Chapter 1
The Hodgkin–Huxley Equations

1.1 The Resting Potential

All living cells have an electrical voltage, or potential difference, between their inside and outside. Since the cell's membrane is what separates the inside from the outside, this potential difference is referred to as the *membrane potential*. In mathematical terms, the membrane potential V_{M} is defined as

$$V_{\mathrm{M}} = V_{\mathrm{in}} - V_{\mathrm{out}},$$

where V_{in} is the potential on the inside of the cell and V_{out} is the potential on the outside. This will change during an action potential, for example.

The *resting potential* refers to the potential across the membrane when the cell is at rest. A typical neuron has a resting potential of about -70 mV. An *inward current* corresponds to a positively charged ion, such as Na^+, entering the cell. This raises the membrane potential; that is, it brings the membrane potential closer to zero. In this case, the cell is said to be *depolarized*. An *outward* current corresponds to a positively charged ion, such as K^+, leaving the cell or a negatively charged ion, such as Cl^-, entering the cell. In this case, the cell becomes *hyperpolarized*.

The potential difference arises from differences in the concentrations of various ions within and outside the cell. The maintenance of the potential difference also involves the transport of ions across the cell membrane and the selective permeability of the membrane to these ions. The principal ions found on either side of the cell membrane are Na^+, K^+, and Cl^-. The concentration of K^+ ions inside a cell is about 10 times that in the extracellular fluid, whereas the concentrations of Na^+ and Cl^- are much higher outside the cell than inside.

The lipid bilayer of the cell membrane is a poor conductor of ionic current because it is not permeable to ions. However, the membrane does contain channel proteins that allow for the ions to move through it. There are two types of ion channels in the membrane: gated and nongated. Nongated channels are always open, whereas gated channels can open and close and the probability of opening often depends on the membrane potential; these are referred to as *voltage-gated channels*. Gated channels are typically selective for a single ion. The *permeability* of the

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membrane to a particular ion depends on the number of open channels selective for that ion. Most gated channels are closed at rest; hence, the nongated ion channels are primarily responsible for establishing the resting potential. An action potential is generated when gated channels open allowing for the flux of ions across the cell membrane.

Because of concentration differences, when the appropriate channels are open, Na^+ and Cl^- ions tend to diffuse into the cell, whereas K^+ ions tend to diffuse outward. Note that ions do not simply diffuse in or out of an open channel until the concentration of that ion on either side of the cell is zero. This is because of the electric field created by separation of positive and negative charges across the cell membrane.

Suppose, for example, the cell is permeable only to K^+. The concentration gradient of K^+ moves K^+ ions out of the cell. However, the continued efflux of K^+ builds up an excess of positive charge on the outside of the cell and leaves behind an excess of negative charge on the inside. The negative charge consists mostly of impermeable organic anions A^-. This buildup of charge acts to impede the further efflux of K^+, so eventually an equilibrium is reached. At this equilibrium, the electrical and chemical driving forces are equal and opposite (Fig. 1.1). The membrane potential at which K^+ ions are in equilibrium across the membrane is called the K^+ *Nernst*, *equilibrium*, or *reversal potential* .

In the next section, we shall derive the following expression for the K^+ Nernst potential:

$$E_{\mathrm{K}} = -\frac{RT}{zF}\ln\frac{[K^+]_{\mathrm{in}}}{[K^+]_{\mathrm{out}}}. \tag{1.1}$$

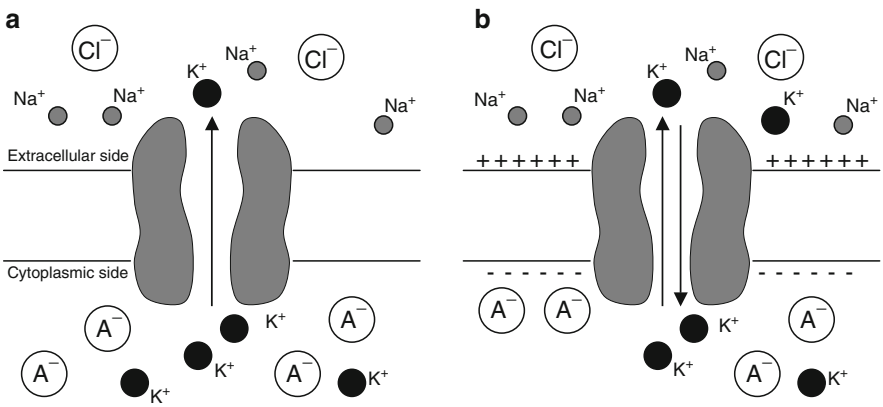

Fig. 1.1 The K^+ flux is determined by both the K^+ concentration gradient and the electrical potential across the membrane. (**a**) For a cell that is permeable only to K^+, the concentration gradient of K^+ moves K^+ ions out of the cell. (**b**) The continued efflux of K^+ builds up an excess of positive charge on the outside and an excess of negative charge on the inside. At equilibrium, the electrical and chemical driving forces are equal and opposite

Here, E_K is the K^+ Nernst potential, R is the gas constant, T is the absolute temperature in kelvin, z is the valence of K^+, F is Faraday's constant, and $[K^+]_{out}$ and $[K^+]_{in}$ are the concentrations of K^+ ions outside and inside the cell. A similar formula holds for the Na^+ and Cl^- Nernst potentials.

Neurons at rest are permeable to Na^+ and Cl^- in addition to K^+. Because of their concentration differences, Na^+ and Cl^- ions move into the cell and K^+ ions move outward. The influx of Na^+ ions tends to depolarize the cell, whereas the efflux of K^+ and the influx of Cl^- have the opposite effect. The resting potential of the cell is the potential at which there is a balance between these fluxes. It depends on the concentrations of the ions both inside and outside the cell, as well as the permeability of the cell membrane to each of the ions. We note that at rest, many more K^+ and Cl^- channels than Na^+ channels are open; hence, the cell's resting potential is determined primarily by the K^+ and Cl^- Nernst potentials. In the following sections, we shall derive the *Goldman–Hodgkin–Katz (GHK) equation*, which gives an explicit expression for how the resting potential depends on the concentrations, both inside and outside, of ions and the permeabilities of the membrane to the ions.

For a cell to maintain a constant resting potential, the efflux of K^+ ions must balance the influx of Na^+ ions (here we are ignoring Cl^- ions). That is, the charge separation across the membrane must be constant. If these steady ion leaks continued unopposed, then K^+ ions within the cell would become depleted, whereas the concentration of Na^+ ions inside the cell would increase. This would eventually result in a loss of the ionic gradients, necessary for maintaining the resting potential. The dissipation of ionic gradients is prevented by active pumps that extrude Na^+ ions from the cell while taking in K^+. The Na^+–K^+ pump is an integral membrane protein that exchanges three Na^+ ions for two K^+ ions. This is probably the most important ion transporter in biological membranes; however, there are many other proteins in the membrane that are capable of pumping ions from one side of the membrane to the other.

1.2 The Nernst Equation

Here we derive the Nernst equation and, in Sect. 1.3 we derive the GHK equation. Recall that if the membrane is permeable to only one ion, then that ion's Nernst potential is the resting potential at which the electrical and chemical driving forces balance. The GHK equation is, in some sense, a generalization of the Nernst equation in which we assume the membrane is permeable to more than just one ion. The GHK equation determines the resting potential at which the electrical and chemical forces, generated by each of these ions, balance each other. The first step in deriving these equations is to derive the *Nernst–Planck* equation.

In what follows, let $[C](x)$ be the concentration of some ion and $V(x)$ the potential at the point x across the membrane. Then, Fick's law of diffusion says that the diffusive flux, J_{diff}, is given by

$$J_{diff} = -D\frac{\partial [C]}{\partial x}.$$

The diffusion constant, D, has units of square centimeters per second and the concentration is in molecules per cubic centimeter, so the diffusive flux has units of molecules per square centimeter second. (Think of the flux as movement across the two-dimensional cell surface.) The direction of movement is from high concentrations to low concentrations. The diffusion constant (empirically measured) depends on the size of the molecule and the medium in which it is diffusing. A typical value for ions such as K^+, Cl^-, and Na^+ is 2.5×10^{-6}cm^2/s. Calcium ion has a diffusion constant about an order of magnitude less.

