

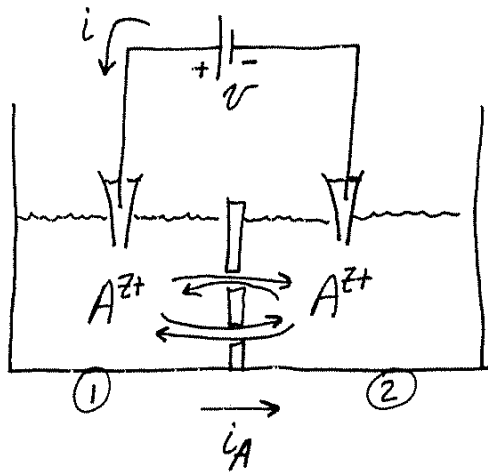
MATHEMATICAL ASPECTS OF NEUROPHYSIOLOGY

by Charles S. Peskin
2000

- I. Membrane Channels
- II. Hodgkin-Huxley Equations
- III. Synaptic Transmission

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Flow of ionic current through membrane channels



$$i = i_A(v, [A^{z+}]_1, [A^{z+}]_2)$$

The goal is to determine the form of this function.

Notation:

i = current in external circuit

i_A = current carried across membrane by ion A^{z+}

z = number of elementary charges carried by ion A^{z+}
(z may be negative or positive)*

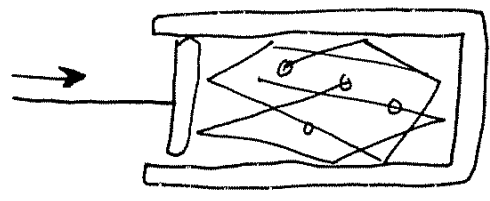
$[]$ = concentration

v = voltage difference across membrane.

* Thus the ion carries a charge ez , where e is the charge on a proton.

Work of concentration

Ions in solution behave much like molecules of an ideal gas. Consider the work required to compress such a gas at constant temperature:



$$PV = nkT$$

P = pressure

V = volume

n = # of molecules

k = Boltzmann's constant

T = absolute temperature.

} constant

$$dW = -PdV = -\frac{nkT}{V}dV = +\frac{nkT}{P}dP$$

let $c = \frac{n}{V}$, $P = kTc$ (c = concentration)

$$dW = nkT \frac{dc}{c}$$

$$W_{1 \rightarrow 2} = nkT \log \frac{c_2}{c_1}$$

Remark: The formula

$$W_{1 \rightarrow 2} = n k T \log \frac{C_2}{C_1}$$

was developed for the situation in which a gas is actually compressed. We assume that it holds also for ions in solution and for the situation in which n particles are removed from a place where the prevailing concentration is C_1 and put in a place where the prevailing concentration is C_2 . (If the particles are charged, there may also be electrical work required. The work of concentration does not include this electrical work and is therefore independent of the charge.)

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Energetic argument to determine the form of i_A :

By conservation of energy: $\dot{W}_b = \dot{W}_c + \dot{H}$, where

$\dot{W}_b = v i = v i_A$ = rate at which the battery does work

$$\dot{W}_c = n i kT \log \frac{[A^{z+}]_2}{[A^{z+}]_1} = \frac{i_A}{z f} kT \log \frac{[A^{z+}]_2}{[A^{z+}]_1}$$

= rate at which work is required to change the concentration of the ions that cross the membrane from $[A^{z+}]_1 \rightarrow [A^{z+}]_2$.

$\dot{H} = ?$ = rate at which heat is generated in the membrane by the ionic current i_A .

There is no universal formula for \dot{H} ; it depends on the details of charge transport through the channel. As a simple example, though, suppose $\dot{H} = r i_A^2$, just as in an ordinary resistor. Then

$$v i_A = i_A \frac{kT}{z f} \log \frac{[A^{z+}]_2}{[A^{z+}]_1} + r i_A^2$$

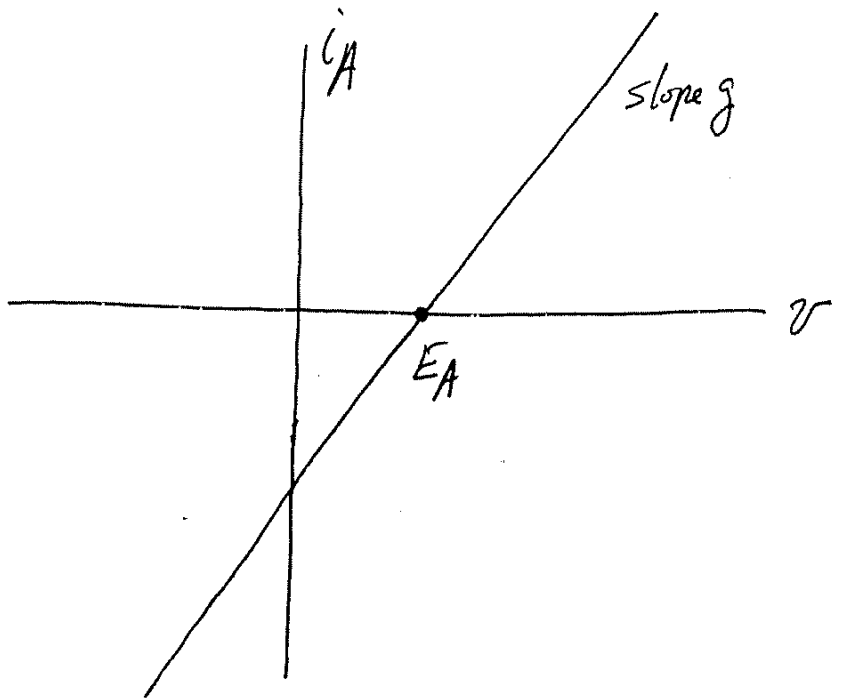
Solve for i_A :

$$i_A = g (v - E_A)$$

Where

$$g = 1/r = \text{conductance}$$

$$E_A = \frac{kT}{zF} \log \frac{[A^{z+}]_2}{[A^{z+}]_1} = \text{equilibrium potential for } A^{z+}$$



Equilibrium potential

In the foregoing, $E_A = \frac{kT}{z_F} \log \frac{[A^{z+}]_2}{[A^{z+}]_1}$ is the

value of v at which $i_A = 0$. Hence it is called the equilibrium potential for the ion A^{z+} . This formula for E_A is universal, as we now show.

Although $\dot{H} \neq r i_A^2$ in general, it is a universal fact that $\dot{H} = 0$ when $i_A = 0$. Moreover, $\dot{H} \geq 0$ for all i_A .

It follows that the Taylor series expansion for \dot{H} about $i_A = 0$ must be of the form

$$\dot{H} = r i_A^2 + \dots$$

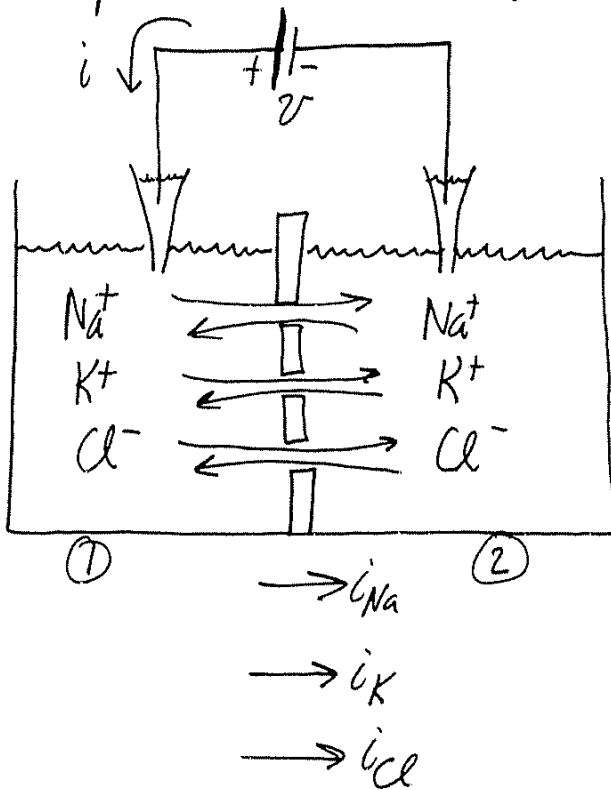
Hence

$$v i_A = i_A \frac{kT}{z_F} \log \frac{[A^{z+}]_2}{[A^{z+}]_1} + r i_A^2 + \dots$$

Divide by i_A and then let $i_A \rightarrow 0$. The result is

$$v = \frac{kT}{z_F} \log \frac{[A^{z+}]_2}{[A^{z+}]_1} = E_A$$

Several ions present simultaneously



(Each ion has channels specific for that ion type only.)

In this situation

$$i = i_{\text{Na}} + i_{\text{K}} + i_{\text{Cl}}$$

Where

$$i_{\text{Na}} = g_{\text{Na}} (v - E_{\text{Na}}), \quad E_{\text{Na}} = \frac{kT}{q} \log \frac{[\text{Na}^+]_2}{[\text{Na}^+]_1}$$

$$i_{\text{K}} = g_{\text{K}} (v - E_{\text{K}}), \quad E_{\text{K}} = \frac{kT}{q} \log \frac{[\text{K}^+]_2}{[\text{K}^+]_1}$$

$$i_{\text{Cl}} = g_{\text{Cl}} (v - E_{\text{Cl}}), \quad E_{\text{Cl}} = \frac{kT}{-q} \log \frac{[\text{Cl}^-]_2}{[\text{Cl}^-]_1}$$

note negative sign.

Membrane potential without the battery

Suppose we replace the battery in the foregoing circuit by a voltmeter. Such a meter has a high input resistance which effectively prevents the flow of current. Thus

$$\begin{aligned}
0 = \dot{v} &= i_{Na} + i_K + i_{Cl} \\
&= g_{Na}(v - E_{Na}) + g_K(v - E_K) + g_{Cl}(v - E_{Cl})
\end{aligned}$$

Solving for v , we get

$$v = \frac{g_{Na} E_{Na} + g_K E_K + g_{Cl} E_{Cl}}{g_{Na} + g_K + g_{Cl}}$$

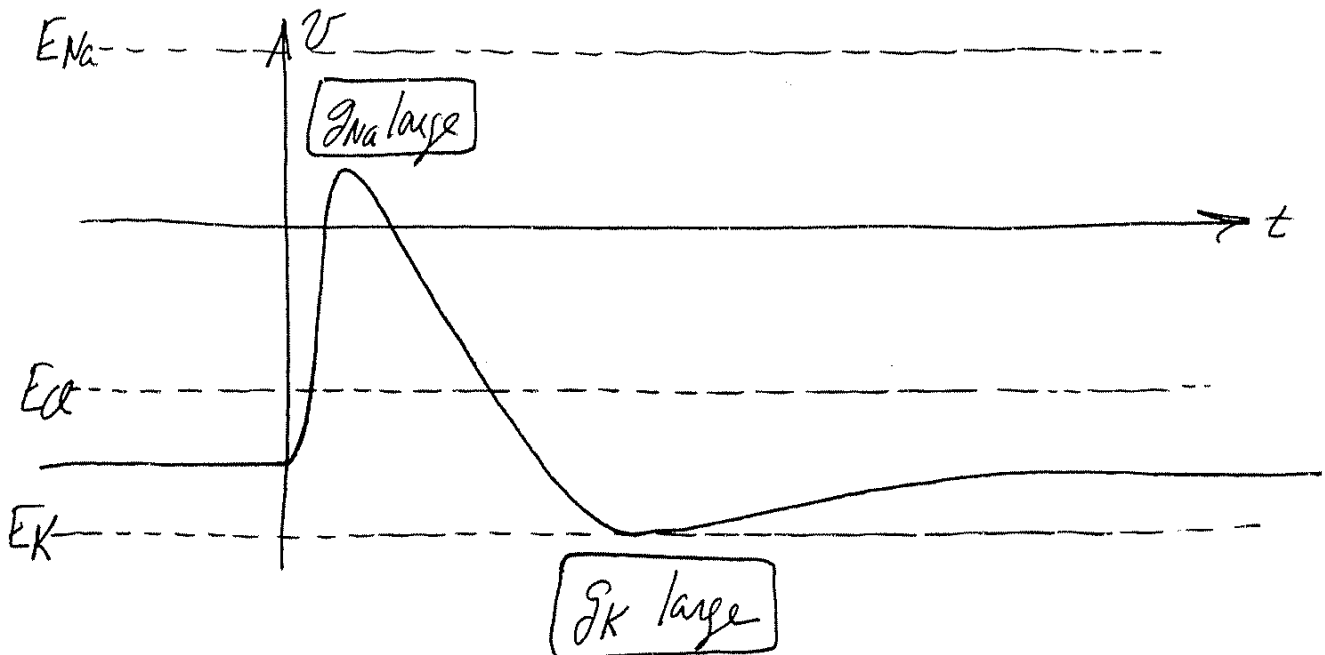
This formula gives the membrane potential when the total ionic current is zero. It is a weighted average of the equilibrium potentials of the different ions, the weights being the conductances. This is an important formula because it shows that a cell can adjust its membrane potential v by changing the conductances of its membrane to the different ions, i.e., by opening and closing channels.

In a nerve action potential this is done as follows. The equilibrium potentials satisfy

$$E_K < E_{Cl} < 0 < E_{Na}$$

At rest, g_{Na} is very small, so V lies between E_K and E_{Cl}

The first event in the action potential is the opening of Na^+ channels. This drives V towards E_{Na} . Then the Na^+ channels close and K^+ channels open. This drives V towards E_K . Finally everything comes back to rest.



Important remark

In the foregoing discussion, we have treated E_K , E_{Cl} , and E_{Na} as constants. This is an excellent approximation. The currents that flow during a nerve action potential are too small to change the bulk ion concentrations on either side of the membrane to any significant extent. The dramatic changes in membrane potential that occur during the nerve impulse are caused not by significant changes in bulk ionic concentrations but instead by small shifts of charge which occur in response to the opening and closing of ionic channels, i.e., in response to changes in the conductances G_{Na} and G_K . These small charge shifts have large consequences because the bulk solutions are electrically neutral (on each side of the membrane, the total concentration of positive charge = the total concentration of negative charge, to an excellent approximation).

Drift-diffusion equation

This equation is needed to take a more detailed look at current flow in ionic channels. It asserts that the current at any point x in the channel is given by

$$i = a q z \left(-D \frac{\partial c}{\partial x} + \mu q z E c \right)$$

where

- a = cross-sectional area of the channel
- q = elementary charge (the charge on a proton)
- qz = charge carried by the ion in question
- D = diffusion coefficient
- c = concentration of the ion in question at x
- x = distance coordinate along the channel
($0 \leq x \leq l$, where l is the length of the channel)
- μ = mobility coefficient
- E = electric field at x (in the x direction)

The drift-diffusion equation may be derived as follows. Let f denote the flux of ions, defined as the number per unit area per unit time crossing a given surface. Then

$$i = qz f = qz (f_{\text{diffusion}} + f_{\text{drift}})$$

where $f_{\text{diffusion}}$ is the flux that would occur for purely statistical reasons even in the absence of an electric field and where f_{drift} is the flux that occurs in response to the electric field.

For $f_{\text{diffusion}}$, we use Fick's law

$$f_{\text{diffusion}} = -D \frac{\partial c}{\partial x}$$

For f_{drift} we recall that the force on the ion in an electric field E will be qzE , that the response to this force in a medium where the ion must undergo multiple collisions is a drift velocity μqzE , where μ is the mobility, and that the flux is therefore

$$f_{\text{drift}} = \mu qz E c$$

The Einstein relation: $D = kT\mu$

Though drift and diffusion appear in the foregoing as independent quantities, they are physically related, since both involve the random walk of the ion through the solvent. Thus, one might suspect that there is a relationship between D and μ . Einstein derived such a relationship from thermodynamic considerations without any explicit reference to the underlying stochastic process.

Consider an equilibrium situation in which $i=0$. Let $E = -\partial\phi/\partial x$, where ϕ is the electrostatic potential. Then the drift-diffusion equation reduces to

$$0 = -D \frac{\partial c}{\partial x} - \mu z e \frac{\partial \phi}{\partial x} c$$

Divide by c and integrate across the membrane. The result is

$$D \log c_1 + \mu z e \phi_1 = D \log c_2 + \mu z e \phi_2$$

$$\mu z e v = D \log \frac{c_2}{c_1}$$

where $v = \phi_1 - \phi_2$ is the membrane potential. Thus,

The current is zero when

$$v = \frac{(D/\mu)}{gz} \log \frac{c_2}{c_1}$$

This agrees with our previous (thermodynamically-derived) result, only if

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

Since D and μ are constants, this relationship between them must hold even in non-equilibrium situations, though we have used an equilibrium situation to derive it. That Einstein was a clever guy!

Making use of the Einstein relation, we rewrite the drift-diffusion equation as follows:

$$i = qgz\mu \left(-kT \frac{\partial c}{\partial x} - gz \frac{\partial \phi}{\partial x} c \right)$$

(In addition to $D = kT\mu$, we have also made the substitution $E = -\frac{\partial \phi}{\partial x}$.)

Constant-field model for ionic current

Consider a channel which admits only one ion type.
Then

$$i = - agz\mu \left(kT \frac{\partial c}{\partial x} + gz \frac{\partial \phi}{\partial x} c \right)$$

In the steady state, charge cannot build up anywhere, so

$$\frac{\partial i}{\partial x} = 0$$

The local charge density is $\rho = gz c$, and the Maxwell equation $\nabla \cdot E = \rho/\epsilon$ becomes

$$-\frac{\partial^2 \phi}{\partial x^2} = \frac{gz c}{\epsilon}$$

(since $E = -\frac{\partial \phi}{\partial x}$), where ϵ is the dielectric constant.

