Mathematical models of chemical reactions

The Law of Mass Action

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:

$$k_-[C] = k_+[A][B] \tag{1}$$

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

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

so that

$$[A] + [C] = A_0 \tag{2}$$

Substituting (2) into (1) yields:

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

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

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

and

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

Gibbs free energy

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 $c = 1\text{M}$, 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 $\Delta G < 0$, i.e. 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:

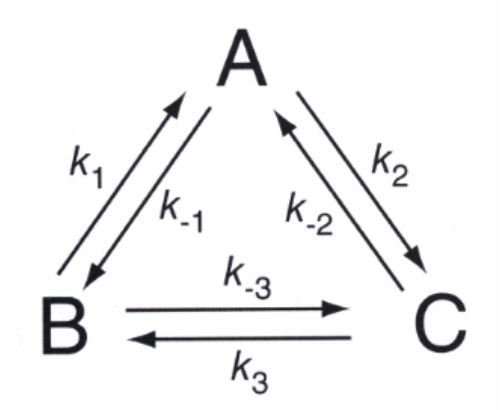
$$\begin{aligned}
\Delta G &= \gamma G_C + \delta G_D - \alpha G_A - \beta G_B \\
&= \gamma G_C^0 + \delta G_D^0 - \alpha G_A^0 - \beta G_B^0 \\
&\quad + \gamma RT \ln([C]) + \delta RT \ln([D]) - \alpha RT \ln([A]) - \beta RT \ln([B]) \\
&= \Delta G^0 + RT \ln\left(\frac{[C]^\gamma [D]^\delta}{[A]^\alpha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

At equilibrium with $\Delta G = 0$:

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

Detailed balance

Consider the cyclic reaction:



In equilibrium all states must have the same energy:

$$G_A = G_B = G_C$$

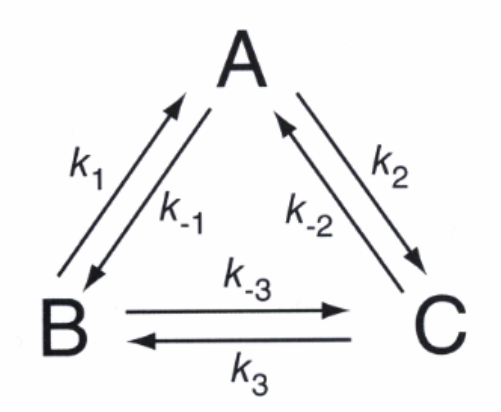
All transitions must be in equilibrium:

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

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

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

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

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

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 $V_{max} = k_2 E_0$.

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:

$$
\begin{aligned}
\frac{ds}{dt} &= -k_1 se + k_{-1} c_1 - k_3 s c_1 + k_{-3} c_2 \\
\frac{dc_1}{dt} &= k_1 se - (k_{-1} + k_2) c_1 - k_3 s c_1 + (k_4 + k_{-3}) c_2 \\
\frac{dc_2}{dt} &= k_3 s c_1 - (k_4 + k_{-3}) c_2
\end{aligned}
$$

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

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

Which gives this reaction speed:

$$
\begin{aligned}
V &= \frac{(k_2K_2 + k_4s)e_0s}{K_1K_2 + K_2s + s^2} \\
&= \frac{(2k_2K + 2k_2s)e_0s}{K^2 + 2Ks + s^2} \\
&= \frac{2k_2(K + s)e_0s}{(K + s)^2} = \frac{2k_2e_0s}{(K + s)}
\end{aligned}
$$

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:

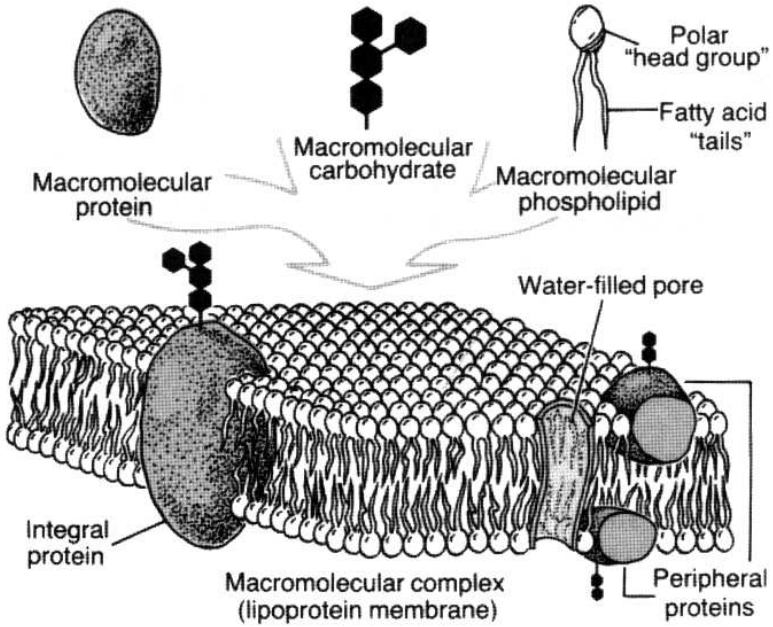
$$V = V_{\max} \frac{s^n}{K_m^n + s^n}$$

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



Two types of transmembrane flow

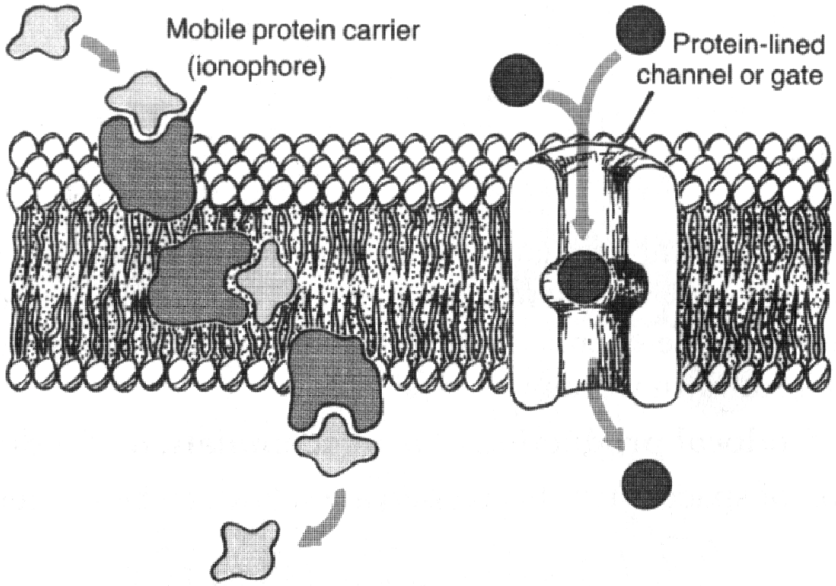
Passive: Diffusion along the concentration gradient

