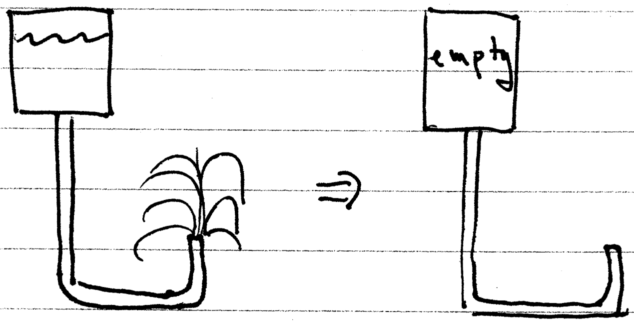
Topic 13 Phys 347 Nov. 20

Ion Channels ~~& Nerve~~ impulses:

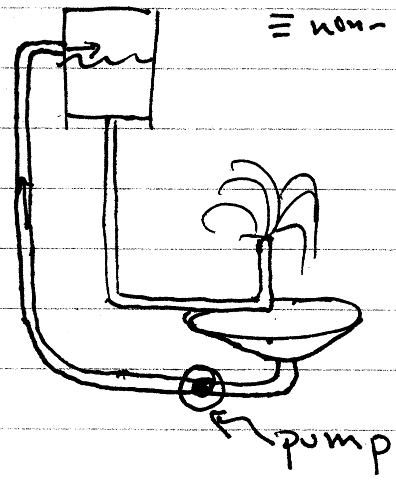
- How do cells generate electricity?
- How do they use electrical signals to send information? (next week's class)
- How do cells balance osmotic pressure and the flow of ionic currents?
- Big picture: The cell is a non-equilibrium system — it is driven. Equilibrium ≡ no change ≡ death.

Analogy:



fountain comes to equilibrium

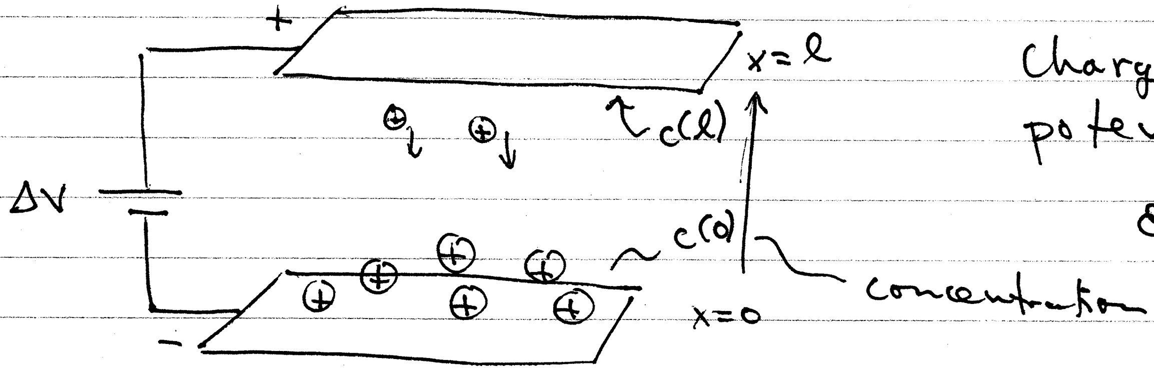
fountain + pump ≡ non-equilibrium



- Cells are constantly using energy to drive pumps and thereby keeping themselves out of equilibrium.

Concentrations Differences ⇒ Voltages

Consider the distribution of charge in the presence of a voltage (battery)



Charge has a potential energy

$$\mathcal{E} = q \cdot V(x)$$

- Energy difference between charges at the top and bottom electrodes is:

$$\Delta\mathcal{E} = \mathcal{E}(\ell) - \mathcal{E}(0) = q\big(V(\ell) - V(0)\big) = q\Delta V$$

- From Boltzmann: $c(\ell) = c(0)\, e^{-\Delta\mathcal{E}/k_BT} = c(0)\, e^{-q\Delta V/k_BT}$

or

$$\boxed{\ln\left(\frac{c(\ell)}{c(0)}\right) = -\frac{q\Delta V}{k_BT}}$$

Nernst relation

- So in the presence of an applied voltage charges will redistribute, with more +ve charge near the −ve electrode.

- Thus to maintain a concentration difference and fight off the flow from diffusion, there must be an applied voltage.

