3.5 The Hodgkin–Huxley Equations for the Nerve Action Potential

The basic mechanism for control of cell volume that we have outlined in this chapter operates in all animal cells. But some of these cells, most notably neurons, have developed the ability to make brief changes in the membrane potential by adjusting the conductances g_K and g_{Na}. The resulting changes in membrane potential typically take the form of a stereotyped, pulse-shaped waveform, which is known as the "action potential." The level of activity of a neuron is measured in terms of the number of action potentials that it generates per unit time. The electrical activity of neurons is responsible for sensation, action, and thought, so it is no exaggeration to say that we are here concerned with a fundamental and important physiological mechanism.

Changes in the membrane conductances g_K and g_{Na} lead to departures from the steady state, so that I_{Na}, I_K and I_{Cl} are no longer equal to zero. Because the changes in question are rapid, taking place on a time scale of milliseconds, the capacitance of the cell membrane cannot be neglected, as it was when we were considering the slower changes associated with cell volume regulation. Under these circumstances of rapid conductance change, the fundamental equation governing the potential difference v across the cell membrane can be derived as follows. First, differentiate equation (3.4.4) with respect to time to obtain

$$C\dot{v} = \frac{d}{dt}(Vq[\mathrm{Na}^+]_i) + \frac{d}{dt}(Vq[\mathrm{K}^+]_i) + \frac{d}{dt}(V(-q)[\mathrm{Cl}^-]_i). \tag{3.5.1}$$

Note that $(Vq[\mathrm{Na}^+]_i)$ is the amount of charge inside the cell that is contributed by the Na^+ ions. Therefore, the rate of change of this quantity is $-I_{Na}$ (since our sign convention is that outward currents are considered positive). Similarly, the rate of change of $(Vq[\mathrm{K}^+]_i)$ is $-I_K$, and the rate of change of $(V(-q)[\mathrm{Cl}^-]_i)$ is $-I_{Cl}$. Therefore, taking into account the formulae for I_{Na}, I_K, and I_{Cl} (equations 3.4.1–3.4.3), we have

$$C\dot{v} + g_{Na}(v - E_{Na}) + g_K(v - E_K) + g_{Cl}(v - E_{Cl}) = 0, \tag{3.5.2}$$

where

$$E_{Na} = \frac{kT}{q}\log\left(\frac{[\mathrm{Na}^+]_o}{[\mathrm{Na}^+]_i}\right), \tag{3.5.3}$$

$$E_K = \frac{kT}{q}\log\left(\frac{[\mathrm{K}^+]_o}{[\mathrm{K}^+]_i}\right), \tag{3.5.4}$$

$$E_{Cl} = \frac{kT}{-q}\log\left(\frac{[\mathrm{Cl}^-]_o}{[\mathrm{Cl}^-]_i}\right). \tag{3.5.5}$$

Note that the pump currents have canceled out. This is because we have made the simplifying assumption of a 1:1 Na^+–K^+ exchange. With other ratios, the pump will make a contribution to equation (3.5.1).

Now we come to an important simplifying assumption: that the cell is so large, and the fluxes of ions are so small, that the internal concentrations of the various ions change only slightly during an action potential. This is a point that is often missed by the student, who imagines large swings of ion concentrations occurring during an action potential. In fact, the changes in concentration are so small that even a cell in which the Na^+–K^+ exchange pump mechanism has been poisoned can generate hundreds of action potentials before the concentrations "run down." Mathematically, we express this by treating the quantities E_{Na}, E_K, and E_{Cl} as given constants. Their values will be specified later. For now, we just note the qualitative relationship

$$E_K < E_{Cl} < 0 < E_{Na}. \tag{3.5.6}$$

For purposes of discussion, it is helpful to rewrite equation (3.5.2) in the following form:

$$C\dot{v} + g(v - E) = 0, \tag{3.5.7}$$

where

$$g = g_{Na} + g_K + g_{Cl} \tag{3.5.8}$$

is the total membrane conductance, and where

$$E = \frac{g_{Na}E_{Na} + g_K E_K + g_{Cl}E_{Cl}}{g_{Na} + g_K + g_{Cl}} \tag{3.5.9}$$

is a weighted average of the equilibrium potentials E_{Na}, E_K, and E_{Cl}, the weight being given in each case by the corresponding conductance. Given these definitions of g and E, it is easy to check that equations (3.5.7) and (3.5.2) are equivalent.

