4 Reaction kinetics (Murray, Chapter 6)

In Lecture 3 we studied interaction models between populations of biological species. In this lecture we will see that these models show great similarity to simple models of chemical reactions.

4.1 Enzyme reactions (M6.1)

Most chemical reactions in living systems are very slow unless they are sped up by catalysts (substances that increase reaction rates without altering the reaction). In biological systems catalysts are called enzymes. There are thousands of examples of biochemical reactions that are sped up by enzymes. Usually catalysed reactions proceed in two steps. The substrate S reacts with the enzyme E to form a complex SE which is converted into a product P and the enzyme E

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{SE} \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E}$$

Here k_{-1}, k_1, k_2 are rate constants ($\rightleftharpoons$ denotes reversible reactions while $\longrightarrow$ is a one-way reaction). The law of mass action states that the reaction rate R is proportional to the product of the concentrations of the reactants (assuming a well-mixed, not too fast reaction). Apply the law of mass action to the concentrations of reactants:

$$s = [S] \qquad e = [E] \qquad c = [SE] \qquad p = [P]$$

to get:

$$\begin{aligned}
\dot{s} &= -k_1 e s + k_{-1} c\,, & s(0) &= s_0 \\
\dot{e} &= -k_1 e s + (k_{-1} + k_2) c\,, & e(0) &= e_0 \\
\dot{c} &= k_1 e s - (k_{-1} + k_2) c\,, & c(0) &= 0 \\
\dot{p} &= k_2 c\,, & p(0) &= 0\,.
\end{aligned}$$

In systems described by law of mass action, linear combinations of the variables are often conserved. Add second and third equations

$$\dot{e} + \dot{c} = 0 \qquad \Rightarrow \qquad e + c = e_0\,.$$

This reflects that E acts as a catalyst: its concentration in free form (e) plus bound form (c) is constant. Using $e = e_0 - c$ and that the fourth equation is slave to the other three, two equations remain:

$$\begin{aligned}\dot{s} &= -k_1 e_0 s + (k_1 s + k_{-1})c \\ \dot{c} &= k_1 e_0 s - (k_1 s + k_{-1} + k_2)c\,.\end{aligned}$$

Go to dimensionless variables

$$\tau = k_1 e_0 t\,, \qquad u(\tau) = \frac{s(t)}{s_0}\,, \qquad v(\tau) = \frac{c(t)}{e_0}$$

and define dimensionless parameters

$$\lambda = \frac{k_2}{k_1 s_0}\,, \qquad K = \frac{k_{-1} + k_2}{k_1 s_0}\,, \qquad \epsilon = \frac{e_0}{s_0}$$

to get

$$\begin{aligned}\frac{\mathrm{d}u}{\mathrm{d}\tau} &= -u + (u + \underbrace{K - \lambda}_{>0})v \equiv f(u,v)\,, \qquad u(0) = 1 \\ \frac{\mathrm{d}v}{\mathrm{d}\tau} &= \frac{1}{\epsilon}\left[u - (u+K)v\right] \equiv \frac{1}{\epsilon} g(u,v)\,, \qquad v(0) = 0\,.\end{aligned} \tag{1}$$

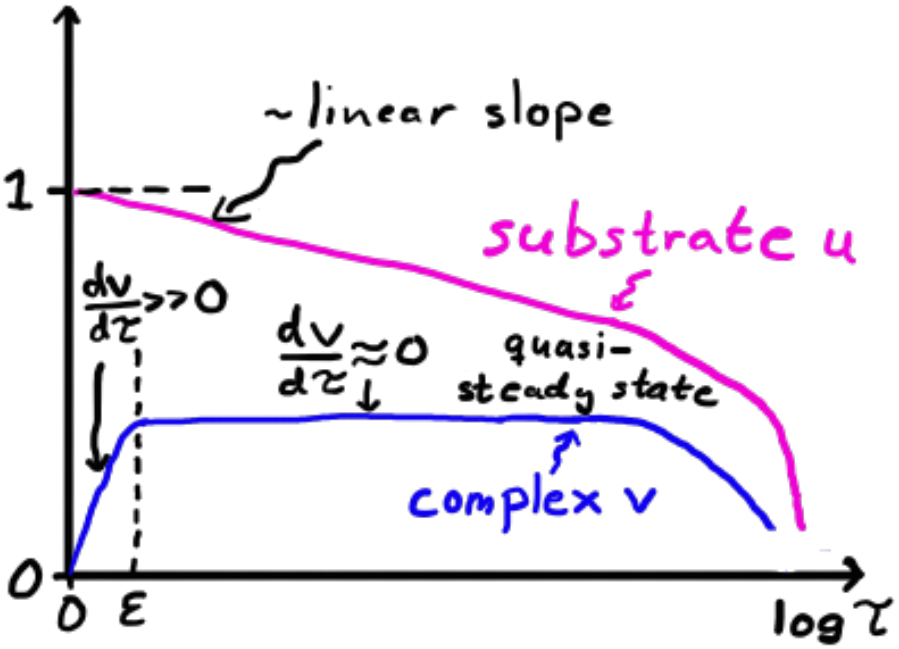
Usually only tiny enzymes concentrations are needed (compared to substrate concentrations): $\epsilon \sim 10^{-2} \cdots 10^{-7}$. The Michaelis-Menten approximation exploits this observation.

