Delays in Model Reduction of Chemical Reaction Networks

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Abstract: A novel engineering model reduction method is proposed in this paper that can be applied to a chemical reaction network (CRN) with chains of linear reactions. The reduced model is a delayed CRN with possibly different delays but with less state variables than the original model. As the first step of the model reduction, a decomposition method is also developed to transform chains with joint reactions into independent chains of linear reactions. The well known example of McKeithan's network is used as a case study to illustrate the basic concepts and the design method.

Keywords: Process control; Delay; Model reduction; Chemical Reaction Networks

1. INTRODUCTION

Mathematical models of complex nonlinear systems derived from engineering principles most often have a large number of state variables that makes them unsuitable for dynamic analysis, model-based control, diagnosis or parameter estimation. Therefore, the need arises to derive more simple versions from these detailed dynamic models that have the same or similar dynamical properties but can be handled by the tools and techniques of nonlinear systems and control theory. Therefore, the aim of model reduction for dynamic analysis and control purposes is to decrease the number of state variables using engineering judgement and operating experience about the parameters of the different mechanisms present in the system.

Chemical Reaction Networks (CRNs) form a wide class of positive (or non-negative) systems attracting significant attention not only among chemists but in numerous other fields such as physics, or even pure and applied mathematics where nonlinear dynamical systems are considered. Beside pure chemical reactions, CRNs are often used to model the dynamics of intracellular processes, metabolic or cell signalling pathways [Haag et al., 2005]. Although chemical reaction network models originate from chemical reaction kinetics, the increasing interest in the systems and control community towards reaction networks as a well-defined special class of positive nonlinear systems is clearly shown by recent tutorial and survey papers, see e.g. the papers of Sontag [2001], Angeli [2009], Chellaboina et al. [2009].

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Because of the high complexity of (bio)chemical reaction networks, different effective model reduction methods have been developed utilizing their specialities (see [Hangos, 2010] for a review). Majority of the approaches use the multiscale nature of such CRNs when fast and slow reactions are both present and preserve the type of nonlinearities (e.g. polynomial) present in the original model. Besides of the usual steady-state approximation based reduction method, more advanced reduction schemes are also proposed, see e.g. Cappelletti and Wiuf [2017] for a recent paper. Another widely applied reduction method for CRNs is the so called variable lumping (see in Farkas [1999] and in Li et al. [1994] for the nonlinear CRN case) that can be applied for state variables with similar dynamics. A model reduction method of complex balanced CRNs based on algebraic approaches has been proposed in Rao et al. [2013], that results in a similar structure than variable lumping.

An alternative way of achieving the reduction of the number of state variables in CRNs is to allow the introduction of delay into the reduced model. In order to have an equivalent dynamics of the non-intermediate species in the original and reduced models, distributed delays are proposed in e.g. [Hinch and Schnell, 2004] or [Leier et al., 2014]. Motivated by this approach and by the so called chain method used for approximated finite delays with a chain of linear reactions (see e.g. Repin [1965] or Krasznai et al. [2010]), the aim of our paper is to propose a model reduction method applicable to CRNs with linear reaction chains.

2. BASIC NOTIONS

In this section, we will introduce the basic notions of chemical reaction networks with and without of time delay.

We will also present our previous result to approximate time delayed CRNs with ordinary differential equations (ODEs).

2.1 CRNs with mass action law

A CRN obeying the mass action law is a closed system where chemical species $X_1, X_2, \ldots, X_n$ take part in r chemical reactions. An *elementary reaction step* has the form

$$C \xrightarrow{\kappa} C', \tag{1}$$

where C and C' are the source and product complexes, respectively. They are defined by the linear combinations of the species $C = \sum_{i=1}^{n} y_i X_i$ and $C' = \sum_{i=1}^{n} y'_i X_i$ where the nonnegative integer vectors y and y' are called stoichiometric coefficients. The positive real number κ is the reaction rate coefficient.

The *reaction rate* ρ of an individual reaction (1) obeying the so-called *mass action law* can be described as

$$\rho(x) = \kappa \prod_{i=1}^{n} x_i^{y_i} = \kappa x^y,$$

where $x_1, x_2, \ldots, x_n$ are the concentration of species $X_1, X_2, \ldots, X_n$.

