Topic 11: Membrane potentials & ion channels
(chapter 17)

Outline:

- How do cells generate electricity?
- How do they use electrical signals to transmit information?
- How do cells balance osmotic pressure and the charge imbalance?
- We will again see how the cell must be kept out of equilibrium in order to solve the above problems and generate function.

Neuron Structure

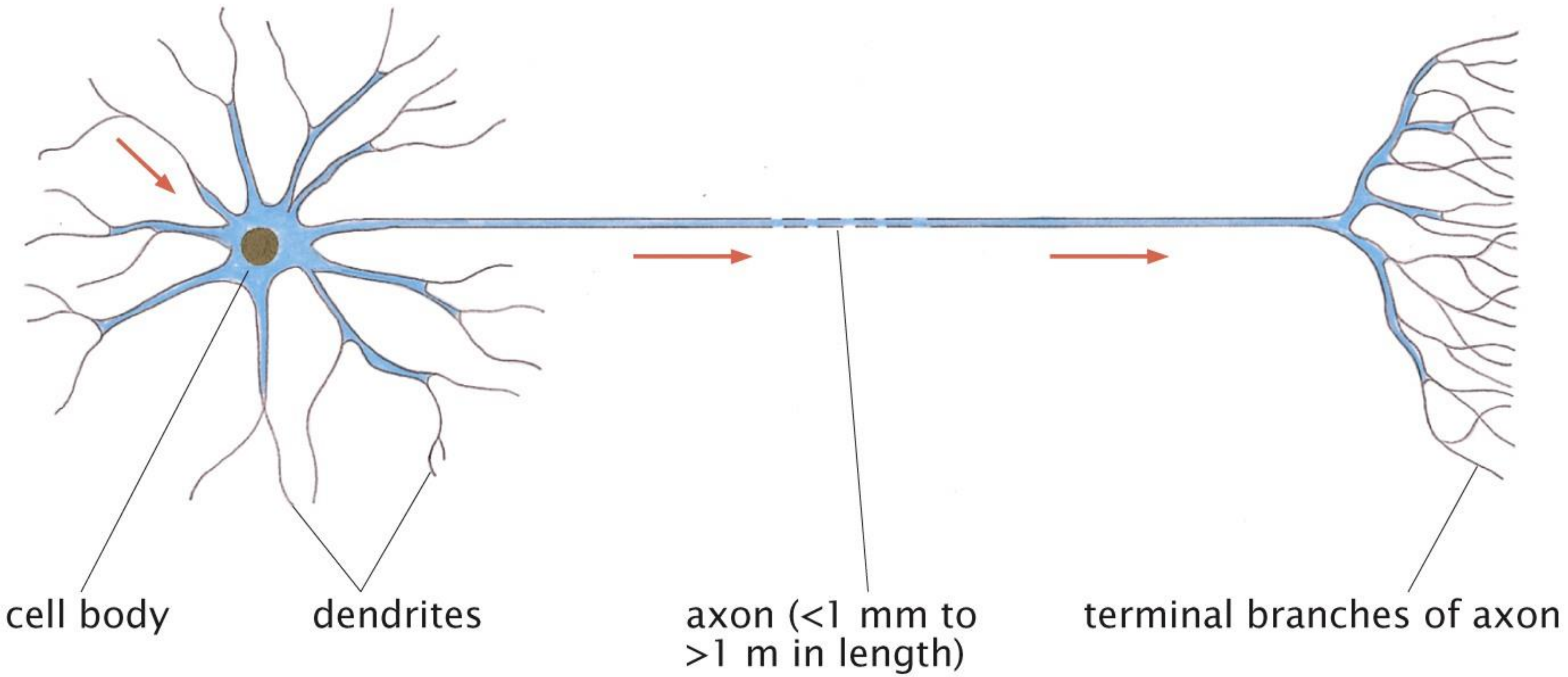


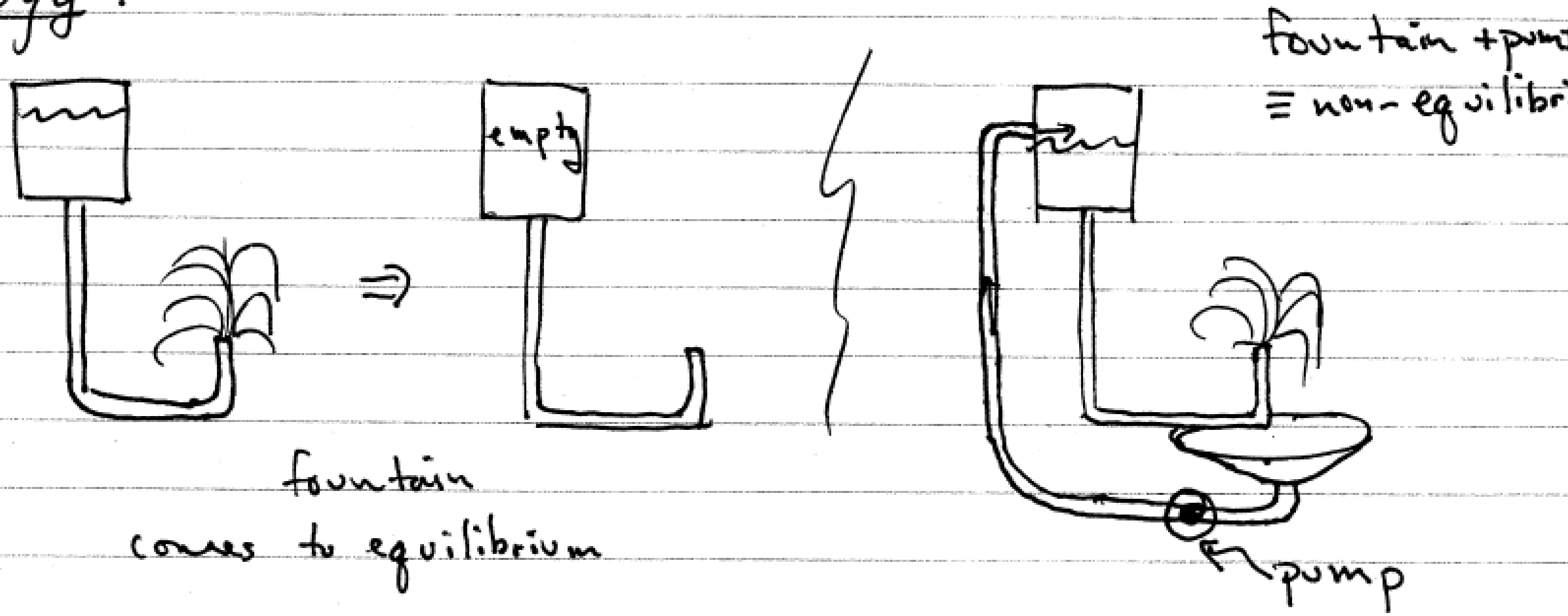
Figure 17.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Ions move across the membrane, generating a current.

This changes the potential across the membrane.

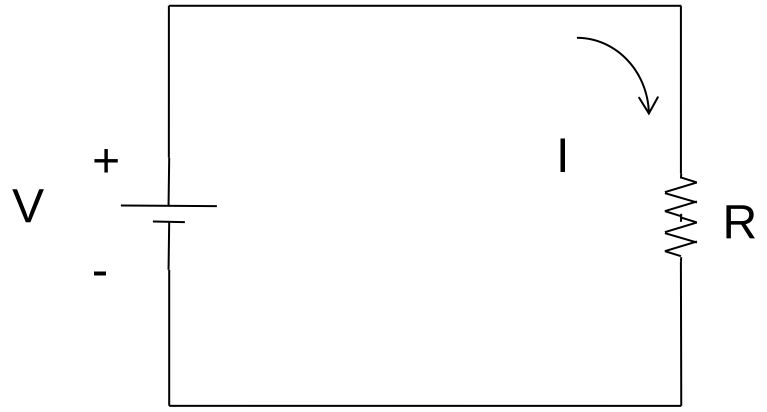
If conditions are right, charge flows and the potential change propagates down axon

Analogy:



