Kinetic realization of delayed polynomial dynamical models

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Background, motivation and goals

Background

- a wide class of (nonnegative) dynamical systems can be modeled in the kinetic (CRN) framework
- in many applications, the incorporation of time delay is essential to describe the observed phenomena
- some earlier results on delayed CRNs: (Roussel, 1996), (Mincheva and Roussel, 2007)
- there are important relations between reaction graph structure and qualitative dynamics (not so many results on delayed networks)

Goals

- to study a class of delayed kinetic systems (reactions are delayed)
- to generalize the well-known inverse (realization) problem for delayed models:
  delayed kinetic differential equations $\Longrightarrow$ reaction graph(s)

CRNs without delays (review)

Differential equations:

$$\dot{x}(t) = \sum_{k=1}^{r} \kappa_k \left(x(t)\right)^{y_k} \left[y_k' - y_k\right], \qquad t \geq 0, \tag{1}$$

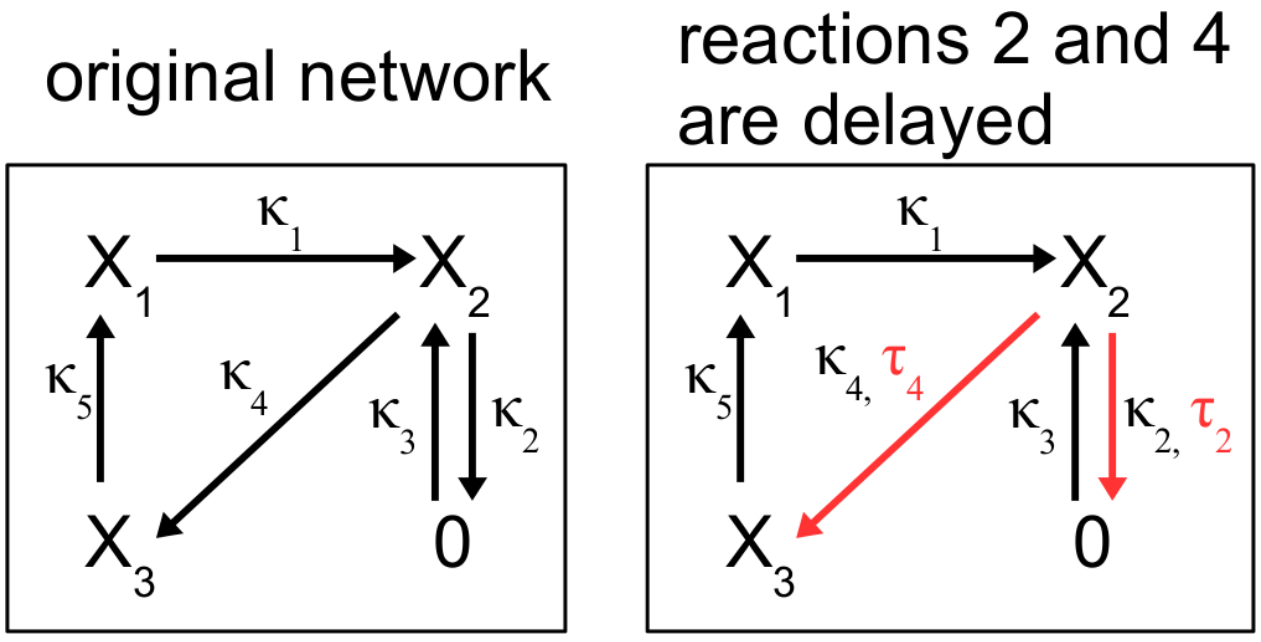
where

- $x(t) \in \overline{\mathbb{R}}_+^N$ is the state (concentration) vector
- $\mathcal{K} \subset \overline{\mathbb{Z}}_+^N$ is the set of complex vectors (containing stoichiometric coefficients)
- $r = |\mathcal{R}|$: number of reactions.
- source and product complex vectors in the kth reaction: $y_k, y_k' \in \mathcal{K}$, the rate coeff. is $\kappa_k > 0$
- $x^y = \prod_{i=1}^N x_i^{y_i}$
- initial condition: $x(0)$