The other physical force that is responsible for the passive movement of ions is the electrical drift described by the microscopic version of Ohm's law:

$$J_{\text{drift}} = -\mu z[C]\frac{\partial V}{\partial x}.$$

The electric field, $E \equiv -\partial V/\partial x$, is the gradient of the potential V (measured in volts) and thus has units of volts per centimeter. z is the valence of the ion ($\pm 1, \pm 2$, etc.). The parameter μ is the mobility and has dimensions of square centimeters per volt second and $[C]$ is the concentration. The higher the concentration, the greater the drift. Note that the drift has the same dimensions as the diffusive flux.

The total flux across the membrane is given by the sum of the diffusive flux and the electrical drift:

$$J_{\text{total}} = -D\frac{\partial [C]}{\partial x} - \mu z[C]\frac{\partial V}{\partial x}.$$

Einstein's relation connects the mobility with the diffusion coefficient:

$$D = \frac{kT}{q}\mu,$$

where k is Boltzmann's constant (J/K), T is the absolute temperature, and q is the charge (measured in coulombs). Thus, we can write the total flux as

$$J_{\text{total}} = -\frac{\mu kT}{q}\frac{\partial [C]}{\partial x} - \mu z[C]\frac{\partial V}{\partial x}.$$

It is convenient to convert this equation, which is in terms of the number of individual molecules, into its molar equivalent, by dividing by Avogadro's number. It is also convenient to introduce RT/F, where R is the ideal gas constant and F is Faraday's constant, instead of kT/q. (A list of these constants is given at the end of the next section.) This will yield the flux per mole. Multiplying this flux by the valence and Faraday's constant yields a current flux

$$I = -\left(uzRT\frac{\partial [C]}{\partial x} + uz^2F[C]\frac{\partial V}{\partial x}\right)$$

measured in amperes per square centimeter. The quantity u is the molar mobility, μ/N_{A}. This equation is the *Nernst–Planck equation*.

The Nernst equation is obtained by setting the current equal to zero. That is, for a given ionic species, at equilibrium, the diffusion and electric effects balance:

$$I = -\left(uzRT\frac{\partial[C]}{\partial x} + uz^2F[C]\frac{\partial V}{\partial x}\right) = 0.$$

As an exercise, it is left to the reader to prove this implies the *Nernst equation*:

$$V_{\text{eq}} \equiv V_{\text{in}} - V_{\text{out}} = -\frac{RT}{zF}\ln\frac{[C]_{\text{in}}}{[C]_{\text{out}}}. \tag{1.2}$$

That is, the equilibrium (or Nernst) potential, which occurs when all the fluxes balance, depends on the logarithm of the ratio of the concentrations of the ions inside and outside the cell.

To illustrate how to use the Nernst equation to compute an equilibrium potential, note that in a typical mammalian cell, there is 140 mM K^+ inside the cell and 5 mM outside. At room temperature, 37°C, $RT/F = 26.73$ mV. Hence, the equilibrium potential of potassium is

$$-62\log\frac{140}{5} = -89.7\text{mV}.$$

1.3 The Goldman–Hodgkin–Katz Equation

The Nernst–Planck equation describes the movement of charged ions in aqueous media. However, the cell membrane has thickness and there may be energy barriers or blocking sites within the channel. In this case, the ions flowing through the open channel may not obey the Nernst–Planck equation and we must model the complex behavior within the membrane to get a true picture of the flux across the cell. This type of biophysics is beyond the details that are needed for this book, but the resulting equation does play a role in later parts. Thus, we will present a shortened derivation of a simplification of what happens within the membrane. Goldman, Hodgkin, and Katz came up with this simplified model called the *constant-field equation*. They assumed (1) the electric field across the lipid membrane is constant, (2) the Nernst–Planck equation holds within the membrane, and (3) the ions all move independently.

Let V_{M} be the total potential across a membrane of width l and let $V(x)$ be the potential at the point x across the membrane. Since the electric field is constant, $E = -V_{\text{M}}/l$. This implies that $\text{d}V/\text{d}x = V_{\text{M}}/l$. The mobility of ions within the membrane will be different from that in the aqueous solution; denote this mobility by u^*. Finally, let β be the ratio of the ion solubility within the membrane to the ion

solubility in the aqueous solution. Thus, if $[C]$ is the aqueous concentration, then $\beta[C]$ is the membrane concentration. With these assumptions, the Nernst–Planck equation for current across the membrane is

$$I = -u^* z^2 F\beta[C]\frac{V_{\mathrm{M}}}{l} - u^* zRT\beta\frac{\mathrm{d}[C]}{\mathrm{d}x}, \quad 0 < x < l.$$

This is just a first-order linear ordinary differential equation for $[C]$ subject to the *two* boundary conditions

$$[C](0) = [C]_{\mathrm{in}}, \quad [C](l) = [C]_{\mathrm{out}}.$$

One cannot, in general, solve a first-order equation with two boundary conditions. However, the current I is unknown, so choosing this correctly will allow us to find a solution that satisfies both boundary conditions. We leave this elementary exercise for the reader. The result is

$$I = \frac{u^* z^2 F V_{\mathrm{M}}\beta}{l}\left(\frac{[C]_{\mathrm{out}}\mathrm{e}^{-\xi} - [C]_{\mathrm{in}}}{\mathrm{e}^{-\xi} - 1}\right),$$

where

$$\xi = \frac{zV_{\mathrm{M}}F}{RT}.$$

This expression is often written in terms of the permeability,

$$P \equiv \frac{\beta u^* RT}{lF};$$

that is,

$$I = PzF\xi\left(\frac{[C]_{\mathrm{out}}\mathrm{e}^{-\xi} - [C]_{\mathrm{in}}}{\mathrm{e}^{-\xi} - 1}\right). \tag{1.3}$$

The permeability has dimensions of centimeters per second. Thus, the dimensions are in terms of current per unit area. Equation (1.3) is called the constant-field equation.

This is the current due to a single ionic species. The current vanishes at the equilibrium or Nernst potential of the ionic species. A current–voltage (I–V) plot is a common plot. If the inside and outside concentrations are identical, then the I–V plot is linear. For $[C]_{\mathrm{out}} > [C]_{\mathrm{in}}$ (respectively, $[C]_{\mathrm{out}} < [C]_{\mathrm{in}}$) the I–V plot is concave down (respectively concave up). The reader is encouraged to plot the current as a function of the voltage for different concentration ratios. If the concentrations are quite different on the inside and outside, then the I–V curve is *strongly rectifying*. This means the magnitude of the current depends strongly on whether or not the potential is above or below the equilibrium.

Given several ionic species, the total current is just a sum of the individual currents. This is a consequence of assumption 3, which says that the ions do not interact. Suppose there are three permeable ions, K^+, Na^+, and Cl^- with corresponding currents, I_K, I_{Na}, and I_{Cl}. At equilibrium, the total current, $I = I_K + I_{Na} + I_{Cl}$, vanishes; that is, $I = 0$. The potential at which this occurs is

$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}}, \tag{1.4}$$

where the P_j's are the permeabilities of each of the three ionic species. This is a generalization of the Nernst equilibrium discussed above and is called the *Goldman–Hodgkin–Katz (GHK) equation*. With one species, the equation reduces to the Nernst potential. For example, in the squid axon, the ratios of the permeabilities, at rest, are $P_K : P_{Na} : P_{Cl} = 1 : 0.03 : 0.1$. The ion concentrations inside the cell are, respectively, for K^+, Na^+, and Cl^-, 400, 50, and 40 mM, whereas outside the cell they are 10, 460, and 540 mM. Thus, at room temperature, the equilibrium or resting potential is −74 mV.

