Distributed delay model of the McKeithan's network

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Outline

Motivation and aim

- *kinetic systems* (CRNs with MAL) are useful and powerful representations of complex biochemical systems
- detailed CRN models in biochemistry are usually too complex for dynamic analysis and control
- *reduced order equivalent models* are needed

Aim: *reduction of the number of state variables in CRNs by allowing the introduction of delays* .

Mass action law CRNs

Elementary reaction step : transforms the complex C to the complex C'

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

- *complex composition matrix* (Y) with non-negative integer elements Y_{ij} such that $C = \sum_{i=1}^{n} y_i X_i$, and the column vector y represents C
- *reaction rate*

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

- *dynamics* (ODEs):

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

CRN: reaction graph and properties

Reaction graph $G = (V_d, E_d)$: weighted directed graph

- *vertices* correspond to complexes: $V_d = \{C_1, C_2, \dots C_m\}$
- *directed edges* represent reactions: $(C_i, C_j) \in E_d$ if complex C_i is transformed to C_j
- *reaction rate coefficients* : κ_{ij}, weights of the corresponding directed edges

Properties

- *weakly reversible CRN* : the reaction graph consists of ℓ strongly connected components
- *complex balanced CRN* : for each positive equilibrium $\overline{x}$ of the CRN

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

- stability implications

Chain of linear reactions

Example: linear CRN with n species participating in $(n-1)$ first order chemical reactions

- dynamics

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

- reaction graph

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

CRNs with discrete and distributed time delays

Extension to the elementary reaction step : a time delay τ or kernel g

$$C \xrightarrow{\kappa,\ \tau} C' \quad \text{or} \quad C \xrightarrow{\kappa,\ g} C'$$

- dynamics: *delay differential equations* (DDEs)
  discrete time delays

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

  distributed time delays: *kernel/distribution function* g_k ,
  $\int_0^\infty g_k(s)\, ds = 1$

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

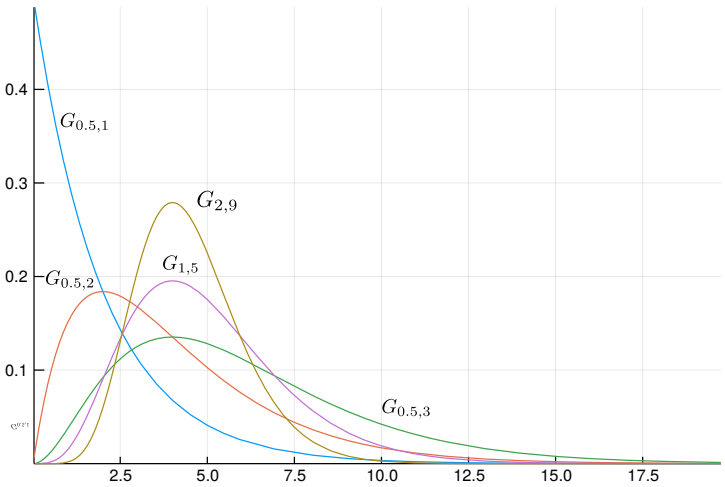
The linear chain trick

Given a delayed CRN which has only one reaction with Gamma distribution

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

Gamma distributions
(a: rate par., p shape par.)

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



Equivalent CRN model: no delay

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

reaction graph

$$C \xrightarrow{\kappa} V_1 \xrightarrow{a} V_2 \xrightarrow{a} \cdots \xrightarrow{a} V_p \xrightarrow{a} C'.$$

Transforming of chains of linear reactions

Given: *a part of a CRN that forms a chain of linear reactions with measurable (important) entrance and exit complexes in the form*

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

Steps of the algorithm

G1 Identify the kth chain

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

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

$$C_k \xrightarrow{\kappa_k,\ g_k} C_k',$$

where the kernel function of the distributed time delay is $g_k = G_{\tilde{\kappa}_k, N_k}$

Decoupling the chains of linear reactions

Aim of decoupling: *to obtain independent chains of linear reactions (with no common linear complexes).*

