Distributed delay model of the McKeithan's network

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Abstract: In this paper CRNs containing linear reaction chains with multiple joint complexes were considered in order to obtain an equivalent reduced order delayed CRN model with distributed time delays. For this purpose, our earlier method (Lipták and Hangos (2018)) for decomposing the chains of linear reactions with multiple joint complexes was used together with the "linear chain trick". An analytical expression for the kernel function of the distributed delay was also derived from the reaction rate coefficients of the linear reaction chains.
Our approach was demonstrated using the example of the well known McKeithan's network model of kinetic proofreading.

1. INTRODUCTION

It is widely accepted, that the class of kinetic systems is a useful representation of nonnegative polynomial system models not only in (bi)ochemistry, but also in other areas like population or disease dynamics, process systems, and even transportation networks, see Érdi and Tóth (1989); Haddad et al. (2010). They can be considered as universal descriptors of smooth nonnegative polynomial systems (Szederkényi et al. (2018)), and their representations can effectively be used for the analysis of their structural stability.

At the same time, the detailed CRN model of a realistic application, e.g. a biochemical reaction network, is usually too complex in its original form, therefore the development of reduced order equivalent models is of great theoretical and practical importance. In order to achieve the *reduction of the number of state variables in CRNs we may allow the introduction of delays* into the reduced model. For enzyme kinetic models (Hinch and Schnell, 2004) or (Leier et al., 2014) proposed to *introduce distributed delays for obtaining equivalent dynamics* of the non-intermediate species in the original and reduced models. 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 generalize the above methods for linear reaction chains with multiple joint complexes, and to demonstrate this approach to the well known McKeithan's network model of kinetic proofreading.

2. BASIC NOTIONS

The basic notions of delayed kinetic systems or delayed CRNs is briefly described here with a special emphasis on CRNs with distributed time delays.

2.1 CRNs with mass action law

A CRN obeying the mass action law is a closed system where chemical species X_i for $1 \leq i \leq n$ take part in r chemical reactions. An *elementary reaction step* has the form

$$C \xrightarrow{\kappa} C', \qquad (1)$$

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 the individual reaction (1) obeying the so-called *mass action law* is

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

where x_i is the concentration of species X_i for $1 \leq i \leq n$.

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

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

where $x(t) \in \overline{\mathbb{R}}_+^n$ is the n dimensional nonnegative state vector which describes the concentrations of species. The

set $\mathcal{K} \subset \overline{\mathbb{Z}}_+^n$ denotes the set of stoichiometric coefficient vectors. In the kth reaction, the nonnegative integer vectors $y_k \in \mathcal{K}$ and $y_k' \in \mathcal{K}$ 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. (A simple reversible chemical reaction).
Consider the following reactions

$$2X_1 + X_2 \xrightarrow{\kappa_1} 2X_3, \quad 2X_3 \xrightarrow{\kappa_2} 2X_1 + X_2.$$
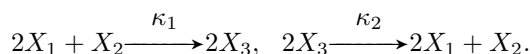
We have three species X_1, X_2, X_3 and two complexes $C_1 = 2X_1 + X_2$, and $C_2 = 2X_3$. Fig. 1. shows the corresponding reaction graph. The corresponding stoichiometric coefficient vectors are $y_1 = [2\ 1\ 0]^T$ and $y_2 = [0\ 0\ 2]^T$. The reaction rates are $\rho_1(x) = \kappa_1 x_1^2 x_2$ and $\rho_2(x) = \kappa_2 x_3^2$. The dynamics is given by the following ODEs

$$\dot{x}(t) = \kappa_1 x_1^2 x_2 [y_2 - y_1] + \kappa_3 x_3^2 [y_1 - y_2],$$

where x_i is the concentration of the species X_i.

$$C_1 \underset{\kappa_2}{\overset{\kappa_1}{\rightleftarrows}} C_2$$
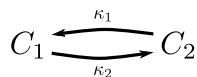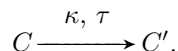
Fig. 1. Reaction graph of Example 1

2.2 Delayed chemical reaction networks

We can extend CRN models with *discrete (time) delays* in such a way, that each reaction has also a nonnegative real number associated with 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

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

where the nonnegative real numbers τ_k for $1 \le k \le r$ represent the time delays. Solutions of (3) are generated by initial data $x(t) = \theta(t)$ for $-\tau \le t \le 0$, where τ is the maximum delay and θ is a nonnegative vector-valued continuous initial function over the time interval $[-\tau, 0]$. In the special case, when each τ_k is zero, the DDEs of the delayed CRN (3) reduces to the ODEs of the undelayed CRN model (2).

