First Principles and Dynamics in Kinetic Systems

Katalin M. Hangos[1,2]

[1] Department of Electrical Engineering and Information Systems, University of Pannonia, Veszprém, Hungary
[2] Institute for Computer Science and Control, Budapest, Hungary

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Outline

Basic notions in *kinetic systems*

G. Szederkényi, A. Magyar, and K.M. Hangos. Analysis and Control of Polynomial Dynamic Models with Biological Applications. Academic Press, London, 2018.

Kinetic systems

Kinetic systems are *positive polynomial systems*

$$\dot{x}(t) = F(x,p) \quad x(0) = x_0 \tag{1}$$

where $F(x,p)$ is a multivariate vector-valued polynomial function with parameters p.

Positivity condition : $F_i(x,p)|_{x_i=0} \geq 0$ *on the positive orthant*
A system is kinetic if $F_i(x,p) = -x_i g_i(x) + h_i(x)$ *where* $g_i(x)$ *and* $h_i(x)$ *are polynomials with positive (non-negative) coefficients.*

Example

$$\frac{dx_1}{dt} = -k_1 x_1 x_2 + k_2 x_3$$
$$\frac{dx_2}{dt} = -k_1 x_1 x_2 + k_2 x_3$$
$$\frac{dx_3}{dt} = k_1 x_1 x_2 - k_2 x_3 + k_0$$

Mass action law CRNs

Elementary reaction step : transforms the complex C_k to the complex C_j

$$C_k \xrightarrow{\kappa_{kj}} C_j$$

- *complex composition matrix* (Y) with non-negative integer elements $Y_{ik} = y_{k,i}$ such that $C_k = \sum_{i=1}^{n} y_{k,i} X_i$, the column vector y_k represents C_k
- *reaction rate* (mass action): $\varphi_\ell(x) = \kappa_{kj} \prod_{i=1}^{n} x_i^{y_{k,i}} = \kappa_{kj} x^{y_k}$, x_i is the concentration of component/specie X_i
- *dynamics* (ODEs):

$$\dot{x}(t) = \sum_{kj=\ell=1}^{r} \kappa_{kj} \left(x(t)\right)^{y_k} [y'_k - y_k] = Y A_K \varphi(x), \qquad t \geq 0, \qquad (2)$$

- *Kirchhoff matrix (column conservation)* : $A_{K,ij} = \begin{cases} \kappa_{ij} & i \neq j \\ -\sum_{k=1}^{m} \kappa_{ik} & i = j \end{cases}$

CRN: reaction graph and properties

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

- *vertices* correspond to complexes: $V_d = \{C_1, C_2, \ldots C_m\}$
- *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
- the Kirchhoff matrix A_K determines the structure of the reaction graph

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

$$\sum_{k:\eta=y_k} \kappa_k(\overline{x})^{y_k} = \sum_{k:\eta=y'_k} \kappa_k(\overline{x})^{y_k}, \tag{3}$$

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

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

Realizations and dynamic equivalence

Given a kinetic system in the form

$$\dot{x}(t) = YA_K\varphi(x) \quad , \quad \varphi_\ell(x) = \kappa_{kj}x^{y_k}$$

Realization : the matrix pair (Y, A_K)

Two realizations (Y, A_K) *and* (Y', A'_K) *are* *dynamically equivalent* , *if* $YA_K = Y'A'_K$.
Usually $Y = Y'$ *is assumed.*

Usually there exist multiple dynamically equivalent realizations of a kinetic system.

Open CRN: a CRN with external elements

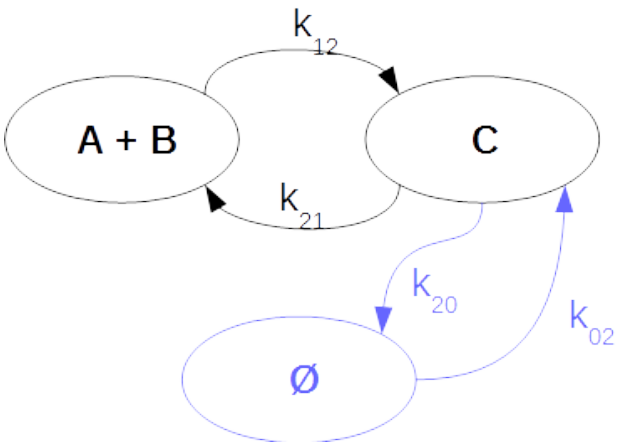
Open CRN: interaction with the environment (external elements)