According to equation (3.5.7), the membrane potential v is always approaching the instantaneous value of E. Whenever $v < E$, we have $\dot{v} > 0$; and when $v > E$, we have $\dot{v} < 0$. It is therefore significant that the cell can adjust E simply by changing the membrane conductances. In the cell at rest, v and E are both close to E_{Cl}. Early in an action potential, Na^+ channels open (how this happens will be discussed below), dramatically increasing g_{Na}. This makes E become close to E_{Na}, and v follows, actually reversing sign in the process. Later on in the action potential, the Na^+ channels close and K^+ channels open. This brings E close to E_K, and the membrane potential v again follows E, thus becoming more negative than the resting potential of the cell. Finally, all of the conductances come back to normal, and E and v return to their resting values, close to E_{Cl}.

We now turn to the important question of how the Na^+ and K^+ conductances actually change. This was discovered by Hodgkin and Huxley,

through experiments on the squid giant axon. (The axon is a fiber that projects out from the cell body of a neuron and carries the signals generated by that neuron to other, possibly distant, locations.) These experimenters employed a "voltage clamp," which is an electronic circuit that uses feedback to force the membrane potential to follow a command signal specified by the experimenter. The current that is needed to keep the voltage tracking the command signal is recorded. Hodgkin and Huxley used command signals in the form of voltage steps, so that in between jumps, the voltage would be constant. The significance of this is that when v is constant, $C\dot{v} = 0$. Thus, except during the jumps in voltage, all of the current generated by the voltage clamp circuit would actually flow through the membrane channels; none of it would be involved in charging or discharging the membrane itself. A constant voltage is also useful for another reason. As we shall see, the properties of the membrane channels turn out to be voltage dependent. These properties are therefore easiest to investigate under constant voltage conditions. It was part of the genius of Hodgkin and Huxley to realize that voltage was the right variable to control.

Another experimental simplification made by Hodgkin and Huxley was to thread a silver wire down the length of the nerve axon that they were investigating. (Only in a *giant* axon would this be possible!) Since silver is an excellent conductor of electricity, this has the effect of eliminating any voltage differences that might otherwise develop between one location and another along the length of the axon. Mathematically speaking, this "space clamp" has the effect of ensuring that the membrane potential v is a function only of the time t, and not also of the position x along the axon. A major triumph of the theory introduced by Hodgkin and Huxley is that it was able to predict the behavior of the nerve action potential in an axon without a space clamp, despite the fact that the theory was derived from experiments performed with the space clamp in place. Specifically, Hodgkin and Huxley were able to predict the speed with which the action potential propagates along the (non-space-clamped) axon. Propagation, of course, cannot even be discussed without introducing the spatial variable x. Here, however, we shall restrict consideration to the space-clamped case. For this reason, the version of the Hodgkin–Huxley equations that we consider will be a system of *ordinary* differential equations, with time as the sole independent variable. This version is adequate for modeling essentially all phenomena associated with the nerve action potential *except* for the propagation of the action potential as a traveling wave. For that, the Hodgkin–Huxley *partial* differential equations are needed, and these are beyond the scope of this book.