Delayed chemical reaction networks: idea

Basic idea (not new): assign different nonnegative delays to the reactions

Simple compartmental (linear) example (e.g. a mass convection network):



Delayed chemical reaction networks: set description

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

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

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

  stoichiometric coefficients: α_{ij}

  stoichiometric coefficient vector of complex C_j:

  $[\alpha_{1j} \; \ldots \; \alpha_{nj}]^T \in \mathbb{R}^n$.

  zero complex: all stoichiometric coefficients are zero.
- A set of *reactions*: $\mathcal{R} = \{\mathcal{R}_1, \mathcal{R}_2, \ldots, \mathcal{R}_r\}$ of the form

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

for $j = 1, \ldots, r$, 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**

Delayed chemical reaction networks cont'd

- **complex composition matrix**: $Y_{ij} = \alpha_{ij}$ for $i = 1, \ldots, n$, $j = 1 \ldots, m$
- mass action type **reaction rates** are assumed: $\rho_j(x) = \kappa_j x^{Y_{\cdot,l}}$ for $j = 1, \ldots, r$, where $x_i = [X_i]$
- weighted **directed graph** of a delayed CRN: $D^\tau = \left(V_d, E_d^\tau\right) = \left(V_d, E_d^{\tau_0}, E_d^{\tau_1}, \ldots, E_d^{\tau_p}\right)$ where $\tau_0 = 0$
  1. The vertices correspond to the complexes, i.e. $V_d = \{C_1, \ldots, C_m\}$.
  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.
- delayed loop edges are allowed (non-zero term in the DDEs)
- multiple edges with the same direction are allowed with different delays

Delayed chemical reaction networks: differential equations

General form of delayed kinetic models:

$$\dot{x}(t) = \sum_{k=1}^{r} \kappa_k \left[(x(t-\tau_k))^{y_k} \, y_k' - (x(t))^{y_k} \, y_k \right], \qquad t \geq 0, \qquad (3)$$

- $x(t) \in \overline{\mathbb{R}}_+^N$ is the state (concentration) vector
- $\mathcal{K} \subset \overline{\mathbb{Z}}_+^N$ is the set of complex vectors
- r: number of reactions.
- source and product complex vectors in the kth reaction: $y_k, y_k' \in \mathcal{K}$, rate coeff.: $\kappa_k > 0$, time delay: $\tau_k \geq 0$
- $x^y = \prod_{i=1}^N x_i^{y_i}$
- The initial condition (function) is $x(t) = \theta(t)$ for $-\tau \leq t \leq 0$, where $\tau = \max_{1 \leq k \leq R} \tau_k$ is the maximum delay and $\theta \in \overline{\mathcal{C}}_+$ is a nonnegative continuous initial function
- The segment of the solution $x_t \in \mathcal{C}$ is defined as $x_t(s) = x(t+s)$ for $-\tau \leq s \leq 0$

For any initial function $\theta \in \overline{\mathcal{C}}_+$, the solution x^θ of (3) is nonnegative

'Laplacian'-like description

- notation change : $\bar{\kappa}_{jk}^{\bar{\tau}_i}$: reaction rate of the reaction $C_k \xrightarrow{\bar{\tau}_i} C_j$, and $\bar{\tau}_0 = 0$
  no reaction with source complex C_k, product complex C_j and delay $\bar{\tau}_i \Longrightarrow \bar{\kappa}_{jk}^{\bar{\tau}_i} = 0$
- we can rewrite Eq. (3) as follows

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

- from this, it is easy to show that Eq. (3) can be written as

$$\dot{x}(t) = YA_0\psi\big(x(t)\big) + \sum_{i=1}^{p} YA_i\psi\big(x(t - \bar{\tau}_i)\big) \qquad (5)$$

