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Modeling and control of networked kinetic systems with delayed interconnections

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ABSTRACT

The modeling and control of networks of kinetic systems, also called chemical reaction networks (CRNs), containing distributed delays are considered in this paper. The nodes in the network are sub-CRNs with nonnegative nonlinear dynamics, while the interconnections are modeled as linear connecting CRNs. Distributed delays appearing in the system are described as physically motivated connecting sub-CRNs with asymptotically stable linear compartmental dynamics. A control model is given for the studied system class, where the manipulable inputs are selected inlet concentrations, and the control goal is to achieve global stability by ensuring the complex balanced property of the closed loop system. Besides stabilization, the tracking of prescribed setpoints is also solved using a suitable decentralized feedforward-feedback combination. The operation of the proposed method is illustrated through a network containing three sub-CRNs and several linear interconnections.

1. Introduction

Chemical reaction networks (abbreviated as CRNs) cover a large set of nonlinear polynomial 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 [1,2]. Kinetic models are also universal in the sense that a wide class of possibly complex nonlinear dynamics can be directly transformed or embedded into kinetic form [3,4]. Although kinetic systems are also applied in ecological or transport systems modeling, their primary application areas are biochemical, chemical, and process systems.

CRNs with complex hierarchical structure. In biochemical systems, one often has to face a large number of chemical species reacting over a complicated network of biochemical reactions. Therefore, sub-network based approaches have been successfully used for the simplification of dynamical analysis (see, e.g. [5,6]) Moreover, such complex chemical reaction networks taking place e.g. in a living cell, often have parts that occur in different compartments, i.e. (balance) volumes that are connected by transport channels. In [7], delayed compartmental systems (which form a special subset of kinetic systems) are studied by representing distributed delays as compartmental subsystems without lags and thus forming a network with a hierarchical structure. Networked kinetic systems with sub-CRNs in different compartments in the context of systems biology have also started to gain attention (see e.g. a recent paper [8]), where the connections between compartments with different spatial arrangements and their effect on the reaction rate laws are analyzed. A systematic model-reduction method based on the removal of appropriately selected subnetworks of CRNs is proposed in [9], where it is also proved that under certain topological conditions, the reduced network preserves the steady state of the original model. A network decomposition method for stability analysis is given in [10], where a general CRN is decomposed into a complex balanced subnetwork and several one or two-species subnetworks.

Delayed dynamical systems and CRNs. It is well-known that the explicit modeling of time delays is often necessary to describe dynamical processes with sufficient precision [11]. Some examples are traffic models with delayed reactions of drivers, communication delays in control systems, or delayed growth of bacteria and other populations [12]. In many cases, for example in several biological applications, the use of distributed delay is more realistic from a modeling point of view than a constant point-wise (also referred to as discrete) delay [13]. In such cases, the delay depends on the weighted average over past values of the state variables. It has been long noticed in chemical reaction networks, in particular enzyme kinetics, that the reaction rate of enzyme-catalyzed reactions deviates from the mass action law such

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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 has been extended by introducing delays into the dynamics of the reactions (see e.g. [14] or [15]), where examples of such kinetic schemes can also be found. Besides 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 [16]) or slow inter-cellular convection can also be considered as the cause of the apparent delays. In addition, the usual transport mechanisms (convection, diffusion, and transfer) that are linear and obey conservation laws can also cause apparent delays in CRNs.

Although the presence of delays may destabilize otherwise stable systems, one can show that complex balanced CRNs with arbitrary time delays remain at least locally asymptotically stable [17,18]. These results were extended in [19] using the notion of linear conjugacy. Persistence has a key role in proving global stability of CRN dynamics [20] which is also true in the delayed case [21]. In [22], important conditions were given for the persistence of complex balanced CRNs with time delay using semilocking sets. A graph theoretical condition is given in [23] for the stability of linearized delay networks, which is independent both of rate constants and delay parameters.

Stability and control of CRNs. It was shown in several publications that the entropy-like Lyapunov function candidate, called the 'pseudo-Helmholtz' function [24] can be used as a control Lyapunov function when designing stabilizing feedback for kinetic and nonnegative systems. A linear input structure representing inflow control is assumed in [1], and it is shown that any positive equilibrium can be globally stabilized with appropriate linear state feedback if the number of independent inputs is large enough. A straightforward approach for control is to transform a dynamical system into a (robustly) stable kinetic system via feedback. In this framework, a nonlinear state feedback control design method based on optimization is proposed in [25] for the stabilization of polynomial systems with linear input structure that results in a closed loop system with a complex balanced or weakly reversible realization. This methodology was extended for general polynomial systems with time delay in [25]. A balanced shaping method for finding stabilizing state feedbacks for open mass action systems is given in [26], where the stability of the closed loop system is also proved using the pseudo-Helmholtz Lyapunov function.

Networks of dynamic systems. In many control applications, it is useful to divide a large-scale system [27] into interconnected subsystems [28]. The partitioning can be done using natural principles, or it can yield from engineering design. The control of cyclically interconnected nonlinear systems was discussed in [29]. A review of distributed control approaches for interconnected chemical processes was performed in [30]. The synchronization of passive nonlinear networks having discrete delays in the interconnections was discussed in [31]. Networked CRNs with special conservative network structures enable the development of efficient distributed controller design based on passivity analysis [32]. The synchronization conditions for a general class of networks of nonlinear systems were presented in [33] with biochemical network applications.

Aim and research highlights. The aim of this paper is to give a networked control model for interconnected nonnegative systems described as CRNs containing distributed delays and to propose a novel approach for setpoint tracking nonlinear control.

The main contributions of this study can be summarized as follows:

- A modeling approach is introduced for interconnected CRNs in which the delays in interconnections are distributed. In the model, the delay effects are approximated by physically motivated asymptotically stable linear time-invariant compartmental dynamic systems.
- A comprehensive stabilizing nonlinear feedback design is proposed to ensure the stability of networks of CRNs with distributed delay.
- It is shown that, by suitably extending the stabilizing control for CRN networks, the states of the CRNs can be driven into prescribed setpoints.

2. Delayed dynamical systems and chemical reaction networks

We briefly summarize the most important basic notions on delayed dynamical systems and chemical reaction networks in this section.

2.1. Dynamical models with distributed delay

The general form of delayed differential equations (DDEs) is given by

$$\dot{\mathbf{x}}(t) = F(\mathbf{x}(t), \mathbf{x}_t) \tag{1}$$

where $\mathbf{x} \in \mathbb{R}^n$ is the state variable, $\mathbf{x}_t$ is the delay function, and $F : \mathbb{R}^n \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$. The simplest possibility is a constant delay of $\tau > 0$ when $\mathbf{x}_t = \mathbf{x}(t-\tau)$. In the case of distributed time delays, the delay function is written as

$$\mathbf{x}_t = \int_0^\infty g(s)h(\mathbf{x}(t-s))ds = \int_{-\infty}^t h(\mathbf{x}(s))g(t-s)ds \tag{2}$$

where $h : \mathbb{R}^n \longrightarrow \mathbb{R}^n$, and $g : \mathbb{R}_0^+ \longrightarrow \mathbb{R}$ is the *delay kernel* which is assumed to be at least piecewise continuous [13]. Without the loss of generality, we can assume that $\int_0^\infty g(s)ds = 1$.

Although the convolution in Eq. (1) is not the same as the causal convolution used for computing the output of LTI (Linear Time-Invariant) systems, asymptotically stable linear subsystems of nonlinear models can be described as distributed delays as follows (see [34], Section 7 for the details). Consider the model

$$\dot{\mathbf{x}} = f(\mathbf{x}, \mathbf{x}_I) \tag{3}$$

$$\dot{\mathbf{x}}_I = A\mathbf{x}_I + B\mathbf{x} \tag{4}$$

where $\mathbf{x}(t) \in \mathbb{R}^n$, $\mathbf{x}_I(t) \in \mathbb{R}^m$, $f : \mathbb{R}^n \longrightarrow \mathbb{R}^n$ is a smooth function, $A \in \mathbb{R}^{m\times m}$ is Hurwitz stable, and $B \in \mathbb{R}^{m\times n}$. Then the linear subsystem (4) can be substituted by the distributed delay term given by

$$\mathbf{x}_I(t) = \int_{-\infty}^t G(t-s)\mathbf{x}(s)ds \tag{5}$$

where $G(s) = (sI - A)^{-1}B$ is the transfer function matrix of the linear subsystem (4).

2.2. Dynamical models of CRNs

A CRN obeying the mass action law is a closed system where chemical species $X_1, X_2, \dots, X_n$ 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, that are 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 $\eta, \eta' \in \overline{\mathbb{N}}_+^n$ are called stoichiometric coefficients, and $\overline{\mathbb{N}}_+^n$ denotes the set of n-dimensional vectors with nonnegative integer entries. The positive real number κ is the reaction rate coefficient. Therefore, a CRN can be described by the set of stoichiometric coefficients/complexes $\mathcal{C} \subset \overline{\mathbb{N}}_+^m$ and the set of reactions $\mathcal{R} \subset \mathcal{C} \times \mathcal{C} \times \mathbb{R}_+$:

$$CRN = (\mathcal{C}, \mathcal{R}) \quad , \quad \mathcal{R} = \{(C, C', \kappa) \mid C, C' \in \mathcal{C}\} \tag{6}$$

The set of species $\mathcal{S}_\mathcal{C}$ contains all the species X_i, $i = 1, \dots, n$ that are present in the complexes $\mathcal{C}$.

Let us introduce the following notations. For any matrix M, $M_{i,\cdot}$ and $M_{\cdot,j}$ denotes the ith row and jth column of M, respectively. For $x, y \in \mathbb{R}^n$ and $Y \in \mathbb{R}^{n\times m}$, $x^y = \prod_{i=1}^n x_i^{y_i}$, and

$$x^Y = \begin{bmatrix} cx^{Y_{\cdot,1}} \\ \vdots \\ x^{Y_{\cdot,m}} \end{bmatrix}$$

Definition 1 (*Complex Variable*)**.** A complex variable φ associated to the complex $C \in \mathcal{C}$ of a CRN with the stoichiometric vector η is a reaction monomial

$$\varphi(\mathbf{x}) = \mathbf{x}^\eta \tag{7}$$

where $\mathbf{x}_i$ is the concentration of the ith specie in the specie set $\mathcal{S}_C$.

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

$$\rho_k(\mathbf{x}) = \kappa_k \mathbf{x}^{\eta^{(k)}} = \kappa_k \varphi_k(\mathbf{x}), \tag{8}$$

where $\mathbf{x}(t) \in \overline{\mathbb{R}}_+^n$ is the concentration vector of species, and $\eta^{(k)}$ is the stoichiometric vector corresponding to the source complex of the reaction R_k.

