INF-5610, Matematiske modeller i medisin

Forelesere:

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Topics:

- Chemical reactions
- Ionic channels
- Calcium dynamics in cells
- Signal propegation between cells
- Blood flow

Exam

- There will be six topics given, two weeks prior to the exam
- A 20 minute lecture for each topic should be prepared
- At the exam, one of the topics will be drawn
- There will also be questions given on other subjects

Mathematical models of chemical reactions

The Law of Mass Action, 1.1

Chemical A and B react to produce chemical C:

$$A + B \xrightarrow{k} C$$

The rate constant k determines the rate of the reaction. It can be interpreted as the probability that a collision between the reactants produces the end results.
If we model the probability of a collision with the product [A] [B] we get the law of mass action:

$$\frac{d[C]}{dt} = k[A][B]$$

A two way reaction

The reverse reaction may also take place:

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$$

The production rate is then:

$$\frac{d[C]}{dt} = k_+[A][B] - k_-[C]$$

At equilibrium when $d[C]/dt = 0$ we have:

$$k_-[C] = k_+[A][B] \qquad (1)$$

If $A + B \xrightarrow{k} C$ is the only reaction involving A and C then

$$d[A]/dt = -d[C]/dt$$

so that

$$[A] + [C] = A_0 \qquad (2)$$

Substituting (2) into (1) yields:

$$[C] = A_0 \frac{[B]}{K_{\mathsf{eq}} + [B]}$$

where $K_{\mathsf{eq}} = k_-/k_+$.
Notice that

$$[B] = K_{\mathsf{eq}} \implies [C] = A_0/2$$

and

$$[B] \to \infty \implies [C] \to A_0$$

Gibbs free energy, 1.2

Molecules have different chemical potential energy, quantified by *Gibbs free energy*

$$G = G^0 + RT \ln(c)$$

where c is the concentration of the molecule, T is the temperature, R the gas constant.
G^0 is the energy at $c = 1$M, called the *standard free energy*.

Gibbs free energy

Can be used to compare two states:

$$A \longrightarrow B$$

Change in free energy after this reaction:

$$\begin{aligned}\Delta G &= G_B - G_A \\ &= (G_B^0 + RT\ln(B)) - (G_A^0 + RT\ln(A)) \\ &= (G_B^0 - G_A^0) + (RT\ln(B) - RT\ln(A)) \\ &= \Delta G^0 + RT\ln(B/A)\end{aligned}$$

If $\Delta G < 0$, e.g. there is less free energy after the reaction, then B is the preferred stated.

Gibbs free energy at equilibrium

At equilibrium neither states are favoured and $\Delta G = 0$:

$$\Delta G = \Delta G^0 + RT \ln(B/A) = 0$$

Given G^0, the concentrations at equilibrium must satisfy:

$$\ln(B_{eq}/A_{eq}) = -\Delta G^0/RT$$

or

$$\frac{B_{eq}}{A_{eq}} = e^{-\Delta G^0/RT}$$

Gibbs free energy and rate constants

The reaction

$$A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B$$

is governed by

$$\frac{d[A]}{dt} = k_+[B] - k_-[A]$$

and at equilibrium $\frac{d[A]}{dt} = 0$, so

$$k_+[B] - k_-[A] = 0, \text{ or }, A/B = k_-/k_+ = K_{eq}$$

Comparing with the Gibbs free energy we find:

$$K_{eq} = e^{\Delta G^0/RT}$$

Note:

$$\Delta G^0 < 0 \Longrightarrow K_{eq} < 1 \Longrightarrow B_{eq} > A_{eq}$$

Gibbs free energy with several reactants

The reaction

$$\alpha A + \beta B \longrightarrow \gamma C + \delta D$$

has the following change in free energy:

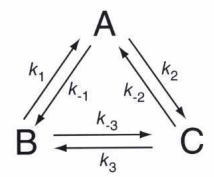
$$\begin{aligned}\Delta G &= \gamma G_C + \delta G_D - \alpha G_A - \beta G_B \\ &= \gamma G_C^0 + \delta G_D^0 - \alpha G_A^0 - \beta G_B^0 \\ &\quad + \gamma RT \ln([C]) + \delta RT \ln([D]) - \alpha RT \ln([A]) - \beta RT \ln([B]) \\ &= \Delta G^0 + RT \ln(\frac{[C]^\gamma [D]^\delta}{[A]^\alpha [B]^\beta})\end{aligned}$$