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

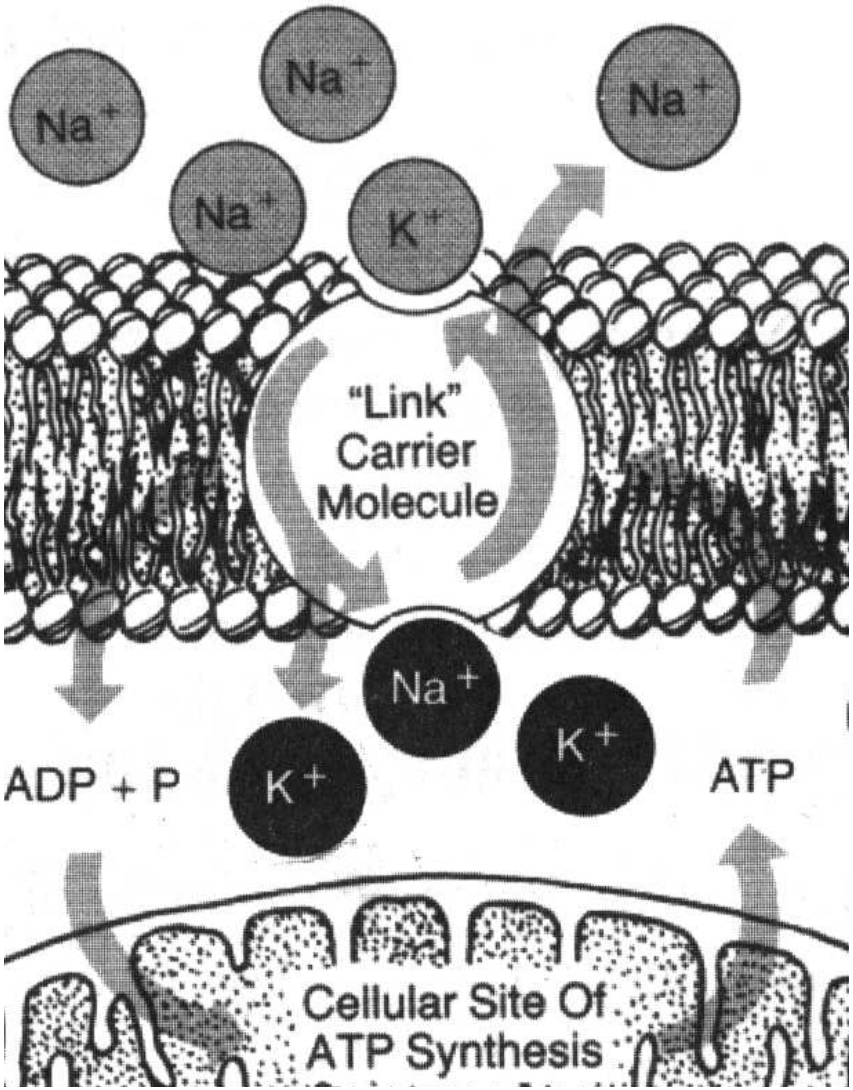
Active: Energy driven flow against the gradients

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

Transmembrane flow



Active Transport



Diffusion

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

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

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

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

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:

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

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

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:

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

Antiport

In antiport the two substances travels in opposite direction (exchangers).
Model:

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

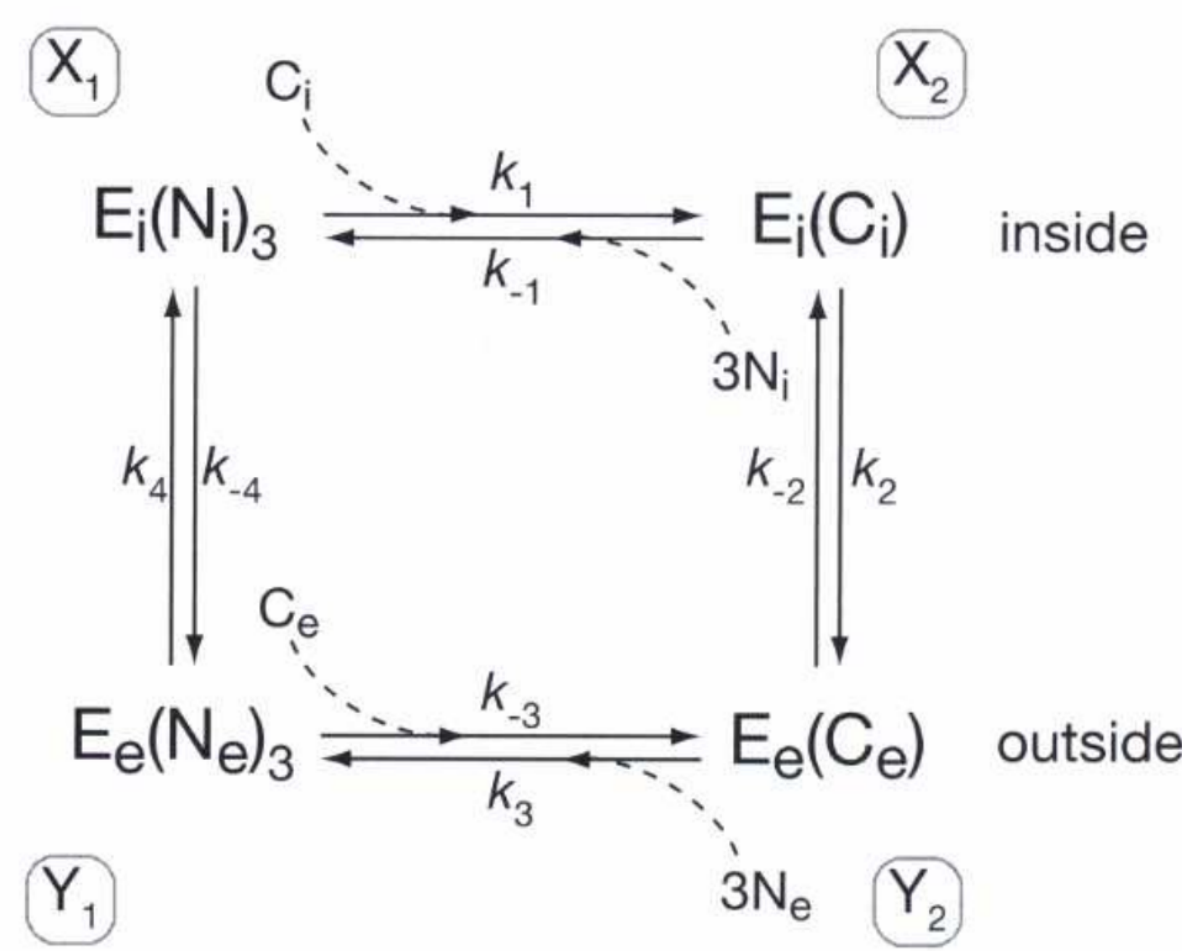
Mathematically almost the same flux, but with subscript of T toggled:

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

Sodium-Calcium exchange

- The sodium calcium exchanger is a membrane protein
- It uses the energy stored in the sodium gradient to do work on calcium ions.
  - Transports one calcium ion out of the cell (against the Calcium gradient)
  - In exchange for letting three sodium ions in (along the Sodium gradient)
- It is electrogenic, i.e. each exchange changes the charge balance over the membrane.
- Net influx: $3 \times \mathrm{Na}^{+} - 1 \times \mathrm{Ca}^{2+} = +e$

Sodium-Calcium exchange



$$\frac{dx_1}{dt} = k_{-1} n_i^3 x_2 + k_4 y_1 - (k_1 c_i + k_{-4}) x_1$$
$$\frac{dx_2}{dt} = k_{-2} y_2 + k_1 c_i x_1 - (k_2 + k_{-1} n_i^3) x_2$$
$$\frac{dy_1}{dt} = k_{-4} x_1 + k_3 n_e^3 y_2 - (k_4 + k_{-3} c_e) y_1$$
$$1 = x_1 + x_2 + y_1 + y_2$$

Flux in steady state:

$$J = \frac{k_1 k_2 k_3 k_4 (c_i n_e^3 - K_1 K_2 K_3 K_4 c_e n_i^3)}{\text{16 positive terms}}$$

An electrogenic exchanger

$$L_i \rightarrow L_e$$

$$\begin{aligned}\Delta G &= G_{L_e} - G_{L_i} \\ &= (G^0_{L_e} + RT\ln([L_e]) + zFV_e) - (G^0_{L_i} + RT\ln([L_i]) + zFV_i) \\ &= RT\ln\left(\frac{[L_e]}{[L_i]}\right) - zFV\end{aligned}$$

Here we have used that $G^0_{L_e} = G^0_{L_i}$ and $V = V_i - V_e$.
At equilibrium

$$K = \frac{[L_i]_{eq}}{[L_e]_{eq}} = \exp\left(\frac{-zFV}{RT}\right)$$

Back to the NCX case

$$3\mathrm{Na}_e^+ + \mathrm{Ca}_i^{2+} \longrightarrow 3\mathrm{Na}_i^+ + \mathrm{Ca}_e^{2+}$$