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

$$\dot{\mathbf{x}}(t) = \sum_{k=1}^{r} \kappa_k \mathbf{x}(t)^{\eta^{(k)}} \left[\eta'^{(k)} - \eta^{(k)}\right] = Y A_\kappa \varphi(\mathbf{x}) \,, \tag{9}$$

where r is the number of reactions, $Y \in \overline{\mathbb{N}}_+^{n\times m}$ is the complex composition matrix composed from the stoichiometric coefficient vectors, and $A_\kappa \in \overline{\mathbb{R}}_+^{m\times m}$ is the Kirchhoff matrix of the reaction graph. The entries of the vector function φ are the complex variables of each complex $C \in \mathcal{C}$ of the CRN.

Reaction graph. Similarly to [35] 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.

2.3. CRNs with delays

By a delayed reaction, we mean that the consumption of reactants is immediate, while product formation is delayed in time. If one assumes the presence of delays in chemical reactions, then the usual CRN structure can be extended with elements describing the properties of the delays.

For *distributed time delays* we associate a *kernel function* g to the reaction step and associate it as an additional weight (besides the reaction rate coefficient κ) to the reaction in the reaction graph, as

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

This way the dynamics can be described by *delayed differential equations (DDEs) of the form* (1). When the reaction steps have distributed time delays with kernel/distribution function g_k, satisfying $\int_0^\infty g_k(s)\, ds = 1$ the model (9) becomes

$$\dot{\mathbf{x}}(t) = \sum_{k=1}^{r} \kappa_k \left[\int_0^\infty g_k(s) \mathbf{x}(t-s)^{\eta^{(k)}}\, ds \cdot \eta'^{(k)} - \mathbf{x}(t)^{\eta^{(k)}} \eta^{(k)}\right] \tag{10}$$

2.4. Open CRNs

The usual way of describing open CRNs is to introduce a zero complex with $\eta = \mathbf{0}$, where $\mathbf{0}$ is the zero vector of appropriate dimension. In order to have a more general way of connecting CRNs into a network we generalize this concept and *enable to have a linear time-invariant input from the environment to a CRN* [36].

Then the state equations of the open CRN system in the non-delayed case are in the following form

$$\dot{\mathbf{x}}(t) = \sum_{(\eta,\eta',\kappa)\in\mathcal{R}} \kappa\, \mathbf{x}(t)^\eta \left[\eta' - \eta\right] + F\mathbf{u} = Y A_\kappa \varphi(\mathbf{x}) + F\mathbf{u} \,, \tag{11}$$

where $\mathbf{u}$ is the input vector $\mathbf{u}(t) \in \overline{\mathbb{R}}_+^p$ and $F \in \overline{\mathbb{R}}_+^{n\times p}$ is a *nonnegative matrix*.

Note that the element-wise nonnegativity of the input vector and the coefficient matrix F ensures the nonnegativity of the state variables for nonnegative initial conditions.

The vector of output variables is defined as:

$$\mathbf{y} = H\mathbf{x} \tag{12}$$

where H is a rectangular matrix with non-negative entries.

This way an open CRN has an input-affine state equation with polynomial non-linearities in the state transformation term, and linear input and output transformation terms.

3. Networked representation of CRNs with delays

Networked systems are described by specifying the network nodes and their connections. In networked kinetic systems the network nodes are independent sub-CRNs and the interconnections are defined by linear connecting CRNs or static connections that are described below.

3.1. Sub-CRNs as CRN subsystems

The network nodes in a networked kinetic system are required to be open CRNs themselves. Let us assume that a sub-CRN $CRN^{(j)} = (\mathcal{C}^{(j)}, \mathcal{R}^{(j)})$ with its complexes $\mathcal{C}^{(j)}$ and reactions $\mathcal{R}^{(j)}$ is considered as the jth subsystem-node of a networked kinetic system that is a CRN $(\mathcal{C}, \mathcal{R})$ itself, such that $\mathcal{C}^{(j)} \subseteq \mathcal{C}$ and $\mathcal{R}^{(j)} \subseteq \mathcal{R}$.

Then the state equation of $CRN^{(j)}$ is in the following form (see Eq. (11))

$$\frac{d\mathbf{x}^{(j)}}{dt} = Y^{(j)} A_\kappa^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \sum_{\ell\in\overline{\mathcal{N}}_I^{(j)}} F_\ell^{(j)} \mathbf{u}_\ell^{(j)} \tag{13}$$

where $\mathbf{x}^{(j)}$ is the concentration vector of the species in $\mathcal{S}_{\mathcal{C}^{(j)}}^{(j)}$.

The *set of generalized input neighborhood* $\overline{\mathcal{N}}_I^{(j)}$ of this sub-CRN is defined as

$$\overline{\mathcal{N}}_I^{(j)} = \{C \mid \exists\, (C, C', \kappa) \in \mathcal{R}^{(j)}, \textit{such that}\ \ C' \in \mathcal{C}^{(j)}\}$$

and $\mathbf{u}_\ell^{(j)} \in \mathbb{R}^{m_j}$ are the vectors of input concentration variables that are the *complex variables associated to the complexes* in $\overline{\mathcal{N}}_I^{(j)}$.

An important special case is when convective material flows, described as first order chemical reactions realize the connections between sub-CRNs. Then it is enough to give the set of subsystem indices the output of which is the input of the jth CRN ($CRN^{(j)}$). Then the *input neighborhood set* $\mathcal{N}_I^{(j)}$ is defined as follows:

$$\mathcal{N}_I^{(j)} = \{\ell \mid \exists\, (C, C', \kappa) \in \mathcal{R}^{(j)}, \textit{such that}\ \ C' \in \mathcal{C}^{(j)}\ \ \textit{and}\ \ C = X_I^{(\ell)} \in \mathcal{C}^{(\ell)}\} \tag{14}$$

In order to be able to handle sub-CRNs relatively separately, the notion of independent sub-CRN should be introduced.

Definition 2 (*Independent Sub-CRNs*)**.** A sub-CRN $(\mathcal{C}^{(j)}, \mathcal{R}^{(j)})$ is independent of another sub-CRN $(\mathcal{C}^{(\ell)}, \mathcal{R}^{(\ell)})$ of the same CRN with complex set $\mathcal{C}$ if their complexes $\mathcal{C}^{(j)}$ and $\mathcal{C}^{(\ell)}$ do not have any common species, i.e.

$$\mathcal{S}^{(j)}_{\mathcal{C}^{(j)}} \cap \mathcal{S}^{(\ell)}_{\mathcal{C}^{(\ell)}} = \emptyset .$$

Independent sub-CRNs will also be called **CRN subsystems**.

Remark 1. It is important to remark that independent sub-CRNs often appear in complex kinetic systems. Chemical reactions taking place in different compartments, or reaction chains describing the gradual formation of a reaction complex are common examples.

Linear connecting CRN subsystems. Linear sub-CRNs will serve as dynamic connecting elements between sub-CRNs.

Definition 3 (*Linear CRN Subsystems*)**.** Let us assume a CRN subsystem given by its complexes $\mathcal{C}^{(j)}$ and reactions $\mathcal{R}^{(j)}$. We call a CRN subsystem a linear CRN subsystem if each complex in $\mathcal{C}^{(j)}$ is a one-specie complex.

The dynamics of linear sub-CRNs can be described by LTI state space models of the following form since their reaction rates are single-variable linear functions:

$$\begin{aligned} \frac{d\mathbf{x}^{(j)}}{dt} &= A^{(j)}_{\kappa}\mathbf{x}^{(j)} + B^{(j)}\mathbf{u}^{(j)} \\ \mathbf{y}^{(j)} &= C^{(j)}\mathbf{x}^{(j)}, \end{aligned} \tag{15}$$

where $\mathbf{x}^{(j)}(t) \in \mathbb{R}^n$, $A^{(j)}_{\kappa}$ is a Metzler compartmental matrix, $B^{(j)}$ is a nonnegative matrix, while $C^{(j)}$ is a binary matrix with all its column sums equal to 1. It is easy to see that $Y^{(j)} = I$ and $\varphi^{(j)}$ is the identity mapping in this case.

In order to describe dynamic connections in a networked kinetic system that connect CRN subsystems as nodes, we will use linear CRN subsystems with additional dynamic properties.

Definition 4 (*Linear Connecting CRN Subsystems*)**.** A linear CRN subsystem with an LTI state space realization (15) is called a linear connecting CRN subsystem if it is asymptotically stable, and jointly controllable and observable (i.e., its minimal state space dimension is n).

As linear connecting CRN subsystems are asymptotically stable positive LTI systems, they are BIBO stable both in the SISO and MIMO cases.

Dynamic properties. It is important to notice that networked kinetic systems possessing overall mass conservation have bounded state trajectories (assuming bounded inputs) for all of its CRN subsystems, including linear connecting CRN subsystems.

3.2. Interconnection of CRNs

Consider a connection from the kth CRN subsystem to the jth CRN subsystem, where $\dim \mathbf{u}^{(j)} = p_j$ and $\dim \mathbf{y}^{(j)} = m_j$.

3.2.1. Static connections

If the connection of the subsystems is assumed to be static, then it can be described by the equation

$$\mathbf{u}^{(j)} = \mathbf{L}^{(jk)}\mathbf{y}^{(k)} \tag{16}$$

where $\mathbf{L}^{(jk)}$ is a constant *interconnection matrix* for the connection from subsystem k to subsystem j. The interconnection matrix is a rectangular matrix $\mathbf{L}^{(jk)} \in \mathbb{R}^{p_j \times m_k}$ such that an *elementary connection* from the output $\mathbf{y}^{(k)}_{\ell}$ to $\mathbf{u}^{(j)}_{\lambda}$ is

$$\mathbf{u}^{(j)}_{\lambda} = L^{(jk)}_{\lambda\ell}\mathbf{y}^{(k)}_{\ell} \tag{17}$$

where the scalar $L^{(jk)}_{\lambda\ell}$ is the connection gain.

3.2.2. Dynamic connections with distributed delay

One can generalize the above static elementary connection by adding a distributed time delay with a distribution or *kernel function* g to the connection. Then an elementary connection with distributed time delay can be written as the following integral equation:

$$\mathbf{u}^{(j)}_{\lambda}(t) = L^{(jk)}_{\lambda\ell} D_{g^{(kj)}_{\lambda\ell}}\left[\mathbf{y}^{(k)}_{\ell}(t)\right] = L^{(jk)}_{\lambda\ell}\left[\int_{-\infty}^{0} g^{(jk)}_{\lambda\ell}(s)\mathbf{y}^{(k)}_{\ell}(t-s)\,ds\right] \tag{18}$$

where the *distribution function* or *weighting kernel* $g^{(jk)}_{\lambda\ell} : [-\infty, 0] \to [0, \infty)$, $1 \le k \le r$, is a piecewise continuous function satisfying

$$\int_{-\infty}^{0} g^{(jk)}_{\lambda\ell}(s)\,ds = 1 \quad .$$

Then this delayed connection is characterized by its gain $L^{(jk)}_{\lambda\ell}$ and delay kernel function $g^{(jk)}_{\lambda\ell}$.

