1 Ion Channel Biophysics

- Describe the main biophysical characteristics of at least one type of ionic channel. How does its biophysical properties contribute to its physiological function. What is thought to be the basis for the channel's ion selectivity?

There are many types of ion channels. I shall talk about some of the ones that are

- interesting,
- typical in neurons, and
- well understood (by me).

For now, I won't talk about the second messenger channels, nor about the glutamate gated channel or its relatives.

I will make numerous simplifying assumptions and generalizations, none of which are completely true.

1.1 Transmitter Gated Channels

The best understood one is the nicotinic acetylcholine receptor (nAChR). The glycine, $GABA_A$ and serotonin receptors are closely related, so they probably have very similar structures.

nAChR can be opened by acetylcholine, nicotine, and a couple of other molecules. There are several known channel blockers, such as QX222 and QX314. When nAChR opens, it is cation selective, i.e. ions with a positive charge (cations) can pass through, but ions with a negative charge (anions) cannot. nAChR is found in the neuromuscular junction and in the brain. It is excitatory. In the CNS, it is thought that nAChR performs a modulator role, not primarily a signalling role ([1]).

In a typical event, ACh will hit the nAChR, and the receptor will open. This causes both sodium and potassium currents, but the sodium gradient is so much higher that it plays a dominant role. This causes the membrane potential to rise and causes an action potential, a muscle contraction, or whatever.

One of the reasons we started with nAChR is that its selectivity is pretty simple. It allows most cations to pass through, while stopping anions. The structure is five-fold symmetric, and each of the five subunits has 3 negatively charged rings: two inside the cell and one on the outside surface. This attracts cations and repels anions. Other than that, the channel is large enough to allow just about any common cation through.

1.2 Voltage Gated Sodium Channel

As far as I know, there's only one of these (as opposed to potassium channels, of which there are many.) The one I'm describing is the classical Hodkin-Huxley sodium channel.

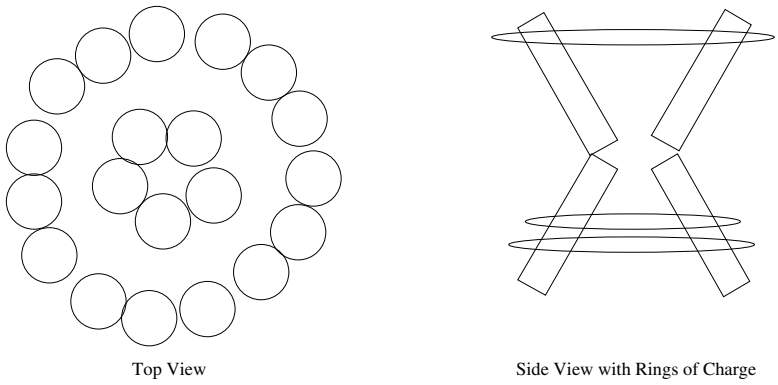

Figure 1: Rings of charge on the nAChR, right

When depolarized, this channel opens for a while, then inactivates. It can only be reactivated by hyperpolarization.

This fulfils its main physiological function: when the cell is depolarized, the channels start to open, then inactivate. At some voltage (called the threshold) gates open faster than inactivation, and the cell spikes.

Sodium channels are inpermeable to anions, and are much more permeable to sodium than potassium. First off, we know the pore has to be small, because there's no way a big pore could distinguish between sodium and potassium. So how does it work? Consider the data in this table.

Ion	$AtomicRadius(\mathring{A})$	$HydrationEnergy(kcal/mol)$
$Sodium$	0.95	-105
$Potassium$	1.33	-85

(The hydration energy is the energy change when a mole of gaseous ions are dissolved in water.)

Sodium is a smaller atom, but has higher hydration energy (i.e. it's harder to pull off the waters of hydration.) Basically, the channel is a pore that's too small for potassium to pass through, but is big enough for sodium to pass through.

(That's only part of the story, because we have to worry about the waters of hydration, too. The channel is too small to leave all of the waters of hydration on, but it must provide stabilization for the molecules as it pulls off the waters of hydration, i.e. there must be residues which can provide hydrogen bonding to replace the water molecules that were doing that before.)

The final part of the sodium gate story is inactivation. The channel contains a "ball and chain [1]," which tend to block the channel at higher voltages. At rest and during hyperpolarization, the channels become unblocked, i.e. de-inactivated, and can respond the next time there's a change in voltage.

