



Formal reaction kinetics and related questions
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Modeling and control of interconnected CRNs

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- ▶ Open CRN Models
- ▶ Modeling Interconnected CRNs
- ▶ Passivity-based Control of CRNs
- ▶ Control of Interconnected CRNs

CRNs and Open CRN Models

The dynamic model of a Chemical Reaction Network (CRN) is built upon the following elements:

- ▶ *Species*: $\mathcal{S} := \{S_1 \dots S_n\}$ are constituent molecules undergoing (a series of) chemical reactions.
- ▶ *Complexes*: $\mathcal{C} := \{\mathcal{C}_1 \dots \mathcal{C}_m\}$ are formally linear combinations of the species, i.e. $\mathcal{C}_k := \sum_{i=1}^n \alpha_{k,i} S_i$, where $\alpha_{k,i}$ are non-negative integer stoichiometric coefficients.
- ▶ *Reactions*: $\mathcal{R} := \{\mathcal{R}_1 \dots \mathcal{R}_r\}$ where $\mathcal{R}_k : \mathcal{C}_i \rightarrow \mathcal{C}_j$. Here $\mathcal{C}_i$ is the reactant (or source) complex, and $\mathcal{C}_j$ is the product complex for $k = 1, \dots, r$.
- ▶ *Reaction rate coefficients*: $\kappa_k > 0$ that is associated to $\mathcal{R}_k$ for $k = 1, \dots, r$.

Under the assumption of mass action law, the dynamic behavior of the species' chemical concentration ($\mathbf{x} = (x_i)^T \in \mathbb{R}_{>0}^n$) during the reactions is given:

$$\dot{\mathbf{x}} = Y A_{\kappa} \varphi(\mathbf{x}), \quad \mathbf{x}(0) = \mathbf{x}_0 \in \mathbb{R}_{>0}^n$$

- ▶ $Y = [Y_{ij}] \in \mathbb{N}^{n \times m}$, $Y_{ij} = \alpha_{ij}$ is the *complex composition matrix*
- ▶ $A_{\kappa} \in \mathbb{R}^{m \times m}$ is the so-called *Kirchhoff matrix* containing the reaction rate coefficients:

$$A_{\kappa}(i, j) = \begin{cases} \kappa_{ji}, & \text{for } j \neq i \\ -\sum_{\ell \neq j} \kappa_{j\ell}, & \text{if } j = i. \end{cases}$$

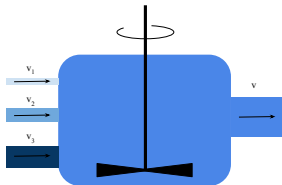
- ▶ $\varphi_j(\mathbf{x}) = \prod_{i=1}^n x_i^{\alpha_{ij}}$ for $j = 1, \dots, m$ are *monomial functions*



Consider *constant volume* $\mathcal{V}$ in the reactor where the reactions take place:

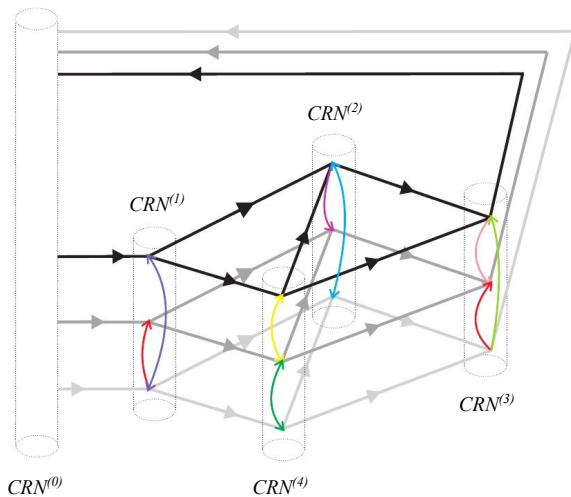
$$\dot{\mathbf{x}} = Y A_{\kappa} \varphi(\mathbf{x}) + \frac{1}{\mathcal{V}} (\text{diag}(v_i) \mathbf{x}_I - v \mathbf{x}), \quad \text{where} \quad v = \sum_{i=1}^n v_i.$$

- ▶ $\mathbf{x}_I$ - concentration of inlet species
- ▶ v - volumetric flow rate



As follows we assume that $\mathcal{V} = 1$.

Physically Motivated Interconnections

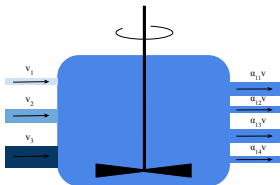


The dynamics of the j th open CRN reads as:

$$\dot{\mathbf{x}}^{(j)} = Y^{(j)} A_{\kappa}^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \sum_{\ell \in \mathcal{N}_I^{(j)}} \alpha_{\ell j} v_{\ell} \mathbf{x}^{(\ell)} - v_j \mathbf{x}^{(j)}$$

The outlet of the j th CRN is divided into fractions with the fraction coefficients α_{ji} and are fed into the neighboring CRNs.

$$\sum_{i \in \mathcal{N}_O^{(j)}} \alpha_{ji} = 1$$



Let the *Kirchhoff convection matrix* of the interconnected CRN structure:

$$\mathbf{C}_\kappa = \begin{bmatrix} -v_1 & \alpha_{21}v_2 & \dots & \alpha_{N1}v_N \\ \alpha_{12}v_1 & -v_2 & \dots & \alpha_{N2}v_N \\ \dots & \dots & \dots & \dots \\ \alpha_{1N}v_1 & \alpha_{2N}v_2 & \dots & -v_N \end{bmatrix}$$

- ▶ Due to the definition of fraction coefficients, the column sum is zero, e.g. $\sum_{j=2}^N \alpha_{1j} = 0$.
- ▶ Due to the constant volume assumption, the row sum is zero, e.g. $\sum_{\ell=2}^N \alpha_{\ell 1} v_\ell = v_1$.

