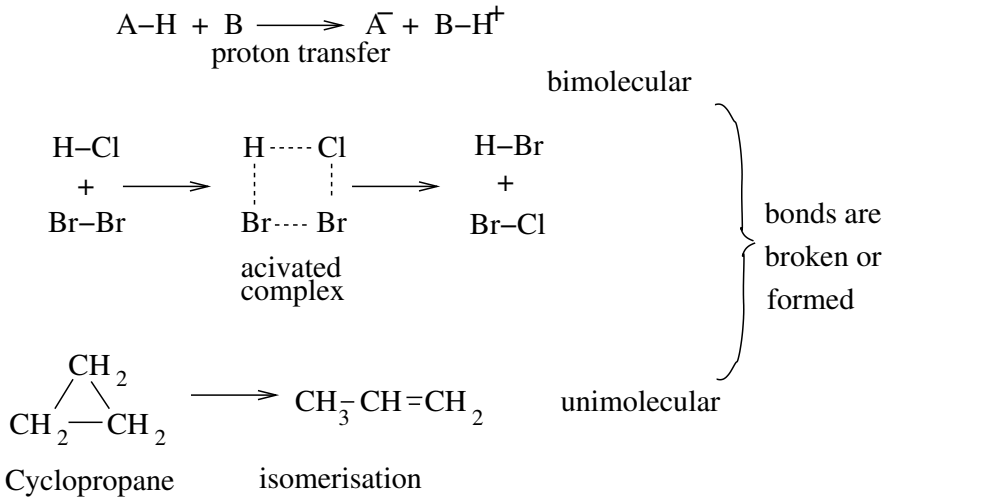
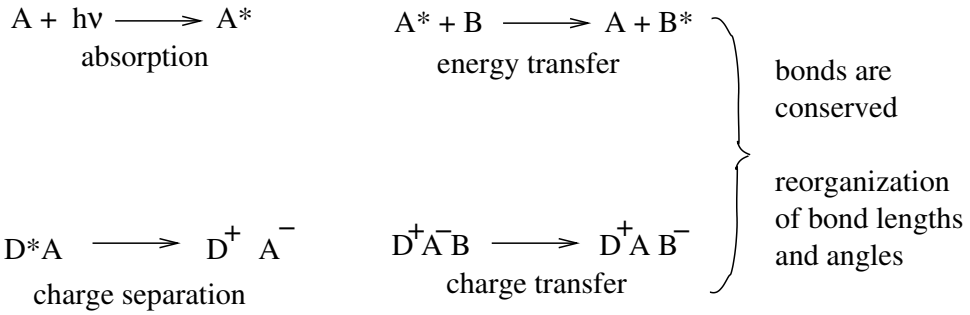
Part III
Reaction kinetics

6 formal kinetics

6.1 elementary chemical reactions

Figure 54: different types of elementary chemical reactions





All elementary reactions are reversible. There is a dynamical equilibrium between forward and back reaction, which are independent, for instance

$$H_2 + J_2 \leftrightharpoons 2HJ$$

6.2 reaction variable and reaction rate

We consider a general stoichiometric equation for the reaction of several species[7]

$$\sum_i \nu_i A_i = 0$$

and define a reaction variable x based on the concentration of the species A_i by

$$c_i = c_{i,0} + \nu_i x$$

as

$$x = \frac{c_i - c_{i,0}}{\nu_i}$$

and the reaction rate as

$$r = \frac{dx}{dt} = \frac{1}{\nu_i}\frac{dc_i}{dt}$$

6.3 reaction order

Frequently the progress of a chemical reaction can be described by a simple rate expression such as

$$r = kc_1^{n_1}c_2^{n_2}\cdots = k\prod_{i\in educts} c_i^{n_i}$$

with the rate constant k. For such a system the exponent[8] of the i-th term is called the order of the reaction with respect to this substance and the sum of all the exponents is called the overall reaction order.

