Introduction to Computational Neuroscience (Spring 2018)

Applications of Current Clamp

In this exercise we'll work with two model HVC neurons, an HVC_{RA} model neuron and an HVC_X model neuron. We will see what can be done in the lab using the current clamp model of electrical recording, and then see what additional things can be done *in silico* (i.e., with a computer).

Exploration

Download the files HVCRA.ode and HVCX.ode from my web site. We'll be using both of these, first as if the model cell were an actual cell and we were in the lab, and then in the *in silico* environment, where we have access to things that can't be observed in the lab.

(1) Start up the HVC_{RA} code and run it. At time 500 ms a depolarizing current pulse of 200 pA is applied. How does the voltage respond? What happens if 400 pA of depolarizing current is added (delta I_{ap})? What happens if -200 pA of hyperpolarizing current is added?

(2) Pharmacological drugs are very useful tools to neuroscientists. Different drugs block different types of channels and if used at the right concentrations they tend to be relatively specific to one channel type. Pretend you are in the lab, and see what happens to the voltage trace when 200 pA of depolarizing current is added in the presence of each of the following drugs individually: tetrodotoxin (TTX: blocks the fast-inactivating Na^+ current), tetraethylammonium (TEA: blocks the delayed rectifying K^+ current), apamin (blocks the small-conductance SK current), linopirdine (blocks the channels for the M current), and 4-aminopyridine (4-AP: blocks A-type K^+ channels).

(3) The ion channels targeted by the drugs above activate upon depolarization. Some channels become active upon hyperpolarization. For example, the T-type Ca^{2+} channels are typically inactivated at the rest potential, but the inactivation is removed if the cell is hyperpolarized. There are two types of channels underlying the h current, and both are activated by hyperpolarization. So I_{CaT} and I_h are typically examined using a pulse of hyperpolarizing current. Using a hyperpolarizing pulse of -200 pA determine what happens to the voltage when I_{CaT} is blocked with the drug mibefradil. What happens when I_h is blocked with the drug ZD 7288?

(4) Now let's see what can be done *in silico* that can't be done in the lab. First, we can look at each of the ionic currents to help us understand how they act on

the voltage trace, and why removing them with a drug changes things. Open up a new XPP window and put the inward currents I_{Na}, I_{h}, and I_{CaT} in it (remember that these are all negative). Open up a second new window and put the outward currents I_{K}, I_{A}, I_{M}, and I_{SK} in it. Then redo the depolarization protocol above, but this time describe what the currents do and how they might be influencing the voltage response. Which currents shape the spikes? Which remain active during the plateau and why? What happens to I_{h} during the depolarizing pulse and why? By plotting activation/inactivation variables you can answer these questions (and you can't measure these in the lab). Can you determine now why blocking one of the currents as we did above has the effect that it has? What effect does blocking one current, like I_{M}, have on the other currents? Why?

(5) Now examine the currents during the hyperpolarizing pulse. Which currents are turned on and why? Why does blocking the h current have the effect on voltage that it does?

(6) Do the depolarizing pulse protocol, looking at both voltage and currents, but with the $\mathrm{HVC_X}$ neuron. Which currents are contributing to the slowdown in the spiking (called *spike frequency adaptation*)?

(7) Do the hyperpolarizing pulse protocol with the $\mathrm{HVC_X}$ neuron. You should notice that V first declines, but then slowly rises during the hyperpolarizing pulse. This is called *sag* or *inward rectification*. What current makes this happen? Why didn't it happen with the $\mathrm{HVC_{RA}}$ neuron? When the hyperpolarization is over the cell produces a spike, called *post-inhibitory rebound*. Why? Why did this not happen with the $\mathrm{HVC_{RA}}$ neuron?