A necessary pre-processing step of the model transformation

- Given a first order complex U with a single incoming $C_{in} \xrightarrow{\kappa_{in}} U$,

  and multiple outgoing reactions $U \xrightarrow{\kappa_{out,i}} C_{out,i}, \quad i = 1, \ldots, N$
- Replace the complex U with a set of first order complexes $V^{(1)}, V^{(2)}, \ldots, V^{(N)}$ such that the corresponding state variables are $v^{(i)} = \frac{\kappa_{out,i}}{\kappa_{sum}} u$ with $\kappa_{sum} = \sum_{i=1}^{N} \kappa_{out,i}$
- Consider the new mutually independent reactions

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

The McKeithan's network

Model elements

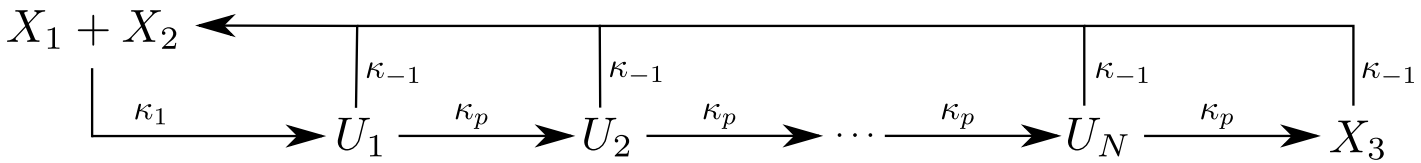
Species
X_1 (TCR=T-cell receptor),
X_2 (MHC=peptide major histocompatibility complex)
X_3 (final complex)
are measurable.

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

$$\dot{x}_3(t) = -\kappa_{-1}x_3(t) + \kappa_p u_N(t),$$

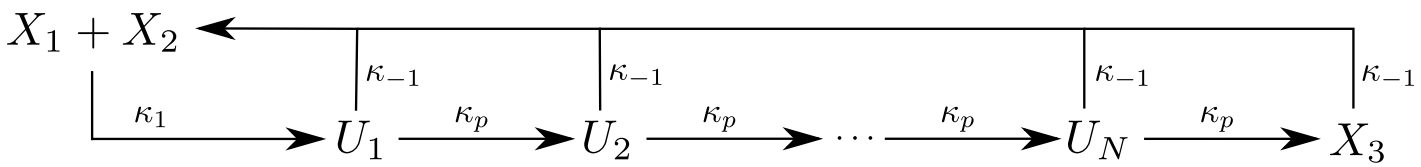
with the intermediates

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

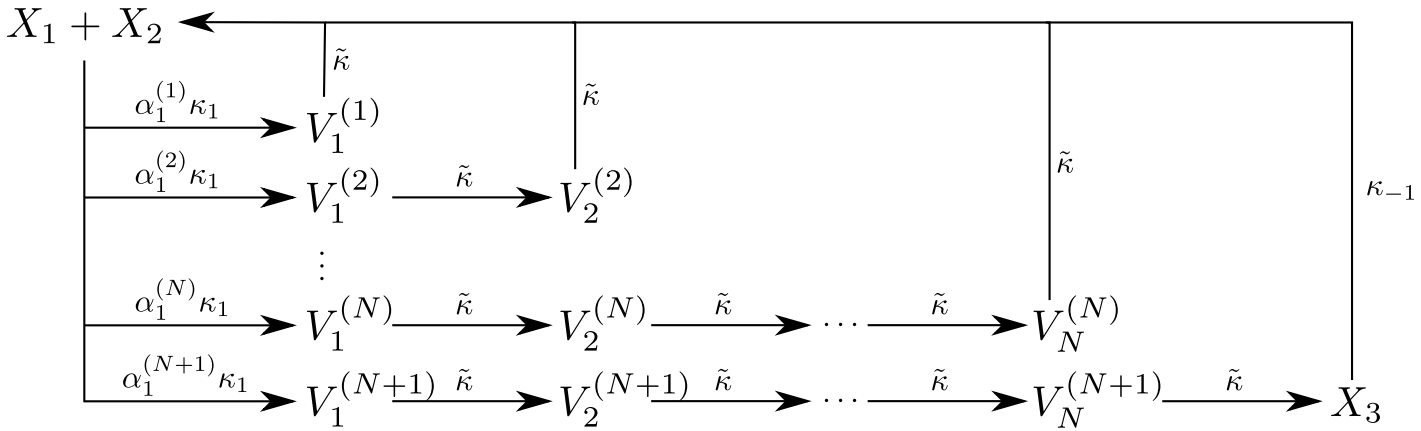


Decoupling the chains of linear reactions

The original reaction graph of the McKeithan's network



The transformed (decoupled) reaction graph



Development of the distributed delay model

Independent chains of linear reactions: $\beta = \left(\frac{\kappa_p}{\tilde{\kappa}}\right)^N$

