

Kinetic realization of delayed polynomial dynamical models

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Abstract: In this paper, we study the kinetic realization problem of nonnegative delayed polynomial systems. Given a set of delayed polynomial differential equations, the task is to assign a chemical reaction network structure that realizes its dynamics. We show that similarly to the non-delayed case, this problem is generally non-uniquely solvable. We extend existing results for the realization of non-delayed models by proposing an algorithm to build delayed realizations and proving that the so-called dense realization defines a superstructure in the delayed case, too. The notions and results are shown on a simple illustrative example.

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1. INTRODUCTION

A very general part of nonnegative dynamical systems is the class of kinetic systems (Érdi and Tóth, 1989; Chellaboina et al., 2009). This system class is capable of describing all important complex dynamical phenomena that are needed for the description of key processes not only in molecular (chemical, biochemical) but also in certain compartmental, process, economic or transportation systems. A particular advantage of kinetic systems is their associated directed graph structure which can be efficiently used to analyze and prove key qualitative dynamical properties such as the existence, structure or stability of equilibria, boundedness of solutions etc. often without the exact knowledge of the model parameters (Feinberg, 1987; Angeli, 2009). Moreover, kinetic differential equations have a mathematically simple enough structure that allows the solution of identification, realization or even control problems (Chis et al., 2011; Craciun and Pantea, 2008; Szederkényi et al., 2011; Lipták et al., 2016).

Delayed systems are ubiquitous in nature and technology, and it is often required to explicitly include time delay into dynamical models to describe the studied processes in a satisfactory way (Erneux, 2009; Haddad et al., 2010). The original motivation of the application of delayed models in chemistry was to avoid the detailed modeling of intermediates and thus to concentrate on the description of key species (Roussel, 1996). An important relevant result in systems biology is Swameye et al. (2003), where nuclear export was described using time delays in a mass-action type signaling pathway model. Moreover, higher level models that are often formally kinetic such as compartmental or process models, may contain inherent (e.g., transport or communication) delays which can be modeled as delayed reactions. A recent result is the generalization of the well-

known logarithmic Lyapunov function and the corresponding stability results for delayed complex balanced reaction networks (Lipták et al., 2018).

The problem of kinetic realization, namely, how to algorithmically construct a reaction network with a prescribed nonnegative dynamics given in the form of polynomial ordinary differential equations was first addressed and solved in (Hárs and Tóth, 1981). It was immediately visible from the solution that the reaction graph of a given set of kinetic ODEs is generally non-unique. This non-uniqueness was used in an optimization framework to compute preferred or even all possible reaction graphs realizing a polynomial dynamics (see, e.g. (Ács et al., 2016) and the related articles).

The purpose of this paper is to propose a solution for the kinetic realization problem of nonnegative polynomial delayed differential equations (DDEs) by using and extending the above mentioned results.

2. BASIC NOTIONS

In this section, we summarize the notations and definitions used throughout the paper. We denote the sets of real numbers and nonnegative integers by $\mathbb{R}$ and $\mathbb{N}_0$, respectively. The positive and nonnegative orthants in the n -dimensional Euclidean space $\mathbb{R}^n$ are denoted by $\mathbb{R}_{>0}^n$ and $\mathbb{R}_{\geq 0}^n$, respectively. For $\tau \geq 0$, let $\mathcal{C} = C([-\tau, 0], \mathbb{R}^n)$ denote the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^n$. Moreover, let $\mathcal{C}_{>0} = C([-\tau, 0], \mathbb{R}_{>0}^n)$ and $\mathcal{C}_{\geq 0} = C([-\tau, 0], \mathbb{R}_{\geq 0}^n)$ denote the set of positive and nonnegative functions in $\mathcal{C}$. For $x, y \in \mathbb{R}_{>0}^n$, $x^y = \prod_{i=1}^n x_i^{y_i}$. For any matrix $P \in \mathbb{R}^{n \times m}$, P_{ij} or $[P]_{ij}$ denotes the entry in row i and column j . Further, $P_{i,\cdot}$ is the i th row, and $P_{\cdot,j}$ is the j th column of P . For $x \in \mathbb{R}_{>0}^n$ and

$Y \in \mathbb{R}_{\geq 0}^{n \times m}$, $x^Y = [f_1(x) \dots f_m(x)]^T$, where $f_i(x) = x^{Y_{\cdot i}}$ for $i = 1, \dots, m$.