3.2.3. Dynamic connections realized by SISO linear connecting CRN subsystems

In this subsection, we consider the simple case, when we assume to have an independent connecting linear CRN subsystem (the jth CRN subsystem) that has only one input, and one output, i.e. it is a SISO subsystem. The LTI state-space model of this CRN subsystem is in Eq. (15).

Let this CRN subsystem connect one of the outputs (the λth) of the ith CRN subsystem to one of the inputs (the ℓth) to the kth one realizing an *elementary connection* $L^{(ik)}_{\lambda\ell}$. In that case, we have the following pseudo-reaction realizing this elementary connection

$$C^{(i)}_{\lambda} \xrightarrow{\kappa} \text{Linear connecting CRN subsystem}^{(j)} \longrightarrow C^{(k)}_{\ell}. \tag{19}$$

We are interested in the input–output behavior of the SISO LTI system (15) that can be obtained by using its impulse response function $h^{(j)}$ in the following form

$$y^{(j)}(t) = \int_0^t h^{(j)}(t-\tau)u^{(j)}(\tau)d\tau \quad , \quad h^{(j)}(t) = C^{(j)}e^{A^{(j)}_{\kappa}t}B^{(j)}. \tag{20}$$

Remark 2. When we apply *structural reduction* [37], we simplify the reaction graph (19) by replacing the CRN subsystem with a distributed delay reaction such that

$$C^{(i)}_{\lambda} \xrightarrow{\overline{\kappa}^{(j)},\, g^{(j)}} C^{(k)}_{\ell},$$

where the delay distribution function $g^{(j)}$ is given by using the impulse response function of the linear connecting CRN subsystem as follows

$$g^{(j)}(r) = \frac{h^{(j)}(-r)}{\int_0^{\infty} h^{(j)}(\tau)d\tau}, \tag{21}$$

and

$$\overline{\kappa}^{(j)} = \kappa \int_0^{\infty} h^{(j)}(\tau)d\tau. \tag{22}$$

3.3. Physically motivated dynamic linear connecting CRN subsystem models

In the general case, it may be difficult to find a suitable finite dimensional realization $(A^{(k)}_{\kappa}, B^{(k)}, C^{(k)})$ of a linear connecting subsystem given the delay kernel function $g^{(k)}$ of a given elementary distributed delay connection. This subsection shows how classical linear CRN models help to construct such realizations.

Irreversible homogeneous chain of linear reactions. The simplest case is when one considers a linear CRN with p intermediate species given by the reaction graph

$$C \xrightarrow{\kappa} V_1 \xrightarrow{a} V_2 \xrightarrow{a} \dots \xrightarrow{a} V_p \xrightarrow{a} C'. \tag{23}$$

The above linear CRN gives rise to the well-known "linear chain trick" [38] that associates to it an *equivalent* delayed CRN model that contains only a single reaction with distributed delay

$$C \xrightarrow{\kappa,\ G_{a,p}} C'$$

The kernel function $G_{a,p}$ of the reaction is the so-called Gamma function with rate parameter a and shape parameter p in the form

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

The dynamic DDE model of the above delayed CRN is in the following form:

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

where $\mathbf{x}$ is the concentration vector, η and η' are the stoichiometric coefficient vectors of the source C and product C' complexes, respectively.

Let us model the dynamics of the CRN (23) with an LTI state space model, where the *input* acts only on the first state variable, and the *output* is the last state variable, i.e. $y(t) = x_N(t)$. It is easy to see that the state space model matrices A_κ, B, C are as follows [18]:

$$A_\kappa = \begin{bmatrix} -v & 0 & 0 & & \dots & & 0 \\ v & -v & 0 & 0 & \dots & & 0 \\ 0 & v & -v & 0 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & 0 \\ 0 & \dots & \dots & \dots & v & -v & 0 \\ 0 & \dots & \dots & \dots & 0 & v & -v \end{bmatrix} \tag{24}$$

$$C = \begin{bmatrix} 0 & 0 & \dots & 0 & 1 \end{bmatrix}, \quad B = \begin{bmatrix} \kappa \\ 0 \\ \dots \\ 0 \end{bmatrix} \tag{25}$$

Remark 3. It is important to note that the state matrix in Eq. (24) is a Metzler-compartmental matrix, which implies the BIBO stability of the system. Moreover, the system is jointly controllable and observable, so it is a linear connecting CRN subsystem.

It is also easy to see, that the kernel (impulse response) function of this CRN subsystem is

$$h(t) = \mathcal{L}^{-1}[H(s)] = \kappa \frac{v^N}{(N-1)!} t^{N-1} e^{-vt} \tag{26}$$

It is seen that $h(t) = G_{v,N-1}(t)$, i.e. that kernel function is a Gamma distribution function.

Irreversible inhomogeneous chain of linear reactions. Here we consider an inhomogeneous *one-directional* (from the kth subsystem to the jth one) *SISO dynamic connection*. This may correspond e.g. to a flow with varying velocity a_i along the pipe caused by its varying cross section containing a single component with concentration x_i from one tank to the other, where $i = 1, \dots, N$ corresponds to the position of a flow element in the pipe.

The state space model matrices (A_κ, B, C) are as follows:

$$A_\kappa = \begin{bmatrix} -a_1 & 0 & 0 & & \dots & & 0 \\ a_1 & -a_2 & 0 & 0 & \dots & & 0 \\ 0 & a_2 & -a_3 & 0 & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & 0 \\ 0 & \dots & \dots & \dots & a_{N-2} & -a_{N-1} & 0 \\ 0 & \dots & \dots & \dots & 0 & a_{N-1} & -a_N \end{bmatrix} \tag{27}$$

$$C = \begin{bmatrix} 0 & 0 & \dots & 0 & 1 \end{bmatrix}, \quad B = \begin{bmatrix} a_0 \\ 0 \\ \dots \\ 0 \end{bmatrix} \tag{28}$$

It is important to note that the state matrix (27) is also a Metzler-compartmental matrix, which implies the BIBO stability of the system. Moreover, the system is jointly controllable and observable, so it is a linear compartmental connecting subsystem.

Assuming that all rate constants $a_i > 0$ are different, the kernel function of the equivalent distributed delay model is a sum of exponential functions [18]:

$$g(s) = \sum_{i=1}^{N} \left(a_i \prod_{j=1, i\neq j}^{N} \frac{a_j}{a_j - a_i} \right) e^{a_i s}, \tag{29}$$

where the coefficients are positive constant elements of the matrix A_κ in Eq. (27).

Recent results on the generalization of the 'linear chain trick' to more complex delay models [39] also motivate the ODE (Ordinary Differential Equation) based modeling of distributed delay terms in networks of biochemical systems.

Remark 4. It is important to remark, that for control purposes it is advantageous to have a non-delayed CRN model of the networked kinetic system to be controlled. Therefore, we may artificially introduce SISO linear connecting subsystems to replace distributed delayed chemical reactions, as it will be seen in Section 4.1

3.4. A simple example

A simple example will serve to illustrate the notions and notations above. This example illustrates a possible decomposition of an overall CRN system into independent CRN subsystems, while several other decompositions also exist.

Overall CRN. Consider a CRN $(C, \mathcal{R})$ given with its reaction graph depicted in Fig. 1. The reactions to/from the environment are denoted by idle edges, such that specie X_4 is fed into the system, and specie X_7 leaves it.

Decomposition. One can conveniently perform the decomposition using the reaction graph of the overall CRN. The aim is to form a partition of the complexes such that the species of each complex subset are mutually disjoint, so independent sub-CRNs are formed.

Let us identify three CRN subsystems: $\text{CRN}^{(1)}$, $\text{CRN}^{(2)}$ and $\text{CRN}^{(3)}$ as depicted with rectangles in the figure. The rationale behind this decomposition is to find the linear connecting CRN subsystem part of the overall CRN, that is $\text{CRN}^{(2)}$.

The next step is to form the input neighborhood set $\overline{\mathcal{N}}_I^{(j)}$ of a CRN subsystem $\text{CRN}^{(j)}$. This is done by finding the inward directed reactions to the CRN subsystem in question: every reactant complex of such a reaction is put into the input neighborhood set.

Then the three sub-CRNs are pairwise independent with the following model ingredients:

- $\text{CRN}^{(1)} = (C^{(1)}, \mathcal{R}^{(1)})$ with $C^{(1)} = \{(X_3 + X_2), X_1, X_3\}$, and $\overline{\mathcal{N}}_I^{(1)} = \{X_{3I}\}$;
- $\text{CRN}^{(2)} = (C^{(2)}, \mathcal{R}^{(2)})$ with $C^{(2)} = \{U_1, U_2, U_3, U_4\}$, and $\overline{\mathcal{N}}_I^{(2)} = \{X_1\}$, that is a *linear connecting CRN subsystem*;
- $\text{sub-CRN}^{(3)} = (C^{(3)}, \mathcal{R}^{(3)})$ with $C^{(3)} = \{(X_5 + X_6), X_7\}$, and $\overline{\mathcal{N}}_I^{(3)} = \{U_4\}$;

The overall system has one input x_{3I} and one output x_7.

It is easy to see, that *subsystem* $\text{CRN}^{(2)}$ *is a SISO linear connecting CRN subsystem*. We remark that this CRN subsystem is structurally similar to the well-known McKeithan network [40].

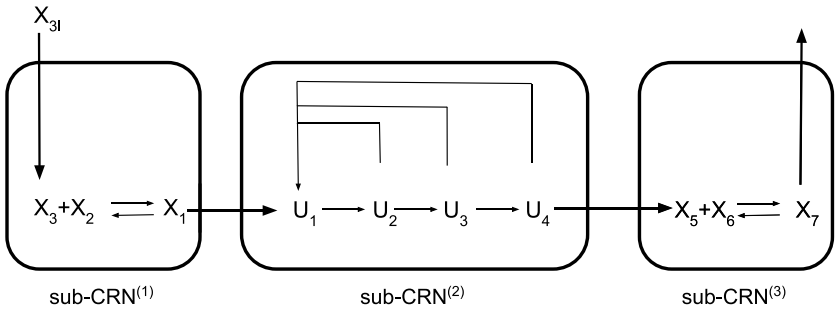

Fig. 1. Reaction graph of the simple example.

4. Control of interconnected CRNs with dynamic linear connecting elements

In this section, such a model of CRN networks with dynamic connections is introduced that is suitable for control design.

First, the *extended subsystem* is defined which includes a CRN subsystem and the dynamic connecting elements at its inputs. With this modeling approach, the investigation of the CRN network is more manageable since the extended subsystems have static interconnections. The reasonable assumption that the inflow rates are equal to the outflow rates in each subsystem is considered during modeling and control design, that implies the overall mass (and the overall volume with constant physico-chemical properties) to be constant.