Subsystem models with *delay*:

$$\dot{\mathbf{x}}^{(j)} = Y^{(j)} A_{\kappa}^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \sum_{\ell \in \mathcal{N}_I^{(j)}} \alpha_{\ell j} v_{\ell} \mathbf{x}_{T_i}^{(\ell)} - v_j \mathbf{x}^{(j)},$$

- ▶ Discrete delay: $x_{T_i}^{(\ell)} = x_i^{(\ell)}(t - T_{\ell j})$, $T_{\ell j} > 0$ delay value.
- ▶ Distributed delay:

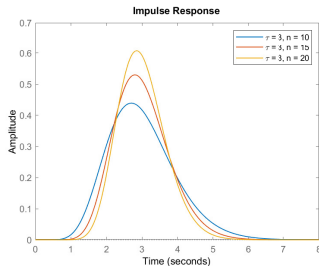
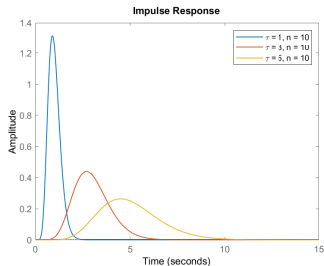
$$x_{T_i}^{(\ell)}(t) = \int_0^{\infty} g(\tau) x_i^{(\ell)}(t - \tau) d\tau = \int_{-\infty}^t g(t - \tau) x_i^{(\ell)}(t) d\tau$$

Here $g(\tau)$ is at least piece-wise continuous *kernel function* such that $\int_0^{\infty} g(\tau) d\tau = 1$.

Example: *Gamma-type kernel function*

$$g(t) = \frac{(n/T)^n e^{-nt/T}}{(n-1)!}$$

- ▶ T is a scaling parameter (time constant)
- ▶ n is a shape parameter (order of the system)



Let a single input – single output *Linear Time-Invariant* (LTI) system with state-space representation

$$\begin{aligned}\dot{\mathbf{x}}(t) &= A\mathbf{x}(t) + Bu(t), & \mathbf{x}(0) &= \mathbf{0} \\ y(t) &= C\mathbf{x}(t)\end{aligned}$$

where $\mathbf{x}(t) : \mathbb{R} \rightarrow \mathbb{R}^n$ are the time-dependent internal states, $y(t), u(t) : \mathbb{R} \rightarrow \mathbb{R}$ are the inputs and outputs respectively. The output of the LTI system:

$$y(t) = \int_0^t \underbrace{Ce^{A\tau}B}_{g(\tau)} u(t - \tau) d\tau$$

Here $g(t)$ is the output when the input is the Dirac-delta.

The output of an LTI system:

$$y(t) = \int_0^t \underbrace{C e^{A\tau} B}_{g(\tau)} u(t - \tau) d\tau$$

The distributed delay operator:

$$y(t) = \int_0^\infty g(\tau) u(t - \tau) d\tau$$

This suggests that LTI systems can be a (truncated) approximation of the distributed delay terms in dynamic models for some types of kernel functions.

Example: *Gamma-type kernel function with $n = 1$*

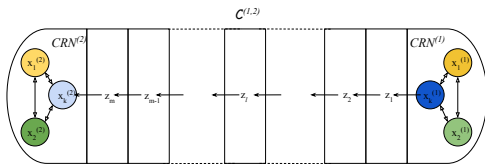
$$y(t) = \int_0^\infty \underbrace{\frac{1}{T} e^{-\tau/T}}_{g(\tau)} u(t - \tau) d\tau$$

The corresponding ODE:

$$\dot{y}(t) = v(u(t) - y(t))$$

Here $v = 1/T$ is the flow rate coefficient.

Example: *Linear chains*



$$\dot{z}_\ell = v(z_{\ell-1} - z_\ell) \quad \dot{z}_1 = v(x_k^{(1)} - z_1)$$

The corresponding LTI approximate model is a *linear chain model* with the following terms

$$A = \begin{bmatrix} -v & 0 & \dots & 0 & 0 \\ v & -v & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & v & -v \end{bmatrix} \quad B = \begin{bmatrix} v \\ 0 \\ \dots \\ 0 \end{bmatrix} \quad C^T = \begin{bmatrix} 0 \\ 0 \\ \dots \\ v \end{bmatrix}$$

Let two CRNs be connected in the following way:

$$\dot{\mathbf{x}}^{(i)} = Y^{(i)} A_{\kappa}^{(i)} \varphi^{(i)}(\mathbf{x}^{(i)}) + \delta(\mathbf{x}^{(j)} - \mathbf{x}^{(i)})$$

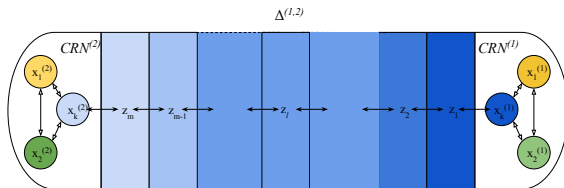
$$\dot{\mathbf{x}}^{(j)} = Y^{(j)} A_{\kappa}^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \delta(\mathbf{x}^{(i)} - \mathbf{x}^{(j)})$$

The interconnection flow is driven by the concentration (state) difference.

The interconnection term $\delta(\mathbf{x}^{(j)} - \mathbf{x}^{(i)})$ represents the simplest *static approximate diffusion model*.

The parameter $\delta > 0$ is the diffusion rate coefficient.