A more general extension is when the *delay has a distribution* in the following form

$$\dot{x}(t) = \sum_{k=1}^{r} \kappa_k \left[\int_0^\infty g_k(s) x(t-s)^{y_k} \, ds\, y_k' - x(t)^{y_k} y_k \right], \quad (4)$$

where the *kernel function* g_k is nonnegative and $\int_0^\infty g_k(s)\, ds = 1$ for $1 \le k \le r$. In the special case, when $g_k(s) = \delta(s - \tau_k)$, then we get back the CRN with discrete delay (3).

Reaction graphs 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 coefficient, but also the time delay distribution (the value of the discrete delay, or the kernel function of the distributed delay). Reactions with same source and product complexes, but different time delays occur as parallel edges in the reaction graph.

It is important to note, that - unlike in the usual reaction graphs - loop edges with time delay related label are also allowed in a reaction graph with time delay.

Underlying physico-chemical mechanisms in delayed CRNs In reaction kinetic systems, the presence of time delays can be the consequence of a physical constraint (for example, the minimal time necessary to carry out transcription and translation, or the time needed to transport chemical species between cellular compartments), or that of a long chain of reaction intermediates (as in a metabolic pathway). Another common source of delays in process systems is the presence of spatially distributed phenomena (see e.g. Hangos and Cameron (2001)), such as convection of different types, or diffusion combined with convection.

2.3 Equilibrium points and complex balancedness in delayed chemical reaction networks

By a *positive equilibrium* of (2), (3) or (4), we mean a positive vector $\overline{x} \in \mathbb{R}_+^N$ such that $x(t) \equiv \overline{x}$ is a solution of (2), (3) and (4), respectively. Note that Eqs. (2), (3) and (4) share the same equilibria satisfying the algebraic equation

$$\sum_{k=1}^{r} \kappa_k \overline{x}^{y_k} [y_k' - y_k] = 0. \qquad (5)$$

A positive equilibrium $\overline{x}$ is called *complex balanced* if for every $\eta \in \mathcal{K}$,

$$\sum_{k:\eta = y_k} \kappa_k \overline{x}^{y_k} = \sum_{k:\eta = y_k'} \kappa_k \overline{x}^{y_k}, \qquad (6)$$

where the sum on the left is over all reactions for which η is the source complex and the sum on the right is over all reactions for which η is the product complex. Finally, an ordinary or delayed kinetic system is called *complex balanced* if it has a positive complexed balanced equilibrium.

It is well-known (van der Schaft et al. (2015)) that if Eq. (2) and hence (3) or (4) has a positive complex balanced equilibrium $\overline{x}$, then any other positive equilibrium is also complex balanced.

The significance of complex balancedness lies in its role in stability analysis of CRNs. Recently, stability analysis results have appeared in (Lipták et al., 2018) for the class of discrete time delayed complex balanced CRNs, too.

2.4 The "linear chain trick" and delayed CRNs

In this subsection, we consider a CRN with Gamma distribution, and we construct its undelayed version which is dynamically equivalent to the delayed system. The delayed reactions are substituted with linear reaction chains of intermediate complexes. The method is based on the so-called linear chain trick (see in MacDonald (1978)).

For the sake of simplicity, consider a delayed CRN which has only one reaction with Gamma distribution. The dynamics is written in the following form

$$\dot{x}(t) = \kappa \left[\int_0^\infty G_{a,p}(s) x(t-s)^y \, ds \, y' - x(t)^y \, y \right], \quad (7)$$

