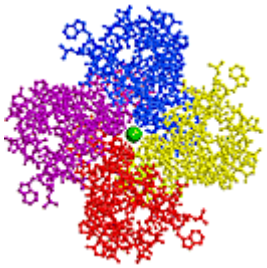
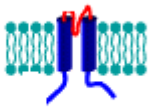
Lecture 3 Membrane Potential

The electrical signals of nerve cells arise from the movement of charges – in the form of ions – across the plasma membrane. The membrane has 2 essential features. First, the lipid bilayer is an impenetrable barrier to the movement of ions. The hydrophobic part of the bilayer, the hydrocarbon "tails" of the phospholipids composing the double layer, will not accommodate polar molecules like water or ions. Thus if an electrical charge is placed inside a cell, it cannot leak out across the bilayer. This means that the membrane acts as a charge storage device – an electrical capacity. It stores charge very well, because the stored charges can get very close to the corresponding but opposite charges that arise on the outside of the membrane, lowering their potential energy. Thus biological membranes have high capacity because they are very thin. The separation of charges generates an electric field, or potential difference, across the membrane, given by V = Q/C (Q = charge; C= capacitance). Typically membranes have a capacity of 1 uF per square centimeter, about 70% of which is due to the lipid bilayer, and the remainder due to embedded proteins.
Electrical charges can arise inside the cell in one of 2 ways. First, because experimenters inject them via microelectrodes, and second, because ion channels are open in the membrane. For example, most of the resting potential of neurons is due to potassium movement through "resting" potassium channels, which are built out of 4 subunits

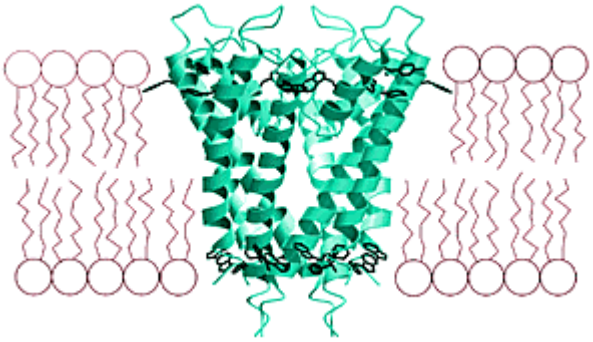


This is a view of the channel looking down onto the membrane, along the axis of the pore along which K ions move. The 4 subunits are shown in blue, purple, yellow and red, and the hole between the subunits (known as the "pore"), is occupied by a potassium ion (green).

Each subunit has the following general topology, where dark blue represents membrane-spanning alpha helix, and red represents the “selectivity filter” or “P-loop” of the



channel.
The whole structure of the channel can be visualized by thinking of an Indian teepee or wigwam, made of 4 poles which cross at the level of the smoke hole. Each one of these poles would be one of the subunits shown above (i.e. most of the pole is made up of the 2 long alpha helices). However, if we visualize the outside of the membrane as being at the top, the teepee is actually upside down (i.e. the smoke hole points down and the wide part of the teepee is pointing up. The 4 P loops, one from each subunit, hang down into the wide part of the upside down teepee and line the interior of a short narrow tube, through which potassium ions pass in single file (i.e. they cannot slide past each other).



Here the picture is from the side, as though the membrane was sliced in 2, through the center of the channel. The widest part of the inverted teepee is filled up by the 4 dangling P-loops which make up the narrow tube, but the rest of the teepee, before reaching the smokehole, is empty of protein, and is filled with a “nanolake” containing about 50 water molecules. The shortness of the narrow tube between the outside surface and this “nanolake” is an important feature allowing potassium ions to cross the membrane. Once the ions reach the nanolake, they are essentially on the cytoplasmic side of the membrane, though they still must cross the smokehole. Another important feature is that the tube can contain only 2 potassium ions at a time, because they strongly repel each other, so if a new ion enters the tube, it forces another out. Thus although potassium ions fit snugly in

the tube (unlike sodium ions), they do not get stuck there. This design ensures both high conductivity and high selectivity (sodium ions, which are chemically very similar, cannot pass through).

