

Approximation of delayed chemical reaction networks

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Abstract Chemical reaction networks with arbitrary constant delays assigned to the reactions are studied in this paper. The delayed models are approximated using the chain method known from the theory of differential equations. It is shown that important structural properties (such as reversibility and deficiency) of the approximated models are preserved in the approximating reaction networks. Moreover, the approximation gives rise to a Lyapunov-Krasovskii functional candidate for the original delayed systems that can be efficiently used for stability analysis.

Keywords Reaction kinetic systems · Mass action kinetics · Time delay systems

1 Introduction

Time delay may fundamentally influence the behaviour of dynamical systems, e.g. it can have both stabilizing or destabilizing effect [10]. Therefore, the

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explicit mathematical description of state, actuation or measurement delays might be necessary in many applications to obtain an acceptable mathematical model for a given goal such as simulation, prediction or control. Well-known examples are the drivers' delayed reactions in modeling traffic jams [23], delayed epidemic models [19], or the role of delays in machine tool vibrations [27].

The original physical picture behind deterministic reaction networks with mass action kinetics does not contain delays. However, the presence of delay might be a key element in the explanation of complex dynamical phenomena (e.g., certain types of oscillations) in biochemical models [9, 22]. Moreover, the introduction of delay can be useful for a simplified description of chemical systems to contain less concentration variables than detailed mass action mechanisms [25].

It is also important to mention that the class of kinetic systems having a reaction network structure is very general within nonlinear nonnegative models [29, 14]. This implies that many processes outside the chemical domain and possibly containing delayed terms, such as population models, compartmental systems, epidemic processes or certain traffic networks can be formally described as chemical reaction networks [2].

Therefore, several authors have elaborated on the analysis of delayed kinetic models. In [25] the notion of a 'chemically acceptable model' is introduced requiring causality and the nonnegativity of the solution. Moreover, conserved quantities in the form of constants of motions are also described for delayed models. In [21], general models are introduced through the extension of mass action reaction networks, where the appearance of products is delayed. Additionally, conditions for delay-induced instability are given using graphs assigned to the models. Series of chemical reactions are simplified using model-specific delay distribution functions in [7].

The chain method as an approximation approach to time delays appeared independently in the theory of delayed differential equations within mathematics [24] and in mathematical modeling within chemical engineering. Convective plug flows causing delays in process networks are commonly approximated using a series of continuously stirred tank reactors resulting in a so called cascade approximation [6]. One of the first attempts to approximate a delayed kinetic (non-mass-action) model with a set of ODEs containing auxiliary state variables was described in [20], where necessary conditions for instability were also given. After its introduction, the chain method has been significantly improved even recently with model class extensions and strong approximation results [12, 16]

Based on the above, the goal of this paper is to analyse delayed reaction networks using the chain method that transforms delayed differential equations to ODEs and preserves the kinetic property of the model. The structure of the paper is the following. Section 2 contains the most important notations and known results on kinetic models and the chain method. The structural and dynamical analysis of the approximated kinetic models is described in Section

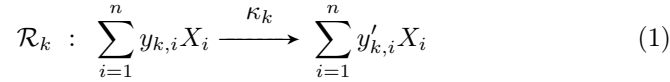
3, while Section 4 contains general stability result for delayed kinetic systems derived from the approximation. Finally, conclusions are drawn in Section 5.

2 Basic notions and tools

This section is devoted to introducing the studied class of chemical reaction networks (CRNs) with and without delays, and our most important tool, the chain method.

2.1 The studied model class: chemical reaction networks obeying mass action law

Chemical reaction networks (abbreviated as CRNs) have been abstracted from chemical kinetics. They consist of simple *elementary irreversible reaction steps* \mathcal{R}_k (with r reaction steps) taking place between n chemical *species* denoted by X_1, \dots, X_n in the form



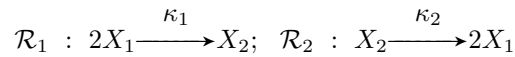
where the nonnegative integers $y_{k,i}$ and $y'_{k,i}$ are the *stoichiometric coefficients*. The positive numbers $\kappa_k > 0$ are the reaction rate constants.

The linear combinations of the species appearing on the left and right hand sides of the reaction steps (1) are called *complexes*

$$\mathbf{C}_k = \sum_{i=1}^n y_{k,i} X_i, \quad \mathbf{C}'_k = \sum_{i=1}^n y'_{k,i} X_i \quad (2)$$

where the stoichiometric coefficients (arranged in vectors) y_k and y'_k describe the composition of the complexes \mathbf{C}_k (the source complex) and \mathbf{C}'_k (the product complex), respectively. In the next, we will refer to the complexes with their stoichiometric coefficients, such that \mathbf{C}_k corresponds to y_k . Therefore, the *set of complexes* is defined as $\mathcal{K} \subset \overline{\mathbb{Z}}_+^n$, and $y_k, y'_k \in \mathcal{K}$.

Example 1: Simple CRN Consider two species, X_1 and X_2 that react in a reversible reaction $2X_1 \rightleftharpoons X_2$. Then the elementary reaction steps are



The complexes are $\mathbf{C}_1 = 2X_1$ and $\mathbf{C}_2 = X_2$ with the stoichiometric coefficient vectors $y_1 = [2 \ 0]^T$ and $y_2 = [0 \ 1]^T$.

