizations and the 4 sparse realizations have only 5 reactions. The T^{-1} matrices and $\mathcal{M}^p$ tensors of the sparse realizations are (rounded to two significant decimals):

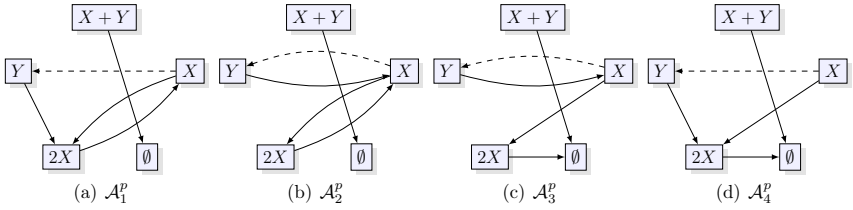
$$T_1^{-1} = \begin{bmatrix} 10 & 0 \\ 0 & 10 \end{bmatrix} \quad [\mathcal{M}_1^p]_{0,\cdot,\cdot} = \begin{bmatrix} 0.2 & -220.00 & 297.75 & -2.46 & 0 \\ -0.1 & -220.00 & 0 & 0 & 0 \end{bmatrix} \quad [\mathcal{M}_1^p]_{1,\cdot,\cdot} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 111.59 & 0 & 0 \end{bmatrix} \tag{67}$$

$$T_2^{-1} = \begin{bmatrix} 10 & 0 \\ 0 & 10 \end{bmatrix} \quad [\mathcal{M}_2^p]_{0,\cdot,\cdot} = \begin{bmatrix} 0.1 & -220.00 & 297.75 & -2.46 & 0 \\ -0.1 & -220.00 & 0 & 0 & 0 \end{bmatrix} \quad [\mathcal{M}_2^p]_{1,\cdot,\cdot} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 111.59 & 0 & 0 \end{bmatrix} \tag{68}$$

$$T_3^{-1} = \begin{bmatrix} 10 & 0 \\ 0 & 10 \end{bmatrix} \quad [\mathcal{M}_3^p]_{0,\cdot,\cdot} = \begin{bmatrix} 0.1 & -220.00 & 297.75 & -2.46 & 0 \\ -0.1 & -220.00 & 0 & 0 & 0 \end{bmatrix} \quad [\mathcal{M}_3^p]_{1,\cdot,\cdot} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 111.59 & 0 & 0 \end{bmatrix} \tag{69}$$

$$T_4^{-1} = \begin{bmatrix} 10 & 0 \\ 0 & 10 \end{bmatrix} \quad [\mathcal{M}_4^p]_{0,\cdot,\cdot} = \begin{bmatrix} 0.2 & -220.00 & 297.75 & -2.46 & 0 \\ -0.1 & -220.00 & 0 & 0 & 0 \end{bmatrix} \quad [\mathcal{M}_4^p]_{1,\cdot,\cdot} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 111.59 & 0 & 0 \end{bmatrix} \tag{70}$$

Figure 5 shows the reaction graphs of the sparse realizations. Delayed reactions are represented by dashed lines.



(a) $\mathcal{A}_1^p$ (b) $\mathcal{A}_2^p$ (c) $\mathcal{A}_3^p$ (d) $\mathcal{A}_4^p$

Figure 5. Reaction graphs of sparse realizations

5.2 Delayed Lotka-Volterra reactions with three species

The Lotka-Volterra equations are used to model biological systems where the different species interact with each other and the environment. Let us consider a Lotka-Volterra system with three species from the literature [28, 29]

$$\dot{x}_1(t) = u + \big(\kappa_1 - d - \kappa_2 x_1(t) - a x_2(t) - b x_3(t)\big) x_1(t) \tag{71}$$

$$\dot{x}_2(t) = u + \big(\kappa_1 - d - b x_1(t) - \kappa_2 x_2(t) - a x_3(t)\big) x_2(t) \tag{72}$$

$$\dot{x}_3(t) = u + \big(\kappa_1 - d - a x_1(t) - b x_2(t) - \kappa_2 x_3(t)\big) x_3(t) \tag{73}$$

where the parameters u and d denote a constant migration into and out of the habitat, the parameters κ_1 and κ_2 denote the birth and death rate coefficients of the species and the parameters a and b denote comptetition between the species. Of course $u, d, \kappa_1, \kappa_2, a, b > 0$ and according to the literature we set $\kappa_1 - d = \kappa_2 = 1$ [29].