ODE model for *spatially discretized diffusion*



$$\dot{z}_\ell = \delta(z_{\ell-1} - z_\ell) + \delta(z_{\ell+1} - z_\ell)$$

$$\dot{z}_1 = \delta(z_2 - z_1) + \delta(x_k^{(1)} - z_1)$$

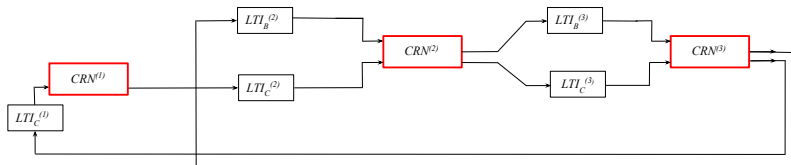
$$\dot{z}_m = \delta(z_{m-1} - z_m) + \delta(x_k^{(2)} - z_m)$$

ODE approximation: Two input – two output LTI system with the following terms

$$\begin{aligned}\dot{\mathbf{x}} &= A\mathbf{x} + B\mathbf{u}, \quad \mathbf{x}(0) = \mathbf{x}_0 \\ \mathbf{y} &= C\mathbf{x}\end{aligned}$$

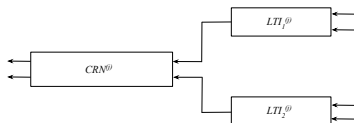
$$A = \begin{bmatrix} -2\delta & \delta & \dots & 0 & 0 \\ \delta & -2\delta & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \delta & -2\delta \end{bmatrix} \quad B = \begin{bmatrix} \delta & 0 \\ 0 & 0 \\ \dots & \dots \\ 0 & \delta \end{bmatrix} \quad C^T = \begin{bmatrix} \delta & 0 \\ 0 & 0 \\ \dots & \dots \\ 0 & \delta \end{bmatrix}$$

These cases (distributed delay, diffusion) motivate the analysis of such networks of CRNs in which the interconnections are LTI systems.



CRN Model of Interconnected CRNs





One directional case: a number of m species is transferred among the CRN subsystems.

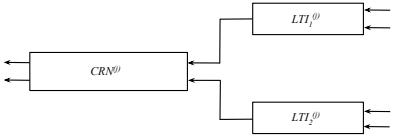
$$CRN^{(j)} : \dot{\mathbf{x}}^{(j)} = Y^{(j)} A_{\kappa}^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \sum_{\ell=1}^m F_{\ell}^{(j)} y_{I\ell}^{(j)} - H^{(j)} \mathbf{x}^{(j)}, \quad \mathbf{x}^{(j)}(0) = \mathbf{x}_0^{(j)}$$

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

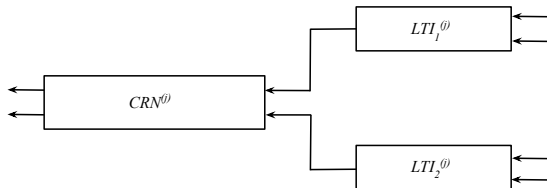
- ▶ Motivated by the physical examples we assume that $A_\ell^{(j)}$ is Metzler and Hurwitz.
- ▶ The inflow rates are considered to be equal to the outflow rates both in the CRNs and LTI connecting subsystems.
Example: The cumulative inflow rate in the open $CRN^{(j)}$ subsystem is equal to the outflow rate from this subsystem, i.e. the row sum of the matrix below is zero:

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

The *extended subsystem* contains a CRN subsystem and the LTI connecting elements from its input neighborhood set.

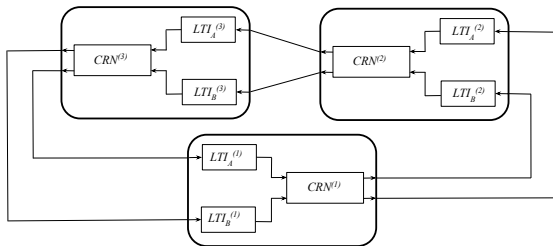


$$\begin{aligned}
 \underbrace{\begin{pmatrix} \dot{\mathbf{x}}^{(j)} \\ \mathbf{x}_{I_1}^{(j)} \\ \mathbf{x}_{I_2}^{(j)} \end{pmatrix}}_{\dot{\mathbf{x}}^{(j)}} &= \underbrace{\begin{pmatrix} Y^{(j)} & O & O & I \\ O & I & O & O \\ O & O & I & O \end{pmatrix}}_{\mathbf{Y}^{(j)}} \underbrace{\begin{pmatrix} A_{\kappa}^{(j)} & O & O & O \\ O & A_1^{(j)} & O & O \\ O & O & A_2^{(j)} & O \\ O & F_1^{(j)} C_1^{(j)} & F_2^{(j)} C_2^{(j)} & -H^{(j)} \end{pmatrix}}_{\mathbf{\bar{A}}_{\kappa}^{(j)}} \underbrace{\begin{pmatrix} \varphi^{(j)}(\mathbf{x}^{(j)}) \\ \mathbf{x}_{I_1}^{(j)} \\ \mathbf{x}_{I_2}^{(j)} \\ \mathbf{x}^{(j)} \end{pmatrix}}_{\Phi^{(j)}(\mathbf{X}^{(j)})} \\
 &+ \underbrace{\begin{pmatrix} O & O & O & O \\ O & O & O & B_{1f}^{(j)} H_1^{(f)} \\ O & O & O & B_{2f}^{(j)} H_2^{(f)} \end{pmatrix}}_{\mathbf{B}_f^{(j)}} \underbrace{\begin{pmatrix} \varphi^{(f)}(\mathbf{x}^{(f)}) \\ \mathbf{x}_{I_1}^{(f)} \\ \mathbf{x}_{I_2}^{(f)} \\ \mathbf{x}^{(f)} \end{pmatrix}}_{\Phi^{(f)}(\mathbf{X}^{(f)})} + \underbrace{\begin{pmatrix} O & O & O & O \\ O & O & O & B_{1g}^{(j)} H_1^{(g)} \\ O & O & O & B_{2g}^{(j)} H_2^{(g)} \end{pmatrix}}_{\mathbf{B}_g^{(j)}} \underbrace{\begin{pmatrix} \varphi^{(g)}(\mathbf{x}^{(g)}) \\ \mathbf{x}_{I_1}^{(g)} \\ \mathbf{x}_{I_2}^{(g)} \\ \mathbf{x}^{(g)} \end{pmatrix}}_{\Phi^{(g)}(\mathbf{X}^{(g)})}
 \end{aligned}$$

