

## Solution 2: Hodgkin and Huxley model

### A. Equilibrium Potential

**Question 1.** (points: 2) Calculate the effect of halving the external sodium concentration. Remember, we're assuming that only passive sodium channels are present. Use the simulator to confirm your answer by looking at the value of passive  $V_r$  in the Membrane window. (You can type new values into any of the boxes in the Membrane window, or use the "<" or ">" buttons to change the values.) Show the calculation and the results.

**Answer 1:** Calculation from the Nernst-equation:

$$V_{eq} = \frac{RT}{zF} \ln \frac{C_{out}}{C_{in}}$$

$$\text{With: } K = \frac{R}{zF} = 0.086173$$

$$\text{Full } C_{Na} = 440 \quad : \quad V_{eq} = (273.16 + 6.3)K * \ln \frac{440}{50} = 52.4mV$$

$$\text{Halve } C_{Na} = 220 \quad : \quad V_{eq} = (273.16 + 6.3)K * \ln \frac{220}{50} = 35.67mV$$

The simulation verified this value.

**Question 2.** (points: 2) Calculate the  $[Na^+]$  external concentration required to achieve  $V_r = 55.5 mV$ . Confirm your answer using the simulator.

**Answer 2:** Used:  $V_{eq} = 55mV$  and  $C_{in} = 50$

Convert the Nerst equation to  $C_{out}$ :

$$V_{eq} = TK * (\ln(C_{out}) - \ln(C_{in}))$$

$$C_{out} = e^{\frac{V_{eq}}{TK} + \ln C_{in}}$$

$$C_{out} = e^{\frac{55.5}{279.46+K} + \ln 50} = 500.7mMol$$

The simulation verified this value.

**Question 3.** (points: 2) Suppose we double the temperature from 6.3 degrees C to 12.6 degrees C. What is the new value of  $V_r$ ? Please explain short, why  $V_r$  doesn't double.

**Answer 3:**  $V_r = 53.6 mV$ . It does not double because the Nernst equation is linear in degrees K, not in degrees C.

## B. Membrane Potential

**Question 1.** (points: 1) Write down the parallel conductance equation for the resting potential as a function of equilibrium potentials and conductances. Given the equilibrium potentials shown in the Membrane window and the conductances shown in the Channels window, calculate the resting potential  $V_r$ . Show your work.

**Answer 1:** We use the parallel conductance equation and set  $I_{leak} = 0$

$$\begin{aligned}I_{leak} = 0 &= g_K(V - E_K) + g_{Na}(V - E_{Na}) + g_{Cl}(V - E_{Cl}) \\0 &= g_K V - g_K E_K + g_{Na} V - g_{Na} E_{Na} + g_{Cl} V - g_{Cl} E_{Cl} \\0 &= V(g_K + g_{Na} + g_{Cl}) - g_K E_K - g_{Na} E_{Na} - g_{Cl} E_{Cl} \\V(g_K + g_{Na} + g_{Cl}) &= g_K E_K + g_{Na} E_{Na} + g_{Cl} E_{Cl} \\V &= \frac{g_K E_K + g_{Na} E_{Na} + g_{Cl} E_{Cl}}{g_K + g_{Na} + g_{Cl}} \\V &= \frac{0.07 * -72.1 + 0.026 * 52.4 + 0.1 * -57.2}{0.07 + 0.026 + 0.1} \\V &= -47.8mV\end{aligned}$$

The simulation verified this value.

**Question 2.** (points: 2) You can see from the Channels window that  $g_K$  is 0.070 micro-Siemens. Calculate to two significant digits the value to which  $g_K$  would have to be reduced in order to make  $V_r$  be -45 mV. Show your work. Verify your answer by changing the value of  $g_K$  in the simulator and seeing how the value of passive  $V_r$  in the Membrane window changes.