2.1 Nonlinear polynomial models with time delay

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

$$\dot{x}(t) = M_0 \psi'(x(t)) + \sum_{i=1}^p M_i \psi'(x(t - \bar{\tau}_i)) \quad (1)$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $M_i \in \mathbb{R}^{n \times m'}$ for $i = 0, \dots, p$ are coefficient matrices with real entries, $\psi'(x) = x^{Y'}$ with $Y' \in \mathbb{N}_0^{n \times m'}$, and $\bar{\tau}_i > 0$ for $i = 1, \dots, p$ are constant time delays. The initial function for the model (1) is $\theta \in \mathcal{C}$, i.e. $x(t) = \theta(t)$ for $-\bar{\tau} \leq t \leq 0$, where $\bar{\tau} = \max_{1 \leq i \leq p} \bar{\tau}_i$ is the maximal delay.

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 (Roussel, 1996). Therefore, we can define *delayed chemical reaction networks* with three sets, analogously to the classical non-delayed case as follows:

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

$$C_j = \sum_{i=1}^n \alpha_{ij} X_i \quad j \in \{1, \dots, m\}$$

$$\alpha_{ij} \in \mathbb{N}_0, \quad i \in \{1, \dots, n\}, \quad j \in \{1, \dots, m\}$$

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 $[\alpha_{1j} \dots \alpha_{nj}]^T \in \mathbb{R}^n$. 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*: $\mathcal{R} = \{\mathcal{R}_1, \mathcal{R}_2, \dots, \mathcal{R}_r\}$ of the form

$$\mathcal{R}_j: C_l \xrightarrow{\kappa_j, \tau_j} C_{l'}, \quad l, l' \in \{1, \dots, m\} \quad (2)$$

for $j = 1, \dots, r$, where C_l and $C_{l'}$ are the *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.

The stoichiometric coefficients are collected into the *complex composition matrix*: $Y_{ij} = \alpha_{ij}$ for $i = 1, \dots, n$, $j = 1, \dots, m$. That is, the j th 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 $j = 1, \dots, r$, 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. (2)).

We assign a weighted directed graph $D^\tau = (V_d, E_d^\tau) = (V_d, E_d^{\tau_0}, E_d^{\tau_1}, \dots, E_d^{\tau_p})$ where $\tau_0 = 0$, to a delayed reaction network as follows.

- (1) The vertices correspond to the complexes, i.e. $V_d = \{C_1, \dots, C_m\}$.

- (2) The directed edges represent reactions, i.e. $(C_j, C_l) \in E_d^{\tau_i}$, if C_j is transformed into C_l in the network with time delay τ_i .
- (3) The reaction rate coefficients κ_j are assigned as positive weights to the edges.

The general dynamic equations of delayed kinetic systems are the following (see, Lipták et al. (2018))

$$\dot{x}(t) = \sum_{k=1}^r \kappa_k [(x(t - \tau_k))^{y_k} y'_k - (x(t))^{y_k} y_k], \quad (3)$$

where κ_k is the reaction rate coefficient of $\mathcal{R}_k$, and $y_k, y'_k \in \mathbb{N}_0^n$ are the stoichiometric coefficient vectors of the source and product complexes in $\mathcal{R}_k$, respectively. Moreover, $\tau_k \geq 0$ and the initial function is $\theta \in \mathcal{C}_{\geq 0}$. In the special case when all $\tau_k = 0$, Eq. (3) gives the classical model of mass action kinetic systems known from the literature (Horn and Jackson, 1972; Érdi and Tóth, 1989).

