One can solve ①–⑥ in steady state to find

$$J = \frac{k_- k C_e}{2k_+} \frac{S_e - S_i}{(K_m + S_i)(K_m + S_e) - K_d^2}$$

where $K_m = \frac{k_- + k_+}{k_+}$, $K_d = \frac{k}{k_+}$

So this tells us the flux of ions transported across the cell membrane in steady state.

Note the similarity in structure to the Michaelis-Menten flux we derived.

Recall: $\frac{dS}{dt'} = -\frac{\gamma S}{S + K'}$ Michaelis-Menten

($\frac{dS}{dt'} = J$)

Active transport: the sodium-potassium pump

The carrier-mediated transport described above moves molecules down chemical gradients.

To move molecules against a chemical gradient requires energy. This is known as an active transport mechanism. One of the most important active transport mechanisms is the $Na^+ - K^+$ pump. [Sodium ions pumped out of the cell against the electrochemical gradient
Potassium ions pumped in]

Thus, the important distinction here to pay attention to is:

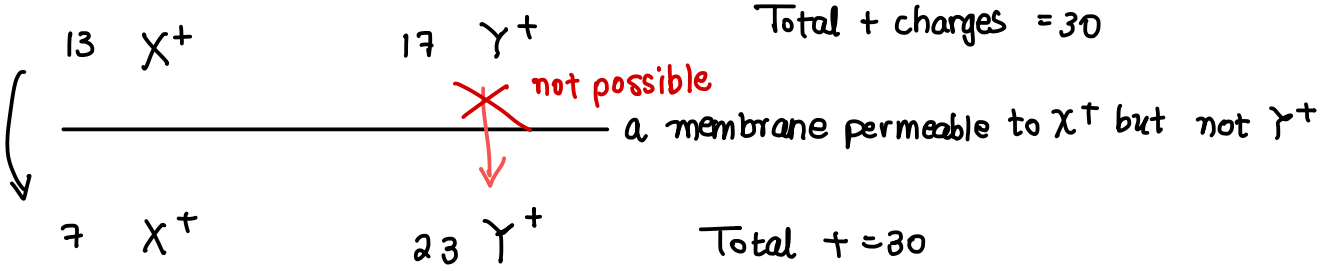
This is like the carrier mediated transport, but now there is a chemical reaction which requires energy. This allows chemicals to move against concentration gradients.

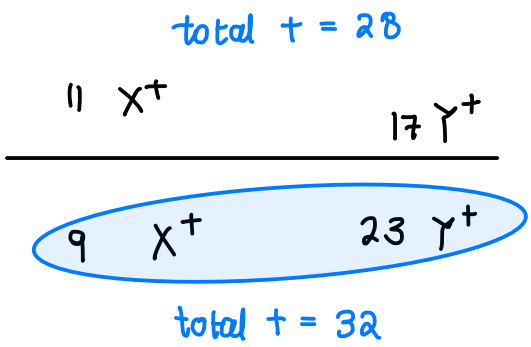
The Nernst potential and the resting potential

The Nernst potential is that obtained when all gates are open and there is a balance between diffusive flux and electric flux. The system is in equilibrium.
high to low concent. ion charges moving

The resting potential is the difference between the potential outside and far from the cell and inside the cell, which may be different to the Nernst potential because gates open and close and ions are moved under different ionic and concentration gradients.

The Nernst potential





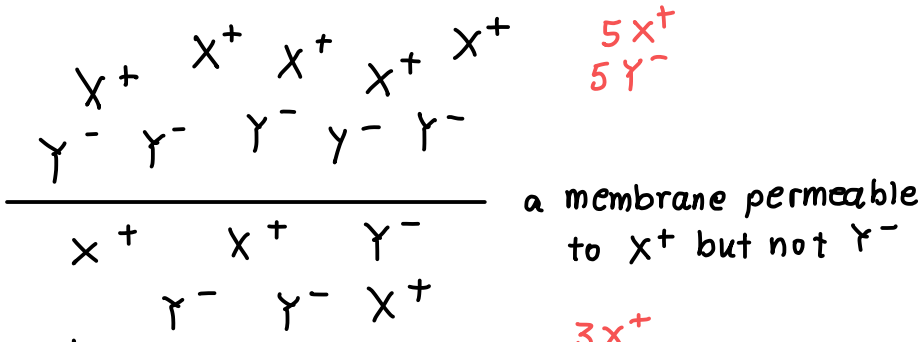
But doesn't reach 10 X^+ on each side because of electrostatic potential pushing back.