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

Review of circuit theory



Current, I, here represents the flow of +ve current around the circuit

Ohm's law:

$$V = I R$$

or

$$I = g V$$

where g = conductance = 1/R

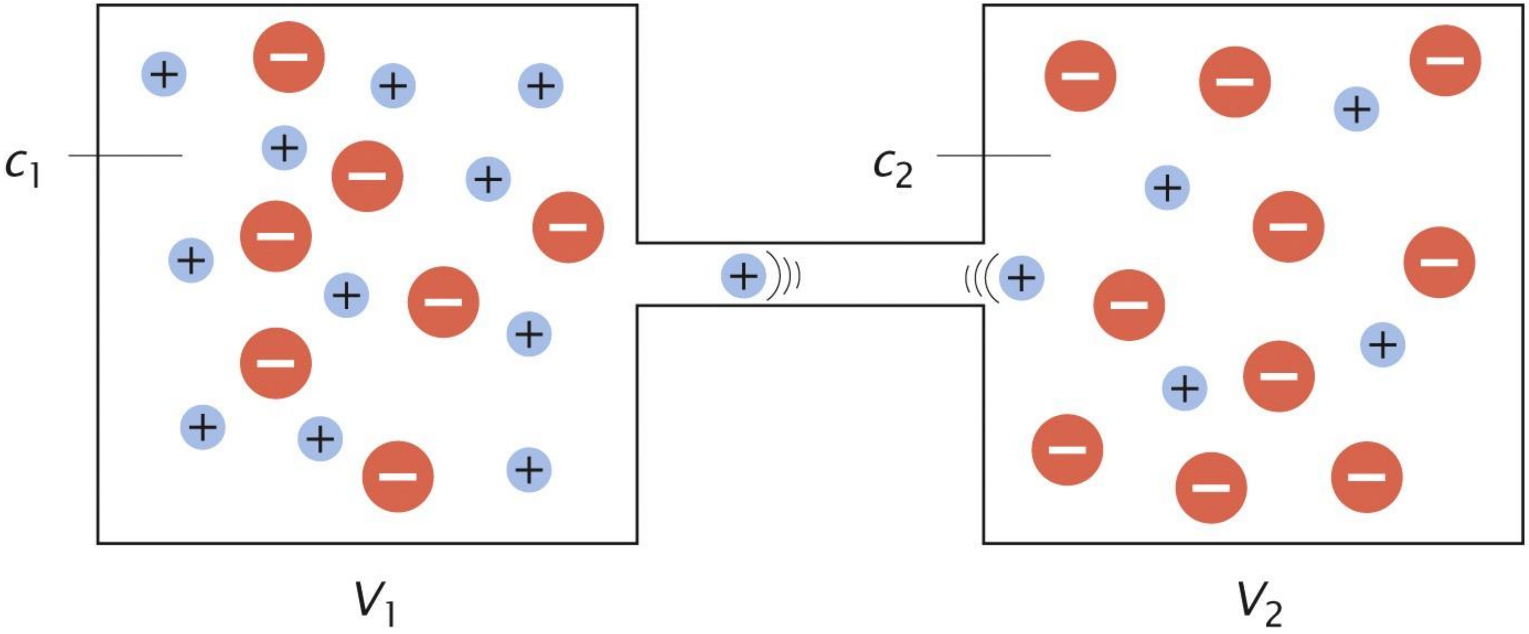


Figure 17.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

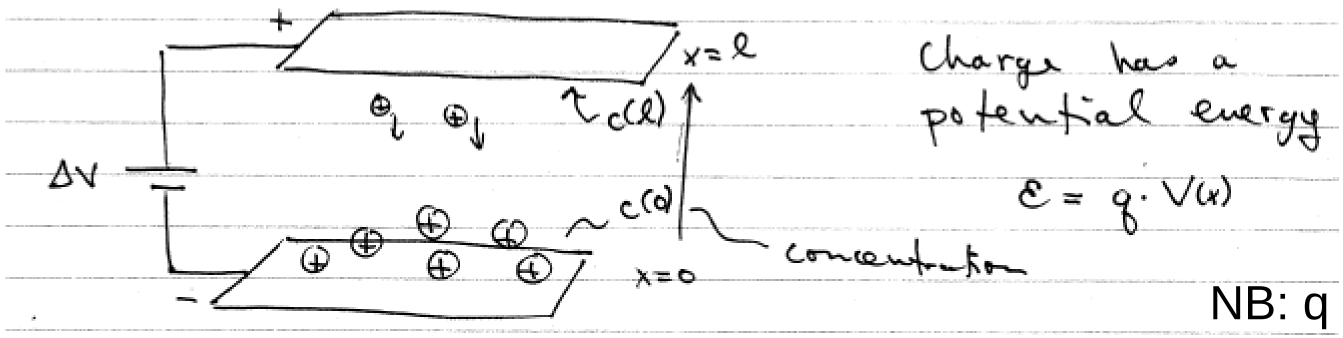
Imagine the situation where there is a charge imbalance between the inside and outside of the cell

Ions will want to move (if they can) across the membrane to make the concentrations uniform

BUT, they have charge, so can we apply a voltage that will counteract this diffusion?