The *mass action law* originates from the reaction rate expressions of chemical reactions in mixtures of ideal gases, where the *reaction rate of the k th reaction step* (1) under isotherm conditions is

$$\rho_k = \kappa_k \prod_{i=1}^n x_i^{y_{k,i}} = \kappa_k x^{y_k} \quad (3)$$

where x_i is the concentration of the specie X_i .

2.1.1 CRNs without time delay

The time evolution of the specie concentrations (i.e. the dynamics) of a CRN obeying the mass action law can be described by an ordinary differential equation model (an *ODE model*) the structure of which is given by a signed directed graph, the so called *structure graph*.

The ODE model The dynamics of an ordinary mass-action kinetic system [8] with reaction steps (1) and reaction rates (3) can be described by an ODE in the form

$$\dot{x}(t) = \sum_{k=1}^r \kappa_k (x(t))^{y_k} [y'_k - y_k], \quad t \geq 0, \quad (4)$$

where $x(t) \in \overline{\mathbb{R}}_+^n$ is the state vector which describes the concentrations of species. Solutions of (4) are determined by nonnegative initial vectors $x(0) = \eta \in \overline{\mathbb{R}}_+^n$.

Kinetic systems Let us consider the following general dynamical model

$$\dot{x}(t) = f(x(t)), \quad (5)$$

where $x(t) \in \mathbb{R}^n$ and the coordinates functions of f are multivariate polynomials in x . We call the system (5) *kinetic*, if there exist $r > 0$, and $\kappa_k > 0$, $y_k, y'_k \in \overline{\mathbb{Z}}_+^n$ for $k = 1, \dots, r$ such that (5) can be written in the form of (4). The kinetic property is easy to check: according to [15], the necessary and sufficient condition for kinetic realizability of a polynomial vector field is that all coordinates functions of f in (5) must have the form

$$f_i(x) = -x_i g_i(x) + h_i(x), \quad i = 1, \dots, n \quad (6)$$

where g_i and h_i are polynomials with nonnegative coefficients. In other words, the model (5) is kinetic if and only if each monomial with a negative sign in f_i contains x_i for $i = 1, \dots, n$, i.e. a kinetic model cannot contain negative cross-effects.

Kinetic systems are known to be *positive*, i.e. the solution remains in the nonnegative orthant if the initial condition was also there. We remark that the representation (4) for a given polynomial model (5) is generally non-unique [5, 28].

Reaction graph The structure of a CRN is described by a signed directed graph called reaction graph. The vertices of a reaction graph are the complexes (i.e. $v_j \sim \mathbf{C}_j$), and the edges correspond to the reactions. There exists a directed edge from v_i to v_j with edge weight κ_k if a reaction step $\mathbf{C}_i \xrightarrow{\kappa_k} \mathbf{C}_j$ can be found in the CRN.

A CRN is called *weakly reversible* if whenever there exists a directed path from v_i to v_j in its reaction graph, then there exists a directed path from v_j to v_i , too. In graph theoretic terms, this means that all components of the reaction graph are strongly connected components.

CRN properties The most important properties of CRNs are their stoichiometric subspaces, complex balance and deficiency.

The *stoichiometric subspace* of a given CRN is defined as

$$\mathcal{S} = \text{span}(\{y'_k - y_k \mid \text{for all } k = 1, \dots, r\}). \quad (7)$$

where $\eta_k = y'_k - y_k$ are the so called reaction vectors.

Then, we can define the first integrals

$$c_a(x(t)) = a^T x(t), \quad a \in \mathcal{S}^\perp, \quad (8)$$

where $\frac{d}{dt}c_a(x(t)) = 0$.

Finally, we can introduce the *positively invariant* stoichiometric compatibility classes as follows

$$\mathcal{S}_p = \left\{ x \in \overline{\mathbb{R}}_+^n \mid c_a(x) = c_a(p), \quad \forall a \in \mathcal{S}^\perp \right\}, \quad (9)$$

where the elements of p are nonnegative. These classes are positively invariant sets of the dynamical system (4), i.e if $x(0) \in \mathcal{S}_p$ then $x(t) \in \mathcal{S}_p$ for all $t \geq 0$. This means that the concentrations remain in the stoichiometric compatibility class that is determined by their initial value.

The notion of *complex balance* originally comes from the study of the thermodynamic compatibility of reaction networks. An equilibrium point $\bar{x} \in \mathbb{R}_+^n$ of the system (4) is called *complex balanced* if for every $\xi \in \mathcal{K}$,

$$\sum_{k:\xi=y_k} \kappa_k(\bar{x})^{y_k} = \sum_{k:\xi=y'_k} \kappa_k(\bar{x})^{y_k}, \quad (10)$$

where the sum on the left is over all reactions for which ξ is the source complex and the sum on the right is over all reactions for which ξ is the product complex. Thus complex balance of an equilibrium point expresses that the reaction fluxes producing and consuming a complex ξ are equal for each complex.