Having ensured by means of voltage clamp and space clamp that all of the measured current would flow through membrane channels, Hodgkin and Huxley then went a step further and used pharmacological intervention to block one channel type or another, and thereby obtain separately the different ionic currents. By studying how these currents varied over

time in response to various voltage steps, they arrived at a mathematical description of the individual currents. We shall present this description in a deductive manner, as though it were derived from first principles, which we shall state. But of course, there was no way to know what those principles would turn out to be until the measurements had been made, and even now, no one is sure what is happening in detail within the channels that control the different ionic currents. Thus, the reader should take the following description with a grain of salt. It is a theory of membrane channels that is consistent with measurements made on the squid giant axon, but its details are not to be taken too seriously or applied too universally, since there are many different types of membrane channels in different types of neurons with quite different properties, and since even in the case of the squid giant axon, there may be many different models of the membrane channels that would be consistent with the experimental data.

The great achievement of Hodgkin and Huxley was to characterize the behavior of the Na^+ and K^+ channels of the squid giant axon. We shall begin with the K^+ channel, which is simpler. Its behavior can be derived from the following postulates:

1. Each K^+ channel has four gates. Each gate can be OPEN or CLOSED. The K^+ channel as a whole is OPEN if and only if all four of its gates are OPEN.

2. All four gates within a K^+ channel are identical. (And since we assume that there is only one type of K^+ channel, all of the different K^+ channels are identical, too.)

3. The different gates within a K^+ channel operate independently of one another. (And of course, the different gates in different K^+ channels also operate independently of one another.)

4. The rate constant (probability per unit time) for opening or closing a gate of a K^+ channel is a specified function of voltage for the opening rate and another specified function of voltage for the closing rate.

Note that the term "OPEN" in the foregoing refers to the conducting state of a gate or a channel. This is opposite to the standard electrical terminology (which comes from switches that use air as an insulator), but when talking about channels and gates it seems irresistible to say that they are "OPEN" when they allow ionic current to flow.

Let us now reduce the foregoing postulates to a mathematical theory. Consider the whole population (which we assume is large) of K^+ channels, and the population of gates within those channels, which we shall call K^+ gates. Let $n(t)$ be the fraction of K^+ gates that are in the OPEN state at time t. Alternatively, one can say that $n(t)$ is the probability that a given K^+ gate is OPEN at time t. Then the dynamics of $n(t)$ are governed by

the following equation:

$$\frac{dn}{dt} = \alpha_{\rm n}(v)(1-n) - \beta_{\rm n}(v)n. \tag{3.5.10}$$

Here $\alpha_{\rm n}(v)$ is the opening rate constant for the K^+ gates, which is a function of voltage. Similarly, $\beta_{\rm n}(v)$ is the closing rate constant for the K^+ gates, which is also a function of voltage. These functions will be specified later. For now we just mention that $\alpha_{\rm n}(v)$ is an increasing function and that $\beta_{\rm n}(v)$ is a decreasing function. Thus, increasing the membrane potential (inside relative to outside) encourages K^+ gates to open and discourages them from closing, thus increasing the K^+ conductance. (We are speaking here of an algebraic increase, i.e., a change that makes the inside potential less negative or more positive relative to the outside potential. Since the rest potential is negative, an increase in the membrane potential starting from rest is, in fact, a decrease in the magnitude of the potential, and for this reason such an increase is often called "depolarization.")

At any particular v, $\alpha_{\rm n}(v)$ and $\beta_{\rm n}(v)$ are just numbers, with units of reciprocal time, i.e., rate. The opening rate constant $\alpha_{\rm n}(v)$ is multiplied by $(1-n)$ in equation (3.5.10) because $(1-n)$ is the fraction of CLOSED K^+ gates, and a gate has to be CLOSED in order to open. For example, if $n = 1$ at some instant, then all of the gates are already OPEN, so the rate of opening has to be zero at that particular instant. Similarly, the closing rate constant $\beta_{\rm n}(v)$ is multiplied by n in equation (3.5.10) because n is the fraction of OPEN K^+ gates, and a gate has to be OPEN in order to close.