These equations are to be solved subject to the boundary conditions

$c(0) = c_1$	$c(l) = c_2$
$\phi(0) = v$	$\phi(l) = 0$

Instead of solving this problem in general, we consider the low-concentration limit. Formally, this can be obtained by setting

$$c_1 = \alpha c_1' \quad c_2 = \alpha c_2' \quad c(x) = \alpha c'(x)$$

$$i = \alpha i'$$

and then letting $\alpha \rightarrow 0$. Note that ϕ is not scaled by α , since its scale is fixed by v . The resulting equations are

$$i' = -\alpha g z \mu \left(kT \frac{\partial c'}{\partial x} + g z \frac{\partial \phi}{\partial x} c' \right)$$

$$\frac{\partial i'}{\partial x} = 0$$

$$-\frac{\partial^2 \phi}{\partial x^2} = 0$$

with

$$c'(0) = c_1'$$

$$c'(l) = c_2'$$

$$\phi(0) = v$$

$$\phi(l) = 0$$

Of course, we can solve for ϕ immediately:

$$\phi(x) = v \left(\frac{l-x}{l} \right)$$

Note that $E = -\frac{\partial\phi}{\partial x} = \frac{v}{l}$, which is constant, independent of x .

That is why this limiting case is called the constant-field approximation. We are now left with

$$i' = -a g z \mu \left(kT \frac{\partial c'}{\partial x} - g z \frac{v}{l} c' \right)$$

$$\frac{\partial i'}{\partial x} = 0$$

$$c'(0) = c_1' \quad c'(l) = c_2'$$

Since i' is constant c' must be of the form

$$c'(x) = A + B \exp \frac{g z v x}{kT l}$$

where A and i' are related by

$$i' = \frac{+ a (g z)^2 \mu v}{l} \mathbf{A}$$

If i' were given, this would determine A . In our situation,

we find A and B from the boundary conditions and use this to find i' . Thus

$$C_1' = A + B$$

$$C_2' = A + B \exp\left(\frac{qzV}{kT}\right)$$

Solving for A, we get

$$A = \frac{C_1' \exp\left(\frac{qzV}{kT}\right) - C_2'}{\exp\left(\frac{qzV}{kT}\right) - 1}$$

Hence

$$i' = \frac{a(qz)^2 \mu V}{l} \frac{C_1' \exp\left(\frac{qzV}{kT}\right) - C_2'}{\exp\left(\frac{qzV}{kT}\right) - 1}$$

In the original variables:

$$i = \frac{a(qz)^2 \mu V}{l} \frac{C_1 \exp\left(\frac{qzV}{kT}\right) - C_2}{\exp\left(\frac{qzV}{kT}\right) - 1}$$

Note that $i=0$ when $C_1 \exp\left(\frac{qzV}{kT}\right) - C_2 = 0$

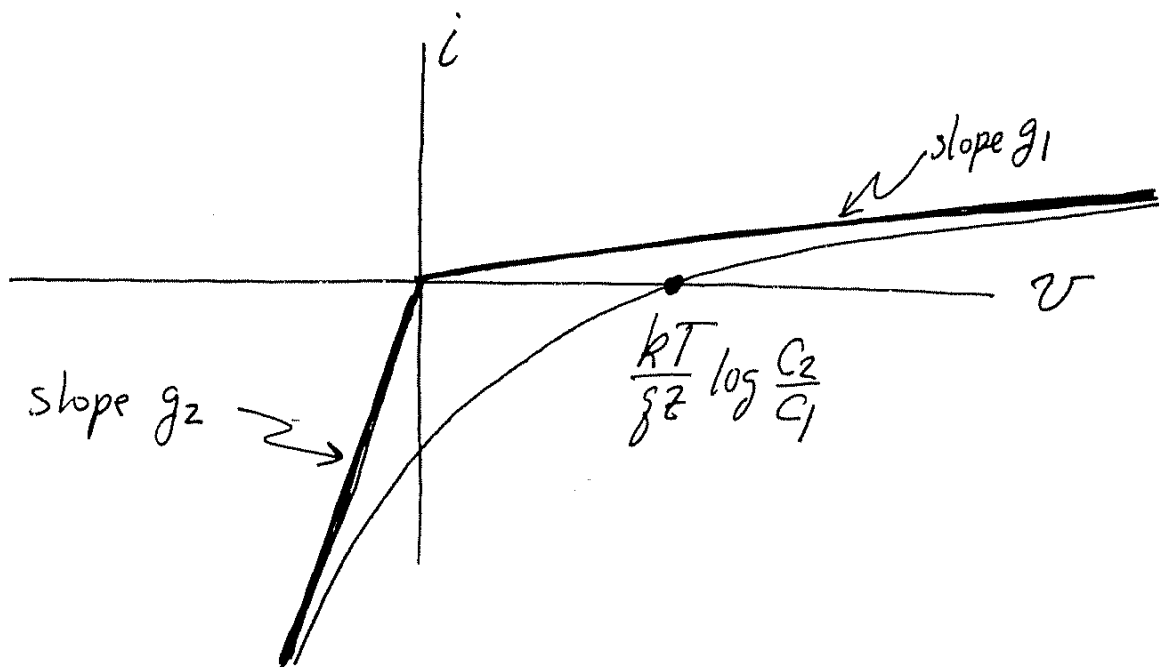
$$\text{or } V = \frac{kT}{qz} \log \frac{C_2}{C_1}$$

(a good thing, too, since we claimed that was universal!)

$$\text{When } \frac{qzV}{kT} \gg 1 \quad i \sim \frac{a(qz)^2 \mu V C_1}{l} = g_1 V$$

$$\text{When } \frac{qzV}{kT} \ll -1 \quad i \sim \frac{a(qz)^2 \mu V C_2}{l} = g_2 V$$

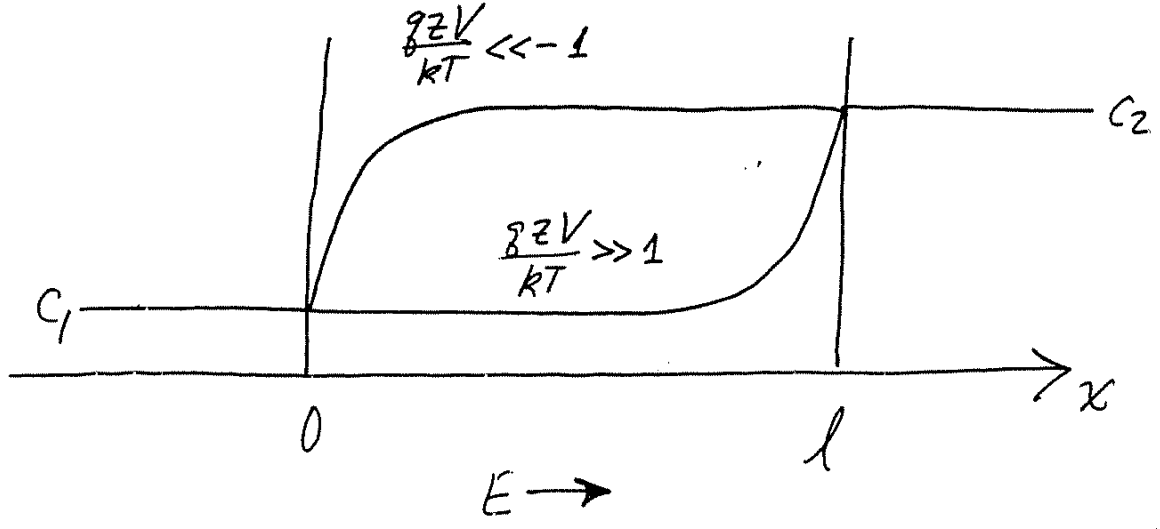
Here is the i - V relation for $z > 0$ and $C_2 > C_1$
(or for $z < 0$ and $C_1 < C_2$)



Such a channel acts as a rectifier. It has a larger conductance for current flow in the direction favored by the concentration difference. This is not merely because the diffusion flux adds to the drift, since the effect persists even at high voltages. The real reason is that the current sweeps the ions into the channel where they can be acted upon by the electric field. When $\frac{qzV}{kT} \gg 1$

the concentration over most of the length of the channel is c_1 , but when $\frac{qzV}{kT} \ll -1$, the concentration over most of the

length of the channel is c_2 . To see this, complete the solution by solving for B and plot $c(x)$ in the two cases. The result should be like this:



$$\text{Let } \theta = \frac{gzv}{kT}$$

Then the constant-field current can be written in the form

$$i = gz P \theta \frac{c_1 \exp(\theta) - c_2}{\exp(\theta) - 1}$$

where $P = \frac{akT\mu}{l} = \frac{aD}{l}$

The coefficient P is called the "permeability". To see its significance, consider the case $v=0$, which is the same as $\theta=0$. Since

$$\lim_{\theta \rightarrow 0} \frac{\theta}{\exp(\theta) - 1} = 1$$

we have

$$\lim_{v \rightarrow 0} i = gz P (c_1 - c_2) = gz \frac{aD(c_1 - c_2)}{l}$$

This is the expected formula for a pure diffusion flux of ions through the channel.

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Mixture of Na^+ , K^+ , and Cl^- channels of the constant-field type

For Na^+ and K^+ , $z=+1$, while for Cl^- $z=-1$.
In this section, we use the notation

$$\theta = \frac{zV}{kT}$$

Hence $\frac{zV}{kT} = \begin{cases} +\theta & \text{for } \text{Na}^+ \text{ and } \text{K}^+ \\ -\theta & \text{for } \text{Cl}^- \end{cases}$

Therefore

$$i_{\text{Na}} = f P_{\text{Na}} \theta \frac{[\text{Na}^+]_1 \exp(\theta) - [\text{Na}^+]_2}{\exp(\theta) - 1}$$

$$i_{\text{K}} = f P_{\text{K}} \theta \frac{[\text{K}^+]_1 \exp(\theta) - [\text{K}^+]_2}{\exp(\theta) - 1}$$

$$i_{\text{Cl}} = (-f) P_{\text{Cl}} (-\theta) \frac{[\text{Cl}^-]_1 \exp(-\theta) - [\text{Cl}^-]_2}{\exp(-\theta) - 1}$$

$$= f P_{\text{Cl}} \theta \frac{[\text{Cl}^-]_1 - [\text{Cl}^-]_2 \exp(\theta)}{1 - \exp(\theta)}$$

$$= f P_{\text{Cl}} \theta \frac{[\text{Cl}^-]_2 \exp(\theta) - [\text{Cl}^-]_1}{\exp(\theta) - 1}$$

Thus the formula for i_{ice} is of precisely the same form as the formula for i_{Na} and i_K , except that the subscripts 1 and 2 have been reversed.

In general $i = i_{Na} + i_K + i_{ice}$, but it is of particular interest to solve for v when $i = 0$. The common factors $z\theta / (\exp(\theta) - 1)$ then cancel out, and we are left with

$$0 = ([Na^+]_1 \exp(\theta) - [Na^+]_2) P_{Na} \\ + ([K^+]_1 \exp(\theta) - [K^+]_2) P_K \\ + ([Cl^-]_2 \exp(\theta) - [Cl^-]_1) P_{Cl}$$

Thus

$$\frac{z\theta}{kT} = \theta = \log \frac{P_{Na} [Na^+]_2 + P_K [K^+]_2 + P_{Cl} [Cl^-]_1}{P_{Na} [Na^+]_1 + P_K [K^+]_1 + P_{Cl} [Cl^-]_2}$$

$$v = \frac{kT}{z} \log \frac{P_{Na} [Na^+]_2 + P_K [K^+]_2 + P_{Cl} [Cl^-]_1}{P_{Na} [Na^+]_1 + P_K [K^+]_1 + P_{Cl} [Cl^-]_2}$$

This is called the Goldman-Hodgkin-Katz formula or simply the constant-field formula for the membrane potential.

Note the similarities and differences between this result and the formula derived on page 8 for the membrane potential without the battery with a mix of channels having a linear $i-v$ relation. There we found

$$v = \frac{g_{Na} E_{Na} + g_K E_K + g_{Cl} E_{Cl}}{g_{Na} + g_K + g_{Cl}}$$

where

$$E_{Na} = \frac{kT}{\delta} \log \frac{[Na^+]_2}{[Na^+]_1}$$

$$E_K = \frac{kT}{\delta} \log \frac{[K^+]_2}{[K^+]_1}$$

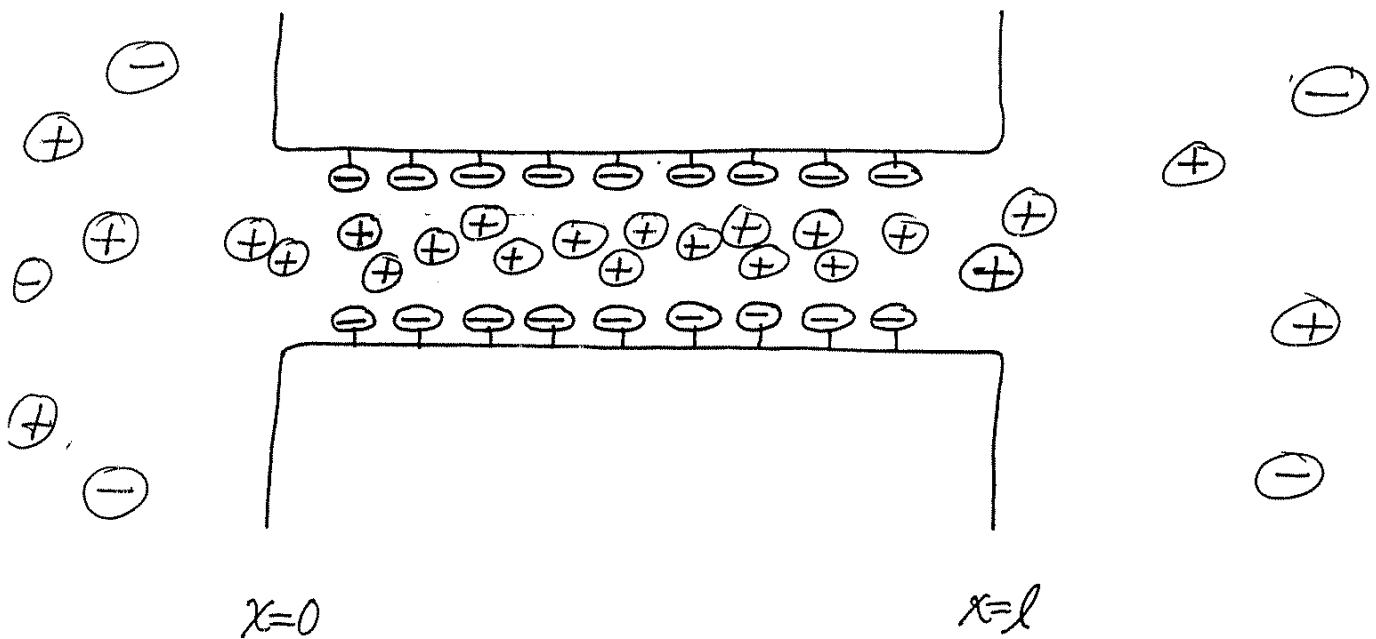
$$E_{Cl} = \frac{kT}{-\delta} \log \frac{[Cl^-]_2}{[Cl^-]_1} = \frac{kT}{\delta} \log \frac{[Cl^-]_1}{[Cl^-]_2}$$

In the case of the linear $i-v$ relation, the equilibrium potentials are computed separately and then averaged. In the constant-field case, the averaging occurs at the level of the concentrations and then an effective equilibrium potential is computed. In both cases, v is driven towards E_{Na} (for example) by opening Na^+ channels or towards E_K by opening K^+ channels.

Channel with a linear $i-v$ relation

Earlier, we derived a linear $i-v$ relation by making the ad-hoc assumption that the rate of heat generation has the form $i^2 r$. This leaves open the question of what physical situation (if any) leads to a linear $i-v$ relation for all choices of C_1 and C_2 . (The constant-field $i-v$ relation becomes linear in the special case $C_1 = C_2$ but is nonlinear in general.)

Consider a channel which admits only one ion type for which $z = +1$, and suppose the channel carries a large number of fixed negative charges distributed along its walls:



We make the (somewhat questionable) assumption that the whole situation can be modeled as one-dimensional.

Then the fixed negative charges have an effective concentration which we denote by C^* , and the equations are

$$i = -aq\mu \left(kT \frac{\partial c}{\partial x} + q \frac{\partial \phi}{\partial x} c \right)$$

$$\frac{\partial i}{\partial x} = 0$$

$$-\frac{\partial^2 \phi}{\partial x^2} = \frac{q(c - C^*)}{\epsilon}$$

$$c(0) = c_1$$

$$c(l) = c_2$$

$$\phi(0) = V$$

$$\phi(l) = 0$$

These are the same as the constant-field equations except that here we specialize to the case $z=+1$, we do not take the limit of small concentrations, and we include the background negative charge concentration C^* .