Second, the CRN subsystems are extended with additional control inflows and outflows. The concentrations of the inflow species are assumed to be adjustable by a control mechanism as a function of a predefined control goal.

The aim of the control is to ensure that the states being the chemical concentrations of each CRN can be driven to prescribed equilibrium states regardless of the delayed flows among the CRN subsystems. The control algorithm is going to be formulated in such a way that the entire controlled CRN network with delays is detailed balanced and stable.

4.1. The control-oriented model of CRN network

In order to facilitate the control design of networked kinetic systems a control-oriented model is developed in this subsection where we assume that the connections between the kinetic subsystems are realized by physically meaningful linear transport (i.e. convection, diffusion, phase transfer) between the subsystems possibly allowing distributed nature (see Section 3.3).

4.1.1. Extended CRN subsystems

Let us consider a network of N open CRN subsystems whose dynamic behavior is described by the model (11). The state vector of each CRN is composed of chemical concentration values of $n \in \mathbb{N}_{>1}$ species ($\mathbf{x}^{(j)} = (x_\ell^{(j)}) \in \mathbb{R}^n_{\geq 0}$).

A number of $m \leq n$ species is transferred among these CRN subsystems. The outflows of an open CRN are linked to the inflows of another open CRN through possibly dynamic elements that can be modeled using LTI systems as in Eq. (15) because of the linear nature of the connecting transfer mechanisms.

Because of this linearity, we use the input neighborhood set of the jth CRN ($\mathcal{N}_I^{(j)}$) introduced in Section 3.1 in Eq. (14). It contains those CRNs whose outputs are connected to the jth extended subsystem.

Similarly, the output neighborhood set of the jth CRN ($\mathcal{N}_O^{(j)}$) contains those extended subsystems, which inputs contain the output of the jth CRN.

The LTI systems implement the transport of the species among the CRNs. The ℓth linear subsystem ($LTI_\ell^{(j)}$) transports the ℓth species to $CRN^{(j)}$.

The model of jth extended subsystem in the network includes the dynamic nonlinear model of $CRN^{(j)}$ (CRN subsystem) and the model of the linear connecting elements ($LTI_\ell^{(j)}$, $\ell = 1 \dots m$) at its inputs:

$$CRN^{(j)}: \begin{cases} y_\ell^{(j)} = H_\ell^{(j)} \mathbf{x}^{(j)}, \ \ell = 1 \dots m, \\ \dot{\mathbf{x}}^{(j)} = Y^{(j)} A_\kappa^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \sum_{\ell=1}^{m} F_\ell^{(j)} y_{I\ell}^{(j)} - H^{(j)} \mathbf{x}^{(j)}, \\ \mathbf{x}^{(j)}(0) = \mathbf{x}_0^{(j)}, \end{cases} \tag{30}$$

where $y_\ell^{(j)}, y_{I\ell}^{(j)} \in \mathbb{R}_{>0}$, the output matrix is

$$H^{(j)} \begin{pmatrix} H_1^{(j)} \\ \dots \\ H_\ell^{(j)} \\ \dots \\ H_m^{(j)} \end{pmatrix}, \text{ and}$$

$$LTI_\ell^{(j)}: \begin{cases} y_{I\ell}^{(j)} = C_\ell^{(j)} \mathbf{x}_{I\ell}^{(j)} \\ \dot{\mathbf{x}}_{I\ell}^{(j)} = A_\ell^{(j)} \mathbf{x}_{I\ell}^{(j)} + \sum_{i \in \mathcal{N}_I^{(j)}} B_{i\ell}^{(j)} y_\ell^{(i)}, \mathbf{x}_{I\ell}^{(j)}(0) = \mathbf{x}_{I\ell 0}^{(j)}, \ell = 1 \dots m. \end{cases} \tag{31}$$

In the dynamics of $CRN^{(j)}$, species outflows are also considered. The outflow is defined by the linear output term $H^{(j)}\mathbf{x}^{(j)}$.

The inputs of $LTI_\ell^{(j)}$ are the ℓth outputs of the CRNs in $\mathcal{N}_I^{(j)}$.

The matrices $B_\ell^{(j)}$, $H_\ell^{(j)}$ and $F_\ell^{(j)}$ are defined as:

$$H_\ell^{(j)} = (0 \dots 0 \ \underbrace{h_{\ell j}}_{\ell\text{th}} \ 0 \dots 0) \tag{32}$$

$$F_\ell^{(j)} = (0 \dots 0 \ \underbrace{f_{\ell j}}_{\ell\text{th}} \ 0 \dots 0)^T \tag{33}$$

$$B_{i\ell}^{(j)} = (b_{i\ell}^{(j)} \ \ 0 \ \dots \ 0)^T \tag{34}$$

The dimensions of the state-, input- and output matrices are considered as:

$Y^{(j)} \in \mathbb{N}_{\geq 0}^{n \times p_j}$, $A_\kappa^{(j)} \in \mathbb{R}^{p_j \times p_j}$, $\varphi^{(j)}(\mathbf{x}^{(j)}) \in \mathbb{R}_{\geq 0}^{p_j \times 1}$, $H_\ell^{(j)} \in \mathbb{R}_{\geq 0}^{1 \times n}$, $H^{(j)} \in \mathbb{R}_{\geq 0}^{m \times n}$, $A_\ell^{(j)} \in \mathbb{R}^{m_j \times m_j}$, $B_{i\ell}^{(j)} \in \mathbb{R}_{\geq 0}^{m_j \times 1}$, $C_\ell^{(j)} \in \mathbb{R}_{\geq 0}^{1 \times m_j}$, $F_\ell^{(j)} \in \mathbb{R}_{\geq 0}^{n \times 1}$.

Motivated by the physical examples presented in Section 3.3, we assume that $A_\ell^{(j)}$ is Metzler and Hurwitz.

On the other hand, the inflow rates are considered to be equal to the outflow rates both in the CRNs and LTI connecting subsystems (constant volume assumption in each extended subsystem). The corresponding modeling assumptions are:

- The row sum of the matrix below is zero:

$$\left(F_1^{(j)} C_1^{(j)} \dots F_\ell^{(j)} C_\ell^{(j)} \dots F_m^{(j)} C_m^{(j)} \ - H^{(j)} \right) \tag{35}$$

This condition shows that the cumulative inflow rate in the open $CRN^{(j)}$ subsystem is equal to the outflow rate from this subsystem.

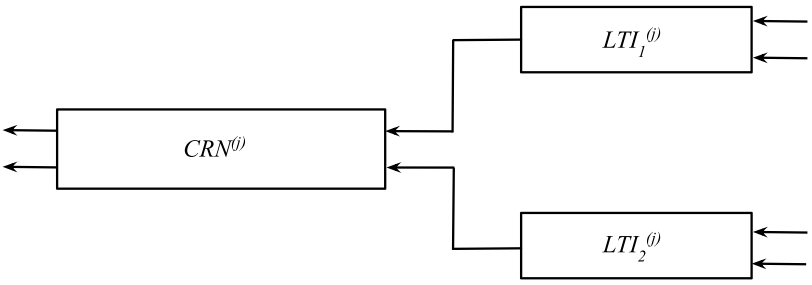

Fig. 2. Open CRN with dynamic elements at inputs ($m = 2$).

- The column sum of the matrix below is zero:

$$\begin{pmatrix} -H_\ell^{(j)} \\ \dots \\ B_\ell^{(i)} H_\ell^{(j)} \\ \dots \end{pmatrix} \tag{36}$$

where $i \in \mathcal{N}_O^{(j)}$. The property shows that the outflow rate of the ℓth specie from the jth CRN subsystem is equal to the cumulative inflow rate of the same specie into the extended subsystems that belong to $\mathcal{N}_O^{(j)}$.

- The row sum of the matrix below is zero:

$$(A_\ell^{(j)} \underbrace{\dots \; B_{i\ell}^{(j)} H_\ell^{(i)} \; \dots}_{\dim(\mathcal{N}_I^{(j)})}) \tag{37}$$

where $i \in \mathcal{N}_I^{(j)}$. This propriety stands for the inflows of $LTI_\ell^{(j)}$. If this condition holds, all the states of the linear connecting element will be equal to the weighted sum of ℓth input states from $\mathcal{N}_I^{(j)}$ in steady state.

- The column sum of the matrix below is zero:

$$\begin{pmatrix} F_\ell^{(j)} C_\ell^{(j)} \\ A_\ell^{(j)} \end{pmatrix} \tag{38}$$

According to this property, the outflow rate from $LTI_\ell^{(j)}$ is equal to the inflow rate of the ℓth species into $CRN^{(j)}$.

The state dynamics of the extended subsystem can be formulated as an open CRN model. This is illustrated in the following example.

Example 1. Let an extended subsystem as it is shown in Fig. 2. In this example, $m = 2$ and the neighboring subsystems are $\mathcal{N}_I^{(j)} = \{f, g\}$. Its dynamic model can be formulated as an open CRN model, the inputs of which are represented by the outputs of the neighboring CRNs. In the view of the general Eqs. (30) and (31), the state dynamics of the extended subsystem reads as:

$$\underbrace{\begin{pmatrix} \dot{\mathbf{x}}^{(j)} \\ \dot{\mathbf{x}}_{I1}^{(j)} \\ \dot{\mathbf{x}}_{I2}^{(j)} \end{pmatrix}}_{\dot{\mathbf{X}}^{(j)}} = \underbrace{\begin{pmatrix} Y^{(j)} & O & O & I \\ O & I & O & O \\ O & O & I & O \end{pmatrix}}_{\mathbf{Y}^{(j)}} \times \underbrace{\begin{pmatrix} A_\kappa^{(j)} & O & O & O \\ O & A_1^{(j)} & O & O \\ O & O & A_2^{(j)} & O \\ O & F_1^{(j)} C_1^{(j)} & F_2^{(j)} C_2^{(j)} & -H^{(j)} \end{pmatrix}}_{\mathbf{A}_\kappa^{(j)}} \underbrace{\begin{pmatrix} \varphi^{(j)}(\mathbf{x}^{(j)}) \\ \mathbf{x}_{I1}^{(j)} \\ \mathbf{x}_{I2}^{(j)} \\ \mathbf{x}^{(j)} \end{pmatrix}}_{\boldsymbol{\Phi}^{(j)}(\mathbf{X}^{(j)})}$$

$$+ \underbrace{\begin{pmatrix} O & O & O & O \\ O & O & O & B_{1f}^{(j)} H_1^{(f)} \\ O & O & O & B_{2f}^{(j)} H_2^{(f)} \end{pmatrix}}_{\mathbf{B}_f^{(j)}} \underbrace{\begin{pmatrix} \varphi^{(f)}(\mathbf{x}^{(f)}) \\ \mathbf{x}_{I1}^{(f)} \\ \mathbf{x}_{I2}^{(f)} \\ \mathbf{x}^{(f)} \end{pmatrix}}_{\boldsymbol{\Phi}^{(f)}(\mathbf{X}^{(f)})}$$

$$+ \underbrace{\begin{pmatrix} O & O & O & O \\ O & O & O & B_{1g}^{(j)} H_1^{(g)} \\ O & O & O & B_{2g}^{(j)} H_2^{(g)} \end{pmatrix}}_{\mathbf{B}_g^{(j)}} \underbrace{\begin{pmatrix} \varphi^{(g)}(\mathbf{x}^{(g)}) \\ \mathbf{x}_{I1}^{(g)} \\ \mathbf{x}_{I2}^{(g)} \\ \mathbf{x}^{(g)} \end{pmatrix}}_{\boldsymbol{\Phi}^{(g)}(\mathbf{X}^{(g)})} \tag{39}$$

O denotes the zero matrix with appropriate dimension.