To complete the theory of the K^+ channel, we need to specify the K^+ conductance, $g_{\rm K}$, in terms of the fraction n of open K^+ gates. This is where the assumed independence of the K^+ gates comes into the picture. Since there are four *independent* gates in each channel, and since n is the probability that each of them is OPEN, then the probability that all four are OPEN (and hence that the channel is OPEN) is equal to n^4. Thus $g_{\rm K}$ should be proportional to n^4. Hodgkin and Huxley used the notation $\bar{g}_{\rm K}$ for the constant of proportionality. Thus

$$g_{\rm K} = \bar{g}_{\rm K} n^4. \tag{3.5.11}$$

Note that $\bar{g}_{\rm K}$ is the K^+ conductance in the hypothetical situation of all K^+ gates in all K^+ channels being open. The value of the constant $\bar{g}_{\rm K}$ will be specified later.

We now turn to the Hodgkin–Huxley theory of the Na^+ channel. The behavior of the Na^+ channel is qualitatively different from that of the K^+ channel in the following respect. When an upward step of voltage is applied, the K^+ conductance rises monotonically and settles down to a new, elevated, level that is maintained as long as the elevated voltage is maintained. In response to the same kind of voltage step, however, the Na^+ conductance rises only briefly, and then falls back to a low level, even when the elevated voltage level is maintained. This phenomenon is known

as Na^+ inactivation. To describe it, Hodgkin and Huxley had to assume that there are two types of gates within each Na^+ channel: fast "m-gates" that are encouraged to open by increasing membrane potential, and slower "h-gates" that have the opposite response to membrane potential. Thus, in the voltage step described above, the transient increase in Na^+ conductance happens when the m-gates have opened but the h-gates have not yet closed. Inactivation is a consequence of the eventual closure of the slower h-gates.

More precisely, the Hodgkin–Huxley theory of the Na^+ channel can be derived from the following postulates:

1. Each Na^+ channel has four gates. Each gate can be OPEN or CLOSED. The Na^+ channel as a whole is OPEN if and only if all four of its gates are OPEN.

2. The four gates, however, are not identical. Three of them are of a type that we shall call an "m-gate," and one is of a type that we shall call an "h-gate." All m-gates are identical to one another (whether they live within the same Na^+ channel or not), and all h-gates are identical to one another, but the m-gates and the h-gates have different properties.

3. The different gates within a Na^+ channel operate independently of one another, regardless of their type. (And of course, the different gates in different Na^+ channels also operate independently of one another.)

4. The rate constant (probability per unit time) for opening or closing a gate of a Na^+ channel is a specified function of voltage for the opening rate and another specified function of voltage for the closing rate. The opening and closing rates of the m-gates are different from those of the h-gates. In fact, they are qualitatively different: The m-gates are encouraged to open by increasing voltage, whereas the h-gates are encouraged to close by increasing voltage.

As we did in the case of the K^+ channel, we now translate these postulates into a mathematical theory. Consider a large population of Na^+ channels. Let $m(t)$ be the fraction of open m-gates at time t, and let $h(t)$ be the fraction of open h-gates at that time. Then $m(t)$ and $h(t)$ satisfy differential equations of the same form as equation (3.5.10):

$$\dot{m} = \alpha_{\mathrm{m}}(v)(1-m) - \beta_{\mathrm{m}}(v)m, \tag{3.5.12}$$

$$\dot{h} = \alpha_{\mathrm{h}}(v)(1-h) - \beta_{\mathrm{h}}(v)h. \tag{3.5.13}$$

The functions $\alpha_{\mathrm{m}}(v)$, $\beta_{\mathrm{m}}(v)$, $\alpha_{\mathrm{h}}(v)$, and $\beta_{\mathrm{h}}(v)$ that give the opening and closing rate constants for the m-gates and the h-gates will be specified later. For now, we note that $\alpha_{\mathrm{m}}(v)$ and $\beta_{\mathrm{h}}(v)$ are increasing functions of v, whereas $\beta_{\mathrm{m}}(v)$ and $\alpha_{\mathrm{h}}(v)$ are decreasing functions of v. Thus, increasing

voltage encourages opening and discourages closure of the m-gates, but has just the opposite effect on the h-gates.