Environment: a CRN with the same species

- no dynamic model is considered for the environment (constant concentrations)

Zero complex ($C_\emptyset = \emptyset$): $y_\emptyset = \underline{0}$

Example: in- and outflow of specie C - a *linear interaction*



$$\frac{dx_A}{dt} = -k_{12}x_Ax_B + k_{21}x_C$$

$$\frac{dx_B}{dt} = -k_{12}x_Ax_B + k_{21}x_C$$

$$\frac{dx_C}{dt} = k_{12}x_Ax_B - k_{21}x_C - k_{20}x_C + k_{02}u_C$$

u_C is the external (manipulable) concentration

First principles in kinetic systems

Conservation
(1st Law of thermodynamics)

A process systems view on CRNs

Model originates from dynamic conservation balances for component masses

State equations: component mass conservation balances in intensive form ($V = const$, $v_I = v_O$)

$$\frac{dx_{X_k}}{dt} = \frac{v_I}{V}(x_{I,X_k} - x_{X_k}) + R_{X_k} + S_{X_k} \qquad (*)$$

where R_{X_k} is the reaction rate and S_{X_k} is a source term (e.g. component mass exchange, diffusion)

System variables:

- *state variables: component concentrations* x_{X_k}, $k = 1, ..., K$
- *input variables: inlet concentrations* x_{I,X_k}, $k = 1, ..., K$

Conservation equation for the overall mass

Mass conservative (physically plausible) chemical reactions

For reaction $C_k \mapsto C_j$

$$\sum_{i=1}^{K} y_{k,i}\mathcal{M}_i \;=\; \sum_{i=1}^{K} y_{j,i}\mathcal{M}_i \;=\; c_s,$$

where $\mathcal{M}_i > 0$ is the molecular weight of the component X_i, k and j are column indexes in Y and $c_s > 0$ is a constant weighted column-sum.

Algebraic characterization

Molecular weight row vector $M = [\mathcal{M}_1, ..., \mathcal{M}_n]$

$$M \cdot y_k \;=\; M \cdot y_j \;=\; c_s, \quad \text{or} \quad M \cdot \rho^{(k,j)} = 0$$

Implications: ***no zero complex***, *no autocatalytic reaction*

The solution trajectories of conservative CRNs are bounded $\Rightarrow$ conservative CRN systems are BIBO stable.

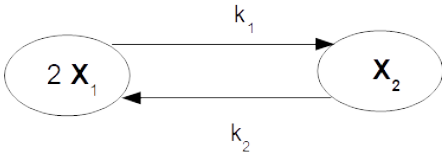
Stoichiometric subspace

Overall mass conservation implies

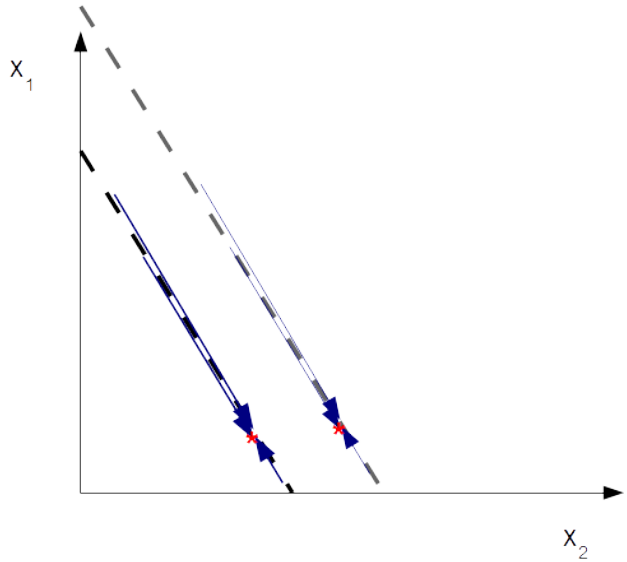
$$\sum_{i=1}^{K} \mathcal{M}_i x_i = C$$

i.e. the trajectories move on a lower dimensional linear manifold determined by the initial conditions .