At equilibrium with $\Delta G = 0$:

$$\Delta G^0 = RT \ln(\frac{[A]_{eq}^\alpha [B]_{eq}^\beta}{[C]_{eq}^\gamma [D]_{eq}^\delta})$$

Detailed balance, 1.3

Consider the cyclic reaction:



In equilibrium all states must have the same energy:

$$G_A = G_B = G_C$$

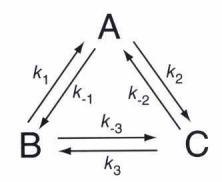
All transitions must be in equilibrium:

$$k_1[B] = k_{-1}[A], \quad k_2[A] = k_{-2}[C], \quad k_3[C] = k_{-3}[B]$$

Which yields:

$$k_1[B] \cdot k_2[A] \cdot k_3[C] = k_{-1}[A] \cdot k_{-2}[C] \cdot k_{-3}[B]$$

Detailed balance



cont.

$$k_1[B] \cdot k_2[A] \cdot k_3[C] = k_{-1}[A] \cdot k_{-2}[C] \cdot k_{-3}[B]$$

so

$$k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$$

This last condition is independent of the actual concentrations and must hold in general. Thus only 5 free parameters in the reaction.

Enzyme Kinetics, 1.4

Characteristics of enzymes:

- Made of proteins
- Acts as catalysts for biochemical reactions
- Speeds up reactions by a factor $> 10^7$
- Highly specific
- Often part of a complex regulation system

Reaction model of enzymatic reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} P + E$$

with

S: Substrate

E: Enzyme

C: Complex

P: Product

Mathematical model of enzymatic reaction

Applying the law of mass action to each compound yields:

$$\begin{aligned}
\frac{d[S]}{dt} &= k_{-1}[C] - k_1[S][E] + J_S \\
\frac{d[E]}{dt} &= (k_{-1} + k_2)[C] - k_1[S][E] \\
\frac{d[C]}{dt} &= k_1[S][E] - (k_2 + k_{-1})[C] \\
\frac{d[P]}{dt} &= k_2[C] - J_P
\end{aligned}$$

Here we also supply the substrate at rate J_S and the product is removed at rate J_P.

Equilibrium, 1.4.1

Note that In equilibrium

$$d[S]/dt = d[E]/dt = d[C]/dt = d[P]/dt = 0$$

it follows that that $J_S = J_P$.
Production rate:

$$J = J_P = k_2[C]$$

In equilibrium we have

$$\frac{d[E]}{dt} = 0$$

that is

$$(k_{-1} + k_2)[C] = k_1[S][E]$$

Since the amount of enzyme is constant we have

$$[E] = E_0 - [C]$$

This yields

$$[C] = \frac{E_0[S]}{K_m + [S]}$$

with $K_m = \frac{k_{-1}+k_2}{k_1}$ and E_0 is the total enzyme concentration.
Production rate: $\frac{d[P]}{dt} = k_2[C] = V_{max}\frac{[S]}{K_m+[S]}$, where $V_{max} = k_2E_0$.

Cooperativity, 1.4.4

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C_1 \xrightarrow{k_2} E + P$$

$$S + C_1 \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} C_2 \xrightarrow{k_4} C_1 + P$$

with

- S: Substrate
- E: Enzyme
- C1: Complex with one S
- C1: Complex with two S
- P: Product

Mathematical model of cooperativ reaction

Applying the law of mass action to each compound yields:

$$\begin{aligned}
\frac{ds}{dt} &= -k_1se + k_{-1}c_1 - k_3sc_1 + k_{-3}c_2 \\
\frac{dc_1}{dt} &= k_1se - (k_{-1} + k_2)c_1 - k_3sc_1 + (k_4 + k_{-3})c_2 \\
\frac{dc_2}{dt} &= k_3sc_1 - (k_4 + k_{-3})c_2
\end{aligned}$$

Equilibrium

Set $\frac{dc_1}{dt} = \frac{dc_2}{dt} = 0$, and use $e_0 = e + c_1 + c_2$,

$$\begin{aligned} c_1 &= \frac{K_2 e_0 s}{K_1 K_2 + K_2 s + s^2} \\ c_2 &= \frac{e_0 s^2}{K_1 K_2 + K_2 s + s^2} \end{aligned}$$

where $K_1 = \frac{k_{-1}+k_2}{k_1}$, $K_2 = \frac{k_4+k_{-3}}{k_3}$

Reaction speed:

$$V = k_2 c_1 + k_4 c_2 = \frac{(k_2 K_2 + k_4 s) e_0 s}{K_1 K_2 + K_2 s + s^2}$$

