

Voltage dependent conductances

9-1. Last time we finished our discussion of the Hodgkin-Huxley equations, showing that the ionic current could be represented by

$$I_{\text{ion}} = \bar{g}_{\text{Na}} m^3 h (V - V_{\text{Na}}) + \bar{g}_{\text{K}} n^4 (V - V_{\text{K}}) + g_{\text{L}} (V - V_{\text{L}})$$

where m , n and h are computed from the corresponding equations for α and β . We saw how to get m , n and h from equations like $m = m_{\infty} - (m_{\infty} - m_0) \exp(-t/\tau_m)$ where $\tau_m = 1/(\alpha_m + \beta_m)$ and then once we had m_{∞} and τ_m we could get α and β and then fit the data points for α and β with empirical functions of a type similar to the constant field equation.

We saw how to get the activation and inactivation curves for m_{∞} , h_{∞} and n_{∞} . When plotted in lab we saw that the slope for m was steeper than that for n and that τ_m was much faster than τ_n or τ_h .

At rest with hh, $m \approx 0.05$, $h \approx 0.7$, and $n \approx 0.3$. Then $m^3 h \approx 0.0009$ and $n^4 \approx 0.0081$ showing that the conductances are very small at rest.

These functions are sometimes described in terms of a Boltzmann-like function, as mentioned earlier, where $V_{1/2}$ is the voltage where the state variable = 0.5 and k describes the slope.

For a calcium channel the data may say that its activation is m^2 and $V_{1/2} = -10$ mV and $k = -10$. Because of the m^2 activation we have $m_{\infty}^2 = (1 + \exp((V - V_{1/2})/k))^{-1}$ and to get m_{∞} we need to take the square root. An example where this is done is Jaffe DB et al., J. Neurophysiology 71:1065, 1994 and they show how to get the α and β from the Boltzmann.

9-2. The standard view of a cell has been that dendrites are passive and the action potential is a property of the axon. However there are a variety of ionic conductances in the soma and dendrites that are responsible for a wide variety of firing patterns as shown here.

In A we see the firing pattern of a regular firing cortical pyramidal cell. Note the adaptation towards the end. In B we see burst firing from a different cortical pyramidal cell. This type of burst discharge is mediated by a calcium conductance. In C we see bursting riding on a plateau potential, probably due to a persistent Na conductance and then later on we see evidence of dendritic calcium spikes. In D and E we see differences in spiking mode of a thalamic relay cell that depend on the resting potential. If rest is -65 we see regular spiking. When rest is -75, we see a burst discharge. T-type calcium channels are involved here. Finally in F we see a pacemaker type pattern that persists in the absence of stimulation.

The physiological behavior is determined by the types and densities of ionic conductances found in the membrane and their interactions.

9-3. At the top we see the firing patterns of 3 types of neurons in the Aplysia. The R3 cell beats regularly. The R15 cell is a regular burster, having bursts followed by silent periods. The L10 cell is an irregularly bursting cell. Again the physiological behavior of these neurons is

determined by the types of conductances and their densities found in cell membranes and the interactions between these conductances.

The Table on the bottom comes from Chap 7 of BoG, although I have corrected a few typos. In this example as well as with the Traub model of a hippocampal CA3 cell that we will discuss later, it is differences in densities of various types of channels that produce the wide variations in the shape and firing patterns of action potentials.

In this table p is the activation variable power and q is the inactivation variable power. The maximum conductance is given in units that GENESIS likes, but not units that we normally think in. Only 2 values are given for τ for each conductance here. Each of these conductances has a different threshold of activation (and inactivation) and different τ s of activation and inactivation.

9-4. So when modeling a particular cell, the first thing we need to know is what types of channels exist and what are the kinetics.

The types of channels is first distinguished by ion selectivity. What ions can pass through the channels? Secondly, channels are distinguished by their pharmacology. What blocks the channel, for example? Third, what are the kinetic properties of the channels? Where do they activate, where do they inactivate and with what time courses? In modeling we hope that Nature is nice and that similar types of channels occur across species, and molecular biology does show that there are lots of similarities across species.

However there are complications. The kinetics for a particular channel may not have yet been studied for the cell you are interested in. Kinetics may be described for different preparations. Also there is some molecular diversity. Ion channels can have different sub-unit compositions. A channel may be composed of 3-6 subunits of more than one type and different combinations may be possible. Ion channels can be in different phosphorylation states. One study suggests that the $V_{1/2}$ value for the Na channel is different for soma Na channels and dendritic Na channels and that this may be related to the different phosphorylation states. Finally, channels can be modified. For example we look to learning in *Aplysia* (from Eric Kandel's lab—recall Kandel got the Nobel Prize a few years back for his work in *Aplysia*). Here an increase in cAMP can activate PKA which can phosphorylate a channel resulting in a decrease in potassium current.