We introduce delays τ_1 to the terms $\kappa_1 x_i(t)$, for $i = 1, \ldots, 3$. (For simplicity, we assume that the delays corresponding to each term are the same for the three species.) Eqs. (74) − (76) below describe the dynamics of the delayed system, and Figure 6 shows a reaction graph drawn using the literature (see [28] for the non-delayed version).

$$\dot{x}_1(t) = u + \kappa_1 x_1(t - \tau_1) - \big(d + \kappa_2 x_1(t) + a x_2(t) + b x_3(t)\big) x_1(t) \tag{74}$$

$$\dot{x}_2(t) = u + \kappa_1 x_2(t - \tau_1) - \big(d + b x_1(t) + \kappa_2 x_2(t) + a x_3(t)\big) x_2(t) \tag{75}$$

$$\dot{x}_3(t) = u + \kappa_1 x_3(t - \tau_1) - \big(d + a x_1(t) + b x_2(t) + \kappa_2 x_3(t)\big) x_3(t) \tag{76}$$

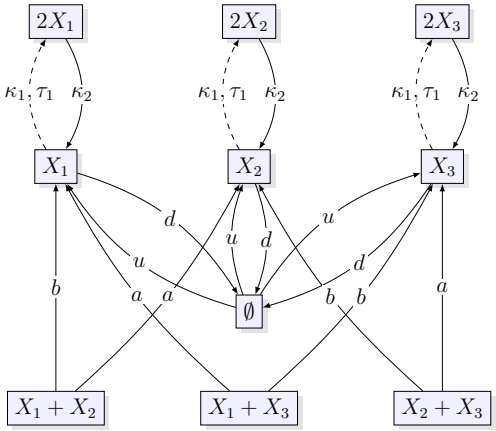


Figure 6. Delayed Lotka-Volterra reactions with three species

Note that this is not the canonical realization (the edges representing the deaths of the species would have X_i as the source complex and $\emptyset$ as the product complex, for $i = 1, \ldots, 3$), but our complex generation algorithm (Algorithm 1 of [18]) computes the same complex set. The matrices describing the system are

$$Y = \begin{bmatrix} 2 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 2 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 2 & 0 & 0 & 1 & 0 & 0 & 1 & 1 \end{bmatrix} \tag{77}$$

$$M_0 = \begin{bmatrix} -\kappa_2 & 0 & 0 & d & 0 & 0 & u & -a & -b & 0 \\ 0 & -\kappa_2 & 0 & 0 & d & 0 & u & -b & 0 & -a \\ 0 & 0 & -\kappa_2 & 0 & 0 & d & u & 0 & -a & -b \end{bmatrix} \tag{78}$$

$$M_1 = \begin{bmatrix} 0 & 0 & 0 & \kappa_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \kappa_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \kappa_1 & 0 & 0 & 0 & 0 \end{bmatrix}. \tag{79}$$

Figure 7 shows the result of Algorithm 5 run with the matrices above, which is the dense weakly reversible realization of the system consisting of 42 reactions (which, incidentally, has identical structure with the dense realization).

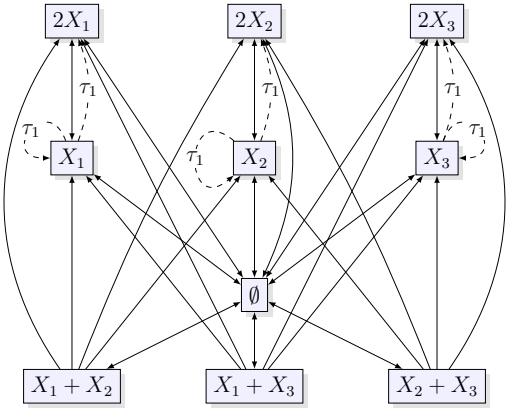


Figure 7. Dense weakly reversible linearly conjugate realization

6 Conclusions

The inverse problem of computing reaction graphs from delayed kinetic polynomial differential equations was addressed in this work. Building on the initial realizability results described in [18], linear conjugacy and parametric uncertainty of the models were added and treated in the same computational framework based on convex optimization. It was shown that similarly to previous results (see, e.g. [16,30]), the dense realization containing the maximum number of reactions is a super-structure containing all admissible reaction graphs corresponding to a given uncertain DDE assuming a fixed complex set. An algorithm was proposed which is able to compute each one of these reaction graphs. It is expected that the presented results can be used in the distinguishability and identifiability analysis of delayed kinetic models identified from imperfect (noisy) measurement data, and also in the design of reaction networks with prescribed dynamical properties. Finally, it is important to note that earlier results on the computational construction of non-delayed CRNs in [23,30] can be considered as special cases of the general framework proposed in this paper.