Case 1: No cooperation

The binding sites operate independently, with the same rates k_+ and k_-. k_1, k_{-3} and k_4 are associated with events that can happen in two ways, thus:

$$k_1 = 2k_3 = 2k_+$$

$$k_{-3} = 2k_{-1} = 2k_-$$

$$k_4 = 2k_2$$

So:

$$K_1 = \frac{k_{-1} + k_2}{k_1} = \frac{k_- + k_2}{2k_+} = K/2$$

$$K_2 = \frac{k_{-3} + k_4}{k_3} = \frac{2k_- + 2k_2}{k_+} = 2K$$

where

$$K = \frac{k_- + k_2}{k_\perp}$$

Which gives this reaction speed:

$$\begin{aligned} V &= \frac{(k_2 K_2 + k_4 s) e_0 s}{K_1 K_2 + K_2 s + s^2} \\ &= \frac{(2k_2 K + 2k_2 s) e_0 s}{K^2 + 2Ks + s^2} \\ &= \frac{2k_2 (K + s) e_0 s}{(K + s)^2} = \frac{2k_2 e_0 s}{(K + s)} \end{aligned}$$

Note that this is the same as the reaction speed for twice the amount of an enzyme with a single binding site.

Case 2: Strong cooperation

The first binding is unlikely, but the next is highly likely, i.e. k_1 is small, and k_3 is large. We go to the limit:

$$k_1 \to 0, k_3 \to \infty, k_1 k_3 = \text{const}$$

so

$$K_2 \to 0, K_1 \to \infty, K_1 K_2 = \text{const}$$

In this case the reaction speed becomes:

$$V = \frac{k_4 e_0 s^2}{K_m^2 + s^2} = V_{\text{max}} \frac{s^2}{K_m^2 + s^2}$$

with $K_m^2 = K_1 K_2$, and $V_{\text{max}} = k_4 e_0$

The Hill equation

In general with n binding sites, the reaction rate in the limit will be:

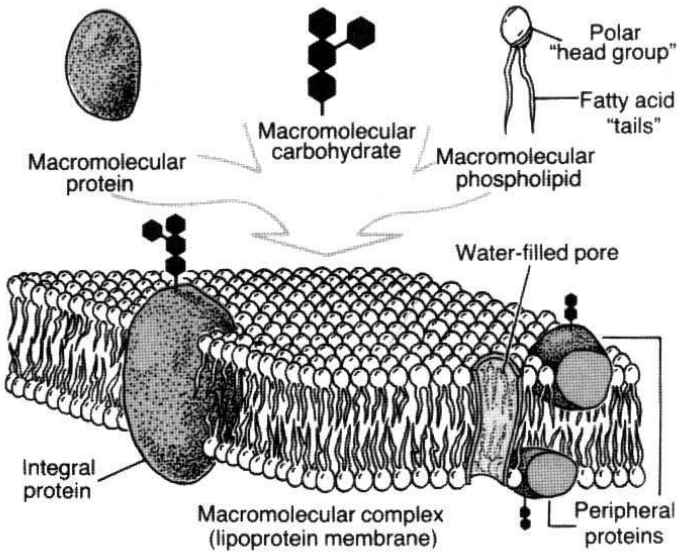
$$V = V_{\text{max}} \frac{s^n}{K_m^n + s^n}$$

This model is often used when the intermediate steps are unknown, but cooperativity suspected. The parameters V_{max}, K_m and n are usually determined experimentally.

The Cell Membrane

- Consist of a bilipid layer
- Embedded proteins for transport control
- Selectively permeable
- Maintains concentration gradients
- Has a transmembrane potential

The Cell Membrane, 2.1



Two types of transmembrane flow

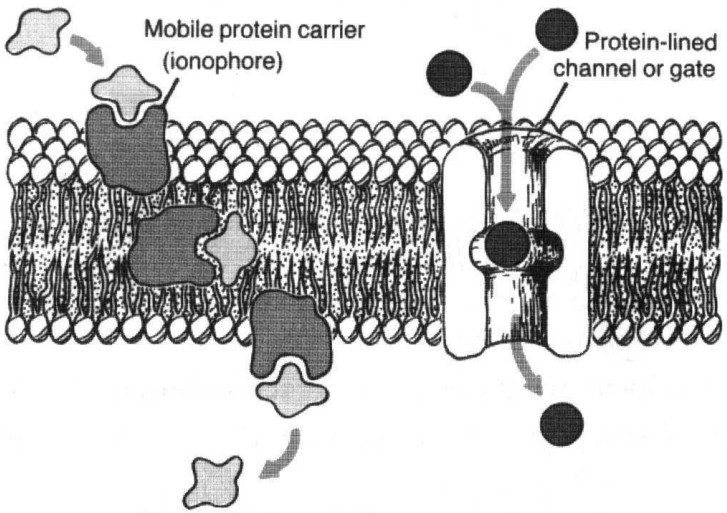
Passive: Diffusion along the concentration gradient

