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Structural reduction of CRNs with linear sub-CRNs

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Abstract: A novel systems theory-based structural reduction method is proposed in this paper that can be applied to chemical reaction networks (CRNs) including subsystems consisting of linear reactions, i.e. a linear sub-CRN. The reduced model is a delayed CRN with distributed delays having less complexes (monomials) and reactions than the original model. The reduction is based on the fact that the input/output response of a linear sub-CNR can be seen as a time-delayed input to output relationship, therefore linear sub-CNRs can be interpreted as reactions with distributed delay from their input to their output complexes. The practically important example of a kinetic model describing the spread of the COVID-19 epidemic is used as a case study to illustrate the basic concepts and the computation method.

Keywords: Delay; Model reduction; Chemical Reaction Networks; COVID

1. INTRODUCTION

Mathematical models of complex nonlinear systems derived from engineering principles often have a large number of state variables and a complicated nonlinear structure 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.

Kinetic systems, also called chemical reaction networks (CRNs) cover a large set of nonlinear nonnegative systems, and their associated directed graph structure (i.e., the reaction graph) can be successfully used in dynamical analysis and even in control design [Sontag, 2001, Chellaboina et al., 2009]. Due to the possible complexity of interactions and the large graph size in biochemical applications, several effective model reduction methods have been proposed utilizing special model properties (see, [Hangos, 2010] for a review). A significant part of the approaches use the multi-scale 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.

A possible 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]. This approach and the so called chain method used for approximating finite delays with a chain of linear reactions (see e.g. Repin [1965] or Krasznai et al. [2010]) show that these linear reaction chains can be reduced to a single reaction between the starting and the ending complex of the chain equipped with a distributed delay. Our earlier work (see [Lipták and Hangos, 2018] and [Lipták and Hangos, 2019]) generalizes these results for arbitrary connected chains of irreversible linear reactions.

Kinetic models often contain linear subsystems of significant size due to e.g., degradations, first order reactions or simple transitions between different compartments. A typical example of these is the presence of linear reaction chains both with reversible and irreversible linear reactions. Therefore, the aim of the present work is to extend

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the above mentioned results to the case of arbitrary linear connected subsystems within a CRN model structure.

2. BASIC NOTIONS

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

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 chemical reactions. An *elementary reaction step* R has the form

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

where C and C' are the source and product complexes, respectively. They are defined by the linear combinations of the species $C = \sum_{i=1}^{n} \eta_i X_i$ and $C' = \sum_{i=1}^{n} \eta'_i X_i$ where the nonnegative integer vectors η and η' are called stoichiometric coefficients. The positive real number κ is the reaction rate coefficient. Therefore, a CRN can be described by the set of stoichiometric coefficients/complexes $\mathcal{C} \subset \overline{\mathbb{R}}_+^n$ and the set of reactions $\mathcal{R} \subset \mathcal{C} \times \mathcal{C} \times \mathbb{R}_+$.

The *reaction rate* ρ of the reaction R_k obeying the so-called *mass action law* can be described as

$$\rho(x) = \kappa \prod_{i=1}^{n} x_i^{\eta_i} = \kappa x^{\eta}, \tag{1}$$

where $x(t) \in \overline{\mathbb{R}}_+^n$ is the concentration of species.

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

$$\dot{x}(t) = \sum_{(\eta,\eta',\kappa)\in\mathcal{R}} \kappa\, x(t)^{\eta}\, [\eta' - \eta]\,. \tag{2}$$

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 between $C \in \mathcal{C}$ and $C' \in \mathcal{C}$ then there is an edge in the reaction graph between the complexes C and C' with the corresponding 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

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

and the corresponding reaction graph 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 the reaction rate of enzyme-catalyzed reactions deviate from the mass action law such that there is a time delay between the availability of the reactants and the starting of the reaction itself. 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.*

Reactions with constant delays 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

$$\dot{x}(t) = \sum_{(\eta,\eta',\kappa,\tau)\in\mathcal{R}} \kappa\, [x(t-\tau)^{\eta}\, \eta' - x(t)^{\eta}\, \eta]\,. \tag{3}$$

In the special case, when each τ is zero, the DDEs of the delayed CRN (3) reduces to the ODEs of the non-delayed CRN model (2).

