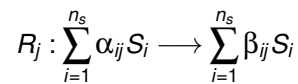


# 1. Continuous modeling

## 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



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

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

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

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

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, ...

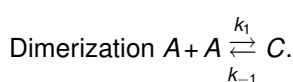
## ODE system of a chemical network

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

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
- $\Gamma$  the stoichiometric matrix

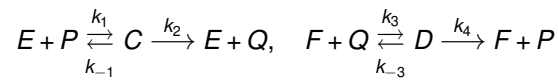
## Example



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

## 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  $D$ .



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

$$\dot{x} = f(t, x) \tag{1.1}$$

- $t \in \mathbb{R}$  scalar, often identified with time.
- $x \in \mathbb{R}^n$  vector, often representing the state of the system.
- $\dot{x} = dx/dt$  derivative
- $f : G \rightarrow \mathbb{R}^n$  continuous,  $G \subseteq \mathbb{R}^{n+1}$  open subset

- Solution:  $x : I \rightarrow \mathbb{R}^n, t \mapsto x(t)$

- $I \subseteq \mathbb{R}$  interval
- $x : I \rightarrow \mathbb{R}^n$  continuously differentiable
- $x(t)$  satisfies (1.1)

## Autonomous equations

- Autonomous vector equation

$$\dot{x} = f(x) \tag{1.2}$$

i.e., the independent variable  $t$  does not occur explicitly.

- **Translation property:** If  $x(t)$  is a solution of (1.2), 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  $\partial f_i / \partial x_j$ ,  $i, j = 1, \dots, n$  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*.
- $x(t) = (x_1(t), \dots, x_n(t))$  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  $i = 1, \dots, n$ .
- A point  $a \in D$  with  $f(a) = 0$  (i.e.,  $f_i(a) = \dot{x}_i = 0$ , for all  $i = 1, \dots, n$ ) 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  $\lim_{t \rightarrow \infty} x(t) = a$ .
- If this property holds for  $t \rightarrow -\infty$ , 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.