where $G_{a,p}$ is the Gamma distribution

$$G_{a,p}(s) = \frac{a^p s^{p-1}}{(p-1)!} \exp(-as),$$

with a positive reaction rate coefficient $a > 0$, and an integer shape parameter $p \geq 1$. Fig. 2 shows the Gamma distribution with different parameters.
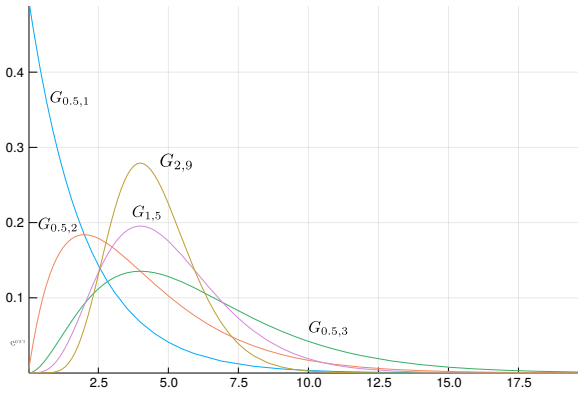

Fig. 2. Gamma distribution with different shape and rate parameters

In order to transform the DDE (7) to an ODE, we introduce new variables v_i for $1 \leq i \leq p$ as follows

$$v_i(t) = \frac{\kappa}{a} \int_0^\infty G_{a,i}(s) \, x(t-s)^y \, ds.$$

The time derivatives of the new variable are

$$\dot{v}_i(t) = \frac{\kappa}{a} G_{a,i}(0) x(t)^y + \frac{\kappa}{a} \int_{-\infty}^t G'_{a,i}(t-s) x(s)^y ds. \quad (8)$$

Next, we will use the following two properties of the Gamma distribution

$$G'_{a,i}(s) = \begin{cases} -a\, G_{a,i}(s) & \text{if } i = 1 \\ -a\, G_{a,i}(s) + a\, G_{a,i-1}(s) & \text{if } i > 1, \end{cases}$$

and

$$G_{a,i}(0) = \begin{cases} a & \text{if } i = 1 \\ 0 & \text{if } i > 1, \end{cases}$$

Then Eq. (8) becomes

$$\dot{v}_i(t) = \begin{cases} \kappa x(t)^y - a v_1(t) & \text{if } i = 1 \\ a v_{i-1}(t) - a v_i(t) & \text{if } i \leq p. \end{cases}$$
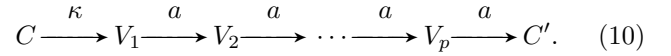
Finally, we get the equivalent ODE version of (7) in the form

$$\begin{aligned} \dot{x}(t) &= a v_p(t)\, y' - \kappa x(t)^y\, y, \\ \dot{v}_1(t) &= \kappa x(t)^y - a v_1(t), \\ \dot{v}_i(t) &= a v_{i-1}(t) - a v_i(t), \quad 2 \leq i \leq p. \end{aligned} \quad (9)$$

The initial conditions for the new variables fulfil

$$v_i(0) = \frac{\kappa}{a} \int_0^\infty G_{a,i}(s)\theta(-s)^y ds, \quad 1 \leq i \leq p,$$

and the corresponding reaction graph is

$$C \xrightarrow{\kappa} V_1 \xrightarrow{a} V_2 \xrightarrow{a} \cdots \xrightarrow{a} V_p \xrightarrow{a} C'. \quad (10)$$

Finally we obtained that the *original delayed CRN with distributed time delay (7) is indeed equivalent to the linear reaction chain of intermediate complexes (9)* with reaction graph (10).

3. A DELAYED CRN MODEL OF KINETIC PROOFREADING

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 method of constructing an equivalent model with distributed time delay of this system is described, and the dynamic response of the original and simplified models are compared.

3.1 The McKeithan's network

The species 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_i for $1 \leq i \leq N$ 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 reaction rate coefficients for each of the uniform steps of phosphorylation or other intermediate modifications, and the constants κ_{-1} are uniform dissociation rate coefficients. Fig. 3 shows the reaction graph of the network.

The dynamics of the McKeithan's network can be described by ODEs 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

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

where x_i, and u_i are the concentrations of the species X_i, and U_i, respectively. The positive parameters κ_1, κ_{-1} and κ_p are the reaction rate coefficients.
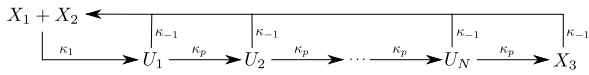

Fig. 3. The reaction graph of the McKeithan's network

3.2 Decomposed McKeithan's network

In order to be able to use the "linear chain trick" described in Subsection 2.4, we need to decompose the original McKeithan's network in Fig. 3 to an equivalent model that contains a set of independent linear chains. We apply the decomposition method reported in Lipták and Hangos (2018).

