## Some points of confusion from our section today.

OK, today there were some blank stares in section. As it turns out, this happens every year with this problem set because this is the time in the course where the different concepts we've covered really start to come together and the individual sources of complexity start being stacked on top of each other. So I wanted to make sure that a few of the key points from today's problem set were emphasized.

We'll assume that we're looking at a glutamatergic CNS synapse with AMPA receptors. But the same principles apply to other ionotropic receptors as well. Let's look at the EPSP from a single presynaptic release event. This is what we'd measure in current clamp (i.e. just measuring the membrane voltage).
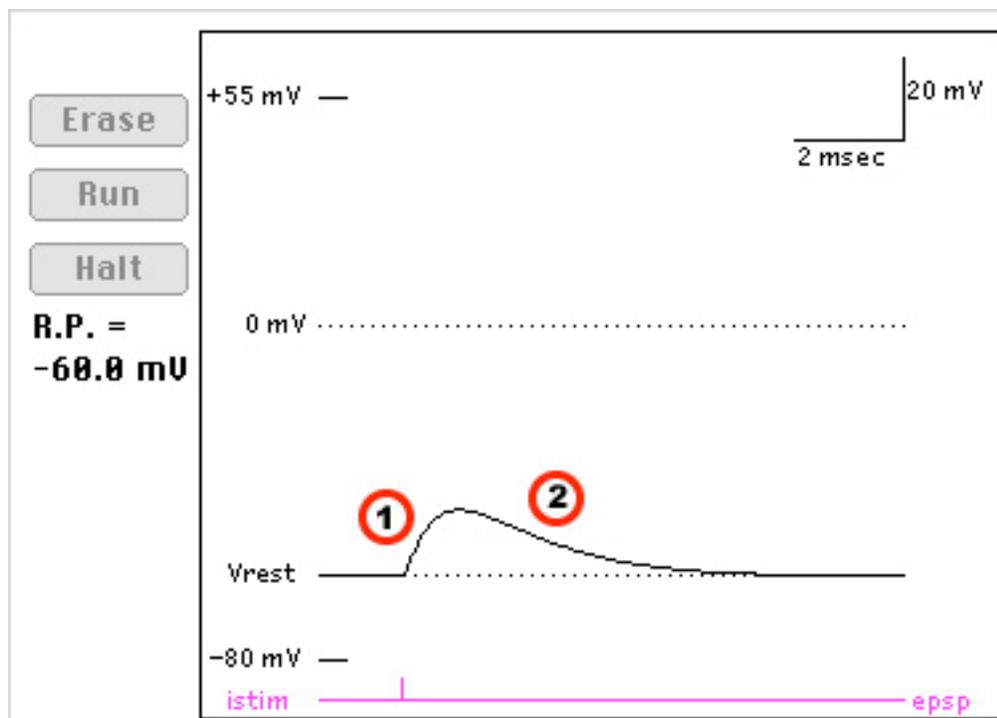
Note that it has a rapid rising/depolarizing phase (1), and a slower repolarizing phase (2). During phase (1) there must be a net inward/depolarizing current. This current flows through the activated AMPAR ion channels (which are permeable to both Na+ and K+ and so have a reversal potential near 0 mV). During phase (2) the membrane is hyperpolarizing, and so there must be a net outward current. This current flows through potassium-selective leak channels which are always open (i.e. they have a constant conductance). These two currents are not strictly separated in time (again, the leak conductance is constant), but the AMPAR current predominates early and the leak current predominates late in the EPSP (as the AMPARs close/desensitize).

Why does the depolarizing phase (1) have a more rapid rise than the repolarizing phase (2)? There are several reasons. Remember that the membrane time constant (τ = Rm*Cm) quantifies how quickly the voltage exponentially approaches a new steady state. For every unit time τ, the membrane voltage will move 63% closer to its new steady state. The membrane capacitance does not change; it is constant. The resistance, of course, can change. The greater the conductance of the opened channels, the shorter the time constant; that is, the more current will flow into the cell and the more rapidly the Vm will approach steady state. Therefore, during phase (1) when AMPAR + leak conductances are present τ is smaller than during phase (2) when the AMPAR conductance has markedly decreased.

But that's not the whole story. The other thing that can change is how far from steady state we are. That is, 63% of a large gap is more (in absolute terms) than 63% of a small gap. In our pspSim model, Vrest is –60 mV. If the AMPAR could be opened and kept open, the new steady state membrane potential would be –30 mV (halfway between –60 mV and 0 mV because the maximum value of the leakage and EPSP conductances are equal). What we see is that the Vm only gets halfway there or so before it starts relaxing back down to rest. So, the rising phase is the steep portion at the beginning of an exponential approach to –30 mV while the repolarizing phase is the slow portion at the "end" of an exponential approach back to –60 mV (loosely speaking). That is, the repolarizing phase would have a shallower slope (and therefore appear slower) even if the membrane τ was constant (which it is not).
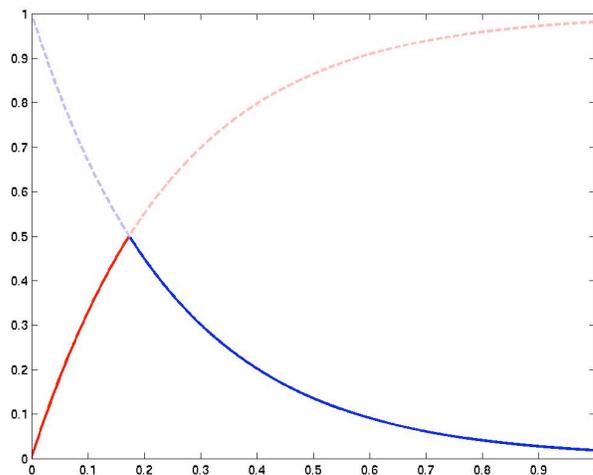

A exponential rise (in red) and decay (in blue) with the same tau. Note that for an exponential process the slope of the change depends on how far from steady state you are.