Table 1.1 Typical ion concentrations in cells (from Johnston and Wu [139])

Ion	Inside (mM)	Outside (mM)	Equilibrium potential (mV), $E_i = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}}$
Frog muscle			$T = 20°C$
K^+	124	2.25	$58 \log \frac{2.25}{124} = -101$
Na^+	10.4	109	$58 \log \frac{109}{10.4} = +59$
Cl^-	1.5	77.5	$-58 \log \frac{77.5}{1.5} = -99$
Ca^{2+}	10^{-4}	2.1	$29 \log \frac{2.1}{10^{-4}} = +125$
Squid axon			$T = 20°C$
K^+	400	20	$58 \log \frac{20}{400} = -75$
Na^+	50	440	$58 \log \frac{440}{50} = +55$
Cl^-	40–150	560	$-58 \log \frac{560}{40-150} = -66$ to -33
Ca^{2+}	10^{-4}	10	$29 \log \frac{10}{10^{-4}} = +145$
Mammalian cell			$T = 37°C$
K^+	140	5	$62 \log \frac{5}{140} = -89.7$
Na^+	5–15	145	$62 \log \frac{145}{5-15} = +90 - (+61)$
Cl^-	4	110	$-62 \log \frac{110}{4} = -89$
Ca^{2+}	10^{-4}	2.5–5	$31 \log \frac{2.5-5}{10^{-4}} = +136 - (+145)$

Table 1.2 Elementary constants

N_A	6.022×10^{23} mol (Avogadro's number)
k	1.380658×10^{-23} J/K (Boltzmann's constant)
R	8.31451 J/(mol K) (ideal gas constant)
e	1.602177×10^{-19} C (electron charge)
F	96, 485.3 C/mol (Faraday's constant)
ϵ_0	8.85×10^{-12} F/m (permittivity constant)
K	Kelvin (degrees centigrade +273.16)
L	Liter
N	Newton
J	Joule (N m); 1 J = 0.238845 cal
V	Volt (J/C)
C	Coulomb
A	Ampere (C/s)
Ω	Ohm (V/A)
S	Siemens (A/V)
F	Farad (s A/V or C/V)

1.4 Equivalent Circuits: The Electrical Analogue

We saw in Sect. 1.3 that the electrical properties of cells are determined by the ionic species that move through the membrane. Currents flow according to the permeabilities of ion channels and concentration gradients across the cell membrane. However, all of our discussion so far has been in a steady-state environment. The GHK equation does not determine how the membrane potential changes in response to changes in the permeabilities. For this reason, it cannot be used to understand how these changes in permeabilities may generate an action potential. A very useful way to describe the behavior of the membrane potential is in terms of electrical circuits; this is commonly called the *equivalent circuit model*. The circuit consists of three components: (1) conductors or resistors, representing the ion channels; (2) batteries, representing the concentration gradients of the ions; and (3) capacitors, representing the ability of the membrane to store charge. The equivalent circuit model leads to both an intuitive and a quantitative understanding of how the movement of ions generates electrical signals in the nerve cell.

We first consider a membrane that is only permeable to potassium. The equivalent circuit is shown in Fig. 1.2. The lipid bilayer that constitutes the cell membrane has dielectric properties and as such behaves in much the same manner as a capacitor. Recall that capacitors store charge and then release it in the form of currents. The relationship between the charge stored and the potential is given by

$$q = C_M V_M; \tag{1.5}$$

that is, the total charge q is proportional to the potential V_M with a proportionality constant C_M called the *membrane capacitance*. Note that the total capacitance depends on the total area of the dielectric; thus, larger neurons have a larger total capacitance than smaller ones. The capacitance per square centimeter is called the *specific membrane capacitance* and will be denoted as c_M. Hence, the total

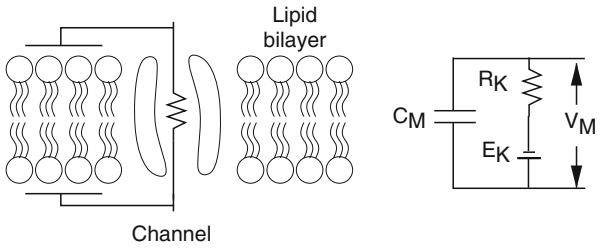

Fig. 1.2 The cell membrane showing the insulating lipid bilayer and a K^+ channel, which allows current to flow. The equivalent electrical circuit is shown on the *right*

membrane capacitance C_M is the specific membrane capacitance c_M times the total surface area of the cell. In general, the specific membrane capacitance may depend on the potential; however, for most cell membranes, the specific membrane capacitance is very close to 1 μF/cm^2.

Since current is the time derivative of charge, we can differentiate (1.5), divide by the cell's area, and obtain an expression for the specific capacitance current:

$$i_{\text{cap}} = c_M \frac{dV_M}{dt}. \tag{1.6}$$

This gives the capacitance current per unit area. We will denote the total capacitance current as I_{cap}.

In the equivalent circuit, K^+ channels are represented as a conductor in series with a battery. If $\hat{g}_K$ is the conductance of a single K^+ channel, then, using Ohm's law, the ionic current through this channel is

$$\hat{I}_K = \hat{g}_K(V_M - E_K). \tag{1.7}$$

Here, E_K is the potential generated by the battery; this is given by the K^+ Nernst potential. The *driving force* is $V_M - E_K$. Now suppose there are N_K K^+ channels in a unit area of membrane. These can all be combined into the single equivalent circuit shown in Fig. 1.2. The conductance per unit area, or specific membrane conductance (S/cm^2), is given by $g_K = N_K \times \hat{g}_K$ and the specific membrane resistance (Ω cm^2) is $r_K \equiv 1/g_K$. Since the Nernst potential depends only on the concentration gradient of K^+, and not on the number of K^+ channels, it follows that the K^+ current, per unit area, is given by

$$I_K = g_K(V_M - E_K) = \frac{V_M - E_K}{r_K}. \tag{1.8}$$

Kirchhoff's current law states that the total current into the cell must sum to zero. Together with the equivalent circuit representation, this leads to a differential equation for the membrane potential:

$$0 = i_{\text{cap}} + I_K = c_M \frac{dV_M}{dt} + \frac{V_M - E_K}{r_K} \tag{1.9}$$

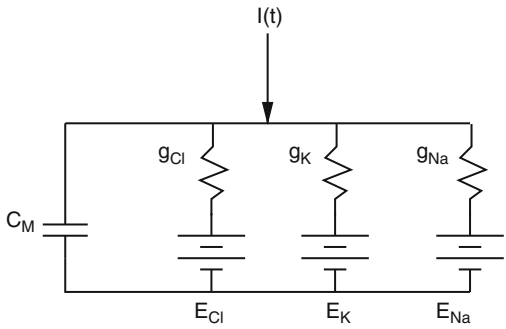

Fig. 1.3 Equivalent circuit for a membrane with three channels

or

$$c_M \frac{dV_M}{dt} = -\frac{V_M - E_K}{r_K} = -g_K(V_M - E_K). \tag{1.10}$$

Figure 1.3 shows an equivalent circuit with three parallel conductances and a current source, $I(t)$. Here the capacitance current must be equal to the sum of the ionic currents and the current source. As before, the capacitance current, per unit area, is given by (1.6) and the ionic current, per unit area, is given by

$$i_{ion} = -g_{Cl}(V_M - E_{Cl}) - g_K(V_M - E_K) - g_{Na}(V_M - E_{Na}). \tag{1.11}$$

The current source is not typically expressed as current per unit area, so we must divide $I(t)$ by the total surface area of the neuron, A. It then follows that

$$c_M \frac{dV_M}{dt} = -g_{Cl}(V_M - E_{Cl}) - g_K(V_M - E_K) - g_{Na}(V_M - E_{Na}) + I(t)/A. \tag{1.12}$$

Note that we can rewrite this equation as

$$c_M \frac{dV_M}{dt} = -\frac{(V_M - E_R)}{r_M} + I(t)/A, \tag{1.13}$$

where

$$E_R = (g_{Cl}E_{Cl} + g_K E_K + g_{Na}E_{Na})r_M$$

is the cell's resting potential and

$$r_M = \frac{1}{g_{Cl} + g_K + g_{Na}}$$

is the specific membrane resistance.

For a passive membrane in which the conductances and currents are all constant, V_M will reach a steady state:

$$V_{ss} = \frac{g_{Cl}E_{Cl} + g_K E_K + g_{Na}E_{Na} + I/A}{g_{Cl} + g_k + g_{Na}}.$$

In the absence of the applied current, the steady-state potential is a weighted sum of the equilibrium potentials of the three currents. This is similar to the GHK equation (1.4), in which the contribution to the resting potential by each ion is weighted in proportion to the permeability of the membrane to that particular ion. Note, however, that in the equivalent circuit model, the equilibrium is a linear weighted sum of the equilibrium potentials, whereas in the GHK equation, the sum is nonlinear.