6.3.1 zero-order reactions

these are reactions which proceed at the same rate regardless of concentration. The rate expression for a reaction of this type is

$$-\frac{dc}{dt} = k_0$$

which can be integrated

$$c = c_0 - k_0 t$$

zero order reactions appear when the determining factor is an outside source of energy (light) or when the reaction occurs on the surface of a catalyst.

6.3.2 first order reactions

describe the decay of an excited state, for instance a radioactive decay

$$A^* \rightarrow A$$

The rate expression is

$$-\frac{dc_{A*}}{dt} = \frac{dc_A}{dt} = k_1 c$$

[7] The stochiometric coefficients ν_i are postive for products and negative for educts.

[8] For more complicated reactions the exponents need not to be integers. For simple reactions they are given by the stochiometric coefficients $n_i = |\nu_i|$

which gives an exponential decay

$$c_{A*} = c_{A*}(0)e^{-kt}$$

with a constant half-period

$$\tau_{1/2} = \frac{\ln(2)}{k}$$

6.3.3 second order reactions

A second order reaction between two different substances obeys the eqations

$$A + B \rightarrow \cdots$$

$$-\frac{dc_A}{dt} = -\frac{dc_B}{dt} = k_2 c_A c_B$$

which can be written using the reaction variable x and the initial concentrations a,b as

$$c_A = a - x \qquad c_B = b - x$$

$$\frac{dx}{dt} = k_2(a-x)(b-x)$$

which can be integrated to give

$$\frac{1}{a-b}\ln\frac{b(a-x)}{a(b-x)} = k_2 t$$

if two molecules of the same type react with each other we have instead

$$-\frac{dc_A}{dt} = -k_2 c_A^2$$

which gives an algebraic decay

$$c_A(t) = \frac{1}{k_2 t + \frac{1}{a}}$$

where the half-period now depends on the initial concentration

$$\tau_{1/2} = \frac{1}{k_2 a}$$

An example is the exciton-exciton annihilation in the light harvesting complex

$$A^* + A^* \rightarrow A + A$$

6.4 dynamical equilibrium

We consider a first order reaction together with the back reaction

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} B$$

The reaction variable of the back reaction will be denoted by y.

$$c_A(t) = a - x + y$$

$$c_B(t) = b + x - y$$

$$\frac{dx}{dt} = k_1 c_A = k_1(a - x + y)$$

$$\frac{dy}{dt} = k_{-1} c_B = k_{-1}(b + x - y)$$

defining an overall reaction variable

$$z = x - y$$

and the equilibrium value

$$s = \frac{k_1 a - k_{-1} b}{k_1 + k_{-1}}$$

we have

$$\frac{dz}{dt} = k_1 a - k_{-1} b - (k_1 - k_{-1})z = (k_1 + k_{-1})(s - z)$$

which for $z(0) = 0$ has teh solution

$$z = s(1 - e^{-(k_1 + k_{-1})t})$$

The reaction approaches the equilibrium with a rate constant $k_1 + k_{-1}$. In equilibrium $z = s$ and $\frac{dz}{dt} = 0$. The equilibrium concentrations are

$$c_A = a - s = (a + b)\frac{k_{-1}}{k_1 + k_{-1}}$$

$$c_B = b + s = (a + b)\frac{k_1}{k_1 + k_{-1}}$$

and the equilibrium constant is

$$K = \frac{c_A}{c_B} = \frac{k_{-1}}{k_1}$$

6.5 competing reactions

If one species decays via seperate independent channels (fluorescence,electron transfer, radiationless transitions $\cdots$) the rates are additive

$$\frac{dc_A}{dt} = -(k_1 + k_2 + \cdots)c_A$$

6.6 consecutive reactions

We consider a chain consisting of two first order reactions[9]

$$A \underset{\rightarrow}{\overset{k_1}{}} B \underset{\rightarrow}{\overset{k_2}{}} C$$

The reaction variables are denoted by x and y, the initial concentrations by a,b,c.