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

'Laplacian'-like description

- it can be shown that the exact structure of A_i is

$$[A_0]_{jk} = \begin{cases} -\sum_{l=1}^{m} \bar{\kappa}_{jl}^{\bar{\tau}_0} - \sum_{i=1}^{p} \sum_{l=1}^{m} \bar{\kappa}_{jl}^{\bar{\tau}_i} = -\sum_{i=0}^{p} \sum_{l=1}^{m} \bar{\kappa}_{jl}^{\bar{\tau}_i}, & j = k \\ \bar{\kappa}_{kj}^{\bar{\tau}_0}, & j \neq k \end{cases} \tag{6}$$

$$[A_i]_{jk} = \bar{\kappa}_{kj}^{\bar{\tau}_i} \qquad i = 1, \ldots, p. \tag{7}$$

- note that if $\bar{\tau}_i = 0$ for $i = 1, \ldots, p$, then Eq. (5) reduces to the classical CRN representation

$$\dot{x} = Y \cdot A \cdot \psi(x) \tag{8}$$

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 $\psi(x) = x^Y$.

Delayed polynomial models

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

$$\dot{x}(t) = M_0 \psi'\big(x(t)\big) + \sum_{i=1}^{p} M_i \psi'\big(x(t-\bar{\tau}_i)\big) \tag{9}$$

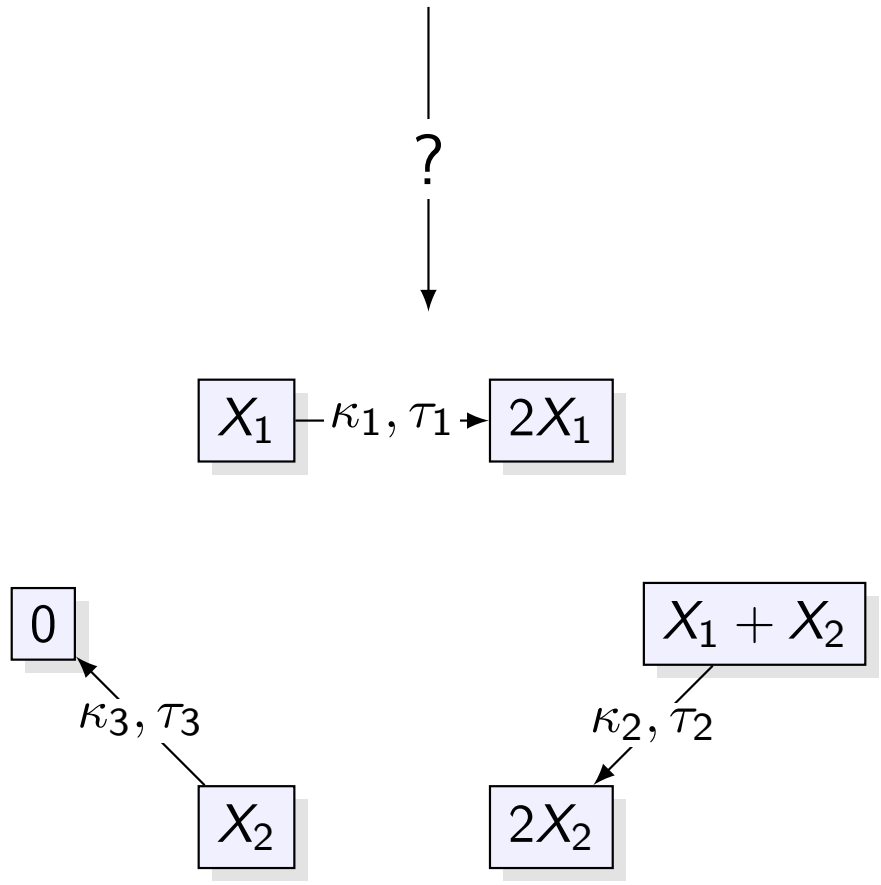
where $x(t) \in \mathbb{R}^n$ is the state vector, $M_i \in \mathbb{R}^{n \times m'}$ for $i = 0, \ldots, p$ are coefficient matrices with real entries, $\psi'(x) = x^{Y'}$ with $Y' \in \mathbb{N}_0^{n \times m'}$, and $\bar{\tau}_i > 0$ for $i = 1, \ldots, p$ are constant time delays.