Another qualitative point worth making about the different gates that we have considered is that the m-gates respond to voltage changes about 10 × faster than the h-gates. The gates of the K^+ channel (which we may now call "n-gates") are comparable in speed to the slower gates of the Na^+ channel, i.e., to the h-gates.

To complete the theory of the Na^+ channel, we have to specify the Na^+ conductance, g_{Na}, as a function of m and h, which are the fractions of open m-gates and h-gates, respectively. Here again we are helped by the probability interpretation of m and h and by the assumption that the different gates of the Na^+ channel operate independently. Since there are three m-gates and one h-gate in each channel, with probability m that any particular m-gate is OPEN and probability h that any particular h-gate is OPEN, and since the gates open and close independently, the probability that all four gates are OPEN, and hence that the channel as a whole is OPEN, is equal to m^3h. The Na^+ conductance is proportional to this, and hence is given by

$$g_{Na} = \bar{g}_{Na} m^3 h, \tag{3.5.14}$$

where the constant $\bar{g}_{Na}$ is the hypothetical Na^+ conductance when all of the gates in all of the Na^+ channels are simultaneously open. The value of $\bar{g}_{Na}$ will be specified later.

In addition to the Na^+ and K^+ channels, Hodgkin and Huxley also found a third type of channel in the membrane of the squid giant axon. They called this a "leakage" channel. Unlike the Na^+ and K^+ channels, the leakage channel population has a constant conductance

$$g_L = \bar{g}_L. \tag{3.5.15}$$

The leakage channel corresponds roughly to the Cl^- channel that was considered earlier in this chapter, but it is not specific to Cl^- ions. When a channel allows more than one ion type to flow through it, the current-voltage relation of that channel may still be of the form $I = g(v - E)$, but there is no longer a simple formula for E in terms of the ion concentrations on the two sides of the membrane. Under these circumstances, E is called the "reversal potential," a more general term that includes "equilibrium potential" as a special case. This change in terminology conveys an important physical distinction. In a channel that is specific for a single ion, when the voltage across the membrane is equal to the equilibrium potential, the situation is one of true thermodynamic equilibrium. No heat is being generated, for example, and the ion concentrations are not running down. In a channel that admits more than one species of ion, though, even when the voltage is at the reversal potential and there is no net current, there are nevertheless opposing currents of the different ions that do generate heat and that will eventually tend to equalize the concentrations on the two sides

of the membrane. This is *not* a case of thermodynamic equilibrium; hence the change in terminology. The reversal potential of the leakage channel, which we shall call E_{L}, turns out to be somewhat less negative than the resting potential of the squid giant axon. This would not be possible for a pure Cl^- channel. Since Cl^- is not pumped, its equilibrium potential has to coincide with the rest potential. In the equations that follow, the leakage channel, denoted by the subscript L, will replace the chloride channel considered earlier.

We may now summarize the Hodgkin–Huxley equations for the nerve action potential in the space-clamped case (no propagation). Those equations are as follows:

$$C\frac{dv}{dt} + g(v - E) = i_0(t), \tag{3.5.16}$$

where $i_0(t)$ is an applied current (per unit area of membrane) as a function of time. It may represent current applied through an electrode by an investigator, or synaptic current flowing naturally into a neuron because channels have been opened by a neurotransmitter. In either case, we regard $i_0(t)$ as a known function of time.