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

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

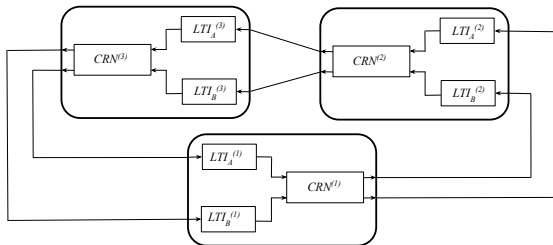


The state-space realization of the networks has the form:

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

Proposition: The matrices $\mathbf{B}_i^{(j)}$, can be factorized as:

$$\mathbf{B}_i^{(j)} = \mathbf{Y}^{(j)} \mathbf{B}_{Ei}^{(j)}, \text{ where } \mathbf{B}_{Ei}^{(j)} = \begin{pmatrix} \mathbf{B}_i^{(j)} \\ \mathbf{O} \end{pmatrix}$$

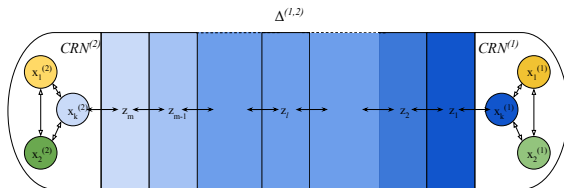


The dynamic network model can be rewritten in the form:

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

The model of the interconnected system has CRN form:

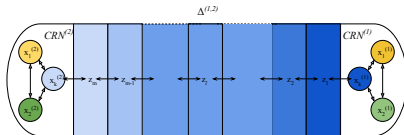
$$\dot{\mathbf{X}} = \mathbf{Y} \mathbf{A}_{\kappa} \Phi(\mathbf{X}).$$



$$\dot{z}_1 = \delta(z_2 - z_1) + \delta(x_k^{(1)} - z_1)$$

$$\dot{z}_m = \delta(z_{m-1} - z_m) + \delta(x_k^{(2)} - z_m)$$

The highlighted terms are included in the CRN models at the boundaries. Let the terms of the modified model be $(\bar{Y}^{(1)}, \bar{A}_\kappa^{(1)})$, and $(\bar{Y}^{(2)}, \bar{A}_\kappa^{(2)})$ respectively.



$$\mathbf{x} = \begin{bmatrix} \mathbf{x}^{(1)} \\ \mathbf{z} \\ \mathbf{x}^{(2)} \end{bmatrix} \quad \mathbf{Y} = \begin{bmatrix} \overline{\mathbf{Y}}^{(1)} & 0 & 0 \\ 0 & I & 0 \\ 0 & 0 & \overline{\mathbf{Y}}^{(2)} \end{bmatrix} \quad \mathbf{A}_\kappa = \begin{bmatrix} \overline{\mathbf{A}}_\kappa^{(1)} & Q_{11} & 0 \\ Q_{12} & A_\Delta & Q_{21} \\ 0 & Q_{22} & \overline{\mathbf{A}}_\kappa^{(2)} \end{bmatrix}$$

$$Q_{11} = \begin{bmatrix} 0 & 0 \\ \cdots & \cdots \\ 0 & \delta \end{bmatrix} \quad Q_{12} = \begin{bmatrix} 0 & \cdots & 0 \\ 0 & \cdots & \delta \end{bmatrix} \quad A_\Delta = \begin{bmatrix} -2\delta & \delta & \cdots & 0 & 0 \\ \delta & -2\delta & \cdots & 0 & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & \delta & -2\delta \end{bmatrix}$$

$$Q_{22} = \begin{bmatrix} 0 & 0 \\ \cdots & \cdots \\ \delta & 0 \end{bmatrix} \quad Q_{21} = \begin{bmatrix} 0 & \cdots & \delta \\ 0 & \cdots & 0 \end{bmatrix}$$

The global model of the interconnected system:

$$\dot{\mathbf{x}} = \mathbf{Y} \mathbf{A}_\kappa \varphi(\mathbf{x})$$

Control – Theory of Passive Systems

Let the open dynamic system:

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}), \quad \mathbf{x}(0) = \mathbf{x}_0$$

$$\mathbf{y} = \mathbf{h}(\mathbf{x})$$

- ▶ *Control problem:* Design $\mathbf{u}$ in the function of $\mathbf{y}$ such to achieve desired dynamic and steady-state proprieties for the (controlled) system states.
- ▶ Example: all the states remain bounded and the output converge to a prescribed constant *setpoint*.

$$\lim_{t \rightarrow \infty} \mathbf{y} = \mathbf{y}_{SP}$$

Let the same open dynamic system:

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}), \quad \mathbf{x}(0) = \mathbf{x}_0$$

$$\mathbf{y} = \mathbf{h}(\mathbf{x})$$

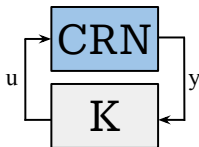
- Static *feedback control*:

$$\mathbf{u} = \mathbf{u}(\mathbf{y})$$

- Example: *linear control*

$$\mathbf{u} = -K\mathbf{y}, \quad K = (k_{ij})$$

- The controlled system is autonomous: $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}(\mathbf{h}(\mathbf{x})))$



Let a dynamic system

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad \mathbf{x}(0) = \mathbf{x}_0,$$

Notions from Lyapunov's stability theory:

- ▶ Let $\mathbf{x}^*$ be an *equilibrium point* of the system, i.e. $\mathbf{f}(\mathbf{x}^*) = \mathbf{0}$
- ▶ The equilibrium point $\mathbf{x}^* = \mathbf{0}$ is *asymptotically stable* if $\forall \rho > 0 \exists r > 0$ such that $\|\mathbf{x}_0\| < r$ implies $\|\mathbf{x}(t)\| < \rho, \quad \forall t$ and $\lim_{t \rightarrow \infty} \|\mathbf{x}(t)\| = 0$.
- ▶ *Lyapunov's direct method:* Let a *storage function* $S(\mathbf{x}) : \mathbb{R}^n \rightarrow \mathbb{R}$ assigned to the system such that $S(\mathbf{x}) > 0, \forall \mathbf{x} \neq \mathbf{0}$ and $S(\mathbf{0}) = 0$. If $\dot{S}(\mathbf{x}) < 0, \forall \mathbf{x} \neq \mathbf{0}$, then the system is asymptotically stable.
Note that for uniform and global stability decreasency or radial unboundedness proprieties of S are required.