It is important to remark that in contrast to non-delayed chemical reaction networks (CRNs), we allow delayed loop edges in delayed CRNs since a non-zero term in the differential equations can be assigned to them. To see this, consider the simplest delayed loop reaction $X \xrightarrow{\kappa, \tau} X$. According to Eq. (3), the DDE corresponding to this reaction is $\dot{x} = -kx + kx(t - \tau)$. Furthermore, multiple identically directed edges can be present between the same pair of vertices if the corresponding reactions have different time delays.

We now show that similarly to the non-delayed case, the model (3) 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 notations. Let $\bar{\kappa}_{jk}^{\bar{\tau}_i}$ be the reaction rate of the reaction $C_k \xrightarrow{\bar{\tau}_i} C_j$, and $\bar{\tau}_0 = 0$. If there is no reaction with source complex C_k , product complex C_j and delay $\bar{\tau}_i$ then $\bar{\kappa}_{jk}^{\bar{\tau}_i} = 0$. (The reason for notation change is that the rate coefficients and delays are indexed differently from (3). Moreover, zero rate coefficients are also used for denoting non-existent reactions.)

We can rewrite (3) as follows

$$\dot{x}(t) = \sum_{i=0}^p \sum_{j=1}^m \sum_{k=1}^m \bar{\kappa}_{jk}^{\bar{\tau}_i} [(x(t - \bar{\tau}_i))^{y_j} y_j - (x(t))^{y_k} y_k] \quad (4)$$

Now we can rearrange (4) as

$$\begin{aligned} \dot{x}(t) = & \sum_{j=1}^m \sum_{k=1}^m \left[\bar{\kappa}_{jk}^{\bar{\tau}_0} (x(t))^{y_j} y_j - \sum_{i=0}^p \bar{\kappa}_{jk}^{\bar{\tau}_i} (x(t))^{y_k} y_k \right] \\ & + \sum_{i=1}^p \sum_{j=1}^m \sum_{k=1}^m \bar{\kappa}_{jk}^{\bar{\tau}_i} (x(t - \bar{\tau}_i))^{y_j} y_j \end{aligned} \quad (5)$$

It is easy to see that the second term of (5) can be rewritten using matrix and vector multiplications as

$$\begin{aligned} \sum_{i=1}^p \sum_{j=1}^m \sum_{k=1}^m \bar{\kappa}_{jk}^{\bar{\tau}_i} (x(t - \bar{\tau}_i))^{y_j} y_j &= \sum_{i=1}^p Y K_i \psi(x(t - \bar{\tau}_i)) \\ &= \sum_{i=1}^p Y A_i \psi(x(t - \bar{\tau}_i)) \end{aligned} \quad (6)$$

where Y is the complex composition matrix, $\psi(x) = x^Y$, and the $K_i \in \mathbb{R}^{m \times m}$ rate constant matrices contain the

reaction rate constants so that $[K_i]_{jk} = \bar{\kappa}_{kj}^{\bar{\tau}_i}$. Similarly, the first term of (5) can also be rewritten using the rate constant matrices as

$$\sum_{j=1}^m \sum_{k=1}^m \left[\bar{\kappa}_{jk}^{\bar{\tau}_0} (x(t))^{y_k} y_j - \sum_{i=0}^p \bar{\kappa}_{jk}^{\bar{\tau}_i} (x(t))^{y_k} y_k \right] = \quad (7)$$

$$Y \left[K_0 - \sum_{i=0}^p \text{diag}(K_i^T \mathbf{1}) \right] \psi(x(t)) = Y A_0 \psi(x(t))$$

Therefore, the dynamics of a delayed CRN with reaction steps (2) can be described by a system of delay differential equations (DDEs) of the form

$$\dot{x}(t) = Y A_0 \psi(x(t)) + \sum_{i=1}^p Y A_i \psi(x(t - \bar{\tau}_i)) \quad (8)$$

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

From Eqs. (6) and (7) we can see that the exact structure of A_i is

$$[A_0]_{jk} = \begin{cases} -\sum_{l=1}^m \bar{\kappa}_{jl}^{\bar{\tau}_0} - \sum_{i=1}^p \sum_{l=1}^m \bar{\kappa}_{jl}^{\bar{\tau}_i} = -\sum_{i=0}^p \sum_{l=1}^m \bar{\kappa}_{jl}^{\bar{\tau}_i}, & j = k \\ \bar{\kappa}_{kj}^{\bar{\tau}_0}, & j \neq k \end{cases} \quad (9)$$

$$[A_i]_{jk} = \bar{\kappa}_{kj}^{\bar{\tau}_i} \quad i = 1, \dots, p. \quad (10)$$