Lastly, as we drew on the board today, the presence of glutamate in the cleft also looks something like this with a quick rise time as the synaptic vesicle fuses and releases its glutamate into the cleft, and then a slower decay as the glutamate is pumped out and diffuses out of the cleft. The AMPAR conductance will track along with the glutamate concentration, but slightly delayed (because the channels have a time constant that defines how quickly they open in response to changes in ligand concentration). AMPAR conductance will also be affected by the amount of desensitization.

Each of these processes contributes to the difference in the absolute slope of the rising and falling phase of the EPSP. The fact that the AMPAR conductance, the membrane time constant, and the driving force are all changing in time means that neither phase would be fit well by a single exponential function. Nevertheless, these concepts are still very helpful in understanding the basic shape of the EPSP.

OK, now let's look at the currents, as displayed by the pspSim program:
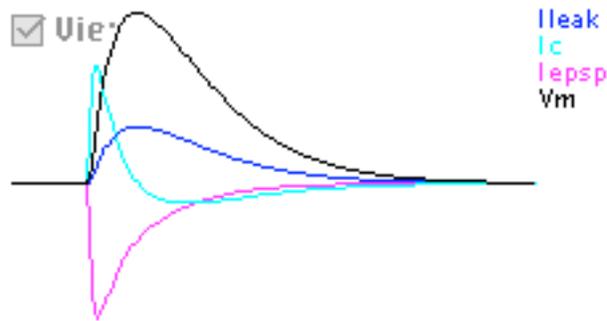
The membrane voltage (Vm) is plotted in black. We also plot the current through the leakage conductance (Ileak), the current through the AMPARs (Iepsp), and the total current flowing onto the membrane capacitance (Ic). Ic is just the total current; in this case the sum of Ileak and Iepsp (with the sign reversed).

Note that the Iepsp rises rapidly as glutamate binds to the AMPARs and opens the channels, and then decays more slowly as the channels close due to glutamate unbinding and channel desensitization. Ileak, you will note, is essentially a scaled version of the membrane voltage. This is because the leak conductance does not change, and so the only thing influencing the leak current is the driving force ($\Delta V = Vm - E_K$) according to Ohm's law: Ileak = ΔV * Gleak.

Note that the voltage increases until the total current (Iepsp + Ileak, or Ic) shifts from being outward (positive) to inward (negative).

Now for a subtlety. What's the difference between the Iepsp plotted here and the EPSC we discussed? The difference is that the EPSC is recorded in voltage clamp, and so Vm does not change. This gives us a profile of the current flowing through the AMPARs at different times after a vesicle release, *but at a fixed membrane voltage*. Or, since $I = \Delta V * G_{AMPAR}$, and ΔV is being held constant, it gives us a current which is proportional to the conductance of our AMPARs. The Iepsp, on the other hand, is affected both by the conductance of the AMPARs at any given point in time and by the driving force applied across that conductance (i.e. $\Delta V = Vm - E_{AMPAR}$) where, E_{AMPAR} is 0 mV as discussed above.)

That difference is illustrated by comparing the current and conductance plots in the experiment with five pulses (question number 3c):
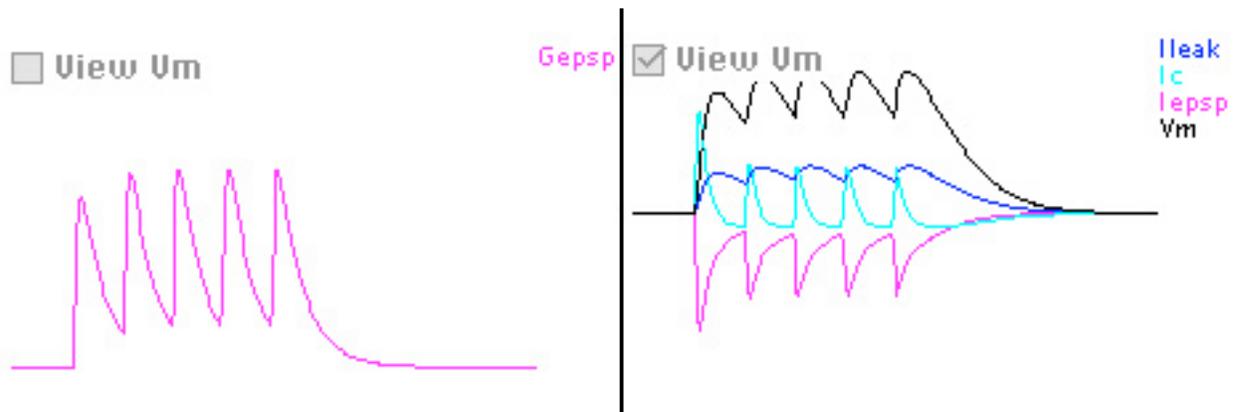
I have increased the maximal conductance of the postsynaptic receptors (Iepsp) here to accentuate the effect. Note that the conductance achieved for the final four pulses is actually larger than the first, but the Iepsp for the final four pulses is less. Why? The Vm for the final four pulses is closer to the reversal potential (0 mV) for the AMPAR channels, and so there is less driving force across the Gepsp.