↳ charge imbalance sets up an electric field, which produces a force on the ions opposing further diffusion of X^+

Important: the actual amount of X^+ which diffuses through the membrane is small, and the excess charge all accumulates near the interface, so that to a good approx. the solutions on either side remain electrically neutral. The potential difference at which eqm is established and diffusion and electric-field-generated fluxes balance is the Nernst potential.

The membrane potential

Consider the following set-up:



Equal positive and negative charges in each respective side but different amounts on the two sides.

X^+ will diffuse through the membrane to balance the charge of X^+ on both sides.

The balancing will happen in a small region near the membrane (so far from the membrane the liquids will remain electroneutral).

The potential difference that builds up across the cell membrane as a result is called the Nernst potential.

- What is this potential? There will be a flux of ions due to a concentration gradient.

$$\vec{J}_1 = -D\vec{\nabla}c$$

(D: ion diffusivity; c: concentration; regular diffusive flux)

There will be a flux of ions due to a potential difference (the ion carries a charge & is in the presence of an electric field)

$$\vec{J}_2 = -\frac{uzc}{|z|}\vec{\nabla}\phi$$

- u = ion mobility = velocity under a constant electric field
- z = valence of the ion (i.e. valence = charge of ion (e.g. Na^+ has valence +1, O^{2-} has valence -2))
- $\frac{z}{|z|} = \pm 1$ giving ion charge (+ve ions move down potential gradients, -ve ions move up potential gradients)
- ϕ = electric potential $\Rightarrow \nabla\phi$ = electric field

So the total flux is $\vec{J} = \vec{J}_1 + \vec{J}_2 = -D\nabla\vec{c} - \frac{uzc}{|z|}\vec{\nabla}\phi$

or $\boxed{J = -D\frac{\partial c}{\partial x} - \frac{uzc}{|z|}\frac{\partial \phi}{\partial x}}$ (*) assuming set-up is one-dimensional.

Einstein's relation connects the diffusivity with the ion mobility: (look up Einstein relation in diffusion, or, kinetic theory)

$$\boxed{D = \frac{uRT}{|z|F}}$$

R = universal gas constant

T = absolute temperature

F = Faraday's constant. (total electric charge divided by elementary charge carriers)

Note that (*) can be rewritten as $J = -D\left(\frac{\partial c}{\partial x} + \frac{Fzc}{RT}\frac{\partial \phi}{\partial x}\right)$, where x is a coordinate normal to the membrane.

In equilibrium, $J = 0$ (no flux) $\Rightarrow$ $\frac{\partial c}{\partial x} + \frac{zFc}{RT}\frac{\partial \phi}{\partial x} = 0$

We can integrate the flux J in (*) from $x = 0$ (interior) to $x = L$ (exterior of membrane) to get:

$$V \overset{def}{=} \phi_i - \phi_e = \frac{RT}{zF}\log\left(\frac{c_e}{c_i}\right)$$

Nernst potential across cell membrane

e : exterior
i : interior

Ionic currents

The flow of ions across a membrane causes a build up of charge which means the membrane acts as a capacitor.

The voltage across the membrane is $V = \frac{Q}{C}$ (Q: charge difference, C: capacitance)

The current across the membrane is $I = -\frac{dQ}{dt}$

here I is the ionic current out of the cell (i.e. rate of flow of +ve charges outwards)

Combining these gives $C\frac{dV}{dt} + I = 0$ (assuming C = constant)

since $CV = Q$

$\frac{d}{dt}(CV) = \frac{dQ}{dt} \Rightarrow C\frac{dV}{dt} = -I$ if C = const

This eqn is the basis for much theoretical electrophysiology

We link the current of each species of ion S to the voltage via $I_S = g_S(V - V_S)$

V_S: Nernst potential

g_S: ion-specific membrane conductance

$I_S = 0$ when $V = V_S$

The total current is $I = \sum_S I_S$.