We remark that membrane conductance and permeability are related concepts; however, they are not the same. The permeability depends on the state of the membrane, whereas conductance depends on both the state of the membrane and the concentration of the ions. The permeability to K^+, for example, may be high if there are a large number of open K^+ channels. However, if the concentration of K^+ ions is low on both sides of the membrane, then the K^+ conductance will be low.

1.5 The Membrane Time Constant

In this section, we consider how a passive, isopotential cell responds to an applied current. This will help explain how each component of the electrical circuit contributes to changes in the membrane potential. The cell is said to be *passive* if its electrical properties do not change during signaling. Such a cell cannot generate an action potential; however, it is important to understand how a cell's passive, or constant, properties influence changes in the membrane potential before considering active signaling. Moreover, many dendrites do not have gated channels, so their behavior is influenced primarily by their passive properties. The cell is said to be *isopotential* if the membrane potential is uniform at all points of the cell; that is, the membrane potential depends only on time. To simplify the analysis, we will consider a spherical cell with radius ρ.

Suppose this cell is injected with an applied current, $I(t)$, that is turned on at $t = 0$ to some constant value, I_0, and turned off at $t = T$. Here, we assume $I_0 > 0$; however, this is really not necessary. Note that for an isopotential cell, the injected current distributes uniformly across the surface. It follows that for a spherical cell, the current flowing across a unit area of the membrane is

$$I_{\mathrm{M}}(t) = \frac{I(t)}{4\pi\rho^2} = \begin{cases} \frac{I_0}{4\pi\rho^2} & \text{if } 0 < t < T \\ 0 & \text{otherwise.} \end{cases} \tag{1.14}$$

As before, suppose c_{M} is the specific membrane capacitance, r_{M} is the specific membrane resistance, and E_{R} is the cell's resting potential. To simplify things, we take $E_{\mathrm{R}} = 0$ so that V_{M} measures the deviation of the membrane potential from rest. From (1.13), the membrane potential satisfies the ordinary differential equation

$$c_{\mathrm{M}} \frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -\frac{V_{\mathrm{M}}}{r_{\mathrm{M}}} + I_{\mathrm{M}}(t). \tag{1.15}$$

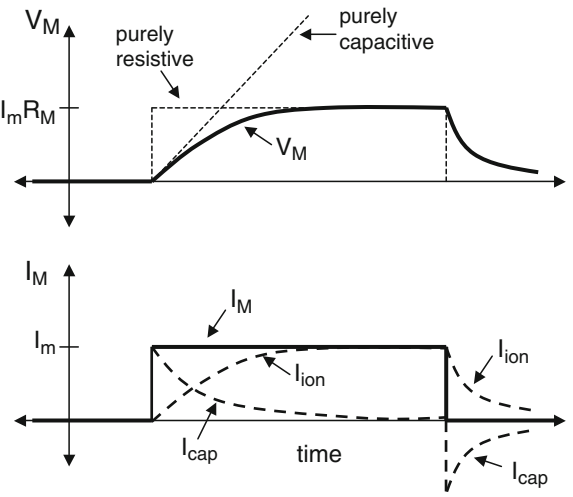

Fig. 1.4 The change of membrane potential in response to a step of current. The membrane potential is shown with a *solid line*. The *dashed lines* show the time courses of the purely capacitive and resistive elements. The *bottom panel* shows the time course of the total membrane current, the ionic current, and the capacitive current

If the cell starts at rest, then the solution of this linear equation satisfies

$$V_{\mathrm{M}}(t) = \frac{r_{\mathrm{M}} I_0}{4\pi\rho^2}\left(1 - \mathrm{e}^{-\frac{t}{\tau_{\mathrm{M}}}}\right) \quad \text{for } 0 < t < T, \tag{1.16}$$

where $\tau_{\mathrm{M}} \equiv c_{\mathrm{M}} r_{\mathrm{M}}$ is the *membrane time constant* and

$$V_{\mathrm{M}}(t) = V_{\mathrm{M}}(T)\mathrm{e}^{-\frac{t}{\tau_{\mathrm{M}}}} \quad \text{for } t > T. \tag{1.17}$$

The solution is shown in Fig. 1.4. Once the current is turned on, the membrane potential asymptotically approaches the steady-state value $r_{\mathrm{M}} I_0/(4\pi\rho^2)$. The approach is exponential with the time constant τ_{M}. The membrane time constant also determines the rate at which the membrane potential decays back to rest after the current is turned off. The steady-state membrane potential satisfies

$$I_0 \frac{r_{\mathrm{M}}}{4\pi\rho^2} \equiv I_0 R_{\mathrm{INP}}, \tag{1.18}$$

where R_{INP} is the *input resistance* of the cell. Note that if the input current changes by ΔI, then the steady-state membrane potential changes by $R_{\mathrm{INP}}\Delta I$; that is, the input resistance is the slope of the I–V curve obtained by plotting the steady-state voltage against the injected current.

The initial rise in membrane potential is determined primarily by the membrane capacitance. Initially, the voltage across the resistor and that across the capacitor are both zero. From Ohm's law, it follows that initially no current flows through the resistor and all the current is due to the capacitor. Because of the capacitive current, the potential across the capacitor, and hence the membrane potential, will become

more positive. As V_M increases, the membrane potential difference begins to drive current across the membrane resistance, resulting in less current across the capacitor. Eventually, the membrane potential reaches a value where all the membrane current flows through the resistor. This value is given by $V_M = I_0 R_{INP}$.

Figure 1.4 also shows responses in which there are purely resistive or purely capacitive elements. If there is no membrane capacitance, then V_M satisfies

$$V_M(t) = r_M I_M(t). \tag{1.19}$$

That is, V_M jumps to the steady-state potential, $I_0 R_{INP}$, as soon as the injected current is turned on and it jumps back to rest as soon as the current is turned off. If there is only a capacitive element, then the membrane potential changes linearly as long as there is an applied current.

1.6 The Cable Equation

We have, so far, considered the passive properties of an isopotential cell. This analysis may be used to describe signaling within the cell body, which can be approximated by a sphere. However, it is clearly not appropriate for studying electrical properties of the axon or dendrites. These are better approximated by cylinders that are not isopotential. A subthreshold voltage signal that is initiated at one point along the axon or dendrite will decrease in amplitude with distance from the point of initiation. It is important to understand how the geometry of the cell affects the spread of the signal. The signal may, for example, correspond to synaptic input from another neuron. Understanding how geometry affects the spread of the signal will help determine whether the synaptic input will cause the cell to fire an action potential. Here, we assume the membrane is passive, so the analysis is more applicable to dendrites than to axons. However, as we shall describe later, the passive spread of current flow helps determine the velocity of propagating action potentials in the axon.

We consider a cell that is shaped as a long cylinder, or cable, of radius a. We assume the current flow is along a single spatial dimension, x, the distance along the cable. In particular, the membrane potential depends only on the x variable, not on the radial or angular components. The cable equation is a partial differential equation that describes how the membrane potential $V_M(x,t)$ depends on currents entering, leaving, and flowing within the neuron. The equivalent circuit is shown in Fig. 1.5. In what follows, we will assume $R_e = 0$, so that the extracellular space is isopotential. This assumption is justified if the cable is in a bath with large cross-sectional area.