The initial function for the model (9) 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.

Main problem statement

Q: How to obtain a reaction graph from a delayed differential equation (DDE)?

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



Realizability in the non-delayed case (revision)

- 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.

$$\text{if } [M_0]_{ij} < 0 \text{ then } Y'_{ij} > 0 \text{ for } i = 1, \ldots, n,\ j = 1, \ldots, m \qquad (10)$$

  constructive proof: algorithm to construct the so-called canonical structure

- also known: the polynomial dynamics $\dot{x} = f(x)$ where $f(x) = [f_1(x)\ \ldots\ f_n(x)]^T$ is invariant to the nonnegative orthant if and only if

$$f_i(x)|_{x_i=0} \geq 0, \quad i = 1, \ldots, n \qquad (11)$$

- we will also call a vector field $f(x) = M_0 x^{Y'}$ **kinetic** or **nonnegative invariant**, if it fulfills (10) or (11), respectively

The basic observation for delayed realization

- consider a model with a single delayed monomial:

$$\dot{x}(t) = kx(t-\tau) \tag{12}$$

this can be realized with the reactions

$$R_1: \; X \xrightarrow{\gamma,\tau} nX \tag{13}$$

$$R_2: \; X \xrightarrow{\gamma} 2X \tag{14}$$

where $\gamma > 0$, $n \in \mathbb{Z}^+$, $\gamma \cdot n = k$, since (12) can be written as

$$\dot{x}(t) = \underbrace{\gamma n x(t-\tau) - \gamma x(t)}_{R_1} \underbrace{+\gamma x(t)}_{R_2} \tag{15}$$

- generally, the realization of delayed monomials requires the addition of extra non-delayed monomials with positive coefficients which can be realized as normal (non-delayed) reactions
- the same principle can be generalized to delayed multivariable monomials

Dynamically equivalent delayed CRN

- a DDE given in the form (9) is called **kinetic** if it can be rewritten to the form (3) or, equivalently, to (5)
- a delayed kinetic system $(Y, A_0, \ldots, A_p)$ is called **dynamically equivalent to a DDE** $(Y', M_0, \ldots, M_p)$ if

$$M_0\psi'\big(x(t)\big) + \sum_{i=1}^{p} M_i\psi'\big(x(t-\bar{\tau}_i)\big) \tag{16}$$

$$= YA_0\psi\big(x(t)\big) + \sum_{i=1}^{p} YA_i\psi\big(x(t-\bar{\tau}_i)\big) \tag{17}$$

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

Condition for realizability

Proposition

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

Proof.

$\Rightarrow$ Assume that $(Y', M_0, \ldots, M_p)$ 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.
$\Leftarrow$ Assume that $M_0\psi'\big(x(t)\big)$ 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. $\square$

The dense realization is a super-structure

- dynamically equivalent realizations are generally non-unique
- **dense realization**: contains the maximum number of reactions

Proposition

Let us consider a delayed kinetic system $(Y', M_0, \ldots, M_p)$*. Then it's dense dynamically equivalent realization* $(Y, A_0^d, \ldots, A_p^d)$ *has superstructure property.*

Proof.

