Exercise 1. 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 2. 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.

Exercise 3. Consider a two-state gate with the kinetic diagram

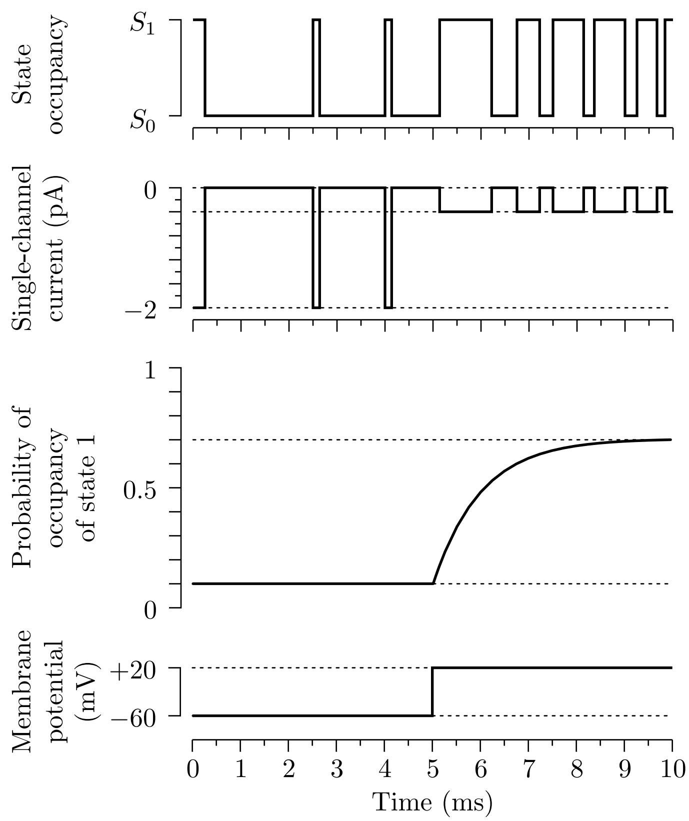
$$C_g \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} O_g.$$

Determine a kinetic diagram for the Hodgkin-Huxley model of the potassium channel which consists of 4 independent two-state activation gates. Determine all the states and the transition rates between states.

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.

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

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 2. Three three-state voltage-gated channels (channels a, b, and c) have the kinetic diagram and state occupancy probabilities shown in Figure 1. These channels have the same voltage dependent rate constants and the same equilibrium potential which is +40 mV. For the membrane

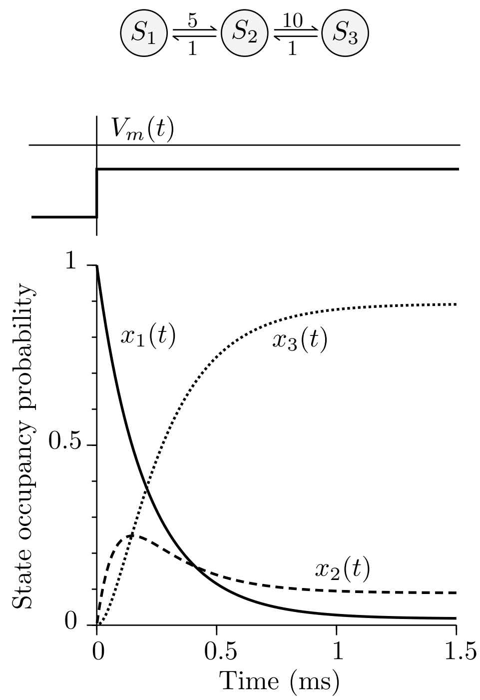


Figure 1: State diagram and occupancy probabilities for a three-state channel. The state occupancy probabilities for states S_1, S_2, and S_3 are $x_1(t)$, $x_2(t)$, and $x_3(t)$, respectively.