We first consider the axial current flowing along the neuron due to voltage gradients. Note that the total resistance of the cytoplasm grows in proportion to the length of the cable and is inversely proportional to the cross-sectional area of the cable. The specific intracellular resistivity, which we denote as r_L, is the constant of proportionality. Hence, a cable of radius a and length Δx has a total resistance of

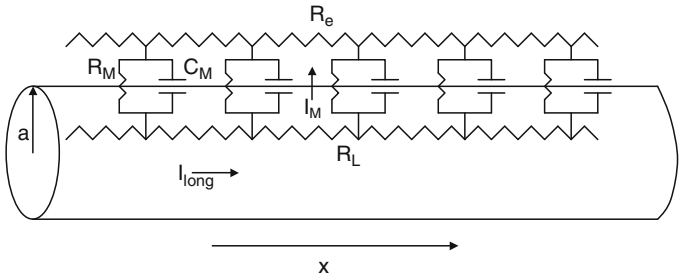

Fig. 1.5 Equivalent circuit for a uniform passive cable. I_{long} is the current along the inside of the cable, I_{M} is the current across the membrane, R_{L} is the resistance of the cytoplasm, R_{e} is the resistance of the extracellular space, R_{M} is the membrane resistance, and C_{M} is the membrane capacitance

$R_{\text{L}} = r_{\text{L}}\Delta x/(\pi a^2)$. It follows from Ohm's law that at any point x, the decrease in V_{M} with distance is equal to the current times the resistance. That is,

$$V_{\text{M}}(x + \Delta x, t) - V_{\text{M}}(x, t) = -I_{\text{long}}(x, t)R_{\text{L}} = -I_{\text{long}}(x, t)\frac{\Delta x}{\pi a^2}r_{\text{L}}. \tag{1.20}$$

There is a minus sign because of the convention that positive current is a flow of positive charges from left to right. If voltage decreases with increasing x, then the current is positive. In the limit $\Delta x \to 0$,

$$I_{\text{long}}(x, t) = -\frac{\pi a^2}{r_{\text{L}}}\frac{\partial V_{\text{M}}}{\partial x}(x, t). \tag{1.21}$$

Let i_{ion} be the current per unit area due to ions flowing into and out of the cell. Then the total ionic current that flows across a membrane of radius a and length Δx is given by $I_{\text{ion}} = (2\pi a\Delta x)i_{\text{ion}}$.

Recall that the rate of change of the membrane potential is determined by the capacitance. The total capacitance of a membrane is equal to the specific membrane capacitance c_{M} multiplied by the total surface area of the membrane. Hence, for a cable of radius a and length Δx, the total capacitance is given by $C_{\text{M}} = (2\pi a\Delta x)c_{\text{M}}$ and the amount of current needed to change the membrane potential at a rate $\partial V_{\text{M}}/\partial t$ is

$$I_{\text{cap}}(x, t) = (2\pi a\Delta x)c_{\text{M}}\frac{\partial V_{\text{M}}}{\partial t}. \tag{1.22}$$

From Kirchhoff's law, the change in intracellular axial current is equal to the amount of current that flows across the membrane. Hence,

$$I_{\text{cap}}(x, t) + I_{\text{ion}}(x, t) = -I_{\text{long}}(x + \Delta x, t) + I_{\text{long}}(x, t), \tag{1.23}$$

from which it follows that

$$(2\pi a\Delta x)c_{\mathrm{M}}\frac{\partial V_{\mathrm{M}}}{\partial t}+(2\pi a\Delta x)i_{\mathrm{ion}}=\frac{\pi a^2}{r_{\mathrm{L}}}\frac{\partial V_{\mathrm{M}}}{\partial x}(x+\Delta x,t)-\frac{\pi a^2}{r_{\mathrm{L}}}\frac{\partial V_{\mathrm{M}}}{\partial x}(x,t).$$

We divide both sides of this equation by $2\pi a\Delta x$ and let $\Delta x\to 0$ to obtain the cable equation:

$$c_{\mathrm{M}}\frac{\partial V_{\mathrm{M}}}{\partial t}=\frac{a}{2r_{\mathrm{L}}}\frac{\partial^2 V_{\mathrm{M}}}{\partial x^2}-i_{\mathrm{ion}}. \tag{1.24}$$

For a passive cable, in which the resting potential is assumed to be zero,

$$i_{\mathrm{ion}}=V_{\mathrm{M}}(x,t)/r_{\mathrm{M}}, \tag{1.25}$$

where r_{M} is the specific membrane resistance. Then (1.24) becomes

$$c_{\mathrm{M}}\frac{\partial V_{\mathrm{M}}}{\partial t}=\frac{a}{2r_{\mathrm{L}}}\frac{\partial^2 V_{\mathrm{M}}}{\partial x^2}-\frac{V_{\mathrm{M}}}{r_{\mathrm{M}}}. \tag{1.26}$$

We can rewrite this equation as

$$\tau_{\mathrm{M}}\frac{\partial V_{\mathrm{M}}}{\partial t}=\lambda^2\frac{\partial^2 V_{\mathrm{M}}}{\partial x^2}-V_{\mathrm{M}}, \tag{1.27}$$

where

$$\lambda=\sqrt{\frac{ar_{\mathrm{M}}}{2r_{\mathrm{L}}}}\quad\text{and}\quad\tau_{\mathrm{M}}=c_{\mathrm{M}}r_{\mathrm{M}} \tag{1.28}$$

are the *space* or *length constant* and the *membrane time constant*, respectively. Note that the space constant depends on the geometry of the cable, that is, the cable's diameter; however, the time constant does not.

Later, we shall give a detailed analysis of solutions to the cable equation and properties of passive dendrites. For now, it is instructive to consider steady-state solutions. Suppose, for example, we consider a semi-infinite cable (defined for $x>0$) and we inject a step of current, I_0, at $x=0$. As $t\to\infty$, the solution $V_{\mathrm{M}}(x,t)$ approaches a steady-state solution $V_{\mathrm{ss}}(x)$ that does not depend on time. Setting $\frac{\partial V_{\mathrm{M}}}{\partial t}=0$ in (1.27), we find that V_{ss} satisfies

$$\lambda^2\frac{\mathrm{d}^2V_{\mathrm{ss}}}{\mathrm{d}x^2}-V_{\mathrm{ss}}=0. \tag{1.29}$$

To solve this equation, we need boundary conditions. Recall from (1.21) that

$$I_0=-\frac{\pi a^2}{r_{\mathrm{L}}}\frac{\partial V_{\mathrm{M}}}{\partial x}.$$

It follows that V_{ss} must satisfy the boundary condition

$$\frac{dV_{ss}}{dx}(0) = -\frac{r_L}{\pi a^2} I_0. \tag{1.30}$$

The solution of (1.29) and (1.30) is

$$V_{ss}(x) = \frac{\lambda r_L}{\pi a^2} I_0 e^{-x/\lambda}. \tag{1.31}$$

Note that the membrane potential decays exponentially. The distance at which the potential has decayed to $1/e$ is the space constant λ. Since the space constant is proportional to the square root of the cable's radius, we conclude that thicker axons or dendrites have larger space constants than narrower processes. That is, thicker processes transmit signals for greater distances. As we discuss later, this is important because it influences the ability of the neuron to spatially summate incoming synaptic potentials. Moreover, the electrotonic, or passive, conductance plays an important role in the propagation of the action potential. Thicker cells with a larger space constant are more easily excited and are able to generate faster action potentials.

The input resistance is defined to be the steady-state membrane potential, evaluated at $x = 0$, divided by the injected current. That is,

$$R_{inp} = V_{ss}(0)/I_0 = \frac{r_L \lambda}{\pi a^2} = \frac{1}{\pi a^{3/2}} \sqrt{r_M r_L/2}. \tag{1.32}$$

Note that the input resistance of the cable varies with the $-3/2$ power of the cable radius. Therefore, the input conductance is directly proportional to the $3/2$ power of the cable radius. The input resistance is important because it is something that can be measured experimentally. Since it is also possible to measure the space constant λ, one can compute r_M and r_L from experimental data.

1.7 The Squid Action Potential

We have so far viewed the membrane as a passive cable. However, linear cables cannot transmit information over long distances unless the cable has an enormous diameter. For example, the squid axon is more than 5 cm long, has a diameter of about a 0.5 mm, a resting membrane resistance of $r_M = 700\ \Omega\ \text{cm}^2$, and a transmembrane resistance of $r_L = 30\,\Omega$ cm. Thus, the space constant for the squid axon is $\lambda = 5.4$ mm. This is an order of magnitude smaller than the length. If the potential at one end of the axon is held at 120 mV above rest, then the potential at the other end is about 10 μV above the rest, a 10,000-fold decrement. For neural signals to reach any distance, there must be another way to carry them so that they do not degrade.

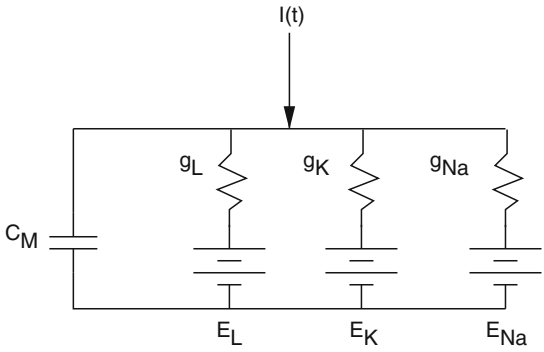

Fig. 1.6 Equivalent circuit underlying the Hodgkin–Huxley equations

Nature has solved this problem by inserting *voltage-gated* channels into the membranes of many cell types. These channels are proteins which selectively let different ionic species into the cell. Furthermore, the permeability of the channels depends on the local environment near the channel. In particular, for voltage-gated channels, whether the channel is open or closed depends on the local potential near the channel. It is the opening and closing of voltage-gated channels that is responsible for the generation of the action potential that propagates along the axon.