The voltages across cell membranes arise from 2 factors: the selective passage (or "permeation") of ions through ion channels, and the fact that ion concentrations may differ on either side of the membrane. Typically there is ten times more sodium out than in, and even more than ten times more internal potassium than external potassium. If only potassium could move through the membrane (for example, via completely selective potassium channels) then if the initial membrane potential Vm were zero, potassium ions would leave the cell by diffusion. Diffusion refers to the tendency of molecules to move from regions of high concentration to regions of lower concentration. This happens because of the disordering effect of thermal motion. But as potassium potassium ions leave, a negative electrical charge builds up inside the cell. This charge (Q) causes the development of a membrane potential, given by Vm = Q/C. The membrane potential tends to oppose the further diffusion of ions (since a negative Vm pulls K+ ions back into the cell. In fact , as with the ferromagnet, a balance is reached between the disordering effect of concentration, and the ordering effect of Vm. This equilibrium point arises when the ratio of the probability of finding an ion on the high energy side (i.e. outside) to that on the inside Phi/Plo = exp – deltaE/kT (i.e. the Boltzmann distribution). The energy difference for the ion is given by the charge times V, and because concentrations are proportional to probabilities, the result is the Nernst equation

Vm = Ek = (kT/ze) ln [K]o/[K]i

Where e is the electronic charge, and ln is the natural logarithm, with Ek the equilibrium Nernst potential for potassium. This can also be written (at room temperature) as

Ek = 58 log [K]o/[K]I

For the typical values of [K]o and [K]I found in cells, Ek is about –90 mV. This would be Vm if the membrane were permeable only to K.

It is important to realize that only a very tiny fraction of the potassium ions have to leave the cell for Vm to reach Ek – typically less than 1 part in a million.

(It is very instructive to calculate this fraction for cells around 50 um in diameter (a typical figure) and for individual synaptic vesicles (diameter as small as 20 nm). To do this calculation assume that there are 100,000 coulombs in the Faraday (an Avogadro's number of univalent ions).

However, the Vm of nerve cells is typically around –70 mV, because the membrane also is permeable to sodium ions, because some open sodium-selective channels are also present. The overall Vm represents a compromise between the Nernst potentials for K (-90mV) and Na (+50 mV). One way to quantitate this compromise is to represent the membrane as an electric circuit, with the contribution of K represented as a battery (Ek)

and a conductance (Gk) , and similarly for sodium. The Gs represent the ease with which the ions cross the membrane (i.e, the number of open channels times their conductance) If it is assumed that the ionic currents follow Ohm's law (I = VG) with fixed G, then at the resting potential Vm the inward sodium current INa (= [$V-E_{Na}G_{Na}$]) plus the outward potassium current Ik must sum to give zero, and

Vm = (Gna Ena + Gk Ek)/(Gna + Gk)

i.e. the resting potential is a weighted sum of the Nernst potentials of the permeating ions. This can be extended to any number of different ions.

[Advanced material: another way to set the compromise is with the Goldmann equation, which calculates the ionic currents based on electrodiffusion, rather than simply assuming they obey Ohm's law. The result is that the potential is given by the log of the ratio of the weighted concentrations, the weights being the permeabilities. The circuit-based equation above weights the logs of the concentration ratios. Both the circuit approach and the Goldmann approach are widely used, though they do not give the same answers. They were formulated before we knew exactly how ions cross the membrane. Now we have a much clearer picture, especially of how potassium ions move through the potassium channel. This has lead to a detailed mathematical model, but the older pictures are still roughly correct]

In general the membrane potential of a cell lies somewhere between Ek and Ena (i.e. about – 90 mV and about +50 mV. Where is lies depends on the relative sodium and potassium conductances. In neurons in the CNS these conductances constantly change as a result of synaptic and spike activity.

References

A good summary for the structure of potassium channels is:
http://search.msn.com/results.aspx?q=mckinnon+nobel+lecture+angewandte&FORM=QBRE

see also

http://www.hhmi.org/news/mackinnon.html

Jiang YX, Lee A, Chen JY, Ruta V, Cadene M, Chait BT, MacKinnon R X-ray structure of a voltage-dependent K+ channel. NATURE 2003 MAY 1;423(6935):33-41

Zhou YF, MacKinnon R The occupancy of ions in the K+ selectivity filter: Charge balance and coupling of ion binding to a protein conformational change underlie high conduction rates. J MOL BIOL 2003 NOV 7;333(5):965-975

Morais-Cabral JH, Zhou YF, MacKinnon R Energetic optimization of ion conduction rate by the K+ selectivity filter. NATURE 2001 NOV 01;414(6859):37-42

Doyle DA, Cabral JM, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait BT, MacKinnon R The structure of the potassium channel: molecular basis K+ conduction and selectivity. SCIENCE 1998 APR;280(5360):69-77