Generally, the open CRN model of an extended subsystem can be written in the following compact form:

$$\dot{\mathbf{X}}^{(j)} = \mathbf{Y}^{(j)} \mathbf{A}_\kappa^{(j)} \boldsymbol{\Phi}^{(j)}(\mathbf{X}^{(j)}) + \sum_{i \in \mathcal{N}_I^{(j)}} \mathbf{B}_i^{(j)} \boldsymbol{\Phi}^{(i)}(\mathbf{X}^{(i)}), \tag{40}$$

4.1.2. Global model of the CRN network

By employing the extended subsystem model (40), the state space realization of the entire dynamic network can be formulated.

Example 2. Consider the network presented in Fig. 3. The input neighbor sets are $\mathcal{N}_I^{(1)} = \{3\}$, $\mathcal{N}_I^{(2)} = \{1\}$, $\mathcal{N}_I^{(3)} = \{2\}$. By Eq. (40) the state space realization of the networks has the form:

$$\begin{pmatrix} \dot{\mathbf{X}}^{(1)} \\ \dot{\mathbf{X}}^{(2)} \\ \dot{\mathbf{X}}^{(3)} \end{pmatrix} = \begin{pmatrix} \mathbf{Y}^{(1)} \mathbf{A}_\kappa^{(1)} & O & \mathbf{B}_3^{(1)} \\ \mathbf{B}_1^{(2)} & \mathbf{Y}^{(2)} \mathbf{A}_\kappa^{(2)} & O \\ O & \mathbf{B}_2^{(3)} & \mathbf{Y}^{(3)} \mathbf{A}_\kappa^{(3)} \end{pmatrix} \begin{pmatrix} \boldsymbol{\Phi}^{(1)}(\mathbf{X}^{(1)}) \\ \boldsymbol{\Phi}^{(2)}(\mathbf{X}^{(2)}) \\ \boldsymbol{\Phi}^{(3)}(\mathbf{X}^{(3)}) \end{pmatrix} \tag{41}$$

Proposition 1. *The matrices $\mathbf{B}_i^{(j)}$, introduced in (40), can be factorized as:*

$$\mathbf{B}_i^{(j)} = \mathbf{Y}^{(j)} \mathbf{B}_{Ei}^{(j)}, \tag{42}$$

where the matrix $\mathbf{B}_{Ei}^{(j)}$ has the form:

$$\mathbf{B}_{Ei}^{(j)} = \begin{pmatrix} \mathbf{B}_i^{(j)} \\ O \end{pmatrix} \tag{43}$$

The affirmation above can be shown by direct computation. For an example, refer to $\mathbf{Y}^{(j)}$ and $\mathbf{B}_1^{(j)}$ in Eq. (39).

In the view of this proposition, the dynamic network model (41) can be rewritten in the form:

$$\underbrace{\begin{pmatrix} \dot{\mathbf{X}}^{(1)} \\ \dot{\mathbf{X}}^{(2)} \\ \dot{\mathbf{X}}^{(3)} \end{pmatrix}}_{\dot{\mathbf{X}}} = \underbrace{\begin{pmatrix} \mathbf{Y}^{(1)} & O & O \\ O & \mathbf{Y}^{(2)} & O \\ O & O & \mathbf{Y}^{(3)} \end{pmatrix}}_{\mathbf{Y}} \underbrace{\begin{pmatrix} \mathbf{A}_\kappa^{(1)} & O & \mathbf{B}_{E3}^{(1)} \\ \mathbf{B}_{E1}^{(2)} & \mathbf{A}_\kappa^{(2)} & O \\ O & \mathbf{B}_{E2}^{(3)} & \mathbf{A}_\kappa^{(3)} \end{pmatrix}}_{\mathbf{A}_\kappa}$$

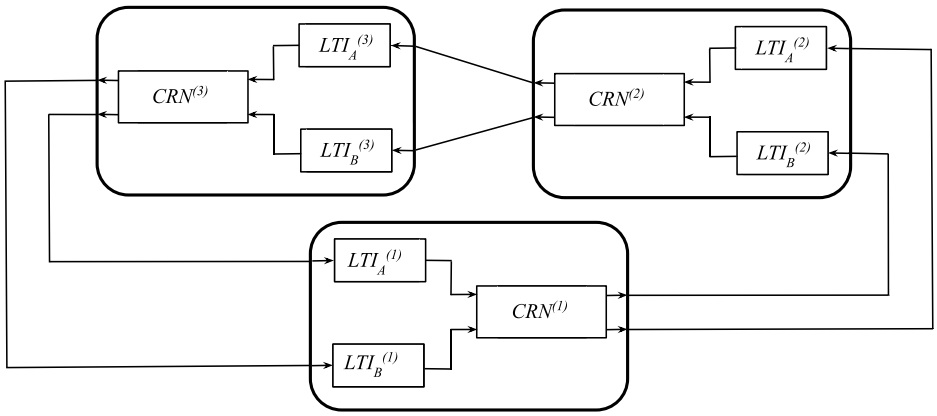

Fig. 3. CRN network example with dynamic connections.

$$\times \underbrace{\begin{pmatrix} \Phi^{(1)}(\mathbf{X}^{(1)}) \\ \Phi^{(2)}(\mathbf{X}^{(2)}) \\ \Phi^{(3)}(\mathbf{X}^{(3)}) \end{pmatrix}}_{\Phi(\mathbf{X})} \tag{44}$$

By the proprieties (36) and (38) yields that the row sums of the matrix $\mathbf{A}_\kappa^{(1)}$ are zero.

Generally, it can be affirmed that the model of the CRN network with linear connecting elements can be formulated as a CRN model:

$$\dot{\mathbf{X}} = \mathbf{Y}\mathbf{A}_\kappa \Phi(\mathbf{X}). \tag{45}$$

4.2. Control of CRN network

4.2.1. Complex balancedness

Let $\mathbf{x}^* = (x_\ell^*) \in \mathbb{R}^n_{>0}$ be an equilibrium state of the kinetic system (9). The kinetic system is called complex balanced if

$$A_\kappa \varphi(\mathbf{x}^*) = \mathbf{0}. \tag{46}$$

It is known that, if (46) is satisfied for an equilibrium point, then it is fulfilled for all the other equilibrium points of the model [41]. Hence the complex balance is a property of the whole CRN and not only of the equilibrium point. If a CRN is complex balanced, then the system (9) is at least locally stable in the equilibrium point $\mathbf{x}^*$ with a known entropy-like logarithmic Lyapunov function which is independent of the rate coefficients of the system [4]. If the reaction graph of a complex balanced system contains one connected component (which we can assume in our case) then the stability is global with respect to the nonnegative orthant [42].

Remark 5. In the case of linear CRNs ($\varphi(\mathbf{x}) = \mathbf{x}$, $Y = I$) the vector $\mathbf{x}^* = \alpha\mathbf{1}$, $\alpha > 0$ is an equilibrium point, and $A_\kappa \mathbf{x}^* = \mathbf{0}$ if A_κ is *row conservation matrix* (i.e. the sum of the elements in each row is zero).

4.2.2. Control problem

Generally, it cannot be assumed that the CRN subsystems possess complex balanced property. On the other hand, in many biochemical systems, it is desirable to have different prescribed equilibrium states in the CRN subsystems of the network. To tackle this problem, the CRN subsystems are extended with additional control flows that are designed in function of the desired equilibrium states and measured states.

Control inputs. The state-space model (30) is extended as:

$$\dot{\mathbf{x}}^{(j)} = Y^{(j)} A_\kappa^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \sum_{\ell=1}^{m} F_\ell^{(j)} y_{I\ell}^{(j)} - H^{(j)}\mathbf{x}^{(j)} + B_c^{(j)} \underbrace{\left(\mathbf{x}_c^{(j)} - \mathbf{x}^{(j)}\right)}_{\mathbf{u}_c^{(j)}} \tag{47}$$

where $B_c^{(j)} \in \mathbb{R}^{n\times n}_{\geq 0}$ is the control input matrix, and $\mathbf{u}_c^{(j)} = \mathbf{x}_c^{(j)} - \mathbf{x}^{(j)} \in \mathbb{R}^{n\times 1}$ implements the control input. The term $\mathbf{x}_c^{(j)} \in \mathbb{R}^n_{\geq 0}$ represents the species concentration vector which is considered to be adjustable by a control mechanism.

It is important to remark, that the last, additional input term in Eq. (47) corresponds to the situation when an additional inflow-outflow pair of constant mass flowrate $B_c^{(j)}$ is used for control purposes with adjustable inflow concentration $\mathbf{x}_c^{(j)}$ in order to keep the constant overall mass condition in each CRN subsystem. Here $B_c^{(j)}\mathbf{x}_c^{(j)}$ is the component mass inflow and $B_c^{(j)}\mathbf{x}^{(j)}$ is the balancing component mass outflow of the subsystem.

Control objective. Let the set of prescribed equilibrium states as:

$$\{\mathbf{x}^{(1)*}, \ \dots \ , \mathbf{x}^{(j)*}, \ \dots \ \mathbf{x}^{(n)*}\}. \tag{48}$$

Design a decentralized control $\mathbf{u}_c^{(j)}$ for each CRN subsystem such that the entire CRN network with delayed connections is stable, and the steady state value of $\mathbf{x}^{(j)}$ is equal to $\mathbf{x}^{(j)*}$.

By *decentralized control*, we mean that the control inputs $\mathbf{u}_c^{(j)}$ may only depend on the states of the jth CRN subsystem.

4.2.3. Control design

Let the controlled CRN subsystem be defined by the relation (47). The control will be designed in three steps.

(1) First, kinetic state feedback is designed to ensure the complex balanced property of the CRN subsystems.
(2) Second, the control is extended by logarithmic feedback to ensure setpoint tracking in the CRN subsystems.
(3) Third, the control is further extended by a feed-forward term which is meant to compensate for the setpoint differences in the neighboring CRN subsystems.

4.2.4. Reference Kirchhoff matrix to ensure complex balancedness

The Kirchhoff matrix ($A_{\kappa ref}^{(j)}$) for $CRN^{(j)}$ will be constructed such to ensure the complex balanced property of the CRN subsystem.