Let an *open* dynamic system

$$\begin{aligned}\dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}, \mathbf{u}), \quad \mathbf{x}(0) = \mathbf{x}_0 \\ \mathbf{y} &= \mathbf{h}(\mathbf{x})\end{aligned}$$

$\mathbf{u}, \mathbf{y} : \mathbb{R} \rightarrow \mathbb{R}^m$ are the (control) input and output vectors.

- ▶ The system is *passive* if $\exists \beta$ constant such that

$$\int_0^t \mathbf{y}^T \mathbf{u} d\tau \geq \beta \quad \forall \mathbf{u}(t).$$

- ▶ If there exists a continuously differentiable storage function $S(\cdot) \geq 0$ such that

$$S(t) \leq \int_0^t \mathbf{y}^T \mathbf{u} d\tau + S(t=0) \quad \text{or} \quad \dot{S}(t) \leq \mathbf{y}^T \mathbf{u},$$

then the system is passive.



Let an *input-affine* system:

$$\begin{aligned}\dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}) + G(\mathbf{x})\mathbf{u}, \quad \mathbf{x}(0) = \mathbf{x}_0 \\ \mathbf{y} &= \mathbf{h}(\mathbf{x})\end{aligned}$$

$G(\mathbf{x}) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times m}$ is a state-dependent input matrix.

- If there exists a continuously differentiable storage function $S(\cdot) \geq 0$, $S(\mathbf{0}) = 0$ such that

$$\begin{aligned}\frac{\partial S}{\partial \mathbf{x}} \mathbf{f}(\mathbf{x}) &\leq 0 \\ \text{and} \quad \frac{\partial S}{\partial \mathbf{x}} G(\mathbf{x}) &= \mathbf{h}(\mathbf{x})\end{aligned}$$

then the system is passive.

Let the dynamic system:

$$\begin{aligned}\dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}, \mathbf{u}), \quad \mathbf{x}(0) = \mathbf{x}_0 \\ \mathbf{y} &= \mathbf{h}(\mathbf{x})\end{aligned}$$

- ▶ The system is *zero state detectable* if $\mathbf{y} = \mathbf{0}$ and $\mathbf{u} = \mathbf{0}$ implies that the steady-state of $\mathbf{x} = \mathbf{0}$.
- ▶ If the system is zero state detectable and *passive*, then the linear diagonal control $\mathbf{u} = -K\mathbf{y}$ *asymptotically stabilizes* the equilibrium state $\mathbf{0}$. Here $K = \text{diag}(k_i)$, $k_i > 0$.

Let the input-affine system:

$$\begin{aligned}\dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}) + G(\mathbf{x})\mathbf{u}, \quad \mathbf{x}(0) = \mathbf{x}_0 \\ \mathbf{y} &= \mathbf{h}(\mathbf{x})\end{aligned}$$

- ▶ Let the control transformation:

$$\mathbf{u} = \mathbf{f}_p(\mathbf{x}) + G_p(\mathbf{x})\mathbf{u}_p$$

- ▶ The system with control:

$$\begin{aligned}\dot{\mathbf{x}} &= \underbrace{\mathbf{f}(\mathbf{x}) + G(\mathbf{x})\mathbf{f}_p(\mathbf{x})}_{f_c(\mathbf{x})} + \underbrace{G(\mathbf{x})G_p(\mathbf{x})}_{G_c(\mathbf{x})} \mathbf{u}_p, \\ \mathbf{y} &= \mathbf{h}(\mathbf{x})\end{aligned}$$

- ▶ The selection of the output ($\mathbf{y}$) and the construction of the feedback transformation $\mathbf{u}$ called *feedback passivation*.

Passivity-based Control of CRNs

Let the CRN model

$$\dot{\mathbf{x}} = Y A_{\kappa} \varphi(\mathbf{x}), \quad \mathbf{x}(0) = \mathbf{x}_0$$

- ▶ An equilibrium point of a CRN's dynamic model satisfies

$$Y A_{\kappa} \varphi(\mathbf{x}^*) = \mathbf{0}$$

- ▶ The CRN is called *complex balanced* if

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

i.e. the signed sum of incoming and outgoing reaction rates at equilibrium is zero for each complex.

- ▶ If the complex balanced property is satisfied for an equilibrium point, then it is fulfilled for all the other equilibrium points.

Let the open CRN model

$$\dot{\mathbf{x}} = Y A_{\kappa} \varphi(\mathbf{x}) + \mathbf{u}, \quad \mathbf{x}(0) = \mathbf{x}_0$$

The model is passive from the input $\mathbf{u}$ to the output

$$\mathbf{y} = \text{Ln}(\mathbf{x}) - \text{Ln}(\mathbf{x}^*)$$

with respect to the storage function

$$S(\mathbf{x}) = \sum_{i=1}^n \left[x_i \left(\ln \frac{x_i}{x_i^*} - 1 \right) + x_i^* \right].$$

if the CRN is complex balanced.

L. Márton, K. M. Hangos, G. Szederkényi, Disturbance Attenuation via Nonlinear Feedback for
Chemical Reaction Networks, IFAC-PapersOnLine, Vol. 53, No. 2, 2020, pp 11497-11502.