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We seek an approximate solution to these equations when c^* is large. To answer the question "large compared to what?" and to simplify the notation, we introduce dimensionless variables:

$$x = lX$$

$$c_1 = c^* C_1 \quad c_2 = c^* C_2 \quad c(x) = c^* C\left(\frac{x}{l}\right) = c^* C(X)$$

$$v = \frac{kT}{q} V \quad \phi(x) = \frac{kT}{q} \Phi\left(\frac{x}{l}\right) = \frac{kT}{q} \Phi(X)$$

$$i = \frac{a_2 \mu kT c^*}{l} I$$

In other words, we choose l as the unit of length, c^* as the unit of concentration, (kT/q) as the unit of voltage, and $(a_2 \mu kT c^* / l)$ as the unit of current.

In dimensionless variables, the equations read as follows:

$$I = - \left(\frac{\partial C'}{\partial X} + \frac{\partial \Phi}{\partial X} C' \right) \quad \frac{\partial I}{\partial X} = 0$$

$$-\beta^2 \frac{\partial^2 \Phi}{\partial X^2} = C' - 1$$

where β is a dimensionless parameter given by

$$\beta = l_D / l$$

where

$$l_D = \sqrt{\frac{kT\epsilon}{q^2 C^*}}$$

The constant l_D is called the "Debye length". Note that it decreases with increasing C^* . We assume that C^* is sufficiently large ^{that} l_D is small in comparison to the length of the channel. In other words, we assume that $\beta \ll 1$. The dimensionless boundary conditions are:

$$C'(0) = C_1$$

$$C'(1) = C_2$$

$$\Phi(0) = V$$

$$\Phi(1) = 0$$

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Consider the limit of the foregoing problem as $\beta \rightarrow 0$. Let

$$I_0 = \lim_{\beta \rightarrow 0} I(\beta) \quad C_0(X) = \lim_{\beta \rightarrow 0} C(X, \beta)$$

$$\Phi_0(X) = \lim_{\beta \rightarrow 0} \Phi(X, \beta)$$

(When it seems useful to emphasize the dependence of a variable on β , we shall write it explicitly as an argument. Otherwise, it will be omitted.) It seems reasonable to guess that these limiting variables satisfy the equations obtained by setting $\beta=0$:

$$I_0 = - \left(\frac{\partial C_0}{\partial X} + \frac{\partial \Phi_0}{\partial X} C_0 \right) \quad \frac{\partial I_0}{\partial X} = 0$$

$$0 = C_0' - 1$$

From these equations we derive

$$C_0 = 1 \quad \text{and} \quad \frac{\partial \Phi_0}{\partial X} = -I_0 = \text{constant}$$

Note, however, that this cannot satisfy the boundary conditions unless it happens that $C_1 = C_2 = 1$.

This limiting solution can only be valid away from the boundaries. Perhaps there are thin boundary layers that connect (C_0, Φ_0) to the prescribed boundary values. To study the boundary layer near $X=0$, make the following change of variables in the original (dimensionless) equations:

$$X = \beta X' \quad I = I'$$

$$C(X) = C(\beta X') = C'(X')$$

$$\Phi(X) = \Phi(\beta X') = \Phi'(X')$$

The resulting equations are

$$\beta I' = - \left(\frac{\partial C'}{\partial X'} + \frac{\partial \Phi'}{\partial X'} C' \right) \quad \frac{\partial I'}{\partial X'} = 0$$

$$- \frac{\partial^2 \Phi'}{\partial (X')^2} = C' - 1$$

As before, we consider the limit $\beta \rightarrow 0$. Let

$$I_0 = \lim_{\beta \rightarrow 0} I'(\beta)$$

$$C_0'(X') = \lim_{\beta \rightarrow 0} C'(X', \beta) \quad \Phi_0'(X') = \lim_{\beta \rightarrow 0} \Phi'(X', \beta)$$

Note that these limits are taken with X' fixed which implies that $X \rightarrow 0$. For example

$$C_0'(X') = \lim_{\beta \rightarrow 0} C'(X', \beta) = \lim_{\beta \rightarrow 0} C(\beta X', \beta)$$

Then C_0' and Φ_0' satisfy the following system of equations

$$0 = \frac{\partial C_0'}{\partial X'} + \frac{\partial \Phi_0'}{\partial X'} C_0'$$

$$-\frac{\partial^2 \Phi_0'}{\partial (X')^2} = C_0' - 1$$

(The constant I_0' has dropped out.) The first of these is essentially an equilibrium equation. It says that concentration and potential are related as if the current were zero. We integrate this equation by dividing by C_0' and rewriting the result as

$$\frac{\partial}{\partial X'} (\log C_0' + \Phi_0') = 0$$

which implies

$$\log C_0' + \Phi_0' = \text{constant}$$

The constant is evaluated using the conditions at $X=0$:

$$\log C_0' + \bar{\Phi}_0' = \log C_1 + V$$

This is all that we need to know about the boundary layer near $X=0$. The boundary layer near $X=1$ can be studied in a similar way, with the change of variable

$$X = 1 - \beta X''$$

The result of that analysis is:

$$\log C_0'' + \bar{\Phi}_0'' = \log C_2 + 0$$

We are now ready to match the three solutions $(C_0', \bar{\Phi}_0')$, $(C_0, \bar{\Phi}_0)$, and $(C_0'', \bar{\Phi}_0'')$

The matching conditions are

$$C_0'(\infty) = C_0(0)$$

$$C_0(1) = C_0''(\infty)$$

$$\bar{\Phi}_0'(\infty) = \bar{\Phi}_0(0)$$

$$\bar{\Phi}_0(1) = \bar{\Phi}_0''(\infty)$$

Since $C_0(x) \equiv 1$, this yields $C_0'(\infty) = C_0''(\infty) = 1$,
and hence

$$\Phi_0(0) = \Phi_0'(\infty) = \log C_1 + V$$

$$\Phi_0(1) = \Phi_0''(\infty) = \log C_2$$

Finally, since

$$I_0 = - \frac{\partial \Phi_0}{\partial x} = \text{constant}$$

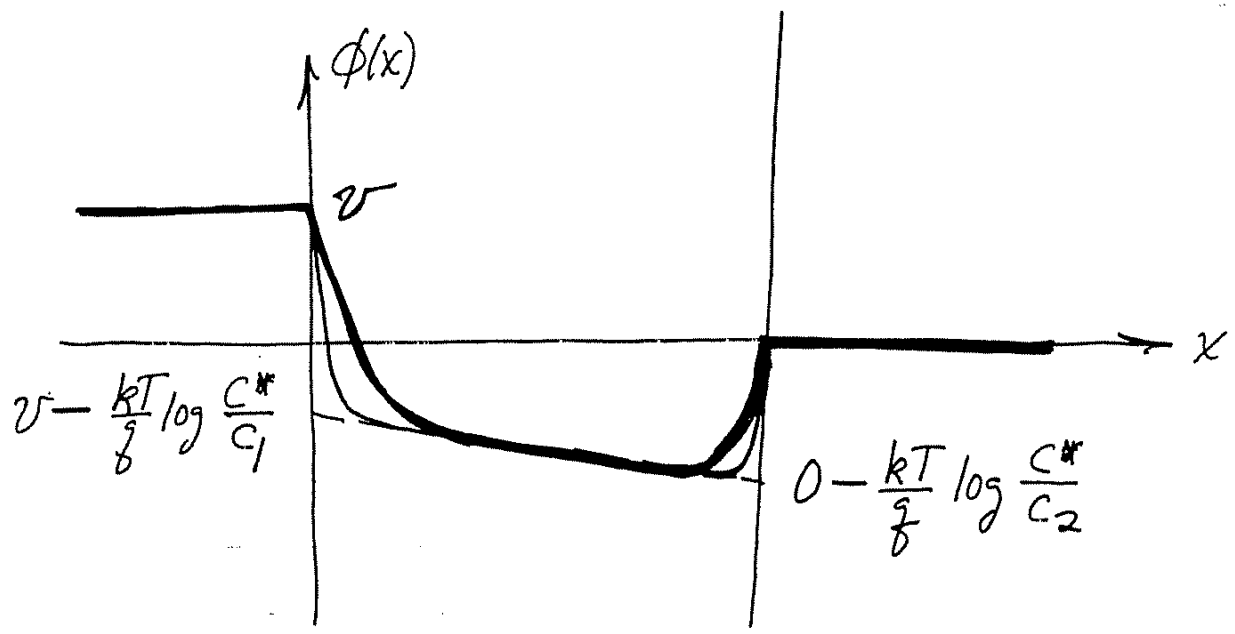
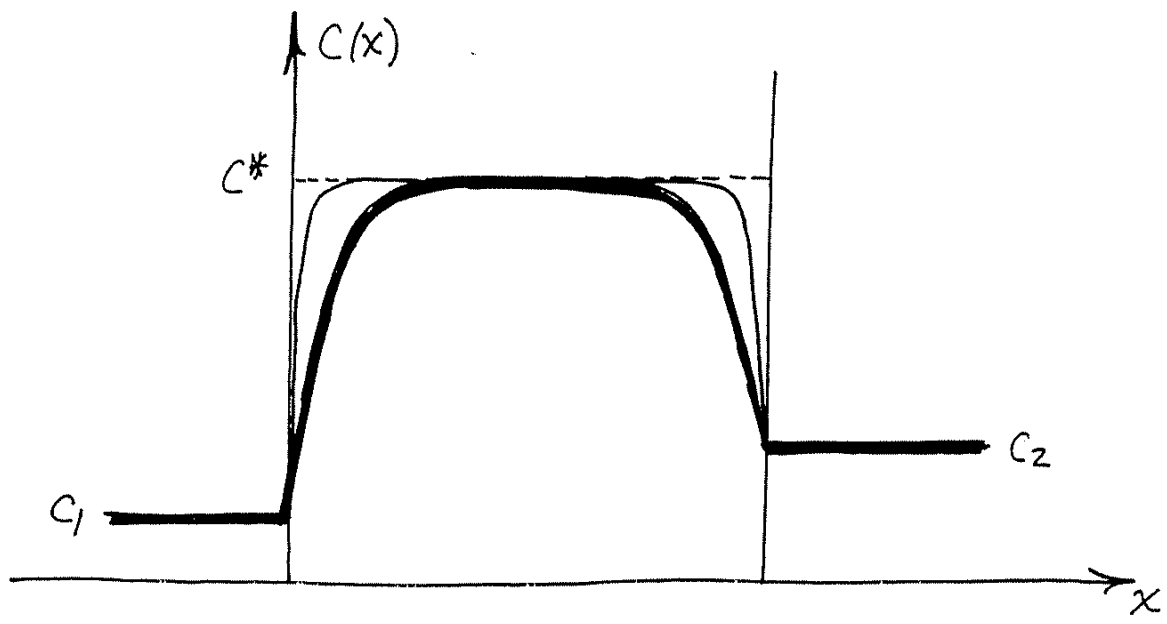
we have

$$I_0 = -(\Phi_0(1) - \Phi_0(0)) = V - \log \frac{C_2}{C_1}$$

In terms of the original variables

$$i = \frac{a \gamma \mu k T c^*}{l} \frac{\gamma}{k T} \left(v - \frac{k T}{\gamma} \log \frac{C_2}{C_1} \right)$$

$$= \frac{a \gamma^2 \mu c^*}{l} \left(v - \frac{k T}{\gamma} \log \frac{C_2}{C_1} \right)$$



Concentration and voltage profile in a membrane channel containing a fixed background of negative charge. Two examples are sketched corresponding to different values of β .

Intuitively, such a channel works like this:

Across most of its length, the concentration of mobile ions is clamped at c^* . At the ends of the channel, there are rapid transitions to the bulk concentrations c_1 and c_2 . These could not be sustained unless they were balanced by corresponding voltage transitions. Near the ends of the channel but far enough from the ends to be past the boundary layers, the voltages are therefore

$$\left(V - \frac{kT}{f} \log \frac{c^*}{c_1} \right) \quad \text{and} \quad \left(0 - \frac{kT}{f} \log \frac{c^*}{c_2} \right)$$

Thus, the electric field in the interior of the channel is given by

$$E = \frac{\left(V - \frac{kT}{f} \log \frac{c_2}{c_1} \right)}{l}$$

This produces a force on each ion fE , a drift velocity $\mu f E$, a flux $\mu f E c^*$, and a current $af(\mu f E c^*)$. Thus

$$i = \frac{af^2 \mu c^*}{l} \left(V - \frac{kT}{f} \log \frac{c_2}{c_1} \right)$$

just as we found above.

An intriguing feature of the channel that we have just described is that the conductance

$$g = \frac{aq^2 \mu c^*}{l}$$

is independent of C_1 and C_2 . In fact, we can change C_1 and C_2 without changing the i - V relation at all provided only that we hold C_2/C_1 constant. The physical reason for this is clear. The background charge regulates the concentration of mobile ions in the channel, independent of C_1 and C_2 . This peculiar behavior should provide a straightforward way to recognize such a channel.

Channel selectivity for ions of one sign

One of the central mysteries of membrane biophysics is how channels can be selective for specific ions. Here we attack only an easy version of that problem by discussing discrimination between ions on the basis of their charge. To do this, we consider the same physical model as above, a channel containing fixed negative charges distributed along its walls, but we now see what happens if charges with $z = -1$ as well as charges with $z = +1$ are allowed to enter the channel. Clearly, the channel will discriminate against the negative ions, but how much? The equations of such a channel are as follows:

$$j^+ = -a_f \mu \left(kT \frac{\partial c^+}{\partial x} + f \frac{\partial \phi}{\partial x} c^+ \right) \quad \frac{\partial j^+}{\partial x} = 0$$

$$j^- = a_f \mu \left(kT \frac{\partial c^-}{\partial x} - f \frac{\partial \phi}{\partial x} c^- \right) \quad \frac{\partial j^-}{\partial x} = 0$$

$$\frac{\partial^2 \phi}{\partial x^2} = \frac{f(c^+ - c^- - c^*)}{\epsilon}$$

$$c^+(0) = c_1^+$$

$$c^+(l) = c_2^+$$

$$c^-(0) = c_1^-$$

$$c^-(l) = c_2^-$$

$$\phi(0) = v$$

$$\phi(l) = 0$$

where i^+ is the current carried by the positive ions which have concentration $C^+(x)$ and i^- is the current carried by the negative ions which have concentration $C^-(x)$. The two currents are separately constant because we assume that the ions remain ionized; they do not combine to form a neutral species.

These equations can be made dimensionless in the same way as before. The result is

$$I^+ = - \left(\frac{\partial C^+}{\partial X} + \frac{\partial \Phi}{\partial X} C^+ \right) \quad \frac{\partial I^+}{\partial X} = 0$$

$$I^- = \left(\frac{\partial C^-}{\partial X} - \frac{\partial \Phi}{\partial X} C^- \right) \quad \frac{\partial I^-}{\partial X} = 0$$

$$\beta^2 \frac{\partial^2 \Phi}{\partial X^2} = (C^+ - C^- - 1)$$

$$C^+(0) = C_1^+ \quad C^+(1) = C_2^+$$

$$C^-(0) = C_1^- \quad C^-(1) = C_2^-$$

$$\Phi(0) = V \quad \Phi(1) = 0$$

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Letting $\beta \rightarrow 0$, we obtain the equations

$$I_0^+ = - \left(\frac{\partial C_0^+}{\partial X} + \frac{\partial \Phi_0}{\partial X} C_0^+ \right) \quad \frac{\partial I_0^+}{\partial X} = 0$$

$$I_0^- = \left(\frac{\partial C_0^-}{\partial X} - \frac{\partial \Phi_0}{\partial X} C_0^- \right) \quad \frac{\partial I_0^-}{\partial X} = 0$$

$$0 = C_0^+ - C_0^- - 1$$

which, in general, is inconsistent with the boundary conditions.

To study the boundary layer near $X=0$, let $X = \beta X'$ and then let $\beta \rightarrow 0$. The resulting equations can be integrated to read

$$\log(C_0^+)' + \Phi_0' = \log C_1^+ + V$$

$$\log(C_0^-)' - \Phi_0' = \log C_1^- - V$$

Adding these equations gives the important result that

$$(C_0^+)' (C_0^-)' = C_1^+ C_1^-$$

That is, the product of the two ion concentrations is constant across the boundary layer.