Solutions of (3) are generated by initial data $x(t) = \theta(t)$ for $-\overline{\tau} \le t \le 0$, where $\overline{\tau}$ is the maximum delay and θ is a nonnegative vector-valued continuous initial function over the time interval $[-\overline{\tau}, 0]$.

Reaction graph with constant 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 the 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., 2018] for this class, too.

Reactions with distributed delays We can further extend CRN models with delays if we consider that the delay associated to a reaction is not a real number, but it has a distribution given by the so called *distribution functions* or *weighting kernels* $g : (-\infty, 0] \to [0, \infty)$, are piecewise continuous functions satisfying

$$\int_{-\infty}^{0} g(r)\, dr = 1.$$

Then the delay differential equation that describes the dynamics of a *CRN with distributed delay* is an integro-differential equation

$$\dot{x}(t) = \sum_{(\eta,\eta',\kappa,\tau)\in\mathcal{R}} \kappa \left[\int_{-\infty}^{0} g(r) x(t+r)^{\eta}\, ds\, \eta' - x(t)^{\eta}\, \eta \right]. \tag{4}$$

Similarly to the constant time delay case, we can extend the reaction graph of a CRN to have a directed and labelled multigraph, where the label of an edge is not only the reaction rate constant, but also the distribution function.

3. STRUCTURAL REDUCTION OF CRNS WITH LINEAR SUB-CRNS

3.1 Linear connecting sub-CRNs

We start with defining sub-CRNs with different properties.

Definition 2. (sub-CRN). Let us assume a CRN given by its complexes $\mathcal{C}$ and reactions $\mathcal{R}$. Then, for a given subset of complexes $\mathcal{C}_{sub} \subseteq \mathcal{C}$, we can define a sub-CRN with its complexes $\mathcal{C}_{sub}$, and reactions $\mathcal{R}_{sub}$, such that

$$\mathcal{R}_{sub} = \{(C, C', \kappa) \in \mathcal{R} \mid C, C' \in \mathcal{C}_{sub}\}.$$

Definition 3. (Entrance and exit of a sub-CRN). Let us assume a sub-CRN given by its complexes $\mathcal{C}_{sub}$ and reactions $\mathcal{R}_{sub}$. Then we can define the entrance $\mathcal{R}_{sub,in}$, and exit reactions $\mathcal{R}_{sub,out}$ such that

$\mathcal{R}_{sub,in} = \{(C, C', \kappa) \in \mathcal{R} \mid C \in \mathcal{C} \setminus \mathcal{C}_{sub}, \text{ and } C' \in \mathcal{C}_{sub}\}$,
$\mathcal{E}_{sub} = \{C \mid \exists\, (C, C', \kappa) \in \mathcal{R}_{sub,in}\}$,
and
$\mathcal{R}_{sub,out} = \{(C, C', \kappa) \in \mathcal{R} \mid C \in \mathcal{C}_{sub}, \text{ and } C' \in \mathcal{C} \setminus \mathcal{C}_{sub}\}$,
$\mathcal{X}_{sub} = \{C' \mid \exists\, (C, C', \kappa) \in \mathcal{R}_{sub,out}\}$,
respectively, where $\mathcal{E}_{sub}$ and $\mathcal{X}_{sub}$ are the sets of entrance and exit complexes.

Definition 4. (Independent sub-CRNs). Let us assume two sub-CRNs such that their source complexes (the complexes that appear only as reactants in the reactions) do not have any common species. Then, we say that two sub-CRNs are independent.

Definition 5. (Complementary sub-CRN). Let us assume a sub-CRN given by its complexes $\mathcal{C}_{sub}$ and reactions $\mathcal{R}_{sub}$. Then, we define the complementary sub-CRN such that $\mathcal{C}_{sub,c} = \mathcal{C} \setminus \mathcal{C}_{sub}$ and $\mathcal{R}_{sub,c} = \mathcal{R} \setminus (\mathcal{R}_{sub} \cup \mathcal{R}_{sub,in} \cup \mathcal{R}_{sub,out})$.