Let the open CRN model

$$\dot{\mathbf{x}} = Y A_{\kappa} \varphi(\mathbf{x}) + B \mathbf{u} + \mathbf{d}, \quad \mathbf{x}(0) = \mathbf{x}_0$$

Here $\mathbf{d}$ is an unknown *disturbance* rate, B is the input matrix.

The control problem:

- ▶ Let a *setpoint* concentration $\mathbf{x}_{SP} > \mathbf{0}$ chosen from the equilibrium point set of the CRN.
- ▶ If $\mathbf{d} = \mathbf{0}$, design the control $\mathbf{u}$ such that $\lim_{t \rightarrow \infty} \mathbf{x} = \mathbf{x}_{SP}$ or equivalently $\lim_{t \rightarrow \infty} \mathbf{y} = \lim_{t \rightarrow \infty} (\text{Ln}(\mathbf{x}) - \text{Ln}(\mathbf{x}_{SP})) = \mathbf{0}$.
- ▶ If $\mathbf{d} \neq \mathbf{0}$, ensure *disturbance attenuation*, i.e. “minimize” the effect of $\mathbf{d}$ on $\mathbf{y}$.

The control has a passivation feedback term and a setpoint tracking term:

$$\mathbf{u} = \mathbf{u}_p + \mathbf{u}_t$$

- ▶ The first term ($\mathbf{u}_p$) modifies the rate such that the dynamics of the controlled CRN “mimics” the dynamics of a complex balanced CRN with the same monomial vector.
- ▶ The second term ($\mathbf{u}_t$) ensures the setpoint tracking of the CRN in the presence of disturbances.

- ▶ First, design a reference Kirchhoff matrix $A_{\kappa ref}$ such that

$$A_{\kappa ref} \varphi(\mathbf{x}_{SP}) = \mathbf{0}$$

- ▶ Let the passivation feedback in the form:

$$\mathbf{u}_p = K_p \varphi(\mathbf{x})$$

- ▶ We can design such feedback iff

$$BB^\dagger Y (A_{\kappa ref} - A_\kappa) = Y (A_{\kappa ref} - A_\kappa)$$

- ▶ If the solvability condition holds, the solution is

$$K_p = B^\dagger Y (A_{\kappa ref} - A_\kappa) + \left(I - B^\dagger B \right) Z$$

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

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

- ▶ Let a diagonal matrix P_j in the form:

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

- ▶ Let $a_j > 0$ and

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

- ▶ The reference Kirchhoff matrix can be constructed as:

$$A_{\kappa ref}^{(j)} = a_j A_0^{(j)} P_j^{-1} = \begin{pmatrix} -\frac{a_j}{x_1^{(j)*} x_2^{(j)*}} & \frac{a_j}{x_3^{(j)*}} \\ \frac{a_j}{x_1^{(j)*} x_2^{(j)*}} & -\frac{a_j}{x_3^{(j)*}} \end{pmatrix}.$$

Let $\mathbf{u}_t = -K_t \mathbf{y} = -K_t (\text{Ln}(\mathbf{x}) - \text{Ln}(\mathbf{x}^*))$.

- ▶ With this control, the CRN model has the form:

$$\dot{\mathbf{x}} = Y A_{\kappa ref} \varphi(\mathbf{x}) - K_t \mathbf{y} + \mathbf{d}.$$

- ▶ The time-derivative of the storage function satisfies

$$\dot{S} \leq \mathbf{y}^T (-K_t \mathbf{y} + \mathbf{d})$$

- ▶ If the controller gain matrix is chosen such that $k_t > \frac{1}{2} \left(1 + \frac{1}{\gamma}\right)$, where $\gamma > 0$ is the *prescribed disturbance attenuation level*, then the disturbance attenuation control objective $\int_0^t \mathbf{y}^T \mathbf{y} \leq \gamma \int_0^t \mathbf{d}^T \mathbf{d} + S(0)$ is achieved.

Realistic implementation of the control:

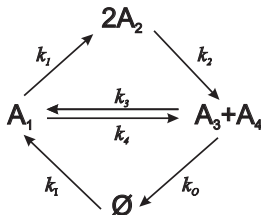
$$\mathbf{u} = \mathbf{u}_p + \mathbf{u}_t =: \text{diag}(v_i)\mathbf{x}_I - v\mathbf{x}$$

The input concentration ($\mathbf{x}_I > \mathbf{0}$) is manipulated by the control mechanism.

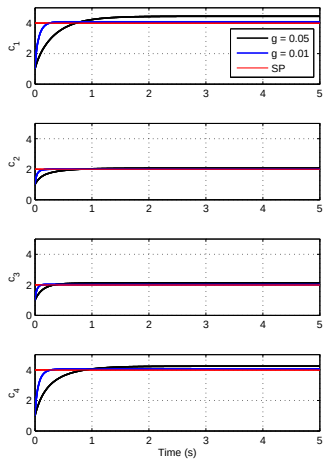
Ensuring *positivity* for $\mathbf{x}_I$ by manipulating the volumetric flow rate v :

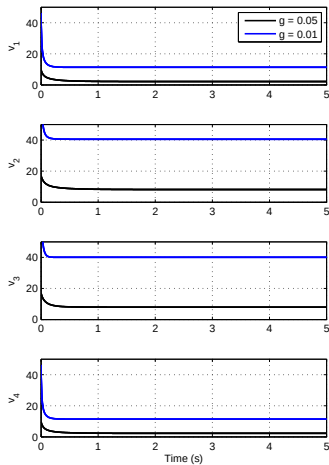
- ▶ Technical assumption 1: $0 < \varepsilon < x_i < x_M$
- ▶ Technical assumption 2: $-u_M < u_i < u_M$
- ▶ Design v_i such that $x_{Ii} = \frac{1}{v_i}(u_i + vx_i) > 0$ regardless of the sign of u_i .