Change in chemical potential:

$$\Delta G = RT \ln\left(\frac{n_i^3 c_e}{n_e^3 c_i}\right) + FV$$

At equilibrium we have $\Delta G = 0$ thus:

$$\frac{n_{i,eq}^3 c_{e,eq}}{n_{e,eq}^3 c_{i,eq}} = \exp\left(-\frac{FV}{RT}\right)$$

Detailed balance require that the product of the rates in each direction is equal:

$$k_1 c_{i,eq} \cdot k_2 \cdot k_3 n_{e,eq}^3 \cdot k_4 = k_{-1} n_{i,eq}^3 \cdot k_{-4} \cdot k_{-3} c_{e,eq} \cdot k_{-2}$$

Defining $K_j = k_{-j}/k_j$ this becomes

$$K_1 K_2 K_3 K_4 = \frac{c_{i,eq}}{c_{e,eq}} \frac{n_{e,eq}^3}{n_{i,eq}^3}$$

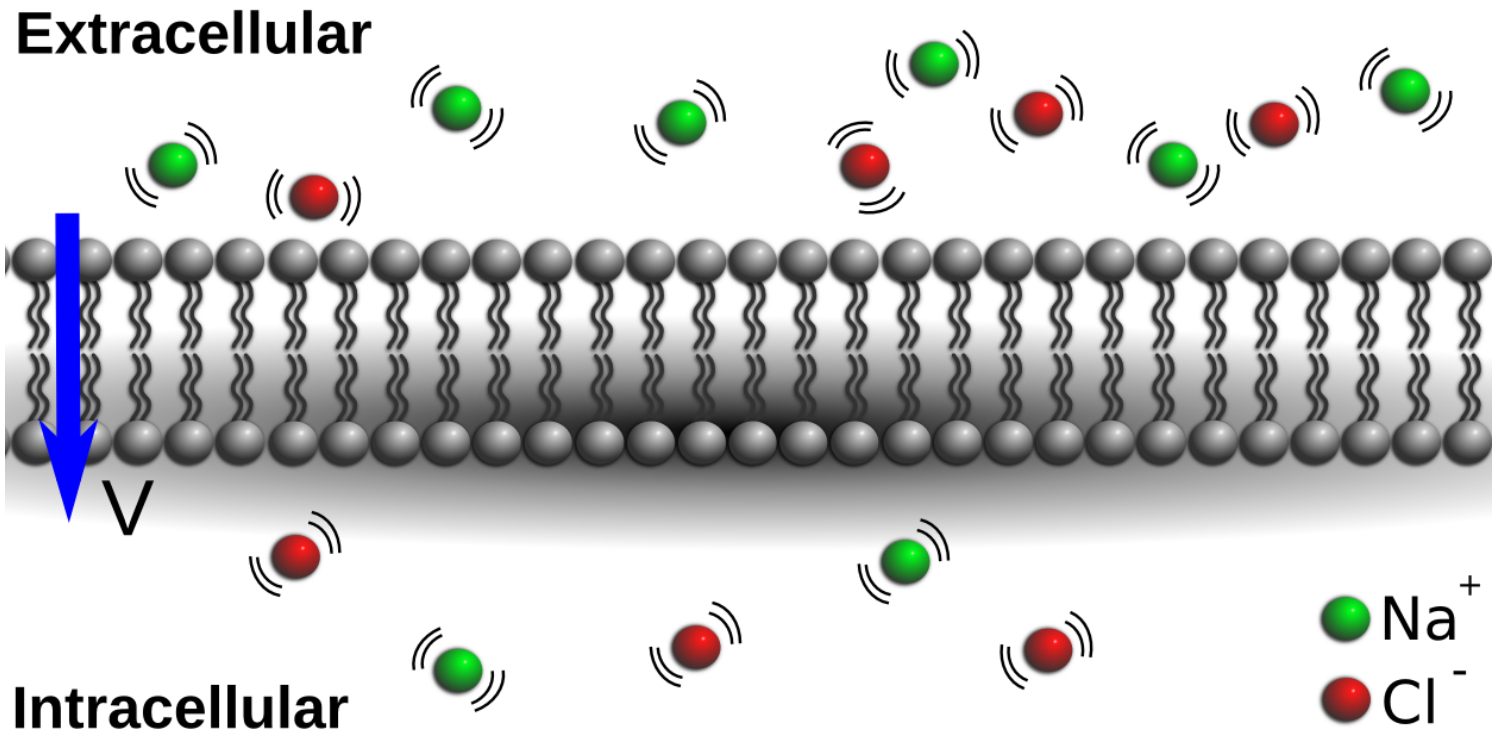
Inserting into previous expression:

$$K_1 K_2 K_3 K_4 = \exp\left(\frac{FV}{RT}\right)$$

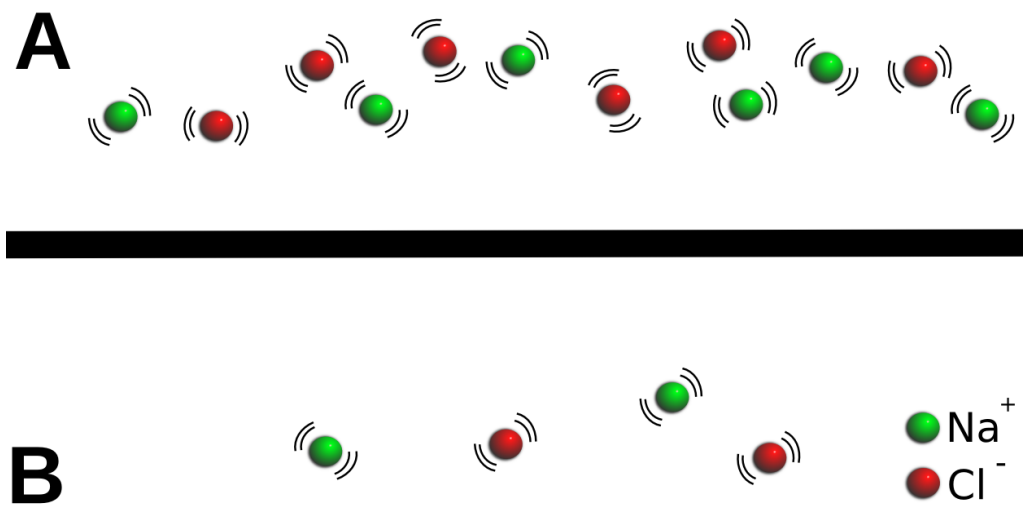
The current expression then becomes:

$$J = \frac{k_1 k_2 k_3 k_4 (c_i n_e^3 - e^{\frac{FV}{RT}} c_e n_i^3)}{\text{16 positive terms}}$$

The membrane potential



Flow through a semi-permeable membrane

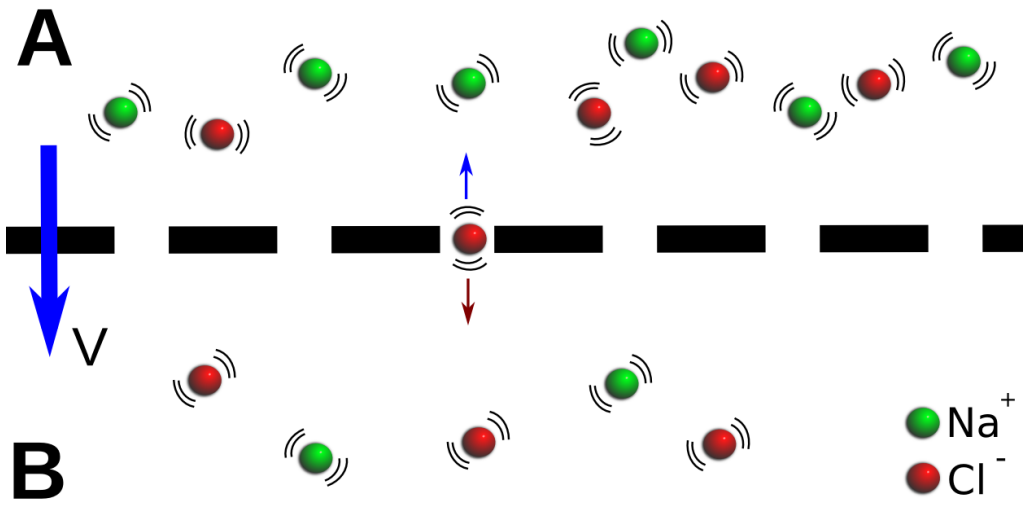


Consider two solutions:

- A: Contains 100mM Cl^- ions and 100mM Na^+ ions
- B: Contains 10mM Cl^- ions and 10mM Na^+ ions

Both are neutral.

