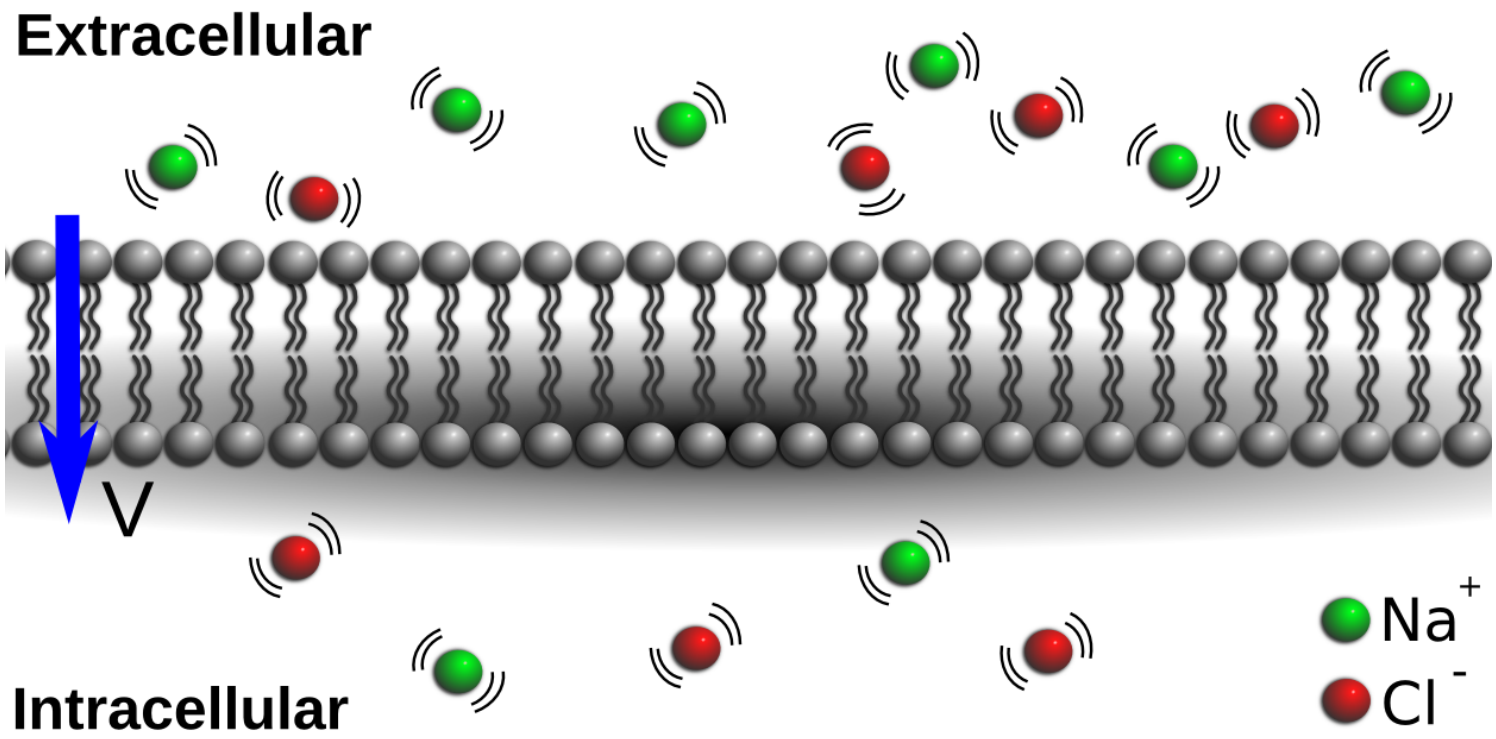
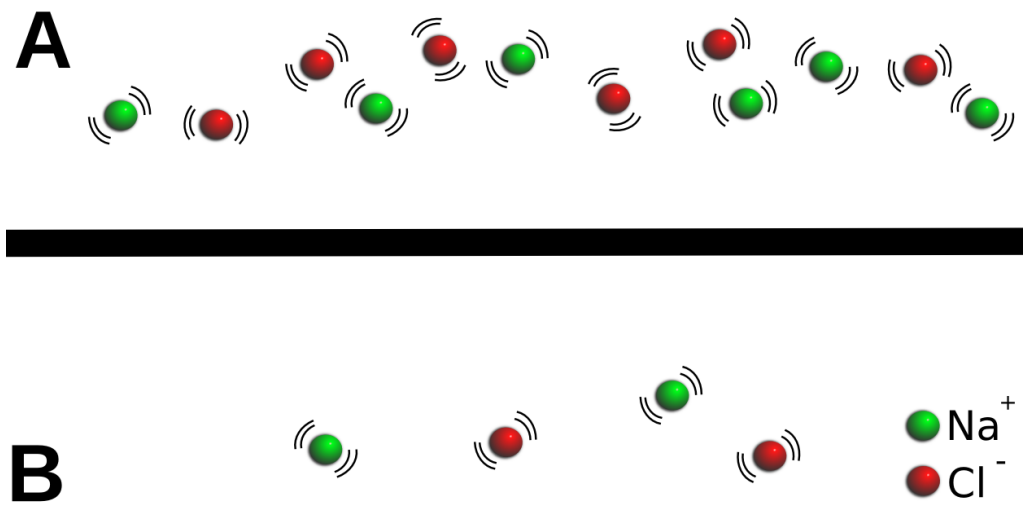
The membrane potential