Note that if $\bar{\tau}_i = 0$ for $i = 1, \dots, p$, then Eq. (8) reduces to the classical CRN representation

$$\dot{x} = Y \cdot A \cdot \psi(x) \quad (11)$$

with $A = \sum_{i=0}^p A_i$ being the negative transpose of the weighted Laplacian of the reaction graph (also called a Kirchhoff matrix), and $\psi(x) = x^Y$.

From now on, we denote a delayed polynomial system (1) by $(Y', M_0, \dots, M_p)$. Similarly, a delayed CRN (8) is denoted by $(Y, A_0, \dots, A_p)$, where A_0 is a Metzler matrix, and each A_i has nonnegative entries for $i = 1, \dots, p$.

We have an important structural connection between the reaction graph of delayed and non-delayed systems. Let us consider a delayed kinetic system $(Y, A_0, \dots, A_p)$ with reactions

$$\sum_{l=1}^n [Y]_{lk} X_l \xrightarrow{[A_i]_{kj}, \bar{\tau}_i} \sum_{l=1}^n [Y]_{lj} X_l. \quad (12)$$

Then the kinetic system $(Y, \sum_{i=0}^p A_i)$ has reactions

$$\sum_{l=1}^n [Y]_{lk} X_l \xrightarrow{\sum_{i=0}^p [A_i]_{kj}} \sum_{l=1}^n [Y]_{lj} X_l \quad (13)$$

i.e., by setting all delays to zero, we obtain a classical kinetic system (Y, A_k) with $A_k = \sum_{i=0}^p A_i$, where the multiple identically directed edges between the same pairs of vertices are merged and delayed loop edges are removed.

3. KINETIC REALIZATION OF DELAYED MODELS

In this section, we address the inverse problem, i.e. how to compute a delayed reaction graph from the model (1). We give a necessary and sufficient condition for realizability and then we extend the algorithm published in (Hárs and Tóth, 1981) to the delayed case.

3.1 Realizability in the non-delayed case

Consider the polynomial system (1) with $p = 0$. According to (Hárs and Tóth, 1981), $\dot{x} = M_0 \psi'(x)$ is *kinetically realizable* or briefly *kinetic* if and only if the model does not contain negative cross-effects, i.e.

$$\text{if } [M_0]_{ij} < 0 \text{ then } Y'_{ij} > 0 \text{ for } i = 1, \dots, n, j = 1, \dots, m \quad (14)$$

The proof in (Hárs and Tóth, 1981) is constructive and it contains a simple procedure to construct one possible reaction graph, the so-called canonical structure for any kinetic system. We will also use the term ‘canonical’ for the algorithmically computed reaction graph.

It is also known from the literature that the dynamics of a polynomial system $\dot{x} = f(x)$ where $f(x) = [f_1(x) \dots f_n(x)]^T$ is invariant to the nonnegative orthant if and only if

$$f_i(x)|_{x_i=0} \geq 0, \quad i = 1, \dots, n \quad (15)$$

It is easy to check that the kinetic property implies nonnegativity of the dynamics but not vice versa.

With some abuse of notation, we will also call a vector field $f(x) = M_0 x^{Y'}$ kinetic or nonnegative invariant, if it fulfills (14) or (15), respectively.