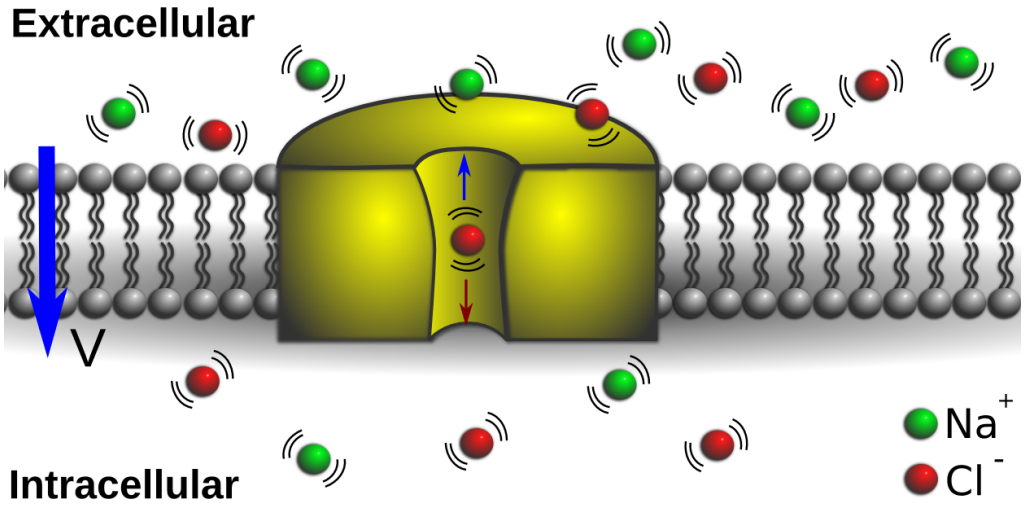
Flow through a semi-permeable membrane



If they are only separated by a membrane permeable to Cl^- but not Na^+, this will happen:

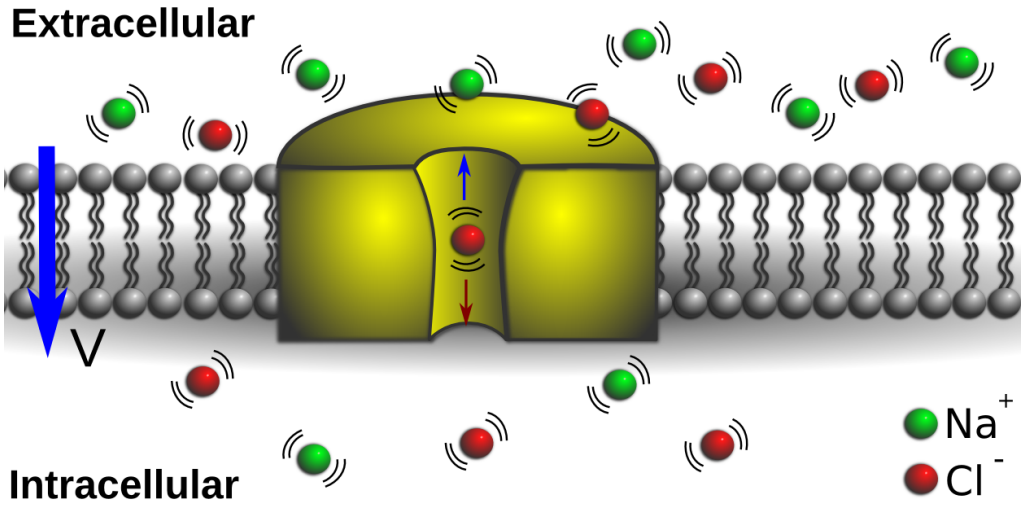
- Cl^- will diffuse from A to B due the concentration gradient
- $[Cl^-]_A$ will drop and $[Cl^-]_B$ will increase
- $[Na^+]_A$ and $[Na^+]_B$ will remain fixed (no flow)
- A and B will no longer be neutral
- An electrical force will attract Cl^- towards A

Flow through a semi-permeable membrane



- The cell membrane is semi-permeable.
- The semi-permeability is provided by for example ion channels
- V is called the *membrane potential* and is defined by $V_i - V_e$

The Nernst Equilibrium Potential



We now have two forces driving Cl^- across the membrane:

- Flow from A to B due to the concentration gradient
- Flow from B to A due to the charge gradient

At some point an equilibrium is reached were the net flow is zero. The transmembrane potential at that point is called the Nernst Equilibrium Potential.

The Nernst Equilibrium Potential, via Gibbs

Gibb's free energy on either side of the membrane:

$$G_{S,i} = G_S^0 + RT \ln([S]_i) + zFV_i$$
$$G_{S,e} = G_S^0 + RT \ln([S]_e) + zFV_e$$

Electro-chemical potential difference:

$$\Delta G_S = G_{S,i} - G_{S,e} = RT \ln([S]_i/[S]_e) + zFV$$

At equilibrium, $\Delta G_S = 0$:

$$V_S = \frac{RT}{zF} \ln\left(\frac{[S]_e}{[S]_i}\right)$$

Nernst Equilibrium Potential via Planck's equation

Models the ion-flux caused by an electrical field (Planck's equation):

$$J = -\mu \frac{z}{|z|} c \nabla \phi$$

with

μ - mobility of the ions in the liquid

$z/|z|$ - sign of the charge of the ion

c - the concentration of the ion

$\nabla \phi$ - the electrical field

Nernst Equilibrium Potential via Planck's equation

Given Fick's law of diffusion

$$J = -D\nabla c$$

and using Einstein's relationship between μ and D:

$$\mu = D\frac{|z|F}{RT}$$

to substitute for μ in Plank's law, we can combine the effect of concentration gradient (Fick's law) and the electric field (Plank's law):

$$J = -D(\nabla c + \frac{zF}{RT}c\nabla\phi)$$

and we get Nernst-Planck equation for electro diffusion.

Nernst Equilibrium Potential via Planck's equation

Consider equilibrium in 1D flow:

$$\frac{dc}{dx} + \frac{zF}{RT} c \frac{d\phi}{dx} = 0$$

$$\frac{1}{c}\frac{dc}{dx} + \frac{zF}{RT}\frac{d\phi}{dx} = 0$$

Integrating from inside (x=0) to outside (x=L) yields:

$$\ln(c)|_{c(0)}^{c(L)} = -\frac{zF}{RT}(\phi(L) - \phi(0))$$

We define the transmembrane potential to be $v = \phi_i - \phi_e$ The value of the transmembrane potential at zero flux is then

$$V_e = \frac{RT}{zF} \ln(\frac{c_e}{c_i}) \tag{3}$$

Ionic currents across the membrane

Ionic currents across the membrane can in general be expressed by:

$$I = N\, p(V, t)\mathcal{I}(V)$$

where:

- $\mathcal{I}(V)$ is an $I - V$ relationship
- N the number of open channels
- $p(V, t)$ the proportion of open channels

Ionic currents across the membrane

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Next we will go through:

- 2 common versions of $\mathcal{I}(V)$
- How I change the membrane potential V
- Different models for $p(V,t)$

Linear and nonlinear $I - V$ relationship for which both $\mathcal{I}(V_e) = 0$

Linear

$$\mathcal{I}(V) = \bar{g}(V - V_e)$$

$$\mathcal{I}(V_e) = 0$$

where $\bar{g}$ is a maximal channel conductance.

