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Quantitative Physiology: Cells and Tissues

Homework Assignment #10 Issued: December 7, 2006
Not to be submitted or graded

Exercise 1. Explain the origin of gating current.

Exercise 2. State whether each of the following are true or false and give a reason for your answer.

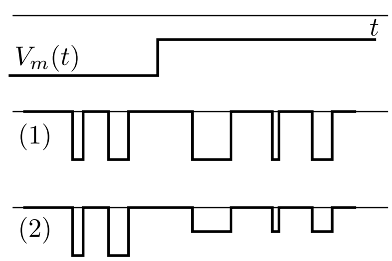
a) Tetrodotoxin blocks the flow of potassium through the sodium channel.

b) The macroscopic sodium current recorded by an electrode in a cell is a sum of the single-channel sodium currents that flow through single sodium channels.

c) The macroscopic sodium current recorded by an electrode in a cell is the average of the single-channel sodium currents that flow through single sodium channels.

d) Ionic and gating currents give identical information about channel kinetic properties.

Exercise 3. The following figure shows two putative records of membrane currents recorded from two membrane patches, each of which contains a single channel, in response to a step of depolarizing membrane potential.

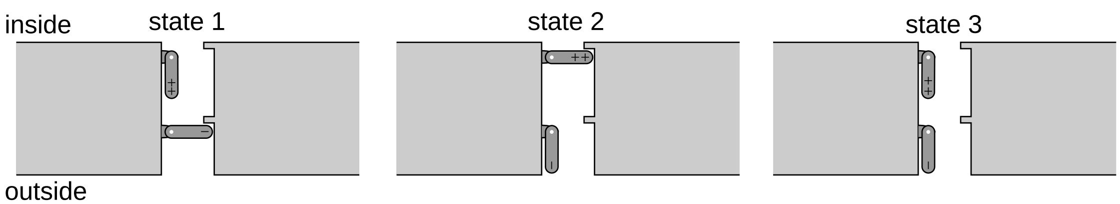


Each of these channels has a linear voltage-current characteristic when the channel is open.

a) Which, if any, of these records could be from a single, voltage-gated channel? Explain.

b) Which, if any, of these records could be from a single channel that is not voltage-gated? Explain.

Exercise 4. Consider a model for an ion channel that consists of 2 two-state gates. One of the gates has a positive gating charge while the other has a negative gating charge, and the magnitude of the positive gating charge is twice that of the negative gating charge. Furthermore, the channel can be in one of **ONLY 3 STATES**, which are illustrated in the following figure.



Assume that the gates open and close very rapidly, and that we can ignore the possibility that the positive gate and negative gate change state at the same time. Assume that the channel is open only if both gates are open and that the open-channel current-voltage relation is linear with a reversal potential equal to 0. Consider the response of such a channel in a voltage clamp experiment in which the voltage is changed from a very negative V_m^i to a very positive V_m^f at $t = 0$. Determine whether the following statements are true or false. Briefly explain your reasoning.

Part a. State 1 is most likely when the membrane potential is very negative.

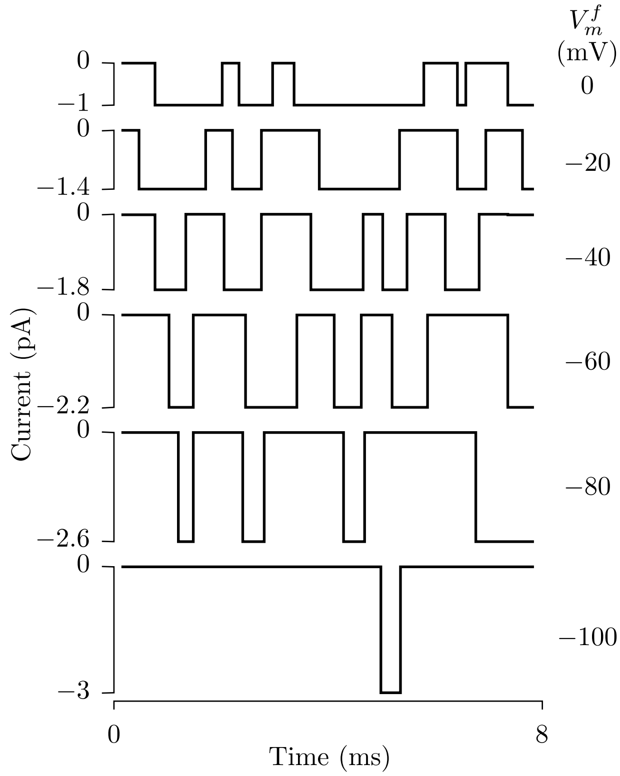
Part b. The average gating current for $t > 0$ will contain a transient outward component followed by a transient inward component.