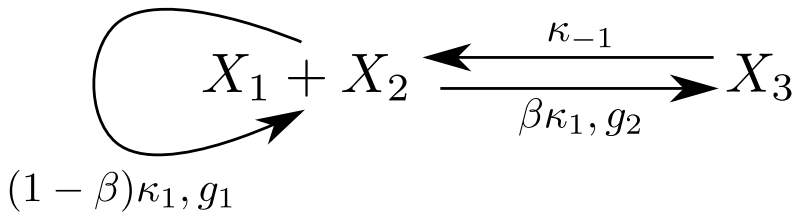
- final chain

$$X_1 + X_2 \xrightarrow{\alpha_1^{(N+1)}\kappa_1} V_1^{(N+1)} \xrightarrow{\tilde{\kappa}} V_2^{(N+1)} \xrightarrow{\tilde{\kappa}} \cdots \xrightarrow{\tilde{\kappa}} V_N^{(N+1)} \xrightarrow{\tilde{\kappa}} X_3 \quad \Rightarrow \quad \mathbf{X_1 + X_2} \xrightarrow{\beta\kappa_1,\ g_2} \mathbf{X_3}$$

- intermediate chains: $j = 1, ..., N$

$$X_1 + X_2 \xrightarrow{\alpha_1^{(j)}\kappa_1} V_1^{(j)} \xrightarrow{\tilde{\kappa}} V_2^{(j)} \xrightarrow{\tilde{\kappa}} \cdots \xrightarrow{\tilde{\kappa}} V_j^{(j)} \xrightarrow{\tilde{\kappa}} X_1 + X_2 \quad \Rightarrow \quad \mathbf{X_1 + X_2} \xrightarrow{(1-\beta)\kappa_1,\ g_1} \mathbf{X_1 + X_2}$$

Overall distributed delay model



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

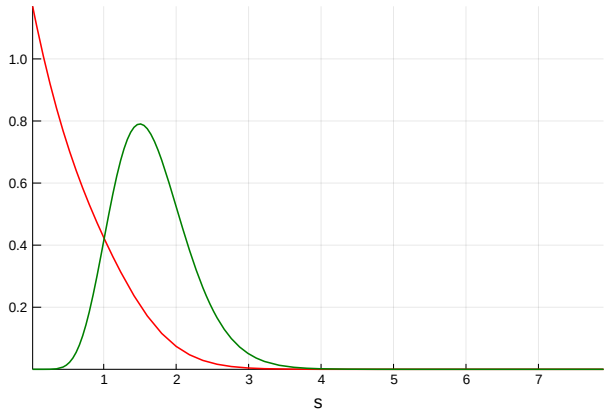
$$g_2(s) = G_{\tilde{\kappa},N}(s).$$

Distributed delay model of the McKeithan's network

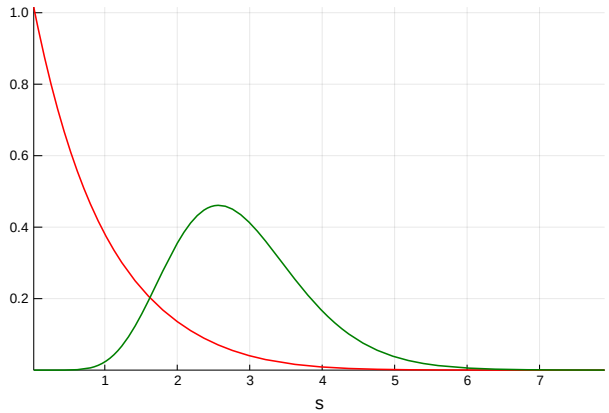
$$\dot{x}_{\{1,2\}}(t) = -\kappa_1 x_1(t)x_2(t) + \kappa_{-1}x_3(t) + (1-\beta)\,\kappa_1 \int_0^\infty g_1(s)x_1(t-s)x_2(t-s)ds,$$