[1] Some sodium gates contain more than one.

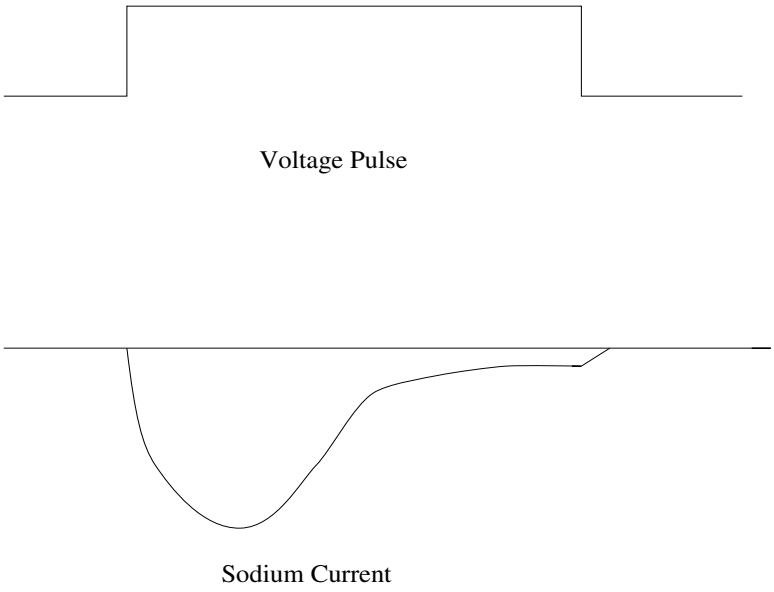

Figure 2: Inactivation of the voltage gated sodium channel

1.3 Potassium Channels - Delayed Rectifier

There are more types of potassium channels than you can shake a stick at (not meant as a pun about the Shaker potassium channel.) One important one is the delayed rectifier potassium channel in axons, often called $I_{K(DR)}$ or something similar.

The biophysics of this channel are simple, yet complex. When the cell is depolarized, there is a brief delay, then the channel opens. (See figure.) The channel is selective for potassium — sodium is only 2–3% as permeable.

So what is the basis of its selectivity? Again, as with the sodium channel, this channel must be small to have any hope of telling the difference between sodium and potassium. In fact, this channel is probably the smallest pore of any ion channel. It strips off *most or all* of the waters of hydration before allowing an ion to pass through. As is shown in the table, it takes more energy to take the waters of hydration off of sodium, so fewer sodium atoms have enough energy to get through the channel.

Another interesting effect is why the rectifier is delayed (i.e. why there's a brief pause before there's any current.) We won't talk about that here, but if you're interested, let us know.

1.4 Potassium channels - other kinds

- A-type K^+ channel — activates when cell is hyperpolarized then depolarized. Important in graded firing rate responses.