Reaction graph



Stoichiometric subspace



Entropy-based Lyapunov function
(2nd Law of thermodynamics)

Equilibrium points and complex balance

The equilibrium (steady state) points can be obtained by solving the algebraic equations

$$0 = YA_K\varphi(\overline{x}) \quad , \quad \varphi_\ell(x) = \kappa_{kj}x^{y_k}$$

for element-wise non-negative $\overline{x}$.

There may be none or multiple equilibrium points due to the possible rank deficiency of the matrices Y and A_k, and the nonlinearity of φ.

Complex balance *(implies weak reversibility)*
An equilibrium point $\overline{x} \in \mathbb{R}^n_{>0}$ of the system is called complex balanced if $A_k \cdot \varphi(\overline{x}) = 0$.
It is known that if any equilibrium point of a CRN given by the pair (Y, A_k) is complex balanced, then all other equilibrium points are complex balanced, too.

Stability and Lyapunov function candidate

Given a positive equilibrium point $\overline{x}$ of a kinetic system

Relative entropy

$$V(x) = \sum_{i=1}^{n} x_i(\ln x_i - \ln \overline{x}_i) + (\overline{x}_i - x_i)$$

is a Lyapunov function candidate.
$V(x)$ does not depend on the parameters and additive with the species.

Deficiency Zero Theorem
Deficiency zero weakly reversible CRNs have precisely one positive equilibrium point in their stoichiometric compatibility class that is at least locally stable with the Lyapunov function $V(x)$.

CRNs with delays

Kinetic systems = mass action law chemical reaction networks

First principles in kinetic systems

CRNs with delays

- Formal description of CRNs with delays
- Physically plausible delays in kinetic systems
- "Linear chain trick" and delayed CRNs
- Example: delayed CRN model of McKeithan's network
- CRN models of spatially distributed mechanisms
- Stability of delayed CRNs with discrete delays

Conclusions

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

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

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

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

CRN models of delay-causing mechanisms

(reduced order, accurate or approximate)

What is the origin of delays in kinetic systems?

Possible mechanisms

- Sequence (chain) of consecutive linear reactions
- Spatial transport mechanisms: convection, diffusion
- Transport through phase boundaries
- Combination of the above

Possible delay types

- Discrete
- Distributed
- Combined discrete and distributed

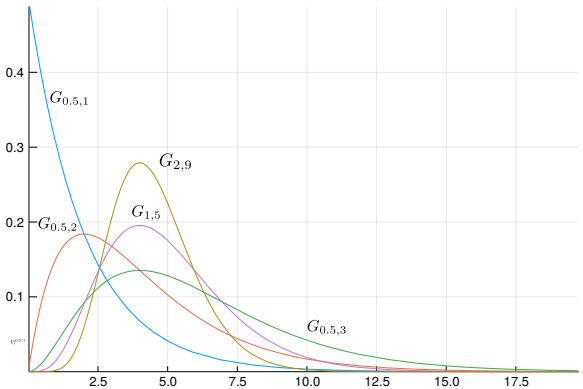
The linear chain trick for delayed CRNs

Given a delayed CRN $C \xrightarrow{\kappa,\ G_{a,p}} C'$ *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

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

Chain of linear reactions

(reduced order accurate models)

The McKeithan's network

Model elements

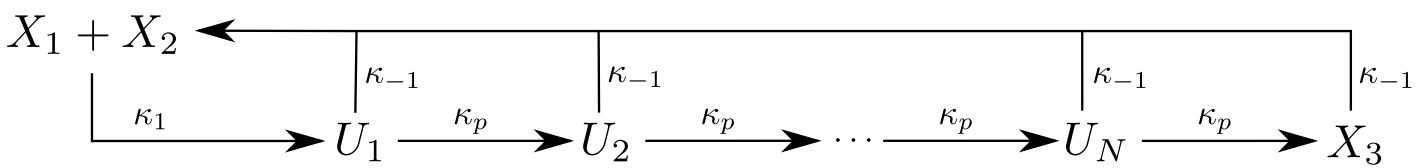
Species
X_1 (TCR=T-cell receptor),
X_2 (MHC=peptide major histocompatibility complex)
X_3 (final complex)
are measurable.