The matching conditions

$$(C_0^+)'(\infty) = C_0^+(0)$$

$$(C_0^-)'(\infty) = C_0^-(0)$$

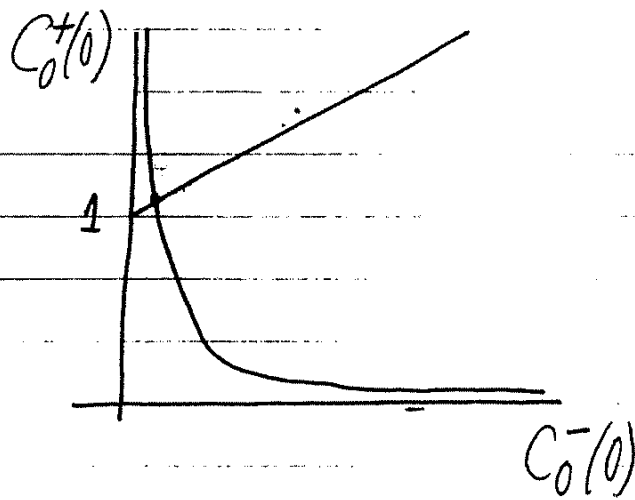
therefore yield

$$C_0^+(0)C_0^-(0) = C_1^+C_1^-$$

But we also have

$$C_0^+(0) - C_0^-(0) = 1$$

These two equations in the two unknowns $C_0^+(0)$ and $C_0^-(0)$ have a unique positive solution:



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Instead of solving these equations exactly, we shall use the approximate result which holds when

$$C_1^+ C_1^- \ll 1 \quad C_2^+ C_2^- \ll 1$$

This is

$$C_0^+(0) \approx 1 \quad C_0^-(0) \approx C_1^+ C_1^- \ll 1$$

Once $C_0^+(0)$ and $C_0^-(0)$ are determined, we can use either of them to determine $\Phi_0(0)$. The more convenient choice is $C_0^+(0) \approx 1$. To find $\Phi_0(0)$, proceed as follows

$$\begin{aligned} \Phi_0(0) &\approx \bar{\Phi}_0(0) + \log C_0^+(0) = \bar{\Phi}_0'(\infty) + \log (C_0^+)'(\infty) \\ &= V + \log C_1^+ \end{aligned}$$

A similar analysis of the situation near $X=1$ yields

$$C_0^+(1) \approx 1 \quad C_0^-(1) \approx C_2^+ C_2^- \ll 1$$

$$\Phi_0(1) \approx 0 + \log C_2^+$$

Thus C_0^+ , C_0^- , Φ_0 satisfy

$$I_0^+ = - \left(\frac{\partial C_0^+}{\partial X} + \frac{\partial \Phi_0}{\partial X} C_0^+ \right)$$

$$\frac{\partial I_0^+}{\partial X} = 0$$

$$I_0^- = \left(\frac{\partial C_0^-}{\partial X} - \frac{\partial \Phi_0}{\partial X} C_0^- \right)$$

$$\frac{\partial I_0^-}{\partial X} = 0$$

$$0 = C_0^+ - C_0^- - 1$$

with boundary conditions

$$C_0^+(0) \approx 1$$

$$C_0^+(1) \approx 1$$

$$C_0^-(0) \approx C_1^+ C_1^- \ll 1$$

$$C_0^-(1) \approx C_2^+ C_2^- \ll 1$$

$$\Phi_0(0) \approx V + \log C_1^+$$

$$\Phi_0(1) \approx \log C_2^+$$

These equations have the following approximate solutions

$$C_0^+(x) \approx 1$$

$$-\frac{\partial \Phi_0}{\partial x} \approx I_0^+ \approx \Phi_0(0) - \Phi_0(1) \approx V - \ln \frac{C_2^+}{C_1^+}$$

and C_0^- is the solution of

$$I_0^- = \left(\frac{\partial C_0^-}{\partial x} + I_0^+ C_0^- \right) \quad \frac{\partial I_0^-}{\partial x} = 0$$

$$C_0^-(0) \approx C_1^+ C_1^- \quad C_0^-(1) \approx C_2^+ C_2^-$$

Thus

$$C_0^-(x) = \left(\frac{I_0^-}{I_0^+} \right) + A \exp(-I_0^+ x)$$

$$C_1^+ C_1^- \approx \left(\frac{I_0^-}{I_0^+} \right) + A$$

$$C_2^+ C_2^- \approx \left(\frac{I_0^-}{I_0^+} \right) + A \exp(-I_0^+)$$

Eliminating A , we can solve for I_0^-/I_0^+ which gives an indication of the selectivity of the channel. The result is

$$\frac{I_0^-}{I_0^+} \approx \frac{C_2^+ C_2^- \exp(I_0^+) - C_1^+ C_1^-}{\exp(I_0^+) - 1}$$

As $I_0^+ \rightarrow \infty$, $(I_0^-/I_0^+) \rightarrow C_2^+ C_2^- \ll 1$

As $I_0^+ \rightarrow -\infty$, $(I_0^-/I_0^+) \rightarrow C_1^+ C_1^- \ll 1$

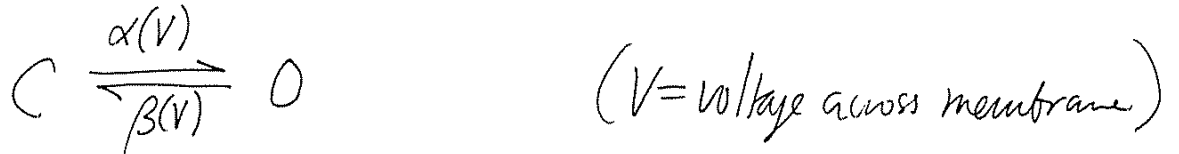
Thus the channel is quite selective at both extremes of current. (Of course, it is not selective at all by this measure near the equilibrium potential for positive ions, where $I_0^+ = 0$.)

An amazing feature of this type of channel is that the selectivity for the positive ions actually improves as their concentrations in the bulk solutions are reduced. As we have seen, such reduction does not affect the conductance of the channel, since the concentration of the positive ions in the channel is clamped at C^* . When C_1^+ and C_2^+ are lowered, however, this increases the size of the voltage steps across the boundary layers, an effect which makes it even harder for negative ions to enter the channel than before! This paradoxical effect could be useful for recognizing channels of this type.

Charles S. Peskin 9/26/91

Opening and closing of membrane channels

Simplest case: a 2-state channel



Macroscopic theory

$[C]$ = fraction of closed channels

$[O]$ = fraction of open channels

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

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

$$\frac{d}{dt} ([C] + [O]) = 0$$

This is as it should be, since $[C] + [O] = 1$

/c

$$\text{let } s = [O] \quad 1-s = [C]$$

$$\begin{aligned} \frac{ds}{dt} &= \alpha(V)(1-s) - \beta(V)s \\ &= \alpha(V) - (\alpha(V) + \beta(V))s \end{aligned}$$

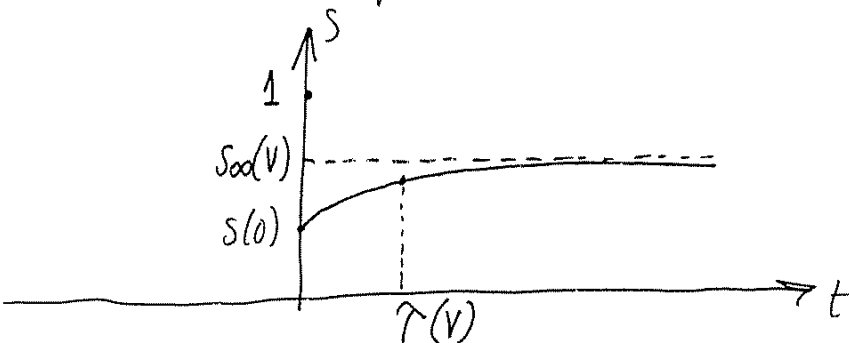
$$\tau(V) \frac{ds}{dt} = s_{\infty}(V) - s$$

Where

$$\tau(V) = \frac{1}{\alpha(V) + \beta(V)}$$

$$s_{\infty}(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)}$$

When $V = \text{constant}$ ("voltage-clamp" conditions)



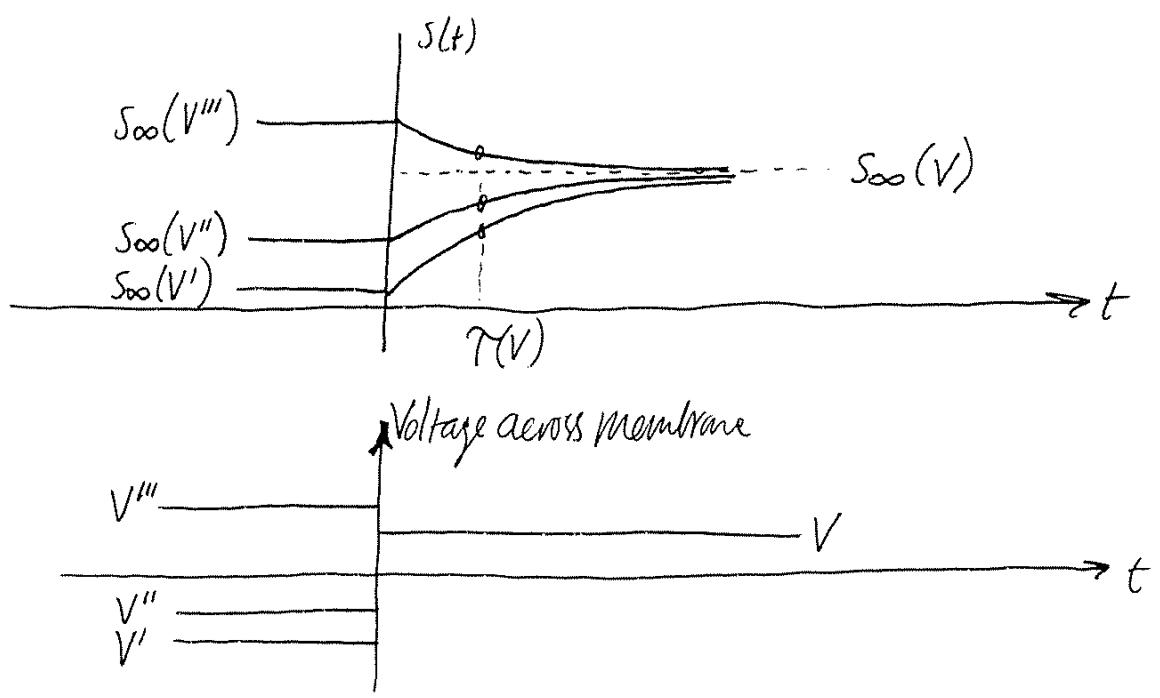
$$s(t) = s_{\infty}(V) + (s(0) - s_{\infty}(V)) \exp(-t/\tau(V))$$

In voltage step from $V' \rightarrow V$, $s(0) = S_{\infty}(V')$ provided that membrane has been held at V' for a long time. From such a transient, one can measure $S_{\infty}(V)$ and $\tau(V)$. Then $\alpha(V)$ and $\beta(V)$ can be found, since

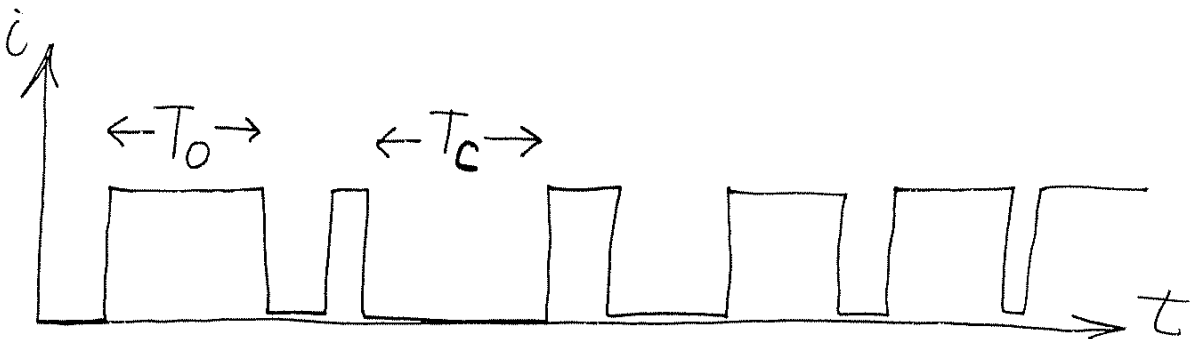
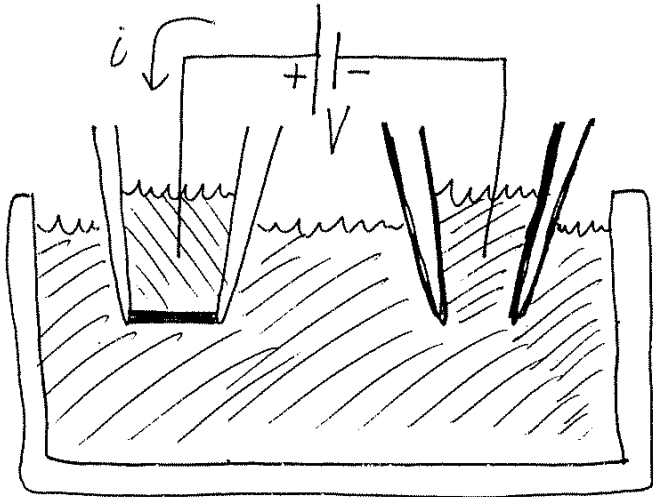
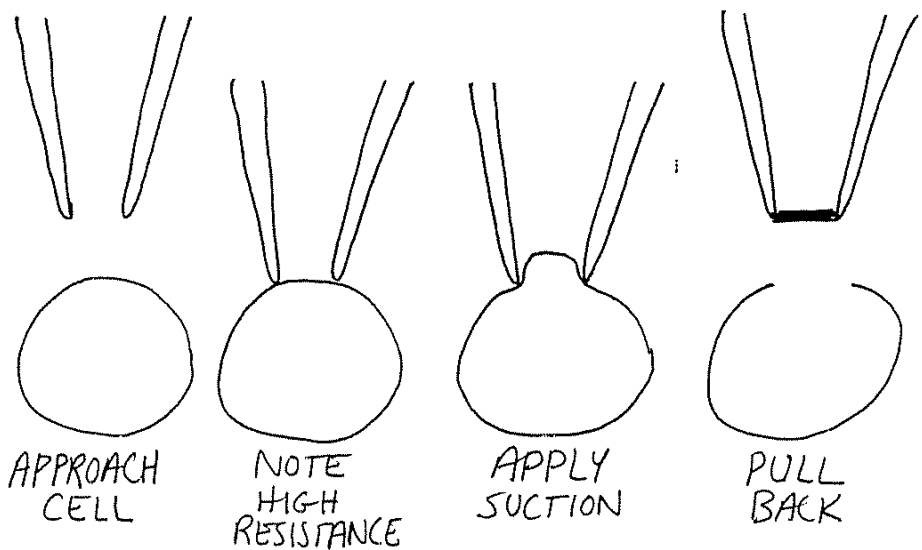
$$\alpha(V) = \frac{S_{\infty}(V)}{\tau(V)}$$

$$\beta(V) = \frac{1 - S_{\infty}(V)}{\tau(V)}$$

As a check on the theory, one can do voltage steps from several different levels $V', V'', \dots \rightarrow V$. The measured $S_{\infty}(V)$ and $\tau(V)$ should be the same



Patch-clamp technique:



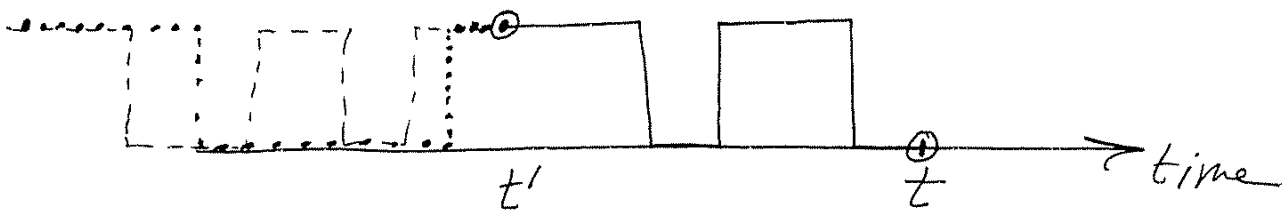
Microscopic analysis of 2-state channel:

$$\text{Let } S(t) = \begin{cases} 1 & \text{if channel is open} \\ 0 & \text{if channel is closed} \end{cases}$$

(random variable)

Markov property: for $t' < t$

$S(t) | S(t')$ is independent of $\{S(t''), t'' < t'\}$



If we know $S(t')$ and want to predict $S(t)$, it does no good to be told $S(t'')$ for $t'' < t'$.

$$\begin{aligned} P(S(t)=k | S(t')=k') \\ = P(S(t)=k | S(t')=k' \text{ and } S(t'')=k'') \end{aligned}$$

for all $t'' < t' < t$

Transition probabilities

$$P(S(t+dt)=1 | S(t)=0) = \alpha(V)dt$$

$$P(S(t+dt)=0 | S(t)=1) = \beta(V)dt$$

$$P(\text{No transition in } (0, t) | S(0)=0)$$

$$= \lim_{n \rightarrow \infty} (1 - \alpha(V) \frac{t}{n})^n = e^{-\alpha(V)t}$$

$$P(\text{First transition in } (t, t+dt) | S(0)=0)$$

$$= P(S(t+dt)=1 | S(t)=0) \cdot$$

$$P(\text{No transition in } (0, t) | S(0)=0)$$

$$= \alpha(V)dt e^{-\alpha(V)t}$$

T_{CLOSED} has pdf $\alpha(V)e^{-\alpha(V)t}$
↙ probability density function

Similarly

T_{OPEN} has pdf $\beta(V)e^{-\beta(V)t}$

$\alpha(V)$ and $\beta(V)$ can be found by measuring pdf for T_{CLOSED} and T_{OPEN}