Let us assume that there is a reaction that does not appear in the dense realization $(Y, A_0^d, \ldots, A_p^d)$ but appears in another dynamically equivalent realization $(Y, A_0, \ldots, A_p)$ (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

$$\bar{A}_i = \lambda A_i^d + (1-\lambda)A_i,\ 0 < \lambda < 1,\ i = 0, \ldots, p \tag{18}$$

Then, it can be seen from (5) that $(Y, \bar{A}_0, \ldots, \bar{A}_p)$ is also a dynamically equivalent realization of $(Y', M_0, \ldots, M_p)$ but contains more reactions than $(Y, A_0^d, \ldots, A_p^d)$ which is a contradiction. □

The following result directly follows from Proposition 2.

Corollary

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

Realization algorithm

- input: $(Y', M_0, \ldots, M_p)$
  output: $(Y, A_0, \ldots, A_p)$
- divided into two parts:
  Algorithm 1: complex generation
  Algorithm 2: construction of the delayed reaction graph
- time-complexity is polynomial (in the number of monomials of the DDE)
- the dense realization can also be computed in polynomial time
- our earlier results (Ács et. al., 2016) can be adapted to compute each distinct reaction graph realizing a kinetic delayed polynomial dynamics

Delayed Lotka-Volterra model

- Let us study the following delayed Lotka-Volterra model

$$\begin{aligned} X_1 &\xrightarrow{\kappa_1,\tau_1} 2X_1 \\ X_1 + X_2 &\xrightarrow{\kappa_2,\tau_2} 2X_2 \\ X_2 &\xrightarrow{\kappa_3} 0. \end{aligned} \tag{19}$$

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

$$\dot{x}(t) = \begin{bmatrix} -\kappa_1 x_1(t) - \kappa_2 x_1(t) x_2(t) + 2\kappa_1 x_1(t-\tau_1) \\ -\kappa_2 x_1(t) x_2(t) - \kappa_3 x_2(t) + 2\kappa_2 x_1(t-\tau_2) x_2(t-\tau_2) \end{bmatrix} \tag{20}$$

- The matrices of the representation (9) for the model are

$$\begin{aligned} Y' &= \begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \end{bmatrix}, \; M_0 = \begin{bmatrix} -\kappa_1 & -\kappa_2 & 0 \\ 0 & -\kappa_2 & -\kappa_3 \end{bmatrix}, \\ M_1 &= \begin{bmatrix} 2\kappa_1 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \; M_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 2\kappa_2 & 0 \end{bmatrix}, \end{aligned} \tag{21}$$

Delayed Lotka-Volterra model

- The complex composition matrix is given by

$$Y = \begin{bmatrix} 1 & 2 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 2 & 1 & 0 \end{bmatrix} \tag{22}$$

- The nonzero elements of the A_i matrices defined in (5) are

$$\begin{aligned} &[A_0]_{11} = -\kappa_1, [A_0]_{33} = -\kappa_2, [A_0]_{55} = -\kappa_3, [A_0]_{65} = \kappa_3 \\ &[A_1]_{21} = \kappa_1, [A_2]_{43} = \kappa_2, \end{aligned} \tag{23}$$