It is well-known [26] that if (4) has a positive complex balanced equilibrium \bar{x} , then any other positive equilibrium is complex balanced and the set of all positive equilibria \mathcal{E} can be characterized by

$$\mathcal{E} = \{\tilde{x} \in \mathbb{R}_+^n \mid \text{Ln}(\tilde{x}) - \text{Ln}(\bar{x}) \in \mathcal{S}^\perp\}. \quad (11)$$

Every positive complex balanced equilibrium \bar{x} is at least locally asymptotically stable relative to its positive stoichiometric compatibility class $\mathcal{S}_{\bar{x}}$ with the known logarithmic Lyapunov function which is independent of the rate coefficients and it has the form

$$V(x) = \sum_{i=1}^n \bar{x}_i g\left(\frac{x_i}{\bar{x}_i}\right), \quad (12)$$

where $g(r) = r \ln r + 1 - r$.

According to the *Global Attractor Conjecture*, the complex balanced equilibrium \bar{x} is not only local, but a global attractor in the positive stoichiometric compatibility class $\mathcal{S}_{\bar{x}}$ [4]. Important special cases were proven in [1] and [11]. Moreover, the possible general proof of the conjecture has recently appeared in [3].

Deficiency (denoted by δ) is a fundamental property of a reaction network and it is defined as [8]:

$$\delta = m - l - s, \quad (13)$$

where m is the number of distinct complexes, l is the number of linkage classes (graph components) and s is the dimension of the stoichiometric subspace. The deficiency depends only on the structure of the CRN, so it is a robust (i.e. parameter-independent) property.

According to the *Deficiency Zero Theorem*, the positive equilibrium points of a weakly reversible CRN with zero deficiency are complex balanced [8]. Therefore, the deficiency is a very useful measure for studying the dynamical properties of reaction networks and for establishing parameter-independent (at least) local stability conditions.

2.1.2 Chemical reaction networks with time delay

In bio- or enzyme-kinetics one often faces with reactions that have a certain dormant period, i.e. there is a time delay between the availability of the reactants and the starting of the reaction itself. This may be a consequence of a non-modelled slow initializing reaction step (or steps) that produce an enzyme or a catalyst to the reaction. Examples of such kinetic schemes are e.g. in [21] and [7].

Motivated by the above, the mass-action CRN with time delays will be considered in the form of a *delay differential equation*

$$\dot{x}(t) = \sum_{k=1}^r \kappa_k [(x(t - \tau_k))^{y_k} y_k' - (x(t))^{y_k} y_k], \quad t \geq 0, \quad (14)$$

where $\tau_k \geq 0$, $k = 1, \dots, r$ are the time delays. In the special case of $\tau_k = 0$, $k = 1, \dots, r$, Eq. (14) reduces to the ordinary mass action law CRN model (4).

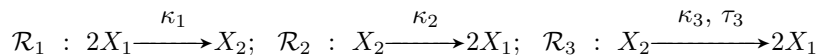
Solutions of (14) are generated by initial data $x(t) = \theta(t)$ for $-\tau \leq t \leq 0$, where $\tau = \max_{1 \leq k \leq r} \tau_k$ is the maximum delay and $\theta \in \bar{\mathcal{C}}_+$ is a nonnegative vector-valued continuous initial function over the time interval $[-\tau, 0]$, and $\bar{\mathcal{C}}_+$ is a set of such functions. For every $t \geq 0$, $x_t \in \bar{\mathcal{C}}_+$ is defined by $x_t(s) = x(t+s)$ for $-\tau \leq s \leq 0$ which is a segment of the solution.

Reaction graph with time delay We can simply extend the reaction graph describing the structure of a CRN with delays as follows. In case of a delayed reaction \mathcal{R}_k with a reaction rate constant $\kappa_k > 0$ and a delay $\tau_k > 0$, the edge weight of the edge corresponding to the reaction will be the pair κ_k, τ_k .

Note that multiple parallel edges between complexes may exist in this case with different delays.

The properties of CRNs with time delay It is easy to see, that the most important properties of CRNs, (weak) reversibility, complex balance and deficiency, can be simply extended to the case with time delay.

Example 2: Simple CRN with delay Consider again two species, X_1 and X_2 that react in a reversible reaction $2X_1 \rightleftharpoons X_2$, and let us have a third reaction converting X_2 to $2X_1$ with a delay. Then the elementary reaction steps are



The corresponding reaction graph is depicted in Fig. 1. The time evolution is described by the following delay differential equations

$$\begin{aligned} \dot{x}_1(t) &= -2\kappa_1 x_1^2(t) + 2\kappa_2 x_2(t) + 2\kappa_3 x_2(t - \tau_3) \\ \dot{x}_2(t) &= \kappa_1 x_1^2(t) - \kappa_2 x_2(t) - \kappa_3 x_2(t) \end{aligned} \quad (15)$$

where $x = [x_1, x_2]^T \in \bar{\mathbb{R}}_+^2$ are the states, $\kappa_i > 0$ are the reaction rate constants and $\tau_3 > 0$ is the time delay of the third reaction.

The stoichiometric subspace is

$$\mathcal{S} = \text{span} \left(\begin{bmatrix} -2 \\ 1 \end{bmatrix} \right) \quad \text{and} \quad \mathcal{S}^\perp = \text{span} \left(\begin{bmatrix} 1 \\ 2 \end{bmatrix} \right).$$

The deficiency of this model is $\delta = 2 - 1 - 1 = 0$, and the reaction graph is weakly reversible, so this model is complex balanced, too.