$$c_A = a - x$$

$$c_B = b + x - y$$

$$c_C = c + y$$

and the time derivatives are

$$\frac{dc_A}{dt} = -\frac{dx}{dt} = -k_1 c_A = -k_1(a - x)$$

$$\frac{dc_B}{dt} = \frac{dx}{dt} - \frac{dy}{dt} = k_1 c_A - k_2 c_B = k_1 a - k_2 b + (k_2 - k_1)x - k_2 y$$

$$\frac{dc_C}{dt} = \frac{dy}{dt} = k_2 c_B = k_2(b + x - y)$$

The first equation gives an exponential decay

$$c_A = a e^{-k_1 t}$$

Integration of

$$\frac{dc_B}{dt} + k_2 c_B = k_1 a e^{-k_1 t}$$

gives the concentration of the intermediate state

$$c_B = \frac{k_1 a}{k_2 - k_1} e^{-k_1 t} + (b - \frac{k_1 a}{k_2 - k_1}) e^{-k_2 t}$$

if at time zero only the species A is present the concentration of B has a maximum at

$$t_{max} = \frac{1}{k_1 - k_2} \ln \frac{k_1}{k_2}$$

with the value

$$c_{B,max} = a \left(\frac{k_2}{k_1} \right) e^{\frac{k_2}{k_1 - k_2}}$$

6.7 enzymatic catalysis

is very important for biochemical reactions. It can be described schematically by formation of a enzyme-substrate complex followed by decomposition into enzyme and product

$$E + S \underset{k_{-1}}{\overset{k_1}{\leftrightharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\leftrightharpoons}} E + P$$

[9] with negligible back reactions

We consider the limiting case of negligible $k_{-2} \ll k_2$ and large concentration of substrate $c_S \gg c_E$. Then we have to solve the equations

$$\dot{c}_S \approx -k_1 c_E c_S^0 + k_{-1} c_{ES}$$

$$\dot{c}_E \approx -k_1 c_E c_S^0 + (k_{-1} + k_2) c_{ES}$$

$$\dot{c}_{ES} \approx k_1 c_E c_S^0 - (k_{-1} + k_2) c_{ES}$$

$$\dot{c}_P = k_2 c_{ES}$$

First we solve the equations for $\dot{c}_E$ and $\dot{c}_{ES}$:

$$\frac{d}{dt} \begin{pmatrix} c_{ES} \\ c_E \end{pmatrix} = \begin{pmatrix} -k_{-1} - k_2 & k_1 c_S^0 \\ k_{-1} + k_2 & -k_1 c_S^0 \end{pmatrix} \begin{pmatrix} c_{ES} \\ c_E \end{pmatrix}$$

The matrix has one Eigenvalue $\lambda = 0$ corresponding to a stationary solution

$$\begin{pmatrix} -k_{-1} - k_2 & k_1 c_S^0 \\ k_{-1} + k_2 & -k_1 c_S^0 \end{pmatrix} \begin{pmatrix} \frac{k_1 c_S^0}{k_{-1}+k_2} \\ 1 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

The stationary concentration of the ES complex is

$$c_{ES}^{stat} = \frac{k_1}{k_{-1} + k_2} c_S c_E = \frac{c_S c_E}{K_M}$$

with the Michaelis constant

$$K_M = \frac{k_{-1} + k_2}{k_1}$$

The second eigenvalue relates to the time constant for reaching the stationary state

$$\begin{pmatrix} -k_{-1} - k_2 & k_1 c_S^0 \\ k_{-1} + k_2 & -k_1 c_S^0 \end{pmatrix} \begin{pmatrix} 1 \\ -1 \end{pmatrix} = -(k_1 c_S^0 + k_{-1} + k_2) \begin{pmatrix} 1 \\ -1 \end{pmatrix}$$

For the initial conditions

$$c_{ES}(0) = c_P(0) = 0$$

we find

$$c_{ES}(t) = \frac{c_E^0}{1 + \frac{K_M}{c_S^0}} (1 - e^{-(k_1 + k_{-1} + k_2)t})$$

$$c_E(t) = \frac{c_E^0}{1 + \frac{c_S^0}{K_M}} (1 + \frac{c_S^0}{K_M} e^{-(k_1 + k_{-1} + k_2)t})$$

The stationary state is stable since any deviation will decrease exponentially.