3.2 Basic observation for delayed realization

Example 1. As a simple illustration, let us consider the kinetic realization of the following system containing only a single delayed monomial:

$$\dot{x} = kx(t - \tau) \quad (16)$$

where $k, \tau > 0$. It can be checked that the following reactions realize (16)

$$R_1 : X \xrightarrow{\gamma, \tau} nX, \quad R_2 : X \xrightarrow{\gamma} 2X \quad (17)$$

where $\gamma > 0$, $n \in \mathbb{Z}^+$, $\gamma \cdot n = k$, since the delayed kinetic model (3) for the reactions R_1 and R_2 can be written as

$$\dot{x}(t) = \underbrace{\gamma n x(t - \tau)}_{R_1} + \underbrace{\gamma x(t)}_{R_2} \quad (18)$$

It is visible from the above example that generally, the realization of delayed monomials necessitates the addition of extra non-delayed monomials with positive coefficients which can be realized as normal (non-delayed) reactions using the results of e.g. (Hárs and Tóth, 1981). Delayed monomials with positive coefficients containing several state variables in higher dimensional DDEs can always be realized in a similar way. This will be a basic principle of our realization method.

3.3 Dynamical equivalence to a delayed nonnegative model

A DDE given in the form (1) is called *kinetic* if it can be rewritten to the form (3) or, equivalently, to (8).

A delayed kinetic system $(Y, A_0, \dots, A_p)$ is called *dynamically equivalent to a DDE* $(Y', M_0, \dots, M_p)$ if

$$M_0 \psi'(x(t)) + \sum_{i=1}^p M_i \psi'(x(t - \bar{\tau}_i)) \quad (19)$$

$$= Y A_0 \psi(x(t)) + \sum_{i=1}^p Y A_i \psi(x(t - \bar{\tau}_i)) \quad (20)$$

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

3.4 Conditions for realizability

Clearly, delayed kinetic models should have the property that for any nonnegative initial function, the state variables remain in the nonnegative orthant. The necessary and sufficient condition of nonnegative invariance for a delayed DDE (1) is that $M_0\psi'$ is nonnegative invariant, and all the entries of M_i for $i = 1, \dots, p$ are nonnegative (Haddad et al., 2010). The kinetic realizability of the system (1) can be checked as follows.

Proposition 1. A delayed system $(Y', M_0, \dots, M_p)$ is kinetic if and only if $M_0\psi'(x(t))$ is kinetic and M_i has only nonnegative elements for $i = 1, \dots, p$.

Proof 1. (draft). Assume that $(Y', M_0, \dots, M_p)$ is kinetic. Then it can be written into the form (3), where the delayed monomials have positive coefficients and the coefficient matrix of the non-delayed monomials is kinetic.

Assume that $M_0\psi'(x(t))$ is kinetic and M_i has nonnegative elements. Delayed monomials with positive coefficients can be realized by delayed reactions, and the added positive non-delayed monomials can be realized by non-delayed reactions (see, Example 1).

3.5 Algorithm for determining the canonical realization

For convenience, we divided the realization algorithm into two parts: **Algorithm 1** contains complex generation, and **Algorithm 2** describes the method for the construction of the delayed reaction graph using the generated complex set. Due to formatting reasons, we present the complete pseudocodes of the algorithms in the Appendix.

The inputs of the whole procedure are the matrices $(Y', M_0, \dots, M_p)$ of the DDE (1), while the outputs are $(Y, A_0, \dots, A_p)$ of the kinetic model (8).

3.6 The dense realization is a superstructure

It is straightforward to extend the results of (Johnston et al., 2012) for delayed CRNs as follows. Let us consider a delayed system $(Y', M_0, \dots, M_p)$ and a dynamically equivalent realization $(Y, A_0, \dots, A_p)$. It is said that $(Y, A_0, \dots, A_p)$ is

- (1) a *sparse realization*, if it contains the minimum number of reactions (i.e. the minimum number of nonzero elements in A_i for $i = 0, \dots, p$),
- (2) a *dense realization*, if it contains the maximum number of reactions.

For more details on the above special realizations, see also (Ács et al., 2016).

We say that a dynamically equivalent realization $(Y, A_0, \dots, A_p)$ of $(Y', M_0, \dots, M_p)$ has superstructure property if its reaction graph contains the reaction graphs of all other dynamically equivalent realizations using the same complex set Y of the delayed kinetic system as subgraphs.

Using the above we can now state the following result.

Proposition 2. Let us consider a delayed kinetic system $(Y', M_0, \dots, M_p)$. Then its dense dynamically equivalent realization $(Y, A_0^d, \dots, A_p^d)$ has superstructure property.