- Through the membrane (H_2O, O_2, CO_2)
- Through specialized channels (Na^+, K^+, Cl^-)
- Carrier mediated transport

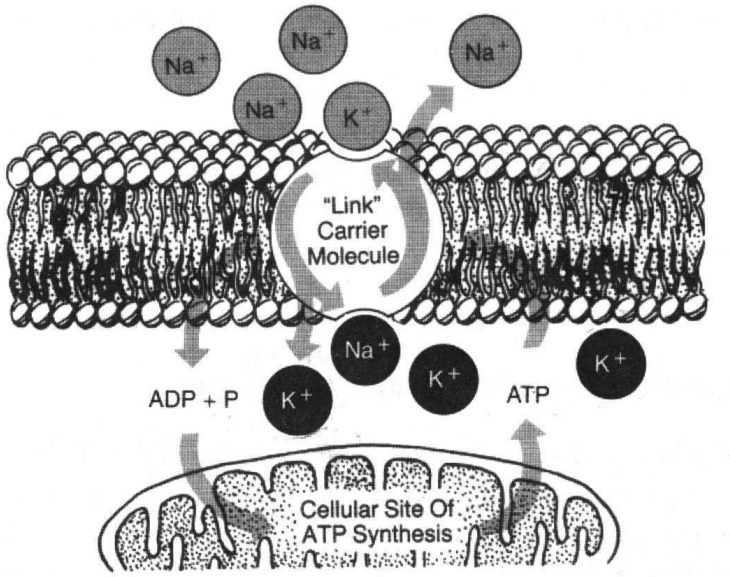
Active: Energy driven flow against the gradients

- ATP driven pumps ($Na^+ - K^+$, Ca^{2+})
- Exchangers driven by concentration gradients ($Na^+ - Ca^{2+}$)

Transmembrane flow



Active Transport



Diffusion, 2.2

The conservation law for a compound with concentration c:
rate change of c = local production + accumulation due to transport.
Model:

$$\frac{d}{dt}\int_\Omega c\,dV = \int_\Omega p\,dV - \int_{\partial\Omega} \mathbf{J}\cdot\mathbf{n}\,dA$$

Here p represents the production and $\mathbf{J}$ is the flux of c.
The divergence theorem:

$$\int_{\partial\Omega} \mathbf{J}\cdot\mathbf{n}\,dA = \int_\Omega \nabla\cdot\mathbf{J}\,dV$$

The law is valid for every volume, thus:

$$\frac{\partial c}{\partial t} = p - \nabla\cdot\mathbf{J}$$

Models for p and $\mathbf{J}$ are needed to compute c.

Fick's Law, 2.2.1

$$\mathbf{J} = -D\nabla c$$

The diffusion coefficient D depends upon the solute and the temperature of the embedding fluid:

$$D = \frac{kT}{f}$$

T is the temperature measured on Kelvin, f is a frictional constant and k is the Boltzmann's constant.
The conservation law with this assumption is a reaction-diffusion equation:

$$\frac{\partial c}{\partial t} = \nabla\cdot(D\nabla c) + p$$

Diffusion coefficients, 2.2.2

The diffusion coefficient of a solute in a solvent is given by

$$D = \frac{kT}{f}$$

where k is Boltzmann's constant and T the temperature. f is the *frictional* constant of the solute and for a sphere with radius a given as

$$f = 6\pi\mu a$$

where μ is called the coefficient of viscosity of the solute.

1D Diffusion through a pore in the membrane,

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial^2 x}$$

Fixed intra and extra cellular concentration:

$$c(0,t) = [C]_i \quad c(L,t) = [C]_e$$

At steady state:

$$\frac{\partial c}{\partial t} = 0 \implies D\frac{\partial^2 c}{\partial^2 x} = 0 \implies \frac{\partial c}{\partial x} = a \implies c(x) = ax + b$$

Taking the boundary condition into consideration yields:

$$c(x) = [C]_i + ([C]_e - [C]_i)\frac{x}{L}$$

and a constant flux: $J = -D\frac{\partial c}{\partial x} = \frac{D}{L}([C]_i - [C]_e)$

Carrier-Mediated Transport, 2.4

Some substances can not pass the membrane on their own, but are helped by a carrier protein.

