## C. The Action Potential

Question 1. (points: 2) *Why does hyperpolarization cause a spike?*

Answer 1: Hyperpolarization causes a spike because of the very different time constants of the activation particles and inactivation particles of the sodium channels with respect to membrane voltage. At the beginning of the hyperpolarization h (deactivation particle) is close to 1, which means that the opening of the sodium channels depends on m, which rises exponentially in this situation. This causes the membrane to depolarize faster and faster. Now, the different responsiveness of h (slow) and m (fast) in this voltage-range causes that the channels are not closed fast enough to stay at the resting potential, but the fast depolarization overshoots this and causes a spike. This point is called the "Anodal break". After the membrane potential is around -40mV the response of h becomes faster again and the sodium channels close again, so that the membrane potential can get to its resting potential quite fast (through the now open potassium channels). The figure shows this characteristics. On the left side you can see a long stimulus I_e (blue line) and on the right a short one. The potential V_m (red line) and n, m, h were plotted in both cases.
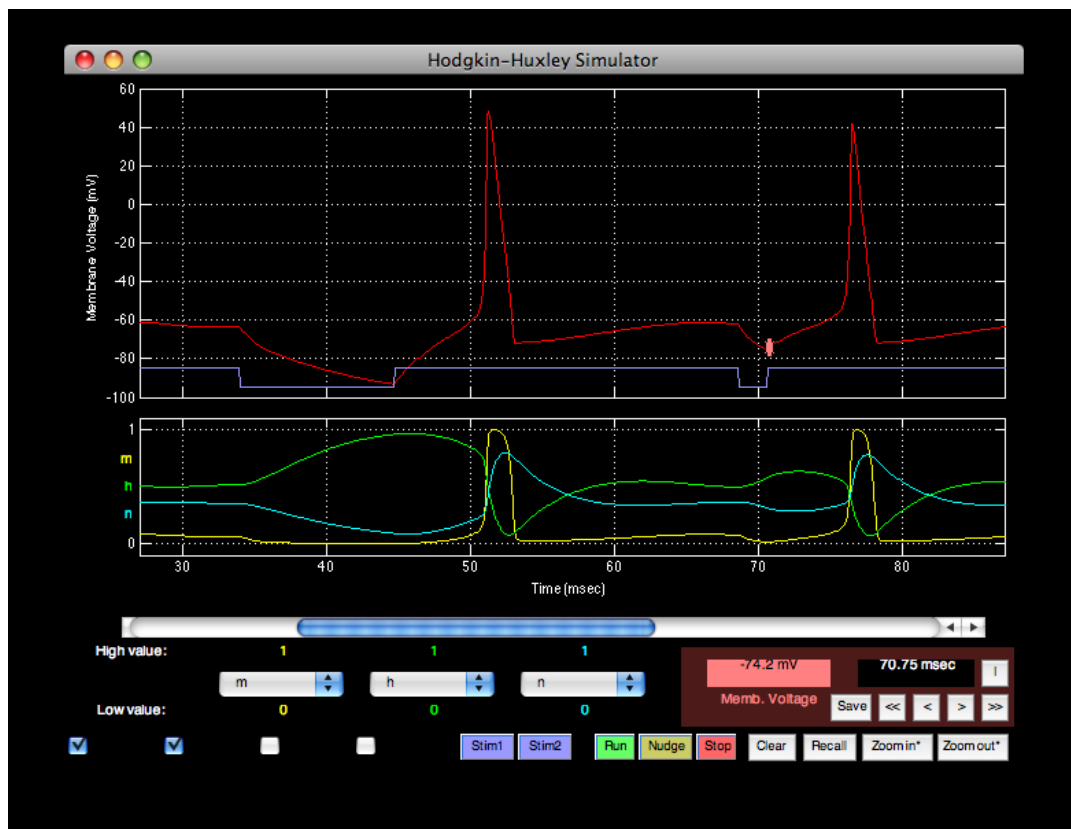
Question 2. (points: 2) *Why doesn't this second pulse cause a second spike? Phrase your answer in terms of gates and voltages. Consider the plot (yellow, green, and cyan lines) of m, h and n below the voltage. Recall that the fast sodium channel conductance is proportional to m^3h, and potassium channel conductance is proportional to n^4.*

Answer 2: Directly after a spike occurs, the Na inactivation gates h are still closed (e.g. $h = 0.05$) so that there can be no sodium influx. In addition K(V) gates are open (e.g. $n = 0.75$), pulling down the membrane potential (Vm).

Question 3. (points: 1) *How much time must elapse between the end of the first pulse and the beginning of the second in order for the second pulse to cause a second spike? (Use the simulator to experiment.)*

Answer 3: At minimum 8 msec must elapsed between the end of the first pulse and the beginning of the second.

Question 4. (points: 1) *To the nearest 10th of a millisecond, what is the longest delay after a 1 msec 5 nA positive pulse that a 1 msec -5 nA pulse can block a spike? Note: in order to get accurate results, be sure that Vm has returned to its asymptotic value of -62.7 mV before supplying the next stimulus. Click on the "Nudge" or "Run" buttons to give the simulator time to reach asymptote.*

Answer 4: 0.3 msec

D. The Fast Sodium Channel

Question 1. (points: 1) *Looking at the simulator output, at approximately what potential does the cell settle after the spike has subsided, i.e., what is the new resting value of Vm?*

Answer 1: $V_m = 6.25mV$

Question 2. (points: 3) *Starting with the equation,*

$$c_m \frac{dV(t)}{dt} = -i_m$$

calculate the conductance of the fast sodium channel in this new resting condition.

Answer 2: In the equilibrium the membrane potential does not change anymore so that:

$$0 = i_m$$
$$0 = g_L(V - E_L) + g_{Na}m^3h(V - E_{Na})$$

since we do not consider the potassium current here. With

$$g_L(V - E_L) = g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl})$$

the conductance g_{Na} can be calculated

$$0 = g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl}) + g_{Na}m^3h(V - E_{Na})$$
$$g_{Na}m^3h(V - E_{Na}) = -\left(g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl})\right)$$
$$g_{Na} = -\frac{1}{m^3h(V - E_{Na})}\left(g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl})\right)$$
$$g_{Na} = 0.2303 \text{ micro-Siemens}$$

Question 3. (points: 1) *Stimulating the cell again (using the "Stim1" button) in this condition will not cause another spike. Even if you raise the stimulus intensity to 20 nA and the duration to 10 msec, the cell will not spike. (Try it. Turn off the cyan plot by selecting "blank" in the pop-up menu so you can see the yellow and green plots clearly when you hit "Stim1".) What is the explanation for this?*

Answer 3: In this condition m and h are almost not affected by the stimulation. The activation and inactivation are balanced and no spike will occur.