**Answer 2:**

$$\begin{aligned}0 &= g_K(V - E_K) + g_{Na}(V - E_{Na}) + g_{Cl}(V - E_{Cl}) \\g_K(V - E_K) &= -g_{Na}(V - E_{Na}) - g_{Cl}(V - E_{Cl}) \\g_K &= \frac{-g_{Na}(V - E_{Na}) - g_{Cl}(V - E_{Cl})}{V - E_K} \\g_k &= \frac{-0.026 * (-45 - 52.4) - 0.1 * (-45 - -57.2)}{-45 - -72.1} \\g_k &= 0.0484 \text{ micro-Siemens}\end{aligned}$$

**Question 3.** (points: 1) Set  $g_K$  back 0.070 micro-Siemens. We can also manipulate the resting potential  $V_r$  by changing the ion concentrations. Obviously it is easier to change the concentrations outside the cell than inside. Suppose we want to raise the cell's resting potential to

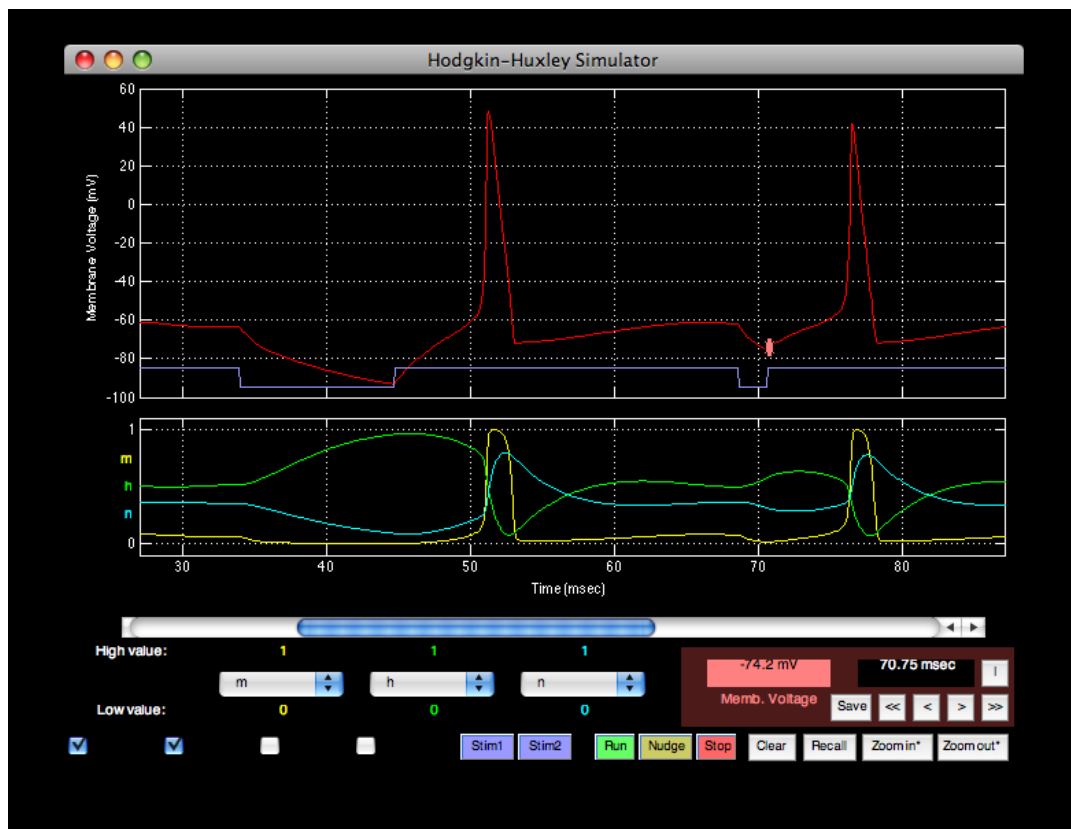
*-39 mV, while maintaining a constant osmolarity and not disturbing the charge balance. What ion concentrations should we change, and what should their new values be? Use the simulator to find the answer empirically.*

**Answer 3:** We should only change the concentrations outside the cell. Constant osmolarity means the number of ions must be constant. And we shouldn't disrupt the charge balance, so we can increment the  $Na^+$  ions and decrement the  $K^+$  ions or vice versa. The new values for -39 mV can be:  $K$  from 20 to 57.5 mMol;  $Na$  from 440 to 402.5 mMol.