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Appendix

FindPositive

The linear program solved by the FindPositive$\big([\mathcal{P}, L, Y], H\big)$ procedure is given below:

maximize $\quad \sum_{j \in H} q_j$

subject to

$$\cdot \sum_{j=1}^{(p+1)nm} [n_i]_j q_{n+j} \leq b_i \qquad i = 1, \ldots, l \tag{80}$$

$$\cdot \sum_{j=1}^{n} [\alpha_i]_j q_j + \sum_{j=1}^{(p+1)m^2-m} [\beta_i]_j q_{n+(p+1)nm+j} \leq d_i \qquad i = 1, \ldots, r \tag{81}$$

$$\begin{aligned} \cdot\, q_{n+(j-1)m+k} - \sum_{l=1}^{k-1} \big([Y]_{j,l} - [Y]_{j,k}\big) q_{n+(p+1)nm+(k-1)(m-1)+l} - \\ - \sum_{l=k+1}^{m} \big([Y]_{j,l} - [Y]_{j,k}\big) q_{n+(p+1)nm+(k-1)(m-1)+l-1} + \\ + [Y]_{j,k} \sum_{i=1}^{p} \sum_{l=1}^{m} q_{n+(p+1)nm+im^2+(k-2)m+l} = 0 \qquad j = 1, \ldots, n,\ k = 1, \ldots, m \end{aligned} \tag{82}$$

$$\begin{aligned} \cdot\, q_{n+inm+(j-1)m+k} - \sum_{l=1}^{m} [Y]_{j,l} q_{n+(p+1)nm+im^2+(k-2)m+l} = 0 \\ i = 0, \ldots, p,\ j = 1, \ldots, n,\ k = 1, \ldots, m \end{aligned} \tag{83}$$

$$\cdot\, q_j \geq 0 \qquad j = 1, \ldots, n, n + (p+1)nm + 1, \ldots, n + (p+1)nm + (p+1)m^2 - m. \tag{84}$$

Derivation of the dimensionless delayed Oregonator model

The non-delayed Oregonator model [10] is

$$A + Y \xrightarrow{k_1} X + P \tag{85}$$

$$X + Y \xrightarrow{k_2} 2P \tag{86}$$

$$A + X \xrightarrow{k_3} 2X + Z \tag{87}$$

$$2X \xrightarrow{k_4} A + P \tag{88}$$

$$Z \xrightarrow{k_5} fY. \tag{89}$$

The concentration of A is taken to be constant by replenishment from a large external reservoir and P is a product species that we can omit from the network, since it does not

take part in any further reaction.
The ODEs of the reactions are

$$\dot{X} = k_1 AY + k_3 AX - k_2 XY - 2k_4 X \tag{90}$$
$$\dot{Y} = k_5 fZ - k_1 AY - k_2 XY \tag{91}$$
$$\dot{Z} = k_3 AX - k_5 Z. \tag{92}$$

By defining

$$\theta = k_1 At \qquad \epsilon = k_1 A\tau \tag{93}$$
$$x(\theta) = \frac{X}{A}\sqrt{\frac{k_2 k_4}{k_1 k_3}} \qquad y(\theta) = \frac{Y}{A}\frac{k_2}{fk_3} \tag{94}$$
$$\alpha = \sqrt{\frac{k_3}{k_1}} \qquad \beta = \sqrt{\frac{k_4}{k_2}} \tag{95}$$
$$z(\theta) = \frac{Z}{A}\frac{k_5}{k_3 A}\sqrt{\frac{k_2 k_4}{k_1 k_3}} \qquad \gamma = \frac{k_5}{k_1 A} \tag{96}$$

we get the so-called dimensionless form of the ODEs of the reactions (suppressing the rescaled time variable θ)

$$\dot{x} = \alpha\big(f\beta y - f\alpha xy + \alpha x - 2\beta x^2\big) \tag{97}$$
$$\dot{y} = -y - \frac{\alpha}{\beta}xy + \frac{\alpha}{\beta}z \tag{98}$$
$$\dot{z} = \gamma(x - z). \tag{99}$$

It is claimed in the literature that the only role of the species Z is to imitate delayed feedback, hence the introduction of a delayed reaction is a suitable approximation [10]. For this we have to separate the product complex of the reaction in Eq. (87)

$$A + X \xrightarrow{\frac{1}{2}k_3} 4X \tag{100}$$
$$A + X \xrightarrow{\frac{1}{2}k_3} 2Z. \tag{101}$$