The dimension of \mathcal{S} is one, therefore the system (15) has infinitely many positive equilibria. It is easily verified that $\bar{x}_1 = \bar{x}_2 = \frac{\kappa_2 + \kappa_3}{\kappa_1}$ is an equilibrium of (15). Then, we can construct the set of the positive equilibria by (11) as follows

$$\mathcal{E} = \left\{ \bar{x} \in \mathbb{R}_+^2 \mid \begin{bmatrix} \ln(\bar{x}_1) - \ln\left(\frac{\kappa_2 + \kappa_3}{\kappa_1}\right) \\ \ln(\bar{x}_2) - \ln\left(\frac{\kappa_2 + \kappa_3}{\kappa_1}\right) \end{bmatrix} \in \mathcal{S}^\perp \right\}. \quad (16)$$

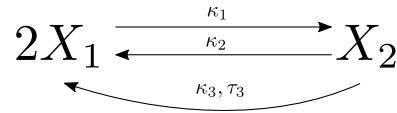


Fig. 1 Reaction graph of the example model (15)

2.2 Summary of the chain method

The analysis of nonlinear delayed differential equations is generally difficult due to the infinite dimension of the phase-space [10]. To overcome this difficulty, delayed terms were approximated by a sequence of first order differential equations in [24] thus approximating delayed differential equations by a set of ODEs. It was shown in [24] that if the initial function of the delayed system is sufficiently smooth, then the solution of the approximating ODE converges uniformly to the solution of the original delayed model on any finite time interval $[0, T]$.

An important generalization of the chain method was proposed in [13], where the authors showed that under additional conditions often fulfilled by physical models, the approximation uniformly converges to the original solution on the whole infinite time-horizon $[0, \infty)$. These results were further improved in [17], where sufficient conditions were given for the convergence of the approximation on $[0, \infty)$ for a more general class of ODEs with Lipschitz-continuous nonlinearities.

In order to formally introduce the chain approximation method, we assume that the system model has the following form

$$\dot{x}(t) = f(x(t)) + h(x(t - \tau))H, \quad \forall t \geq 0, \quad (17)$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $\tau > 0$, $f : \mathbb{R}^n \rightarrow \mathbb{R}^n$, $h : \mathbb{R}^n \rightarrow \mathbb{R}$ are continuous functions, $H \in \mathbb{R}^n$ is a constant vector, and $x(t) = \theta(t)$ for $-\tau \leq t \leq 0$ is the continuous initial function. The approximating set of ODEs with a chain containing N new state variables ('compartments') denoted by v_i for $i = 1, \dots, N$ is the following

$$\begin{aligned}
 \dot{z}(t) &= f(z(t)) + \frac{N}{\tau} v_N(t)H \\
 \dot{v}_1(t) &= h(z(t)) - \frac{N}{\tau} v_1(t) \\
 \dot{v}_i(t) &= \frac{N}{\tau} v_{i-1}(t) - \frac{N}{\tau} v_i(t), \quad 2 \leq i \leq N
 \end{aligned} \quad (18)$$

with $z(0) = \theta(0)$, and $v_i(0) = \int_{-i\frac{\tau}{N}}^{-i\frac{\tau}{N} + \frac{\tau}{N}} h(\theta(s)) ds$, $1 \leq i \leq N$. Note that $z(t) \in \mathbb{R}^n$ and $v_i(t) \in \mathbb{R}$, $i = 1, \dots, N$.

We remark that the model (18) forms a special case of the one studied in [16], since the delayed term in (17) is written as the product of a scalar-valued function h and a constant vector H . Therefore, $v_i(t)$ for $i = 1, \dots, N$

are scalars in (18). Naturally, the results proved in [16] are valid for our model, too.

In the next section, we will show that considering a delayed kinetic system (14), its approximation in the form of (18) is formally a non-delayed kinetic system with additional first order reactions, and we will study its relation to the original delayed model.

3 Analysis of delayed kinetic models through approximation

In order to analyse the properties of approximated delayed kinetic models, we will first apply the chain method in this section for a special case of such systems with just a single delayed reaction. The results can be then easily generalised for the multiple delay case.

3.1 Model equations of approximated delayed kinetic models

Let us assume that only the last (r th) reaction is delayed (i.e. $\tau_k = 0$ for $k = 1, \dots, (r-1)$ and $\tau_r > 0$). With this assumption, the delayed kinetic system (14) can be written as

$$\dot{x}(t) = \sum_{k=1}^{r-1} \kappa_k (x(t))^{y_k} [y'_k - y_k] + \kappa_r [(x(t - \tau_r))^{y_r} y'_r - (x(t))^{y_r} y_r]. \quad (19)$$

Then, we can construct the approximating system by using the *chain method* described in eq. (18) with $h(x(t - \tau_r)) = \kappa_r (x(t - \tau_r))^{y_r}$ and $H = y'_r$ as follows

$$\begin{aligned} \dot{z}(t) &= \sum_{k=1}^{r-1} \kappa_k (z(t))^{y_k} [y'_k - y_k] + \frac{N}{\tau_r} v_N(t) y'_r - \kappa_r (z(t))^{y_r} y_r \\ \dot{v}_1(t) &= \kappa_r (z(t))^{y_r} - \frac{N}{\tau_r} v_1(t) \\ \dot{v}_i(t) &= \frac{N}{\tau_r} v_{i-1}(t) - \frac{N}{\tau_r} v_i(t), \quad 2 \leq i \leq N, \end{aligned} \quad (20)$$

with the initial conditions

$$z(0) = \theta(0), \quad \text{and} \quad v_i(0) = \kappa_r \int_{-i \frac{\tau_r}{N}}^{- (i-1) \frac{\tau_r}{N}} (\theta(s))^{y_r} ds. \quad (21)$$