Nernst Relation

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



NB: q has sign, here it is positive

The energy difference between charges on the top and bottom plate is:

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

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

or

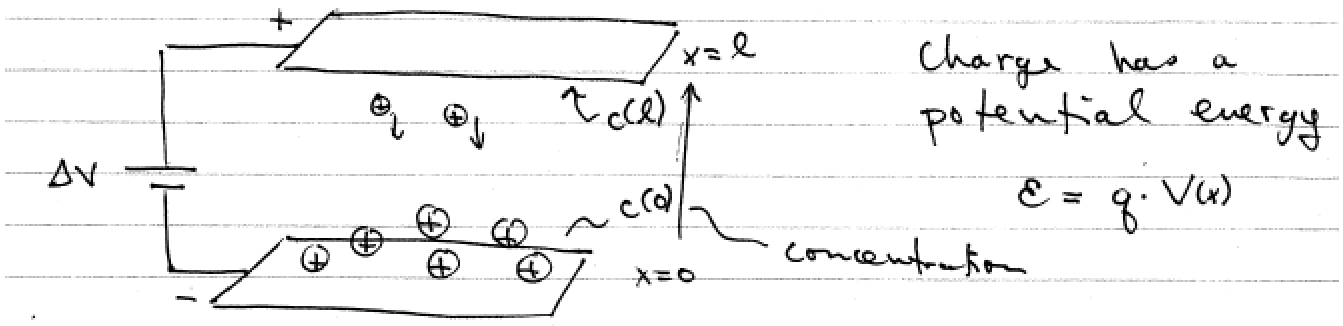
$$\ln\left(\frac{c(l)}{c(0)}\right) = -\frac{q\Delta V}{k_B T}$$

Nernst relation

So in the presence of an applied voltage charges will redistribute in this way

OR, if there is a difference in charge distribution, there will be a voltage

Nernst Relation: Rules of thumb



or

$$\ln\left(\frac{c(l)}{c(0)}\right) = -\frac{q\,\Delta V}{k_B T}$$

Nernst relation

If q is +ve, and let’s take c(l) as concentration inside cell and c(0) as concentration outside the cell then,

1) if c(in) < c(out) → dV > 0, i.e. voltage is greater than 0

2) if c(in) > c(out) → dV < 0, i.e voltage difference is < 0

For –ve ions these above relationships switch sign.

Membrane voltages:

Let’s look at Na+ ions in a typical neuron. There is 10x more Na outside (c(0)) than inside the cell (c(l)) . So c(0)/c(l) = 10

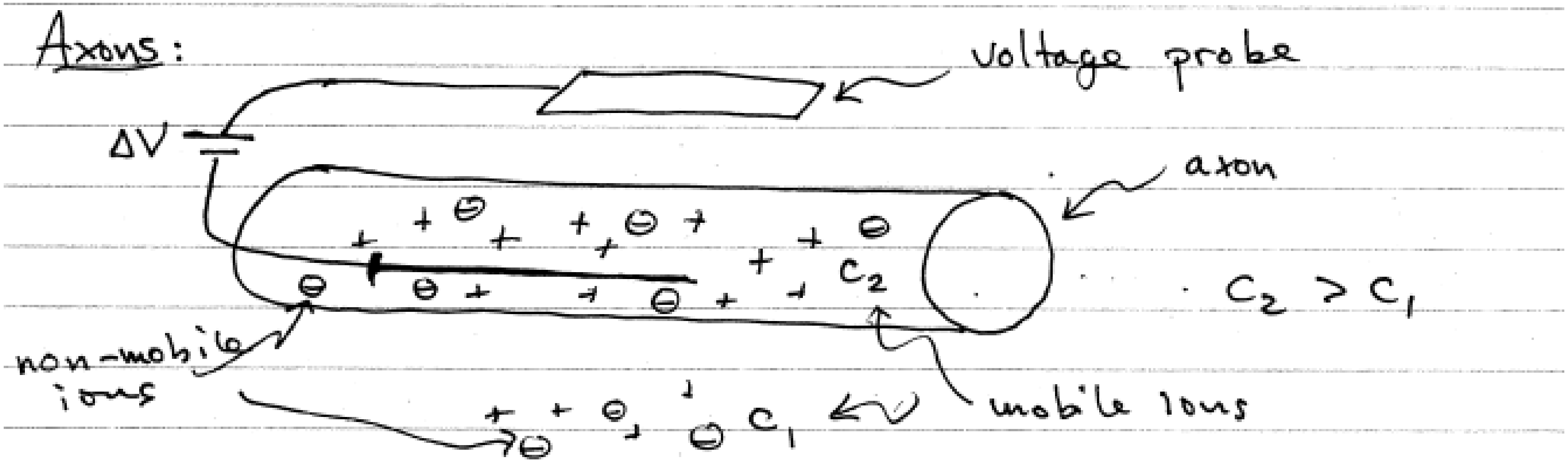
Diffusion would like to generate a current of Na from inside the cell to the outside to overcome this difference