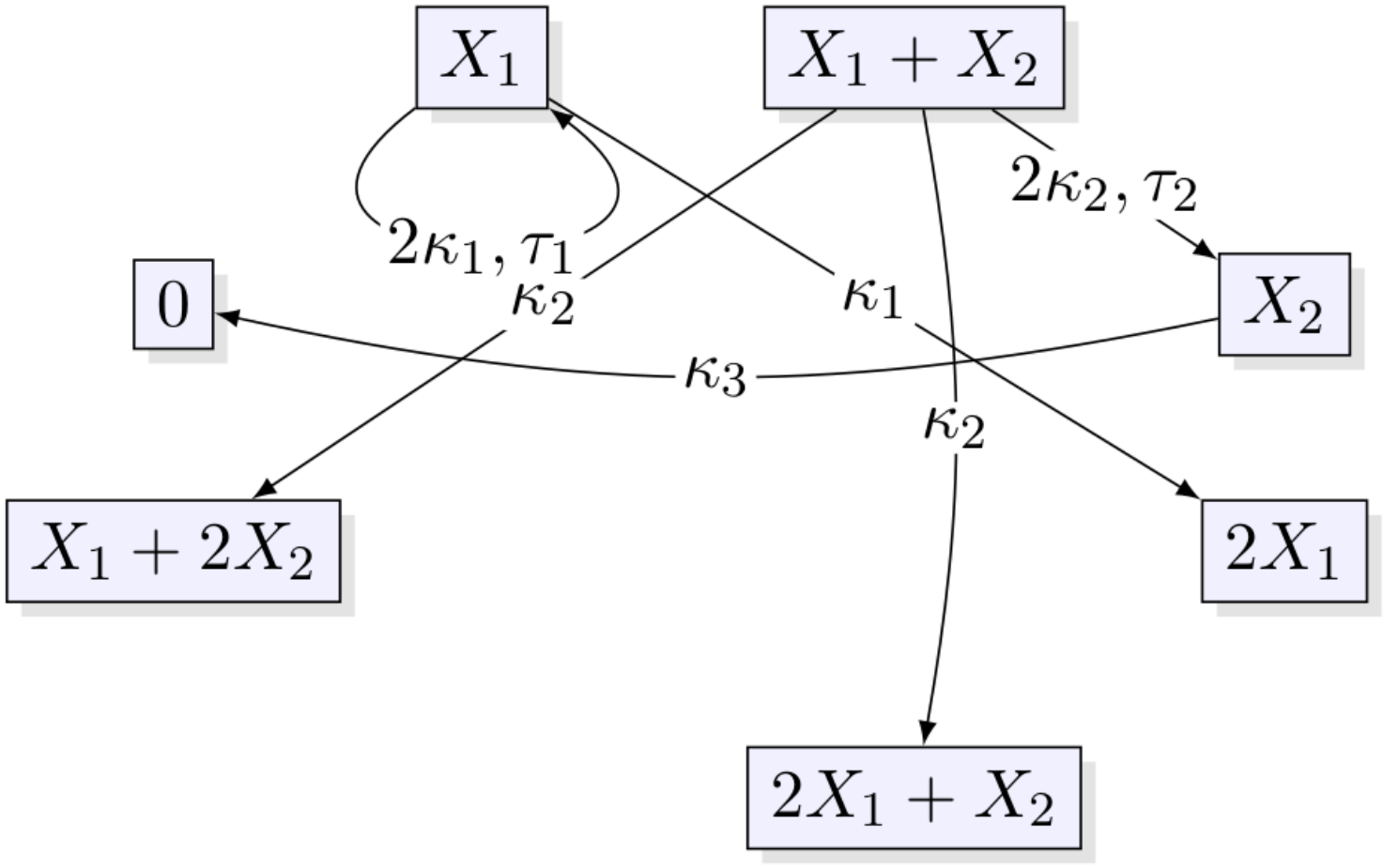
- One can check that the DDE

$$\dot{x} = YA_0\psi(x) + YA_1\psi(x(t-\tau_1)) + YA_2\psi(x(t-\tau_2)) \tag{24}$$

with $\psi(x) = x^Y$ is indeed the same as (20)