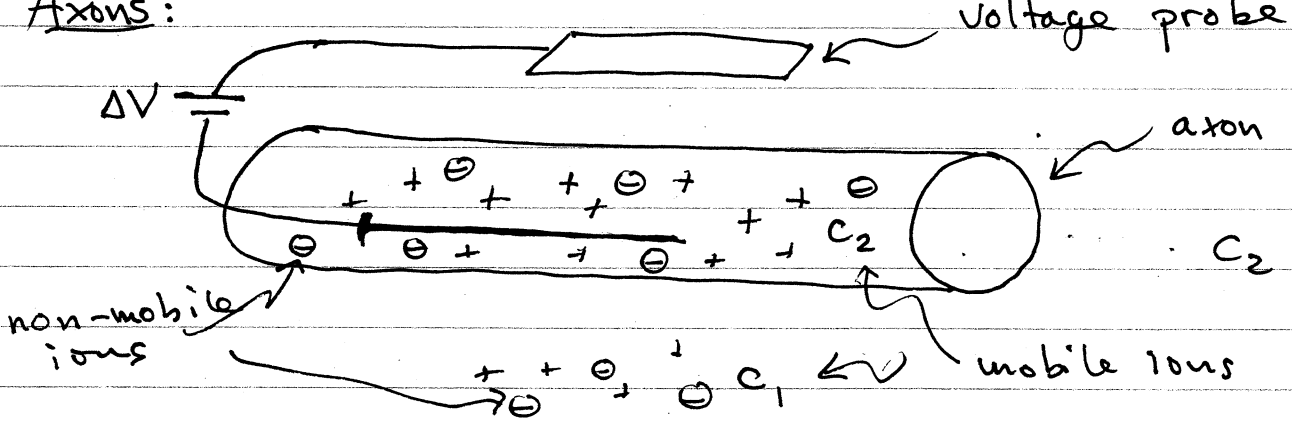
- Cells maintain voltage drops across their membranes in order to sustain concentration differences between the inside and outside of cells.

e.g. for Na^+, $\frac{c(0)}{c(\ell)} = 10$ (10 x more Na inside than outside)

so $$\Delta V = -\frac{k_B T}{e} \ln\left(\frac{1}{10}\right) = 58 \text{ m Volt}$$

- This is the voltage that a cell's membrane would need to generate in order to maintain this concentration difference in Na^+.

Axons:



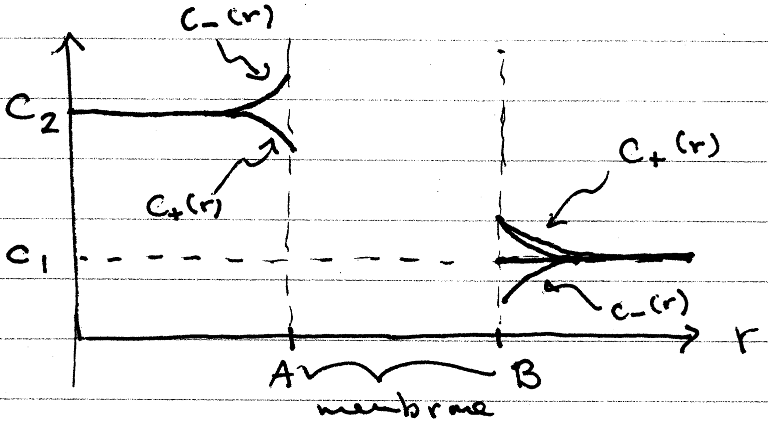
(History: "giant" axon from squid has a diameter of 1mm. Most human axons have diameters ~ 5-20 μm).

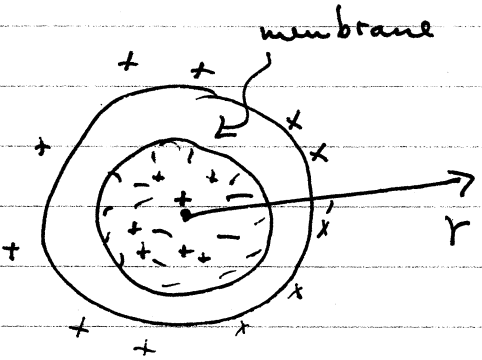
- The ⊕ ions are mobile/permeant. The ⊖ ions can <u>not</u> cross the membrane.

- How will the charge distribute?

- The $\oplus$ ions would like to diffuse away from the cell in order to make $c_2 = c_1$. <u>But</u>, doing so pulls them away from the $\ominus$ ions and this <u>costs</u> energy. So they compromise.

- The result is:





- <u>Explanation</u>:

i) Some of the +ve ions will flow out to try and make $c_1 = c_2$

ii) this makes the cell ~~opp~~ have a net −ve charge ∴ there will be an increase in c_+ just outside the cell (point B). And a correspondin decrease in c_-

iii) Inside the cell, the $\ominus$ ve ions will be attracted to the membrane since the outer world has a net +ve charge. Correspondingly the +ve ions will be repelled.

iv) At large distances $c_+ = c_-$. Deep within the cell $c_+ = c_-$

v) The differences in c_+ & c_- lead to a ΔV!