Hodgkin and Huxley (1952) were the first to provide a comprehensive, quantitative description of the regenerative currents generating the action potential. The choice of the squid axon was fortuitous since the electrical properties rely primarily on Na^+ and K^+ ions. Consider the equivalent circuit shown in Fig. 1.6 and assume the cell is isopotential. Then the membrane potential satisfies

$$c_M \frac{dV}{dt} = -g_{Na}(V - E_{Na}) - g_K(V - E_K) - g_L(V - E_L).$$

Here, we write V instead of V_M and $I_L \equiv g_L(V - E_L)$ is called the *leak current*. It corresponds to passive flow of ions through nongated channels. The leak conductance, g_L, is constant. Since most nongated channels are permeable to K^+ ions, E_L is close to E_K. The conductances g_{Na} and g_K may change with time since these correspond to the opening and closing of Na^+ and K^+ channels, respectively. At rest, g_K is about 30-fold bigger than g_{Na}, so the resting state is near E_K at about -65 mV. Suppose we could increase the conductance of g_{Na} 100-fold, then the resting potential would be much closer to the Nernst potential of Na^+, which is about $+55$ mV. Thus, the amplification of the potential, such as during an action potential, involves changes in the relative conductances of the dominant ionic species. Hodgkin and Huxley's insight was that voltage-gated channels provide the substrate for this dynamic regulation of the conductances.

The basic mechanisms underlying action potentials are the following (Fig. 1.7). At rest, most of the Na^+ channels are closed, so the membrane potential is determined primarily by the K^+ Nernst potential. If the cell is depolarized above some threshold, then Na^+ channels open and this further depolarizes the cell. This allows

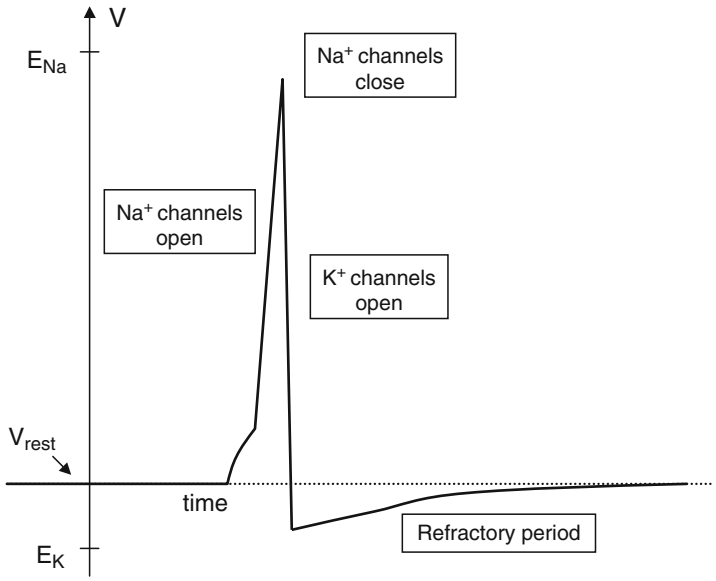

Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

even more Na^+ channels to open, allowing more Na^+ ions to enter the cell and forcing the cell toward the Na^+ Nernst potential. This is the upstroke of the action potential. The Na^+ channel is transient, so even when they are depolarized, the Na^+ channels eventually shut down. In the meantime, the depolarization opens K^+ channels and K^+ ions exit the cell. This hyperpolarizes the cell as the membrane potential moves toward the K^+ equilibrium potential. Until the voltage-gated K^+ channels close up again, the membrane is refractory. During this time, pumps exchange excess Na^+ ions inside the cell with excess K^+ ions outside the cell.

Only a very small change in the concentration of Na^+ ions is needed to generate an action potential. From the exercises, we find that approximately 53 million Na^+ ions must diffuse across the membrane to depolarize it from -60 to $+50$ mV. This influx of Na^+ ions represents only a 0.012% change in the internal Na^+ concentration, which is typically around 12 mM. Hence, changes in local charge separation, not in concentration, are required for an action potential.

1.8 Voltage-Gated Channels

In the Hodgkin–Huxley model, each channel is viewed as a transmembrane protein that forms a pore through which ions can diffuse down their concentration gradients. The pores have gates that can be either open or closed; the probability that a

gate is open or closed depends on the membrane potential. The gate model can be summarized by the diagram

$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O, \tag{1.33}$$

where C and O correspond to the closed and open states, respectively, and $\alpha(V)$ and $\beta(V)$ are the voltage-dependent rate constants at which a gate goes from the closed to the open and from the open to the closed states, respectively. If we let m be the fraction of open gates, then $1 - m$ is the fraction of closed gates, and, from the law of mass action,

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha(V)(1-m) - \beta(V)m = (m_\infty(V) - m)/\tau(V), \tag{1.34}$$

where

$$m_\infty(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)} \quad \text{and} \quad \tau(V) = \frac{1}{\alpha(V) + \beta(V)}. \tag{1.35}$$

It is easy to solve this equation if V is constant. The solution starting at $m(0)$ is

$$m(t) = m_\infty(V) + (m(0) - m_\infty(V))\mathrm{e}^{-t/\tau(V)}.$$

Note that the solution approaches the steady-state $m_\infty(V)$ at a rate determined by the time constant $\tau(V)$.

One must obtain expressions for the voltage-dependent rate constants α and β. In the Hodgkin–Huxley model, these functions were derived by fitting the data. Borg-Graham [17] and others have suggested a simple formulation based on thermodynamics. The idea is that the probability of opening or closing a channel depends exponentially on the potential. Thus,

$$\alpha(V) = A_\alpha \exp(-B_\alpha V) \quad \text{and} \quad \beta(V) = A_\beta \exp(-B_\beta V). \tag{1.36}$$

From this, we find that

$$m_\infty(V) = \frac{1}{1 + \exp(-(V - V_\mathrm{h})/V_\mathrm{s})},$$

where V_h and V_s are constants. We leave as an exercise the calculation of these constants in terms of the constants A and B. The time constant, $\tau(V)$, will generally be a skewed bell-shaped function of V. If $B_\beta = -B_\alpha$, then $\tau(V)$ is a hyperbolic secant.

1.9 Hodgkin–Huxley Model

We are now ready to derive the Hodgkin–Huxley model for the propagation of an action potential along the squid's giant axon. We view the axon as a cylinder of fixed radius, a, so the membrane potential depends on the spatial variable x and time t. Here, we assume there are voltage-gated K^+ and Na^+ channels and a leak current. Then balancing currents, as in (1.23), we have

$$I_{\mathrm{L}} = I_{\mathrm{cap}} + I_{\mathrm{ion}} \tag{1.37}$$

or, using (1.6) and (1.24),

$$\frac{a}{2r_{\mathrm{L}}}\frac{\partial^2 V_{\mathrm{M}}}{\partial x^2} = c_{\mathrm{M}}\frac{\partial V_{\mathrm{M}}}{\partial t} + I_{\mathrm{K}} + I_{\mathrm{Na}} + I_{\mathrm{L}}. \tag{1.38}$$

If each ionic current is ohmic, then this can be written as

$$c_{\mathrm{M}}\frac{\partial V_{\mathrm{M}}}{\partial t} = \frac{a}{2r_{\mathrm{L}}}\frac{\partial^2 V_{\mathrm{M}}}{\partial x^2} - g_{\mathrm{K}}(V_{\mathrm{M}} - E_{\mathrm{K}}) - g_{\mathrm{Na}}(V_{\mathrm{M}} - E_{\mathrm{Na}}) - g_{\mathrm{L}}(V_{\mathrm{M}} - E_{\mathrm{L}}). \tag{1.39}$$

To complete the model, we need to describe how one computes the membrane conductances $g_{\mathrm{K}}, g_{\mathrm{Na}}$, and g_{L}. Note that the voltage-gated conductances g_{K} and g_{Na} change with time during an action potential.