The overall rate of the enzyme catalysed reaction is given by the rate of product formation

$$r = \dot{c}_P = -\dot{c}_S = k_2 c_{ES}$$

and with the total concentration of enzyme

$$c_{E,tot} = c_E + c_{ES}$$

we have

$$c_{ES} = \frac{c_E c_S}{K_M} = \frac{(c_{E,tot} - c_{ES}) c_S}{K_M}$$

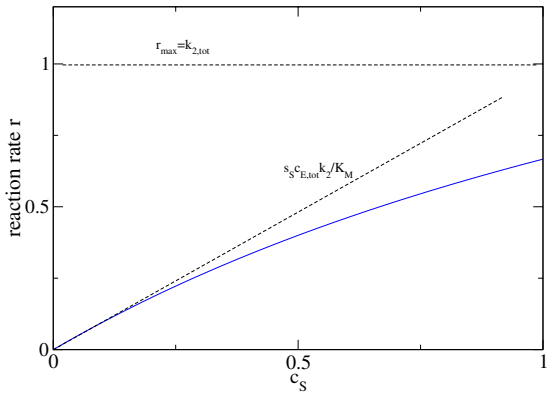
and hence

$$c_{ES} = \frac{c_{E,tot} c_S}{c_S + K_M}$$

and the overall reaction rate is given by the Michaelis-Menten equation

$$r = \frac{k_2 c_{E,tot} c_S}{K_M + c_S}$$

$$\frac{r}{r_{max}} = \frac{c_S}{c_S + K_M} \qquad r_{max} = k_2 c_{E,tot}$$

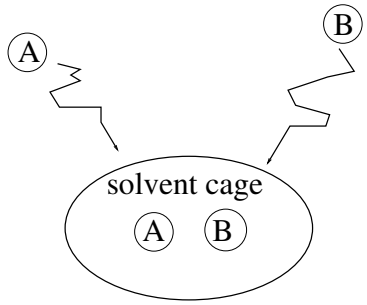


6.8 Reactions in Solutions

In solutions the reacting molecules approach each other by diffusive motion forming a reactive complex within a solvent cage which has a lifetime of typically 100 ps. Formally this can be described by an equilibrium between the free reactands A and B and a reactive complex $\{AB\}$

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \{A\,B\} \overset{k_2}{\rightarrow} C$$

Figure 56: formation of a reactive complex

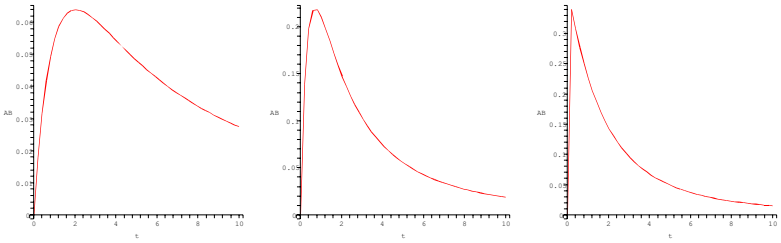


$$\dot{c}_A = \dot{c}_B = -k_1 c_A c_B + k_{-1} c_{\{AB\}}$$

$$\dot{c}_C = k_2 c_{\{AB\}}$$

$$\dot{c}_{\{AB\}} = (k_1 c_A c_B - (k_{-1} + k_2) c_{\{AB\}}$$

Figure 57: transition from reaction controlled to diffusion controlled limit



$r = k_2 c_{\{AB\}}$ is calculated numerically for $k_2 = 1$, $k_1 = k_{-1} = 0.1, 1, 10$

consider the following two limiting cases:

6.8.1 diffusion controlled limit

If the reaction rate k_2 is large compared to $k_{\pm 1}$ we find for the stationary solution approximately

$$k_2 c_{\{AB\}} \approx k_1 c_A c_B$$

and hence for the overall reaction rate

$$\dot{c}_C = k_2 c_{\{AB\}} \approx k_1 c_A c_B$$

and formation of the reactive complex determines the reaction rate

6.8.2 reaction controlled limit

If on the other hand $k_2 \ll k_{\pm 1}$ an equilibrium between reactands and reactive complex will be established

$$A + B \leftrightharpoons \{A\,B\} \qquad \frac{c_{\{AB\}}}{c_A c_B} = K = \frac{k_1}{k_{-1}}$$

Now the overall reaction rate is

$$\dot{c}_c = k_2 c_{\{AB\}} = k_2 K c_A c_B$$

determined by the reaction rate k_2 and the constant of the diffusion equilibrium

11 Ion transport through a membrane

11.1 Nernst potential

In the rest state of a neuron the potassium concentration is higher in the interior whereas there are more sodium and chlorine ions outside. Example data are shown in the following table.
[28]

Table 1: ion concentrations for the squid giant axon

Ion	inside(mM)	outside(mM)
K^+	400	20
Na^+	50	440
Cl^-	52	560
A^- (organic anions)	385	-

Let us first consider only one type of ions and constant temperature. The thermodynamic force is

$$\vec{K}_k = -\frac{1}{T}\vec{\bigtriangledown}(\mu_k + Z_k e\Phi) = -k\vec{\bigtriangledown}\ln c_k - \frac{1}{T}\vec{\bigtriangledown}(Z_k e\Phi)$$

This force and the corresponding ion current vanish if the contributions from concentration gradient and potential difference compensate each other

$$\Phi + \frac{kT}{Z_k e}\ln c_k = \text{const}$$

Usually the potential is defined as zero on the outer side and

$$V_k = \Phi_{inside} = \frac{kT}{Z_k e}\ln\frac{c_{k,outside}}{c_{k,inside}}$$

is the so called Nernst potential. For the example concentrations we find

$$V_{K+} \approx -75mV$$

$$V_{Ka+} = +54mV$$

$$V_{Cl-} = -59mV$$

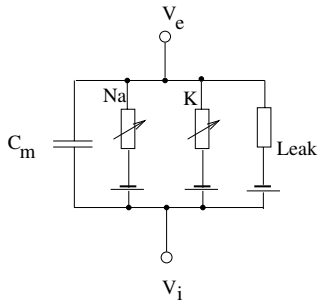
The concentration gradient has to be produced by (energy consuming) ion pumps.

[28] E.Kandel,J.Schwartz,T.Jessel, Neurowissenschaften-Eine Einführung. Spektrum Akademischer Verlag 1996

11.2 Hodgkin-Huxley model

In 1952 Hodgkin and Huxley won the Nobel prize for their quantitative description of the squid qiant axon dynamics. They thought of the axon membrane as an electrical circuit

Figure 67: Hodgkin-Huxley model



They assumed independent currents of sodium and potassium , a capacitive current and a catch-all leak current. The total current is the sum of these

$$I_{app} = I_C + I_{Na} + I_K + I_L$$

The capacitive current is

$$I_C = C_m \frac{dV}{dt}$$

For the ionic currents we have

$$I_s = g_s(V - V_s)$$

where g_k is the channel conductance which depends on the membrane potential and on time and V_k is the specific Nernst potential

11.3 Nernst-Planck model

We consider the thermodynamic force in one dimension

$$\vec{K_k} = -\frac{1}{T}\vec{\bigtriangledown}(\mu_k + Z_k e\Phi) = -\frac{1}{T}\frac{kT}{c_k}\vec{\bigtriangledown}c_k - \frac{1}{T}\vec{\bigtriangledown}\left(Z_k e\Phi\right)$$

as a force acting upon a particle with mass m_k given by

$$\vec{F} = -\frac{kT}{c_k}\vec{\bigtriangledown}c_k - \vec{\bigtriangledown}\left(Z_k e\Phi\right)$$

The phenomenological equation for the corresponding particle flux is

$$\vec{J_k} = c_k\vec{v_k} = -D\vec{\bigtriangledown}c - \frac{G}{Z_k e}\vec{\bigtriangledown}\Phi$$