It is easy to see, that *the approximating equations are kinetic*, since all the functions on the right hand side of (20) match the sign conditions given in Eq. (6). Moreover, it is also clear from the equations that the delayed reaction is replaced by a chain of first order reaction steps where the concentrations of the newly introduced first-order complexes are v_i for $i = 1, \dots, N$.

In a similar way, *any delayed reaction can be approximated by a series of first order reaction steps involving new auxiliary species forming new complexes by themselves.*

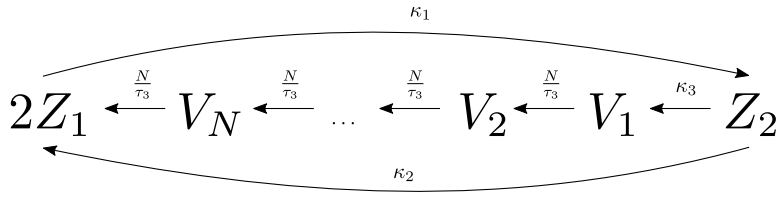


Fig. 2 Reaction graph of the approximating model of *Example 2* with model Eqs. (22). The delayed reaction is replaced by a chain of first order reactions compared to the original reaction graph in Fig. 1.

Example 2 (Continued) Using the above described chain method, we can construct the approximating ODEs of the original model (15) as follows

$$\begin{aligned}
 \dot{z}_1(t) &= -2\kappa_1 z_1^2(t) + 2\kappa_2 z_2(t) + \frac{N}{\tau_3} v_N(t) \\
 \dot{z}_2(t) &= \kappa_1 z_1^2(t) - \kappa_2 z_2(t) - \kappa_3 z_2(t) \\
 \dot{v}_1(t) &= \kappa_3 z_2(t) - \frac{N}{\tau_3} v_1(t) \\
 \dot{v}_i(t) &= \frac{N}{\tau_3} v_{i-1}(t) - \frac{N}{\tau_3} v_i(t), \quad 2 \leq i \leq N,
 \end{aligned} \tag{22}$$

where $z = [z_1, z_2]^T \in \overline{\mathbb{R}}_+^2$ and $v \in \overline{\mathbb{R}}_+^N$ are the states, and $N \geq 2$ is the number of the auxiliary states v . The initial conditions are $z(0) = \theta(0)$ and $v_i(0) = \kappa_3 \int_{-i\frac{\tau_3}{N}}^{-\frac{(i-1)\tau_3}{N}} \theta_2(s) ds$.

Fig. 2 shows the reaction graph of the approximation *with the auxiliary species, complexes and reactions but without delay*.

In order to illustrate the effect of the approximation on the dynamics of the original system and its approximations, Fig. 3 depicts the time domain simulation of the delayed system and the approximating system with different number of compartments, i.e. with different values of N .

3.2 Important properties of approximating kinetic models

We have already seen in Subsection 3.1, that the approximating model of a kinetic system with time delays is kinetic, therefore it is positive, too. In addition, any delayed reaction was approximated by a chain of first order reaction steps involving new auxiliary species forming new complexes by themselves, that implies the properties of the resulting approximating CRN model.

Connectivity and weak reversibility The delayed reaction is replaced by a chain of first order reaction. Therefore, the number and strong connectivity of the reaction graph components are not changing. This means that the number of linkage classes remains the same ($l' = l$), and if the original reaction graph is weakly reversible, then the reaction graph of the approximation is weakly reversible, too.

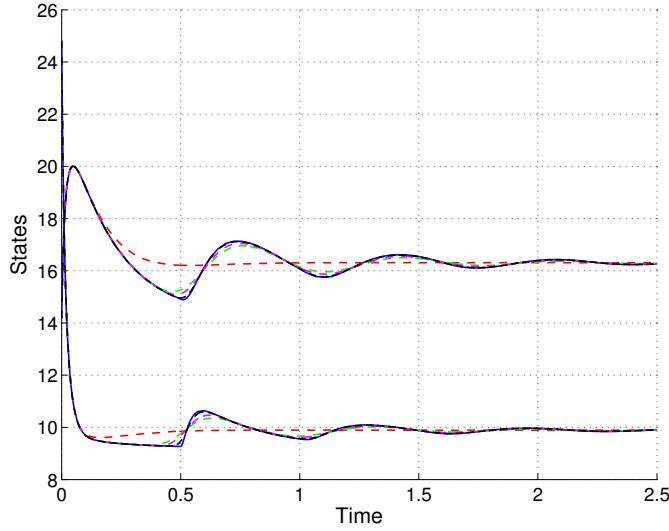


Fig. 3 Time domain simulation of the delayed system (15) and the approximating system (22) with the parameters $\kappa_1 = 1$, $\kappa_2 = 1$, $\kappa_3 = 5$, $\tau_3 = 0.5$ and constant initial condition. The blue lines correspond to the states of the original delayed system $x(t)$. The dashed lines correspond to the first two states of the approximation $z(t)$ with different number of compartments. The red, green, magenta and black dashed lines show the case $N = 2, 50, 100, 500$, respectively. The larger N results in better approximation.