Proof 2. Let us assume that there is a reaction that does not appear in the dense realization $(Y, A_0^d, \dots, A_p^d)$

but appears in another dynamically equivalent realization $(Y, A_0, \dots, A_p)$ (i.e., there exist indices i, j, k , $j \neq k$ such that $[A_i]_{jk} > 0$ but $[A_i^d]_{jk} = 0$). Let us define the convex combination of the matrices

$$\bar{A}_i = \lambda A_i^d + (1 - \lambda) A_i, \quad 0 < \lambda < 1, \quad i = 0, \dots, p \quad (21)$$

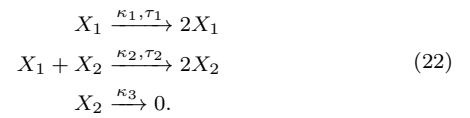
Then, it can be seen from (8) that $(Y, \bar{A}_0, \dots, \bar{A}_p)$ is also a dynamically equivalent realization of $(Y', M_0, \dots, M_p)$ but contains more reactions than $(Y, A_0^d, \dots, A_p^d)$ which is a contradiction.

The following result directly follows from Proposition 2.

Corollary 1. Let us consider a delayed kinetic system $(Y', M_0, \dots, M_p)$ and a dense realization $(Y, A_0^d, \dots, A_p^d)$. Then the structure of the unweighted directed reaction graph of the dense realization is unique.

4. EXAMPLE

Let us study the following delayed Lotka-Volterra model



The DDE of the form (3) corresponding to the above system is

$$\dot{x}(t) = \begin{bmatrix} -\kappa_1 x_1(t) - \kappa_2 x_1(t)x_2(t) + 2\kappa_1 x_1(t - \tau_1) \\ -\kappa_2 x_1(t)x_2(t) - \kappa_3 x_2(t) + 2\kappa_2 x_1(t - \tau_2)x_2(t - \tau_2) \end{bmatrix}. \quad (23)$$

The matrices of the representation (1) for the model are

$$\begin{aligned} Y' &= \begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \end{bmatrix}, \quad M_0 = \begin{bmatrix} -\kappa_1 & -\kappa_2 & 0 \\ 0 & -\kappa_2 & -\kappa_3 \end{bmatrix}, \\ M_1 &= \begin{bmatrix} 2\kappa_1 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad M_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 2\kappa_2 & 0 \end{bmatrix}, \end{aligned} \quad (24)$$

The complex composition matrix is given by

$$Y = \begin{bmatrix} 1 & 2 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 2 & 1 & 0 \end{bmatrix} \quad (25)$$

The nonzero elements of the A_i matrices defined in (8) are

$$\begin{aligned} [A_0]_{11} &= -\kappa_1, [A_0]_{33} = -\kappa_2, [A_0]_{55} = -\kappa_3, [A_0]_{65} = \kappa_3 \\ [A_1]_{21} &= \kappa_1, [A_2]_{43} = \kappa_2, \end{aligned} \quad (26)$$

One can check that the DDE

$$\dot{x} = Y A_0 \psi(x) + Y A_1 \psi(x(t - \tau_1)) + Y A_2 \psi(x(t - \tau_2)) \quad (27)$$

with $\psi(x) = x^Y$ is indeed the same as (23). Note that Y and Y' are not identical, since the monomials of pure product complexes do not appear in the kinetic DDEs. These monomials are naturally cancelled in (27), but this description contains all information about the reaction graph.

Using **Algorithm 1** and **Algorithm 2**, we can compute the canonical realization of (Y', M_0, M_1, M_2) which is depicted in Fig. 1. Note that the complex sets in the original model (22) and in the canonical realization are different. Let us take the union of these complex sets and compute the dense realization of the system model using the parameter values $\kappa_1 = 0.1$, $\kappa = 0.02$, and $\kappa_3 = 0.15$ (see, Fig. 2.) It is visible that both the reaction graph of the original model and that of the canonical realization are the subgraphs of the dense structure.