Because for these complications we may have to shift voltage activation curves left or right by a certain number of mV compared to reported values. Also we may have to adjust the time constant of activation or inactivation, perhaps to account for temperature. We saw before how to apply a q_{10} value to the rate constants.

Experimentally, how do we study the kinetics of voltage dependent channels? Clearly, we can do voltage clamp like HH, but today it is more common to do patch clamp studies so that we can control the space clamp, which can be a problem with voltage clamp studies. If we have a patch, we can block all conductances not relevant to us and do voltage clamp studies on the patch.

9-5. The second thing we need to know is where the channels are located.

In general the axon is almost exclusively Na and K

The soma has lots of different Na, K and Ca conductances.

The dendrites have a similar variety as in the soma but the densities may vary.

Invertebrates may have an axon that begins from a dendrite, so this makes things very interesting to study, shall we say.

How can we determine the locations of the channels? Again the typical means is to patch various areas and use pharmacological manipulations and see what channels are present in the patch. Repeated sampling can tell us where various channels are located.

Thirdly, we need to know the channel densities. How can these be determined experimentally? HH got this from voltage clamp in a preparation where densities were uniform. In other cells the densities are not uniform. Again you can patch clamp and measure the current in the patch for a particular conductance while voltage clamping. The one problem is that it is not always clear what the membrane area of the patch is that you are looking at. This can be estimated, but accuracy is a problem.

Models must be calibrated appropriately to be able to reproduce a representative response of the neuron. In the face of limited information, modelers can get density values by: i) trial and error (used very often with varying success), ii) Systematic and exhaustive search of parameter space using NEURON or GENESIS on parallel computers, iii) a purely stochastic search of parameter space, or iv) the use of optimization methods such as genetic algorithms, conjugate gradient methods, simulated annealing, etc. NEURON has a multiple run fitter built into it which we will explore later in the course. Work to find parameter values is an active area of research going on here at this university.

One problem with these search methods is that they need a comparison metric and it is not clear what the best choice for a comparison should be. Do we want to match a voltage trace at every point? But then how repeatable is this voltage trace experimentally? We may not be able to match long spike trains precisely in experiments, so why require this of models? Maybe we just want number of spikes, or the times of spikes. One interesting metric is to plot dV/dt vs. V of both the experimental trace and the model output and minimize the difference. Some studies say that a white noise input produces a very repeatable spike train, so perhaps this type of stimulus would be useful here.

Metrics chosen then to be very ad hoc. However, mathematics has some criteria that a metric should satisfy and unfortunately many of the ad hoc metrics do not satisfy these criteria. Again this is an active area of research.

9-6. Here are some activation and inactivation functions used by Traub in his hippocampal CA1 and CA3 pyramidal cell models. These were determined completely ad hoc and with trial and error to match qualitatively properties of spiking behavior noted in these cells. Traub's morphology in this model was a cylinder with the soma closer to one end than the other to separate apical and basilar dendrites.

9-7. Here are activation and inactivation curves for the molluscan neuron model. We saw the table at the bottom earlier. The C conductance is a calcium activated potassium conductance. The voltage activation curve here is shown for a fixed calcium concentration. To model this appropriately we need to construct an activation function on a 3-d plot where there are axes for both Voltage and calcium concentration.

9-8. Here are some of the variety of ionic currents that have been characterized. We will go into these in more detail from a quantitative point of view.

9-9. Here is another list of voltage dependent conductances. This table gives a threshold voltage for the activation of the conductance, lists the relative speed of inactivation, if present, lists some pharmacological blockers and modulators.

9-10. We will begin with a discussion of the Na currents. These are comparatively simple in that only 2 types have been reported, the fast sodium responsible for the action potential and the persistent Na current.

Note the crossing of the activation and inactivation curves for the fast Na conductance at the top of the page. Below where they meet is a shaded area representing what is called a “window current”. If voltage is clamped into this area, a constant Na current will result. In fact when HH did a voltage clamp to 6 mV positive to rest they saw a sustained Na current with no inactivation which was probably the result of being in this window area where Na is persistently on.

The slow or persistent Na conductance was thought at one time to be just a variation of the fast Na current or merely the window current of the fast Na current. However, these days we think that this is a separate current in its own right. It turns on slower than the fast Na current and does not show inactivation. This current may amplify small depolarizations and sustain repetitive firing.