

## Voltage-dependent conductances\_2

**9-11.** Calcium conductances should be handled with particular care.  $[Ca]_o$  is about 2 mM while  $[Ca]_i$  is about 100 nM, or in other words there is a 2000-fold gradient. But because  $[Ca]_i$  is so low, there really is no true reversal potential for calcium currents. There are not enough calcium ions to support an outward current! How can we get around this? There are 2 basic approaches.

The first approach is to use the constant field equation to model calcium currents. Instead of

$$I_{Ca} = g_{Ca}(V - V_{Ca}) \text{ we can use } I_{Ca} = P_{Ca} \frac{4F^2}{RT} V \left( \frac{[Ca]_i \exp\left(\frac{2VF}{RT}\right) - [Ca]_o}{\exp\left(\frac{2VF}{RT}\right) - 1} \right) \text{ where } P_{Ca} \text{ is}$$

calcium permeability and  $P_{Ca} = \bar{P}_{Ca} m^x h^y$ . An example of the use of this form is given by Huguenard and McCormick, 1992. Examples are Cachan.mod and fh.mod in the /nrn59/examples/nrniv/nmodl directory.

$$\text{An alternate form used by Jaffee et al 1994 is } I_{Ca} = \bar{g}_{Ca} m^x h^y V \left( \frac{1 - \frac{[Ca]_i}{[Ca]_o} \exp\left(\frac{2VF}{RT}\right)}{1 - \exp\left(\frac{2VF}{RT}\right)} \right)$$

If we were to use the HH form,  $I_{Ca} = g_{Ca}(V - V_{Ca})$  with  $g_{Ca} = \bar{g}_{Ca} m^x h^y$ , then we really should keep track of  $[Ca]_i$  and update  $V_{Ca}$  with the Nernst equation at each time step. Because  $[Ca]_i$  starts out so low, it does not take much to change  $V_{Ca}$ . This procedure works well as long as the voltage does not go above -20 mV very often or for very long, at least according to DeSchutter and Bower, 1994).

**9-12.** There are several types of calcium currents, L, T, N, P, R each with their own activation and inactivation kinetics. Some reported activation and inactivation curves are shown here.

The L current is a high-threshold current meaning that it is activated only when the cell is depolarized considerably. It is Long Lasting (hence the L) and has negligible inactivation. What little inactivation it has is both calcium and voltage dependent, but it is so small that we usually neglect it. A functional form is  $I_{Ca(L)} = \bar{P}_{Ca} m^2 h(Ca)h(V) I_{Ca}(V)$  but again, we neglect the h parts. Here and for all calcium currents, we let  $I_{Ca}(V)$  equal the terms on the right hand side of the large equations above. This notation is not the best, but the exact form will vary depending on which of the above representations are used. The L channels are found primarily in somatic and proximal dendrites, at least in cortical cells, and may be involved in calcium spikes. The threshold for activation is very high, about -25 mV and the Boltzmann  $V_{1/2}$  is about 4 mV with a slope k near 5.

**9-13.** The T current is a low threshold calcium current that inactivates relatively quickly, making its duration Transient (hence the T). This calcium current can be activated near rest and is involved in spontaneous burst firing, because it is only partially inactivated at rest. When the cell is hyperpolarized, inactivation is removed and upon repolarization there can be rebound firing. A possible representation is  $I_{Ca(T)} = \bar{P}_{Ca(T)} m^2 h I_{Ca}(V)$ . This current has a threshold near -60 mV. Activation  $V_{1/2}$  and slope are typically -31 mV and 6.5. Inactivation  $V_{1/2}$  and slope are -75 mV and 6.4.

NOTE, the  $V_{1/2}$  and slope values I give here are one example of what is found in the literature. There is considerable variation in these values, so please look these up for the cell you are modeling.

The N current is a high threshold current that is Neither long-lasting nor transient (hence the N). This type of current is often found at pre-synaptic terminals and is responsible for neurotransmitter release. Inactivation depends on voltage. A much slower component of inactivation depends of calcium concentration, but this is usually neglected. A possible representation is  $I_{Ca(N)} = \bar{P}_{Ca(N)} m^2 h(V) h(Ca) I_{Ca}(V)$ . This current has a threshold near -35 mV for activation. Activation  $V_{1/2}$  and slope are typically -15 mV and 6.5. Inactivation  $V_{1/2}$  and slope are -70 mV and 12.5.

Other calcium current types are P and R. These are high threshold. P is for Purkinje and this current has characteristics similar to the L current or maybe also the N current. R type channels have been found in dendritic spines. Kinetics are similar to the L and N types with activation  $V_{1/2}$  near -10 mV. Kinetics are faster than the T current

**9-13. 9-14.** Potassium currents. There is a great diversity of potassium channels. They i) contribute to the resting potential, ii) may be activated at sub-threshold voltages, iii) are activated by action potentials, iv) contribute to afterpotentials (late hyperpolarizations), v) and may be involved in spike train adaptation during repetitive firing.

One K channel that we have already seen is the fast K current, the delayed rectifier,  $I_{KDR}$ . It has slower kinetics than the fast Na current and so is called “delayed”. This is the HH K channel. Inactivation is very slow and so is ignored. In HH the form is  $I_{K(DR)} = \bar{g}_{K(DR)} n^4 (V - V_k)$ . This conductance has a threshold near -40 mV (note  $n^4$ , not n) and it repolarizes the cell after an action potential.