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

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

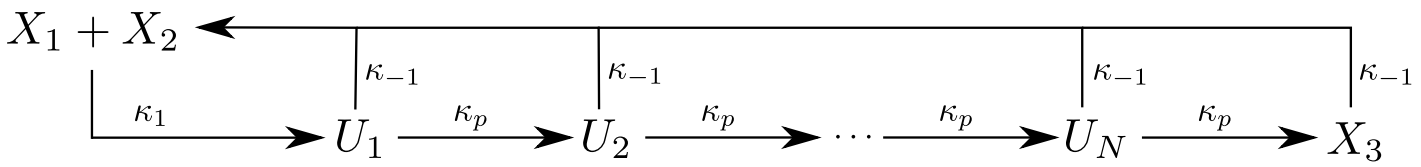
with the intermediates

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

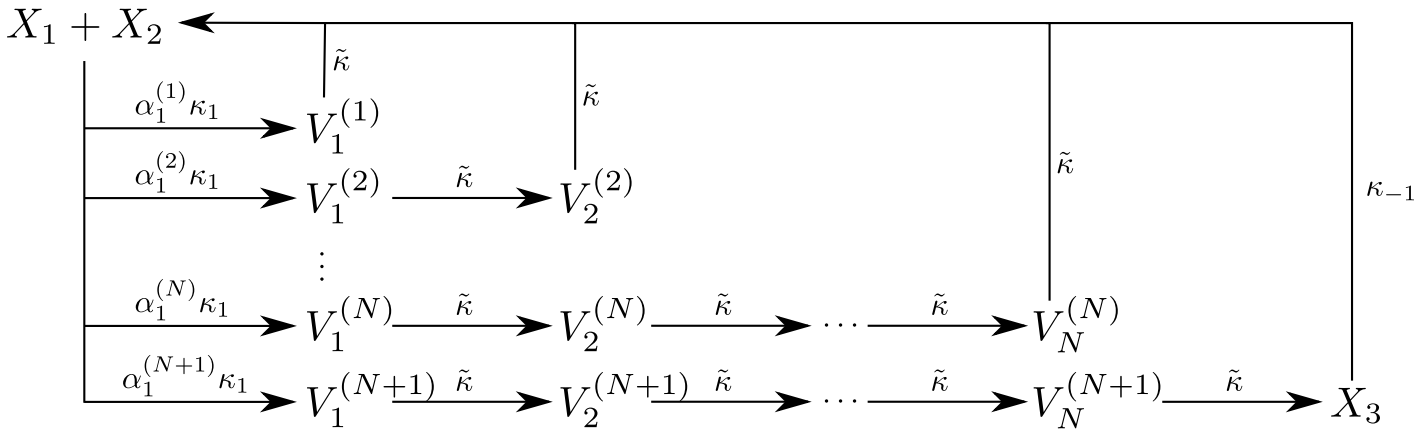


Decoupling the chains of linear reactions

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

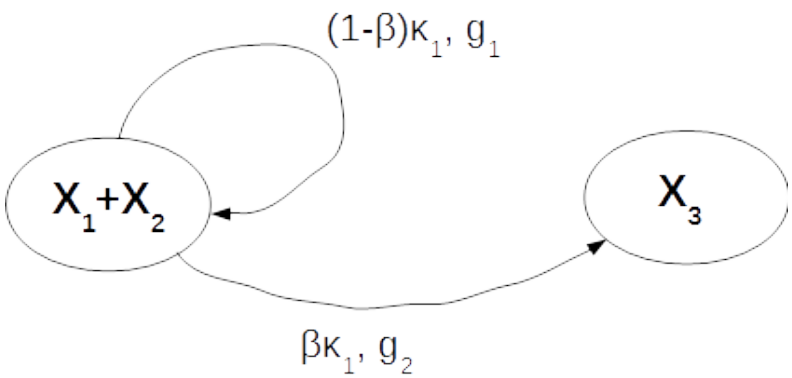
- final chain

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

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

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

Overall distributed delay model



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

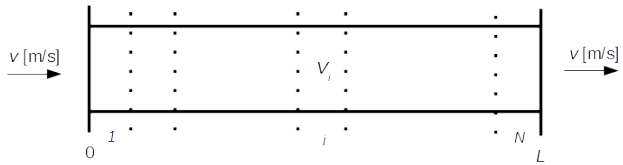
$$g_2(s) = G_{\tilde{\kappa},N}(s).$$

CRN models of spatially distributed linear mechanisms

(convection, diffusion)