Definition 6. (Linear sub-CRN). Let us assume a sub-CRN given by its complexes $\mathcal{C}_{sub}$ and reactions $\mathcal{R}_{sub}$. We call a sub-CRN as a linear sub-CRN if each complex in $\mathcal{C}_{sub}$ is a one-specie complex.

3.2 State space description and decomposition

Assume we have a CRN $(\mathcal{C}, \mathcal{R})$ and it has a linear sub-CRN $(\mathcal{C}_L, \mathcal{R}_L)$ with the complementary sub-CRN $(\mathcal{C}_{L,c}, \mathcal{R}_{L,c})$. Furthermore, we assume that $(\mathcal{C}_L, \mathcal{R}_L)$ and $(\mathcal{C}_{L,c}, \mathcal{R}_{L,c})$ are independent. Therefore, we can partition the states into $x_{L,c}$ and x_L, without loss of generality. This partition decompose the original dynamics system into two parts

$$\begin{aligned} \dot{x}_{L,c}(t) = & \sum_{(\eta,\eta',\kappa)\in\mathcal{R}_{L,c}} \kappa\, x_{L,c}(t)^{\eta}\, [\eta' - \eta] \\ & - \sum_{(\eta,\eta',\kappa)\in\mathcal{R}_{L,in}} \kappa\, x_L(t)^{\eta}\, \eta \\ & + \sum_{(\eta,\eta',\kappa)\in\mathcal{R}_{L,out}} \kappa\, x_{L,c}(t)^{\eta}\, \eta', \end{aligned} \tag{5}$$

and

$$\begin{aligned} \dot{x}_L(t) = & \sum_{(\eta,\eta',\kappa)\in\mathcal{R}_{L}} \kappa\, x_{L}(t)^{\eta}\, [\eta' - \eta] \\ & + \sum_{(\eta,\eta',\kappa)\in\mathcal{R}_{L,in}} \kappa\, x_{L,c}(t)^{\eta}\, \eta' \\ & - \sum_{(\eta,\eta',\kappa)\in\mathcal{R}_{L,out}} \kappa\, x_{L}(t)^{\eta}\, \eta. \end{aligned} \tag{6}$$

The second equation (6) is a linear sub-system with constant parameters, so we can write its dynamics in an LTI from such that

$$\begin{aligned} \dot{x}_L(t) &= A_L x_L(t) + B_L u_L(t), \\ y_L(t) &= C_L x_L(t). \end{aligned} \tag{7}$$

3.3 Structural reduction in the SISO case

In this subsection, we consider the simple case, when the independent linear sub-CRN has only one entrance, and one exit. In that case, we have the following reaction

$$C \xrightarrow{\kappa} \text{ Linear sub-CRN } \longrightarrow C'. \tag{8}$$

We can represent this subsystem with a SISO LTI

$$\dot{x}_L = A_L x_L + B_L u_L \;\;,\;\; y_L = C_L x_L. \tag{9}$$

We are interested in the input-output behavior of this SISO LTI system that can be obtained by using its impulse response function h_L in the following form

$$y_L(t) = \int_0^t h_L(t-\tau) u_L(\tau) d\tau \;\;,\;\; h_L(t) = C_L e^{A_L t} B_L. \tag{10}$$

In the structural reduction, we simplify the reaction graph (8) by replacing the sub-CRN with a distributed delay reaction such that

$$C \xrightarrow{\overline{\kappa},\, g} C',$$

where the delay distribution function g is given by using the impulse response function of the linear sub-CRN as follows

$$g(r) = \frac{h_L(-r)}{\int_0^{\infty} h_L(\tau) d\tau},$$

and

$$\overline{\kappa} = \kappa \int_0^{\infty} h_L(\tau) d\tau.$$

In the next subsections, we show three special cases of this reduction.