This reference Kirchhoff matrix can be designed by applying the following algorithm:

- INPUTS: $\mathbf{x}^{(j)*} \in \mathbb{R}^n_{>0}$, $\varphi^{(j)}(\cdot) : \mathbb{R}^n_{\geq 0} \to \mathbb{R}^{p_j}_{\geq 0}$
- Let $P_j = \operatorname{diag}\left(\varphi^{(j)}(\mathbf{x}^{(j)*})\right) \in \mathbb{R}^{p_j \times p_j}_{\geq 0}$.
- Let a free design parameter (rate coefficient) $\gamma^{(j)} \in \mathbb{R}_{>0}$.
- Let $A_0^{(j)} \in \mathbb{R}^{p_j \times p_j}$ such that $A_{0ii}^{(j)} = -1$ and $0 \leq A_{0ij}^{(j)} \leq 1$ otherwise, and both the row and column sums of it are zero.
- Compute

$$A_{\kappa ref}^{(j)} = \gamma^{(j)} A_0^{(j)} P_j^{-1} \in \mathbb{R}^{p_j \times p_j}. \tag{49}$$

- OUTPUT: $A_{\kappa ref}^{(j)}$

With the design parameter $\gamma^{(j)} > 0$, the transient performances (such as reaction rates) of the reactions can be adjusted.

The obtained reference Kirchhoff matrix has the following proprieties:

- $A^{(j)}_{\kappa ref}\varphi^{(j)}(\mathbf{x}^{(j)*}) = \mathbf{0}$.
- The column sums of $A^{(j)}_{\kappa ref}$ are zero.

Example 3. Let equilibrium sate: $\mathbf{x}^{(j)*} = (x_1^{(j)*}\ x_2^{(j)*}\ x_3^{(j)*})^T \in \mathbb{R}^3_{>0}$ and the vector of monomial functions:

$$\varphi^{(j)} : \mathbb{R}^3_{\geq 0} \to R^2_{\geq 0} \quad \varphi^{(j)}(\mathbf{x}^{(j)}) = \begin{pmatrix} x_1^{(j)}x_2^{(j)} \\ x_3^{(j)} \end{pmatrix} \tag{50}$$

The diagonal matrix P_j has the form:

$$P_j = \begin{pmatrix} x_1^{(j)*}x_2^{(j)*} & 0 \\ 0 & x_3^{(j)*} \end{pmatrix}. \tag{51}$$

Let $\gamma^{(j)} > 0$ and

$$A_0^{(j)} = \begin{pmatrix} -1 & 1 \\ 1 & -1 \end{pmatrix}. \tag{52}$$

In this case, the reference Kirchhoff matrix has the form:

$$A^{(j)}_{\kappa ref} = \begin{pmatrix} -\frac{\gamma^{(j)}}{x_1^{(j)*}x_2^{(j)*}} & \frac{\gamma^{(j)}}{x_3^{(j)*}} \\ \frac{\gamma^{(j)}}{x_1^{(j)*}x_2^{(j)*}} & -\frac{\gamma^{(j)}}{x_3^{(j)*}} \end{pmatrix}. \tag{53}$$

4.2.5. Kinetic state feedback

Let the reference Kirchhoff matrix for the jth CRN subsystem $\mathbf{A}^{(j)}_{\kappa ref}$ which was designed using the method presented in Section 4.2.4.

Consider the kinetic feedback in the form [25]:

$$\mathbf{u}_{c1} = K^{(j)}_{\varphi}\varphi^{(j)}(\mathbf{x}^{(j)}) \tag{54}$$

where $K^{(j)}_{\varphi} \in \mathbb{R}^{n\times p_j}$ is the controller gain matrix.

To ensure the complex balancedness of the jth CRN subsystem, in the view of the Eq. (47), $K^{(j)}_{\varphi}$ can be designed by using the equation:

$$Y^{(j)}A^{(j)}_{\kappa} + B^{(j)}_c K^{(j)}_{\varphi} = Y^{(j)}A^{(j)}_{\kappa ref}. \tag{55}$$

The equation above is solvable iff

$$B^{(j)}_c B^{(j)\dagger}_c Y^{(j)}\left(A^{(j)}_{\kappa ref} - A^{(j)}_{\kappa}\right) = Y^{(j)}\left(A^{(j)}_{\kappa ref} - A^{(j)}_{\kappa}\right), \tag{56}$$

see e.g. [43]. Here $B^{(j)\dagger}_c$ denotes the Moore–Penrose inverse of $B^{(j)}_c$. Note that if $B^{(j)}_c$ has full rank, e.g. $B^{(j)}_c = I$, the condition above is conclusively satisfied.

If the solvability condition holds, the solution is

$$K^{(j)}_{\varphi} = B^{(j)\dagger}_c Y^{(j)}\left(A^{(j)}_{\kappa ref} - A^{(j)}_{\kappa}\right) + \left(I - B^{(j)\dagger}_c B^{(j)}_c\right)Z, \tag{57}$$

where Z is arbitrary with an appropriate dimension.

4.2.6. Logarithmic feedback for setpoint tracking

The control (54) ensures the stability of the CRN subsystems. To ensure the convergence of a specific equilibrium point $\mathbf{x}^{(j)*}$ the control input can be extended with the logarithmic feedback [44]:

$$\mathbf{u}^{(j)}_{c2} = K^{(j)}_p\left(Ln(\mathbf{x}^{(j)*}) - Ln(\mathbf{x}^{(j)})\right) \tag{58}$$

where the mapping $Ln(\cdot)$ applies the natural logarithm element-wise to a vector, and $K^{(j)}_p \in \mathbb{R}^{n\times n}_{>0}$ is a diagonal gain matrix.

For the discussion and setpoint tracking performances and the positivity of the controller above, see [44].

4.2.7. Feedforward compensation for setpoint difference

If different setpoints for the different CRN subsystems are prescribed, it has to be considered that the inflows from the neighboring CRNs could shift the equilibrium state of the CRN subsystem from the prescribed value. To compensate for this, the control is extended with a feed-forward term.

The effect of the neighboring CRN subsystems on the steady states has to be computed by taking into account the connecting elements given by (31).

By assuming that the states of the CRN subsystems from the neighborhood set $\mathcal{N}^{(j)}_I$ have reached their setpoint values ($\mathbf{x}^{(i)*}$), the output of $LTI^{(j)}_{\ell}$ in equilibrium reads as:

$$y^{(j)*}_{I\ell} = -C^{(j)}_{\ell}A^{(j)-1}_{\ell}\sum_{i\in\mathcal{N}^{(j)}_I} B^{(j)}_{i\ell}H^{(i)}_{\ell}\mathbf{x}^{(i)*} \tag{59}$$

Note that $A^{(j)}_{\ell}$ is Hurwitz, hence it is invertible.

To compensate for the effect of the inputs on the equilibrium state of $CRN^{(j)}$, in the view of Eq. (30), the feedforward term of the control $\mathbf{u}^{(j)}_{ff}$ has to be formulated such that

$$\sum_{\ell=1}^{m} F^{(j)}_{\ell}y^{(j)*}_{I\ell} - H^{(j)}\mathbf{x}^{(j)*} + \mathbf{u}^{(j)}_{ff} = \mathbf{0}. \tag{60}$$

By this equation, the final form of the feedforward term of the control yields as:

$$\mathbf{u}^{(j)}_{ff} = H^{(j)}\mathbf{x}^{(j)*} + \sum_{\ell=1}^{m} F^{(j)}_{\ell}C^{(j)}_{\ell}A^{(j)-1}_{\ell}\sum_{i\in\mathcal{N}^{(j)}_I} B^{(j)}_{i\ell}H^{(i)}_{\ell}\mathbf{x}^{(i)*} \tag{61}$$

The final form of the control input yields from (54), (58) and (61):

$$\mathbf{u}^{(j)}_c = \mathbf{u}^{(j)}_{c1} + \mathbf{u}^{(j)}_{c2} + \mathbf{u}^{(j)}_{ff} \tag{62}$$

The decentralized controller above ensures that each controlled CRN subsystem is complex balanced. As it was presented in Eqs. (35)–(38), the inflow rates are equal to the outflow rates in every CRN subsystem and we consider stable linear connecting elements. Moreover, the control input was also formulated in such a way that it does not distort the balancedness of the sub-CRNs, see (47). Hence, the entire controlled network is also balanced.

4.3. The summary of the control

The control design, and the steps of the control algorithm of the connected open CRN subsystems are summarized below. The control is implementable using only local measurements.

- *Let* $\mathbf{x}^{(j)*}$, $\mathbf{x}^{(i)*}$ $(i \in \mathcal{N}^{(j)}_I)$, *and* $K^{(j)}_p$ be given.
- *Compute* $A^{(j)}_{\kappa}$ *by using Eq.* (49)
- *Check condition* (56)

For each $CRN^{(j)}$ *repeat*:

- *INPUT: Measure* $\mathbf{x}^{(j)}$
- *Compute* $\mathbf{u}^{(j)}_c$ *by using Eqs.* (62), (54), (58) and (61)
- *OUTPUT:* $\mathbf{u}^{(j)}_c$

5. Case study

5.1. General description of the process

A case study consisting of three sub-CRNs and several linear interconnections is considered. The process system is designed to extract carbon dioxide (CO_2) from flue gases using lime hydrate ($Ca(OH)_2$). This case study is a simplified version of the process used in industrial practice, during simulations fictive parameters were used.

The network presented in Fig. 4 consists of three operating units, where the LTI connecting subsystems represent the effect of nonideal

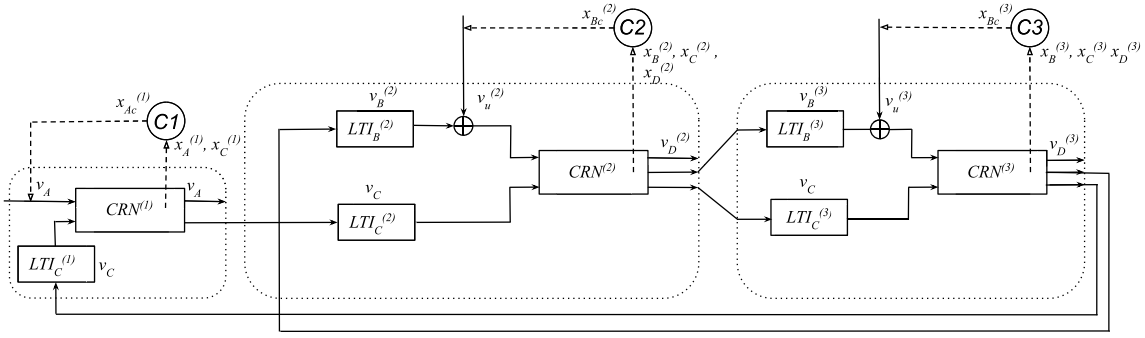

Fig. 4. Controlled process network.

convection [37] along the tubes connecting the operating units that are perfectly stirred.