For this, we introduce a set of new state variables $v_i^{(j)} = \alpha_i^{(j)} u_i$ for $1 \le i \le \min(j, N)$ and $1 \le j \le N+1$ where $\alpha_i^{(j)}$ is defined as follows

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

where $\tilde{\kappa} = \kappa_p + \kappa_{-1}$. This results in the following relation between u_i and $v_i^{(j)}$

$$\sum_{j=i}^{N+1} v_i^{(j)} = \left(\sum_{j=i}^{N+1} \alpha_i^{(j)}\right) u_i = u_i, \quad 1 \le i \le N.$$

By using the new variables $v_i^{(j)}$, we get the following ODEs

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

$$\dot{x}_3(t) = -\kappa_{-1} x_3(t) + \tilde{\kappa} v_N^{(N+1)}(t),$$

with the intermediates

$$\dot{v}_1^{(j)}(t) = -\tilde{\kappa} v_1^{(j)}(t) + \alpha_1^{(j)} \kappa_1 x_1(t) x_2(t), \quad 1 \le j \le N+1$$

$$\dot{v}_2^{(j)}(t) = -\tilde{\kappa} v_2^{(j)}(t) + \tilde{\kappa} v_1^{(j)}(t), \quad 2 \le j \le N+1,$$

$$\dot{v}_3^{(j)}(t) = -\tilde{\kappa} v_3^{(j)}(t) + \tilde{\kappa} v_2^{(j)}(t), \quad 3 \le j \le N+1,$$

$$\vdots$$

$$\dot{v}_N^{(N)}(t) = -\tilde{\kappa} v_N^{(N)}(t) + \tilde{\kappa} v_{N-1}^{(N)}(t),$$

$$\dot{v}_N^{(N+1)}(t) = -\tilde{\kappa} v_N^{(N+1)}(t) + \tilde{\kappa} v_{N-1}^{(N+1)}(t).$$

Fig. 4 shows the corresponding reaction graph where the $N+1$ linear chains are independent. Note that the last two chains have same length.
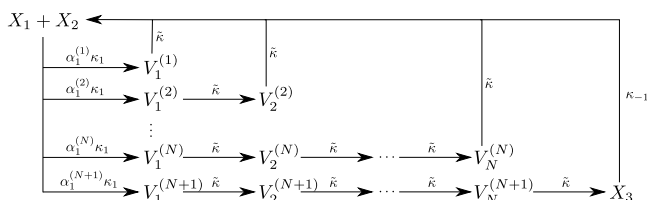

Fig. 4. The reaction graph of the transfomed McKeithan's network. The chains of linear reactions become independent

3.3 Distributed delayed model of McKeithan's network

In this subsection, we use the linear chain trick method of Subsection 2.4 in the reverse direction. As a result, we get a distributed delay version of McKeithan's network.

According to Subsection 2.4, we can describe each intermediate specie $v_i^{(j)}$ by a distributed delay element such that

$$v_i^{(j)}(t) = \frac{\alpha_1^{(j)} \kappa_1}{\tilde{\kappa}} \int_0^\infty G_{\tilde{\kappa},i}(s) x_1(t-s) x_2(t-s)\, ds. \quad (11)$$

By using (11), we get the distributed delay version of McKeithan's network as follows

$$\dot{x}_{\{1,2\}}(t) = -\kappa_1 x_1(t) x_2(t) + \kappa_{-1} x_3(t)$$
$$+ (1-\beta)\,\kappa_1 \int_0^\infty g_1(s) x_1(t-s) x_2(t-s)\, ds,$$
$$\dot{x}_3(t) = -\kappa_{-1} x_3(t)$$
$$+ \beta \kappa_1 \int_0^\infty g_2(s) x_1(t-s) x_2(t-s)\, ds,$$

where $\beta = \left(\frac{\kappa_p}{\tilde{\kappa}}\right)^N$, and

$$g_1(s) = \frac{\kappa_{-1}}{(1-\beta)\tilde{\kappa}} \sum_{j=1}^{N} \left(\frac{\kappa_p}{\tilde{\kappa}}\right)^{j-1} G_{\tilde{\kappa},j}(s),$$

$$g_2(s) = G_{\tilde{\kappa},N}(s).$$

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

C1 $x(0) = \theta(0)$,
C2 $\tilde{\kappa} u_i(0) = \kappa_1 \int_0^\infty G_{\tilde{\kappa},i}(s) \theta_1(-s) \theta_2(-s)\, ds$,
C3 θ is a continuous function.