Relationship between microscopic and macroscopic picture

$$\text{let } s(t) = P(S(t) = 1)$$

$$s(t+dt) = P(S(t+dt) = 1)$$

$$= P(S(t+dt) = 1 | S(t) = 1) P(S(t) = 1)$$

$$+ P(S(t+dt) = 1 | S(t) = 0) P(S(t) = 0)$$

$$= (1 - \beta(V)dt) s(t) + \alpha(V)dt (1 - s(t))$$

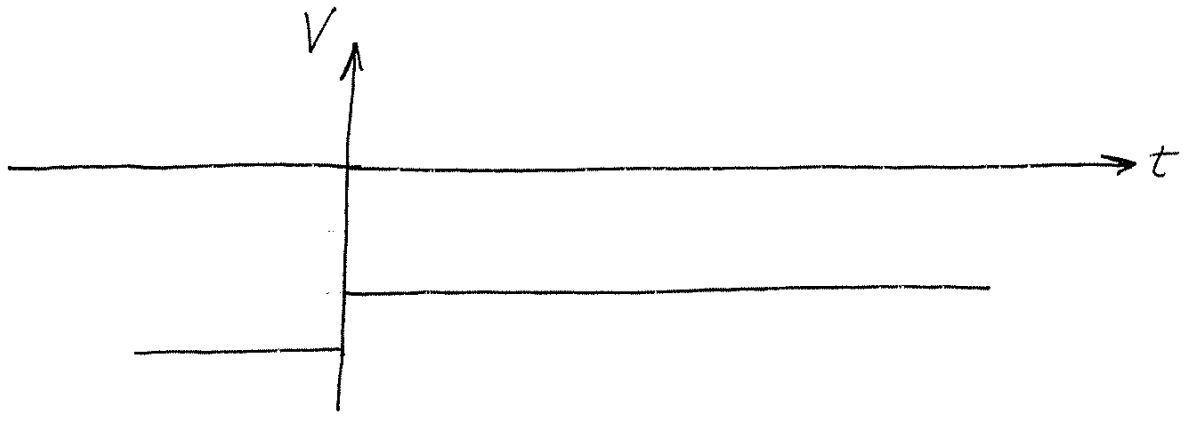
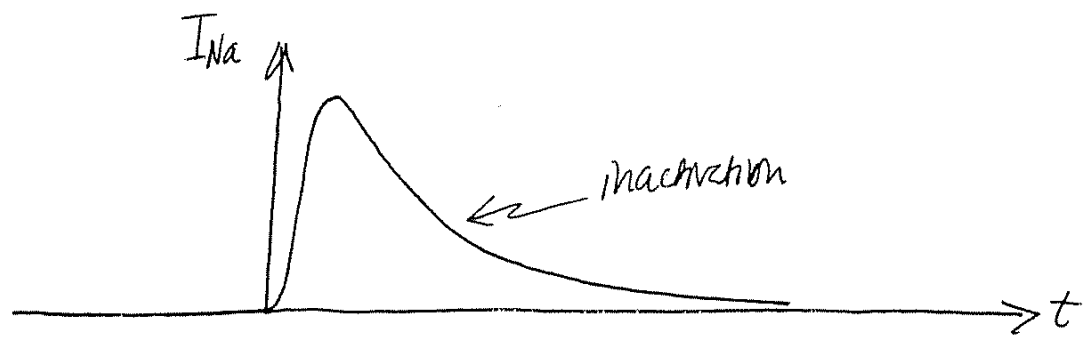
$$\frac{s(t+dt) - s(t)}{dt} = \alpha(V)(1 - s(t)) - \beta(V)s(t)$$

$$\frac{ds}{dt} = \alpha(V)(1 - s(t)) - \beta(V)s(t)$$

which is the macroscopic equation that we used previously.

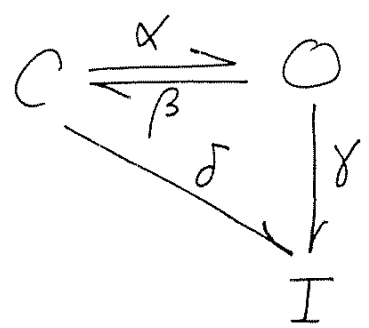
Channels with more states*

In the two-state case, we could get complete information (i.e. $\alpha(V)$ and $\beta(V)$) either from macroscopic or microscopic data. The situation changes when there are more states. As an example, consider the Na^+ channel, the description of which requires at least 3 states, only one of which is an open channel.



* Aldrich RW, Corey DP, and Stevens CF
 A reinterpretation of mammalian sodium channel gating based on single channel recording. Nature 306: 436-441, 1983

Model of the Na⁺ channel



At $t=0$, all channels are in state C

For $t > 0$, voltage is constant and sufficiently high that I is an absorbing state.

Macroscopic analysis:

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

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

$$[C]_{t=0} = 1$$

$$[O]_{t=0} = 0$$

(We don't need the equation for [I] !)

Since only $[O]$ is observable, eliminate $[C]$

$$\begin{aligned} \frac{d^2 [O]}{dt^2} &= \alpha \frac{d[C]}{dt} - (\beta + \gamma) \frac{d[O]}{dt} \\ &= \alpha \left(-(\alpha + \delta)[C] + \beta[O] \right) - (\beta + \gamma) \frac{d[O]}{dt} \\ &= -(\alpha + \delta) \left(\frac{d[O]}{dt} + (\beta + \gamma)[O] \right) + \alpha\beta[O] \\ &\quad - (\beta + \gamma) \frac{d[O]}{dt} \end{aligned}$$

$$\frac{d^2 [O]}{dt^2} + [(\alpha + \delta) + (\beta + \gamma)] \frac{d[O]}{dt} + [(\alpha + \delta)(\beta + \gamma) - \alpha\beta][O] = 0$$

Initial conditions: $[O]_{t=0} = 0$

$$\left. \frac{d[O]}{dt} \right|_{t=0} = \alpha$$

Solution: $[O] = a(e^{\lambda_1 t} - e^{\lambda_2 t})$

where

$$\alpha = a(\lambda_1 - \lambda_2) \quad \lambda_2 < \lambda_1 < 0 \quad \text{and} \quad a > 0$$

λ_1, λ_2 are roots of: $\lambda^2 + [(\alpha + \delta) + (\beta + \gamma)]\lambda + (\alpha + \delta)(\beta + \gamma) - \alpha\beta = 0$

Inverse problem

Given $a > 0$ and $\lambda_2 < \lambda_1 < 0$ find $\alpha, \beta, \gamma, \delta > 0$

Such that

$$\alpha + \delta + \beta + \gamma = -(\lambda_1 + \lambda_2)$$

$$(\alpha + \delta)(\beta + \gamma) - (\alpha\beta) = \lambda_1 \lambda_2$$

$$\alpha = a(\lambda_1 - \lambda_2)$$

α is determined but then there are 3 unknowns (β, γ, δ) and only 2 equations, so we expect many solutions

Use β as a parameter and solve for γ, δ . Even for fixed β there may be 2 solutions. Example: $\beta = 0$

$$(\alpha + \delta) + \gamma = -(\lambda_1 + \lambda_2)$$

$$(\alpha + \delta)\gamma = \lambda_1 \lambda_2$$

where $\alpha = a(\lambda_1 - \lambda_2)$. There are 2 solutions:

- I) $\alpha + \delta = -\lambda_1$ $\gamma = -\lambda_2$ "fast inactivation"
- II) $\alpha + \delta = -\lambda_2$ $\gamma = -\lambda_1$ "slow inactivation"

Each solution is valid iff it yields $\delta \geq 0$. This gives the following requirements

$$\text{I) } -\lambda_1 - a(\lambda_1 - \lambda_2) \geq 0$$

$$\frac{-\lambda_1}{\lambda_1 - \lambda_2} \geq a$$

$$\text{II) } -\lambda_2 - a(\lambda_1 - \lambda_2) \geq 0$$

$$\frac{-\lambda_2}{\lambda_1 - \lambda_2} \geq a$$

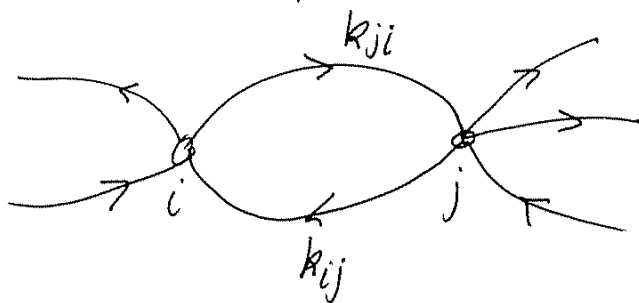
Both solutions are valid if:

$$a \leq \frac{-\lambda_1}{\lambda_1 - \lambda_2} \quad \text{since} \quad \frac{-\lambda_1}{\lambda_1 - \lambda_2} \leq \frac{-\lambda_2}{\lambda_1 - \lambda_2}$$

Conclusion: we cannot determine the rate constants uniquely, in general, from macroscopic data.

Microscopic theory

General case of a channel with several states



$S(t)$ = state at time t $S(t) \in \{1, 2, \dots, n\}$

Markov property (same as 2-state case):

For $t' < t$ $S(t) | S(t')$ is independent of $\{S(t''), t'' < t'\}$

Transition probability:

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

Non-transition probability:

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

$$= 1 - K_i dt$$

(K_i = sum of rate constants for leaving state i)

Given $S(0)=i$ we consider the following events:

$N(t)$ = There is no transition in $(0, t)$

$F(t_1, t_2)$ = The first transition is in (t_1, t_2)

$Tr(j)$ = The first transition is to state j

(N, F, Tr are random variables taking the values "true" or "false")

$$P(N(t) | S(0)=i) = \lim_{m \rightarrow \infty} \left(1 - K_i \frac{t}{m}\right)^m = \exp(-K_i t)$$

$$P(F(t, t+dt) \text{ and } Tr(j) | S(0)=i)$$

$$= P(N(t) | S(0)=i) P(S(t+dt)=j | S(t)=i)$$

$$= \exp(-K_i t) k_{ji} dt$$

$$P(F(t, t+dt) | S(0)=i)$$

$$= \sum_{\substack{j=1 \\ j \neq i}}^n P(F(t, t+dt) \text{ and } Tr(j) | S(0)=i)$$

$$= \sum_{\substack{j=1 \\ j \neq i}}^n \exp(-K_i t) k_{ji} dt = \exp(-K_i t) K_i dt$$

$$P(\text{Tr}(j) | S(0)=i)$$

$$= \int_0^{\infty} P(F(t, t+dt) \text{ and } \text{Tr}(j) | S(0)=i)$$

↖
note: dt

$$= \int_0^{\infty} \exp(-K_i t) dt k_{ji} = \frac{k_{ji}}{K_i} = \frac{k_{ji}}{\sum_{\substack{j'=1 \\ j' \neq i}}^n k_{j'i}}$$

Note that:

$$P(\text{Tr}(j) | S(0)=i) \cdot P(F(t, t+dt) | S(0)=i)$$

$$= \frac{k_{ji}}{K_i} \exp(-K_i t) K_i dt$$

$$= k_{ji} \exp(-K_i t) dt$$

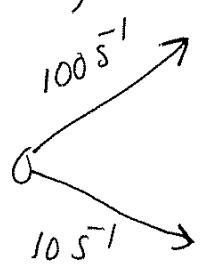
$$= P(\text{Tr}(j) \text{ and } F(t, t+dt) | S(0)=i)$$

In summary, we have shown

- 1) The waiting time to leave a given state is independent of the paths by which the system leaves.*
- 2) The waiting time to leave state i has pdf $K_i \exp(-K_i t)$
- 3) The probability that state j is the next state after state i is given by k_{ji} / K_i

where
$$K_i = \sum_{\substack{l=1 \\ l \neq i}}^n k_{li}$$

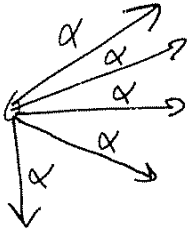
* This may be surprising, since the different paths may have different rate constants, e.g.



One might think there would be an association between long waiting times and the slow pathway. This is not correct.

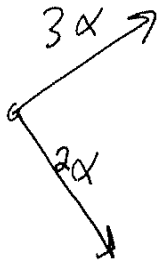
More intuitive proof that the waiting time and the path are independent (Alan Finkelstein):

Step 1: Consider the case of equal rates



The conclusion is obvious by symmetry.

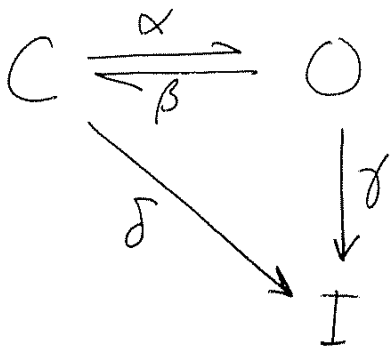
Step 2. Lump together some of the processes!



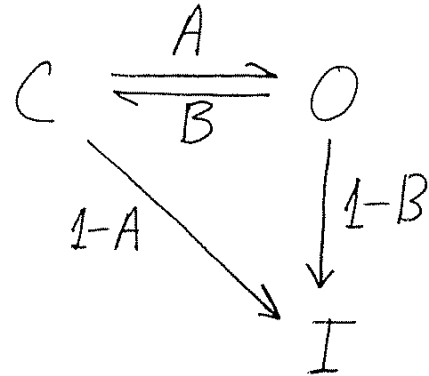
The conclusion is still true because it was true before. Any set of rates which are rationally related can be realized this way.

Step 3: For rates which are not rationally related, approximate them arbitrarily closely by rates which are ,

Application to the Na⁺ channel:



rate constants



probabilities

$$A = \frac{\alpha}{\alpha + \delta}$$

$$1-A = \frac{\delta}{\alpha + \delta}$$

$$B = \frac{\beta}{\beta + \gamma}$$

$$1-B = \frac{\gamma}{\beta + \gamma}$$

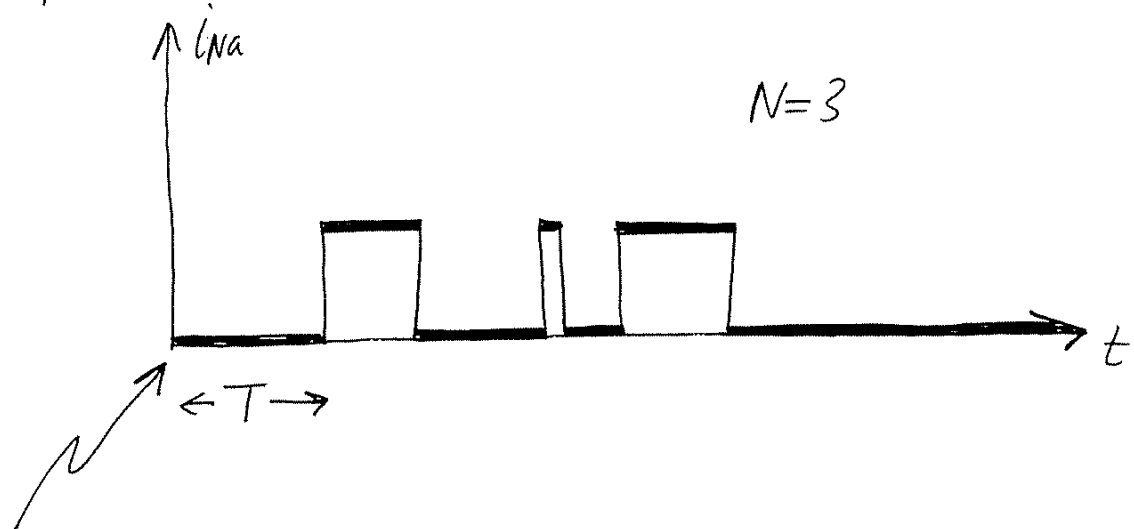
Waiting times

$$\tau_C = \frac{1}{\alpha + \delta}$$

$$\tau_O = \frac{1}{\beta + \gamma}$$

$$\tau_I = \infty$$

Sample record:



$t=0$ is time at which voltage step is applied.

Channel is in state C at $t=0$ and in state I at $t=\infty$.

$T =$ time to first opening ($T = \infty$ if the channel never opens. This happens if it goes direct to state I.)

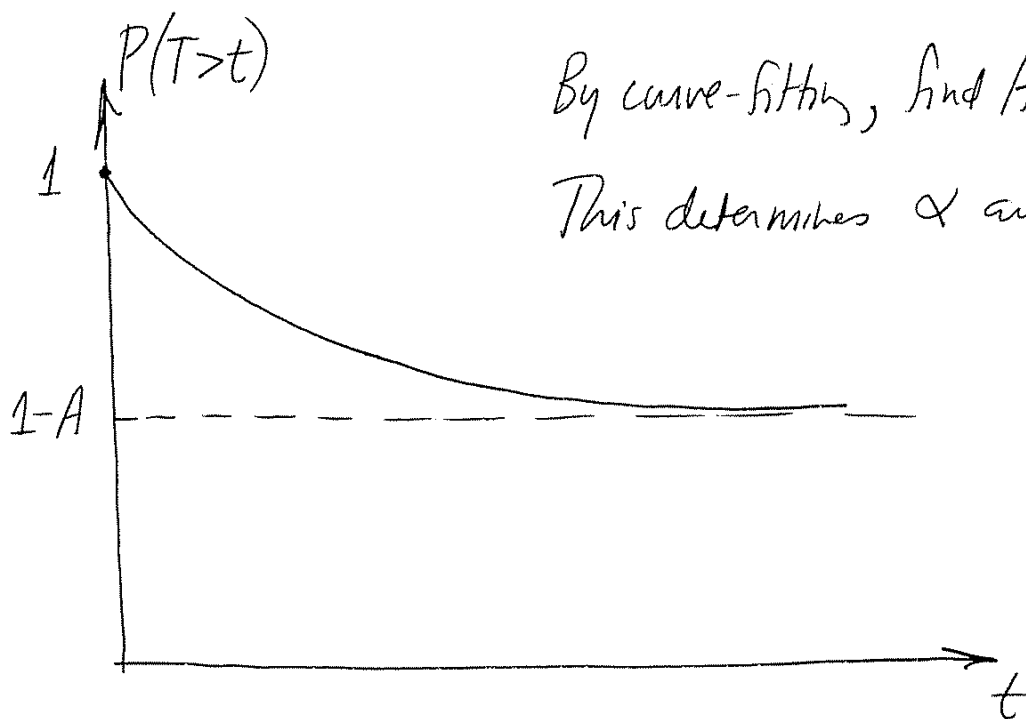
$N =$ # of times the channel opens.