From the Nernst equation, if the membrane can be at a potential

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

then this potential will counteract the diffusive current and maintain the charge imbalance across the membrane

Membrane voltages: mobile and immobile ions



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

Using probes, one can measure the voltage difference between the inside and outside of an axon

Also find that +ve ions are mobile across the membrane, but –ve ions tend not to be.

What happens when you have a population of mobile and immobile charges?

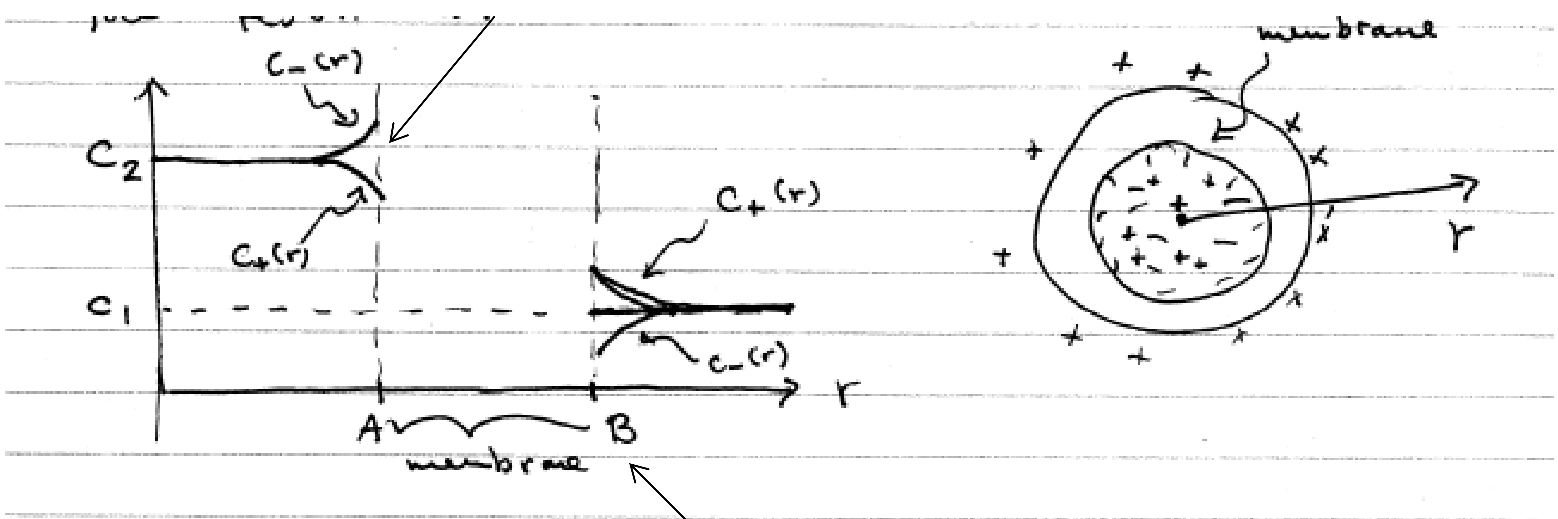
A potential gets generated

The +ve ions would like to diffuse away from the cell in order to make c1 = c2

BUT, doing so pulls them away from the –ve ions and this costs electrostatic energy

So an equilibrium is set up

net -ve



net +ve

Setting the potential:

Some of the +ve ions will flow out

So the cell has net –ve charge → cloud of +ve charge outside the cell

The –ve charges inside will be attracted to the inner membrane due to the +ve charge outside

This is like a parallel plate capacitor with +/- q on the surfaces

This sets up a voltage difference across the membrane

And the voltage is given by Nernst,

- From Nernst, the +ve ions at equilibrium will move so that

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

- Note: the –ve ions cannot cross the membrane, and are therefore NOT in equilibrium.