Spatially distributed plug flow convection

Tube of length L, plug flow with flow rate v, one specie U with concentration $u(\ell, t)$



Cascade approximation (method of lines) with spatial *uniform* sampling

$$\frac{\partial u(t,z)}{\partial t} = -\overline{v}\frac{\partial u(t,z)}{\partial z}$$

$$u(t,0) = u_0(t), \quad u(0,z) = u_0\left(-\tfrac{z}{\overline{v}}\right)$$

$$v = \frac{\overline{v}}{\Delta x}$$

$$\begin{aligned}
\dot{u}_1(t) &= -v\, u_1(t), \\
\dot{u}_i(t) &= v\, u_{i-1}(t) - v\, u_i(t), \\
\dot{u}_N(t) &= v\, u_{N-1}(t) \\
i &= 2, ..., (N-1).
\end{aligned}$$

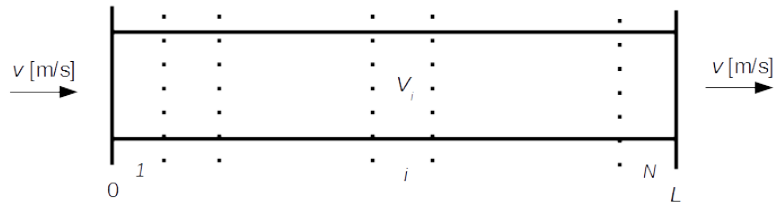
Reaction graph

$$U_1 \xrightarrow{v} U_2 \xrightarrow{v} \ldots \xrightarrow{v} U_{n-1} \xrightarrow{v} U_N.$$

*Plug flow convection results in a chain of **linear irreversible** reactions.*

Plug flow convection with chemical reaction

Tube of length L, plug flow with flow rate v, chemical reaction $C \longrightarrow C'$ forms an intermediate complex U that travels in the tube.



- The spatially distributed CRN model is

$$\frac{\partial u(\ell,t)}{\partial t} = -v\frac{\partial u(\ell,t)}{\partial \ell}, \quad u(0,t) = \beta(x(t))^y,$$
$$\dot{x}(t) = vu(L,t)y' - v\beta(x(t))^y y.$$

- Solution of the spatially distributed part: $u(\ell,t) = \beta(x(t-\frac{\ell}{v}))^y$
- By substitution of $u(L,t)$ into the ODE, we get the **delayed** CRN model

$$\dot{x}(t) = \kappa\left[\left(x\left(t-\tau\right)\right)^y y' - \left(x(t)\right)^y y\right],$$

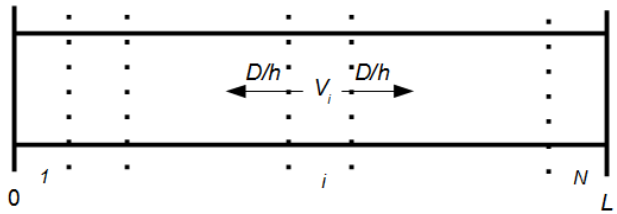
where $\kappa = v\beta$, $\tau = \frac{L}{v}$ and the delayed reaction is $C \xrightarrow{\kappa,\tau} C'$

Chemical reaction with **discrete delay**

Spatially distributed diffusion

Distributed parameter model:

Tube of length L, diffusion coefficient D, reaction forming the intermediate complex U with κ



Cascade approximation (method of lines) with spatial *uniform* sampling

$$\frac{\partial u(\ell,t)}{\partial t} = D\frac{\partial^2 u(\ell,t)}{\partial \ell^2}$$
$$u(\ell,0) = 0;\ \ u(0,t) = u_0(t);\ \ \frac{\partial u(0,t)}{\partial \ell} = 0$$

$$\frac{du_i}{dt} = du_{i-1} - 2du_i + du_{i+1}$$

$$i = 1,...,N, u_0(t)\ \textit{given}$$

CRN model

$$C_0 = U_0 \underset{d}{\overset{d}{\rightleftharpoons}} U_1 \underset{d}{\overset{d}{\rightleftharpoons}} \dots \underset{d}{\overset{d}{\rightleftharpoons}} C$$

reaction rate coefficients: $d = \frac{D}{L^2/N^2}$

*Diffusion results in a chain of **linear reversible** reactions.*

Diffusion and plug flow convection

The following figure shows different delay kernel functions obtained with different v and D values.