Unit 1 is for absorbing the carbon dioxide (specie A) in water that is in great excess and produces dissolved H_2CO_3 (specie C), so we have the reaction

$$A \xrightarrow{k^{(1)}} C \tag{63}$$

The water solvent is recycled from the extractors, i.e. from unit 3.

Thereafter units 2 and 3 realize a two-stage extractor where specie B (lime hydrate, $Ca(OH)_2$) and specie C (dissolved H_2CO_3) react to form specie D (rag-stone, $CaCO_3$) that is deposited, and also water. Here the chemical reactions (taking into account that water is in great excess) are in the simple form

$$B + C \xrightarrow{k^{(j)}} D\ , \quad j = 2, 3. \tag{64}$$

After the second stage, the unreacted solvable species (B and C) are recycled together with the water.

The control inflow contains in unit 1 only specie A. In units 2 and 3, only specie B is in the control inflow.

The control aim is to set the outflow concentration of specie C in $CRN^{(1)}$ high enough to consume most of the specie A (the carbon dioxide) in the inflow gas. Then we set the outflow concentration of specie C in $CRN^{(2)}$ and $CRN^{(3)}$ gradually smaller such that the resulting specie D can be safely withdrawn as a solid from these units. Meanwhile, we would like to maintain the stability of the overall network against the disturbances caused by the delays and recycling.

5.2. Control-oriented model and control design

The controlled network corresponding to the process described in the previous subsection is presented in Fig. 4.

The first subsystem consists of $CRN^{(1)}$, it only has specie A in its gas phase controlled inflow. This gas phase flow leaves the unit with less specie A contents. The liquid phase outflow from $CRN^{(3)}$ also enters this unit through linear connecting elements.

It is important to note, that both specie B and specie C are present in the recycled inflow from $CRN^{(3)}$, as shown in Fig. 4. However, only reaction (63) takes place in $CRN^{(1)}$, the specie B reacts only in $CRN^{(2)}$.

The second extended subsystem contains $CRN^{(2)}$ with control inflow for specie B and two linear connecting elements describing the connections among $CRN^{(2)}$ and its input neighbors.

The third extended subsystem contains $CRN^{(3)}$ with control inflow for specie B. The interconnections from $CRN^{(2)}$ to $CRN^{(3)}$ are also included in this extended subsystem.

Without losing the generality during control design, it is assumed that all the linear connecting subsystems $LTI_C^{(1)}$, $LTI_B^{(2)}$, $LTI_C^{(2)}$, $LTI_B^{(3)}$ and $LTI_C^{(3)}$ have unit steady-state gains. Hence, in steady state, the species concentrations at the connecting output of the connecting elements are equal to the input concentration.

Control-oriented modeling for $CRN^{(1)}$. The dynamic model of the $CRN^{(1)}$ subsystem is given by

$$\left\{ \begin{array}{l} \dot{x}_A^{(1)} = -k^{(1)} x_A^{(1)} + v_A x_{Ac}^{(1)} - v_A x_A^{(1)} \\ \dot{x}_C^{(1)} = \ k^{(1)} x_A^{(1)} + v_C y_{IC}^{(1)} - v_C x_C^{(1)} \end{array} \right. , \quad \left(\begin{array}{c} x_A^{(1)}(0) \\ x_C^{(1)}(0) \end{array} \right) = \left(\begin{array}{c} x_{A0}^{(1)} \\ x_{C0}^{(1)} \end{array} \right), \tag{65}$$

where $y_{IC}^{(1)}$ is the output of the linear connecting element ($LTI_C^{(1)}$) of the extended subsystem, $k^{(1)} > 0$ is the reaction rate coefficient, the inflow concentration $x_{Ac}^{(1)}$ is also applied as control, $v_A, v_C > 0$ are the in- and outflow rate coefficients (in units $[1/s]$, that are the real in- or outflow rates divided by the volume).

Control design for $CRN^{(1)}$. Consider that $x_C^{(1)*}$ represents the prescribed setpoint for specie C. The control goal is to ensure that $\lim_{t\to\infty} x_C^{(1)} = x_C^{(1)*} > 0$ in addition to stable dynamics.

Assuming that the controlled dynamics is stable, the steady states satisfy:

$$v_C(x_C^{(1)*} - x_C^{(3)*}) = k^{(1)} x_A^{(1)*}, \tag{66}$$

where $x_C^{(1)*}$ is prescribed in the control goal, and $x_C^{(3)*} < x_C^{(1)*}$ is the steady state value of C in $CRN^{(3)}$.

The reference Kirchhoff matrix ($A_{kref}^{(1)}$) is formulated as in Section 4.2.4, see Eq. (49). The state of the specie C is not directly influenced by the control input, so the first row in $A_{kref}^{(1)}$ is kept the same as in the original Kirchhoff matrix:

$$\begin{aligned} A_{kref}^{(1)} &= v_C(x_C^{(1)*} - x_C^{(3)*}) \left[\begin{array}{cc} -1 & 1 \\ 1 & -1 \end{array} \right] \left[\begin{array}{cc} \frac{1}{x_A^{(1)*}} & 0 \\ 0 & \frac{1}{x_C^{(1)*} - x_C^{(3)*}} \end{array} \right] \\ &= \left[\begin{array}{cc} -k^{(1)} & v_C \\ k^{(1)} & -v_C \end{array} \right]. \end{aligned} \tag{67}$$

The equilibrium states satisfy the steady-state Eq. (66).

The control is formulated as in Eq. (62):

$$C1: \quad x_{Ac}^{(1)} = \frac{v_C}{v_A}(x_C^{(1)} - x_C^{(3)*}) + k_p^{(1)} \left(ln(x_A^{(1)*}) - ln(x_A^{(1)}) \right) + x_A^{(1)*} \tag{68}$$

where $k_p^{(1)} > 0$, and $x_A^{(1)*} = v_C(x_C^{(1)*} - x_C^{(3)*})/k^{(1)}$ according to Eq. (66). The first term ensures the complex balancedness of the controlled system, and the second term guarantees the setpoint tracking. The feedforward term compensates for the control inflow.

Control-oriented modeling for $CRN^{(2)}$. In this unit, specie A is not present; therefore reaction (63) does not take place here. The dynamic

model corresponding to the reaction (64) has the form:

$$\begin{cases} \dot{x}_C^{(2)} = -k^{(2)} x_B^{(2)} x_C^{(2)} + v_C y_{IC}^{(2)} - v_C x_C^{(2)} \\ \dot{x}_B^{(2)} = -k^{(2)} x_B^{(2)} x_C^{(2)} + v_B^{(2)} y_{IB}^{(2)} - v_B^{(3)} x_B^{(2)} + v_u^{(2)} x_{Bc}^{(2)} \\ \dot{x}_D^{(2)} = \quad k^{(2)} x_B^{(2)} x_C^{(2)} - v_D^{(2)} x_D^{(2)} \end{cases}, \quad \begin{pmatrix} x_C^{(2)}(0) \\ x_B^{(2)}(0) \\ x_D^{(2)}(0) \end{pmatrix} = \begin{pmatrix} x_{C0}^{(2)} \\ x_{B0}^{(2)} \\ x_{D0}^{(2)} \end{pmatrix}, \tag{69}$$

where $y_{IC}^{(2)}$, $y_{IB}^{(2)}$ are the outputs of the linear connecting elements ($LTI_C^{(2)}$, $LTI_B^{(2)}$) of the extended subsystem. $k^{(2)} > 0$ is the reaction rate coefficient, $v_B^{(2)}, v_B^{(3)}, v_D^{(2)} > 0$ are the flow rate coefficients, and $v_u^{(2)} > 0$ is the control inflow rate coefficient such that $v_B^{(2)} + v_u^{(2)} = v_B^{(3)}$.

Control design for $CRN^{(2)}$. The control goal is to ensure that $\lim_{t\to\infty} x_C^{(2)} = x_C^{(2)*}$ beside stable dynamics, where $x_C^{(2)*} < x_C^{(1)*}$ is the prescribed concentration setpoint for specie C in $CRN^{(2)}$.

Note that only the dynamics of $x_B^{(2)}$ is influenced directly by the control.

By Eq. (69) the steady state concentration of the specie D in the controlled CRN satisfies

$$x_D^{(2)*} = \frac{v_C}{v_D^{(2)}} \left(x_C^{(1)*} - x_C^{(2)*} \right), \tag{70}$$

where $x_C^{(2)*}$ is prescribed in the control goal.

The steady-state value of the specie B can also be computed in function of the prescribed steady-state values of specie C:

$$k^{(2)} x_B^{(2)*} x_C^{(2)*} = v_C (x_C^{(1)*} - x_C^{(2)*}). \tag{71}$$

The reference Kirchhoff matrix is expressed as:

$$A_{kref}^{(1)} = \begin{bmatrix} -k^{(2)} & v_D \\ k^{(2)} & -v_D \end{bmatrix}. \tag{72}$$

The control is formulated as in (62):

$$C2: \quad x_{Bc}^{(2)} = \frac{v_D^{(2)}}{v_u^{(2)}} x_D^{(2)} + k_p^{(2)} \left(ln(x_B^{(2)*}) - ln(x_B^{(2)}) \right) - \frac{v_B^{(2)}}{v_u^{(2)}} x_B^{(3)*} + \frac{v_B^{(3)}}{v_u^{(2)}} x_B^{(2)*}, \tag{73}$$

where $k_p^{(2)} > 0$.

The control of the extended $CRN^{(3)}$ subsystem can be formulated and designed in the same manner. Here, the prescribed concentration state for specie C satisfies $x_C^{(3)*} < x_C^{(2)*}$.

Connections. Through the linear connecting elements, the species C and B circulate among the reactions as it is shown in Fig. 4. Each element is considered to be described by an irreversible homogeneous chain with four states, as it is presented in Section 3.3.

$$LTI_C^{(j)}: \begin{pmatrix} \dot{x}_{I1}^{(j)} \\ \dot{x}_{I2}^{(j)} \\ \dot{x}_{I3}^{(j)} \\ \dot{x}_{I4}^{(j)} \end{pmatrix} = \underbrace{\begin{pmatrix} -v_C & 0 & 0 & 0 \\ v_C & -v_C & 0 & 0 \\ 0 & v_C & -v_C & 0 \\ 0 & 0 & v_C & -v_C \end{pmatrix}}_{A_C^{(j)}} \begin{pmatrix} x_{I1}^{(j)} \\ x_{I2}^{(j)} \\ x_{I3}^{(j)} \\ x_{I4}^{(j)} \end{pmatrix} + \underbrace{\begin{pmatrix} v_C \\ 0 \\ 0 \\ 0 \end{pmatrix}}_{B_C^{(j)}} u_C^{(\ell)}$$

Table 1
Initial states.