Cells have more than 2 species of ions, they also contain charged proteins

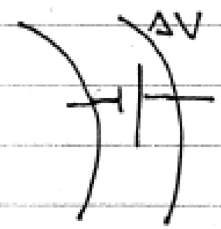
How do all these charges come to equilibrium? and what is the voltage?

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

$c_{Na^+,2}$

$c_{K^+,2}$

$c_{Cl^-,2}$



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

$\rho_{protein} = 125\,mM$ (−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 $\Delta V = -\frac{k_B T}{e} \ln \frac{c_{Na^+,2}}{c_{Na^+,1}} = -\frac{k_B T}{e} \ln \frac{c_{K^+,2}}{c_{K^+,1}} = \frac{k_B T}{e} \ln \frac{c_{Cl^-,2}}{c_{Cl^-,1}}$

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

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

$$\Rightarrow \quad \Delta V = -10\,\text{mV}$$

Thus these 3 species come to equilibrium and generate a potential difference across the membrane

Cells can maintain this voltage without using any energy – it’s a minimum in energy

Q: What about the osmotic pressure?

Q: Do these equilibrium concentration differences and membrane potential match what is seen experimentally?

Osmotic pressure due to charge imbalance:

The total concentration difference between inside and out is:

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

So there are more ions inside the cell than out → osmotic pressure

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

Such a pressure would cause the cell to burst!

Q: How to resolve this pressure problem?

A: Pump ions out of the cell, in particular Na ions

Charges not in equilibrium:

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	

Table 17.1: Ion concentrations and the Nernst potential for small ions within the cell. The numbers are typical of mammalian skeletal muscle cells, which have a resting potential of $V_{mem} = -90$ mV. (Data adapted from B. Hille, Ion Channels of Excitable Membranes. Sinauer Associates, 2001.)

Ion species	Intracellular concentration (mM)	Extracellular concentration (mM)	Nernst potential (mV)
K^+	155	4	−98
Na^+	12	145	67
Ca^{2+}	10^{-4}	1.5	130
Cl^-	4	120	−90

So Na+ is way out of equilibrium → known as the sodium anomaly

Charge out of equilibrium: ion pumps

The massive Na+ difference between in & out balances the osmotic pressure (along with other ionic species too – like calcium ions)

So the cell is not in equilibrium

It burns energy to pump Na+ out of the cell

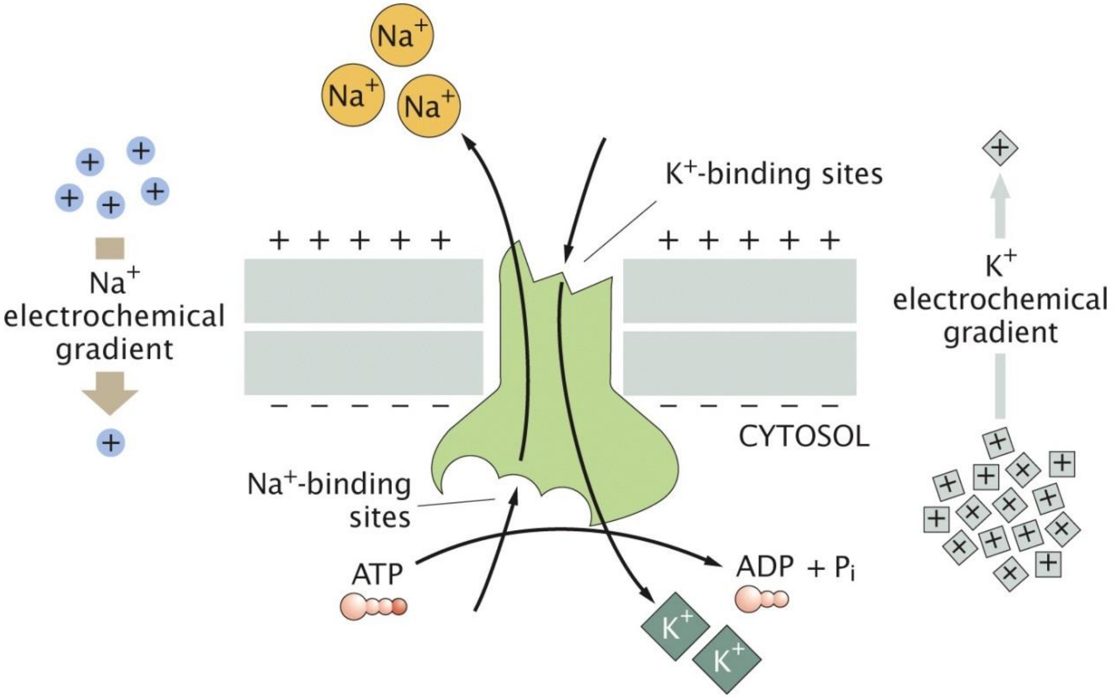
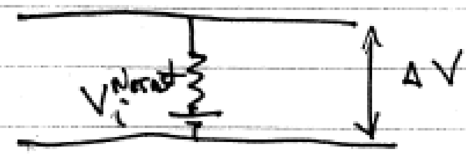