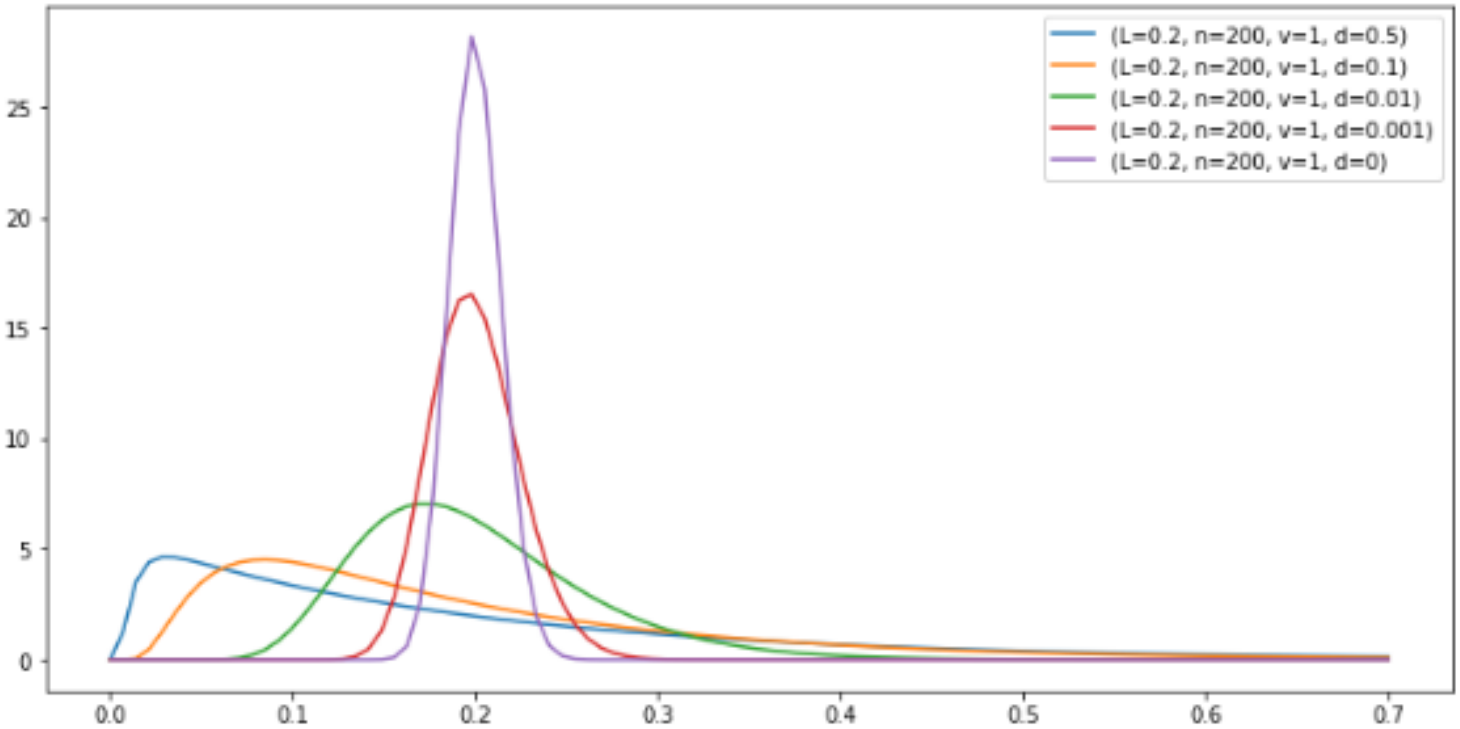


Figure: Kernel functions of combined plug flow convection and diffusion

Dynamics of delayed CRNs

(with discrete delays)