4.1.1 Michaelis-Menten approximation (M6.3)

From Eq. (1) it follows that the reaction for the complex v is initially very fast (if $g(u,v)$ is not close to zero). Initially we have

$$\frac{\mathrm{d}v}{\mathrm{d}\tau} \gg 1\,.$$

It is therefore plausible that the v-reaction is more or less in equilibrium ($\frac{\mathrm{d}v}{\mathrm{d}\tau} \approx 0$) until the substrate is nearly all used up:



Strictly speaking this state is not a steady state, it is called Michaelis-Menten's quasi-steady state. It is valid until the substrate starts to get depleted. For $\tau \gg \epsilon$ approximate Eq. (1) by

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = f(u,v)\,, \qquad g(u,v) = 0\,, \qquad u(0) = 1\,. \tag{2}$$

Solving $g = 0$ for v gives

$$v = \frac{u}{u+K}$$
$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -u + (u + K - \lambda)\frac{u}{u+K} = -\lambda\frac{u}{u+K}\,. \tag{3}$$

The relevant initial reaction rate r_0 is defined as the magnitude of the initial linear decay of the substrate u in the quasi-steady state:

$$r_0 \equiv \left|\frac{\mathrm{d}u}{\mathrm{d}\tau}\right|_{\tau\approx 0} = \lambda\frac{u(0)}{u(0)+K} = \frac{\lambda}{1+K}\,.$$

Here $\tau \approx 0$ means the start of the quasi-steady range, $\epsilon \ll \tau \ll 1$.

In dimensional variables

$$R_0 = \left|\frac{\mathrm{d}s}{\mathrm{d}t}\right|_{\tau\approx 0} = s_0 e_0 k_1 r_0 = \frac{Q s_0}{s_0 + K_\mathrm{m}}$$

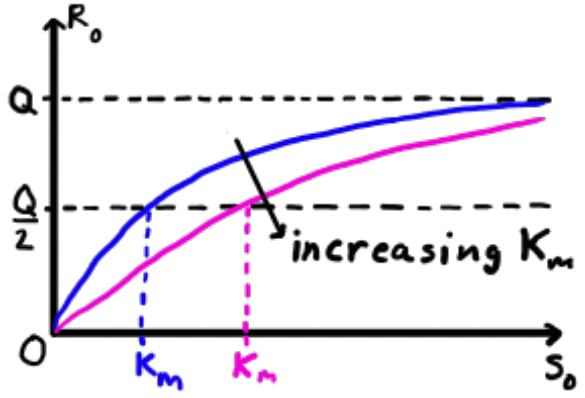
with Michaelis constant

$$K_{\mathrm{m}} \equiv K s_0 = \frac{k_{-1} + k_2}{k_1}$$

and maximal reaction rate (obtained for $s_0 \gg K_{\mathrm{m}}$)

$$Q \equiv k_2 e_0 \,.$$

The reaction rate R_0 determines how efficient the enzyme is in converting the substrate. Parameter dependence:



Two remarks:

- In dimensional terms, Eq. (3) becomes

$$\dot{s} = -\frac{Qs}{s + K_{\mathrm{m}}} \,.$$

  If $s \ll K_{\mathrm{m}}$ the right-hand side is approximately $-Qs/K_{\mathrm{m}}$ (well known from Chemistry textbooks).

- $Q = k_2 e_0$ depends on the rate constant k_2 (for the conversion $\mathrm{SE} \xrightarrow{\mathrm{k_2}} \mathrm{P} + \mathrm{E}$). This conversion is called the rate-limiting step for the reaction.

Single-substrate biochemical reactions are often assumed to follow the Michaelis-Menten kinetics (even in situations where the law of mass action does not apply, such as unevenly distributed reactants in the gel-like structure of the protein-filled cytoplasm).

4.2 Examples of biochemical reactions (M6.6)

In addition to the two-step reaction above, living organisms host a large variety of biochemical reactions between enzymes and substrates. For example, the efficiency of an enzyme as a catalyst can be modified by other molecules: inhibitors decrease enzyme activity and activators increase activity.