potential shown, the channels are in state 1 with probability 1 for $t < 0$ and have the indicated rate constants for $t > 0$. The channels differ only in their state conductances and state gating charges as shown in Figure 2. Denote the expected values of the single-channel random variables as follows: the conductance as $g_a(t)$, $g_b(t)$, and $g_c(t)$; the ionic currents as $i_a(t)$, $i_b(t)$, and $i_c(t)$; the gating charges as $q_a(t)$, $q_b(t)$, and $q_c(t)$; the gating currents as $i_{ga}(t)$, $i_{gb}(t)$, and $i_{gc}(t)$.

a) Which of the waveforms shown in Figure 3 best represents $g_b(t)$? Explain.

b) Which of the waveforms shown in Figure 3 best represents $g_c(t)$? Explain.

c) Which of the waveforms shown in Figure 3 best represents $i_{ga}(t)$? Explain.

d) Which of the waveforms shown in Figure 3 best represents $i_{gc}(t)$? Explain.

e) Which of these channel models exhibits activation followed by inactivation of the ionic current? Explain.

f) Which of these channel models exhibits an ionic current that does not inactivate? Explain.

g) Which of these channel models represents a channel that closes on depolarization? Explain.

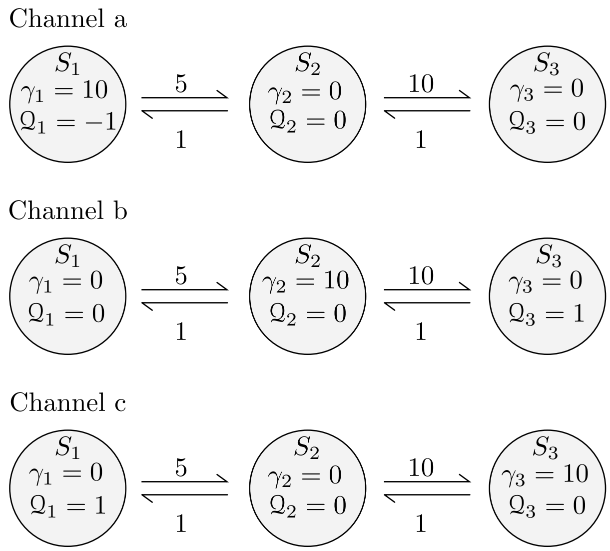


Figure 2: State diagrams of three three-state channel models. The models differ in state conductances and state gating charge but not in rate constants.

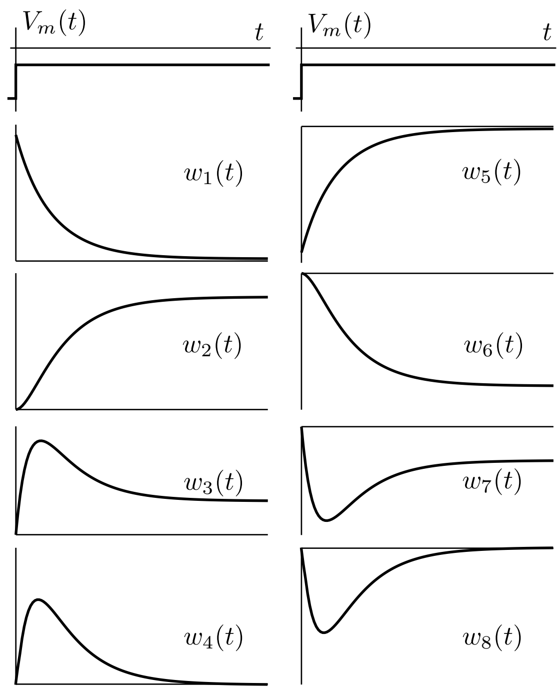


Figure 3: Waveforms of responses. The horizontal axis corresponds to $w(t) = 0$, and the vertical axis to $t = 0$.

Problem 3. A single channel contains one two-state activation gate whose kinetic diagram is

$$C \underset{\beta(V_m)}{\overset{\alpha(V_m)}{\rightleftharpoons}} O,$$

where C is the closed state and O is the open state. $\alpha(V_m)$ and $\beta(V_m)$ are the voltage-dependent forward and reverse rate constants, respectively. The channel is permeable to sodium ions only. The current through the open channel is

$$\mathcal{I} = \gamma(V_m - V_{Na}),$$

where V_{Na} is the Nernst equilibrium potential for sodium.