Figure 17.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Ionic current:

- Recall Ohm's Law: $I = \dfrac{\Delta V}{R}$ or $I = G \cdot \Delta V$ (← G: conductance)

- Flow on ions:



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

so for ionic species i, the current flux is

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

(A ← area)

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

Membrane conductance:

The membrane conducts the +ve charged ions differently

<u>Experimentally</u> it's found that $g(K+) \sim 25\, g(Na+)$

So Na+ is the least conductive ionic species across the membrane

Experimentally with $dV = 0$ and $c1 = c2$ it is found that there is still a current flowing across the membrane → ion pumps

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

For the Na/K pump it is found that Na is actively pumped out while K+ is actively pumped in

The sodium-potassium pump

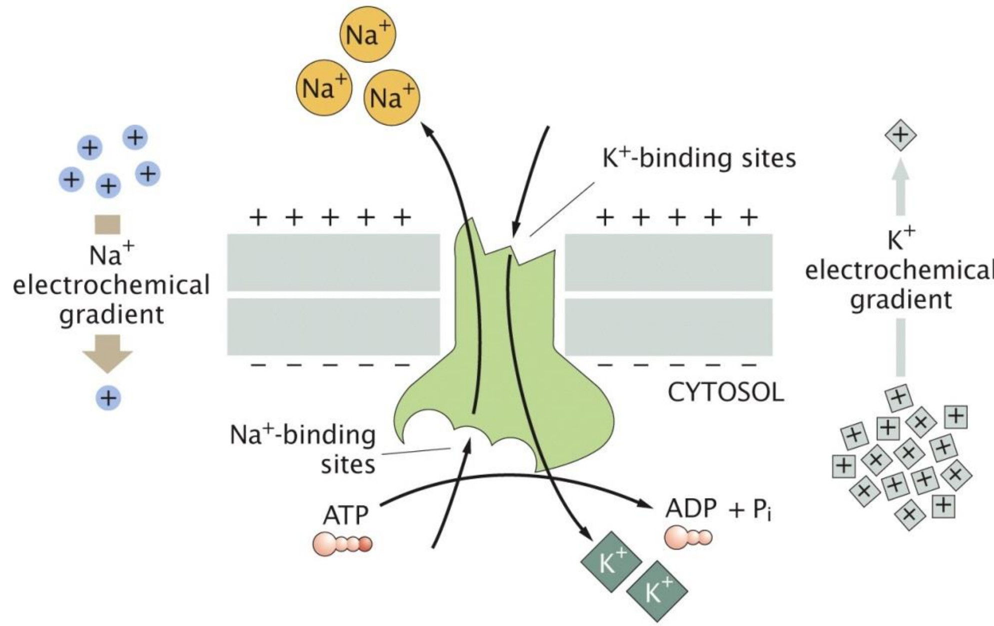
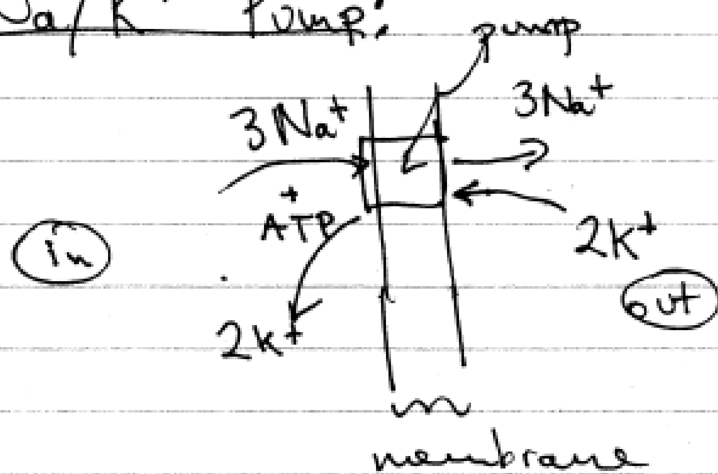


