

VOLTAGE ACTIVATED CHANNELS

A. Background

An excitable nerve has voltage activated Na^+ and K^+ channels. We can no longer use the constant values for g_K and g_{Na} we used in the last exercise on the passive cells. We will begin with the axon model we developed in the last exercise and patch in some voltage activated K channels (slow K gates). The Na channels will be dealt with later.

Hodgkin and Huxley assumed that the K conductance, g_K , is controlled by 4 independently operating charge “gating charges”. In order for the channel to open each of these charges must be in its correct configuration. They assumed that the *fraction* of these charges in the “open” state, denoted by $n(t)$, followed the equation:

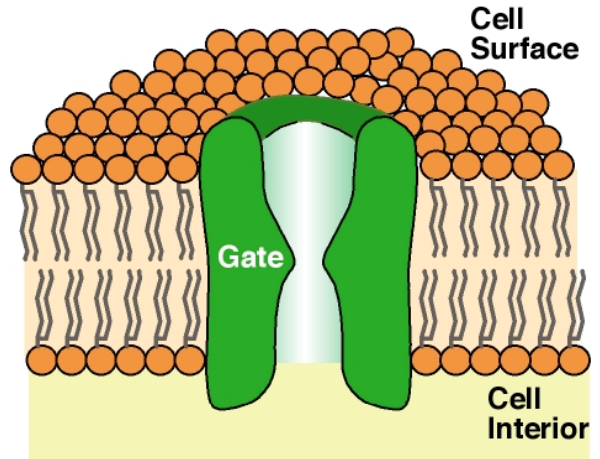


Figure 1

$$\frac{dn}{dt} = \underbrace{a_n(1-n)}_{\text{production rate}} - \underbrace{b_n n}_{\text{decay rate}}, \quad 0 < n < 1 \quad (1)$$

and that the conductance of the channels depended very nonlinearly on n :

$$g_k = G_k \cdot n^4 \quad (2)$$

where G_K is the maximum K^+ conductance ($= 36 \text{ mmho/cm}^2$). For now, we set this equal to a constant. In general n will vary with both membrane potential (it is voltage activated) and time. Our immediate problem is to specify how this happens).

To solve this equation we have to supply initial values for n as well as values for the constants a_n and b_n . Initial values for n are obtained by assuming that, prior to stimulation, the nerve has been in a steady (resting) state with $E = E_r$. In the resting state nothing is changing, including n ; therefore, the rate of production is equal to the rate of decay:

$$n_{\text{initial}} = \frac{a_n}{(a_n + b_n)} \quad (3)$$

In general, the values of a_n and b_n depend on E ; values for a_n and b_n corresponding to any particular E are obtained from the following empirical equations:

$$\begin{aligned} a_n &= 0.01 (E+55)/(1-\exp(-(E+55)/10)) \\ b_n &= 0.125 \cdot \exp(-(E+65)/80) \end{aligned} \quad (4)$$

This is how the voltage activation enters into the simulation. The correct values to use in the above equation for the initial value of n correspond to $E = E_r$. (This will automatically occur if you don't start the stimulus at $t = 0$; i.e. make sure that $\text{ontime} > 0$).

B. Procedure

1. Begin by running your simulation for 8 msec with a $dt = 0.03$ msec. Use a square wave stimulus with $intensity = 100$, $ontime = 1$, and $offtime = 1.3$. Plot the stimulus and membrane potential on the same graph.
2. Increase the size of the stimulus. Is there a threshold? Is the response “all or none”?
3. Increase the $intensity$ to 500, and include the number of open K channels (either n^4 or g_K) in your plot. You can see from the plot how n^4 or g_K lags behind the stimulus; the K gates are slow to respond. Following the stimulus, notice how E dips below its resting value only to return to it several msec later. This same dip is seen in fully formed action potentials and is due to the slow response of the K gates—they are not only slow in responding to a depolarization, they are also slow in returning to their normal configuration once the depolarization is removed.
4. Set the intensity to 500 and the duration (i.e. $offtime - ontime$) to 5 msec. Interpret the results.

You can modify the expression for g_K in your simulation in the following way to make it easier to take out or patch in the voltage activated K channels. Remembering that for the passive axon $g_K = 0.425 \text{ mmho/cm}^2$ (Table 1 of that exercise) we can write

$$g_k = G_{k0} G_k n^4 + 0.425(1 - G_{k0}) \quad (5)$$

Now by simply setting each $G_{K0} = 1$ we simulate an axon with voltage activated K channels present. With $G_{K0} = 0$ we simulate an axon with passive (non voltage activated) K channels.