The dynamics of a mass action CRN can be described by a system of ordinary differential equations as follows

$$\dot{x}(t) = \sum_{k=1}^{r} \kappa_k \left(x(t)\right)^{y_k} \left[y'_k - y_k\right], \qquad t \geq 0, \tag{2}$$

where $x(t) \in \overline{\mathbb{R}}_+^n$ is the n dimensional nonnegative state vector which describes the concentrations of species. In the kth reaction, nonnegative integer vectors y_k and y'_k denote the stoichiometric coefficients of source and product complexes, respectively, and the positive number κ_k is the reaction rate coefficient.

Reaction graph Similarly to Feinberg [1979] and many other authors, we can represent the set of individual reaction steps by a weighted directed graph called *reaction graph*. The reaction graph consists of a set of vertices and a set of directed edges. The vertices correspond to the complexes, while the directed edges represent the reactions, i.e. if we have a reaction $C \xrightarrow{\kappa} C'$ then there is an edge in the reaction graph between the complexes C and C' with the weight κ.

Example 1. (Chain of linear reactions). Let us consider the simple case, when n species participate in $n-1$ first order (i.e. linear) chemical reactions. Then, the dynamics can be described by ODEs as follows

$$\begin{aligned} \dot{x}_1(t) &= -\kappa_1 x_1(t), \\ \dot{x}_i(t) &= \kappa_{i-1} x_{i-1}(t) - \kappa_i x_i(t) \quad i = 2, ..., (n-1), \\ \dot{x}_n(t) &= \kappa_{n-1} x_{n-1}(t). \end{aligned} \tag{3}$$

The corresponding reaction graph of the CRN (3) has the form

$$X_1 \xrightarrow{\kappa_1} X_2 \xrightarrow{\kappa_2} \ldots \xrightarrow{\kappa_{n-2}} X_{n-1} \xrightarrow{\kappa_{n-1}} X_n.$$

2.2 Delayed chemical reaction networks

It has been long noticed in chemical reaction networks, in particular enzyme kinetics, that enzyme-catalysed reactions deviated from the mass action law. Here 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 non-modelled slow initializing reaction steps that produce an enzyme or a catalyst to the reaction. Therefore, the usual notion of CRNs have been extended by introducing delays into the dynamics of the reactions (see e.g. [Mincheva and Roussel, 2007] or [Erneux, 2009]), where examples of such kinetic schemes can also be found.

Besides of the above mentioned slow initialization steps, other mechanisms, such as the fixed lifetime of the enzyme-substrate complex that leads to the product with this fixed delay (see [Hinch and Schnell, 2004]) or a slow inter cellular convection can also be considered as the cause of the apparent delays. In these cases, too, *delays are most often associated to or approximated with a series of activation steps that form a chain of linear activation reactions involving species that are difficult or even impossible to measure.*

Motivated by the above, we can extend CRN models with delays in such a way, that each reaction has also a nonnegative real number associated to it that represents the time delay of the reaction

$$C \xrightarrow{\kappa,\ \tau} C'.$$

The dynamics of a CRN with time delay will be considered in the form of *delay differential equations* (DDEs) as follows

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

where the nonegative real numbers $\tau_1, \tau_2, \ldots, \tau_r$ represent the time delays. In the special case, when each τ_k is zero, the DDEs of the delayed CRN (4) reduces to the ODEs of the undelayed CRN model (2).

Solutions of (4) are generated by initial data $x(t) = \theta(t)$ for $-\tau \leq t \leq 0$, where τ is the maximum delay and θ is a nonnegative vector-valued continuous initial function over the time interval $[-\tau, 0]$.

Reaction graph with time delay We can simply extend the reaction graph of a CRN with time delays. In this case, it is a directed and labelled multigraph, where the label of an edge is not only the reaction rate constant, but also the time delay. Reactions with same source and product complexes, but different time delays occur as parallel edges in the reaction graph.

Recently, stability analysis results have appeared in [Lipták et al., 2018b] for this class, too.

2.3 The chain method

The analysis of nonlinear delayed differential equations is generally difficult due to the infinite dimension of

the phase-space, see [Fridman, 2014]. To overcome this difficulty, delayed terms are approximated by a sequence of first order differential equations (see [Repin, 1965]), thus one can approximate delayed differential equations by a set of ODEs. It was shown in Repin [1965] 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.