Flow through a semi-permeable membrane

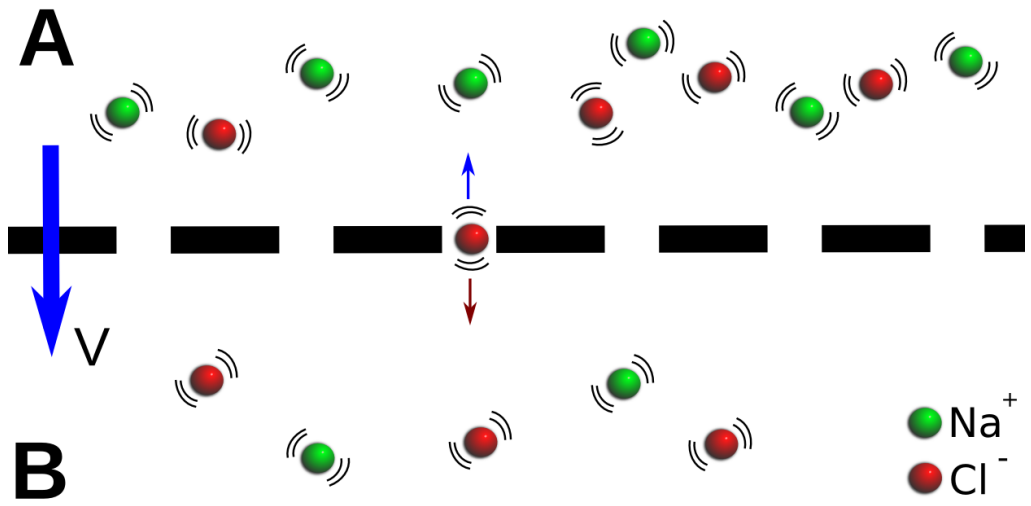


Consider two solutions:

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

Both are neutral.