This can be interpreted as the compensation of the driving force $\vec{F}$ by a frictional force

$$\vec{F}_{fr} = -m_k\gamma\vec{v}_k = -\frac{m_k\gamma}{c_k}\vec{J}_k = \frac{m_k\gamma D}{c_k}\vec{\bigtriangledown}c_k + \frac{m_k\gamma G}{Z_k e c_k}\vec{\bigtriangledown}\Phi$$

with

$$D = \frac{kT}{m_k\gamma}$$

$$G = \frac{Z_k^2 e^2 c_k}{\gamma m_k} = \frac{Z_k^2 e^2 c_k D}{kT}$$

which leads to the Nernst-Planck-equation

$$J = -D\frac{dc}{dx} - \frac{ZecD}{kT}\frac{d\Phi}{dx}$$

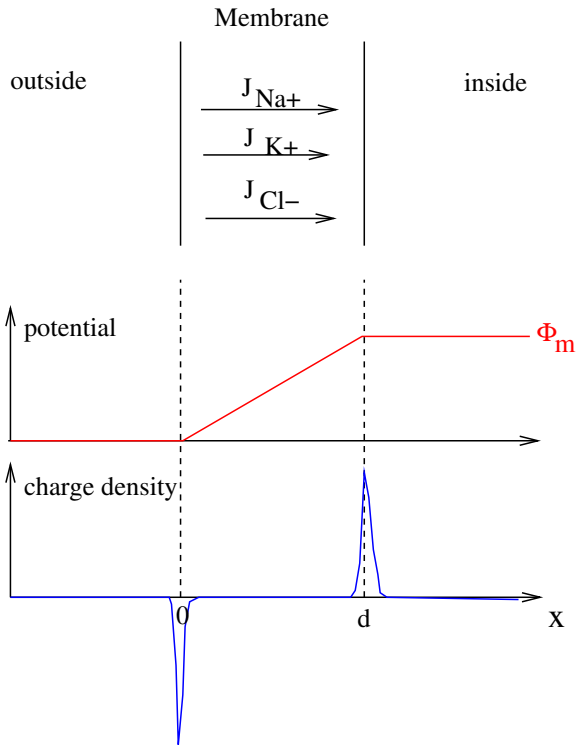
The electric potential obeys the Poisson-Boltzmann equation

$$\frac{d}{dx}\epsilon\frac{d}{dx}\Phi = -\sum Z_k e c_k$$

11.4 Goldman-Hodgkin-Katz model

We now want to calculate the potential for a steady state with more than one ionic species present. If we take the ionic species Na^+, K^+, Cl^- which are most important in nerve excitation that will define the so called Goldman-Hodgkin-Katz model.

Figure 68: coupled ionic fluxes



We may specify at will the chemical potentials or alternatively the concentrations of n-1 species on both sides of the membrane. The concentration of the n-th species is then given by electroneutrality

$$\rho = \sum Z_k e c_k = 0$$

Tp proceed we have to calculate the dependence of the fluxes J_k on the concentrations $c_{k,in}$ and $c_{k,out}$.To that end we multiply the Nernst-Planck equation by e^{y_k} with

$$y_k = Z_k e \frac{\Phi}{kT}$$

to get

$$J_k e^{y_k} = -D_k e^{y_k} \left(\frac{dc_k}{dx} + c_k \frac{dy_k}{dx} \right) = -D_k \frac{d}{dx}(c_k e^{y_k})$$

This can be integrated over the thickness d of the membrane

$$\int_0^d J_k e^{y_k} dx = -D \int_0^d \frac{d}{dx}(c_k e^{y_k}) dx = -D \left(c_{k,in} e^{Z_k e \Phi_m / kT} - c_{k,out} \right)$$