Now we can omit the intermediate Z species and get the reactions

$$A + Y \xrightarrow{k_1} X + P \tag{102}$$
$$X + Y \xrightarrow{k_2} 2P \tag{103}$$
$$A + X \xrightarrow{\frac{1}{2}k_3} 4X \tag{104}$$
$$A + X \xrightarrow{\frac{1}{2}k_{3,\tau}} 2fY \tag{105}$$
$$2X \xrightarrow{k_4} A + P. \tag{106}$$

From these reactions we get the following DDE

$$\dot{X}(t) = k_1 AY(t) + k_3 AX(t) - k_2 X(t)Y(t) - 2k_4 X^2(t) \tag{107}$$

$$\dot{Y}(t) = -k_1 AY(t) - k_2 X(t)Y(t) + k_3 f AX(t-\tau) \tag{108}$$

which becomes

$$\dot{x}(\theta) = \alpha\big(f\beta y(\theta) - f\alpha x(\theta)y(\theta) + \alpha x(\theta) - 2\beta x^2(\theta)\big) \tag{109}$$

$$\dot{y}(\theta) = -y(\theta) - \frac{\alpha}{\beta}x(\theta)y(\theta) + \frac{\alpha}{\beta}x(\theta-\epsilon) \tag{110}$$

after transformed to the dimensionless form using Eqs. (93) – (96).

Interpreting the results of the realization algorithms

Omitting the species A and P from Eqs. (102) – (106) we get

$$Y \xrightarrow{k_1} X \tag{111}$$

$$X + Y \xrightarrow{k_2} \emptyset \tag{112}$$

$$X \xrightarrow{\frac{1}{2}k_3} 4X \tag{113}$$

$$X \xrightarrow{\frac{1}{2}k_{3,\tau}} 2fY \tag{114}$$

$$2X \xrightarrow{k_4} \emptyset. \tag{115}$$

Since the complexes present in the equation are sufficient for realization the complexes $4X$ and $2fY$ do not appear, although we can ensure the ubiety of these complexes. Figure 8 shows the dense realization with the additional complexes. The reactions of the sparse realization from Figure 5(c) are highlighted.

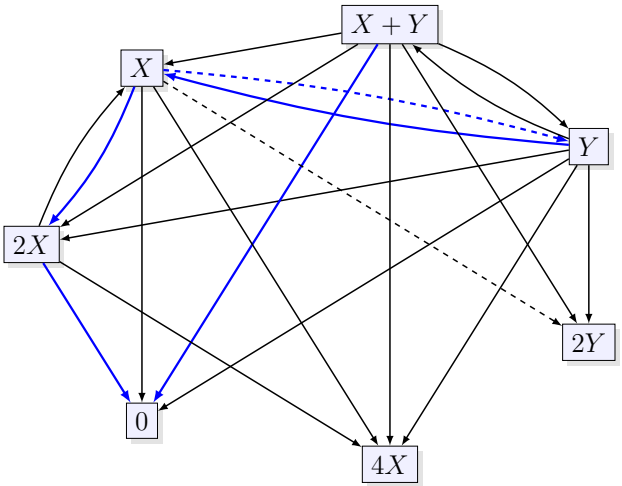

Figure 8. Dense realization with additional complexes

Note that our computational framework can handle non-integer stoichiometric coefficients, however for the sake of simplicity we consider the f scalar to affect the reaction rate.

References

[1] W. M. Haddad, V. Chellaboina, Q. Hui, *Nonnegative and Compartmental Dynamical Systems*, Princeton Univ. Press, New Jersey, 2010.

[2] P. Érdi, J. Tóth, *Mathematical Models of Chemical Reactions. Theory and Applications of Deterministic and Stochastic Models*, Manchester Univ. Press, Manchester, 1989.

[3] M. Feinberg, *Foundations of Chemical Reaction Network Theory*, Springer, Cham, 2019.

[4] B. S. Hernandez, E. R. Mendoza, A. A. de los Reyes V, Fundamental decompositions and multistationarity of power–law kinetic systems, *MATCH Commun. Math. Comput. Chem.* **83** (2020) 403–434.

[5] G. Stépán, *Retarded Dynamical Systems: Stability and Characteristic Functions*, Longman Sci. Tech., Harlow, 1989.

[6] P. D. Christofides, N. El-Farra, *Control of Nonlinear and Hybrid Process Systems: Designs for Uncertainty, Constraints and Time-Delays*, Springer–Verlag, Berlin, 2005.

[7] Y. M. Repin, On the approximate replacement of systems with lag by ordinary dynamical systems, *J. Appl. Math. Mech.* **29** (1965) 254–264.