In the paper of Lipták et al. [2018a], we have presented a method to approximate delayed reactions with linear reaction chains. For simplifying the notations, only the rth reaction with positive time delay τ_r

$$C_r \xrightarrow{\kappa_r,\ \tau_r} C'_r$$

is considered here, that is replaced by the chain of N_r elements

$$C_r \xrightarrow{\kappa_r} V_1^{(r)} \xrightarrow{\tilde{\kappa}_r} \cdots \xrightarrow{\tilde{\kappa}_r} V_{N_r}^{(r)} \xrightarrow{\tilde{\kappa}_r} C'_r.$$

To describe the dynamics of the approximation, we introduce a new n dimensional nonnegative approximating state vector $z \in \overline{\mathbb{R}}_+^n$ and the scalar variables $v_1^{(r)}, v_2^{(r)}, \ldots, v_{N_r}^{(r)}$ with the initial conditions

$$z(0) = \theta(0) \text{ and } v_i^{(r)}(0) = \kappa_r \int_{-i\tilde{\kappa}_r^{-1}}^{-(i-1)\tilde{\kappa}_r^{-1}} (\theta(s))^{y_r} ds.$$

Then, the equations of the approximation have the form

$$\begin{aligned} \dot{z}(t) = &\sum_{k=1}^{r-1} \kappa_k \left[(z(t-\tau_k))^{y_k} y'_k - (z(t))^{y_k} y_k\right] - \\ &- \kappa_r (z(t))^{y_r} y_r + \tilde{\kappa}_r v_{N_r}^{(r)}(t) y'_r, \end{aligned} \tag{5}$$

and

$$\begin{aligned} \dot{v}_1^{(r)}(t) &= \kappa_r (z(t))^{y_r} - \tilde{\kappa}_r v_1^{(r)}(t) \\ \dot{v}_i^{(r)}(t) &= \tilde{\kappa}_r v_{i-1}^{(r)}(t) - \tilde{\kappa}_r v_i^{(r)}(t), \quad 2 \le i \le N_r, \end{aligned} \tag{6}$$

where the reaction rate coefficient of the chain is $\tilde{\kappa}_r = \frac{N_r}{\tau_r}$ and the chain has $N_r \ge 1$ elements. The new state vector $z(t)$ uniformly converges to the original one $x(t)$ on a finite time interval when N_r goes to infinity.

3. MODEL REDUCTION OF CRNS USING DELAYS

The aim of model reduction for dynamic analysis and control purposes is to reduce the number of state variables such that the dynamic properties of the input-output model remains close to that of the original detailed one. This implies that certain state variables, that determine the output of the model should remain unchanged while the reduction may leave out some of the other, non-interesting state variables.

Motivated by the mechanisms behind delayed chemical reactions in Subsection 2.2 and by the approximation of delayed CRNs in Subsection 2.3, we may *introduce delays into the reduced model in order to decrease the number of its state variables that appear as intermediate, usually non-measurable concentrations in the linear chains of the model.* If the delay does not destroy the nice dynamic properties (e.g. structural stability) of the model (see [Lipták et al., 2018b] for such a sub-class of CRNs), the reduced model with a delay may be advantageous for controller design purposes, too. This motivates the model reduction method proposed here.

3.1 The reduction method

The reduction method can be applied for CRNs which have independent linear reaction chains (i.e. the intermediate complexes of the chains have only one incoming reaction and outgoing reaction) with large number of intermediates and with same reaction constants.

For each chain of linear reactions the method consists of three consecutive steps.

G1 The kth chain is identified in the form

$$C_k \xrightarrow{\kappa_k} V_1^{(k)} \xrightarrow{\tilde{\kappa}_k} \cdots \xrightarrow{\tilde{\kappa}_k} V_{N_k}^{(k)} \xrightarrow{\tilde{\kappa}_k} C'_k,$$

where $V_1^{(k)}, V_2^{(k)}, \ldots, V_{N_k}^{(k)}$ denote the intermediate first order complexes of the chain.

G2 Delete all intermediate complexes (species) and all reactions adjacent to them belonging to the chain.

G3 Insert a new delayed reaction between the entrance C_k and exit C'_k of the chain to obtain

$$C_k \xrightarrow{\kappa_k,\ \tau_k} C'_k,$$

where the time delay is computed as $\tau_k = N_k \tilde{\kappa}_k^{-1}$.