Linear irreversible homogeneous reaction chains The simplest linear sub-CRN is a stand alone linear irreversible homogeneous reaction chain with a uniform reaction rate constant $v > 0$, where we can compare our approach to the well known "linear chain trick" from the literature (see e.g. Repin [1965] or Krasznai et al. [2010]).

The reaction graph is in the form

$$C \xrightarrow{\kappa} X_1 \xrightarrow{v} X_2 \xrightarrow{v} \cdots \xrightarrow{v} X_N \xrightarrow{v} C'.$$

where the single specie complexes $X_1, X_2, \ldots, X_N$ form the linear sub-CRN.

Let us model the dynamics of a reaction chain with an LTI state space model, where the concentration at the entrance reaction is considered as its *input*, and the concentrations of the linear complexes $x_{L,i}(t)$ are the state variables. The *output* is the exit reaction, i.e. $y_L(t) = vx_{L,N}(t)$.

The state space matrices of the linear sub-CRN (9) has the form

$$A_L = \begin{bmatrix} -v & 0 & \cdots & \cdots & \cdots & 0 \\ v & -v & 0 & \cdots & \cdots & 0 \\ 0 & v & 0 & 0 & \cdots & 0 \\ & & \vdots & & & \\ 0 & \cdots & \cdots & v & -v & 0 \\ 0 & \cdots & \cdots & 0 & v & -v \end{bmatrix}, \; B_L = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

$$C_L = [\,0\;0\;\ldots\;v\,].$$

In this special case, the impulse response function h_L can be analytically derived using the inverse Laplace transform $\mathcal{L}^{-1}$ of the transfer function $H_L(s) = C_L(sI - A_L)^{-1}B_L$ This results in the following transfer function

$$H_L(s) = \frac{v^N}{(s+v)^N}.$$

From this we obtain for the impulse response function

$$h_L(t) = \mathcal{L}^{-1}[H_L(s)] = \frac{v^N}{(N-1)!}t^{N-1}e^{-vt}.$$

We can compare the above impulse response function with the one obtained by using the well known linear chain trick for the chain of linear irreversible reactions. *It is seen that h_L is a Gamma distribution function.*

Note that the well-known "linear chain trick" (see e.g. Repin [1965] or Krasznai et al. [2010]) from the theory of delay differential equations (DDEs) establishes an *equivalence* between a set of linear ODEs and a DDE with Gamma distribution function. This coincides with the above result.

Generalization to linear inhomogeneous irreversible reaction chains Let us now consider the inhomogeneous case of stand alone linear irreversible reaction chains with the following reaction graph

$$C \xrightarrow{\kappa} X_1 \xrightarrow{v_1} X_2 \xrightarrow{v_2} \cdots \xrightarrow{v_{N-1}} X_N \xrightarrow{v_N} C'.$$

The state space matrices of the linear sub-CRN (9) have the form

$$A_L = \begin{bmatrix} -v_1 & 0 & \cdots & \cdots & \cdots & 0 \\ v_1 & -v_2 & 0 & \cdots & \cdots & 0 \\ 0 & v_2 & 0 & 0 & \cdots & 0 \\ & & \vdots & & & \\ 0 & \cdots & \cdots & v_{N-2} & -v_{N-1} & 0 \\ 0 & \cdots & \cdots & 0 & v_{N-1} & -v_N \end{bmatrix}, \; B_L = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix},$$

$$C_L = [\,0\;0\;\ldots\;v_N\,].$$

The transfer function of this model is

$$H_L(s) = \prod_{i=1}^{N} \frac{v_i}{s+v_i}.$$

Assuming that all reaction rate constants $v_i > 0$ are different, the kernel function of the equivalent distributed delay model is a sum of exponential functions

$$h_L(t) = \mathcal{L}^{-1}[H_L(s)] = \sum_{i=1}^{N} \pi_i e^{-v_i t},$$

where the coefficients π_i are positive constants.