Part c. The average ionic current for $t > 0$ will be persistent and outward.

Part d. The positive and negative gates cannot be statistically independent of each other.

Part e. There are only 4 possible state transitions.

Problem 1. The voltage across a membrane patch is stepped from V_m^o to V_m^f at $t = 0$ and single-channel ionic currents are recorded as a function of time. Typical records at 6 different values of V_m^f are shown in the following figure.



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

b) What is the conductance of the open channel?

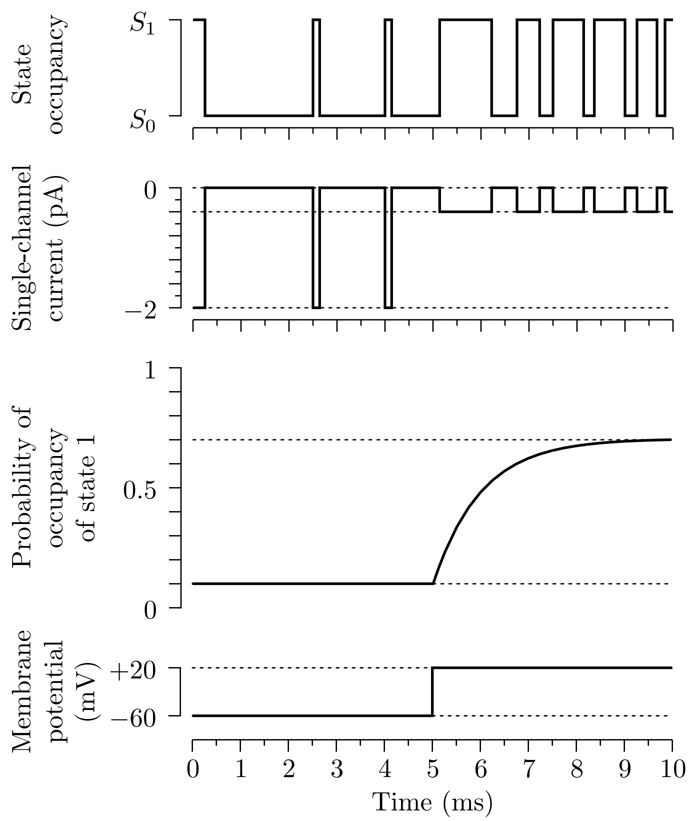
c) What is the equilibrium (reversal) potential for this channel?

d) It is proposed that this channel is the voltage-gated sodium channel responsible for sodium-activated action potentials. Discuss this suggestion.

Problem 2. 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.

$$S_0 \underset{\beta(V_m)}{\overset{\alpha(V_m)}{\rightleftharpoons}} S_1.$$

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.



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.

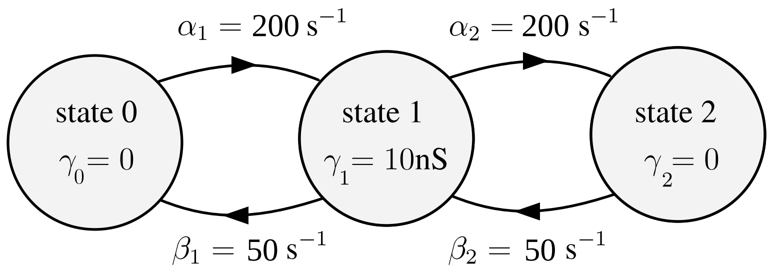
c) For $V_m = 20$ mV determine the rate constant $\alpha(20)$ and $\beta(20)$ where the voltage is expressed in mV.