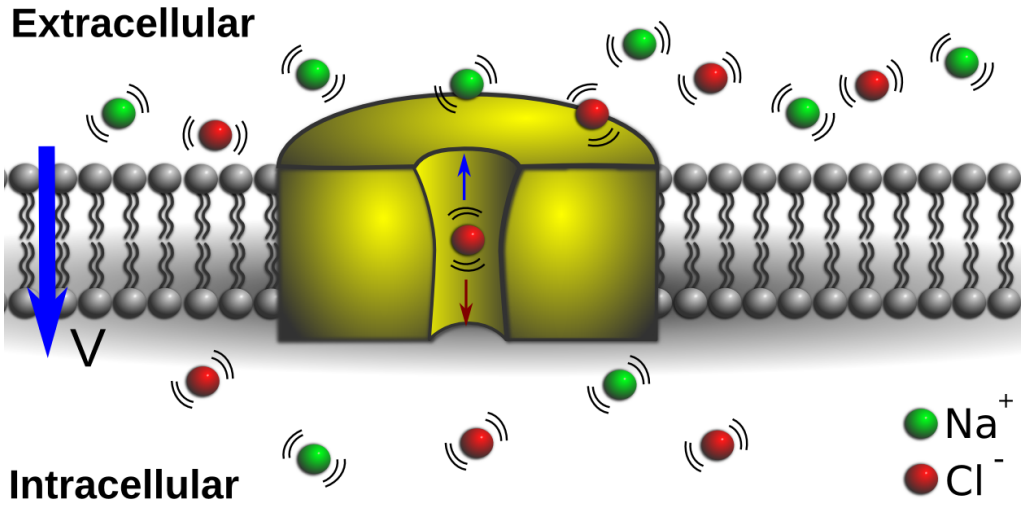
Flow through a semi-permeable membrane



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

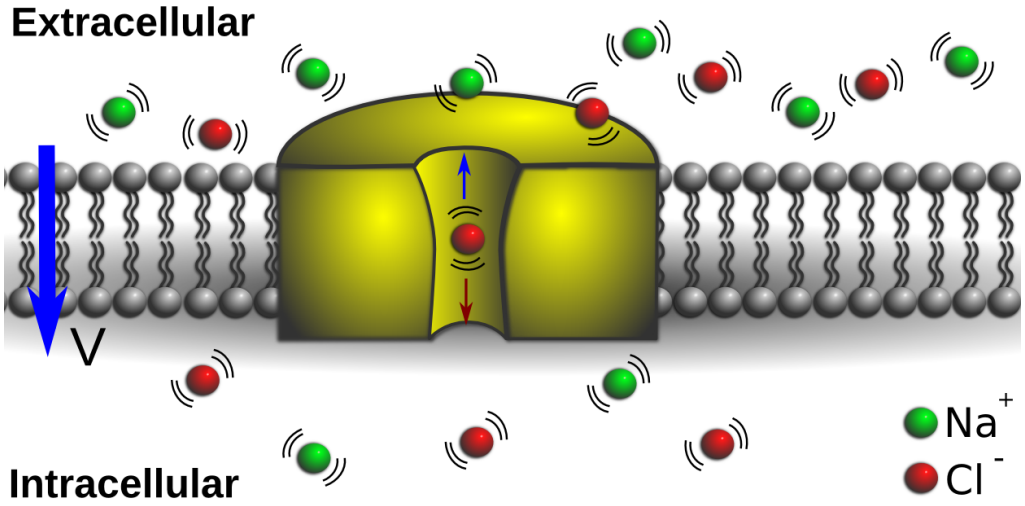
- Cl^- will diffuse from A to B due the concentration gradient
- $[Cl^-]_A$ will drop and $[Cl^-]_B$ will increase
- $[Na^+]_A$ and $[Na^+]_B$ will remain fixed (no flow)
- A and B will no longer be neutral
- An electrical force will attract Cl^- towards A

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.

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

$$V_e = \frac{RT}{zF} \ln(\frac{c_e}{c_i}) \tag{1}$$

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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- $p(V,t)$ the proportion of open channels

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.

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

Goldman-Hodgkin-Katz current equation

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

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 $c(0) = c_i$:

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

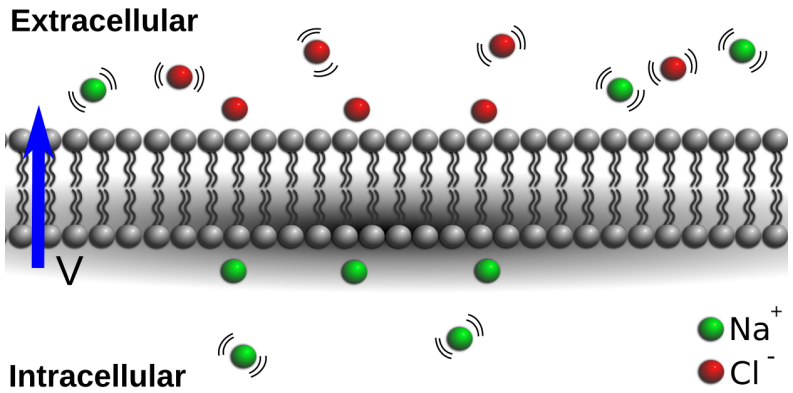
We determine J by using $c(L) = c_e$:

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

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.

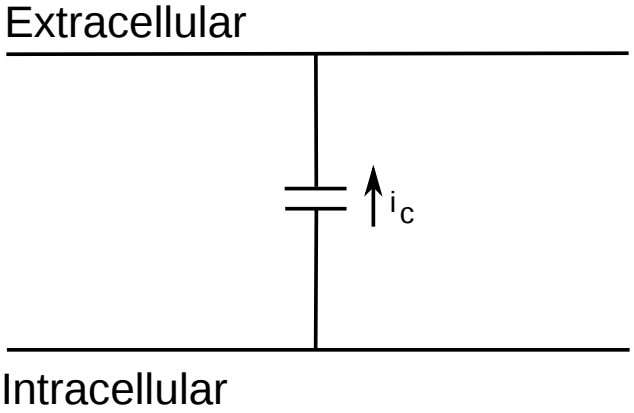
The cell membrane modeled as a leaky capacitor

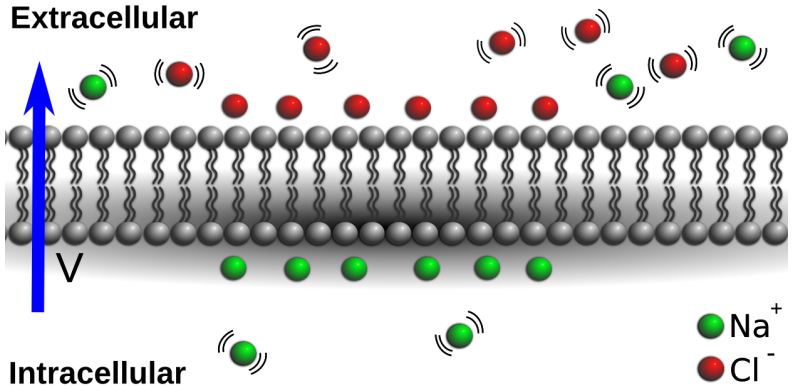
As any real capacitor the membrane conducts some current. The flux of ions (I_{ion}) will cause a change in Q and thus V.

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:

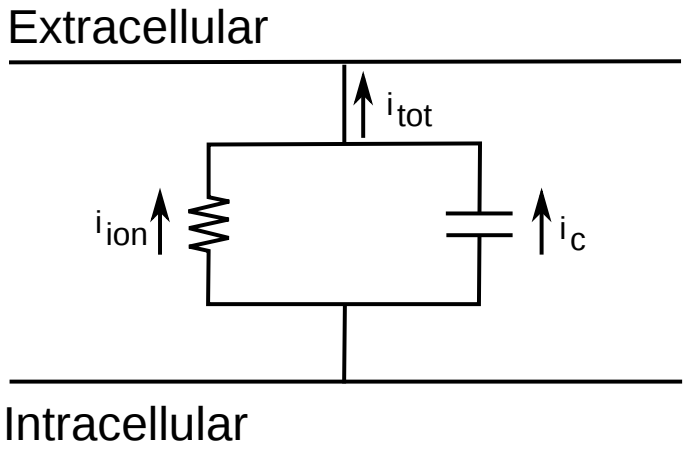
$$\frac{dV}{dt} = \frac{1}{C_m}\frac{dQ}{dt}$$

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

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

Channel gating, 3.5

- Channels with a single and several identical gates
- Channels with different but independent gates

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.