Figure 4 shows single channel ionic current variables in response to a voltage step. Row 1

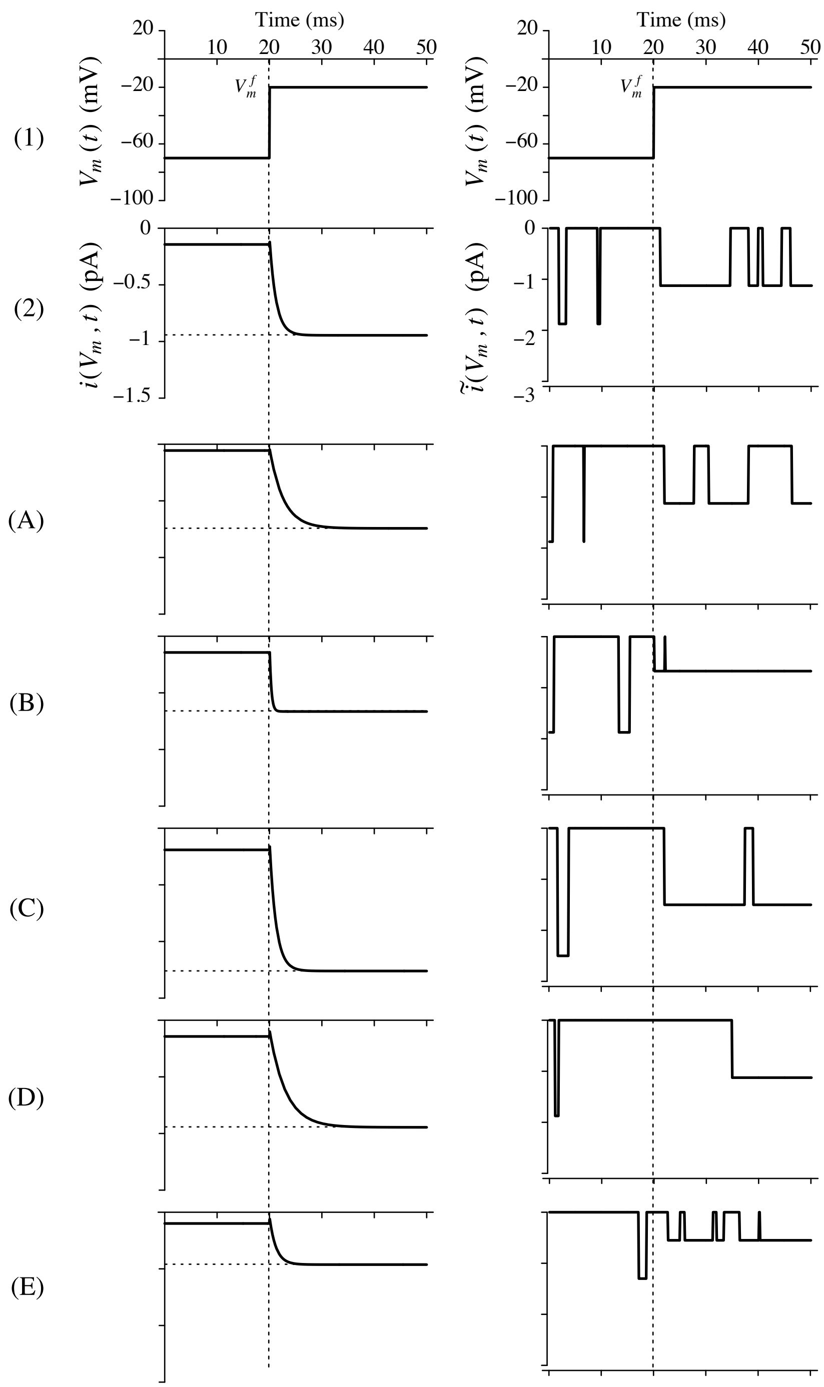


Figure 4: Single channel currents of a channel with one two-state activation gate. The scales for the results shown in rows A-E are the same as for row 2.