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

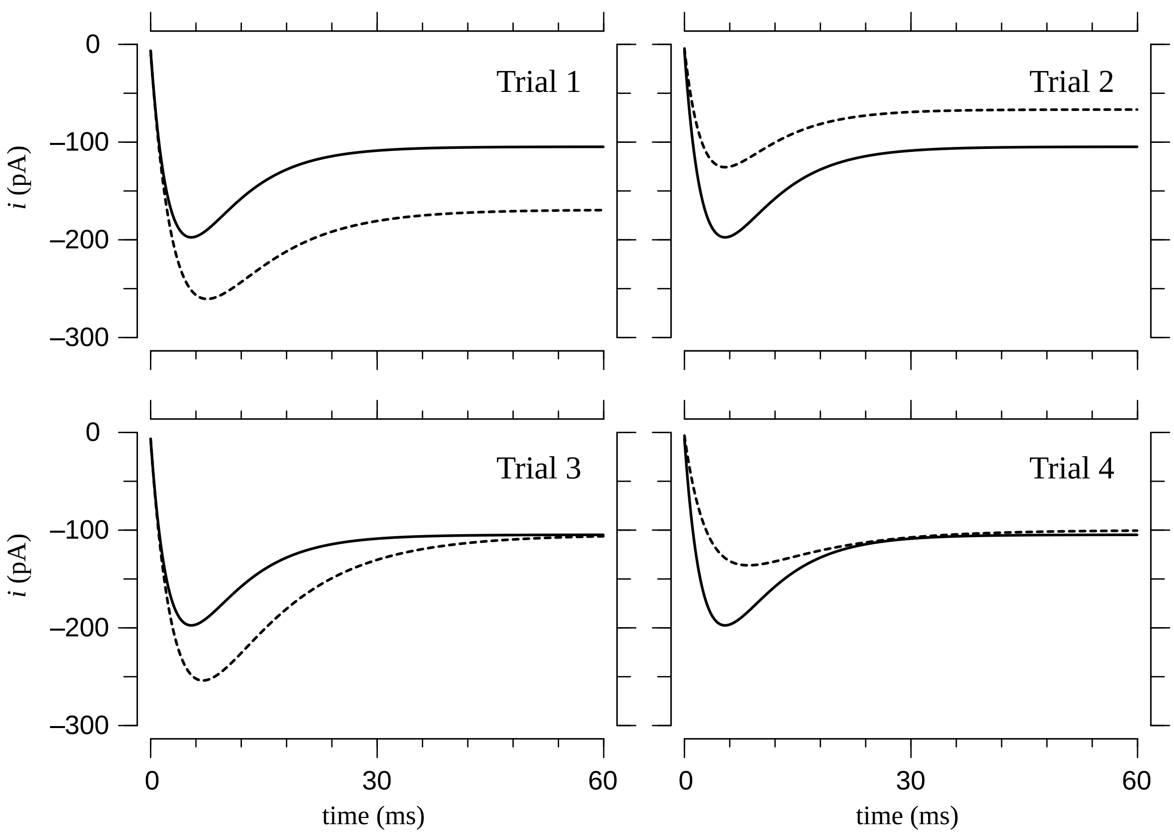
e) Briefly describe one experimental method that can provide an estimate of channel density. Be specific about which data you propose to use and how you propose to estimate the density from these data.

f) Measurements indicate that there are 1000 channels per μm^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 3. The following figure shows the state transition diagram for a three-state model of a voltage-gated sodium channel. The conductivity of the channel is 10 nS in state 1 and is zero otherwise. The Nernst potential for sodium is 55 mV.



The solid curves in the following panels show the average channel current under voltage clamp conditions. For $t < 0$, the membrane potential is held at $V_m^i = -60$ mV and the channel is in state 0. For $t > 0$, the membrane potential is stepped to $V_m^f = 0$ and the forward and backward rates are constants, as shown in the figure.



The dashed curves in each of the panels show the average channel current that results when one or two of the parameters of the model are changed, as follows:

- α_1 is decreased by a factor of 2
- α_2 is decreased by a factor of 2
- c^o_{Na} is decreased by a factor of 2
- α_2 and β_2 are both decreased by factors of 2

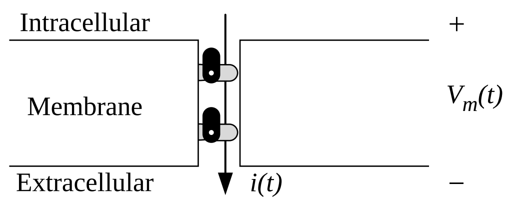
Part a. Which trial shows results when α_1 is decreased by a factor of 2? Briefly explain.

Part b. Which trial shows results when α_2 is decreased by a factor of 2? Briefly explain.

Part c. Which trial shows results when c^o_{Na} is decreased by a factor of 2? Briefly explain.

Part d. Which trial shows results when α_2 and β_2 are both decreased by factors of 2? Briefly explain.

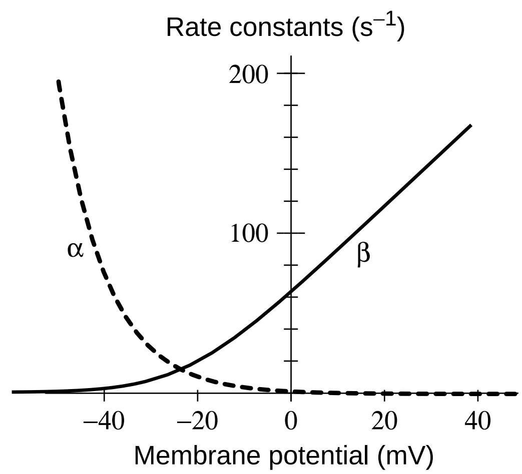
Problem 4. Consider a model of an ion channel with 2 identical, statistically independent gates. Each gate has 2 states: open (up) and closed (down). The channel is open if both gates are open and is closed if one or both of the gates are closed, as shown in the following diagram.