Recall that

$$g = g_{\mathrm{Na}} + g_{\mathrm{K}} + g_{\mathrm{L}} \tag{3.5.17}$$

is the total membrane conductance (per unit area), and that

$$E = \frac{g_{\mathrm{Na}}E_{\mathrm{Na}} + g_{\mathrm{K}}E_K + g_{\mathrm{L}}E_{\mathrm{L}}}{g_{\mathrm{Na}} + g_{\mathrm{K}} + g_{\mathrm{L}}} \tag{3.5.18}$$

is the weighted average of the reversal potentials weighted by the conductances. The reversal potentials E_{Na}, E_{K}, and E_{L} are constants. Their values will be given below. The conductances g_{Na}, g_{K}, and g_{L} are given by

$$g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}}m^3h, \tag{3.5.19}$$

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}}n^4, \tag{3.5.20}$$

$$g_{\mathrm{L}} = \bar{g}_{\mathrm{L}}, \tag{3.5.21}$$

where $\bar{g}_{\mathrm{Na}}$, $\bar{g}_{\mathrm{K}}$, and $\bar{g}_{\mathrm{L}}$ are constants whose values will be given below.

The gating variables m, h, and n obey the following differential equations (all of the same form):

$$\dot{m} = \alpha_{\mathrm{m}}(v)(1 - m) - \beta_{\mathrm{m}}(v)m, \tag{3.5.22}$$

$$\dot{h} = \alpha_{\mathrm{h}}(v)(1 - h) - \beta_{\mathrm{h}}(v)h, \tag{3.5.23}$$

$$\dot{n} = \alpha_{\mathrm{n}}(v)(1 - n) - \beta_{\mathrm{n}}(v)n. \tag{3.5.24}$$

The six functions of v that appear as coefficients in these equations represent the opening and closing rate constants for the different types of gates described earlier. These rates were measured by Hodgkin and Huxley, who then fit formulae to the data they obtained. This curve-fitting technique

yields the following expressions for the opening and closing rate constants as functions of voltage. These formulae are written in a specific system of units in which v is in millivolts (10^{-3} volts), and the α and β rate constants are all in reciprocal milliseconds ($1/(10^{-3}$seconds) or 10^3/second).

$$\alpha_m(v) = 1.0\frac{(v+45)/10}{1-\exp(-(v+45)/10)}, \tag{3.5.25}$$

$$\beta_m(v) = 4.0\exp(-(v+70)/18), \tag{3.5.26}$$

$$\alpha_h(v) = 0.07\exp(-(v+70)/20), \tag{3.5.27}$$

$$\beta_h(v) = 1.0\frac{1}{1+\exp(-(v+40)/10)}, \tag{3.5.28}$$

$$\alpha_n(v) = 0.1\frac{(v+60)/10}{1-\exp(-(v+60)/10)}, \tag{3.5.29}$$

$$\beta_n(v) = 0.125\exp\left(-\frac{v+70}{80}\right). \tag{3.5.30}$$

Note that some of the above expressions evaluate to 0/0 at particular values of voltage. In those special cases, L'Hospital's rule may be used to find the missing value.

Finally, the constants appearing in the Hodgkin–Huxley equations have the following values:

$$C = 1.0\,\frac{\text{microamperes} \times \text{milliseconds}}{\text{centimeter}^2}, \tag{3.5.31}$$

$$\bar{g}_{Na} = 120\,\frac{\text{microamperes/millivolt}}{\text{centimeter}^2}, \tag{3.5.32}$$

$$\bar{g}_K = 36\,\frac{\text{microamperes/millivolt}}{\text{centimeter}^2}, \tag{3.5.33}$$

$$\bar{g}_L = 0.3\,\frac{\text{microamperes/millivolt}}{\text{centimeter}^2}, \tag{3.5.34}$$

$$E_{Na} = 45\,\text{millivolts}, \tag{3.5.35}$$

$$E_K = -82\,\text{millivolts}, \tag{3.5.36}$$

$$E_L = -59\,\text{millivolts}. \tag{3.5.37}$$

3.6 Computer Simulation of the Nerve Action Potential

In this section we describe a numerical method and Matlab program for solving the (space-clamped) Hodgkin–Huxley equations that were introduced in the previous section. The numerical method is derived by replacing the derivatives that appear in the Hodgkin–Huxley equations by the corresponding difference quotients. To save writing, we shall exploit the fact