Stoichiometric subspace The dimension of the state space increases from the original n (reflecting the number of species) to $(n+N)$ with the N new auxiliary species. Therefore, we extend the original complex vectors with N zeros $\hat{y}_i = [y_i^T \ \mathbf{0}^T]^T$ and $\hat{y}'_i = [y_i'^T \ \mathbf{0}^T]^T$ for $i = 1, \dots, r$. Then, we can partition the stoichiometric subspace of the approximating model $\mathcal{S}' \subseteq \mathbb{R}^{n+N}$ as follows

$$\mathcal{S}' = \mathcal{S}'_1 \oplus \mathcal{S}'_2 \oplus \mathcal{S}'_3, \quad (23)$$

where \oplus denotes the direct sum of the vector spaces. The vector spaces \mathcal{S}'_1 , \mathcal{S}'_2 and \mathcal{S}'_3 are defined as follows

$$\begin{aligned} \mathcal{S}'_1 &= \text{span}(\{\hat{y}'_i - \hat{y}_i \mid i = 1, \dots, r\}), \\ \mathcal{S}'_2 &= \text{span}(\{\mathbf{e}_{i+1} - \mathbf{e}_i \mid i = (n+1), \dots, (n+N-1)\}), \\ \mathcal{S}'_3 &= \text{span}(\mathbf{e}_{n+1} - \hat{y}_r). \end{aligned} \quad (24)$$

The intersection of these vector spaces $\mathcal{S}'_1 \cap \mathcal{S}'_2 \cap \mathcal{S}'_3$ contains only $\mathbf{0}$. The dimensions are $\dim(\mathcal{S}'_1) = s$, $\dim(\mathcal{S}'_2) = N - 1$ and $\dim(\mathcal{S}'_3) = 1$. Therefore, $s' = \dim(\mathcal{S}') = s + N$.

Deficiency As it is shown above, the chain approximation of a delay kinetic model changes the structural properties in such a way that the *deficiency*

remains the same with the approximation. This is seen if one substitutes the modified properties l' , m' and s' to the defining equation (13):

$$\delta' = m' - l' - s' = m + N - l - s - N = m - l - s = \delta \quad (25)$$

Equilibrium points and complex balance It is easy to check that when the original system (19) has the positive equilibrium point \bar{x} , then the approximation system (20) has a positive equilibrium (\bar{z}, \bar{v}) in the form

$$\begin{aligned} \bar{z} &= \bar{x}, \\ \bar{v}_i &= \kappa_r \frac{\tau_r}{N} \bar{z}^{y_r} = \kappa_r \frac{\tau_r}{N} \bar{x}^{y_r}, \quad i = 1, \dots, N. \end{aligned} \quad (26)$$

The reaction rates of the chain in the equilibrium (\bar{z}, \bar{v}) are equal to the reaction rate of the delayed reaction in the equilibrium \bar{x} , i.e. $\kappa_r \bar{x}^{y_r}$. Therefore, if the equilibrium point of the original system \bar{x} is complex balanced, then the equilibrium point of the approximation system (\bar{z}, \bar{v}) is complex balanced, too.

3.3 Stability analysis of delayed kinetic models

First integrals of the approximation Let us consider the following linear function of the states

$$c_a^N(z(t), v(t)) = a^T \left[z(t) + \sum_{i=1}^N v_i(t) y_r \right], \quad a \in \mathcal{S}^\perp, \quad (27)$$

where \mathcal{S} is the stoichiometric subspace of the original delayed system (19). The linear function (27) is a first integral of the approximation system (20), because

$$\begin{aligned} \frac{d}{dt} c_a^N(z(t), v(t)) &= a^T \left[\dot{z}(t) + \sum_{i=1}^N \dot{v}_i(t) y_r \right] \\ &= \sum_{k=1}^{r-1} \kappa_k (z(t))^{y_k} \underbrace{a^T [y'_k - y_k]}_0 + \frac{N}{\tau_r} v_N(t) \underbrace{a^T [y'_r - y_r]}_0 = 0, \end{aligned} \quad (28)$$

where $y'_k - y_k \in \mathcal{S}$ for $k = 1, \dots, r$ and $a \in \mathcal{S}^\perp$.

Then, we would like to conclude the first integrals of the delayed system (19). For this, we are looking for the 'limit functional' $c_a : \mathcal{C}_+ \rightarrow \mathbb{R}$ such that if $N \rightarrow \infty$ then $c_a^N(z(t), v(t)) \rightarrow c_a(x_t)$. By using the properties of the chain method, we consider the following approximations denoted by the sign \approx

$$z(t) \approx x(t), \quad v_i(t) \approx \kappa_r \int_{t-i\frac{\tau_r}{N}}^{t-(i-1)\frac{\tau_r}{N}} (x(s))^{y_r} ds \approx \kappa_r \frac{\tau_r}{N} \left(x\left(t - i\frac{\tau_r}{N}\right) \right)^{y_r}. \quad (29)$$

Let us substitute (29) into (27), then

$$c_a^N(z(t), v(t)) \approx c_a^N(x_t) = a^T \left[x(t) + \kappa_r \sum_{i=1}^N \frac{\tau_r}{N} \left(x(t - i \frac{\tau_r}{N}) \right)^{y_r} y_r \right]. \quad (30)$$

If $N \rightarrow \infty$, then

$$c_a^N(x_t) \rightarrow c_a(x_t) = a^T \left[x(t) + \kappa_r \int_{t-\tau_r}^t (x(s))^{y_r} ds y_r \right]. \quad (31)$$

that gives the first integral of the original delayed model.