Transitions between the open and closed states are governed by first-order kinetics:

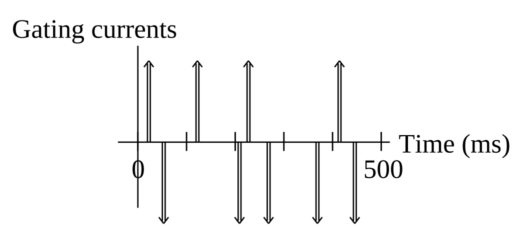
$$C_g \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O_g$$

where the transition from the closed state C_g to the open state O_g has a forward rate constant $\alpha(V_m)$ and reverse rate constant $\beta(V_m)$, both of which depend on membrane potential V_m as shown in the following plot.



a) Estimate the steady-state probability that the channel will be open if the membrane potential is clamped at $V_m = -20$ mV. Briefly explain.

b) The channel is voltage clamped with $V_m = -25$ mV for several minutes and then gating currents for a single channel are observed. The following plot shows results during the time from $t = 0$ to 500 ms.



Which of the following statements are true? Briefly explain your reasoning.

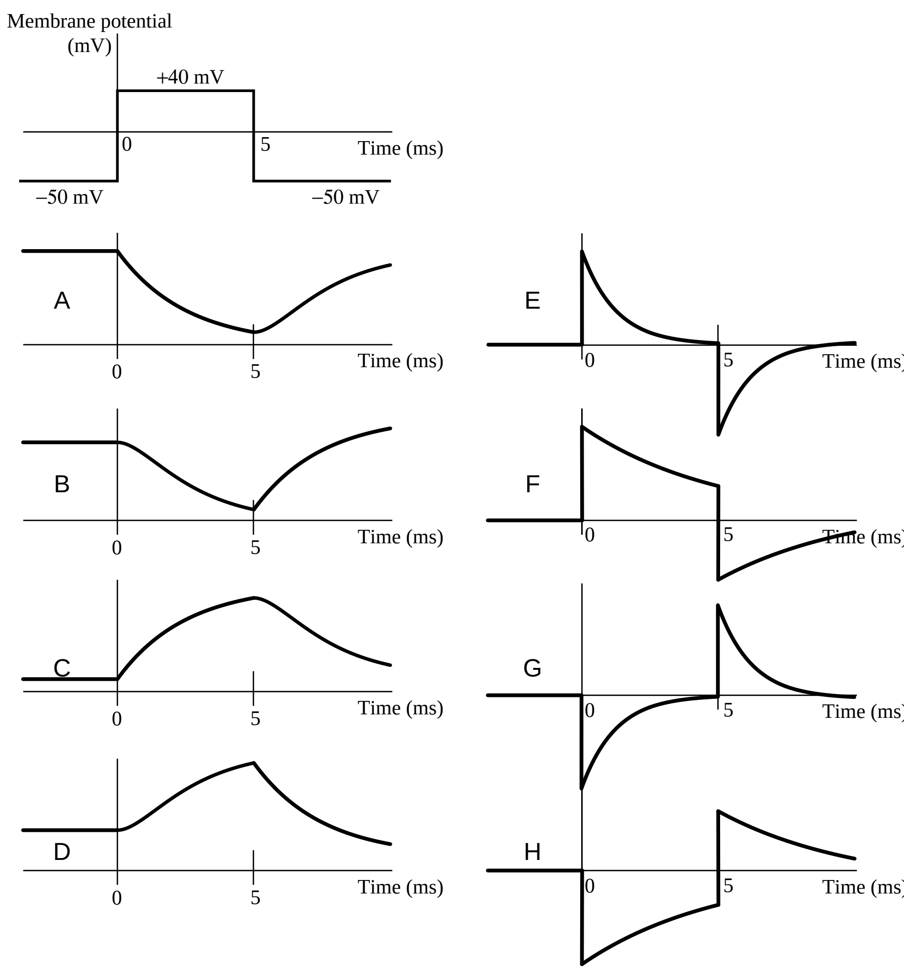
b1) Positive gating currents occur when a gate opens and negative gating currents occur when a gate closes.

b2) Both gates are closed at time $t = 400$ ms.

b3) The channel is open for less than 100 ms between times $t = 0$ and 400 ms.

b4) If the experiment were repeated with V_m clamped at $+20$ mV, the average number of gating current impulses per second should decrease.

c) The membrane potential is held at -50 mV for a long time and stepped to $+40$ mV at $t = 0$ and then returned to -50 mV at $t = 5$ ms.



c1) Which if any of plots A to H represents the average conductance of the channel? Briefly explain.

c2) Which if any of plots A to H represents the average gating current of the channel? Briefly explain.