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

$$g_1(s) = \frac{\kappa_{-1}}{(1-\beta)\tilde{\kappa}} \sum_{j=1}^{N} \left(\frac{\kappa_p}{\tilde{\kappa}}\right)^{j-1} G_{\tilde{\kappa},j}(s), \quad g_2(s) = G_{\tilde{\kappa},N}(s), \quad \beta = \left(\frac{\kappa_p}{\tilde{\kappa}}\right)^N$$

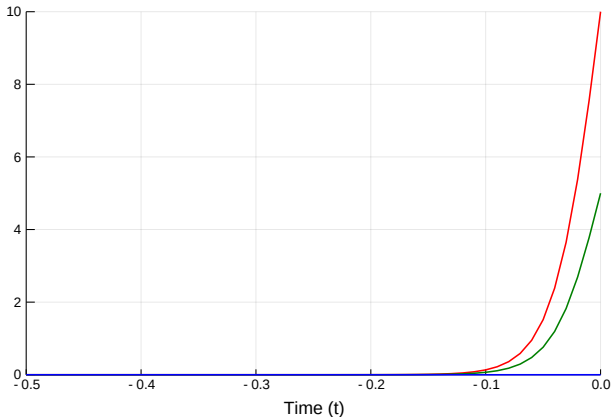


$\kappa_1 = 1$, $\kappa_p = 5$, $\kappa_{-1} = 1$, and $N = 10$,
red: g_1, green: g_2



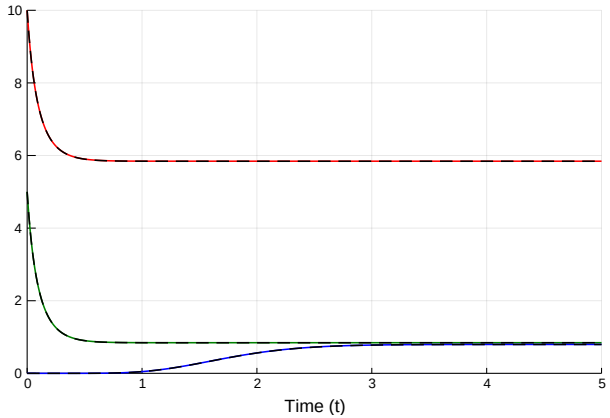
$\kappa_1 = 1$, $\kappa_p = 2.5$, $\kappa_{-1} = 1$, and $N = 10$

The dynamics of the time delayed and the original model of the McKeithan's network

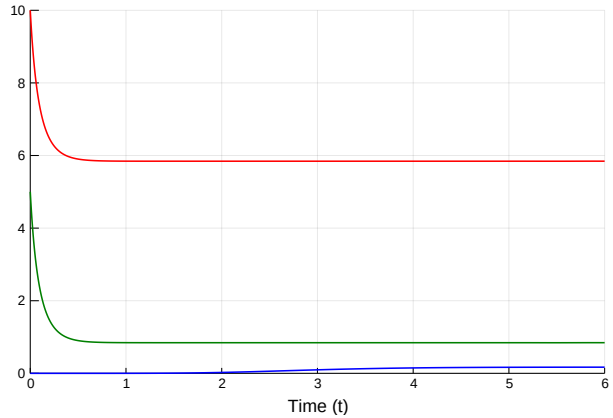


Initial functions: blue: θ_1, green: θ_2, red: θ_3

Time plots



$\kappa_1 = 1$, $\kappa_p = 5$, $\kappa_{-1} = 1$, and $N = 10$



$\kappa_1 = 1$, $\kappa_p = 2.5$, $\kappa_{-1} = 1$, and $N = 10$

Conclusions and future work

A novel model simplification method is proposed for complex ***CRN models with linear chains of reactions****. The method includes two steps:*

1. *Decomposition of coupled linear chains into independent ones*
2. *Replacing linear chains with single reactions using distributed time delays*

An equivalent model with less state variables but distributed delays is obtained.

Future work

- generalization to include description of **linear spatially distributed phenomena** (such as convection and diffusion)
- generalization to the bi-directional linear chain case