G4 Determine the initial function for the remaining state variables.

3.2 Decomposing linear complexes

In this subsection, we will present a simple procedure to decompose a first order complex with a single incoming and multiple outgoing reactions into an equivalent model with new independent first order complexes that have a single incoming and a single outgoing reaction. By applying this procedure multiple times on a given CRN with linear joint complexes participating in chains of linear reactions, we can get an equivalent CRN with first order chains of independent linear complexes. Therefore, this method can be used as a preprocessing step before the model reduction.

Let us consider a first order complex U (i.e. U is a specie and it does not appear in any other complexes) with a single incoming reaction

$$C_{in} \xrightarrow{\kappa_{in}} U, \tag{7}$$

and multiple outgoing reactions

$$U \xrightarrow{\kappa_{out,i}} C_{out,i}, \quad i = 1, \ldots, N. \tag{8}$$

Let us replace the complex U with a set of first order complexes $V^{(1)}, V^{(2)}, \ldots, V^{(N)}$ such that the corresponding state variables are $v^{(i)} = \frac{\kappa_{out,i}}{\kappa_{sum}} u$ with $\kappa_{sum} = \sum_{i=1}^{N} \kappa_{out,i}$. Then, the new reactions have the form

$$C_{in} \xrightarrow{\frac{\kappa_{out,i}}{\kappa_{sum}}\kappa_{in}} V^{(i)} \xrightarrow{\kappa_{sum}} C_{out,i}, \quad i = 1, \ldots, N. \tag{9}$$

This way the reactions $V^{(i)} \xrightarrow{\kappa_{sum}} C_{out,i}, \quad i = 1, \ldots, N$ in (9) become mutually independent, i.e. they do not have any common complex. At the same time, we can get back the original concentrations and dynamics of the original reactions (7)-(8) by applying the equation $u = \sum_{i=1}^{N} v^{(i)}$.

Fig. 1 illustrates the decomposition method when $N = 2$.

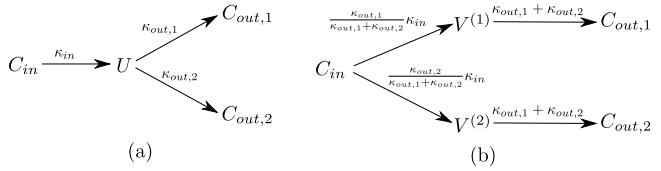

Fig. 1. Decomposition of the reactions (a) into independent ones (b)

4. CASE STUDY

The proposed model reduction method will be illustrated using the famous *kinetic proofreading* model proposed by McKeithan [1995]. This CRN is a simple way to describe how a chain of modifications of the T-cell receptor complex, via tyrosine phosphorylation and other reactions, may give rise to both increased sensitivity and selectivity of the response.

The proposed reduction method with delay is applied to this CRN, and the dynamic response of the original and reduced models are compared.

4.1 McKeithan's network

The specie X_1 represents the concentration of T-cell receptor (TCR), and X_2 denotes a peptide-major histocompatibility complex (MHC). The constant κ_1 is the association rate constant for the reaction which produces an initial ligand-receptor complex U_1 from TCRs and MHCs. The various intermediate T-cell receptor complexes are denoted by $U_1, U_2, \ldots, U_N$ and the final complex is denoted by X_3. McKeithan postulates that *the recognition signals are determined by the concentrations of the final complex* X_3. Clearly, the species X_1, X_2 and X_3 are of primary interest for this model, where X_3 is the model output.

The constants κ_p are the rate constants for each of the uniform steps of phosphorylation or other intermediate modifications, and the constants κ_{-1} are uniform dissociation rates. Fig. 2 shows the reaction graph of the network.

The dynamics of the McKeithan's network can be described by an ODE in the form

$$\dot{x}_{\{1,2\}}(t) = -\kappa_1 x_1(t) x_2(t) + \kappa_{-1} x_3(t) + \kappa_{-1} \sum_{i=1}^{N} u_i(t),$$
$$\dot{x}_3(t) = -\kappa_{-1} x_3(t) + \kappa_p u_N(t),$$

with the intermediates

$$\dot{u}_1(t) = -(\kappa_p + \kappa_{-1}) u_1(t) + \kappa_1 x_1(t) x_2(t),$$
$$\dot{u}_i(t) = -(\kappa_p + \kappa_{-1}) u_i(t) + \kappa_p u_{i-1}(t), \quad 2 \le i \le N,$$

where the states x_1, x_2, x_3 and $u_1, u_2, \ldots, u_N$ are the concentrations of the species.