The dynamics of delayed CRNs – 1

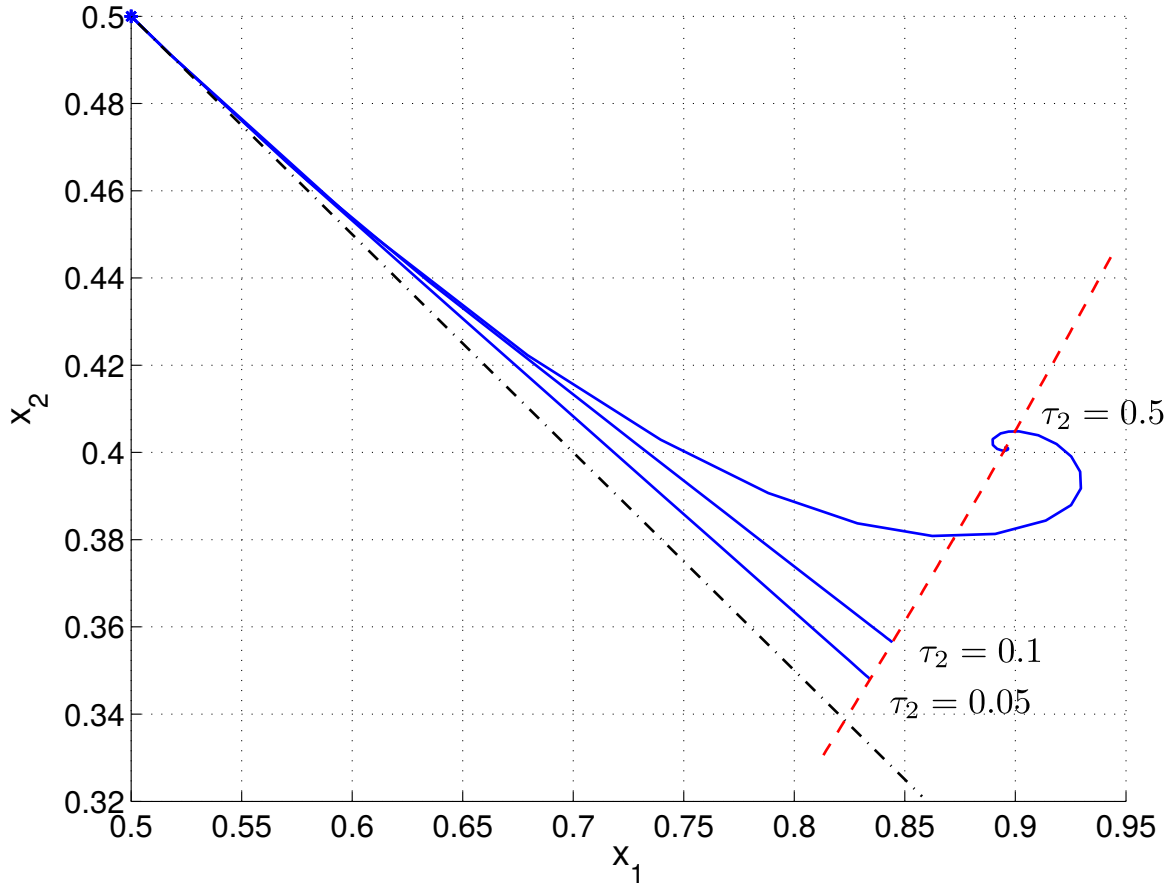


Figure: The phase portrait of the system $2X_1 \leftrightarrows X_2$ with different time delays $\tau_2 = \{0.05, 0.1, 0.5\}$ in reaction $X_2 \leftarrow 2X_1$ and with the same constant initial function defined by $\eta = [0.5\ 0.5]^T$. The red dashed line shows the equilibrium set $\mathcal{E}$ of the network.