Generalization to linear reversible reaction chains Let us consider a chain of linear reversible reactions with an initial irreversible step with the following reaction graph

$$C \xrightarrow{\kappa} X_1 \underset{d_1+v_1}{\overset{d_1}{\rightleftharpoons}} \ldots \underset{d_{N+1}+v_{N+1}}{\overset{d_{N+1}}{\rightleftharpoons}} X_N \xrightarrow{d_N+v_N} C'.$$

Note that the homogeneous case is obtained when $d_i = d,\; v_i = v$ for $i = 1, ..., N$.

In this case, the state space matrices in the linear sub-CRN (9) are in the form

$$A_L = \begin{bmatrix} -(d_1+v_1) & d_1 & \cdots & 0 \\ d_1+v_1 & -(d_1+d_2+v_2) & \cdots & 0 \\ 0 & d_2+v_2 & \cdots & 0 \\ & & \ddots & \\ 0 & \cdots & \cdots & 0 \\ 0 & \cdots & \cdots & d_{N-1} \\ 0 & \cdots & \cdots & -(d_{N-1}+d_N+v_N) \end{bmatrix}$$

$$B_L = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \; C_L = \begin{bmatrix} 0 & 0 & \ldots & d_N+v_N \end{bmatrix}.$$

Here we can only have the general analytical expression $h_L(t) = C_L e^{A_L t} B_L$ for the impulse response function, where the equivalent chemical reaction with distributed delay can be obtained by straightforward numerical computations. Note that A_L is a Metzler compartmental matrix (weakly diagonally dominant with nonnegative off-diagonal elements). Therefore, its the matrix exponential can be computed analytically [Varon et al., 2012].

The following figure (Fig. 1) shows different kernel (impulse response) functions in the homogeneous case obtained with different v and d values.

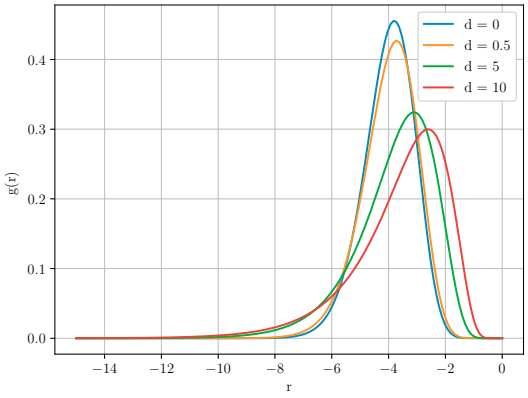

Fig. 1. Distribution functions of different linear reversible reaction chains

3.4 Structural reduction in the MIMO case

We have already seen in subsection 3.3 that a linear independent sub-CRN $\mathcal{S}_{CRN}$ with one entrance and one exit

can be substituted with a distributed delayed reaction. We can generalize this idea to the case of multiple entrances and multiple exits in a straightforward way.

We consider the product of entrance and exit reactions $\mathcal{R}_{in,out} = \mathcal{R}_{L,in} \times \mathcal{R}_{L,out}$. We have for each $(C_{in}, C'_{in}, \kappa_{in}, C_{out}, C'_{out}, \kappa_{out}) \in \mathcal{R}_{in,out}$ a corresponding impulse response function h. When $\int_0^\infty h_L(\tau)d\tau > 0$, there will be a distributed delay reaction

$$C_{in} \xrightarrow{\overline{\kappa}, g} C'_{out}$$

with the distribution function

$$g(r) = \frac{h_L(-r)}{\int_0^\infty h_L(\tau)d\tau},$$

and reaction rate coefficient

$$\overline{\kappa} = \kappa \int_0^\infty h_L(\tau)d\tau.$$

4. CASE STUDY: A DISTRIBUTED DELAY CRN MODEL OF THE COVID-CRN SYSTEM

By using the structural reduction method in Section 3 one can derive a distributed delay CRN model of the COVID-CRN system.