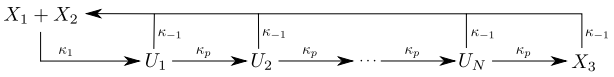

Fig. 2. The reaction graph of the McKeithan's network

4.2 Model reduction with delay

In order to apply the model reduction method described in Subsection 3.1, we introduce an equivalent CRN of the McKeithan's network, where the network is decomposed into independent chains of linear reactions.

Decomposition of the chains The decomposition *uses the procedure for decomposing linear complexes* described before in Subsection 3.2 in an iterative way starting from the final intermediate complex U_N and processing backwards the complexes.

For this, we introduce a set of new state variables $v_1^{(1)}$, $v_1^{(2)}, v_2^{(2)}$, $v_1^{(3)}, v_2^{(3)}, v_3^{(3)}$, $\ldots$, $v_1^{(N)}, v_2^{(N)} ..., v_N^{(N)}$, $v_1^{(N+1)}, v_2^{(N+1)}, \ldots, v_N^{(N+1)}$ such that $v_i^{(j)} = \alpha_i^{(j)} u_i$ where $\alpha_i^{(j)}$ is defined for $1 \le i \le \min(j, N)$ as follows

$$\alpha_i^{(j)} = \begin{cases} \dfrac{\kappa_{-1}}{\kappa_p} \left(\dfrac{\kappa_p}{\kappa_p + \kappa_{-1}} \right)^{j-i+1} & \text{if } 1 \le j \le N \\ \left(\dfrac{\kappa_p}{\kappa_p + \kappa_{-1}} \right)^{j-i} & \text{if } j = N+1 \end{cases}.$$

This results in the following relation between u_i and $v_i^{(j)}$

$$\sum_{j=i}^{N+1} v_i^{(j)} = u_i, \quad i = 1, \ldots, N.$$

By using the new variables $v_i^{(j)}$ and introducing the notation $\tilde{\kappa} = \kappa_p + \kappa_{-1}$, we get the following ODEs

$$\dot{x}_{\{1,2\}}(t) = -\kappa_1 x_1(t) x_2(t) + \kappa_{-1} x_3(t) + \tilde{\kappa} \sum_{i=1}^{N} v_i^{(i)}(t),$$
$$\dot{x}_3(t) = -\kappa_{-1} x_3 + \tilde{\kappa} v_N^{(N+1)},$$

with the intermediates

$$\dot{v}_1^{(j)}(t) = -\tilde{\kappa} v_1^{(j)}(t) + \alpha_1^{(j)} \kappa_1 x_1(t) x_2(t), j = 1, \ldots, N+1$$
$$\dot{v}_2^{(j)}(t) = -\tilde{\kappa} v_2^{(j)}(t) + \tilde{\kappa} v_1^{(j)}(t), \quad j = 2, \ldots, N+1,$$
$$\dot{v}_3^{(j)}(t) = -\tilde{\kappa} v_3^{(j)}(t) + \tilde{\kappa} v_2^{(j)}(t), \quad j = 3, \ldots, N+1,$$
$$\vdots$$
$$\dot{v}_N^{(N)}(t) = -\tilde{\kappa} v_N^{(N)}(t) + \tilde{\kappa} v_{N-1}^{(N)}(t),$$
$$\dot{v}_N^{(N+1)}(t) = -\tilde{\kappa} v_N^{(N+1)}(t) + \tilde{\kappa} v_{N-1}^{(N+1)}(t).$$

Fig. 3 shows the corresponding reaction graph where the $N + 1$ linear chains are independent.

Reducing the chains of independent linear reactions Executing repeatedly the steps of our model reduction method for each of the independent chains of linear reactions in Fig. 3, one can arrive at the reaction graph of the reduced CRN that is seen in Fig. 4.