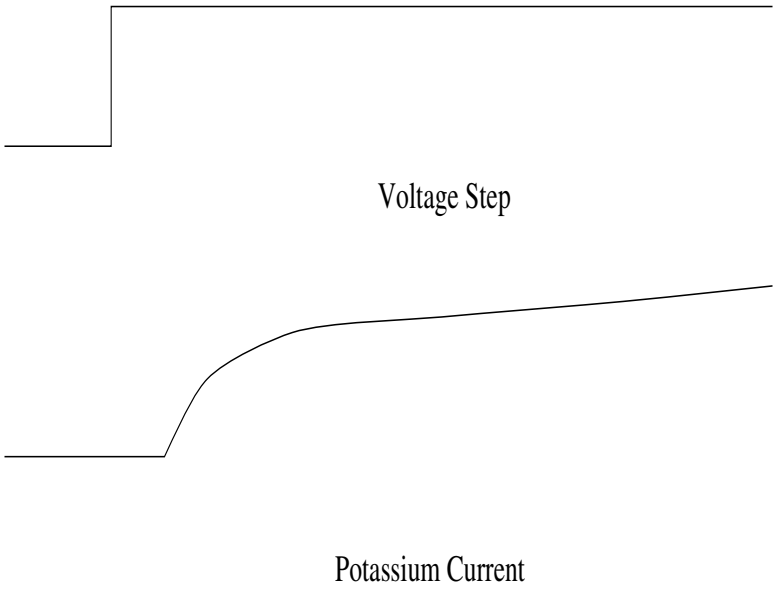

Figure 3: Current response of the delayed rectifier potassium channel

- Ca-dependent K^+ channel — Dependent on the concentration of intracellular calcium. Not really voltage dependent.
- Inward rectifiers — Close under depolarization. Act to stabilize the cell around its resting potential.
- S-channels — Voltage insensitive K^+ channel in *Aplysia*, which is shut by cAMP-dependent phosphorylation.
- ATP gated channel — Open in absense of ATP, closes when ATP is abundant. E.g. causes insulin release to drop off when nutrient supply is low.
- M-channels — Affected by a second messanger from the muscarinic acetylcholine receptor.

1.5 Calcium channels

Calcium channels open in response to depolarization and allow calcium to flow freely into the cell. At rest, the internal calcium concentration is incredibly low, so just a small amount of flux changes the internal concentration a lot. Once calcium gets into the cell, it causes various effects, such as release of neurotransmitter.

In biological conditions, calcium channels are inpermeable to sodium and potassium, but if no calcium (or other divalent cation) is present in the solution, they become permeable to sodium (and to a lesser extent potassium).

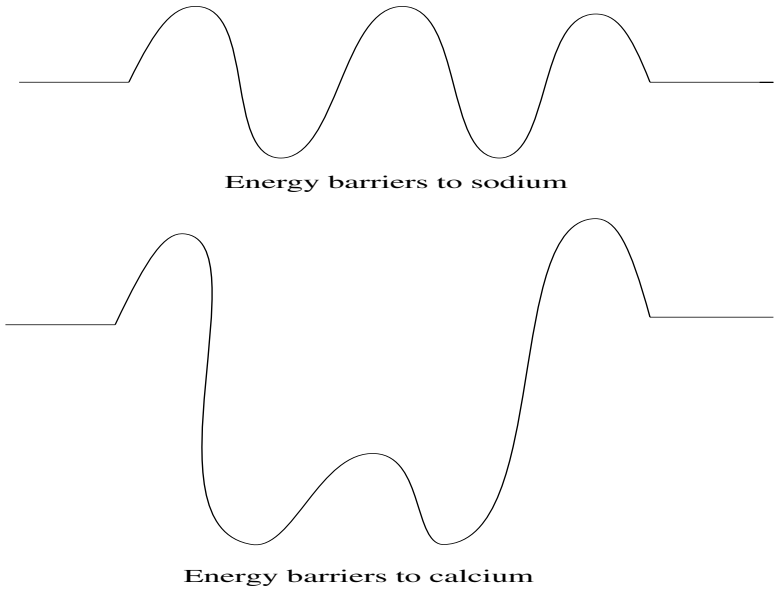

Figure 4: Energy as a function of position in the membrane.

How does this work? Consider the energy barriers that an ion has to get past to go from the extracellular side to the intracellular side of the membrane. (See figure.) Once a calcium ion gets into the pore, it will tend to stay there, because it will get caught in the energy well shown. On the other hand, sodium has much smaller energy wells. So if a calcium is in the pore (one usually is) and a sodium ion comes into the pore, they'll feel a mutual repulsion and each try to get out. The sodium will generally be able to get back out, whereas the calcium will not, so the channel will not allow sodium to pass through when calcium is present in solution.

But wait, you say. If calcium is so stable in the pore, how do you get any flow through the current? Suppose *another* calcium ion comes along. Then all hell breaks loose, and both are really repulsed. Very quickly, one will go out one side of the pore or the other. The fact that the concentration of calcium is higher on the outside means that, on average, more calcium will flow from outside to inside, hence net inward current.

In the absense of calcium, the same thing happens with sodium ions, and so you get a sodium current through the channel.

In fact, researchers have found a single amino acid (repeated four times around the channel due to symmetry), which they believe causes the energy wells. The residue in question is a conserved glutamate ([2]).

References

[1] McGehee, D.S., M.S.J. Heath, S. Gelber, P. Devay, L.W. Role (1995) Nicotine enhancement of fast exitatory synaptic transmission in CNS by presynaptic receptors. *Science* 269, 1692-1696

[2] Yang, J., P.T. Ellinor, W.A. Sather, J.F. Zhang, R.W. Tsien (1993) Molecular determinants of Ca^{2+} selectivity and ion permeation in L-type Ca^{2+} channels. *Nature* 366, 158-161