Figure 17.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Na/K+ Pump:



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

Membrane at steady state:

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

Despite being out of equilibrium the cell is in a steady-state (i.e. dV and the concentrations do not change with time)

Steady state: the fluxes of each ion must be zero

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

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

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

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

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

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

Solving the equation gives the resting potential of the cell,

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

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 quite well with the measured value ~ -68 mV for squid axon

The result is that the rest potential lies nearest the Nernst potential of the most conductive ion, in this case K+

Making a switch: Voltage sensitve ion chanels

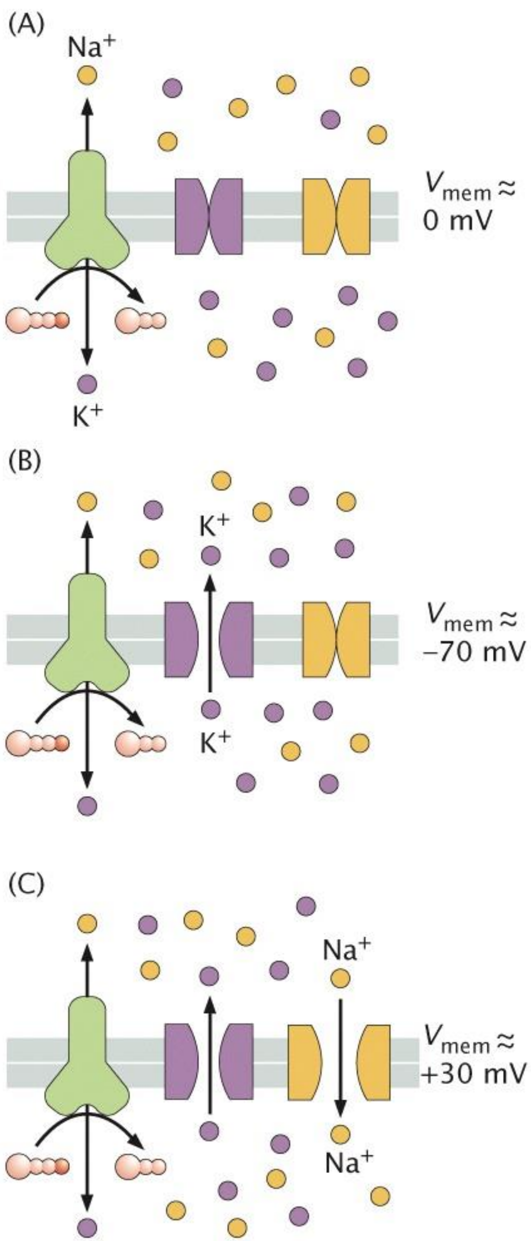


Figure 17.9 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

What this result shows is that if we could make Na be more conductive than K+, then the potential would switch dramatically to +50 mV

There are voltage sensitive ion pumps that make the membrane conductance in favour of Na

So the potential flips → generates a voltage pulse

Under the right conditions this voltage pulse can propagate → to action potential

or a nerve pulse, that we'll look at in the next section

Summary:

Cells generate electricity by maintaining an out of equilibrium charge distribution across it's membrane

Imbalanced charge distribution leads to a potential across membrane

If cell could come to equilibrium, the osmotic pressure would be too great

cell's actively pump ions out of the cell to balance osmotic forces

Rest potential is determined by the conductance of most conductive ion

If you can change the ionic conductance → flip the potential → action potential

… now on to how doe nerve pulses get generated