In the reduced model, we have N different time delays and the ith time delay is $\tau_i = i\tilde{\kappa}^{-1}$. *The reduction results in a*

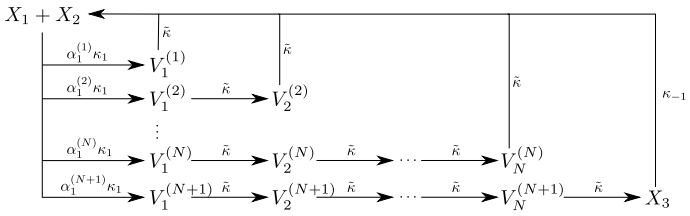

Fig. 3. The reaction graph of the transfomed McKeithan's network. The chains of linear reactions become independent

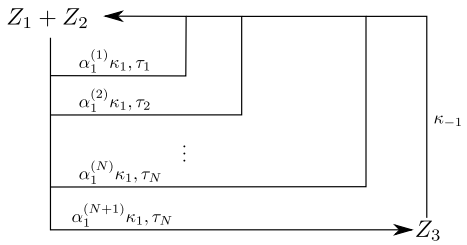

Fig. 4. The reaction graph of the reduced McKeithan's network using delays

delay differential equation system with only 3 *states*. The equations have the form

$$\dot{z}_{\{1,2\}}(t) = -\kappa_1 z_1(t) z_2(t) + \kappa_{-1} z_3(t) + \sum_{i=1}^{N} \alpha_1^{(i)} \kappa_1 z_1(t-\tau_i) z_2(t-\tau_i),$$

$$\dot{z}_3(t) = -\kappa_{-1} z_3(t) + \alpha_1^{(N+1)} \kappa_1 z_1(t-\tau_N) z_2(t-\tau_N).$$

where z_1, z_2, and z_3 are the concentration of species Z_1, Z_2, and Z_3 in the reduced model, that approximate the states X_1, X_2, and X_3 in the original model.

The initial function θ is a a nonnegative vector-valued continuous function over the time interval $[-\tau_N, 0]$. The initial function has to fulfill the following conditions:

C1 $\theta(0) = x(0)$,
C2 $\frac{\alpha_1^{(N)}}{\alpha_i^{(N)}} \kappa_1 \int_{-i\tilde{\kappa}^{-1}}^{-(i-1)\tilde{\kappa}^{-1}} \theta_1(s)\theta_2(s)ds = u_i(0)$,
C3 θ is a continuous function.

Remark Note, that a similar structure has been obtained for the McKeithan's network using a stochastic model and a stochastic reduction method by Leier et al. [2014]. However, instead of the fixed delays associated with the reduced reaction steps in our approach, the authors used distributed delays: this way they did not approximate the solution but computed it in an other equivalent way.

4.3 Analyzing the dynamic responses of the original and the reduced model

In this subsection, we will compare the original and reduced McKeithan's network using simulation in the time domain.

Initial function We used an initial function that describes the situation when a signal arrives at the start of the reaction network. This is described with the following sigmoid function in the species Z_1 ($\sim X_1$) and Z_2 ($\sim X_2$)

$$\theta(t) = \frac{1}{1+e^{-50t}} \begin{bmatrix} 20 \\ 10 \\ 0 \end{bmatrix},$$

while the concentration of the final complex Z_3 ($\sim X_3$) is zero. This situation is depicted in Fig. 5.

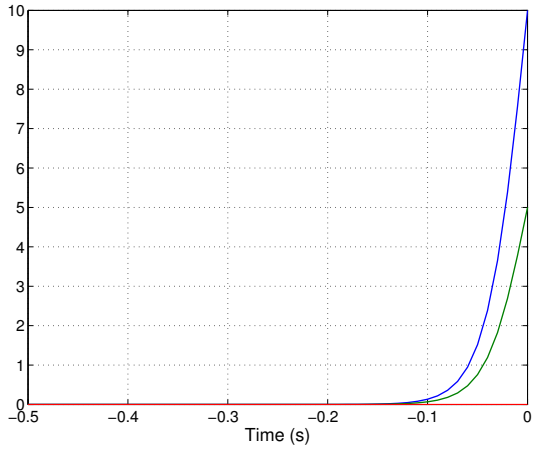

Fig. 5. Plot of the initial function θ of the reduced order McKeithan's network. The blue, green, and red lines show the values $\theta_1(t)$, $\theta_2(t)$, and $\theta_3(t)$, respectively

The response of the reduced model In order to show the effect of the key model parameters on the approximation error, we have investigated two different cases where the obtained delay in the reduced models were the same but with different conditions.