Lyapunov function of the approximating system Let us assume that the delayed system (19) has the complex balanced equilibrium \bar{x} . Then, the equilibrium point of the approximation system (\bar{z}, \bar{v}) is complex balanced, too.

Therefore, we can construct the logarithmic Lyapunov function $V^N(z(t), v(t))$ of the approximation as follows

$$\begin{aligned} V^N(z(t), v(t)) &= \sum_{i=1}^n \bar{z}_i(t) g\left(\frac{z_i(t)}{\bar{z}_i}\right) + \sum_{i=1}^N \bar{v}_i g\left(\frac{v_i(t)}{\bar{v}_i}\right) \\ &= \sum_{i=1}^n \bar{x}_i g\left(\frac{z_i(t)}{\bar{x}_i}\right) + \kappa_r \bar{x}^{y_r} \sum_{i=1}^N \frac{\tau_r}{N} g\left(\frac{1}{\kappa_r} \frac{N}{\tau_r} \frac{v_i(t)}{\bar{x}^{y_r}}\right), \end{aligned} \quad (32)$$

where $g(r) = r \ln r + 1 - r$. Here we used Eqs. (26) relating the equilibrium points of the original and the approximated models.

Similarly to the previous paragraph, we are looking for the 'limit functional' $V : \mathcal{C}_+ \rightarrow \mathbb{R}_+$ such that if $N \rightarrow \infty$ then $V^N(z(t), v(t)) \rightarrow V(x_t)$. For this, let us substitute (29) into (32), then

$$\begin{aligned} V^N(z(t), v(t)) \approx V^N(x_t) &= \sum_{i=1}^n \bar{x}_i g\left(\frac{x_i(t)}{\bar{x}_i}\right) + \\ &+ \kappa_r \bar{x}^{y_r} \sum_{i=1}^N \frac{\tau_r}{N} g\left(\left(\frac{x(t - i \frac{\tau_r}{N})}{\bar{x}}\right)^{y_r}\right). \end{aligned} \quad (33)$$

If $N \rightarrow \infty$, then

$$V^N(x_t) \rightarrow V(x_t) = \sum_{i=1}^n \bar{x}_i g\left(\frac{x_i(t)}{\bar{x}_i}\right) + \kappa_r \bar{x}^{y_r} \int_{t-\tau_r}^t g\left(\left(\frac{x(s)}{\bar{x}}\right)^{y_r}\right) ds. \quad (34)$$

and we obtain the Lyapunov function of the original delayed model, that is used for stability analysis in [18].

Example 2 (Continued) Fig. 4 demonstrates the convergence property of $V^N(z(t), v(t))$ with the example system (15) comparing the functional $V(x_t)$ and its approximations $V^N(z(t), v(t))$ with different N s.

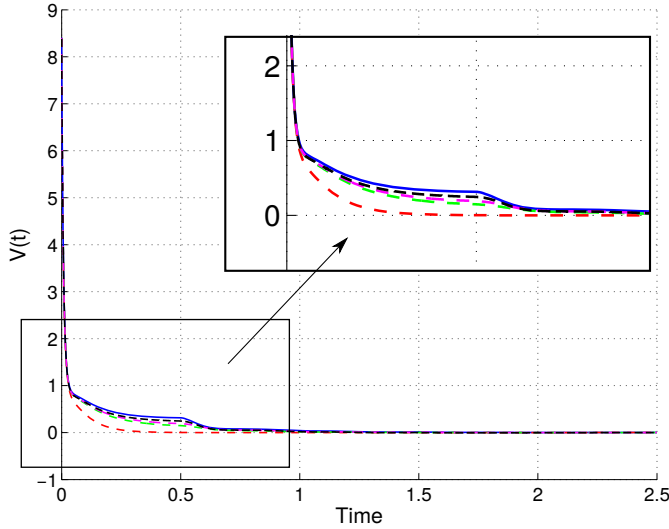


Fig. 4 This figure corresponds to the simulation of the delayed (15) and the approximation system (22) with same parameters and initial conditions as Fig. 3. The blue lines shows the value of the functional $V(x_t)$. The dashed lines correspond to the values of the function $V^N(z(t), v(t))$ with different N s. The red, green, magenta and black dashed lines show the case $N = 2, 50, 100, 500$, respectively. The plot shows the convergence $V^N(z(t), v(t)) \rightarrow V(x_t)$.

4 General stability results

The results of the previous section can be generalized to kinetic models of the form (14) containing multiple constant delays. The detailed stability proofs of complex balanced delayed kinetic systems using the Lyapunov-Krasovskii functional presented in this section can be found in [18].

