1. Continuous modeling

Chemical networks

- A *chemical reaction network (CRN)* is given by
  - a set of chemical *species* $S_i, i \in \{1,\dots,n_s\}$ and
  - a set of chemical *reactions* $R_j, j \in \{1,\dots,n_r\}$, where

$$R_j : \sum_{i=1}^{n_s} \alpha_{ij} S_i \longrightarrow \sum_{i=1}^{n_s} \beta_{ij} S_i$$

    with stoichiometric coefficients $\alpha_{ij}, \beta_{ij} \in \mathbb{N}$.
- The *stoichiometric matrix* $\Gamma \in \mathbb{N}^{n_s \times n_r}$ is defined by

$$\Gamma_{ij} = \beta_{ij} - \alpha_{ij}, \;\; i = 1,\dots,n_s, \;\; j = 1,\dots,n_r.$$

  If $R_j : S_j \longrightarrow \cdot$, then $\beta_{ij} = 0$, for all $i = 1,\dots,n_s$.

Dynamics

- Change in concentrations over time
- Describe the state of the system by a *state vector*

$$([S_1(t)],\dots,[S_{n_s}(t)])^T = (S_1,\dots,S_{n_s})^T.$$

- The rate of a reaction j depends on a *rate law* $R_j(S)$.
- **Mass action kinetics:** Assume

$$R_j(S) = k_j \prod_{i=1}^{n_s} S_i^{\alpha_{ij}}, \;\; j = 1,\dots,n_r, \text{ with } \textit{rate constant } k_j > 0$$

  i.e., the *reaction rate* is proportional to the product of concentrations of the reactants, with higher exponents if more than one molecule is needed.
- Other kinetics: Michaelis-Menten, Hill, ...

ODE system of a chemical network

$$\frac{dS}{dt} = \Gamma \cdot R(S),$$

with

- $S = (S_1(t),\dots,S_{n_s}(t))^T$ the state vector,
- $R(S) = (R_1(S),\dots,R_{n_r}(S))^T$ the vector of rate laws, and
- Γ the stoichiometric matrix

Example

Dimerization $A + A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C$.

$$\Gamma = \begin{pmatrix} -2 & 2 \\ 1 & -1 \end{pmatrix}, \quad R(S) = \begin{pmatrix} k_1 A^2 \\ k_{-1} C \end{pmatrix} \quad \text{gives} \quad \begin{cases} \frac{dA}{dt} &= -2k_1 A^2 + 2k_{-1} C \\ \frac{dC}{dt} &= k_1 A^2 - k_{-1} C \end{cases}$$

Example

Activation of a protein substrate P with intermediate complex C and enzyme E (kinase), Deactivation of Q using a phosphatase F and intermediate complex D.

$$E + P \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} E + Q, \quad F + Q \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} D \xrightarrow{k_4} F + P$$

ODE system: $\frac{dS}{dt} = \Gamma \cdot R(S)$, with

$$S = \begin{pmatrix} P \\ Q \\ E \\ F \\ C \\ D \end{pmatrix}, \quad \Gamma = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ -1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 1 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{pmatrix}, \quad R(S) = \begin{pmatrix} k_1 EP \\ k_{-1} C \\ k_2 C \\ k_3 FQ \\ k_3 D \\ k_4 D \end{pmatrix}$$

For the first ODE we get:

$$\frac{dP}{dt} = (-1) \cdot k_1 EP + 1 \cdot k_{-1} C + 1 \cdot k_4 D = -k_1 EP + k_{-1} C + k_4 D$$

Differential equations

- System of first-order differential equations
$$\dot{x} = f(t, x) \tag{2.1}$$
  - $t \in \mathbb{R}$ scalar, often identified with time.
  - $x \in \mathbb{R}^n$ vector, often representing the state of the system.
  - $\dot{x} = dx/dt$ derivative
  - $f : G \to \mathbb{R}^n$ continuous, $G \subseteq \mathbb{R}^{n+1}$ open subset
- Solution: $x : I \to \mathbb{R}^n, t \mapsto x(t)$
  - $I \subseteq \mathbb{R}$ interval
  - $x : I \to \mathbb{R}^n$ continuously differentiable
  - $x(t)$ satisfies (2.1)

Autonomous equations

- Autonomous vector equation
$$\dot{x} = f(x) \tag{2.2}$$
  i.e., the independent variable t does not occur explicitly.
- **Translation property:** If $x(t)$ is a solution of (2.2) , then $x(t - t_0)$ with t_0 a constant is also a solution.

Existence and uniqueness

Theorem
Consider the *initial value problem*

$$\dot{x} = f(x), \quad x(0) = x_0.$$

Suppose f is continuous and all partial derivatives $\partial f_i / \partial x_j$, $i, j = 1, \ldots, n$ are continuous for x in some open connected set $D \subseteq \mathbb{R}^n$.

Then for $x_0 \in D$ the initial value problem has a solution $x(t)$ on some time interval $]-a, a[$, $a > 0$, about $t = 0$ and the solution is unique.

Phase space

- Autonomous equation $\dot{x} = f(x)$, with $x \in D \subseteq \mathbb{R}^n$.
- D is called *phase space.*
- $x(t) = (x_1(t), \ldots, x_n(t))$ is called *phase point.*
- When t varies, $x(t)$ will move through phase space $\rightsquigarrow$ *trajectory / orbit*
- $f(x)$ can be interpreted as velocity vector.
- If the existence and uniqueness theorem applies, **trajectories in phase space never intersect.**

Critical points

- *Nullcline:* $N_i = \{x \in D \mid \dot{x}_i = f_i(x) = 0\}$, for $i = 1, \ldots, n$.
- A point $a \in D$ with $f(a) = 0$ (i.e., $f_i(a) = \dot{x}_i = 0$, for all $i = 1, \ldots, n$) is called a *critical/singular/equilibrium point* or a *steady state.*
- It corresponds to the *equilibrium* or *stationary solution* $x(t) = a$, for all t.
- It follows from the existence and uniqueness theorem that an equilibrium solution can never be reached in finite time (otherwise two solutions would intersect).

Attractors and periodic solutions

- A critical point $x = a$ of the equation $\dot{x} = f(x)$ is called a *positive attractor* if there exists a neighborhood $\Omega_a \subseteq \mathbb{R}^n$ of a such that $x(0) \in \Omega_a$ implies $\lim_{t \to \infty} x(t) = a$.
- If this property holds for $t \to -\infty$, then $x = a$ is called a *negative attractor.*
- A solution $x(t)$ of $\dot{x} = f(x)$ is called *periodic* if there exists $T > 0$ such that $x(t + T) = x(t)$, for all $t \in \mathbb{R}$.
- **Lemma.** Periodic solutions correspond to closed trajectories in phase space and vice versa.
- A *limit cycle* is an isolated closed trajectory. *Isolated* means that neighboring trajectories are not closed; they spiral either toward or away from the limit cycle.