We shall calculate probability distribution functions for T and N .

Probability distribution for T = first opening event

$$\begin{aligned}
P(T > t) &= P(\text{First transition is to state I}) \\
&\quad + P(\text{First transition is to state 0 and } T > t) \\
&= (1-A) + A \cdot \exp\left(-\frac{t}{\tau_c}\right)
\end{aligned}$$

Here, we use independence of path and waiting time.



By curve-fitting, find A and τ_c .
This determines α and β .

Probability distribution for $N = \#$ of times the channel opens

i) $P(N=0) = 1-A$

(since $N=0$ if and only if channel goes directly to state I)

ii) For $k > 0$,

$$P(N=k) = P(N=k \text{ and channel enters I from O}) + P(N=k \text{ and channel enters I from C})$$

$$= A^k B^{k-1} (1-B) + A^k B^k (1-A)$$

$$= A^k B^{k-1} (1-B + B(1-A))$$

$$= A^k B^{k-1} (1-AB) = (AB)^k \left(\frac{1-AB}{B} \right)$$

Determine A from $P(N=0)$

Then determine AB and hence B by curve fitting to the geometric sequence.

$$P(N=k) = (AB)^k \cdot \text{constant} \quad k \geq 1$$

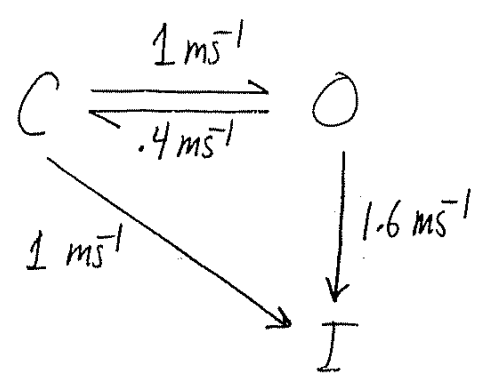
Finally use the (exponential) distribution of open times to determine the parameter

$$\tau_o = \frac{1}{\beta + \gamma}$$

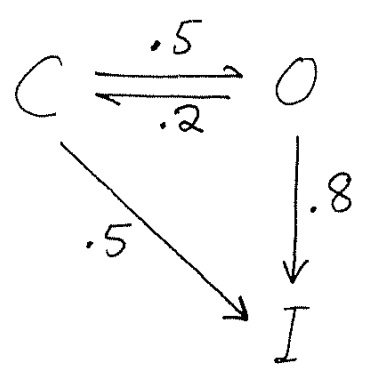
since $B = \frac{\beta}{\beta + \gamma}$ was found above,

we have now determined β and γ . The identification of the model is complete.

Results at $V=0$:



rate constants



probabilities

(Note that inactivation is somewhat faster than activation, contrary to Hodykin-Huxley picture.)

Charles S Peskin 10/3/91

Voltage-dependent gating of membrane channels

Thermodynamics of reaction rates

Let A and B be two possible states of a channel (there may be others as well). Let $W_{A \rightarrow B}$ be the work required to convert a single channel in state A to one in state B.

Now consider a large population of such channels.

Let $[A]$ = fraction of channels in state A
 $[B]$ = fraction of channels in state B

At thermodynamic equilibrium

$$\frac{[B]}{[A]} = \exp\left(-\frac{W_{A \rightarrow B}}{kT}\right)$$

One way to "derive" this result is to treat $[A]$ and $[B]$ as concentrations and to invoke the concept of work of concentration as derived above from the ideal gas law. Then

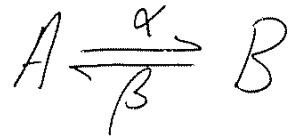
$$W_{A \rightarrow B}^{\text{conc.}} = kT \log \frac{[B]}{[A]}$$

and the condition for thermodynamic equilibrium is

$$0 = W_{A \rightarrow B} + W_{A \rightarrow B}^{\text{conc.}} = W_{A \rightarrow B} + kT \log \frac{[B]}{[A]}$$

which is equivalent to the foregoing formula for $[B]/[A]$.

Now suppose the states A and B are related by a reversible first-order reaction



According to the principle of detailed balance, the rates of the forward and reverse reactions must be equal at thermodynamic equilibrium (see below for further discussion of this principle). Thus, at equilibrium

$$\alpha[A] = \beta[B]$$

$$\frac{\alpha}{\beta} = \frac{[B]}{[A]} = \exp\left(-\frac{W_{A \rightarrow B}}{kT}\right)$$

Since α and β are independent of $[A]$ and $[B]$, the equation

$$\frac{\alpha}{\beta} = \exp\left(-\frac{W_{A \rightarrow B}}{kT}\right)$$

must hold quite generally, whether or not the system is at equilibrium. Thus, thermodynamic considerations determine the ratio of the forward and reverse ~~rate~~ constants.

3

Let the reaction $A \rightleftharpoons B$ take place in a constant electric field E which points in the x direction

Let the channel contain m internal charges $z_i q$, $i=1 \dots m$, and let the x coordinates of these charges be denoted x_i^A when the channel is in state A and x_i^B when the channel is in state B . Then

$$W_{A \rightarrow B} = W_{A \rightarrow B}^0 + \sum_{i=1}^m -E z_i q (x_i^B - x_i^A)$$

where $W_{A \rightarrow B}^0$ is the value of $W_{A \rightarrow B}$ when $E=0$.

If the electric field is constant across the membrane which has thickness l and membrane potential V , then $E=V/l$ and we have

$$W_{A \rightarrow B} = W_{A \rightarrow B}^0 + qzV$$

where

$$z = \sum_{i=1}^m - \left(\frac{x_i^B - x_i^A}{l} \right) z_i$$

Then

$$\frac{\alpha}{\beta} = \frac{\alpha^0}{\beta^0} \exp\left(-\frac{qzV}{kT}\right)$$

where α^0 and β^0 are the rate constants when $V=0$.

Remarks:

1) This formula does not determine α and β separately; only their ratio is determined by thermodynamic considerations. Some choices of α and β consistent with this thermodynamic constraint are

$$\alpha(V) = \alpha^0 \exp\left(-\frac{qzV}{kT}\right) \quad \beta(V) = \beta^0$$

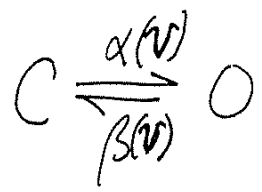
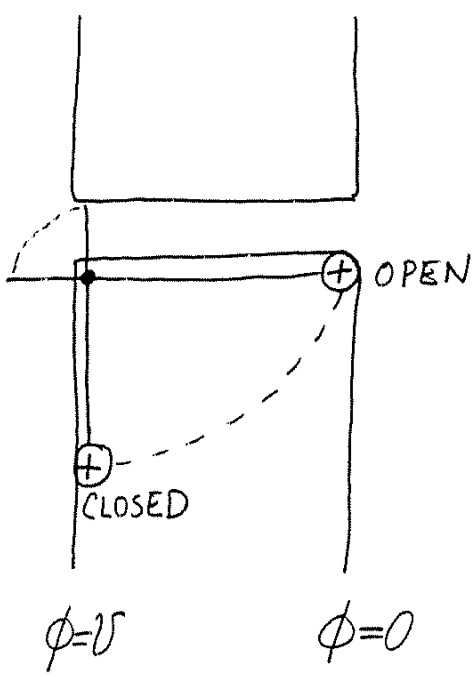
$$\alpha(V) = \alpha^0 \quad \beta(V) = \beta^0 \exp\left(+\frac{qzV}{kT}\right)$$

$$\alpha(V) = \alpha^0 \exp\left(-\frac{1}{2} \frac{qzV}{kT}\right) \quad \beta(V) = \beta^0 \exp\left(+\frac{1}{2} \frac{qzV}{kT}\right)$$

2) The constant qz is the effective gating charge of the channel. From the definition of z it is clear that the same effective gating charge can be achieved either by moving a small amount of charge through a large distance or by moving a large amount of charge through a small distance

Example: a two-state channel with gating charge moving through the dielectric.

Warning: this example is very artificial; a more realistic possibility will be considered below



$$\frac{\alpha(V)}{\beta(V)} = \frac{\alpha^0}{\beta^0} \exp\left(\frac{+gV}{kT}\right)$$

Recall that $s = [0]$ satisfies the differential equation

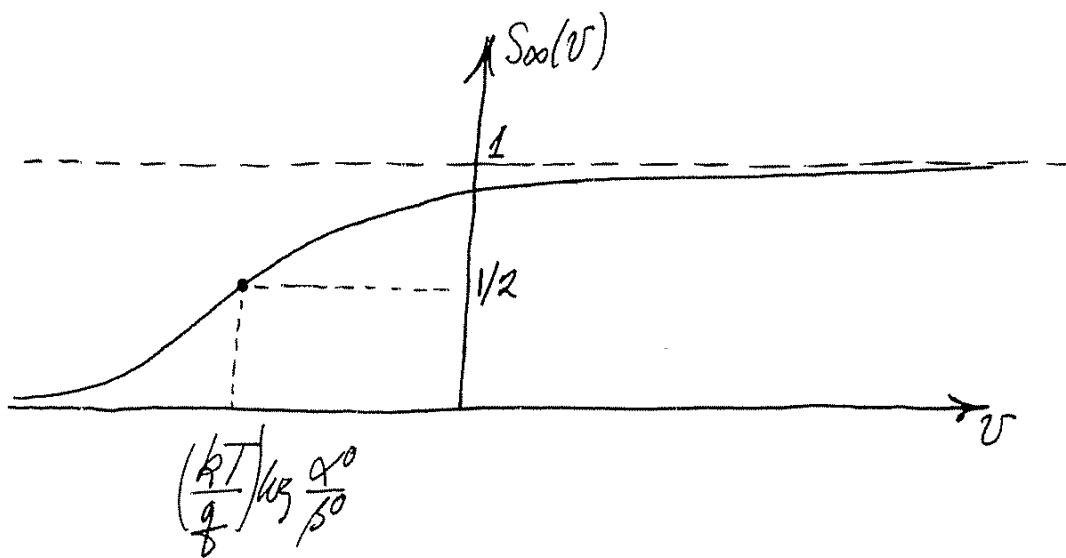
$$\begin{aligned} \frac{ds}{dt} &= \alpha(v)(1-s) - \beta(v)s \\ &= \frac{1}{\tau(v)} (S_{\infty}(v) - s) \end{aligned}$$

where $\tau(v) = \frac{1}{\alpha(v) + \beta(v)}$

$$S_{\infty}(v) = \frac{\alpha(v)}{\alpha(v) + \beta(v)} = \frac{\alpha(v)/\beta(v)}{1 + \alpha(v)/\beta(v)}$$

In our case

$$S_{\infty}(v) = \frac{\frac{\alpha_0}{\beta_0} \exp\left(\frac{qV}{kT}\right)}{1 + \frac{\alpha_0}{\beta_0} \exp\left(\frac{qV}{kT}\right)}$$



The function $\tau(v)$ cannot be predicted from thermodynamic considerations, since $\alpha(v)$ and $\beta(v)$ are not separately determined. However, if we make the symmetrical choice

$$\alpha(v) = \alpha^0 \exp\left(\frac{1}{2} \left(\frac{qv}{kT}\right)\right)$$

$$\beta(v) = \beta^0 \exp\left(-\frac{1}{2} \left(\frac{qv}{kT}\right)\right)$$

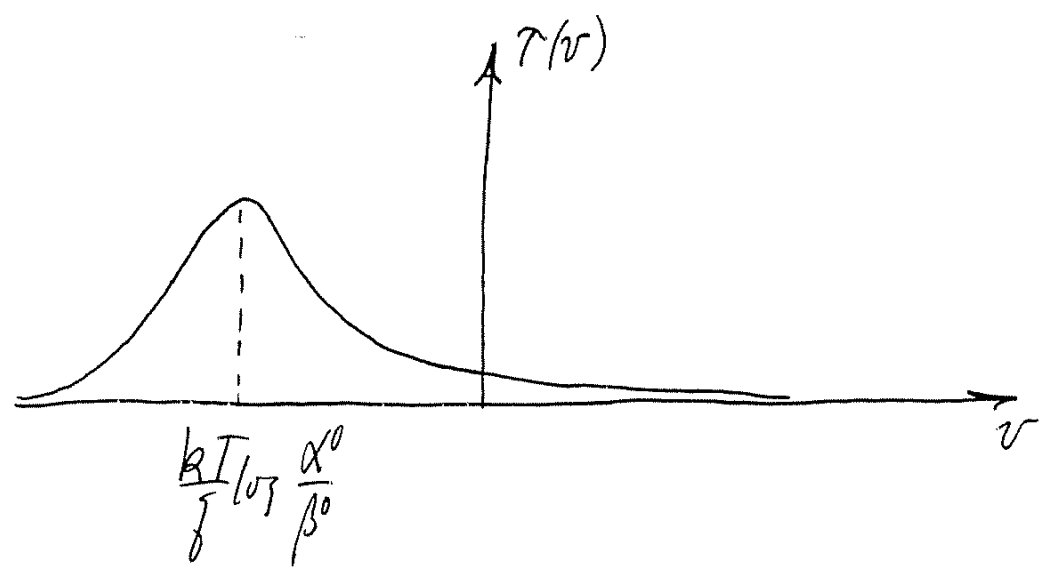
Then

$$\tau(v) = \frac{1}{\alpha^0 \exp\left(\frac{1}{2} \frac{qv}{kT}\right) + \beta^0 \exp\left(-\frac{1}{2} \frac{qv}{kT}\right)}$$

This is a bell-shaped curve with its maximum at

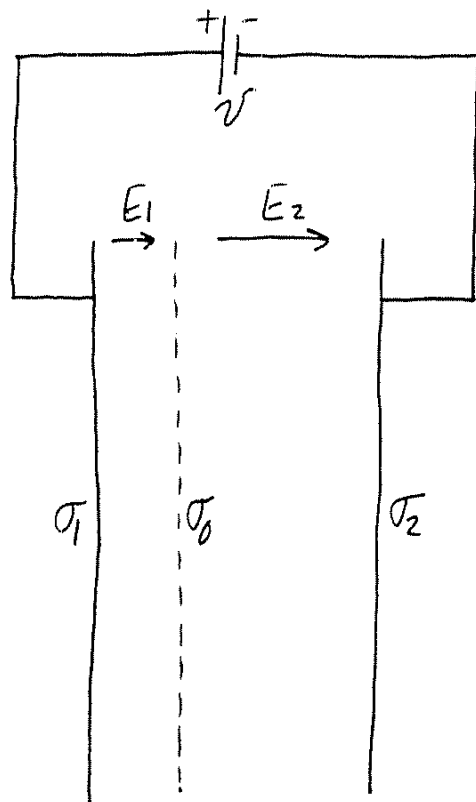
$$v = \frac{kT}{q} \log \frac{\alpha^0}{\beta^0}$$

the same point at which $S_{\infty}(v) = 1/2$



Gating currents

When gating charge moves in the dielectric of the membrane, it induces the flow of charge through the external circuit. To analyze this, we adopt a macroscopic viewpoint.



$$\leftarrow x \rightarrow \leftarrow (l-x) \rightarrow$$

ϵ = dielectric constant of membrane.

σ_0 = gating charge per unit area

σ_1 = charge per unit area on left face of membrane

σ_2 = charge per unit area on right face of membrane

x = distance of gating charge from left face of membrane

l = thickness of membrane

E_1 = electric field to left of gating charge

E_2 = electric field to right of gating charge

Note that the membrane is here regarded as a dielectric (insulator) and that the solution on each side of the membrane is regarded as a perfect conductor.

We take $\epsilon, \sigma, \chi,$ and l as given parameters, and we seek to determine the unknowns:

$$\sigma_1, \sigma_2, E_1, E_2$$

(This problem may look familiar: you probably did it in your introductory course on electricity and magnetism.)

The equations are

$$\sigma_1 = \epsilon E_1 \quad \sigma_2 = -\epsilon E_2$$

$$\sigma_0 = \epsilon (E_2 - E_1)$$

$$V = E_1 x + E_2 (l - x)$$

The first three of these are direct applications of Gauss' law, which relates the flux of E through a surface to the enclosed charge. The last is a special case of the definition of electrostatic potential in terms of the line integral of the electric field.

Solving the last two equations for E_1 and E_2 , we get

$$E_1 = \frac{V}{l} - \left(\frac{l-x}{l}\right) \frac{\sigma_0}{\epsilon}$$

$$E_2 = \frac{V}{l} + \frac{x}{l} \frac{\sigma_0}{\epsilon}$$

Then

$$\sigma_1 = \epsilon E_1 = \frac{\epsilon V}{l} - \left(\frac{l-x}{l}\right) \sigma_0$$

$$\sigma_2 = -\epsilon E_2 = -\frac{\epsilon V}{l} - \left(\frac{x}{l}\right) \sigma_0$$

Now if x changes with all other parameters held constant

$$\frac{d\sigma_1}{dt} = -\frac{d\sigma_2}{dt} = \frac{\sigma_0}{l} \frac{dx}{dt}$$

Let the total area of the membrane be A and $Q_1 = A \sigma_1$, $Q_2 = A \sigma_2$, $Q = A \sigma_0$. Then

$$\frac{dQ_1}{dt} = -\frac{dQ_2}{dt} = \frac{Q_0}{l} \frac{dx}{dt}$$

This charge transfer takes place through the external circuit where it is recorded as a gating current.