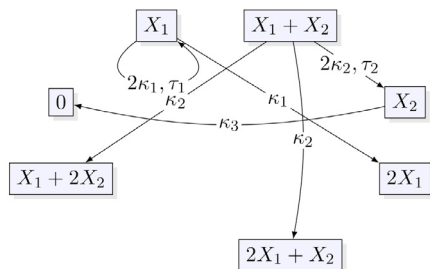
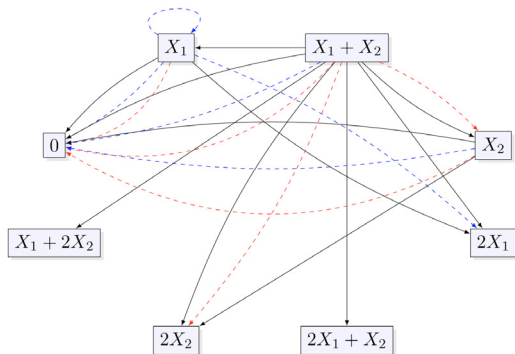
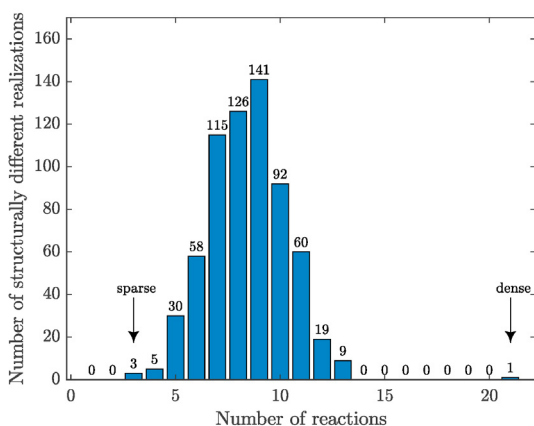


Fig. 1. Reaction graph of the canonical realization

Fig. 2. Reaction graph of the dense realization of (Y', M_0, M_1, M_2) . Solid black arrows show non-delayed reactions, blue and red dashed arrows denote reactions delayed with τ_1 and τ_2 , respectively

Finally, it is possible to adapt the method to enumerate all possible reaction graph structures in (Ács et al., 2016) for delayed CRNs using the superstructure property of the dense realization. The distribution of all distinct structures w.r.t. the number of reactions is shown in Fig. 3.

Fig. 3. The distribution of different reaction graph structures corresponding to (Y', M_0, M_1, M_2) .

5. CONCLUSION

The inverse problem of computing reaction graphs from delayed kinetic polynomial differential equations was addressed in this paper. The necessary and sufficient condition of kinetic realizability was given, and dynamical

equivalence to a delayed kinetic system was defined. An algorithm was presented to compute the so-called canonical reaction graph from delayed differential equations, and some previously published results and computational methods were extended to the delayed case. The proposed representation and approach can be used in the distinguishability analysis of kinetic DDEs. Although currently there are not too many results on the relationship between the reaction graph and the dynamics for delayed CRNs, it is expected that some of the classical results can be extended in the near future such as (Lipták et al., 2018). Then the computational framework proposed can be useful to find reaction graphs with required properties.