Hodgkin and Huxley used two experimental methods to separate the ionic currents and compute how the K^+ and Na^+ conductances depend on voltage. The first was a simple feedback circuit called the *voltage clamp* that allows the experimenter to hold the membrane potential at a constant or holding level V_{C}. The voltage clamp does so by injecting a current into the axon that is equal and opposite to the current flowing through the voltage-gated channels. Electrical details can be found in the book by Johnston and Wu [139]. Note that the voltage clamp separates the total membrane current into its ionic and capacitive components. Recall that the capacitive current satisfies $I_{\mathrm{cap}} = C_{\mathrm{M}}\mathrm{d}V_{\mathrm{M}}/\mathrm{dt}$. If the membrane potential is fixed at some constant, then the capacitive current must be zero. Moreover, the total current can be made spatially uniform by inserting a highly conductive axial wire inside the fiber; the axon is then said to be *space-clamped*. In this case, $\frac{\partial^2 V_{\mathrm{M}}}{\partial x^2} = 0$. It then follows that any changes in current must be due to either the leak or the opening and closing of voltage-gated membrane channels.

We first consider how the voltage clamp can be used to determine the leak conductance, g_{L}. Note that most of the voltage-gated channels are closed at rest. Moreover, if we hyperpolarize the cell, then we may assume all of the voltage-gated channels are closed. It follows that if the membrane potential is clamped at some sufficiently strong hyperpolarized level, then the total current is given by the leak; that is,

$$I_{\mathrm{M}} \approx g_{\mathrm{L}}(V_{\mathrm{C}} - E_{\mathrm{L}}).$$

From this equation, we can easily solve for g_{L}.

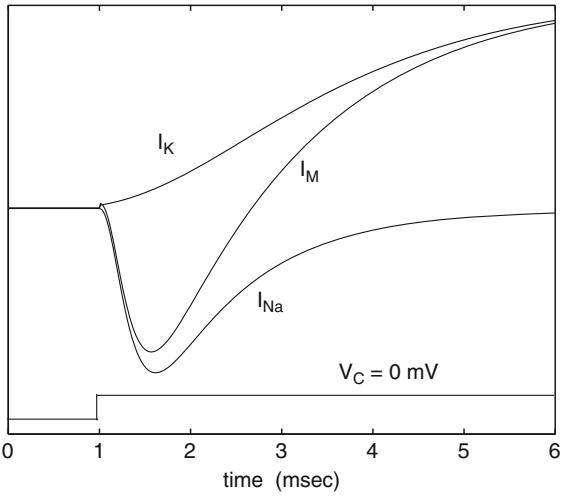

Fig. 1.8 Numerically computed voltage-clamp experiment. The membrane potential is stepped from rest to 0 mV. This results in an inward current followed by an outward current. The separate K^+ and Na^+ currents are also shown

Figure 1.8 shows the results of a (numerically computed) voltage-clamp experiment when the membrane potential is clamped at 0 mV. Note that there is an inward current followed by an outward current. This result suggests the depolarizing voltage step turns on two voltage-gated channels. The inward current is due to the influx of Na^+ ions, whereas the outward current is due to the outward flow of K^+ ions. It is not clear, however, how these two separate ions contribute to the total membrane current. For this it is necessary to isolate the two voltage-gated currents.

Hodgkin and Huxley were able to isolate the K^+ current by replacing Na^+ ions in the external bathing solution with a larger, impermeant cation. This eliminated the inward Na^+ current. Now there are dozens of compounds that selectively block different currents, many derived from natural toxins. (For example, tetrodotoxin, which blocks Na^+ channels, comes from the Pacific puffer fish, a tasty, if slightly dangerous, Japanese delicacy called fugu.) Once Na^+ has been removed, the voltage clamp can be used to determine how I_K depends on the membrane potential. That is, one holds the membrane potential at various levels and determines the time course of the total membrane current I_M. If Na^+ is removed, then the K^+ current is computed by subtracting the leak current from I_M.

It is also now possible to block K^+ channels using the drug tetraethylammonium. This was not available to Hodgkin and Huxley; however, if I_K and I_L are known, then one computes I_{Na} simply by subtracting I_K and I_L from I_M. Once these currents have been determined, we can calculate the I_K and I_{Na} conductances using Ohm's law. That is,

$$g_K(t) = \frac{I_K(t)}{(V_M - E_K)} \quad \text{and} \quad g_{Na}(t) = \frac{I_{Na}(t)}{(V_M - E_{Na})}. \tag{1.40}$$

Figure 1.9 shows the I_K and I_{Na} conductances for different levels of the holding potential. Note than g_{Na} turns on more rapidly that g_K. Moreover, the Na^+ channels

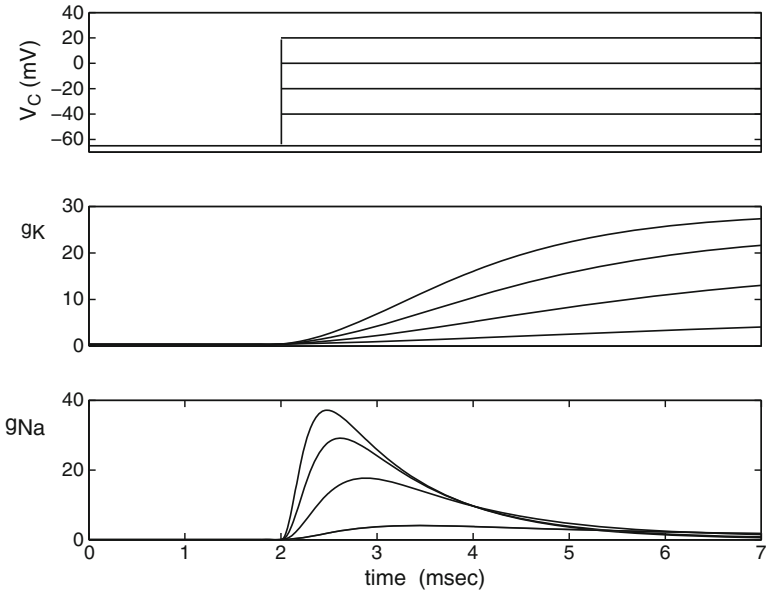

Fig. 1.9 Numerically computed voltage-clamp experiment. The membrane potential is stepped to different values and the resulting K^+ and Na^+ conductances are computed

begin to close before the depolarization is turned off, whereas the K^+ channels remain open as long as the membrane is depolarized. This suggests the Na^+ channel can exist in three states: resting, activated, and inactivated. When the cell is depolarized, the Na^+ channels switch from the resting (closed) to the activated (open) state. If the depolarization is maintained, then the channel switches to the inactivated (closed) state.

A physical interpretation of the Na^+ channel is shown in Fig. 1.10. There are two gates in the Na^+ channel: a fast one (the activation gate), represented by the line, and a slow one (the inactivation gate), represented by the ball. Both gates must be open for the channel to conduct Na^+ ions. At rest, the activation gate is closed and the inactivation gate is open. When the membrane is depolarized, the activation gate opens, which allows Na^+ into the cell. The inactivation gate (ball) closes at the higher potential, so the flow of Na^+ is transient. Hodgkin and Huxley used a more complicated voltage-clamp protocol, first stepping to a fixed voltage and then applying brief voltage steps to probe the fast activation and slow inactivation gates. Details can be found in [144].