shows the membrane potential. In the remaining rows, the right panels show single-channel ionic current random variables and the left panels show average single-channel currents. Row 2 illustrates results for a default set of parameters. Rows A-E show results when one or two parameter values are changed. Determine which of rows A-E corresponds to each of the following changes and give a brief reason for your choice.

a) The single-open-channel conductance γ was increased.

b) The final value of the membrane potential V_m^f was increased.

c) The extracellular concentration of sodium was decreased.

d) Both $\alpha(V_m)$ and $\beta(V_m)$ were decreased without changing the ratio $\alpha(V_m)/\beta(V_m)$.

e) Only $\alpha(V_m)$ was decreased.

Problem 4. Figure 5 shows a model of a voltage-gated ion channel with one three-state gate plus representative single-channel ionic and gating current records.

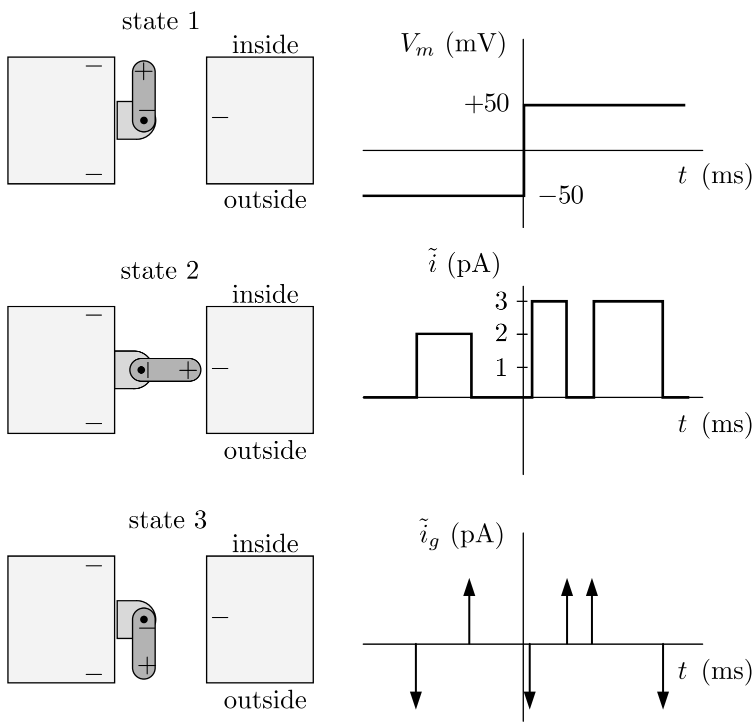


Figure 5: Channel with one three-state gate. The left panels illustrate the three states: states 1 and 3 are open states, state 2 is a closed state. The right panels illustrate the responses of the channel to a step in membrane potential $V_m(t)$ at time $t = 0$ (top right) which gives rise to the ionic 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 5 has three non-zero segments. Determine which state the gate is in during each non-zero segment. Explain your reasoning.

c) Figure 6 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 number of different values of membrane potential V_m. Plot the relation between i_{ss} and V_m. Describe the important features of your plot.

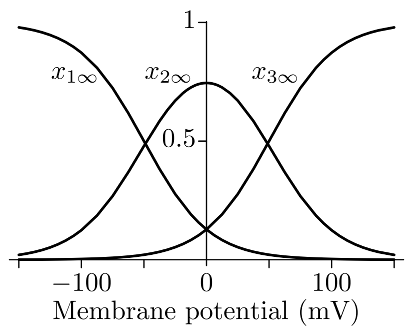


Figure 6: Steady-state probabilities for a channel with one three-state gate. $x_{1\infty}$, $x_{2\infty}$, and $x_{3\infty}$ represent the steady-state probabilities of being in state 1, state 2, and state 3, respectively, as a function of membrane potential.