Voltage activated Na⁺ channel

Now we add voltage activated Na channels. These are more complex; each channel contains two gates, a slow one and a fast one. Both gates have to be open simultaneously before Na can pass through one of these channels. Na conductance is described by

$$g_{Na} = G_{Na} m^3 h \quad (6)$$

where

G_{Na} = maximal Na⁺ conductance = 120 mmho/cm² (constant)

m^3 = the fraction of the total number of *fast* Na gates that are open at any time.

h = the fraction of the total number of *slow* Na gates that are open at any time.

m^3 and h vary between 0 and 1 and depend on both E and t. They accumulate as follows:

	Rate of production	Rate of decay
m	$a_m(1-m)$	$b_m m$
h	$a_h(1-h)$	$b_h h$

As in the case of the K channel, we have to supply initial values for m and h . as well as values for the a 's and b 's. Initial values for m and h are obtained by assuming that, prior to stimulating, the nerve has been in a steady (resting) state with $E = E_r$. Therefore, the production rates of m and h are equal to their decay rates . Using the Table above to apply these criteria, we can solve for initial values as

$$m_{initial} = \frac{a_m}{a_m + b_m}$$

$$h_{initial} = \frac{a_h}{a_h + b_h} \quad (7)$$

In general, the values of the a's and b's depend on E . Again, the correct values to use in the above equations correspond to $E = E_r$, and this will automatically occur if you don't start the stimulus at $t = 0$; i.e. make sure that *ontime* > 0.

Values for a's and b's which reflect their change in E as it departs from E_r are obtained from the following :

$$\begin{aligned} a_h &= 0.07 \exp(-(E+65)/20) \\ a_m &= 0.1 (E+40)/(1 - \exp(-(E+40)/10)) \\ b_h &= 1.0/(\exp(-(E+35)/10)+1) \\ b_m &= 4.0 \exp(-(E+65)/18) \end{aligned} \quad (8)$$

Just as in the case of the K channels, you can modify the expression for g_{Na} in your simulation to make it simple to take out the voltage activated Na channels or patch them back in at your convenience. Remembering that for the passive axon (Table 1 of that exercise) $g_{Na} = 0.0167 \text{ mmho/cm}^2$, we can write

$$g_{Na} = G_{Na0} \cdot G_{Na} \cdot m^3 h + 0.0167(1 - G_{Na0}) \quad (9)$$

With $G_{Na0} = 1$, voltage activated Na channels are active; with $G_{Na0} = 0$, they are deactivated.

Stimulating the axon

Leaving both Na and K voltage activated channels in your model should be sufficient to reproduce most of the excitation behavior of real axons.

5. As before, run your simulation for 8 msec with a $dt = 0.03$ msec. Use a square wave stimulus with *intensity* = 100, *ontime* = 1, and *offtime* = 1.3. At first plot the stimulus and membrane potential on the same graph.

6. Once you have succeeded in obtaining an action potential experiment with:

- a. the *intensity* (e.g. reverse it)
- b. the *offtime*
- c. the shape of the stimulus (e.g. a ramp or an alternating current sine wave)
- d. two stimuli in a row

7. See if you can reproduce some of the classical results described in your text books. E.g.

- a. threshold
- b. all or none behavior
- c. refractory period
- d. accommodation

8. You are now in a position to explore the details of nerve excitation in depth by plotting any of the variables you choose. The Na^+ and K^+ currents yield the actual flow of these ions at each instant. The conductances are a measure of the number of open channels at each moment. m^3 is a measure of the fraction of fast Na gates that are open, while h measures the fraction of slow gates. You can measure the

actual amount of Na that moves in with each impulse and estimate how fast the Na pump would have to operate to pump it back out during rest. You can mimic a TTX poisoned axon simply by reducing (or abolishing) G_{Na} . You can study the effects of hyperpolarization and find that at more negative resting potentials, there are more Na channels available. You can replace the equilibrium potentials with converters that calculate them in terms of ion concentrations (as in the passive cell exercise) and study effects of changing ion concentrations on excitation.

Optional

Plot the parameters a and b as a function of E . Plot the steady state values of n , m , and h —given by $a_X/(a_X+b_X)$ —as a function of E and compare them in terms of opening or closing with depolarization (E becoming more positive). The apparent time constants of n , m , and h are given by $1/(a_X+b_X)$. Plot these as a function of voltage and compare them in terms of fast and slow gates.

1. Set $I_{stim} = 0$ and plot the steady state E that results when K_o takes on values of 1, 5, 10, 50, 100, and 200 mM. (Get the results from Madonna, but you will have to plot them yourself on graph paper. Compare these results (on the same plot) with the results you would expect if the membrane was permeable only to K.
2. How do these results change if you increase g_K by a factor of 10? If you decrease it by a factor of 10?
3. Repeat a and b for Na^+