We assume a linear variation of the potential across the membrane

$$\Phi(x) = \frac{x}{d} \Phi_m$$

This is an approximation which is consistent with electroneutrality. In the bulk solution on either side of the membrane the potential will be constant, again in accordance with electroneutrality. On the boundary between liquid and membrane the first derivative of Φ will be discontinous corresponding to a surface charge distribution. [29] Assuming a stationary state with $\partial J / \partial x = 0$ we can evaluate the second integral

$$J_k \frac{kTd}{Z_k e \Phi_m} \left(e^{Z_k e \Phi_m / kT} - 1 \right) = -D \left(c_k(d) e^{Z_k e \Phi_m / kT} - c_k(0) \right)$$

$$J_k = -\frac{D}{d} \frac{Z_k e \Phi_m}{kT} \frac{c_{k,in} e^{Z_k e \Phi_m / kT} - c_{k,out}}{e^{Z_k e \Phi_m / kT} - 1}$$

In a stationary state the total charge current has to vanish

$$I = \sum_k Z_k e J_k = 0$$

and we find

$$\frac{e \Phi_m}{kTd} \sum D_k Z_k^2 \frac{c_{k,in} e^{Z_k e \Phi_m / kT} - c_{k,out}}{e^{Z_k e \Phi_m / kT} - 1} = 0$$

with $Z_{Na+} = Z_{K+} = 1, Z_{Cl-} = -1$ and

$$y_m = \frac{e \Phi_m}{kT} \quad b_m = e^{y_m}$$

we have

[29] We do not consider a possible variation of ϵ here.

$$D_{Na+}\frac{c_{Na,in}b_m - c_{Na,out}}{b_m - 1} + D_{K+}\frac{c_{K+in}b_m - c_{K+,out}}{b_m - 1} + D_{Cl-}\frac{c_{Cl,in}b_m^{-1} - c_{Cl,out}}{b_m^{-1} - 1} = 0$$

Multiplication with $(b_m - 1)$ gives

$$D_{Na+}(c_{Na,in}b_m - c_{Na,out}) + D_{K+}(c_{K+in}b_m - c_{K,out}) - b_m D_{Cl-}(C_{Cl,in}b_m^{-1} - c_{Cl,out})$$

and we find

$$b_m = \frac{D_{Na+}c_{Na,out} + D_{K+}c_{K,out} + D_{Cl-}c_{Cl,in}}{D_{Na+}c_{Na,in} + D_{K+}c_{K,in} + D_{Cl-}c_{Cl,out}}$$

anf finally

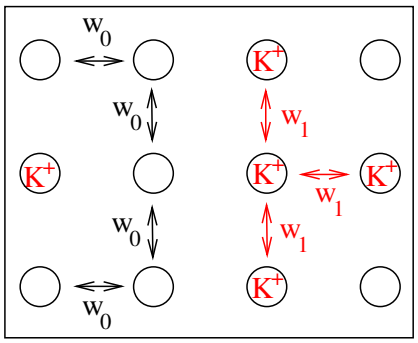
$$\Phi_m = \frac{kT}{e}\ln\frac{D_{Na+}c_{Na,out} + D_{K+}c_{K,out} + D_{Cl-}c_{Cl,in}}{D_{Na+}c_{Na,in} + D_{K+}c_{K,in} + D_{Cl-}c_{Cl,out}}$$

This formula has to be compared with the Nernst equation. The ionic contributions appear weighted with their mobilities. The Nernst equation is obtained if the membrane is permeable for only one ionic species.

11.5 Cooperative transport and membrane excitations: Adam's model

Adam's model for membranes explains the different permeabilities of the membrane in the ground and excited state.

Figure 69: Adam's model



We assume that in the ground state the membrane-pore proteins form preferably complexes with Calcium ions Ca^{2+}while in the excited state the binding of potassium is preferred. The different affinities of the pore proteins- which we will call active centers in the following in the ground and ecited state are

explained as a cooperative phenomenon. The system of active centers is modelled as a lattice with interactions between adjacent sites w_0 and w_1 respectively very much like in the lattice gas models which we studied in the first chapter. An active center in the ground state receives an additional stabilization w_0 for each neighbouring center in the ground state. Similarly an active center having bound K^+ is stabilized by w_1 by every excited center in the neighbourhood. In Adam's model cooperativity is treated in a mean field approximation. We do not want to reproduce the details of the statistical calculations. A change of potential will trigger a phase transition. In biological membranes the interactions w are mediated by direct protein-protein contacts. A similarly well studied cooperative phenomenon occurs in the binding of oxagen by Hemoglobine. Hemoglobine consists of four sub-units. The binding of oxygen to one or more sub-units enhances the affinity for oxygen of the remaining sub-units.