## 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  $-40\text{mV}$  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 ( $V_m$ ).

**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 elapse 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  $V_m$  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  $V_m$ ?*

**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:

$$0 = \dot{i}_m$$

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

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

$$0 = g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl}) + g_{Na}m^3h(V - E_{Na})$$

$$g_{Na}m^3h(V - E_{Na}) = -(g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl}))$$

$$g_{Na} = -\frac{1}{m^3h(V - E_{Na})} (g_K^L(V - E_K) + g_{Na}^L(V - E_{Na}) + g_{Cl}^L(V - E_{Cl}))$$

$$g_{Na} = 0.2303 \text{ micro-Siemens}$$

**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.

## E. The Delayed Rectifier

**Question 1.** (points: 1) *Based on the  $V_m$  plot (red line), what is the approximate peak value reached by the membrane voltage?*

**Answer 1:** The peak is at around  $-15$  mV.

**Question 2.** (points: 2) *After reaching its peak, the membrane voltage quickly declines again, even though the stimulus is still on. What is causing this? Point to some evidence to support your answer.*

**Answer 2:** At the beginning the stimulus causes the  $I_K$  to fall pretty quick and the membrane potential rises rapidly. Then the potassium channels get opened very fast by the quickly rising  $n$  so that the cell hyperpolarises even when a stimulus is still present.

**Question 3.** (points: 2) *When the stimulus ends, the cell does not simply return to its resting value; it undershoots it and then approaches the value from below. Why doesn't it just return to its resting value?*

**Answer 3:** At this potential  $n$  has a significant activation, but a large time constant, which means a slow change. Therefore the channels are not closed fast enough to come to a rest at the resting potential but the membrane potential undershoots a bit.

## F. Voltage-Gated Channel Parameters

**Question 1.** (points: 1) *How does  $g_{max}$  for the fast sodium channel compare with the passive sodium conductance?*

**Answer 1:** The conductance of the sodium leak current is much smaller than  $g_{max}$  for the fast sodium channel.

**Question 2.** (points: 2) *What relationship must hold between the red (alpha) and blue (beta) lines for  $m$  to increase? Please describe first the common case and later the case for  $m = 0.5$ . In this case we assume, that no other mechanisms affect the cell. For  $m = 0.5$ , what is the approximate value of  $V_m$  and how does this compare to the cell's normal resting potential?*

**Answer 2:** The common case is described by the equations:

$$\begin{aligned}\frac{dm}{dt} &= \alpha(1 - m) - \beta m > 0 \\ \frac{m}{1 - m} &> \frac{\alpha}{\beta}\end{aligned}$$

In the case of  $m = 0.5$  the equation resolves to:

$$\begin{aligned}\frac{dm}{dt} &= \alpha(1 - 0.5) - \beta \cdot 0.5 > 0 \\ \alpha &> \beta\end{aligned}$$

So the red line ( $\alpha$ ) must be above the blue ( $\beta$ ) line. This occurs at around  $V_m = -40mV$  judging by the graph.

**Question 3.** (points: 1) *In order to stop the cell from oscillating on its own, we can change the passive channel conductance. Hit the "Run" button in the main simulator window to continue the simulation. By playing with the value of  $g_K$  in the Channels window, find a value close to the original value of 0.07 micro-Siemens that prevents the cell from spiking spontaneously. The cell should of course still spike in response to a stimulus from the Stim1 button. Report the  $g_K$  value you find, to two significant digits.*

**Answer 3:**  $g_K = 0.18$  micro-Siemens