The reactions can, similar to the growth models, be analyzed using a dynamical-system approach. Below, a few reactions are discussed.

4.2.1 Autocatalysis

Describes catalysis in which the products of the reaction act as a catalyst. Consider for instance

$$\mathrm{A} + \mathrm{X} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} 2\,\mathrm{X}\,.$$

Assume that A is maintained at constant concentration $a = [A] =$ const.. Law of mass action gives

$$\dot{x} = k_1 a x - k_{-1} x^2\,.$$

This is a chemical equivalent to logistic growth.

4.2.2 Lotka reaction mechanism

Consider two coupled autocatalytic reactions giving one product:

$$\mathrm{S} + \mathrm{X} \xrightarrow{\mathrm{k}_1} 2\,\mathrm{X}$$
$$\mathrm{X} + \mathrm{Y} \xrightarrow{\mathrm{k}_2} 2\,\mathrm{Y}$$
$$\mathrm{Y} \xrightarrow{\mathrm{k}_3} \mathrm{P}$$

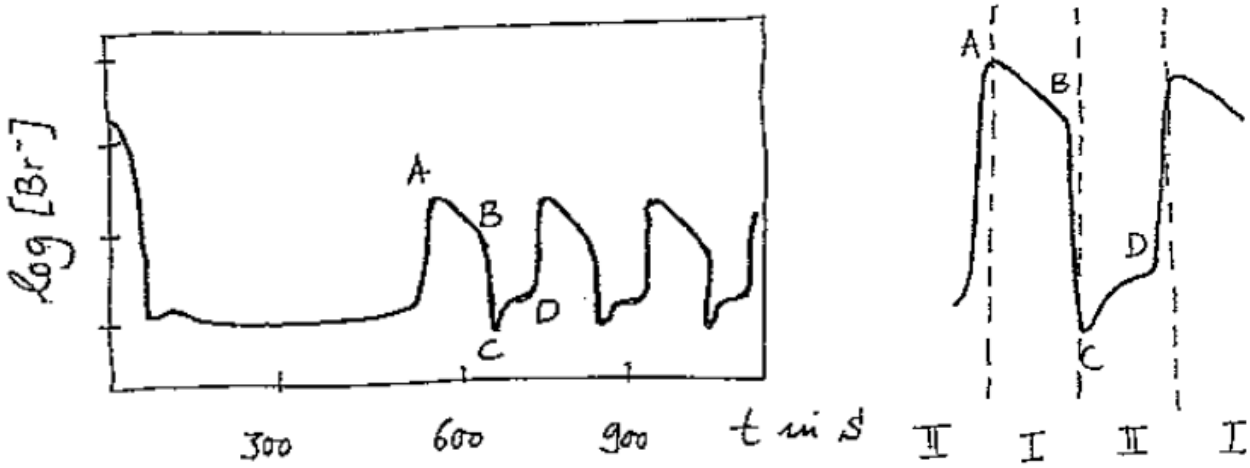
where $s = [S]$ is kept constant. Applying the law of mass action one obtains Lotka-Volterra's predator-prey dynamics:

$$\dot{x} = \underbrace{k_1 s}_{a}\, x - \underbrace{k_2}_{b}\, xy = x(a - by)$$
$$\dot{y} = \underbrace{k_2}_{c}\, xy - \underbrace{k_3}_{d}\, y = y(cx - d)\,.$$

As seen in Lecture 3, these equations are solved by closed orbits in phase-space, leading to periodic oscillations of x and y. One may think that thermodynamics and chemical kinetics imply that chemical reactions quickly and monotonically reach equilibrium states. But, if the system is kept out of equilibrium (here by keeping s constant), complex or chaotic dynamics may emerge in chemical reaction systems.
The Lotka example is not conclusive because the solutions are structurally unstable, but there are other examples where long-lasting concentration oscillations are observed in biochemical and chemical reactions, one being the Belousov-Zhabotinsky reaction.

4.2.3 Belousov-Zhabotinsky reaction (M8.4)

The most intensively studied chemical reaction exhibiting long-lasting oscillatory behaviour is the Belousov-Zhabotinsky reaction. It consists of two chemical processes in which bromide ions (Br^-) are consumed (process I) or created (process II). The reaction is kept out of equilibrium by constant supply of bromat (BrO_3^-). Experimental observation of [Br^-] concentration:



After an initial transient the system shows periodic oscillations in the [Br^-] concentration. Quick transitions occur between states where either process I ($A \to B$) or process II ($C \to D$) are dominant.
The experimental data is of the type of a relaxation oscillator (very slow build-up and sudden discharge). This is also what an analysis of the reaction equations shows.