Let P be the probability to find an active center in the excited state and $1-P$ the probability to find it in the groundstate. We assume the temporal development to obey the Master equation

$$\frac{dP}{dt} = -k'P + k(1-P)$$

In Adam's model the rate constants k and k' are found to be functions of P itself and of the interactions w

$$k = k_0 \exp\left(-\frac{\nu w_0}{kT}(1-P)\right)$$

$$k' = k'_0 \exp\left(-\frac{\nu w_1}{kT}P\right)$$

where ν is the average number of adjacent sites. k_0 and k'_0 are functions of the concentrations on both sides of the membrane and the trans-membrane potential difference Φ_m. In a steady state $P = \overline{P}$ will not change in time and we get

$$\frac{\overline{P}}{1-\overline{P}} = \frac{k}{k'} = \frac{k_0(\Phi_m)}{k'_0(\Phi_m)} \exp\left(\frac{\nu\overline{P}}{kT}(w_1+w_0) - \frac{\nu w_0}{kT}\right)$$

which we rewrite as

$$\frac{\overline{P}}{1-\overline{P}} \exp\left(-\frac{\nu\overline{P}}{kT}(w_1+w_0)\right) = \frac{k_0(\Phi_m)}{k'_0(\Phi_m)} \exp\left(-\frac{\nu w_0}{kT}\right) \approx F(\Phi_m)$$

In a certain range of parameters more than one solution for $\overline{P}$ as a function of Φ_m exists. Let us consider the implicit function

$$\frac{P}{1-P} e^{-wP} = x$$

in more detail. for small values of P we find

$$x \to P + (1-w)P^2 + \cdots \text{ as } P \to 0$$

and in the opposite limit

$$x \to \frac{e^{-w}}{P-1} + \cdots \text{ as } P \to 1$$

The function $P(x)$ becomes multiple valued if $x(P)$ has extremal values. Therefore we solve

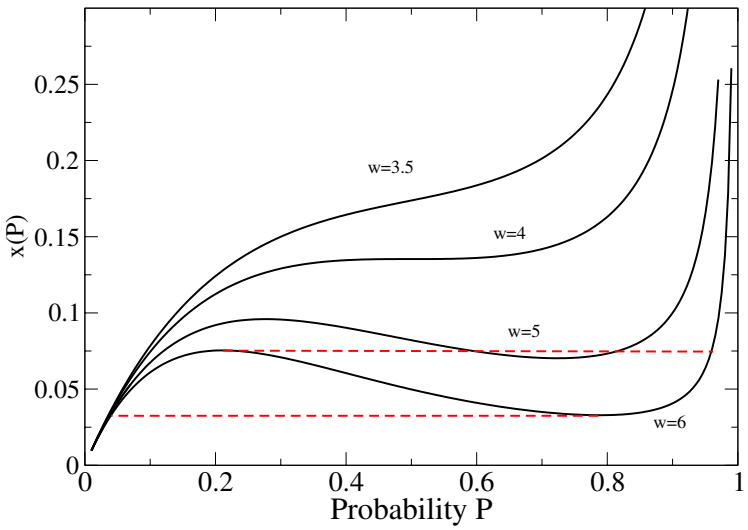
$$0 = \frac{d}{dP}x(P) = e^{-wP}\left(\frac{1 - wP + wP^2}{(1-P)^2}\right)$$

to find

$$P_{extr} = \frac{1}{2} \pm \sqrt{\frac{1}{4} - \frac{1}{w}}$$

A solution with $0 \leq P \leq 1$ is obtained for $w > 4$.

Figure 70: Bistability in Adam's model



By variation of the membrane potential difference it is possible to switch between the ground and excited state.