Announcements

Hodgkin-Huxley reports are due on Day 61. Please note that there is a severe lateness penalty.

Hodgkin-Huxley oral reports will be given on Day 61.

There is no lecture on Day 61.

Please have breakfast with the staff on Day 64. We are interested to hear your comments about the class and your suggestions about ways the class could be improved. Lecture on that day is cancelled.

Exercise 1. Explain why the gating current is outward in response to a depolarization independent of the sign of the charge on the gate.

Exercise 2. A cell contains ionic channels that are permeable to sodium only and have linear voltage-current characteristics. When these channels are open they have a single-channel conductance of 30 pS. The internal and external concentrations of sodium are 20 and 200 mmol/L, respectively, and the membrane potential is maintained at $-20$ mV.

a) Determine the number of sodium ions per second that flow through an open channel.

b) In which direction through the membrane do the ions flow?

Exercise 3. Describe a prediction of the single channel model with one two-state gate that is inconsistent with measurements of ionic currents through the potassium channels in squid giant axons.
Problem 1. Transport of an ion through a cell membrane can be represented by a population of voltage-gated channels where each channel contains one two-state gate. The two states are state $S_0$ and state $S_1$ and transitions between these states obey first-order kinetics with voltage dependent rate constants.

$$S_0 \xrightarrow{\alpha(V_m)} S_1 \xrightarrow{\beta(V_m)} S_0.$$ 

In response to a step of voltage across the channel, the state occupancy of the channel, the single-channel current, and the probability that the channel occupies state $S_1$ are shown in the following figure.

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a) For which state is the channel non-conducting?

b) Determine both the equilibrium (reversal) potential for conduction through this channel and the conductance of the channel when the channel is conducting.

c) For $V_m = 20$ mV determine the rate constant $\alpha(20)$ and $\beta(20)$ where the voltage is expressed in mV.

d) Sketch the probability that the channel occupies state $S_0$ as a function of time.

e) Briefly describe one experimental method that can provide an estimate of channel density. Be specific about which data you propose to use and how you propose to estimate the density from these data.

f) Measurements indicate that there are 1000 channels per $\mu$m$^2$ in the membrane of this cell. Sketch the ionic current density $J_m(t)$ that would be expected with the voltage step shown in the figure. Indicate relevant dimensions on the sketch.
Problem 2. The voltage across a membrane patch is stepped from $V_m^i$ to $V_m^f$ at time $t = 0$. Typical single-channel ionic and single-channel gating currents are shown in Figure 1 as a function of time for 3 different values of $V_m^f$. In each case, $V_m^i = 0$.

![Diagrams of ionic and gating currents](image)

Figure 1: Single-channel ionic and single-channel gating currents.

a) Is the open-channel voltage-current characteristic of this channel linear or nonlinear? Explain.

b) Do the ionic currents show any evidence of that the channel is voltage-gated? If so, what’s the evidence?

c) Compute the conductance of the open channel.

d) Compute the equilibrium (reversal) potential for this channel.

e) Estimate the probability that the channel is open when $V_m^f$ is equal to $-50$, $-100$, and $-150$ mV.

f) Are the measured gating currents consistent with a two-state channel model? Explain.

g) It has been proposed that the three-state model shown in Figure 2 could account for the both ionic and gating currents shown in Figure 1. Assume that $Q_2 = Q_0$, and that $Q_1 > Q_0$. Are
there values of $\gamma_0$, $\gamma_1$, and $\gamma_2$ that are consistent with the measurements? If so, what are they? If not, why not?

**Problem 3.** Figure 3 shows a model of a voltage-gated ion channel with one three-state gate plus representative single-channel ionic and gating current records.

Figure 3: Channel with one three-state gate. The left panels illustrate the three states: states 1 and 3 are open states, state 2 is a closed state. The right panels illustrate the responses of the channel to a step in membrane potential $V_m(t)$ at time $t = 0$ (top right) which gives rise to the ionic current $\tilde{i}(t)$ and gating current $\tilde{i}_g(t)$ illustrated in the middle right and lower right panels, respectively.

a) Assume that the voltage-current characteristic of the channel is the same for states 1 and 3 and is linear. Determine the open channel conductance and equilibrium (reversal) potential for this channel.

b) The ionic current trace shown in Figure 3 has three non-zero segments. Determine which state the gate is in during each non-zero segment. Explain your reasoning.

c) Figure 4 illustrates the dependence of the steady-state probability that the channel will be in each of its three states on the membrane potential. Let $i_{ss}$ represent the average value of the ionic current that results after steady-state conditions are reached in a voltage clamp experiment in which $V_m$ is held constant. Assume that the experiment is repeated for a
Figure 4: Steady-state probabilities for a channel with one three-state gate. \( x_{1\infty} \), \( x_{2\infty} \), and \( x_{3\infty} \) represent the steady-state probabilities of being in state 1, state 2, and state 3, respectively, as a function of membrane potential.

number of different values of membrane potential \( V_m \). Plot the relation between \( i_{as} \) and \( V_m \). Describe the important features of your plot.