- From Nernst, the +ve ions at <u>equilibrium</u> will move so that

$$\Delta V_{Nernst} = -\frac{k_B T}{e} \ln \frac{c_2}{c_1}$$

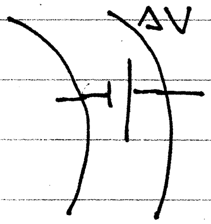
- <u>Note</u>: the −ve ions cannot cross the membrane, and are therefore <u>NOT</u> in equilibrium.

<u>Reality</u>:

- Cells have more than just two species of ions. They also contain charged proteins. How do we balance all these charges?

- Let's consider 3 ions: Na^+, K^+ & Cl^-

$c_{Na^+,2}$
$c_{K^+,2}$
$c_{Cl^-,2}$



$$\left.\begin{aligned} c_{Na^+,1} &= 140\,mM \\ c_{K^+,1} &= 10\,mM \\ c_{Cl^-,1} &= 150\,mM \end{aligned}\right\} \Rightarrow c_{Na^+,1} + c_{K^+,1} - c_{Cl^-,1} = 0$$

$\rho_{protein} \leftarrow$ $= 125\,mM$ (−ve charge) $\Rightarrow c_{Na^+,2} + c_{K^+,2} - c_{Cl^-,2} - \rho_{prot} = 0$

- The inside concentrations & ΔV get set by equilibrium.

Nernst gives $\Delta V = -\frac{k_B T}{e} \ln \frac{c_{Na^+,2}}{c_{Na^+,1}} = -\frac{kT}{e} \ln \frac{c_{K^+,2}}{c_{K^+,1}} = \frac{kT}{e} \frac{c_{Cl^-,}}{c_{Cl^-,}}$

or

$$\frac{c_{Na^+,2}}{c_{Na^+,1}} = \frac{c_{K^+,2}}{c_{K^+,1}} = \frac{c_{Cl^-,1}}{c_{Cl^-,2}}.$$

- Solving these equations gives,

$$c_{2,Na^+} = 210\,mM \; ; \; c_{K^+,2} = 15\,mM \; ; \; c_{Cl^-,2} = 100\,mM$$

$$\Rightarrow \quad \Delta V = -10\,mV$$

- Thus these 3 species come to equilibrium and generate a potential difference ΔV across the membrane. Cells can maintain this voltage without using any energy – it's a minimum free energy state.

- Q: Do these equilibrium concentration differences and ΔV match what is seen experimentally?

Ion ~~pumping~~:

What about the osmotic pressure due to the ion concentration differences? (There's more Na^+ inside)

$$\Delta c_{tot} = c_{2,tot} - c_{1,tot} = 25\,mM$$

(more ions inside cell than out ← flow of water in)

$$P = \Delta c\, k_B T = 6 \times 10^4\, Pa$$

⇒ such pressure would cause the cell to burst!

- How to resolve this pressure problem? (pump out ions)

Equilibrium predicts: $c_{Na^+,2} > c_{Na^+,1}$; $c_{K^+,2} > c_{K^+,1}$; $c_{Cl,2} < c_{Cl,1}$
and $\Delta V < 0$

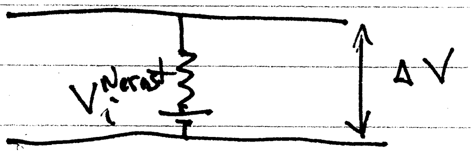
Reality from squid axon.

	c_2 (mM)	c_1 (mM)	ΔV^{Nernst} (mV)	
K^+	400	20	−75	
Na^+	50	440	+54	⇐ way off!!!
Cl^-	52	560	−59	

- Na^+ does not obey the equilibrium conditions. This is known as the <u>sodium anomaly</u>.
- This massive Na^+ difference between in & out balances the osmotic pressure. (There are other ionic species which balance the differences above).
- So the cell is <u>NOT</u> in equilibrium. It burns <u>energy</u> to <u>pump</u> Na^+ out of the cell.