- *Low chain length case* with $N = 6$, $\kappa_p = 20$, $\kappa_{-1} = 1$, and $\kappa_1 = 1$, with the time plot seen in Fig. 6.
- *Long chain length case* with $N = 15$, $\kappa_p = 50$, $\kappa_{-1} = 1$, and $\kappa_1 = 1$, where the time plot is depicted in Fig. 7.

It is seen that a good agreement has been found between the responses of the original and reduced model in the critical concentration of specie X_3, i.e. between $x_3(t)$ and $z_3(t)$.

5. CONCLUSIONS

A model reduction method is proposed in this paper that can be applied to a chemical reaction network (CRN) with chains of linear reactions. For CRNs with chains that contain joint linear reactions, a decomposition method is also developed to transform them into independent chains of linear reactions. This decomposition can be used as the first step of the model reduction.

The proposed method reduces the chains with linear reactions into a single reaction with time delay, therefore one obtains a delayed CRN with possibly different delays but with much less state variables than the original model.

The well-known McKeithan's network is used as a case study to illustrate the basic concepts and the reduction method. Simulation results show that the concentrations in the reduced model approximate well the original ones for a realistic sigmoid type initial function.

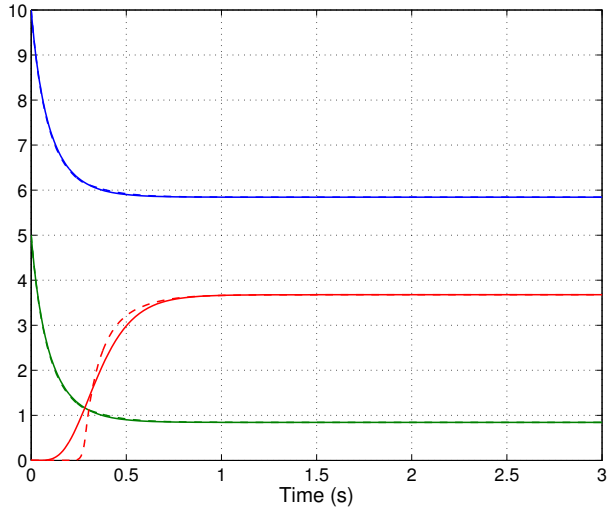

Fig. 6. Time plot of the original and reduced McKeithan's network when $N = 6$, $\kappa_p = 20$, $\kappa_{-1} = 1$, and $\kappa_1 = 1$. The blue, green, and red lines show the values of $x_1(t)$, $x_2(t)$, and $x_3(t)$, respectively. The dashed lines of the same color correspond to the same values in the reduced model.

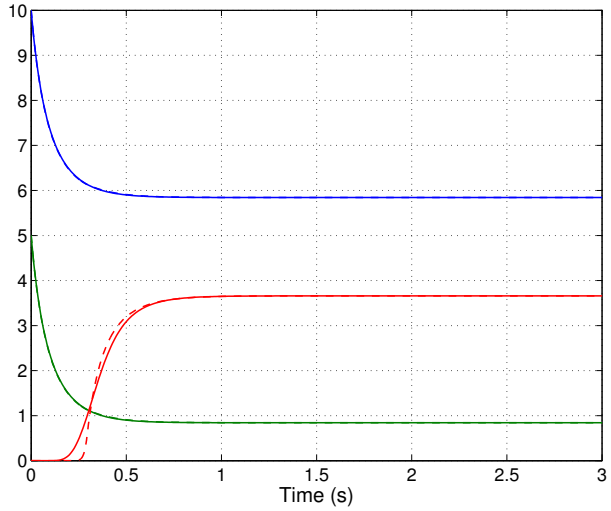

Fig. 7. Time plot of the original and reduced McKeithan's network when $N = 15$, $\kappa_p = 50$, $\kappa_{-1} = 1$, and $\kappa_1 = 1$. The blue, green, and red lines show the values of $x_1(t)$, $x_2(t)$, and $x_3(t)$, respectively. The dashed lines of the same color correspond to the same values in the reduced model.

Further work will be directed to generalize the proposed approximation method such that we *allow different reaction rate coefficients* in the linear chains. Furthermore, we would like to determine the reduction error in the function of chain lengths and reaction rate coefficients.

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