Linear and nonlinear $I - V$ relationship for which both $\mathcal{I}(V_e) = 0$

Linear

$$\mathcal{I}(V) = \bar{g}(V - V_e)$$

$$\mathcal{I}(V_e) = 0$$

where $\bar{g}$ is a maximal channel conductance.

Nonlinear (Goldman-Hodgkin-Katz)

$$\mathcal{I}(V) = gV \frac{c_i - c_e e^{\frac{-zvF}{RT}}}{1 - e^{\frac{-zVF}{RT}}}$$

$$\mathcal{I}(V_e) = \mathcal{I}(\frac{RT}{zF} \ln(\frac{c_e}{c_i})) = 0$$

Goldman-Hodgkin-Katz current equation

Nernst-Planck equation for electro diffusion:

$$J = -D(\nabla c + \frac{zF}{RT} c \nabla \phi)$$

Consider 1D flow through a channel and assume $\nabla\phi$ is constant in space and that c and ϕ are in steady-state and varies linearly inside the channel.

$$\frac{d\phi}{dx} = \frac{\Delta\phi}{\Delta x} = \frac{\phi(L) - \phi(0)}{L - 0} = \frac{\phi_e - \phi_i}{L} = -v/L$$

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The equation is reduced to an ordinary differential equation:

$$J/D = -\frac{dc}{dx} - \frac{zF}{RT} c(-v/L) = -\frac{dc}{dx} + kc$$

where $k = \frac{zFv}{RTL}$

Goldman-Hodgkin-Katz current equation

The differential equation

$$J/D = -\frac{dc}{dx} + kc$$

is solved by setting initial conditions $c(0) = c_i$:

$$e^{-kx}c = c_i + \frac{J}{D}\frac{1}{k}(e^{-kx} - 1)$$

Goldman-Hodgkin-Katz current equation

The differential equation

$$J/D = -\frac{dc}{dx} + kc$$

is solved by setting initial conditions $c(0) = c_i$:

$$e^{-kx}c = c_i + \frac{J}{D}\frac{1}{k}(e^{-kx} - 1)$$

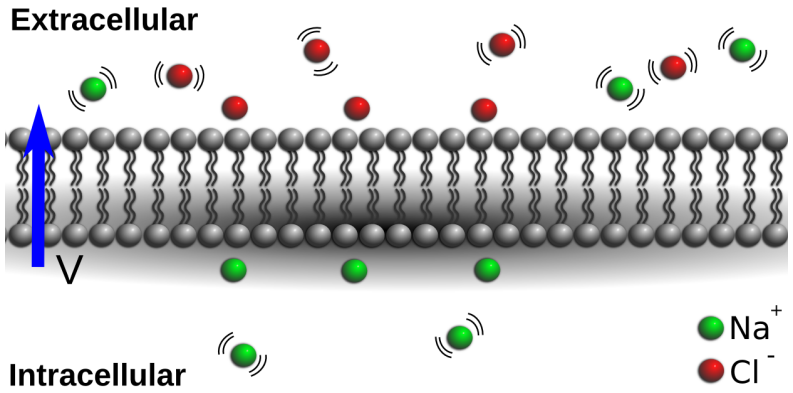
We determine J by using $c(L) = c_e$:

$$J = Dk\frac{c_i - c(L)e^{-kL}}{1 - e^{-kL}} = D\frac{zFv}{RTL}\frac{c_i - c_e e^{\frac{-zvF}{RT}}}{1 - e^{\frac{-zvF}{RT}}}$$

J has dimension moles per area per time, an expression for current is given by

$$I = zFJ = \frac{D}{L}\frac{z^2F^2}{RT}v\frac{c_i - c_e e^{\frac{-zvF}{RT}}}{1 - e^{\frac{-zvF}{RT}}}$$

Ionic currents across the membrane alters the membrane potential as if it was a capacitor



The membrane has properties similar to a capacitor:

- Consists of two conducting medias
- These are separated by an insulating material (the membrane)

The potential over a capacitor is proportional to the separated charge (Q):

$$V = Q/C_m$$

where C_m is the capacitance of the capacitor.

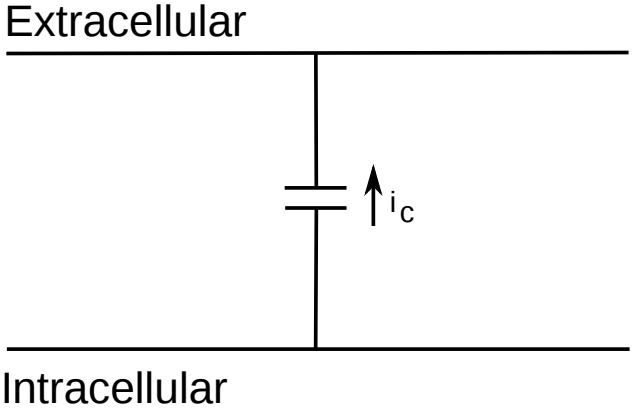
The cell membrane modeled as a leaky capacitor

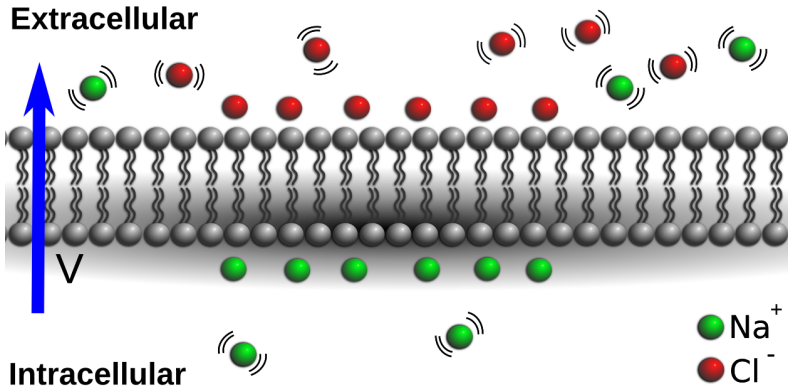
As any real capacitor the membrane conducts some current. The flux of ions (I_{ion}) will cause a change in Q and thus V.

Consider the change over a time interval Δt. It follows that $\frac{\Delta V}{\Delta t} = \frac{1}{C_m}\frac{\Delta Q}{\Delta t}$ and in the limit we get:

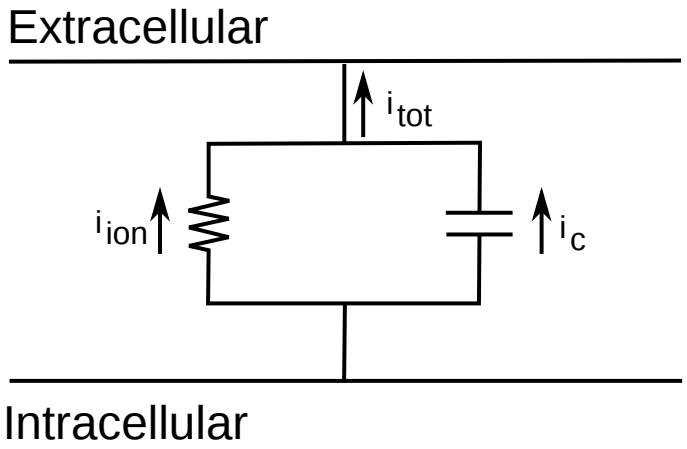
$$\frac{dV}{dt} = \frac{1}{C_m}\frac{dQ}{dt}$$

The term $\frac{dQ}{dt}$ is called the capacitive current and is denoted i_c.