Types of transport:

- Uniport: Transport of single substance
- Symport: Transport of several substances in same direction
- Antiport: Transport of several substances in opposite directions

With symport and antiport the carrier molecule as several binding sites.

Uniport

Substrate S combines with a carrier protein C to form a complex P. The protein has two conformal states.
Model:

$$S_i + C_i \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_i \underset{k}{\overset{k}{\rightleftharpoons}} P_e \underset{k_+}{\overset{k_-}{\rightleftharpoons}} S_e + C_e$$

$$C_i \underset{k}{\overset{k}{\rightleftharpoons}} C_e$$

Model for Carrier Mediated Transport, Uniport

Applying the law of mass action:

$$\begin{aligned}
\frac{d[S_i]}{dt} &= k_-[P_i] - k_+[S_i][C_i] - J \\
\frac{d[S_e]}{dt} &= k_-[P_e] - k_+[S_e][C_e] + J \\
\frac{d[P_i]}{dt} &= k[P_e] - k[P_i] + k_+[S_i][C_i] - k_-[P_i] \\
\frac{d[P_e]}{dt} &= k[P_i] - k[P_e] + k_+[S_e][C_e] - k_-[P_e] \\
\frac{d[C_i]}{dt} &= k[C_e] - k[C_i] + k_-[P_i] - k_+[S_i][C_i] \\
\frac{d[C_e]}{dt} &= k[C_i] - k[C_e] + k_-[P_e] - k_+[S_e][C_e]
\end{aligned}$$

Here J is the influx of the glucose molecules (S).

Size of flux in equilibrium

The flow in equilibrium can be setting the derivatives to zero and solve for J.

This yields a system of six eq. and seven unknowns.

The amount of protein is conserved so we have:

$$[C_i] + [C_e] + [P_i] + [P_e] = C_0$$

Solving for J in equilibrium then gives:

$$J = \frac{1}{2} k K C_0 \frac{[S_e] - [S_i]}{([S_i] + K + K_d)([S_e] + K + K_d) - K_d^2}$$

with $K = k_-/k_+$ and $K_d = k/k_+$.

Size of flux in equilibrium

$$J = \frac{1}{2} k K C_0 \frac{[S_e] - [S_i]}{([S_i] + K + K_d)([S_e] + K + K_d) - K_d^2}$$

Factors affecting the flux:

- The amount of Carrier molecules C_0
- The rate constants
- Substrate gradient

Model for symport

Two different substances S and T are transported in the same direction. The carrier C has m binding sites for S and n for T:

$$mS_i + nT_i + C_i \underset{k_-}{\overset{k_+}{\rightleftarrows}} P_i \underset{k_{-p}}{\overset{k_p}{\rightleftarrows}} P_e \underset{k_+}{\overset{k_-}{\rightleftarrows}} mS_e + nT_e + C_e$$

$$C_i \underset{k}{\overset{k}{\rightleftarrows}} C_e$$

Need to model mathematically the process

$$mS + nT + C \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P$$

Consider the simpler reaction

$$A + B + C \underset{k_-}{\overset{k_+}{\rightleftharpoons}} ABC$$

If we assume that the reaction takes place in two steps

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AB$$

$$AB + C \underset{k_-}{\overset{k_+}{\rightleftharpoons}} ABC$$

cont.

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AB$$

$$AB + C \underset{k_-}{\overset{k_+}{\rightleftharpoons}} ABC$$

If the intermediate step is fast, we can assume it to be in equilibrium:

$$\frac{d[AB]}{dt} = k_1[A][B] - k_{-1}[AB] = 0 \Rightarrow [AB] = k_1/k_{-1}[A][B]$$

For the total reaction:

$$\frac{d[ABC]}{dt} = k_+[AB][C] - k_-[ABC] = k_+\frac{k_1}{k_{-1}}[A][B][C] - k_-[ABC]$$

Flux for symport

With repeated use of similar arguments

$$\frac{d[P]}{dt} = k_+[S]^m[T]^n[C] - k_-[P]$$

The symport model will be identical to the uniport model by substituting $[S]$ with $[S]^m[T]^n$.
Flux:

$$J = \frac{1}{2}K_dKk_+C_0\frac{[S_e]^m[T_e]^n - [S_i]^m[T_i]^n}{([S_i]^m[T_i]^n + K + K_d)([S_e]^m[T_e]^n + K + K_d) - K_d^2}$$