The functional (31) is generalized first in order to prove that it is a first integral of the system (14). The generalized functional $c_a : \bar{\mathcal{C}}_+ \rightarrow \mathbb{R}$ has the form

$$c_a(x_t) = a^T \left[x(t) + \sum_{k=1}^r \left(\kappa_k \int_{t-\tau_k}^t (x(s))^{y_k} ds \right) y_k \right], \quad a \in \mathcal{S}^\perp. \quad (35)$$

that contain a sum of delayed terms (for $k = 1, \dots, r$) compared to the single delay case in Eq. (31).

Then we can define the positive stoichiometric compatibility classes of $\theta \in \bar{\mathcal{C}}_+$ in the case of time delay such that

$$\mathcal{D}_\theta = \{ \psi \in \bar{\mathcal{C}}_+ \mid c_a(\psi) = c_a(\theta), \quad \forall a \in \mathcal{S}^\perp \}. \quad (36)$$

Note that \mathcal{D}_θ is a set of functions and it is a generalization of the stoichiometric compatibility class \mathcal{S}_p of the CRNs without delay (see in Eq. (9)). Similarly to \mathcal{S}_p , the solutions of the delayed model remain in the delayed stoichiometric compatibility class \mathcal{D}_θ if the initial value function θ is in this set, too.

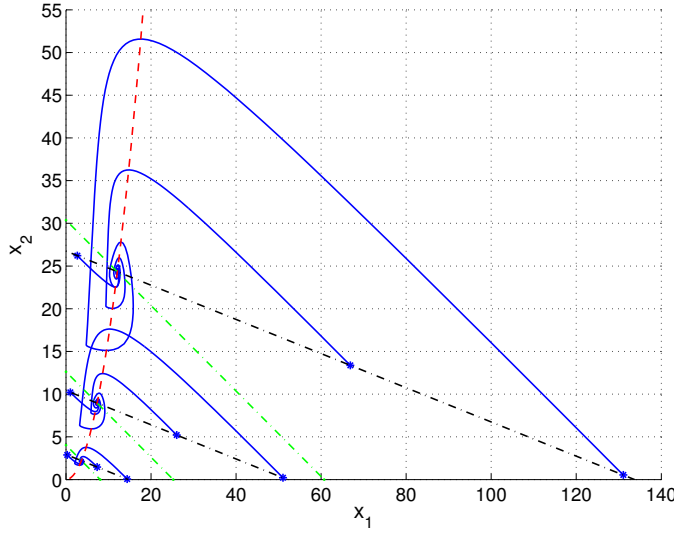


Fig. 5 Phase portrait of the system (20) with the parameters $\kappa_1 = 1$, $\kappa_2 = 1$, $\kappa_3 = 5$, $\tau_3 = 0.2$. The red dashed line shows the set of equilibria. The black dot-dashed lines show the set of initial states (with constant initial functions) corresponding to the same equilibrium. The green dashed lines are the stoichiometric compatibility classes of the non-delayed system. The blue lines show the solution trajectories with different constant initial functions

In the general case, the Lyapunov-Krasovskii functional $V : \mathcal{C}_+ \rightarrow \overline{\mathbb{R}}_+$ of the delayed system has the form

$$V(x_t) = \sum_{i=1}^n \bar{x}_i g\left(\frac{x_i(t)}{\bar{x}_i}\right) + \sum_{k=1}^r \kappa_k \bar{x}^{y_k} \int_{t-\tau_k}^t g\left(\left(\frac{x(s)}{\bar{x}}\right)^{y_k}\right) ds. \quad (37)$$

that also contain a sum of delayed terms (for $k = 1, \dots, r$) compared to the single delay functional in Eq. (34).

The above functional is used to prove that every positive complex balanced equilibrium \bar{x} of the delayed kinetic system (14) is locally asymptotically stable relative to its positive stoichiometric compatibility class $\mathcal{D}_{\bar{x}}$.

Example 2 (Continued) Let us investigate the dynamics of the delayed model (15) assuming positive constant initial functions θ that belong to $\mathcal{D}_{\bar{x}}$ where \bar{x} is from the set of the equilibrium points, i.e. $\bar{x} \in \mathcal{E}$. All these trajectories with such a constant initial value function will go to \bar{x} in the limit with $t \rightarrow \infty$.

At the same time, the equilibrium points of the delayed and no-delayed CRNs coincide, so the trajectories of the non-delayed CRNs will also go to \bar{x} in the limit, and their trajectories will be in $\mathcal{S}_{\bar{x}}$, that is a line in this case.

Fig. 5 shows the phase portrait of the original delayed model in the example (15). The simulation is started from different constant initial functions.

5 Conclusions

Mass action law chemical reaction networks with delays assigned to the reactions were considered in this paper. The delayed models were approximated using the modified chain method known from the theory of delay differential equations.

It was shown that important structural properties (such as weak reversibility and deficiency) of the approximated models are preserved in the approximations. Moreover, a Lyapunov-Krasovskii functional candidate was proposed using the approximation for the original delayed systems that can be efficiently used for stability analysis.

The proposed notions and results were demonstrated using a simple chemical reaction network with two species, two complexes, three reactions and a single delay.

Further work will be directed to use the structural relationship between the delayed and approximated models for model structure simplification for bio-chemical reaction networks.

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