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APPENDIX

Algorithm 1 Compute the necessary complex set Y for the canonical realization of the delayed kinetic system $(Y', M_0, \dots, M_p)$.

```

1: procedure  $(Y, \bar{M}_0, \dots, \bar{M}_p) = \text{GENCOMP}(Y', M_0, \dots, M_p)$ 
2:    $n := \text{size}(Y', 1)$ ;  $m := \text{size}(Y', 2)$ 
3:    $(\bar{M}_0, \dots, \bar{M}_p) := (M_0, \dots, M_p)$ 
4:    $Y := Y'$ 
5:   for  $j := 1, \dots, n$  do
6:     for  $k := 1, \dots, m$  do
7:       if  $\left[\sum_{i=1}^p \bar{M}_i\right]_{jk} > 0$  then
8:         if  $\text{FindComplex}(Y, e_j) > \text{size}(Y, 2)$  then
9:            $Y := [Y \ e_j]$ 
10:        end if
11:        for  $l := 1, \dots, n$  do
12:          if  $[Y']_{lk} > 0$  then
13:             $[\bar{M}_0]_{lk} := [\bar{M}_0]_{lk} + [Y']_{lk} \left[\sum_{i=1}^p \bar{M}_i\right]_{jk}$ 
14:          end if
15:        end for
16:      end if
17:    end for
18:  end for
19:  for  $j := 1, \dots, n$  do
20:    for  $k := 1, \dots, m$  do
21:      if  $[\bar{M}_0]_{jk} \neq 0$  then
22:        if  $\text{FindComplex}(Y, [Y']_{..k} + \text{sign}[\bar{M}_0]_{jk} e_j) >$ 
23:           $\text{size}(Y, 2)$  then
24:             $Y := [Y \ [Y']_{..k} + \text{sign}[\bar{M}_0]_{jk} e_j]$ 
25:          end if
26:        end if
27:      end for
28:    for  $i := 0, \dots, p$  do
29:       $\bar{M}_i := \text{AppendZeroCols}(\bar{M}_i, \text{size}(Y, 2) - \text{size}(\bar{M}_i, 2))$ 
30:    end for
31:  end procedure

```

Algorithm 2 Construct a delayed CRN from a given delayed kinetic system $(Y', M_0, \dots, M_p)$. The algorithm returns the $(Y, A_0, \dots, A_p)$ dynamically equivalent realization.

```

1: procedure  $(Y, A_0, \dots, A_p) = \text{DDE2CRN}(Y', M_0, \dots, M_p)$ 
2:   if  $M_0 \psi'(x(t))$  is not kinetic or any  $M_i$  has nonnegative
   values then
3:     There is no dynamically equivalent realization of the
   delayed kinetic system  $(Y', M_0, \dots, M_p)$ .
4:   end if
5:    $(Y, \bar{M}_0, \dots, \bar{M}_p) := \text{GenComp}(Y', M_0, \dots, M_p)$ 
6:    $n := \text{size}(Y, 1)$ ;  $m := \text{size}(Y, 2)$ 
7:   for  $j := 1, \dots, n$  do
8:     for  $k := 1, \dots, m$  do
9:       for  $i := 1, \dots, p$  do
10:        if  $[\bar{M}_i]_{jk} > 0$  then
11:           $q := \text{FindComplex}(Y, [Y]_{..k})$ 
12:           $r := \text{FindComplex}(Y, e_j)$ 
13:           $[A_i]_{rq} := [A_i]_{rq} + [\bar{M}_i]_{jk}$ 
14:           $[A_0]_{qq} := [A_0]_{qq} - [\bar{M}_i]_{jk}$ 
15:        end if
16:      end for
17:    end for
18:  end for
19:  for  $j := 1, \dots, n$  do
20:    for  $k := 1, \dots, m$  do
21:      if  $[\bar{M}_0]_{jk} \neq 0$  then
22:         $q := \text{FindComplex}(Y, [Y]_{..k})$ 
23:         $r := \text{FindComplex}(Y, [Y]_{..k} + \text{sign}[\bar{M}_0]_{jk} e_j)$ 
24:         $[A_0]_{rq} := [A_0]_{rq} + |[\bar{M}_0]_{jk}|$ 
25:         $[A_0]_{qq} := [A_0]_{qq} - |[\bar{M}_0]_{jk}|$ 
26:      end if
27:    end for
28:  end for
29: end procedure

```

The explanation of the notations and subroutines applied in the algorithms is the following. e_j is the j th standard basis vector in $\mathbb{R}^n$. $\text{size}(A, 1)$ and $\text{size}(A, 2)$ return the number of rows and columns and of any matrix A , respectively. $[A \ B]$ denotes the concatenation of two matrices containing the same number of rows. $\text{FindComplex}(Y, y)$ returns the index q if $[Y]_{..q} = y$ and returns $\text{size}(Y, 2) + 1$ if no such column was found in Y . $\text{AppendZeroCols}(A, n)$ appends (concatenates) n zero columns to the right of matrix A and returns the resulting matrix.