Ionic Current:

- Recall Ohm's Law: $I = \frac{\Delta V}{R}$ or $I = G \cdot \Delta V$ ← conductance
- Flow on ions:



- if $\Delta V = V_{nernt} \rightarrow$ no flow
- Net drop is $(\Delta V - V^i_{nernst})$ for ion species i

so for ionic species i, the current flux is

$$\boxed{j_i = \frac{I_i}{\underset{\underset{\text{area}}{\uparrow}}{A}} = g_i\left(\Delta V - V_i^{Nernst}\right)}$$

where $g_i \equiv$ membrane conductance of species, i.
($i = Na^+, Cl^-, K^+$ etc)

Expt: $g_{K^+} \approx 25\, g_{Na^+} \approx 2 g_{Cl^-}$

so Na^+ has the least conductance

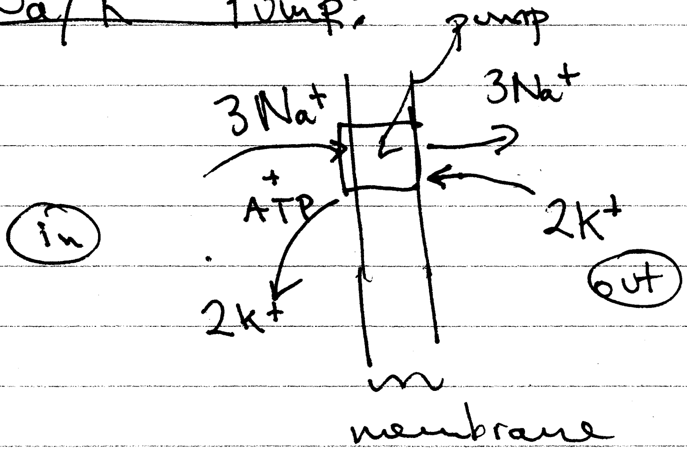
Expt: with $\Delta V = 0$ & $c_1 = c_2 \rightarrow V^{Nernst} = 0$, still find that there is a flow of ions = pumping

so

$$j_i = g_i\left(\Delta V - V_i^{Nernst}\right) + j_i^{pump}$$

- Na^+ is actively pumped out, and K^+ is actively pumped in.

- Na/K$^+$ Pump:



- Net flow of +1 charge out of cell.
- 3 Na^+ get transported out for every 2 K^+

With the pumps, what is the resting potential of the non-equilibrium cell?

- Despite, being in non-equilibrium the cell is in a steady-state i.e. ΔV and the concentrations do not change with time.

Steady state: the fluxs of each ion must be zero

So $$\dot{j}_{Na^+} = 0 = g_{Na^+}(\Delta V - V^{Nernst}_{Na^+}) + \dot{j}^{pump}_{Na^+}$$

and $$\dot{j}_{K^+} = 0 = g_{K^+}(\Delta V - V^{Nernst}_{K^+}) + \dot{j}^{pump}_{K^+}$$

or $$\dot{j}^{pump}_{Na^+} = -g_{Na^+}(\Delta V - V^{Nernst}_{Na^+})$$

and $$\dot{j}^{pump}_{K^+} = -g_{K^+}(\Delta V - V^{Nernst}_{K^+})$$

but expt gives $\dot{j}_{K^+} = -\frac{2}{3}\dot{j}_{Na^+}$ ($3\,Na^+$ out for every $2K^+$ in)

Combining gives: $$-\frac{2}{3}(\Delta V - V^{Nernst}_{Na^+})\,g_{Na^+} = (\Delta V - V^{Nernst}_{K^+})\,g_{K^+}$$

Solve for rest potential ΔV:

~~$\Delta V = (2 g_{Na^+} + V^{Nernst}_{Na^+}$ $3g$~~

$$\Delta V = \frac{2 g_{Na^+} V^{Nernst}_{Na^+} + 3 g_{K^+} V^{Nernst}_{K^+}}{2 g_{Na^+} + 3 g_{K^+}}$$

For the squid axon: $V_{Na^+}^{Nernst} = 54\,mV$; $V_{K^+}^{Nernst} = -75\,mV$

$$g_{K^+} \approx 25\, g_{Na^+}$$

So

$$\Delta V = -72\,mV$$

This compares favourably with the exptly measured value of $\Delta V = -60\,mV$. (The difference lies in effects which are outside the scope of this course).

- Conclusion: the resting membrane potential ΔV is closest to ~~the [illegible] species' Nernst potential~~ Nernst potential of the most conductive ion.

- Since K^+ is the most conductive (biggest g), the $\Delta V = -72\,mV$ is closest to it's Nernst potential $V_{K^+}^{Nernst} = -75\,mV$.

- Note: if we could make the Na^+ conductivity much greater than K^+, then ΔV would move towards $V_{Na^+}^{Nernst} = +54\,mV$. This would be a big change in voltage ≡ voltage pulse

This pump switch leads to voltage pulses ≡ nervous system signalling

≡ nerve impulses! (Next week).