11

Remark: The energetics of the situation we have just described is interesting. Let the gating charge be moved all the way from the right side of the membrane ($x=l$ where $\phi=0$) to the left side ($x=0$ where $\phi=V$). Intuitively, this requires an amount of work equal to Q_0V , but where does the energy go? Not into the electric field, which is V/l throughout the dielectric both before and after the move. (Before, the field is E_1 , which is V/l when $x=l$; after it is E_2 , which is V/l when $x=0$.) In fact, the work is done against the battery (charging it up if it is rechargeable, or just generating heat if it isn't). This work is associated with the gating current

$$i_g(t) = \frac{Q_0}{l} \frac{dx}{dt}$$

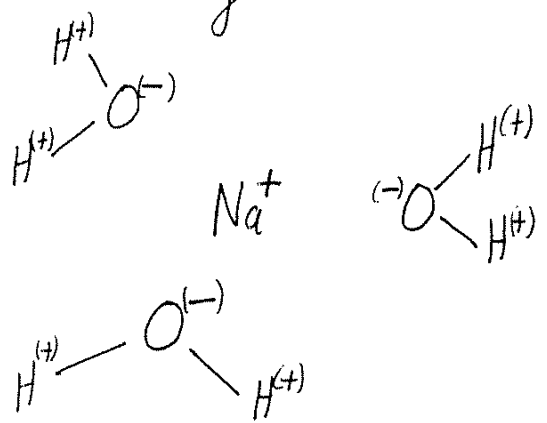
Let W be the work done on the battery during the move from $x=l$ to $x=0$. Then

$$\begin{aligned} W &= - \int V i_g(t) dt = - \frac{VQ_0}{l} \int \frac{dx}{dt} dt \\ &= - \frac{VQ_0}{l} \int_l^0 dx = VQ_0 \end{aligned}$$

as expected.

Critique of the foregoing picture of voltage-dependent gating

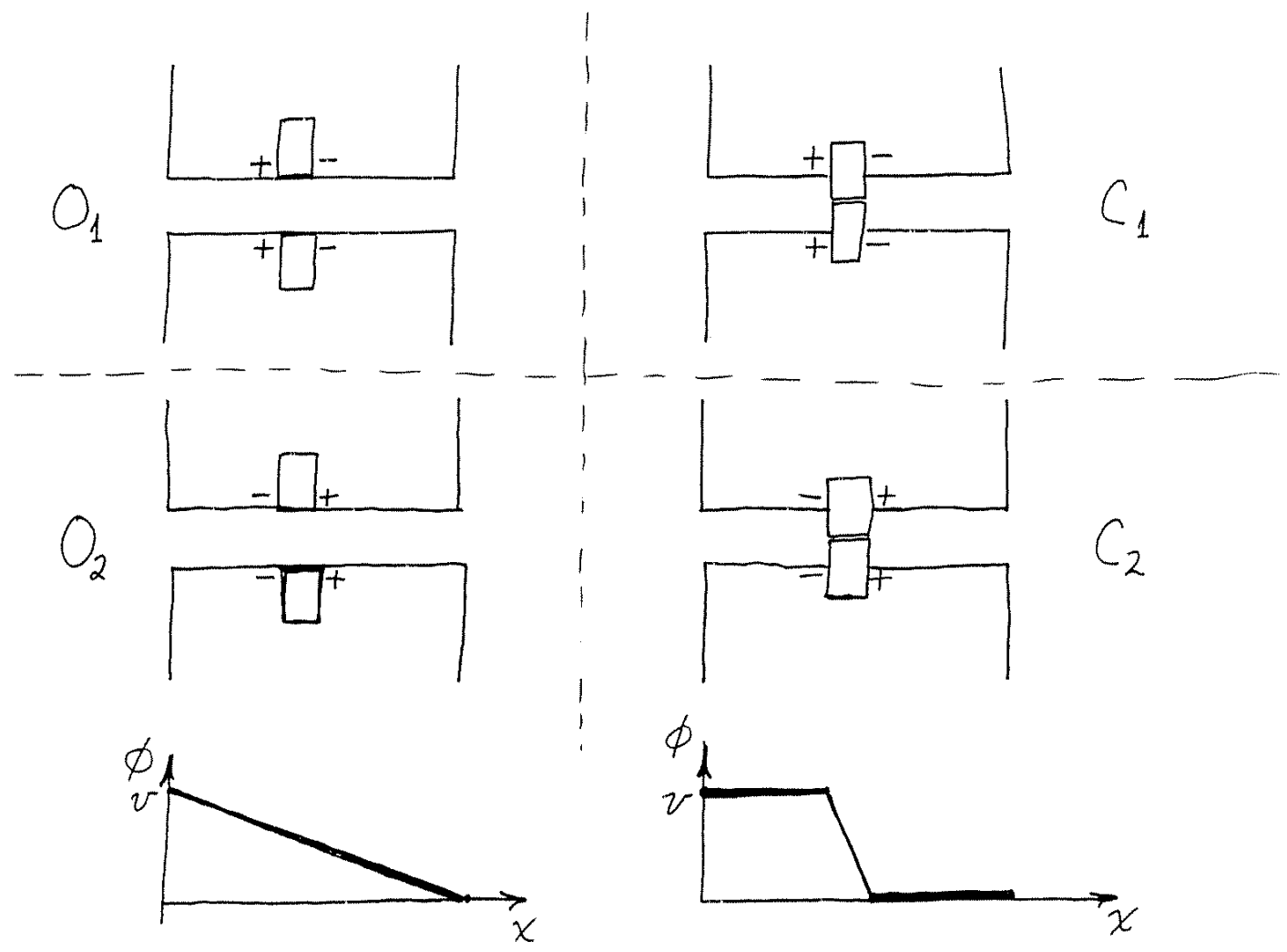
1) It requires the gating charges to move through the oily membrane interior, away from the water. The membrane interior is a very unfavorable place for electric charges to be. Charges are much happier in a polar solvent such as water, the molecules of which orient around it in such a way that the charge is effectively spread over a larger volume.



(The parentheses indicate partial charges.)

2) If only a few charges are involved in gating, the picture we have presented requires that they make large movements (all the way across the membrane) in order to achieve significant sensitivity to the membrane potential. This objection could be overcome by postulating that a large number of gating charges move a small distance, but we shall present a model below which is more economical in that it achieves steep voltage dependence with only a small number of gating charges which move only a small distance.

Voltage-dependent gating with the gating charges on the channel wells*



* Finkelstein A and Peskin CS: Some unexpected consequences of a simple physical mechanism for voltage-dependent gating in biological membranes. Biophysical J 46: 549-558, 1984

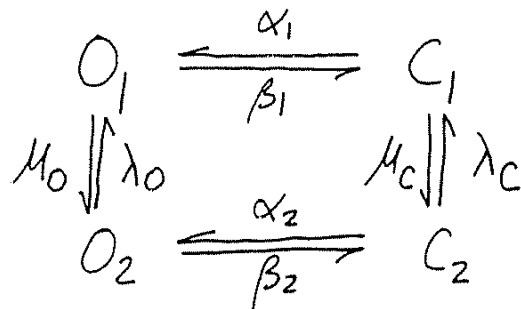
The model channel has a thin gate and a dipole of gating charge located along the channel walls spanning the gate. The channel as a whole has four states, since the gate may be open or closed and since the dipole may point left or right.

The membrane and the gate are modeled as a dielectric (insulator) and the material in the channel is treated as a classical conductor of finite conductivity α . This means that $J = \alpha E$, where J is the current density and E is the electric field. (Note that this leaves out the diffusion term in the drift-diffusion equation considered above.) The solution outside the membrane is considered a perfect conductor so that the voltages are fixed at the two ends of the channel: $\phi(0) = V$ and $\phi(l) = 0$.

The crucial observation concerning such a channel is as follows: when the gate is open, the voltage drop V is spread out over the entire length of the channel, so there is very little voltage difference between the two ends of the dipole. When the gate is closed, on the other hand, the entire voltage drop V appears across the gate (since there is no current and hence no electric field in the channel). Thus the full voltage difference V is felt by the dipole.

Remark: Why don't the gating charges influence the distribution of potential in the channel? This is because they are effectively neutralized by counter-ions which belong to the solution in the channel and which reside on its surface, at the membrane-channel interface. Because of these counter-ions, the gating charges have no electrical effects unless they move. When they do move, however, the counter-ions must adjust accordingly, and this involves the flow of current in the channel and in the external circuit that maintains the membrane potential v .

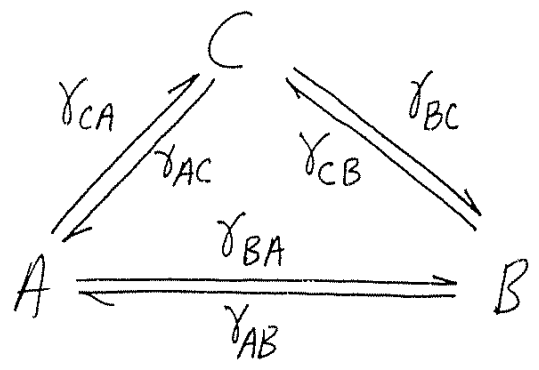
Kinetic scheme



$\alpha, \beta =$ rate constants for opening and closing the gate
 $\lambda, \mu =$ rate constants for flipping the dipole

Detailed balance:

In a system at thermal equilibrium every process runs at the same rate as its own reverse process. This is the principle of detailed balance. To see its significance, consider a kinetic scheme with a cycle



The differential equations of this scheme are

$$\begin{aligned} \frac{d}{dt}[A] &= -(\gamma_{BA} + \gamma_{CA})[A] + \gamma_{AB}[B] + \gamma_{AC}[C] \\ \frac{d}{dt}[B] &= +\gamma_{BA}[A] - (\gamma_{AB} + \gamma_{CB})[B] + \gamma_{BC}[C] \\ \frac{d}{dt}[C] &= \gamma_{CA}[A] + \gamma_{CB}[B] - (\gamma_{AC} + \gamma_{BC})[C] \end{aligned}$$

Note that

$$\frac{d}{dt}([A] + [B] + [C]) = 0$$

$$\Rightarrow [A] + [B] + [C] = \text{constant} = 1$$

The equations of steady state for such a system are

$$0 = -(\gamma_{BA} + \gamma_{CA})[A] + \gamma_{AB}[B] + \gamma_{AC}[C]$$

$$0 = \gamma_{BA}[A] - (\gamma_{AB} + \gamma_{CB})[B] + \gamma_{BC}[C]$$

$$0 = \gamma_{CA}[A] + \gamma_{CB}[B] - (\gamma_{AC} + \gamma_{BC})[C]$$

$$1 = [A] + [B] + [C]$$

One can check that these equations have a unique solution for all positive γ 's. Is this solution a state of thermal equilibrium? If so, it must satisfy detailed balance:

$$\gamma_{BA}[A] = \gamma_{AB}[B]$$

$$\gamma_{CB}[B] = \gamma_{BC}[C]$$

$$\gamma_{AC}[C] = \gamma_{CA}[A]$$

Note that these equations imply

$$[A]/[B] = \gamma_{AB}/\gamma_{BA}$$

$$[B]/[C] = \gamma_{BC}/\gamma_{CB}$$

$$[C]/[A] = \gamma_{CA}/\gamma_{AC}$$

Multiplying these equations together, we conclude that

$$1 = \frac{\gamma_{AB}}{\gamma_{BA}} \cdot \frac{\gamma_{BC}}{\gamma_{CB}} \cdot \frac{\gamma_{CA}}{\gamma_{AC}}$$

We conclude that thermal equilibrium is impossible unless the rate constants satisfy this constraint!

The meaning of this condition is clarified by writing it in terms of work:

$$1 = \exp\left(\frac{W_{A \rightarrow B}}{kT}\right) \exp\left(\frac{W_{B \rightarrow C}}{kT}\right) \exp\left(\frac{W_{C \rightarrow A}}{kT}\right)$$

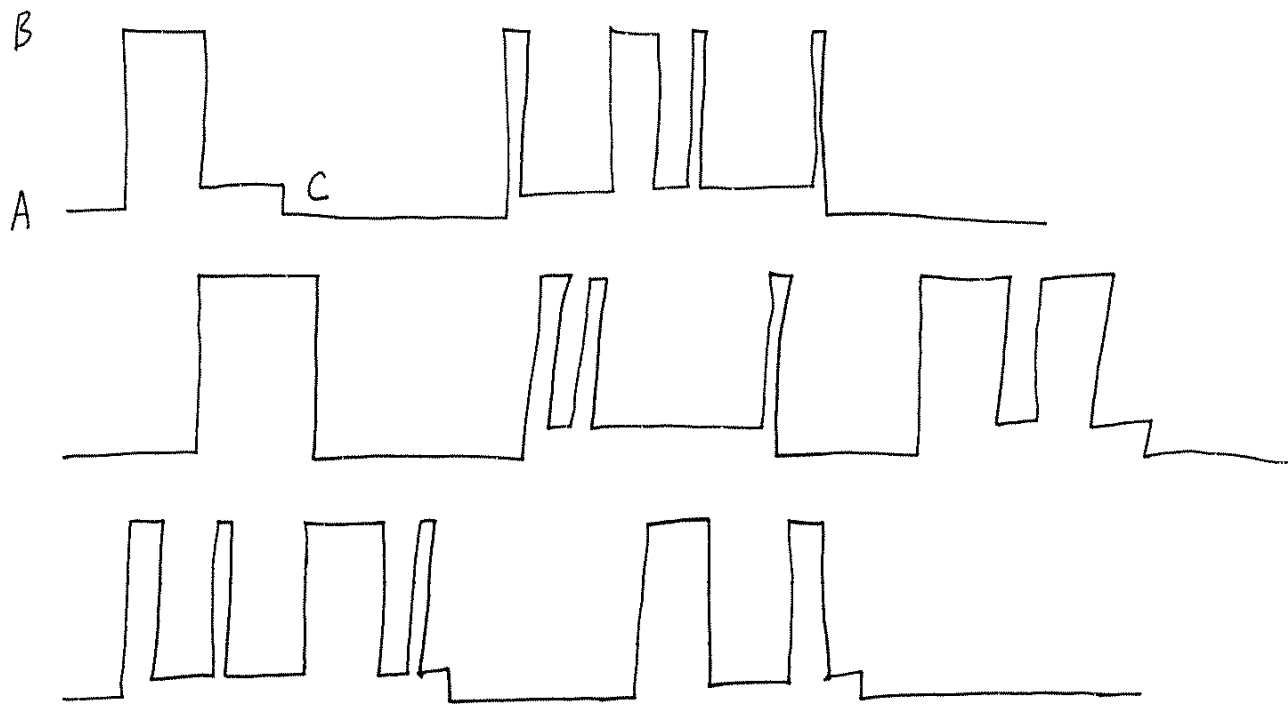
$$0 = W_{A \rightarrow B} + W_{B \rightarrow C} + W_{C \rightarrow A} = W_{A \rightarrow B \rightarrow C \rightarrow A}$$

In short, a necessary condition for the existence of thermal equilibrium is that the net work done going around any cycle of states is zero. When this condition is violated, the system finds a steady state which is not a state of thermodynamic equilibrium. The maintenance of such a state requires an energy source. In our case it will turn out to be the battery that maintains the membrane potential.

Experimental look at detailed balance for membrane channels

If a channel has only 2 distinguishable states, there is nothing to check. The number of opening events in a patch clamp record must equal the number of closing events (± 1).

With 3 distinguishable states, this kind of patch-clamp record can be obtained

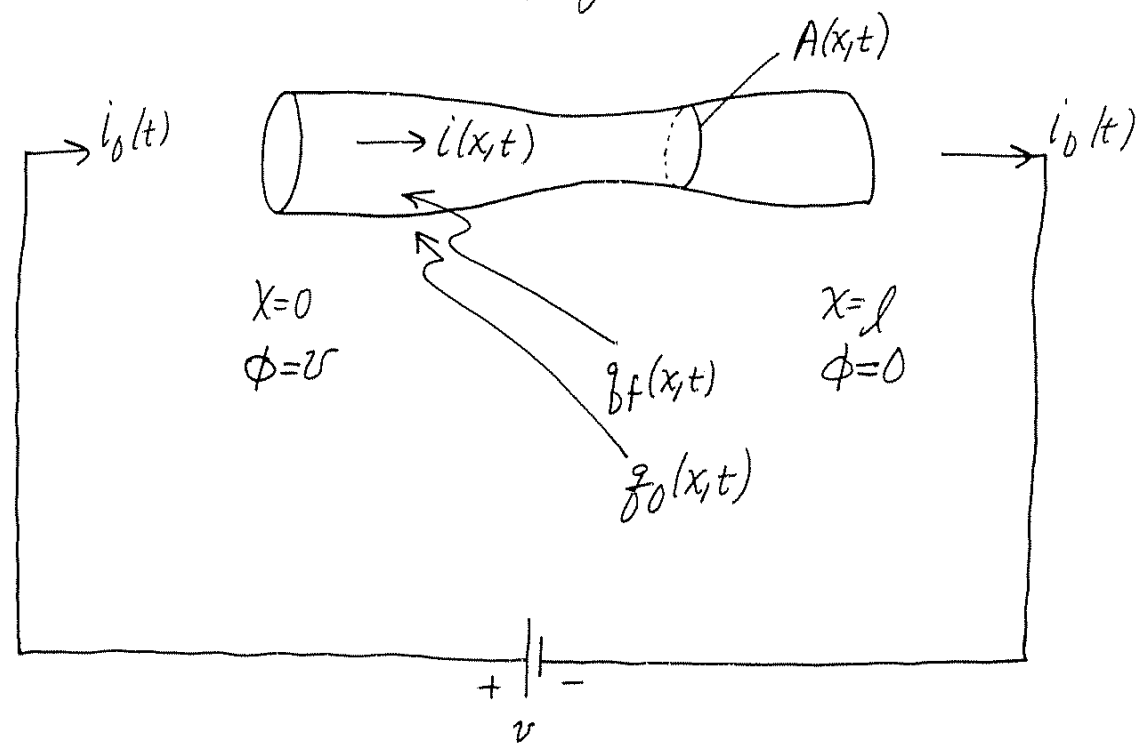


In this example, there are 4 transitions from $C \rightarrow A$ but none from $A \rightarrow C$. Such data* suggest that detailed balance is violated.