→ just $V = IR$ (Ohm's law)

and conductance is $\frac{I}{V} = \frac{1}{R}$

Recall that conductance is a measure of how easily an electric current flows through a material. (It's the reciprocal of resistance)

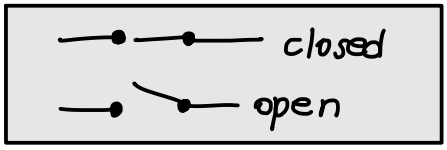
Def protein-lined pores which allow the passage of specific molecules

But what does g_S look like?

This is **not** a constant — it depends on the fraction of gates that are available (i.e that are open) (we know this experimentally) Let's denote the fraction of open channels by n

Then $g_S = n g_{S_{max}}$

↑ conductivity when all gates are open.



depend on the voltage

closed gate $\underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}}$ open gate

Law of mass action gives $\frac{dn}{dt} = \alpha(V)(1-n) - \beta(V)n$

n: fraction of open gates; $(1-n)$: fraction of closed gates

OR $\frac{dn}{dt} = \alpha(V) - n(\alpha(V)+\beta(V))$

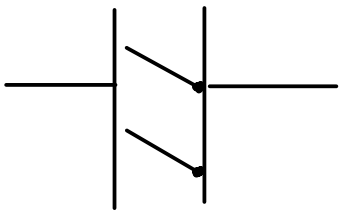
$\Rightarrow \frac{1}{\alpha(V)+\beta(V)} \frac{dn}{dt} = \frac{\alpha(V)}{\alpha(V)+\beta(V)} - n$

$\Rightarrow$ $\boxed{\tau(V)\frac{dn}{dt} = n_\infty - n}$ where $n_\infty = \frac{\alpha}{\alpha+\beta}$ (eqm value of n) and $\tau(V) = \frac{1}{\alpha+\beta}$

We note that both n_∞ and τ are determined experimentally.

$\tau(V)$: timescale for approach of the equilibrium n_∞

You can also have **multiple gates**. Let S_i = density of states with i open gates. Then the transition between gate states is governed by the reaction:



$S_0 \underset{\beta}{\overset{2\alpha}{\rightleftharpoons}} S_1 \underset{2\beta}{\overset{\alpha}{\rightleftharpoons}} S_2$

number of closed gates

the factor of 2 is because there are two configurations for going from 2 open to 1 open gate and similarly for closed to open

Law of mass action gives

$$\frac{dS_0}{dt} = -2\alpha S_0 + \beta S_1$$

$$\frac{dS_2}{dt} = \alpha S_1 - 2\beta S_2$$

We could also write down an equation for S_1 but this equation is superfluous, since we can just infer it from $S_0 + S_1 + S_2 = 1$ (conservation of gates)

We can reduce to one ODE by finding that the solution is

$$S_0 = (1-n)^2, \quad S_1 = 2n(1-n), \quad S_2 = n^2$$ (we can see this by simple substitution)

where n satisfies $\frac{dn}{dt} = \alpha(1-n) - \beta n$ (i.e. the one-gate equation).

[See problem sheet 2, question 1]

In this case, the proportion of open channels is $S_2 = n^2$ so the conductivity in this case is $n^2 g_{s_{max}}$.

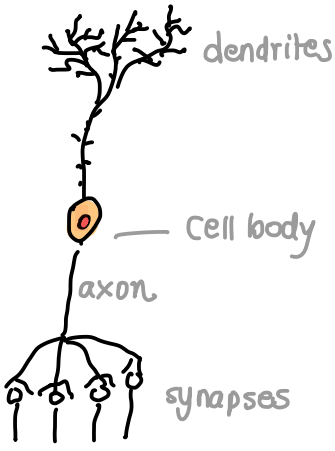
This result generalizes for N gates with a conductivity of $n^N g_{s_{max}}$

You can also look at the case of non-identical gates – see lecture notes on pg 34.