Electrical circuit model of the cell membrane



The membrane behaves like resistor and capacitor in parallel:

$$i_{tot} = i_{\text{ion}} + i_c$$

If no current escapes $I_{tot} = 0$ and all ions passing the membrane, i_{ion} accumulate and change the membrane potential according to

$$C_m \frac{dV}{dt} = i_c = -i_{\text{ion}}$$

L11 Computational physiology

- Channel gating
  - Channels with a single and several identical gates
  - Channels with different but independent gates
  - Rate constants as probabilities
  - Waiting time and channel dynamics

Voltage gated Ion channels

Recall that ion currents across the membrane can be expressed as:

$$I = N\, p(V, t)\mathcal{I}(V)$$

Here $p(V, t)$ determines the proportion of the N channels in the membrane that are open. This propensity function varies with time and membrane potential.

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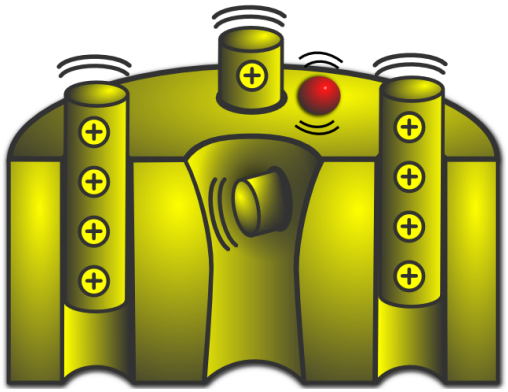
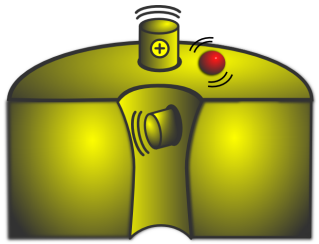


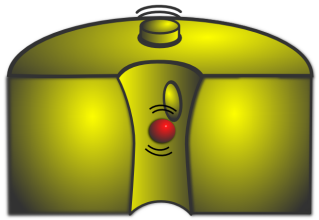
Next we will go through different expressions for how this propensity function can be derived for Voltage gated ion channels.

Voltage gated channel with one gate

Assumes that a channel is gated by one gate that can exist in two states, closed(C) and open(O):



$$C \underset{\beta(v)}{\overset{\alpha(v)}{\rightleftharpoons}} O$$

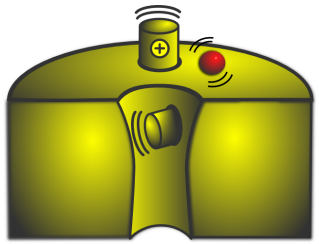


Applying law of mass action:

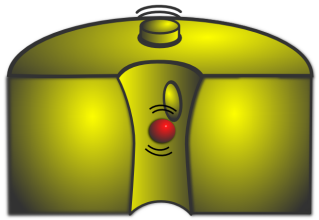
$$\frac{d[0]}{dt} = \alpha(V)[C] - \beta(V)[O]$$

Voltage gated channel with one gate

Assumes that a channel is gated by one gate that can exist in two states, closed(C) and open(O):



$$C \underset{\beta(v)}{\overset{\alpha(v)}{\rightleftharpoons}} O$$



Applying law of mass action:

$$\frac{d[0]}{dt} = \alpha(V)[C] - \beta(V)[O]$$

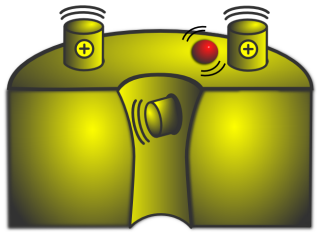
Dividing by the total amount of channels ([C]+[O]) yields

$$\frac{dp}{dt} = \alpha(V)(1-p) - \beta(V)p$$

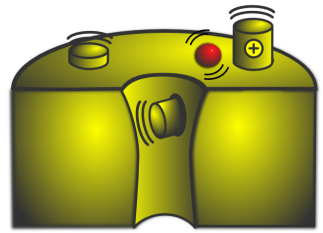
where p is the portion of open channel ([O]/([C]+[O])).

Voltage gated channel with two identical and independent gates

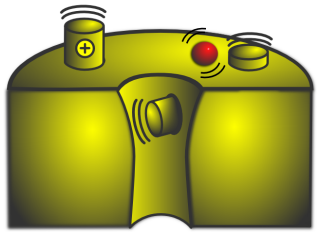
For some channels it is more appropriate to include several gates, which all need to be open for the channel to conduct. Example with two gates:



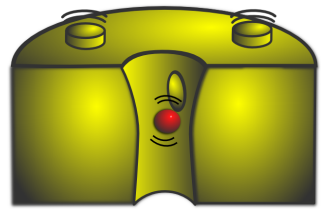
$$S_{00} \underset{\beta}{\overset{\alpha}{\rightleftarrows}} S_{10}$$



$$\alpha \downarrow\uparrow \beta \qquad\qquad \alpha \downarrow\uparrow \beta$$



$$S_{01} \underset{\beta}{\overset{\alpha}{\rightleftarrows}} S_{11}$$



Using the law of mass action we get a system of four equation. Will try to reduce this number to one!

First we make a reasonable claim: $p(V,t) = n^2$ where $\dot{n} = \alpha(1-n) - \beta n$

Further claim:

$$S_{11} = n^2; \quad S_{10} = S_{01} = n(1-n) = (1-n)n; \quad S_{00} = (1-n)^2$$

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Differentiate S_{11}

$$\dot{S}_{11} = 2n\dot{n} = 2n\left[\alpha(1-n) - \beta n\right]$$

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Differentiate S_{11}

$$\dot{S}_{11} = 2n\dot{n} = 2n\left[\alpha(1-n) - \beta n\right]$$

From mass conservation and insertion:

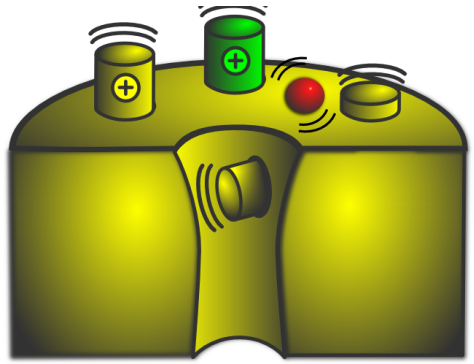
$$\begin{aligned} \dot{S}_{11} &= \alpha\left(S_{01} + S_{10}\right) - 2\beta S_{11} \\ &= \alpha 2n(1-n) - 2\beta n^2 \\ &= 2n\left[\alpha(1-n) - \beta n\right] \end{aligned}$$

Voltage gated channel with three gates, where two are identical and all are independent

Behavior of the Sodium conductance can not be described by a chain of two identical gates.

Two subunits of type m and one of type h.

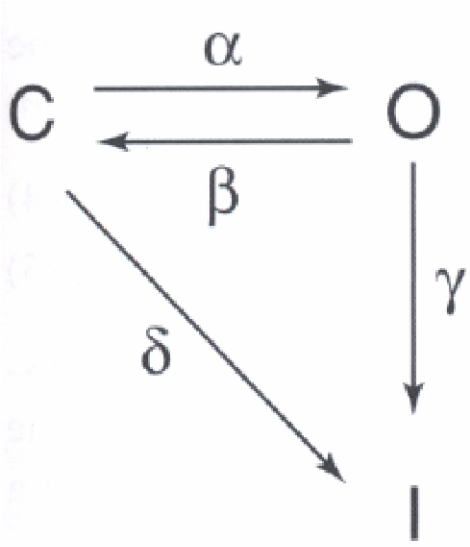
$$\begin{array}{ccccc} S_{00} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{10} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{20} \\ \gamma\downarrow\uparrow\delta & & \gamma\downarrow\uparrow\delta & & \gamma\downarrow\uparrow\delta \\ S_{01} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{11} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{21} \end{array}$$