[8] I. Győri, J. Turi, Uniform approximation of a nonlinear delay equation on infinite intervals, *Nonlin. Anal. Theory, Methods Appl.* **17** (1991) 21–29.

[9] B. Krasznai, I. Győri, M. Pituk, The modified chain method for a class of delay differential equations arising in neural networks, *Math. Comput. Model.* **51** (2010) 452–460.

[10] M. R. Roussel, The use of delay differential equations in chemical kinetics, *J. Phys. Chem.* **100** (1996) 8328–8330.

[11] M. Mincheva, M. R. Roussel, Graph-theoretic methods for the analysis of chemical and biochemical networks. II. Oscillations in networks with delays, *J. Math. Biol.* **55** (2007) 87–104.

[12] G. Lipták, K. M. Hangos, M. Pituk, G. Szederkényi, Semistability of complex balanced kinetic systems with arbitrary time delays, *Syst. Control Lett.* **114** (2018) 38–43.

[13] V. Hárs, J. Tóth, On the inverse problem of reaction kinetics, *Qual. Theory Diff. Eq.* **30** (1981) 363–379.

[14] G. Craciun, M. D. Johnston, G. Szederkényi, E. Tonello, J. Tóth, P. Y. Yu, Realizations of kinetic differential equations, *Math. Biosci. Engin.* **17** (2019) 862–892.

[15] S. M. Shavarani, J. Tóth, B. Vízvári, How to generate species with positive concentrations for all positive times?, *MATCH Commun. Math. Comput. Chem.* **84** (2020) 29–56.

[16] B. Ács, G. Szederkényi, Z. Tuza, Z. A. Tuza, Computing all possible graph structures describing linearly conjugate realizations of kinetic systems, *Comput. Phys. Commun.* **204** (2016) 11-20.

[17] B. Ács, G. Szlobodnyik, G. Szederkényi, A computational approach to the structural analysis of uncertain kinetic systems, *Comput. Phys. Commun.* **228** (2018) 83–95.

[18] M. Vághy, G. Szlobodnyik, G. Szederkényi, Kinetic realization of delayed polynomial dynamical models, *IFAC-PapersOnLine* **52** (2019) 45–50.

[19] F. Horn, R. Jackson, General mass action kinetics, *Arch. Rat. Mech. Anal.* **47** (1972) 81–116.

[20] M. D. Johnston, D. Siegel, Linear conjugacy of chemical reaction networks, *J. Math. Chem.* **49** (2011) 1263–1282.

[21] M. E. Dyer, L. G. Proll, An algorithm for determining all extreme points of a convex polytope, *Math. Program.* **12** (1977) 81–96.

[22] J. Rudan, G. Szederkényi, K. M. Hangos, Polynomial time algorithms to determine weakly reversible realizations of chemical reaction networks, *J. Math. Chem.* **52** (2014) 1386–1404.

[23] B. Ács, G. Szederkényi, Z. A. Tuza, Z. Tuza, Computing linearly conjugate weakly reversible kinetic structures using optimization and graph theory, *MATCH Commun. Math. Comput. Chem.* **74** (2015) 481–504.

[24] L. Gurobi Optimization, Gurobi optimizer reference manual, 2020. [Online]. Available: http://www.gurobi.com

[25] R. J. Field, R. M. Noyes, Oscillations in chemical systems. IV. Limit cycle behavior in a model of a real chemical reaction, *J. Chem. Phys.* **60** (1974) 1877–1884.

[26] R. J. Field, E. Koros, R. M. Noyes, Oscillations in chemical systems. II. Thorough analysis of temporal oscillation in the bromate–cerium–malonic acid system, *J. Am. Chem. Soc.* **94** (1972) 8649–8664.

[27] R. J. Field, H. D. Foersterling, On the oxybromine chemistry rate constants with cerium ions in the Field–Koeroes–Noyes mechanism of the Belousov–Zhabotinskii reaction, *J. Phys. Chem.* **90** (1986) 5400–5407.

[28] E. August, M. Barahona, Solutions of weakly reversible chemical reaction networks are bounded and persistent, *IFAC Proc.* **11** (2010) 42–47.

[29] R. M. May, W. J. Leonard, Nonlinear aspects of competition between three species, *SIAM J. Appl. Math.* **29** (1975) 243–253.

[30] B. Ács, G. Szederkényi, D. Csercsik, A new efficient algorithm for determining all structurally different realizations of kinetic systems, *MATCH Commun. Math. Comput. Chem.* **77** (2017) 299–320.