The Hodgkin-Huxley model

The nervous system is a communication system formed by nerve cells or neurons. Information is propagated along long cylindrical segments called axons by electrochemical signals.

Communication between cells occurs at junctions between synapses to the dendrites.



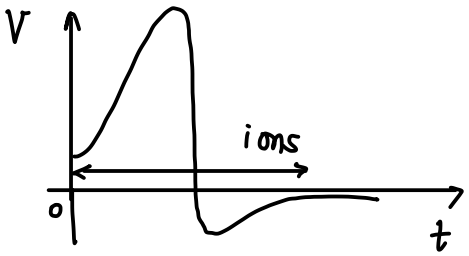
EXCITABILITY OF NEURONS

If a small current is applied for a short time then the membrane potential just returns to its resting potential when the current is removed.

But for a sufficiently high current, the membrane potential undergoes a large excursion — an action potential —

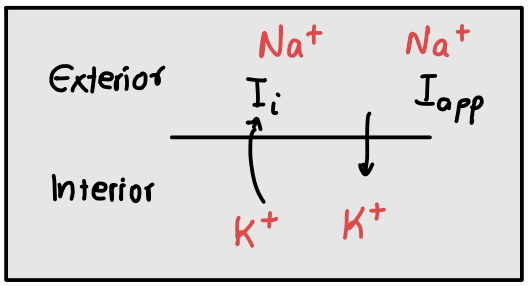
before returning to its resting volve.

Signals are transmitted by the propagation of these action potentials. Later on we will look at this spatial propagation down an axon, but for now we will look at a spatially independent model.



This propagates down the axon like a wave.

This can be achieved in practice by inserting an electrode along the axon to spread the current out. This is called the space clamp technique.



(external inward current)

Apply a current I_{app} to the axon and observe the ionic current that comes out, I_i (outward ionic current)

i.e.
How does I_i respond to I_{app}?
How much energy do we need for this Na^+-K^+ pump?

Our earlier equation $C\frac{dV}{dt} + I = 0$ ①

$$\Rightarrow C_m \frac{dV}{dt} + (I_i - I_{app}) = 0$$

C_m: capacitance of the membrane

$(I_i - I_{app})$: total outward current

Now we'll figure out the eqns that are satisfied by Na & K using the eqns for the gates from before

Potassium flow

Recall we have our link between V (applied voltage) and I_i (resulting current): $I_i = g_s(V - V_s)$ and $g_s = n^N g_{s_{max}}$ (conductivity)

where N = number of gates and $\tau(V)\frac{dn}{dt} = n_\infty(V) - n$ ② ← true regardless of what the N is

What we find is that the potassium conductance may be controlled by this model when $N = 4$

Note, however that this is not due to four gates but just as experimental fit. (the underlying physics is behaving like a 4-gate system but it's a bit more complicated than that)

$g_s = n^4 g_K$, $g_K = g_{s_{max}}$

n is called the potassium activation.

Sodium flow

For the sodium conductance there is a protein that turns the sodium current on and another which turns it off. This can be described by

$$g_s = g_{Na} m^3 h^1$$

again these powers are an experimental fit rather than related to gates

g_{Na} ~ $g_{s_{max}}$

$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m \quad (3)$$

$$\tau_h(V)\frac{dh}{dt} = h_\infty(V) - h \quad (4)$$

is an appropriate model. This is like two gates:

m is called the sodium activation

h is called the sodium inactivation.

The Hodgkin-Huxley model for the outward ionic current is then

resting potentials

$$I_i = g_{Na} m^3 h (V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L) \quad (5)$$

Na^+ current (sodium) | K^+ current (potassium) | leakage (mainly Cl^- chloride ions)

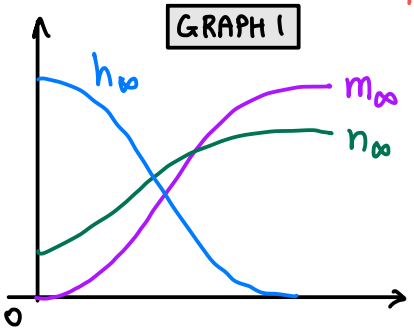
other ions flying around that contribute to the current

(This model also comprises the ODE system (1)–(4)). The closed system is (1)-(5).