* Hamill OP and Sakmann B: Multiple conductance states of single acetylcholine receptor channels in embryonic muscle cells. Nature 294: 462-464, 1981

Analysis of the model: energetic and gating currents

We analyze the general case of a narrow channel with some distribution of gating charge along its walls:



- $l =$ length of channel
- $x =$ distance along channel $0 < x < l$
- $A(x,t) =$ cross-sectional area of channel (given function)
- $q_0(x,t) =$ gating charge per unit length of channel (given function*)
- $q_f(x,t) =$ free charge (on channel walls) per unit length of channel
- $i(x,t) =$ axial current in channel
- $\phi(x,t) =$ potential in the channel
- $\alpha =$ conductivity of solution in the channel

*| but see next page

Consequences of the channel being narrow:

- 1) one-dimensional treatment is appropriate
- 2) electroneutrality ($q_f + q_0 = 0$)
- 3) electrostatic field energy can be neglected

(These statements can be derived by asymptotic analysis of the narrow-channel limit. Here we take them as axioms.)

Equations for distribution of current, voltage, and charge

- i) Conservation of the gating charge:

$$\frac{d}{dt} \int_0^l q_0(x,t) dx = 0$$

(The given function $q_0(x,t)$ must satisfy this constraint.)

- ii) Conservation of the free charge:

$$\frac{\partial q_f}{\partial t} + \frac{\partial i}{\partial x} = 0$$

- iii) Electroneutrality: $q_f + q_0 = 0$

- iv) Ohm's law:

$$i = -\alpha A \frac{\partial \phi}{\partial x}$$

- v) Boundary conditions: $\phi(0) = v$, $\phi(l) = 0$

Note that the current is the same at both ends of the channel:

$$\begin{aligned} i(l,t) - i(0,t) &= \int_0^l \frac{\partial i}{\partial x} dx = - \int_0^l \frac{\partial \rho}{\partial t} dx \\ &= + \int_0^l \frac{\partial \rho_0}{\partial t} dx = \frac{d}{dt} \int_0^l \rho_0 dx = 0 \end{aligned}$$

Hence we may set:

$$i_0(t) = i(0,t) = i(l,t) = \text{current in the external circuit.}$$

This current may be determined as follows:

$$\text{let } R(x,t) = \int_x^l \frac{dx'}{\alpha A(x',t)} = \text{resistance of the part of the channel for which } x \leq x' \leq l$$

$$R_0(t) = R(0,t) = \text{resistance of the entire channel}$$


Then

$$\phi(x,t) = - \int_x^l i(x',t) \frac{\partial R}{\partial x}(x',t) dx'$$


In particular

$$\begin{aligned}
v = \phi(0, t) &= - \int_0^l i(x, t) \frac{\partial R}{\partial x}(x, t) dx \\
&= - i(x, t) R(x, t) \Big|_0^l + \int_0^l \frac{\partial i}{\partial x}(x, t) R(x, t) dx \\
&= i_0(t) R_0(t) + \int_0^l \frac{\partial q_0}{\partial t}(x, t) R(x, t) dx
\end{aligned}$$

$$i_0(t) = \frac{v}{R_0(t)} - \frac{\int_0^l \frac{\partial q_0}{\partial t}(x, t) R(x, t) dx}{R_0(t)}$$



Ohmic current



Gating current

Note: Gating charges have an effect only when they move. Gating current is associated with $\frac{\partial q_0}{\partial t}$ and not with $\frac{\partial R_0}{\partial t}$ or $\frac{\partial R}{\partial t}$. Gating current depends on distribution of resistance in channel.

Narrow-channel energetics

Rate of Joule heating

$$\begin{aligned}\dot{H} &= \int_0^l \left(-\alpha \frac{\partial \phi}{\partial x}\right) \left(-\frac{\partial \phi}{\partial x}\right) A dx \\ &= \int_0^l \alpha A \left(\frac{\partial \phi}{\partial x}\right)^2 dx\end{aligned}$$

Rate of work done by the battery

$$\dot{W}_b = v i_0(t)$$

Rate of work done by the demon that adjusts $j_0(x,t)$ or $A(x,t)$

$$\begin{aligned}\dot{W}_{\text{demon}} &= \dot{H} - \dot{W}_b \\ &= \int_0^l \left(\alpha \frac{\partial \phi}{\partial x} A\right) \frac{\partial \phi}{\partial x} dx - v i_0(t)\end{aligned}$$

Integrating by parts.

$$\begin{aligned}
 \dot{W}_{\text{demon}} &= - \int_0^l \left(\frac{\partial}{\partial x} \left(\alpha \frac{\partial \phi}{\partial x} A \right) \right) \phi \, dx \\
 &\quad + \left(\alpha \frac{\partial \phi}{\partial x} A \right) \phi \Big|_0^l - v i_0(t) \\
 &= \int_0^l \frac{\partial i}{\partial x} \phi \, dx - (i \phi) \Big|_0^l - v i_0(t) \\
 &= \int_0^l \frac{\partial j_0}{\partial t}(x,t) \phi(x,t) \, dx - i_0(t) (\phi(l) - \phi(0)) - v i_0(t) \\
 &= \int_0^l \frac{\partial j_0}{\partial t}(x,t) \phi(x,t) \, dx
 \end{aligned}$$

In summary, the demon doesn't do any work* to adjust $A(x,t)$, but the amount of work he must do to adjust $j_0(x,t)$ depends on ϕ and hence indirectly on $A(x,t)$.

*i.e., any electrical work. There may be other work involved, but it doesn't depend on v .

Shutter model

We now return to the special case pictured on page 13
let the gate extend from x_{g_1} to x_{g_2} where

$$x_{g_2} - x_{g_1} = d \ll l$$

Let the gating change be of the form

$$g_0(x, t) = g_* f_0(t) (\delta(x - x_{g_1}) - \delta(x - x_{g_2}))$$

$$-1 \leq f_0(t) \leq 1$$

Then

$$i_0(t) = \frac{v}{R_0(t)} - \frac{g_* f_0'(t) (R(x_{g_1}, t) - R(x_{g_2}, t))}{R_0(t)}$$

$$W_{\text{demon}} = g_* f_0'(t) (\phi(x_{g_1}, t) - \phi(x_{g_2}, t))$$

Note that $R(x_{g_1}, t) - R(x_{g_2}, t)$ is the resistance of the gate,
which we shall denote R_g :

$$R_g(t) = R(x_{g_1}, t) - R(x_{g_2}, t)$$

Similarly $\phi(x_{g1}, t) - \phi(x_{g2}, t)$ is the voltage drop across the gate which we shall denote v_g

$$v_g = \phi(x_{g1}, t) - \phi(x_{g2}, t)$$

Thus

$$i_0(t) = \frac{v}{R_0(t)} - \frac{g * f_0'(t) R_g(t)}{R_0(t)}$$

$$\dot{W}_{demon} = g * f_0'(t) v_g(t)$$

For an infinitely thin gate which may be OPEN or CLOSED, we have the following results

OPEN: $R_g = 0$, $v_g = 0$, $i_0(t) = \frac{v}{R_0^{OPEN}}$, $\dot{W}_{demon} = 0$

CLOSED: $R_0 = \infty$ but $R_g/R_0 = 1$

$$v_g = v - i_0 R_0^{OPEN}$$

$$i_0(t) = -g * f_0'(t)$$

$$\dot{W}_{demon} = g * f_0'(t) (v + g * f_0'(t) R_0^{OPEN})$$

In the last formula, assume f_0' is small enough that

$$g_* |f_0'(t)| R^{\text{OPEN}} \ll v$$

Then

$$\dot{W}_{\text{demon}} = g_* f_0'(t) v$$

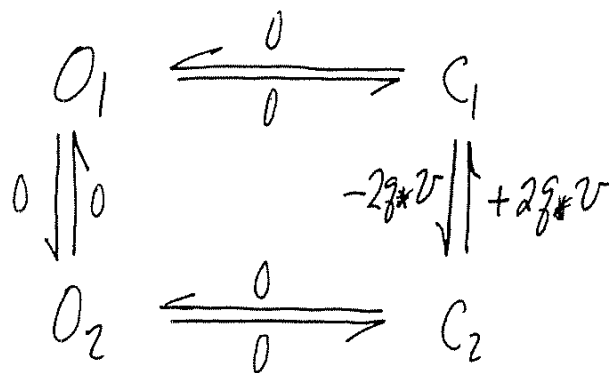
Let the transition from $C_2 \rightarrow C_1$ take place over the time interval $(0, \tau)$.

Then

$$f_0(0) = -1, \quad f_0(\tau) = +1$$

$$W_{C_2 \rightarrow C_1} = g_* v \int_0^\tau f_0'(t) dt = 2g_* v$$

In the pump transition in the loop of channel states, we have found that this is the only one which involves electrical work. (For simplicity, we consider only electrical work in the following.) Thus, we have the following work diagram for the cycle of channel states



— Work required for each transition —

The implications for the rate constants are as follows (see kinetic scheme on p. 15)

$$\alpha_1 = \beta_1$$

$$\mu_0 = \lambda_0$$

$$\alpha_2 = \beta_2$$

$$\frac{\lambda_c}{\mu_c} = \exp\left(-\frac{2z^*v}{kT}\right)$$

We make the following choice (consistent with these equations but not uniquely determined by them):

$$\alpha_1 = \beta_1 = \gamma_1 \quad (\text{independent of } v)$$

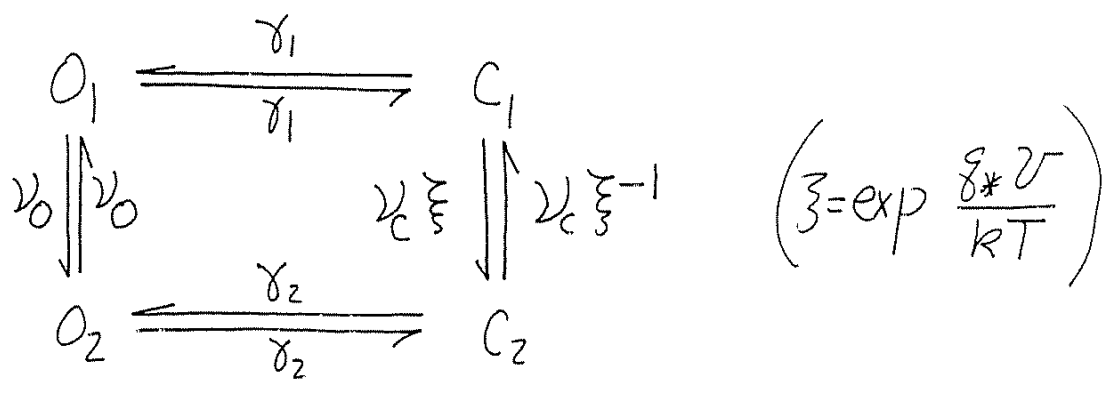
$$\alpha_2 = \beta_2 = \gamma_2 \quad (\text{independent of } v)$$

$$\mu_0 = \lambda_0 = \nu_0 \quad (\text{independent of } v)$$

$$\lambda_c = \nu_c \exp\left(-\frac{z^*v}{kT}\right)$$

$$\mu_c = \nu_c \exp\left(+\frac{z^*v}{kT}\right)$$

Thus, the scheme becomes



Except at $\nu=0$, the thermodynamic constraint on the rate constants is violated. When the system is in a steady state, there is a net flux around the loop: clockwise for $\nu > 0$ ($\xi > 1$) and counterclockwise for $\nu < 0$ ($\xi < 1$). Because of this flux, detailed balance cannot hold, and thermodynamic equilibrium is impossible.

To get some idea of the voltage dependence of this system, consider the two limiting cases $V \rightarrow +\infty$ and $V \rightarrow -\infty$.

At $V = +\infty$, $\bar{z} = +\infty$ and $\bar{z}^{-1} = 0$. Then $[C_1] = 0$, since any channel that enters the state C_1 is immediately converted to the state C_2 . The clockwise flux f in the steady state satisfies the following:

$$f = \gamma_2 ([C_2] - [O_2]) = \nu_0 ([O_2] - [O_1]) = \gamma_1 [O_1]$$

These equations can be used to express $[O_1]$, $[O_2]$, and $[C_2]$ in terms of f :

$$[O_1] = \gamma_1^{-1} f$$

$$[O_2] = [O_1] + \nu_0^{-1} f = (\gamma_1^{-1} + \nu_0^{-1}) f$$

$$[C_2] = [O_2] + \gamma_2^{-1} f = (\gamma_1^{-1} + \nu_0^{-1} + \gamma_2^{-1}) f$$

Hence

$$1 = (3\gamma_1^{-1} + 2\nu_0^{-1} + \gamma_2^{-1}) f$$

It follows that the fraction of open channels (when $V = +\infty$) is given by

$$([O_1] + [O_2])_{V=\infty} = \frac{2\gamma_1^{-1} + \nu_0^{-1}}{3\gamma_1^{-1} + 2\nu_0^{-1} + \gamma_2^{-1}}$$

A similar analysis yields the following result for $V = -\infty$.

$$([O_1] + [O_2])_{V=-\infty} = \frac{2\gamma_2^{-1} + \nu_0^{-1}}{3\gamma_2^{-1} + 2\nu_0^{-1} + \gamma_1^{-1}}$$

in which the roles of γ_1 and γ_2 have merely been interchanged.

To simplify the interpretation of these expressions, let $\nu_0 \rightarrow \infty$. This means that the two open states of the channel are in rapid equilibrium. Then

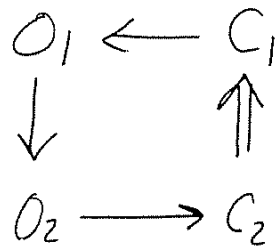
$$([O_1] + [O_2])_{V=+\infty} = \frac{2\gamma_1^{-1}}{3\gamma_1^{-1} + \gamma_2^{-1}} = \frac{2(\gamma_2/\gamma_1)}{3(\gamma_2/\gamma_1) + 1}$$

$$([O_1] + [O_2])_{V=-\infty} = \frac{2\gamma_2^{-1}}{3\gamma_2^{-1} + \gamma_1^{-1}} = \frac{2}{3 + (\gamma_2/\gamma_1)}$$

Thus, the voltage-dependence of the channel depends on the ratio (γ_2/γ_1) . If this ratio is large, nearly 2/3 of the channels are open at large positive voltages whereas very few of the channels are open at large negative voltages.

Homework: the shutter model as a current pump

When a channel of the type we have been considering is forced to go around its cycle of states in the "wrong" direction, it can act as a pump, i.e., it can drive current through the external circuit against the direction set by the battery. Suppose $V > 0$, and consider the cycle



The double arrow from $C_2 \Rightarrow C_1$ indicates that this is the energetically costly step, since it involves the rotation of the dipole against the electric field with the gate closed.

Assume that the gate snaps directly from the open to the closed position and vice versa, so that the transitions $C_1 \rightarrow O_1$ and $O_2 \rightarrow C_2$ are instantaneous. In each cycle, let T^{OPEN} be the time spent with the gate OPEN and let T^{CLOSED} be the time spent with the gate closed. Then

$$T = T^{\text{OPEN}} + T^{\text{CLOSED}}$$

is the period of the cycle.

let the entire time T^{CLOSED} be used for the transition $C_2 \Rightarrow C_1$ with $f_0' = \omega_{\text{constant}} = 2/T^{CLOSED}$ during this time interval.

Similarly, let the entire time T^{OPEN} be used for the transition $O_1 \rightarrow O_2$ with $f_0' = -2/T^{OPEN}$ during this transition.

Use the formulae in the boxes on page 27 to calculate:

i) The mean current through the channel*:

$$\langle i \rangle = \frac{i^{OPEN} T^{OPEN} + i^{CLOSED} T^{CLOSED}}{T^{OPEN} + T^{CLOSED}}$$

ii) The mean power that must be supplied by the demon to sustain the cycle:

$$\langle \dot{W}_{\text{demon}} \rangle = \frac{\dot{W}_{\text{demon}}^{OPEN} T^{OPEN} + \dot{W}_{\text{demon}}^{CLOSED} T^{CLOSED}}{T^{OPEN} + T^{CLOSED}}$$

iii) The efficiency of the channel as a current pump*:

$$E = \frac{-\langle i \rangle v}{\langle \dot{W}_{\text{demon}} \rangle}$$

* Note that the goal of the pump is to produce negative current.

Express the efficiency in terms of the dimensionless parameters β and μ , where

$$\beta = \frac{T^{OPEN}}{T^{CLOSED}}$$

$$\mu = \frac{v T^{CLOSED}}{2g * R_0^{OPEN}}$$

For fixed β , find the value of μ that maximizes the efficiency of the pump. Sketch the graph of E vs μ for several different values of β .