Fig. 5 shows the corresponding reaction graph of the reduced model with distributed time delays. It is important to observe the presence of a *delayed loop* in the reaction graph.
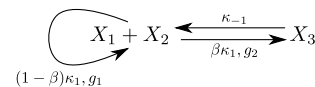

Fig. 5. Reaction graph of the distributed delay version of McKeithan's network

3.4 Simulation results

In this subsection, we will compare the original and the distributed delay version of McKeithan's network using simulation in the time domain. Because of the equivalence of the models, we expect that the dynamic behaviour of the two models should be the same.

We used the Julia programming language and DifferentialEquations.jl package (Rackauckas and Nie (2017)) for the numerical computations.

The parameters $\kappa_1 = 1$, $\kappa_p = 5$ or $\kappa_p = 2.5$, $\kappa_{-1} = 1$, and $N = 10$ were used for the comparison. Figs. 6 and 7
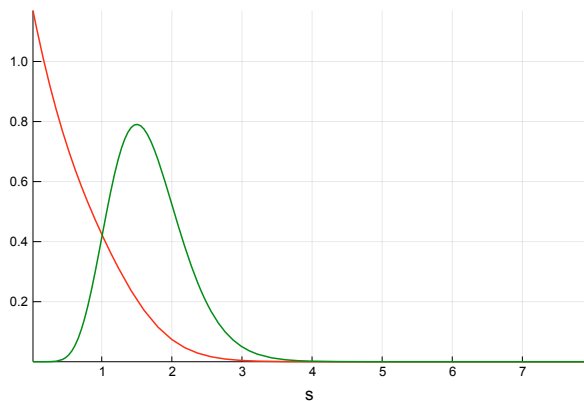
Fig. 6. The red and green lines shows the kernel functions g_1 and g_2 of McKeithan's network with parameters ($\kappa_1 = 1$, $\kappa_p = 5$, $\kappa_{-1} = 1$, and $N = 10$), respectively

Fig. 8. Plot of the initial function θ of the McKeithan's network with distributed delay. The blue, green, and red lines show the functions θ_1, θ_2, and θ_3, respectively
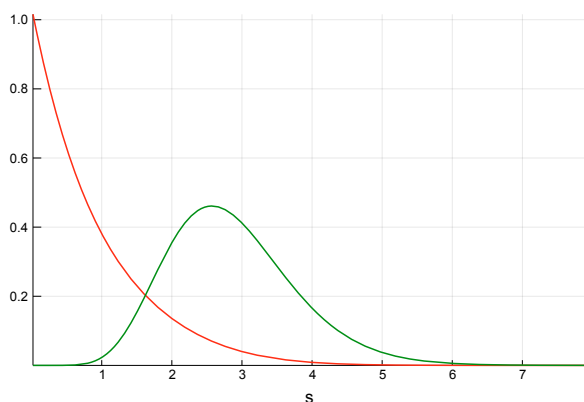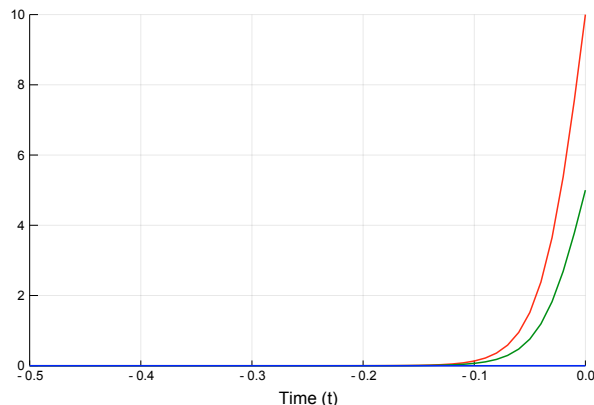