Delayed Lotka-Volterra model

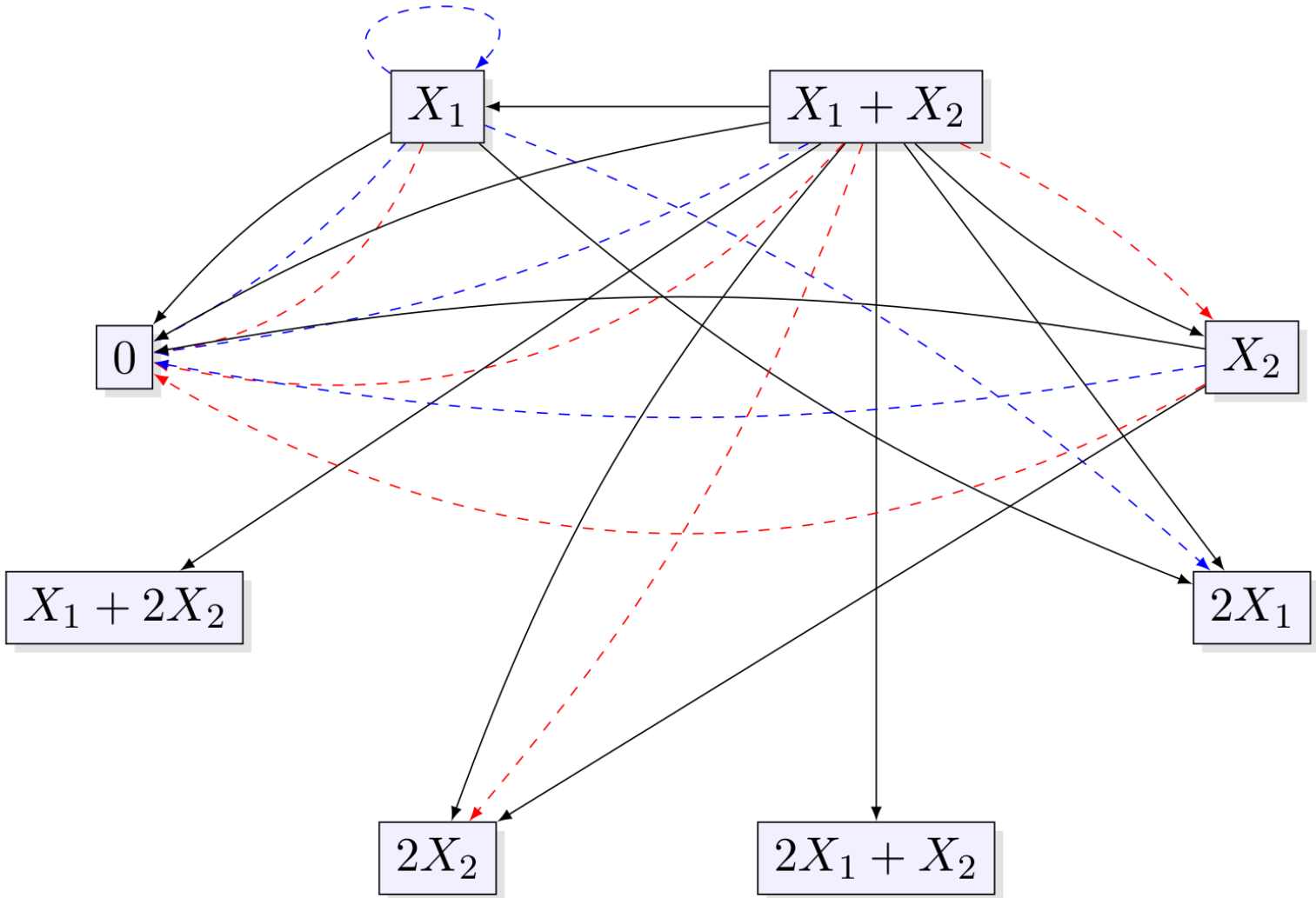
Delayed canonical realization (Algorithms 1, 2)



($2X_2$ is not present)