Arguments similar to the one used above leads to these equations for m and h:

$$\dot{m} = \alpha(1-m) - \beta m, \quad \dot{h} = \gamma(1-h) - \delta h, \quad p(V,t) = m^2 h$$

Voltage gated channel with one gate, which can inactivate in addition to open and close



$$\frac{dc}{dt} = -(\alpha + \delta)c + \beta o$$

$$\frac{do}{dt} = \alpha c - (\beta + \gamma)o$$

$$i = 1 - c - o$$

$$p(V, t) = o$$

Rate constants as probabilities

Consider again the following model:

$$C \underset{\beta(v)}{\overset{\alpha(v)}{\rightleftharpoons}} O$$

Probabilistic interpretation of α and β:

$$\alpha : P(C \to O \text{ in } dt) \simeq \alpha dt$$

$$\beta : P(O \to C \text{ in } dt) \simeq \beta dt$$

Rate constants as probabilities

Consider again the following model:

$$C \underset{\beta(v)}{\overset{\alpha(v)}{\rightleftharpoons}} O$$

Probabilistic interpretation of α and β:

$$\alpha : P(C \to O \text{ in } dt) \simeq \alpha dt$$

$$\beta : P(O \to C \text{ in } dt) \simeq \beta dt$$

Probability that the channel is open at time $t + dt$:

$$\begin{aligned} P(O, t + dt) &= P(C, t) \cdot P(C \to O \text{ in } dt) \\ &\quad + P(O, t) \cdot P(\text{not } \ O \to C \text{ in } dt) \\ &= P(C, t) \cdot (\alpha dt) + P(O, t) \cdot (1 - \beta dt) \end{aligned}$$

$$P(O, t + dt) = P(C, t) \cdot (\alpha dt) + P(O, t) \cdot (1 - \beta dt)$$
$$= (1 - P(O, t)) \cdot (\alpha dt) + P(O, t) \cdot (1 - \beta dt).$$

Divide by dt and rearranges:

$$\frac{P(O, t + dt) - P(O, t)}{dt} = \alpha \cdot (1 - P(O, t)) - \beta \cdot P(O, t)$$

Going to the limit:

$$\frac{dP(O, t)}{dt} = \alpha \cdot (1 - P(O, t)) - \beta \cdot P(O, t)$$

Which we recognize as the usual gating equation!

$$\frac{dp}{dt} = \alpha(V)(1 - p) - \beta(V)p$$

The general case with N different states

Let $S(t) \in [1, 2, \ldots, N]$ being the state of the system at time t.
We define:

$$\phi_j(t) = P(S(t) = j).$$

k_{ij} is the probability rate going from $S = i$ to $S = j$:

$$k_{ij}dt \simeq P(S(t + dt) = j | S(t) = i)$$

Probability of staying $S = i$:

$$P(S(t + dt) = i | S(t) = i) = 1 - \sum_{j}^{j \neq i} k_{ij}dt = 1 - K_i dt$$

where $K_i = \sum_j^{i \neq j} k_{ij}$, total escape rate.

Time evolution of $\phi_j(t)$

$$\begin{aligned}\phi_j(t+dt) &= \phi_j(t)\cdot P(\text{staying in } j \text{ for } dt) \\ &\quad + \sum_{i\neq j}\phi_i(t)P(\text{enter } j \text{ from } i \text{ in } dt) \\ &= \phi_j(t)\cdot(1-K_j dt) + \sum_{i}^{i\neq j}\phi_i(t)k_{ij}dt\end{aligned}$$

Divide by dt and rearrange:

$$\frac{\phi_j(t+dt)-\phi_j(t)}{dt} = -K_j\phi_j(t) + \sum_{i}^{i\neq j}\phi_i(t)k_{ij}$$

And in the limit:

$$\frac{d\phi_j(t)}{dt} = \sum_{i=1}^{n} k_{ij}\phi_i(t), \quad k_{ii} = -K_j$$

Time evolution of $\phi_j(t)$

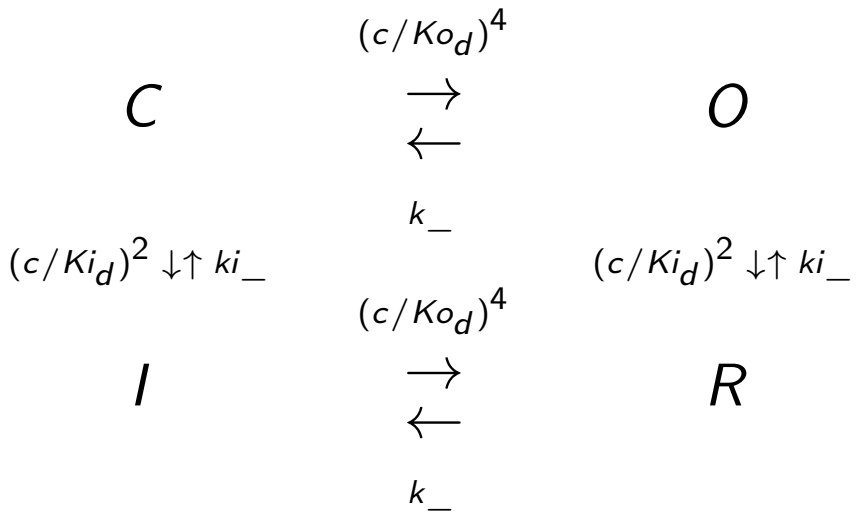
$$\frac{d\phi_j(t)}{dt} = \sum_{i=1}^{n} k_{ij}\phi_i(t), \quad k_{ii} = -K_j$$

can be expressed as a matrix-vector expression:

$$\frac{d\phi(t)}{dt} = K\phi(t)$$

Here K is called a *transition matrix* and multiplied with the probability vector ϕ provides the right hand side function of a system of ODEs.

Example with a four state Markov model



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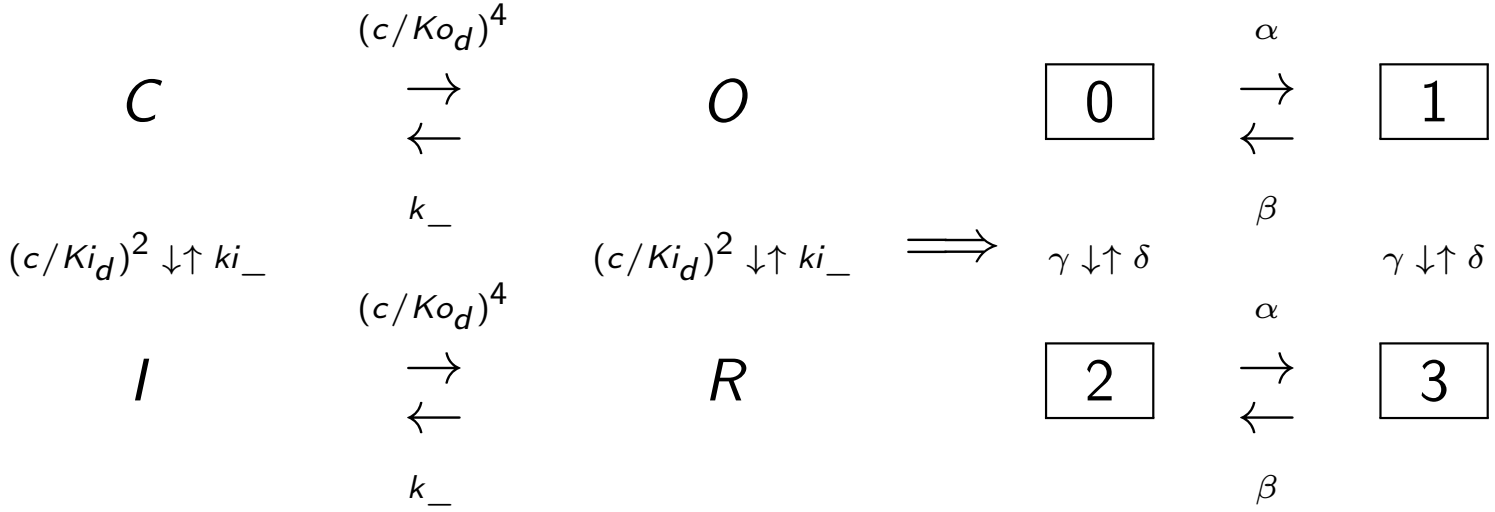


$$\begin{bmatrix} \frac{\phi_0}{dt} \\ \frac{\phi_1}{dt} \\ \frac{\phi_2}{dt} \\ \frac{\phi_3}{dt} \end{bmatrix} = \begin{bmatrix} -(\alpha+\gamma) & \beta & \delta & 0 \\ \alpha & -(\beta+\gamma) & 0 & \delta \\ \gamma & 0 & -(\alpha+\delta) & \beta \\ 0 & \gamma & \alpha & -(\beta+\delta) \end{bmatrix} \begin{bmatrix} \phi_0 \\ \phi_1 \\ \phi_2 \\ \phi_3 \end{bmatrix}$$