The dynamics of delayed CRNs – 2

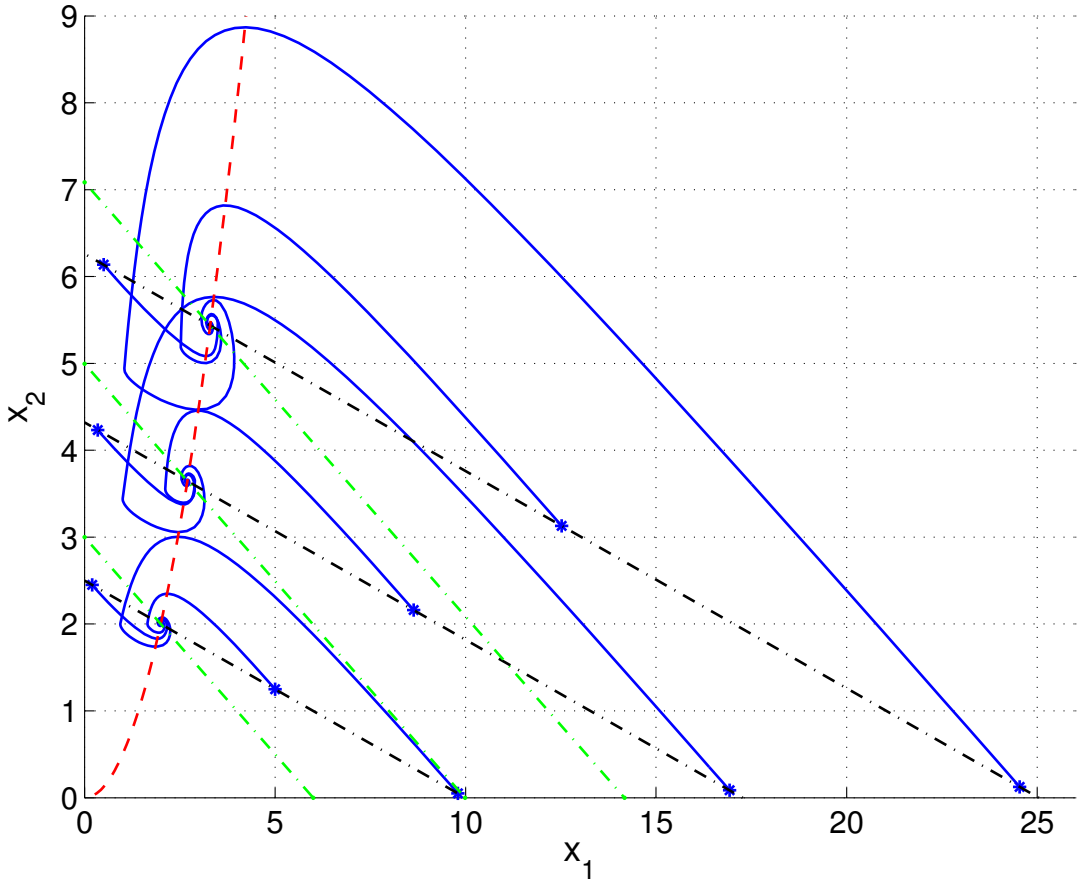


Figure: The phase portrait of the system $2X_1 \leftrightarrows X_2$ with $\tau_2 = 0.5$ in reaction $X_2 \leftarrow 2X_1$ and with different constant initial functions. The red dash curve shows the equilibrium set $\mathcal{E}$ of the network. The black dash-dot lines show the set of points for which the initial functions result in the same equilibrium point.

The Lyapunov-Krasovskii functional and stability

A generalization of the Lyapunov function for delayed ODEs.

(Lyapunov-Krasovskii functional candidate for delayed CRNs)

$$V(\psi) = \sum_{i=1}^{N} [\psi_i(0)(\ln(\psi_i(0)) - \ln(\overline{x}_i) - 1) + \overline{x}_i] +$$

$$+\sum_{k=1}^{M} \kappa_k \int_{-\tau_k}^{0} \{(\psi(s))^{y_k} [\ln((\psi(s))^{y_k}) - \ln(\overline{x}^{y_k}) - 1] + \overline{x}^{y_k}\} \, ds$$

for $\psi \in \mathcal{C}_+$ *with the equilibrium solution* $\overline{x}$.

Theorem (Lipták et al., 2018)

The equilibrium solutions for complex balanced CRNs with arbitrary constant time delays are semistable.

Conclusions and Applications

First principles offer a solid basis of analysing dynamic properties of kinetic systems (CRNs)

1. CRNs are highly nonlinear positive systems
2. Entropy inspired Lyapunov function candidate is available
3. Delays originate from linear mechanisms (chain of linear reactions, convection, diffusion) -> conservation applies
4. A generalized Lyapunov function is proposed for the delayed case

Applications

- networks of CRN with general connection types
- epidemic, biochemical, cellular, transport etc. systems
- reduced models of intracellular processes
- controller design: stabilization, disturbance rejection