$\mathbf{x}_0^{(j)}$	$j=1$	$j=2$	$j=3$
$x_{A0}^{(j)}$	50	–	–
$x_{B0}^{(j)}$	–	0.1	0.1
$x_{C0}^{(j)}$	0	0	0
$x_{D0}^{(j)}$	–	0	0

Table 2
Parameters for simulation.

Parameter	$j=1$	$j=2$	$j=3$
$k^{(j)}$	1	0.1	0.1
$v_A^{(j)}$	1	–	–
$v_C^{(j)}$	1	1	1
$v_B^{(j)}$	–	1	1.2
$v_D^{(j)}$	–	1	1
$v_u^{(j)}$	–	0.2	0.2

Table 3
Controller parameters for simulation.

Parameter	$j=1$	$j=2$	$j=3$
$k_p^{(j)}$	10	10	10
$x_C^{(j)*}$	10	5	2.5

$$y_I^{(j)} = \underbrace{\begin{pmatrix} 0 & 0 & 0 & 1 \end{pmatrix}}_{c_C^{(j)}} \begin{pmatrix} x_{I1}^{(j)} \\ x_{I2}^{(j)} \\ x_{I3}^{(j)} \\ x_{I4}^{(j)} \end{pmatrix}. \tag{74}$$

Here $u_C^{(\ell)}$ denotes the chemical concentration state of the specie C from the corresponding input unit.

The linear connecting elements $LTI_B^{(j)}$, $j = 2, 3$ are defined in the same way.

5.3. Simulation results

The dynamic model of the CRN network presented in the previous subsections, see Fig. 4, was implemented in Matlab/Simulink environment.

The subsystems and connecting elements were implemented based on the models (65), (69), and (74).

The integration of the model was performed using the Dorm-and-Prince solver ('ode45') with $1E-3$ tolerance.

The applied initial states of the dynamic CRN models are presented in Table 1.

In every case, the initial states of the linear connecting elements were chosen as zero.

The parameters of the extended subsystem are chosen as shown in Table 2.

During the simulation experiment, the dynamic behavior of the controlled network with the proposed decentralized control was investigated. The control laws were implemented, as it is presented in (68) and (73).

Table 3 presents the chosen reference states for specie C, and the controller parameters.

Figs. 5, 6, and 7 show the states of the controlled CRNs and the control signals. The network shows stable behavior and the states of the species C converge to their prescribed values. It can also be observed that the steady states of the other species satisfy the Eqs. (66), (70), and (71).

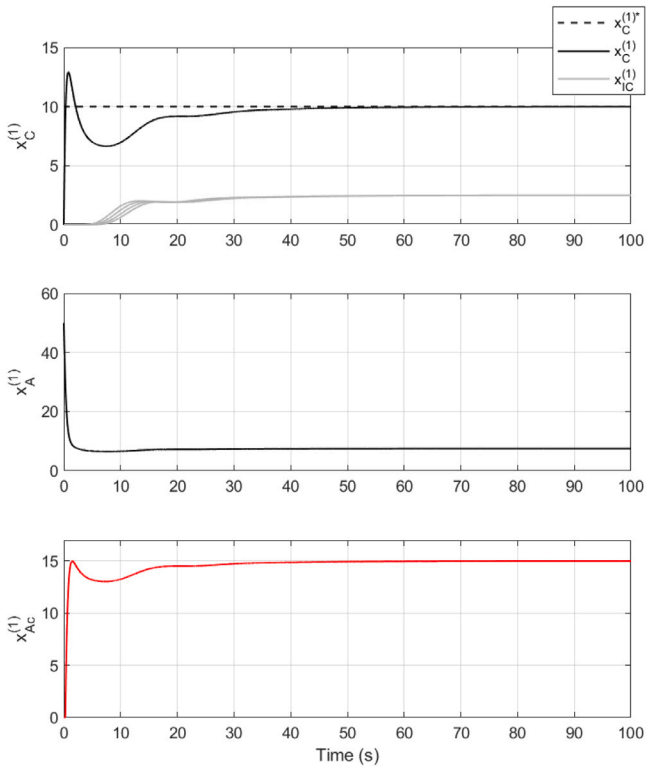

Fig. 5. The controlled states and control signal of subsystem 1.

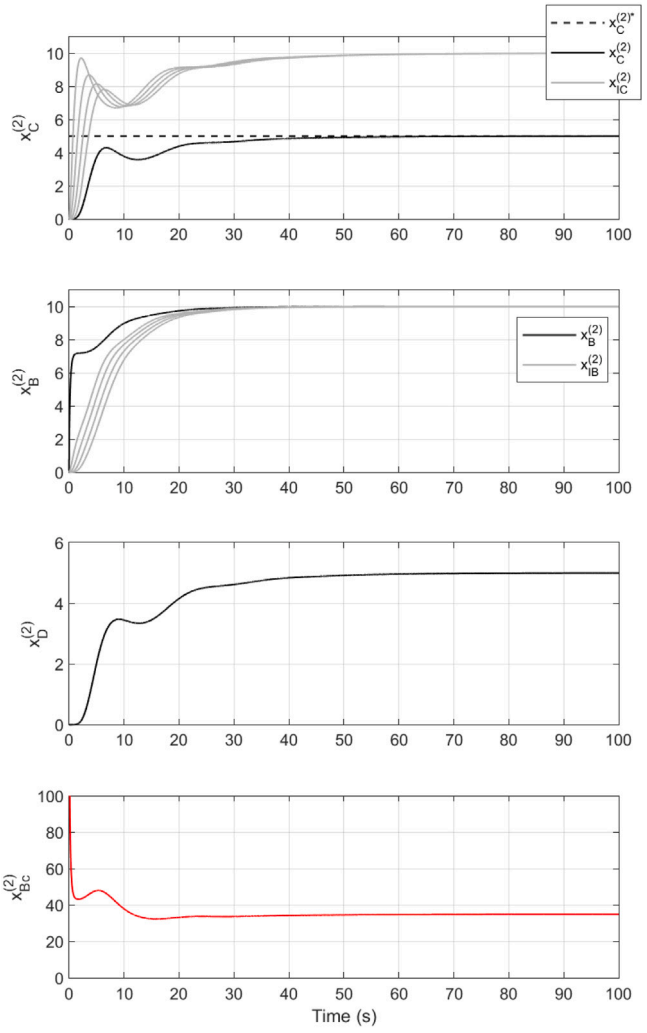

Fig. 6. The controlled states and control signal of subsystem 2.

6. Conclusion and future work

Handling of time delays is often necessary for the modeling and control of dynamic systems. It is known that a large set of general nonlinear systems (especially nonnegative systems) can be formally represented in kinetic form as a set of complexes and abstract chemical reactions. In this paper, the modeling and control of interconnected kinetic systems containing distributed delays were considered. The network structure consists of interconnected chemical reaction networks where the connections are either static or represented as linear connecting CRNs. Distributed delays can also be described as linear sub-CRNs. The manipulable inputs of the network are inlet concentrations, and the control goal is the stabilization of a given positive setpoint.

Stability is achieved by ensuring the complex balanced property of the controlled system using a reference Kirchhoff matrix prescribing a preferred graph structure and interconnection weights, and an appropriate nonlinear feedback. It is an important new result that the stabilizing feedback design is not stated as an optimization problem, but a necessary and sufficient algebraic condition is given for the computability, which also characterizes all possible solutions. Therefore, the computation of the feedback law requires straightforward matrix operations which can be performed efficiently. The control Lyapunov function of the partially closed loop system is an entropy-like logarithmic function ensuring global stability in the positive orthant. The kinetic state feedback is extended by an additional logarithmic feedback and a feedforward compensator which maintain global stability and ensure precise setpoint tracking at the same time.

The proposed computation approach was illustrated through a case study containing 3 sub-CRNs and 5 LTI connecting subsystems representing distributed delays caused by convection properties. The model also contains material recycle loops which are known to potentially complicate control design. It is shown that the computations are feasible, and simulation results show good control performance and simple tunability of the proposed method. Future work will be focused on the selection of feasible solutions and the tuning of controller parameters to satisfy predefined performance requirements. It is also planned to examine the possibility of relaxing certain assumptions and the extension of the approach to time-varying reaction rate coefficients.

CRediT authorship contribution statement

Lőrinc Márton: Conceptualization, Methodology, Investigation, Writing – original draft. **Gábor Szederkényi:** Conceptualization, Validation, Investigation, Writing – review & editing, Funding acquisition. **Katalin M. Hangos:** Conceptualization, Methodology, Investigation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

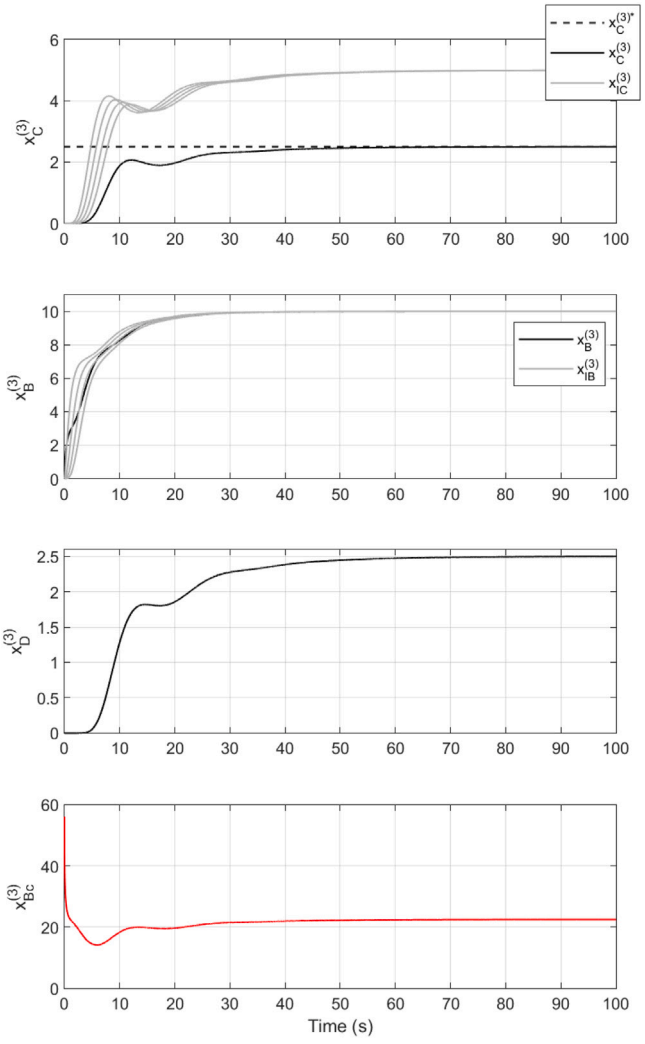

Fig. 7. The controlled states and control signal of subsystem 3.

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