**9-15.** The A current is a transiently activated K current. It activates relatively quickly, in 5-10 ms, and inactivates with a time constant of 20-30 ms. It plays a role in spike repolarization and may delay the onset of the firing of the first action potential in a train. It may contribute to the resting potential, but perhaps not very much. Its form is  $I_{K(A)} = \bar{g}_{K(A)} m h (V - V_k)$ . The activation and inactivation curves are shown here. On the left we see the current when the voltage is clamped to -80 mV holding potential and then is stepped to 0 mV. The summed  $I_{DR}$  and  $I_A$  currents can be isolated pharmacologically to yield the two components shown here. Note that the delayed rectifier shows no inactivation here, while the A current has a prominent inactivation.

**9-16.** The D or delay current has characteristics similar to the A current, but has a much slower inactivation and the activation and inactivation curves are 15-20 mV more hyperpolarized. This current contributes to spike repolarization and it may also be present at the pre-synaptic terminal. The plot on the left shows the inactivation, but note the time scale. It is seconds instead of ms. Its form is  $I_{K(D)} = \bar{g}_{K(D)} m h (V - V_K)$ .

The M or muscarinic sensitive potassium current is slowly activated (time constant of about 50 ms) and shows no inactivation. It is activated at small depolarizations above -65 mV. It may play a role in spike train accommodation, repetitive firing, and in the mAHP (medium after-hyperpolarization). Its form is  $I_{K(M)} = \bar{g}_{K(M)} m (V - V_K)$ .

**9-17.** There are some currents that are activated by hyperpolarization instead of depolarization. There is the potassium inward rectifier or  $I_{K(IR)}$  which passes potassium better into the cell than out. Its activation is sensitive to  $[K]_o$ . Its form is  $I_{K(IR)} = \bar{g}_{K(IR)} m (V - V_K)$ .

The most prominent hyperpolarization activated current is the H current. In the early days it was called  $I_Q$  or  $I_f$  but present notation is  $I_h$ . This is a mixed Na and K current and its reversal potential is about -30 mV (somewhere between the Na and K reversal potentials). This current prevents strong hyperpolarizations from occurring. If a constant hyperpolarizing step current is applied, the voltage will hyperpolarize but then sag back towards the resting potential before reaching a steady-state. Thus hyperpolarization may cause a decrease in input resistance. The  $V_{1/2}$  for this conductance is about -85 mV, although the range of estimates is -68 to -105 mV! Slope is near 8 or so. At depolarizing potentials a slower component becomes evident and models may or may not include it. A representation is  $I_h = \bar{g}_h h_f h_s (V - V_h)$ , where the two h state variables have the same activation curve but different taus. Many people just model the fast component.

**9-18.** Calcium dependent K currents. There are several types of potassium currents that are activated by calcium with or without also being activated by voltage. The  $I_{K(C)}$  or  $I_C$  current, sometimes called  $I_{BK}$  current is one. I believe this is in the nrn/examples/... directory under cagk.mod. The B in BK is for Big single channel conductance. This is a fast calcium-gated K channel and it may be linked or very close to L calcium channels. It is a large current activated in 1-2 ms by calcium and voltage. It deactivates with voltage much more slowly (50-150 ms). It plays a role in spike train accommodation, spike repolarization, and action potential frequency adaptation. It may play a role in the fast and medium AHPs. Its form is  $I_{K(C)} = \bar{g}_{K(C)} m(V,Ca) (V - V_K)$ . Sometimes the  $m(V,Ca)$  is separated into  $m_1(V)m_2(Ca)$ . The activation cannot be illustrated on a 2-d plot as with other conductances. What we see here on the left are activation curves for different fixed levels of calcium. On the right we see the currents for different calcium concentrations.

**9-19.** The  $I_{\text{AHP}}$  current was named because of what it does. It is responsible for an after hyperpolarization. The single channel conductance is smaller than the BK and one form is called the SK current where S is Small and it is activated much more slowly. Furthermore it is not sensitive to voltage, just calcium. There are two forms depending on their sensitivity to apamine. This conductance provides a long, slow hyperpolarization following a single action potential (sAHP). It is responsible for accommodation in the spike train during repetitive firing. Its form is  $I_{\text{AHP}} = \bar{g}_{\text{AHP}} m(\text{Ca}) (V - V_{\text{K}})$ . or  $I_{\text{SK}} = \bar{g}_{\text{SK}} m(\text{Ca}) (V - V_{\text{K}})$ . The upper plots show the response to a single action potential with and without Ca in the external media. Removing calcium removes the after hyperpolarization. The middle and lower traces show the effect of calcium during a train of action potentials

**9-20.** Here are some of the less significant conductances, along with some of the alternate names or similar conductances to those we have discussed. The variety of K currents play specific roles as we have occasionally noted already, but which are shown in more detail in the next overhead.

**9-21.** Here we see that the A and D currents may delay the onset of a spike, the A, D, and DR currents play a role in repolarizing the cell after an action potential, the C current may also help in repolarization and is responsible for the fast after-hyperpolarization, the M and C currents may affect the medium afterhyperpolarization and the AHP is responsible for the late AHP. The relative time courses of these currents are compared in the bottom figure.

**9-22.** Finally, we see here some examples of what happens to a spike train when we include specific subsets of currents. We start with the fast Na and K currents in Fig A, and then add the persistent Na in Fig B and see a higher frequency of action potentials. If on the other hand we had added calcium channels and the  $K_{\text{C}}$  current changes the shape of the voltage profile between spikes and may slightly delay spiking. This is shown in Fig. C. If we use Fig. C as the starting point and add T current and hyperpolarize, we can initiate a burst discharge as shown in D. If instead, we add M and AHP currents and don't hyperpolarize beforehand, we see spike frequency adaptation. There is a lengthening of the time between spikes as shown in E. Finally in F we see the effect of adding an A current.