How long time a state either stays open or stay close tells us something about the rates

How long time (T_i) does the system spend in a state S_i before leaving? We define $P_i(t) := P(T_i < t)$.
Note $P(\text{leaving } S_i \text{ during } dt) \simeq K_i dt$

$$\begin{aligned} P_i(t+dt) &= P(\text{transition has already occurred at } t) \\ &\quad + P(\text{not occurred yet}) \cdot P(\text{it takes place in this interval}) \\ &= P_i(t) + (1 - P_i(t)) \cdot K_i dt \end{aligned}$$

Divides, and goes to the limit:

$$\frac{dP_i(t)}{dt} = K_i(1 - P_i(t))$$

Which has the solution:

$$P_i(t) = 1 - e^{-K_i t}$$

Waiting time

$P_i(t)$ is the cumulative distribution. The probability density function is found by differentiation:

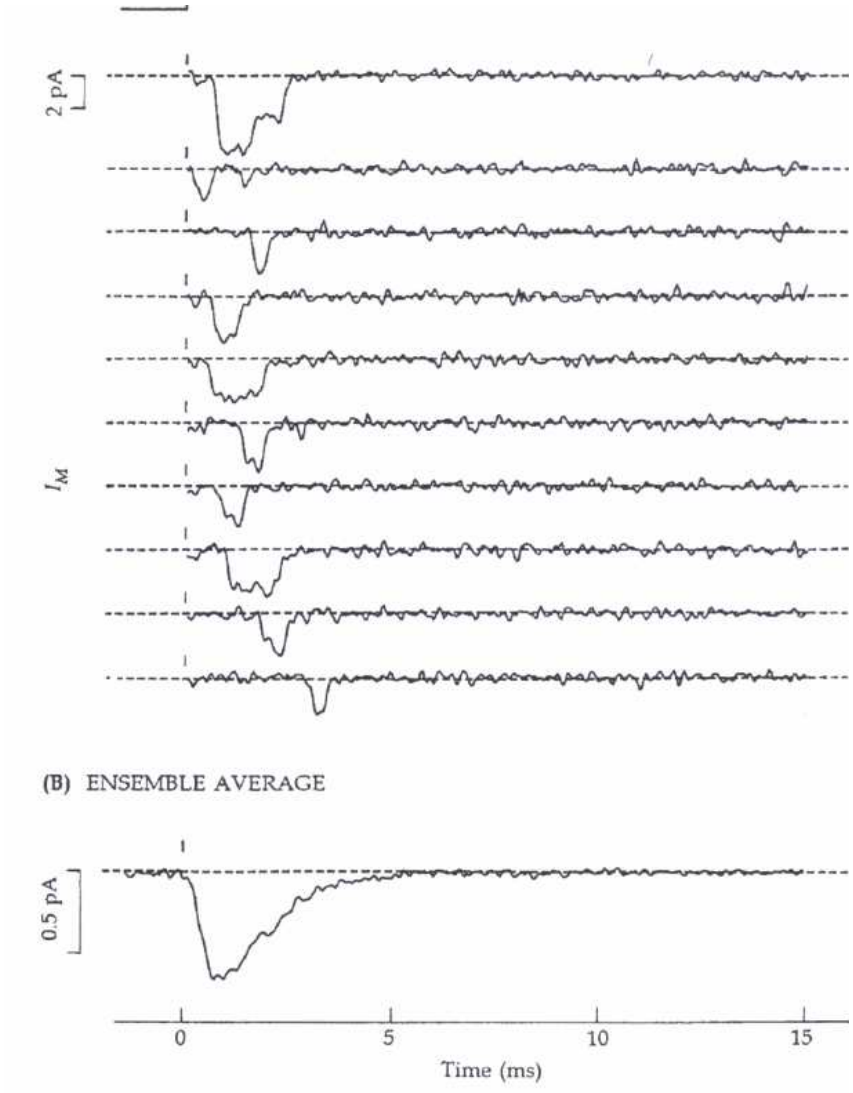
$$p_i(t) = \frac{dP_i(t)}{dt} = K_i e^{-K_i t}$$

The mean waiting time is the expected value of T_i:

$$E(T_i) = \int_0^\infty t p_i(t) dt = \frac{1}{K_i}$$

(If K_i does not depend on t)

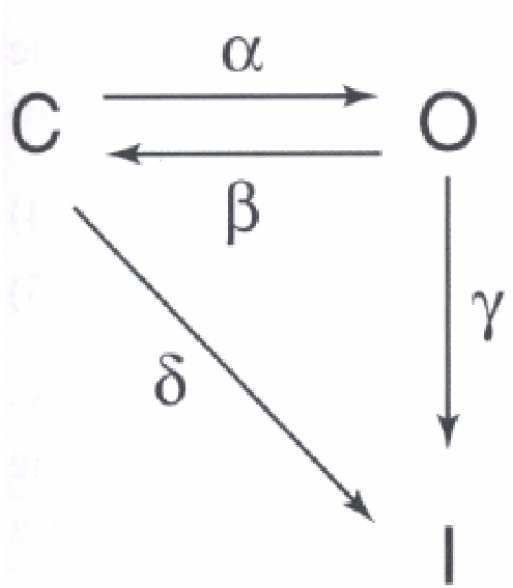
Single channel recordings can be used to fit rates in Markov models



Single channel analysis

Single channel recordings contain statistical information that can be used to estimate transition rate:

- Ratio of experiments where channel directly inactivates
- Distribution of the number of times the channel re-opens before finally inactivating
- Mean open time
- Mean close time



1: If first (and final) transition is $C \rightarrow I$

The channel is initially in the closed state.
As the transmembrane potential is elevated two things can happen:

$$P(C \rightarrow O) = A = \alpha/(\alpha + \delta)$$

$$P(C \rightarrow I) = \delta/(\alpha + \delta) = (\delta - \alpha + \alpha)/(\alpha + \delta) = 1 - A$$

Estimation of $1 - A$: The ratio of experiments where the channel fail to open.

2 & 3: Time spent in C and O

In the experiments where channels do open, record the time spent in C.
The distribution is described by: $P(t) = 1 - \exp(-\alpha)$
The average waiting time will be $E(T) = 1/\alpha$.

Record the duration the channel is open. The distribution is described by: $P(t) = 1 - \exp(-\beta - \gamma)$
The average waiting time will be $E(T) = 1/(\beta + \gamma)$.

4: Number of re-openings

Probability that the channels opens k times before inactivating:

$$\begin{aligned} P[N = k] &= P[N = k \text{ and finally } O \to I] + P[N = k \text{ and finally } C \to I] \\ &= A^k B^{k-1}(1 - B) + A^k B^k (1 - A) \\ &= (AB)^k \left(\frac{1 - AB}{B} \right) \end{aligned}$$

Where $A = \alpha/(\alpha + \delta)$ and $B = \beta/(\beta + \gamma)$
B can be estimated by fitting to the observed data.