Voltage gated Ion channels

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

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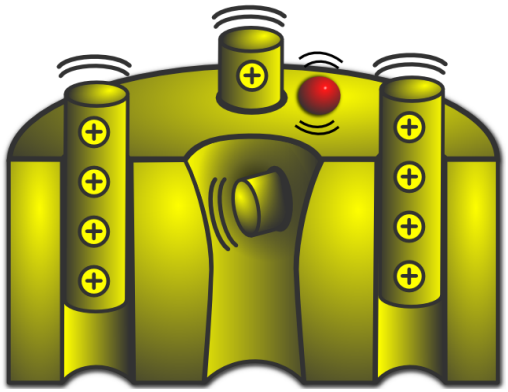
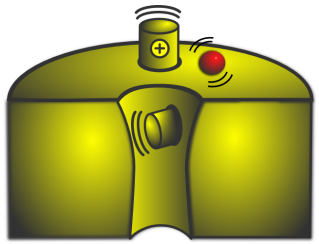


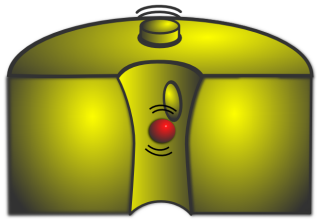
Next we will go through different expressions for how this propensity function can be derived for Voltage gated ion channels.

Voltage gated channel with one gate,3.5.1

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



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

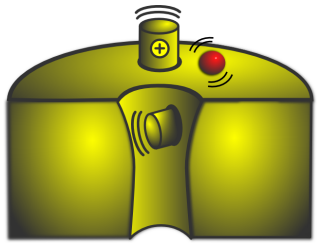


Applying law of mass action:

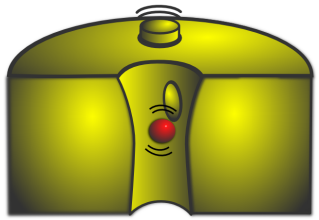
$$\frac{d[0]}{dt} = \alpha(V)[C] - \beta(V)[O]$$

Voltage gated channel with one gate,3.5.1

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:

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

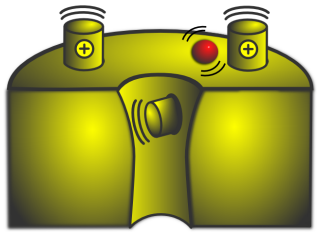
Dividing by the total amount of channels ([C]+[O]) yields

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

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

Voltage gated channel with two identical and independent gates, 3.5.2

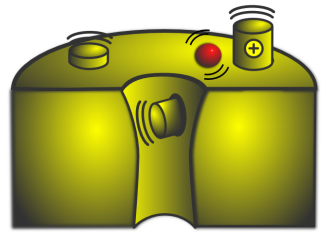
For some channels it is more appropriate to include several gates, which all need to be open for the channel to conduct. Example with two gates:



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

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

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



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

Voltage gated channel with two identical and independent gates

Combine the states S_{01} and S_{10} into $S_1 = S_{01} + S_{10}$:

$$\begin{aligned} & \frac{S_{01}}{dt} &=& \alpha S_{00} + \beta S_{11} - (\alpha + \beta) S_{01} \\ + \quad & \frac{S_{10}}{dt} &=& \alpha S_{00} + \beta S_{11} - (\alpha + \beta) S_{10} \\ \hline = \quad & \frac{S_1}{dt} &=& 2\alpha S_{00} + 2\beta S_{11} - (\alpha + \beta) S_1 \end{aligned}$$

Define $S_0 = S_{00}$ and $S_2 = S_{11}$, we can then write:

$$\mathrm{S}_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} \mathrm{S}_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} \mathrm{S}_2$$