Delayed Lotka-Volterra model

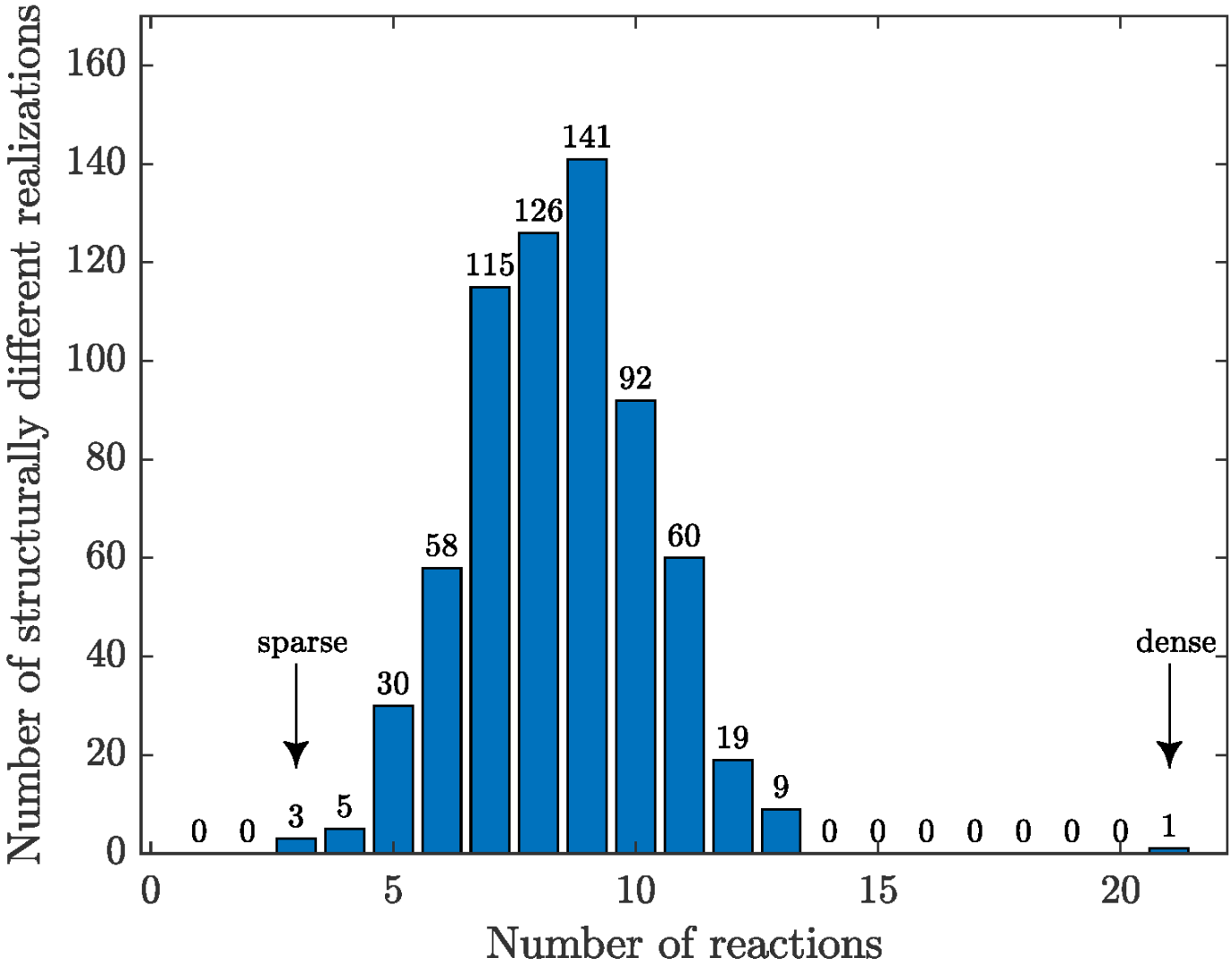
Delayed dense realization (including $2X_2$)



solid black: non-delayed; blue: τ_1; red: τ_2

Delayed Lotka-Volterra model

Enumeration of all possible reaction graphs



Summary

- CRN realization of delayed nonnegative polynomial models was studied
- necessary and sufficient condition: non-delayed part is kinetic, delayed part is nonnegative
- delayed loop-edges and multi-edges are allowed
- notion of dynamically equivalent realization was given (non-unique again!)
- 'Laplacian'-like form of the kinetic DDEs can be given $\Longrightarrow$ can be used in optimization to compute different reaction graphs
- dense reaction graph is unique and forms a super-structure
- several earlier methods (e.g. computing all reaction graphs) can be used for delayed models