4.1 A simple CRN model of the COVID infection system

A simple CRN type dynamic model of the COVID infection mechanism [Péni et al., 2020] is as follows.

$$\begin{aligned}
\dot{S}(t) &= -\beta\left[P(t) + I(t) + \delta A(t)\right] S(t)/N \\
\dot{L}(t) &= \beta\left[P(t) + I(t) + \delta A(t)\right] S(t)/N - \alpha L(t) \\
\dot{P}(t) &= \alpha L(t) - pP(t) \\
\dot{I}(t) &= qpP(t) - \rho_I I(t) \\
\dot{A}(t) &= (1-q)pP(t) - \rho_A A(t) \\
\dot{H}(t) &= \rho_I \eta I(t) - hH(t) \\
\dot{R}(t) &= \rho_I(1-\eta)I(t) + \rho_A A(t) + (1-\mu)hH(t) \\
\dot{D}(t) &= \mu h H(t)
\end{aligned} \tag{11}$$

where the state variables represent the following compartments. S: susceptible, L: latent (not yet infectious), P: pre-symptomatic infectious, I: symptomatic infected, A: asymptomatic, H: hospitalized, R: recovered, D: deceased.

The model parameters were determined using the epidemic data in Hungary (see, Péni et al. [2020]) and have the following values: $\alpha = 0.4$, $p = \beta = 0.33$, $\delta = 0.75$, $\rho_A = \rho_I = 0.25$, $\mu = 0.145$, $N = 9800000$, $h = 0.1$, $q = 0.6$, $\eta = 0.076$.

Fig. 2 shows the reaction graph of a simple CRN form model that describes the dynamics of COVID infection above, with the following reaction rate constants

$$\begin{aligned}
&k_P = \alpha\ , \quad k_A = (1-q)p\ , \quad k_I = qp\ , \quad k_H = \rho_I \\
&k_{1R} = \rho_A\ , \ k_{2R} = (1-\eta)\rho_I\ , \ k_{3R} = (1-\mu)h\ , \ k_D = h
\end{aligned} \tag{12}$$

One can define two possible linear sub-CRNs of the above model.

(1) The full line rectangle depicts a linear sub-CRN $\mathcal{S}^{(1)}_{CRN}$ from the complex **L** (concentration of latent infected people) to the complex **D** (concentration of dead people).

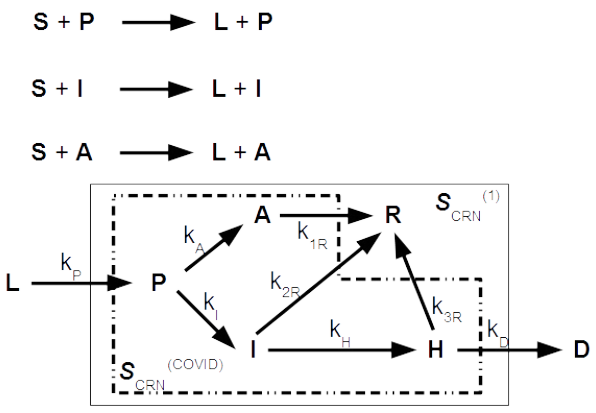

Fig. 2. The reaction graph of a simple COVID-CRN model and two of its linear sub-CRNs

(2) The dashed polygon is also a linear sub-CRN $\mathcal{S}^{(COVID)}_{CRN}$ with its entrance $\mathcal{E}_L = \{\mathbf{L}\}$ and but with an extended exit $\mathcal{X}_L = \{\mathbf{R}, \mathbf{D}\}$.

4.2 Model structure

The reaction graph of the COVID-CRN model in Fig. 2 contains a linear sub-CRN $\mathcal{S}^{(COVID)}_{CRN}$ (depicted by a dash-dotted polygon) that connects the complex **L** to the two exit complexes **R** and **D**. Therefore, we can develop a reduced model of this connecting sub-CRN using two reactions:

$$\mathbf{L} \xrightarrow{\kappa_1, g_1} \mathbf{R} \quad , \quad \mathbf{L} \xrightarrow{\kappa_{COVID,D}, g_{COVID,D}} \mathbf{D} \tag{13}$$

Furthermore, Fig. 2 shows, that the reaction graph of the linear sub-CRN $\mathcal{S}^{(COVID)}_{CRN}$ contains only connected chains of irreversible linear reactions.