Voltage gated channel with two identical and independent gates

Only two independent variables since $S_0 + S_1 + S_2 = S_T$, constant. Define $x_i = S_i/S_T$. Claim:

$$x_2 = n^2, \text{ with } \frac{dn}{dt} = \alpha(1-n) - \beta n$$

and

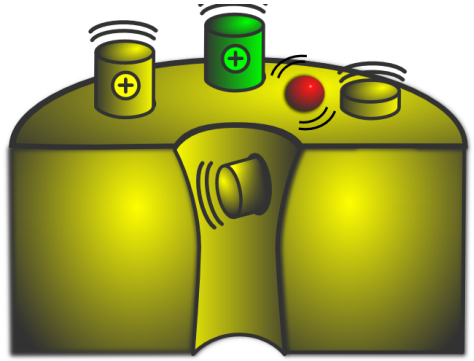
$$p(V,t) = n^2$$

Voltage gated channel with three gates, where two are identical and all are independent, 3.5.3

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.

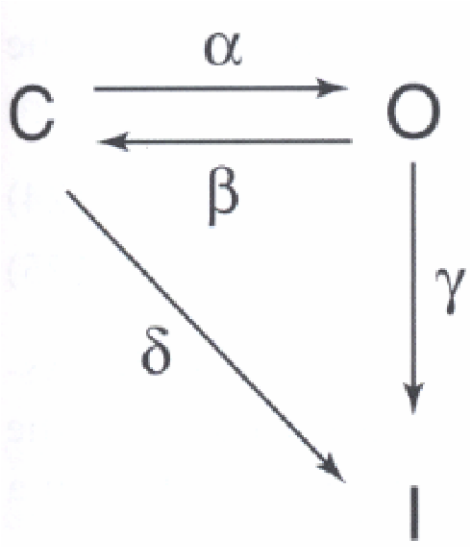
$$\begin{array}{ccccc} S_{00} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{10} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{20} \\ \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta \\ S_{01} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}}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



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

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

Voltage gated channel with one gate, which can inactivate in addition to open and close, 3.5.3



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

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

$$i = 1 - c - o$$

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

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:

$$J = \frac{1}{2} kKC_0 \frac{[S_e] - [S_i]}{([S_i] + K + K_d)([S_e] + K + K_d) - K_d^2}$$

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 travel in opposite direction (exchangers).
Model:

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

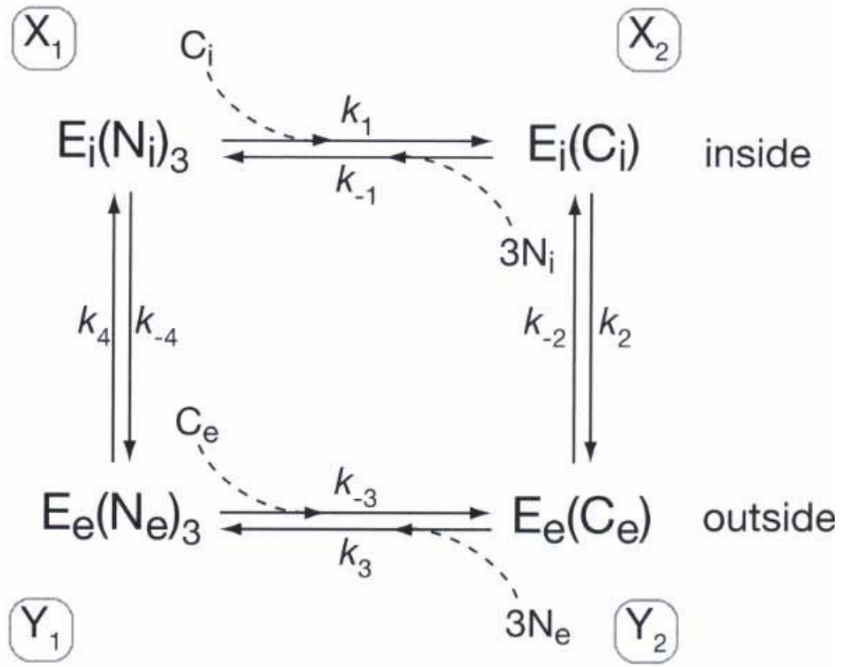
Mathematically almost the same flux, but with subscript of T toggled:

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

Sodium-Calcium exchange, 2.4.3

- 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:

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