CRN with constant inflows and mass action kinetics outflows

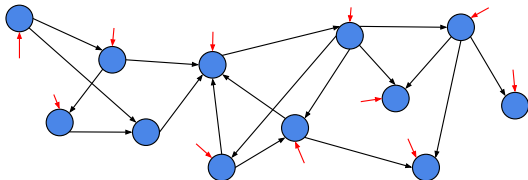


$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix} = \underbrace{\begin{pmatrix} -(k_1 + k_4) & 0 & k_3 \\ 2k_1 & -2k_2 & 0 \\ k_4 & k_2 & -k_3 \\ k_4 & k_2 & -k_3 \end{pmatrix}}_M \begin{pmatrix} x_1 \\ x_2^2 \\ x_3 x_4 \end{pmatrix} - \underbrace{\begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & k_O \\ 0 & 0 & k_O \end{pmatrix}}_{K_O} \begin{pmatrix} x_1 \\ x_2^2 \\ x_3 c_4 \end{pmatrix} + \underbrace{\begin{pmatrix} k_I \\ k_I \\ 0 \\ 0 \end{pmatrix}}_{K_I \mathbf{1}} + \underbrace{\begin{pmatrix} v_1 x_{I1} - v x_1 \\ v_2 x_{I2} - v x_2 \\ v_3 x_{I3} - v x_3 \\ v_4 x_{I4} - v x_4 \end{pmatrix}}_{V \mathbf{x}_I - v \mathbf{x}}.$$





Control of Interconnected CRNs

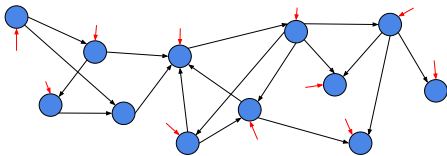


Let a network of subsystems

$$\begin{aligned}\dot{\mathbf{x}}^{(j)} &= \mathbf{f}^{(j)}(\mathbf{x}^{(j)}) + G^{(j)}(\mathbf{x}^{(j)})\mathbf{u}^{(j)}, \quad \mathbf{x}^{(j)}(0) = \mathbf{x}_0^{(j)} \\ \mathbf{y}^{(j)} &= \mathbf{h}^{(j)}(\mathbf{x}^{(j)})\end{aligned}$$

The outputs of the network's subsystems are *synchronized* if

$$\lim_{t \rightarrow \infty} \|\mathbf{y}^{(\ell)}(t) - \mathbf{y}^{(j)}(t)\| = 0, \quad \forall \ell, j$$



The network is synchronized if:

- ▶ All the subsystems are passive.
- ▶ The underlying graph of the network is strongly connected (there is a path from each vertex to each vertex)
- ▶ The inputs of the subsystems are:

$$\mathbf{u}^{(j)}(t) = k \left(\sum_{\ell \in \mathcal{N}_I^{(j)}} \mathbf{y}^{(\ell)}(t) - \mathbf{y}^{(j)}(t) \right), \quad k > 0$$

- CRN subsystem model:

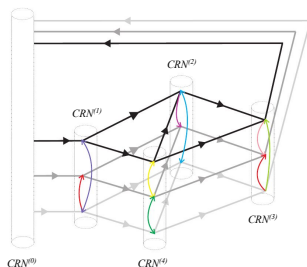
$$\frac{d\mathbf{x}^{(j)}}{dt} = Y^{(j)} A_{\kappa}^{(j)} \varphi^{(j)}(\mathbf{x}^{(j)}) + \underbrace{\sum_{\ell \in \mathcal{N}_{IN}^{(j)}} a_{\ell j} v_{\ell} \mathbf{x}^{(\ell)}(t - T_{\ell j})}_{\text{Interconnection Inflow}} + \underbrace{a_{Lj} v_j \mathbf{x}_C^{(j)}}_{\text{Control Inflow}} - \underbrace{v_{Oj} \mathbf{x}^{(j)}}_{\text{Outflow}} + \underbrace{\mathbf{d}^{(j)}}_{\text{Disturbance}}$$

- *Bounded disturbance* is assumed

$$\|\mathbf{d}^{(j)}\|_2 \leq d_M^{(j)}$$

- Network structure defined by the *Kirchhoff matrix*

$$\mathbf{C}_{\kappa} = \begin{bmatrix} -v_0 & \alpha_{10}v_1 & \dots & \alpha_{N0}v_N \\ \alpha_{01}v_0 & -v_1 & \dots & \alpha_{N1}v_N \\ \dots & \dots & \dots & \dots \\ \alpha_{0N}v_0 & \alpha_{1N}v_1 & \dots & -v_N \end{bmatrix}$$



The CRN network is connected through constant *inflows* (raw material) and constant *outflows* (products) to the *Environment*. Cumulative inflow rates are equal to cumulative outflow rates.

$$v_0 = \sum_{\ell=0}^N \alpha_{0\ell} v_\ell$$

Assume that the underlying graph of the interconnected system has such a *spanning tree* whose root is the Environment.

- ▶ Let the setpoint of the j th CRN be $\mathbf{x}_{SP}^{(j)}$ that belongs to the equilibrium point set of the j th CRN.
- ▶ Design the control input $\mathbf{x}_C$ for each CRN such to assure that

$$\lim_{t \rightarrow \infty} \|\mathbf{y}^{(j)}(t)\| \leq \varepsilon, \quad \forall \ell, j$$

where $\varepsilon > 0$ is a given *control precision* and

$$\mathbf{y}^{(j)} = \text{Ln}(\mathbf{x}^{(j)}) - \text{Ln}(\mathbf{x}_{SP}^{(j)})$$

L. Márton, G. Szederkényi, K. M. Hangos, Distributed control of interconnected Chemical Reaction Networks with delay, Journal of Process Control, Vol. 71, 2018, pp. 52-62



Let the control $\mathbf{x}_C^{(j)} = \mathbf{x}_p^{(j)} + \mathbf{x}_t^{(j)} + \mathbf{x}_{ff}^{(j)}$