Fig. 7. The red and green lines shows the kernel functions g_1 and g_2 of McKeithan's network when the parameters are same as in Fig. 10 with the exception of one parameter $\kappa_p = 2.5$, respectively
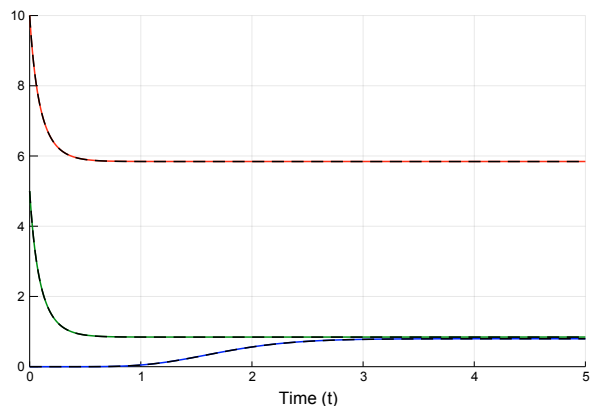

Fig. 9. Time plot of the dynamic response of the original and distributed delayed McKeithan's network when $\kappa_1 = 1$, $\kappa_p = 5$, $\kappa_{-1} = 1$, and $N = 10$. The blue, green, and red lines show the values of x_1, x_2, and x_3, respectively. The black dashed lines correspond to the same values in the distributed delay model. The two dynamic responses are same

show the kernel functions g_1 and g_2 for the case of $\kappa_p = 5$ and $\kappa_p = 2.5$, respectively.

The initial function describes the situation when a signal arrives at the beginning of the reaction network. This is described with the following sigmoid function in the species X_1 and X_2

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

while the initial concentration of the final complex X_3 is zero. This situation is depicted in Fig. 8.

Fig. 10 and Fig. 9 depict the dynamic evolution of the major state variables x_1, x_2, and x_3 from the initial conditions in Fig. 8 with different parameters. Fig. 6 and Fig. 7 show the corresponding kernel functions.

4. CONCLUSION

In this paper CRNs containing linear reaction chains with multiple joint complexes were considered in order to develop a method for reducing the number of state variables (corresponding to the intermediate complexes). An equivalent reduced order delayed CRN model was proposed by introducing distributed time delays.

Our method (presented in Lipták and Hangos (2018)) of decomposing the chains of linear reactions with multiple joint complexes was used together with the "linear chain trick". This way a dynamically equivalent but reduced CRN model with distributed time delays was obtained. The kernel function of the distributed delays can be computed from the reaction rate coefficients of the reactions of the linear reaction chains.

Our approach was demonstrated using the example of the well known McKeithan's network model of kinetic proofreading. The distributed delay version of McKeithan's network with N intermediate was derived, and the analytical expressions for the kernel functions of the distributed delays were derived. The we compared the dynamics of the original and the distributed delay version of McKeithan's network using simulation in the time domain, and indeed the same response was obtained.

Further work includes the generalization of our model reduction method to cover process systems with spatially distributed mechanisms (such as convection), that may
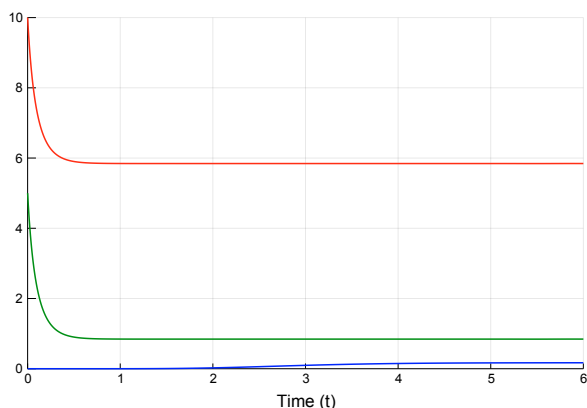
Fig. 10. Time plot of the dynamic response of the McKeithan's network when the parameters are same as in Fig. 10 with the exception of one parameter $\kappa_p = 2.5$. The blue, green, and red lines show the values of x_1, x_2, and x_3, respectively.

lead to apply bi-directional chains of reactions when diffusion is also present on the original model.

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