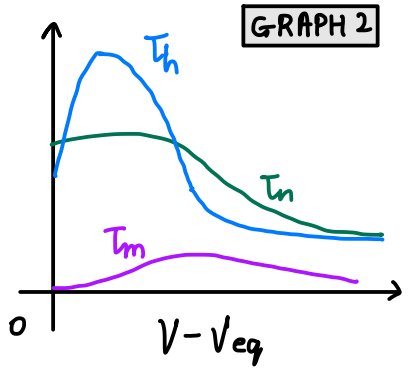
NB. The resting potential is the value of V when the outward ionic current is zero.

What does the potential do?

These values are experimentally measured



Eqm gate variables as fcns of potential relative to resting potential



Relaxation times as fcns of potential relative to resting potential

STEPS

(1) Apply a current I_{app}

(2) V rises due to the current (eqn ①) $C_m \frac{dV}{dt} + (I_i - I_{app}) = 0 \Rightarrow \uparrow C_m \frac{dV}{dt} = I_{app} - I_i \uparrow$

(3) τ_m is small (graph 2) so m rises quickly (eqn ③) $\frac{dm}{dt} = \left(\frac{m_\infty - m}{\tau_m \downarrow}\right) \uparrow$

$\Rightarrow Na^+$ floods into the axon from outside (since $g_s = m^3 h g_{Na}$) m increasing means more gates open for Na

Sodium activation

(4) This causes even more of a potential difference, causing m_∞ to rise (graph 1), which causes even more of a potential difference (from step (3) above) $\frac{dm}{dt} = \left(\frac{m_\infty \uparrow - m}{\tau_m}\right) \uparrow$

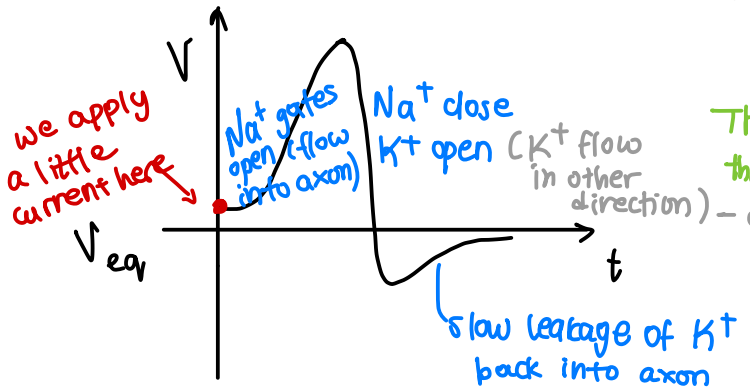
(5) h_∞ falls causing Na^+ flow to slow as g_{Na} falls (gate closes) activation gates ↑ deactivation gates ↓

n_∞ rises (graph 1) causing K^+ to flow out of the axon (g_{K^+} rises - gate opens) $g_s = n g_{Na}$

This causes an overshoot past V_{eq} (because $V_K < V_{eq}$)

Resting potential for K^+

(6) A slow leakage of K^+ back into the axon causes the system to go back to equilibrium (this recovers from the overshoot)



This is an action potential, obtained by solving the Hodgkin-Huxley model. (visualisation)

NB The I_{app} doesn't give a relaxation to V_{eq} immediately, but first an excitation that we are interested in.

The membrane is excitable. The equilibrium is a steady state but a large enough perturbation (which in practice isn't too large) that causes the potential to undergo an excursion – the action potential.

Note If we spatial independence:
We'll basically have a traveling wave of this action potential from the axon to the muscles that tells the muscles to do something

At the moment this is a four-dimensional system (V, n, m, h described by eqns ①–④)
This is not easy to analyse but we can reduce this to a two-dimensional system called the FitzHugh-Nagumo model.