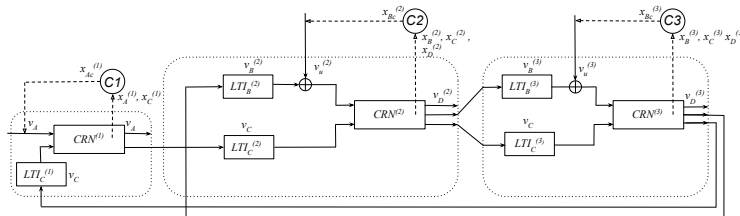
- ▶ $\mathbf{x}_p^{(j)} = K_p \varphi(\mathbf{x}^{(j)})$ - Local feedback to *ensure passivity*.
- ▶ $\mathbf{x}_t^{(j)} = -K_t \mathbf{y}^{(j)}$ - Setpoint tracking term.
- ▶ Feedforward term ($\mathbf{x}_{ff}^{(j)}$) - Compensates for the difference between the physical interconnections and passive outputs.

$$\mathbf{x}_{ff}^{(j)} = \frac{1}{\alpha_{Cj} v_j} \left(\sum_{\ell \in \mathcal{N}_{IN}^{(j)}} \alpha_{\ell j} v_\ell \left(\mathbf{y}^{(\ell)}(t - T_{\ell j}) - \mathbf{x}^{(\ell)}(t - T_{\ell j}) \right) - v_j \left(\mathbf{y}^{(j)} - \mathbf{x}^{(j)} \right) \right).$$

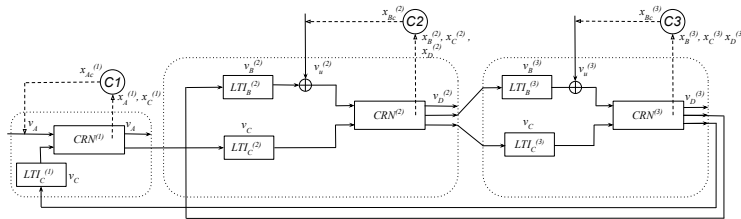
- Consider the Lyapunov-Krasovskii functional:

$$S_{\Sigma} = 2 \sum_{j=0}^N S^{(j)} + \sum_{j=0}^C \sum_{\ell=0}^N \alpha_{\ell j} v_{\ell} \int_{t-T_{\ell j}}^t \mathbf{y}^{(\ell)T} \mathbf{y}^{(\ell)} d\xi.$$

- If the controller gain matrix K_t is chosen such that $k_{ti} > 1 + \frac{d_{Mi}}{\varepsilon}$, it can be shown that $\dot{S}_{\Sigma} < 0$ for $\|\mathbf{y}^{(j)}(t)\| \geq \varepsilon$.



- ▶ The process system is designed to extract carbon dioxide (CO₂) from flue gases using lime hydrate (Ca(OH)₂).
- ▶ Unit 1 is for absorbing the carbon dioxide (specie A) in water that is in great excess and produces dissolved H₂CO₃ (carbonic acid - specie C): $A \xrightarrow{k^{(1)}} C$
- ▶ Units 2 and 3 realize a two-stage extractor where specie B (lime hydrate, Ca(OH)₂) and specie C (dissolved H₂CO₃) react to form specie D (rag-stone, CaCO₃): $B + C \xrightarrow{k} D$



- 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.

Example ($CRN^{(2)}$):

- Control-oriented modeling

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

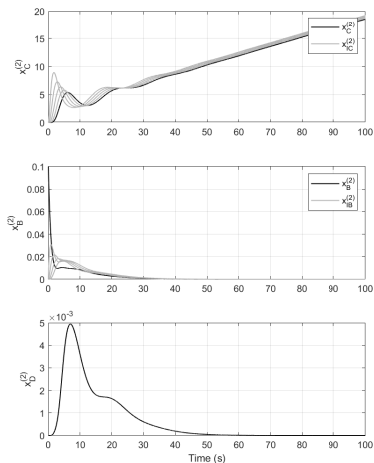
- The steady-state value of the specie B can be computed in function of the prescribed steady-state values of specie C :

$$k^{(2)} x_{BSP}^{(2)} x_{CSP}^{(2)} = v_C (x_{CSP}^{(1)} - x_{CSP}^{(2)})$$

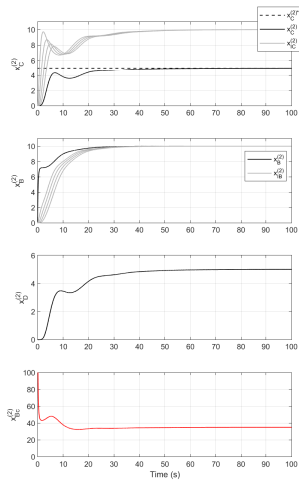
- The control input is the inlet concentration $x_{Bc}^{(2)}$:

$$x_{Bc}^{(2)} = \frac{v_D^{(2)}}{v_u^{(2)}} x_D^{(2)} + \frac{k_P^{(2)}}{v_u^{(2)}} \left(\ln(x_{BSP}^{(2)}) - \ln(x_B^{(2)}) \right) - \frac{v_B^{(2)}}{v_u^{(2)}} x_{BSP}^{(3)} + \frac{v_B^{(3)}}{v_u^{(2)}} x_{BSP}^{(2)}$$

Non-controlled states in subsystem 2



Controlled states and control signal of subsystem 2



- ▶ The global models of some interconnected CRNs with physically motivated interconnections (distributed delay, diffusion) also have a CRN model form with mass-action kinetics. This can be explored for analysis and control of these systems.
- ▶ The passivity theory is a convenient approach to develop setpoint tracking controllers for CRNs in the presence of disturbances.
- ▶ The synchronization problem of passive systems can also be applied to develop control methods for interconnected CRNs.
- ▶ The passivity-based control design approach is also suitable to control interconnected Lotka-Volterra systems see e.g.

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