4.3 Decoupling the reaction chains

The structure of the model enables to apply the decoupling and reducing method presented in [Lipták and Hangos, 2018] and [Lipták and Hangos, 2019] to decompose the chains from the complex L to D and R. The decomposition can be started from the complex **H** at the end of the chain and we proceed backwards towards complex **P**.

Fig. 3 shows the decoupled independent chains of linear reactions in the connecting sub-CRN. The reaction rate constants of the decomposed model are as follows

$$\begin{aligned}
&k_{HS} = k_D + k_{3R}\ , && k_{IS} = k_H + k_{2R}\ , \\
&k_{PS} = k_A + k_I\ , \\
&k_{P1} = \frac{k_P}{k_{PS}} k_A\ , && k_{P2} = \frac{k_P}{k_{PS}} \frac{k_I}{k_{IS}} k_{2R}\ , \\
&k_{P3} = \frac{k_P}{k_{PS}} \frac{k_I}{k_{IS}} \frac{k_H}{k_{HS}} k_{3R}\ , && k_{P4} = \frac{k_P}{k_{PS}} \frac{k_I}{k_{IS}} \frac{k_H}{k_{HS}} k_D
\end{aligned} \tag{14}$$

4.4 The parameters of the delayed reaction from **L** *to* **D**

There is only one stand alone reaction chain that connects complex **L** to **D** that is linear, irreversible and inhomogeneous. So we can use the results in subsection 3.3.2 to

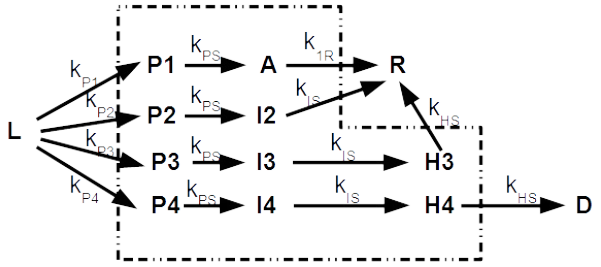

Fig. 3. The decoupled reaction graph of a linear connecting sub-CRN in the COVID-CRN model

obtain the reduced delayed single reaction parameters. The transfer function is now

$$H_{COVID,D}(s) = \frac{k_{P4}}{(s+k_{PS})}\frac{k_{PS}}{(s+k_{IS})}\frac{k_{IS}}{(s+k_{HS})} \qquad (15)$$

Here we can assume that all reaction rate constants k_* are different, so the kernel function of the equivalent distributed delay model is a sum of exponential functions:

$$g_{COVID,D}(t) = \mathcal{L}^{-1}[H_{COVID,D}(s)] = \\ = \pi_1 e^{-k_{PS}t} + \pi_2 e^{-k_{IS}t} + \pi_3 e^{-k_{HS}t} \qquad (16)$$

and $\kappa_{COVID,D} = k_{P4}$ using the parameters in Eq. (14).

4.5 Discussion

We note that the linear sub-CRN $\mathcal{S}_{CRN}^{(COVID)}$ is not independent, as the first equation in the model (11) contains the concentrations of the species **P**, **I** and **A** from the linear sub-CRN. However, these concentrations cannot be measured in practice, so the obtained reaction $\mathbf{L} \xrightarrow{\kappa_{COVID,D}, g_{COVID,D}} \mathbf{D}$ with distributed delay can be applied to construct a simple and numerically stable state estimator for **P** from the measured values of the concentration of specie **D**.

5. CONCLUSIONS

A structure reduction method is proposed in this paper that can be applied to kinetic models with linear independent sub-CRNs consisting of linear reactions. Based on the input-output description of the linear sub-CRNs, the proposed method reduces them into a single reaction with distributed time delay. Therefore, one obtains a delayed CRN with possibly different distributed delays but with less complexes and reactions than the original model.

We emphasize that the result of this reduction is not an approximation of the original model, since the input-output dynamics of the reduced system is the same as that of the original model.

A previously published simple kinetic model of epidemic spread is used as a case study to illustrate the basic concepts and the reduction method.

Further work will be directed to use the reduced complex structures for dynamic analysis and controller design.

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