Using the voltage-clamp data, Hodgkin and Huxley derived expressions for the K^+ and Na^+ conductances. They proposed that

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 \quad \text{and} \quad g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h, \tag{1.41}$$

where $\bar{g}_{\mathrm{K}}$ and $\bar{g}_{\mathrm{Na}}$ are maximum conductances and n, m, and h are gating variables that take values between 0 and 1. Hence, n^4 represents the probability that a K^+

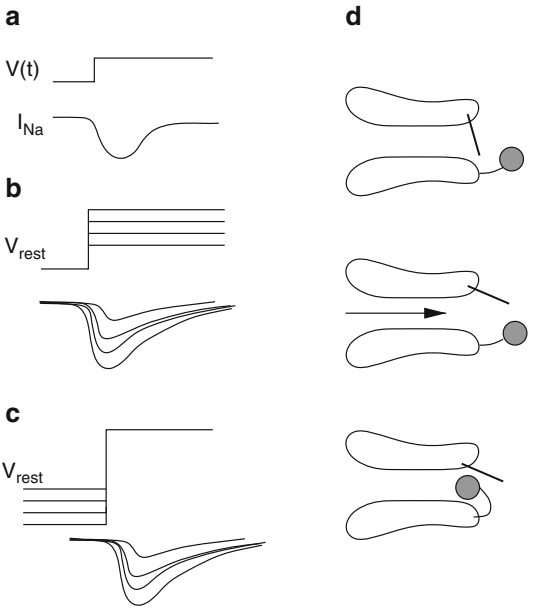

Fig. 1.10 The Hodgkin–Huxley Na^+ channel. (**a**–**c**) Voltage-clamp dynamics. (**d**) Physical model of the channel. If the voltage step is small (**d**, *top*) then the Na^+ channel's activation gate (*line*) is closed but the inactivation gate (*ball*) is open. At intermediate steps (**d**, *middle*), both gates are partially open. For large steps (**d**, *bottom*), the activation gate is open and the inactivation gate is closed

channel is open: the K^+ channel has four independent components, all of which are identical. The probability that the sodium activation gate is open is m^3 and the probability that the sodium inactivation gate is open is h. Each of the gating variables satisfies a first-order differential equation of the form (1.34). That is, they satisfy equations of the form

$$\begin{aligned}
\frac{\mathrm{d}n}{\mathrm{d}t} &= \alpha_n(V)(1-n) - \beta_n(V)n = (n_\infty(V) - n)/\tau_n(V),\\
\frac{\mathrm{d}m}{\mathrm{d}t} &= \alpha_m(V)(1-m) - \beta_m(V)m = (m_\infty(V) - m)/\tau_m(V),\\
\frac{\mathrm{d}h}{\mathrm{d}t} &= \alpha_h(V)(1-h) - \beta_h(V)h = (h_\infty(V) - h)/\tau_h(V).
\end{aligned}$$

If $X = n$, m, or h, then

$$X_\infty(V) = \frac{\alpha_X(V)}{\alpha_X(V) + \beta_X(V)} \quad \text{and} \quad \tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}. \tag{1.42}$$

To match the data, Hodgkin and Huxley chose the following parameters and gating functions: $\bar{g}_{\mathrm{Na}} = 120\,\mathrm{mS/cm^3}$, $\bar{g}_{\mathrm{K}} = 36\,\mathrm{mS/cm^3}$, $\bar{g}_{\mathrm{L}} = 0.3\,\mathrm{mS/cm^3}$, $E_{\mathrm{Na}} = 50\,\mathrm{mV}$, $E_{\mathrm{K}} = -77\,\mathrm{mV}$, $E_{\mathrm{L}} = -54.4\,\mathrm{mV}$,

$$\begin{aligned}
\alpha_n(V) &= 0.01(V + 55)/(1 - \exp(-(V + 55)/10)),\\
\beta_n(V) &= 0.125\exp(-(V + 65)/80),\\
\alpha_m(V) &= 0.1(V + 40)/(1 - \exp(-(V + 40)/10)),
\end{aligned}$$

$$\beta_m(V) = 4\exp(-(V+65)/18),$$
$$\alpha_h(V) = 0.07\exp(-(V+65)/20),$$
$$\beta_h(V) = 1/(1+\exp(-(V+35)/10)).$$

In Fig. 1.11, we plot the *activation curves* $n_\infty(V), m_\infty(V)$, and $h_\infty(V)$ along with $\tau_n(V), \tau_m(V)$, and $\tau_h(V)$. Note that n_∞ and m_∞ are increasing functions that approach 0 for hyperpolarizing currents and approach 1 for depolarizing currents. Hence, n and m become activated when the membrane is depolarized. On the other hand, $h_\infty(V)$ is a decreasing function, so the Na^+ channels inactivate when the membrane is depolarized. It is also important to note that $\tau_m(V)$ is considerably smaller than τ_n or τ_h. Hence, Na^+ channels activate much faster than they inactivate or K^+ channels open. In Fig. 1.12, we show the response of m, h, and n to a step in voltage.

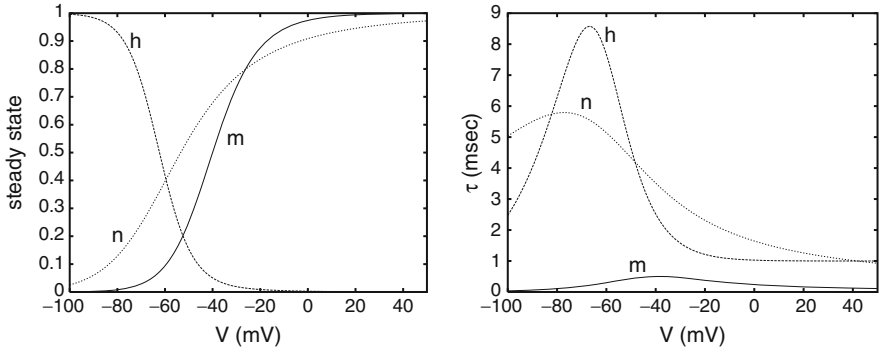

Fig. 1.11 Hodgkin–Huxley functions. *Left* the steady-state opening of the gates and *right* the time constants

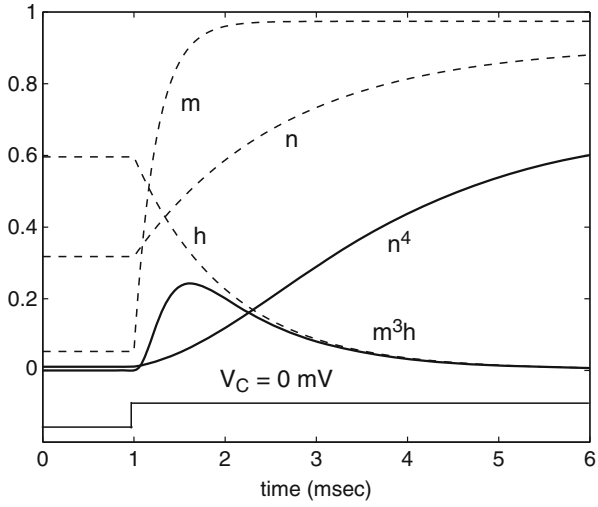

Fig. 1.12 Response of the activation and inactivation variables m, h, and n to a step in voltage

1.10 The Action Potential Revisited

In summary, the Hodgkin–Huxley model is a system of four differential equations; there is one equation for the membrane potential and three equations for channel gating variables. In the case of a space-clamped squid axon, we write these equations as

$$\begin{aligned} c_{\mathrm{M}}\frac{\mathrm{d}V}{\mathrm{d}t} &= -\bar{g}_{\mathrm{Na}}m^3h(V-E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}n^4(V-E_{\mathrm{K}}) - \bar{g}_{\mathrm{L}}(V-E_{\mathrm{L}}),\\ \frac{\mathrm{d}n}{\mathrm{d}t} &= \phi[\alpha_n(V)(1-n) - \beta_n(V)n],\\ \frac{\mathrm{d}m}{\mathrm{d}t} &= \phi[\alpha_m(V)(1-m) - \beta_m(V)m],\\ \frac{\mathrm{d}h}{\mathrm{d}t} &= \phi[\alpha_h(V)(1-h) - \beta_h(V)h]. \end{aligned} \tag{1.43}$$

Here, we added a parameter ϕ; this is the *temperature factor*. It is important to realize that the temperature at which an experiment is done can be very important. Since channels are stochastic in nature, they are sensitive to the temperature, so the rates of switching states depend exponentially on the temperature. Higher temperatures cause faster switching. Thus, there is a factor

$$\phi = Q_{10}^{(T-T_{\mathrm{base}})/10}. \tag{1.44}$$

Q_{10} is the ratio of the rates for an increase in temperature of 10°C. For the squid giant axon, $T_{\mathrm{base}} = 6.3°\mathrm{C}$ and $Q_{10} = 3$.

Figure 1.13 shows solutions of these equations in response to different levels of steps in currents. Note that there is "all-or-none" behavior: When the applied current is below some threshold, the membrane potential returns quickly to the rest; when the current is above some threshold, there is an action potential. If the applied current is sufficiently large and held for a sufficiently long time, then the model generates a periodic response.

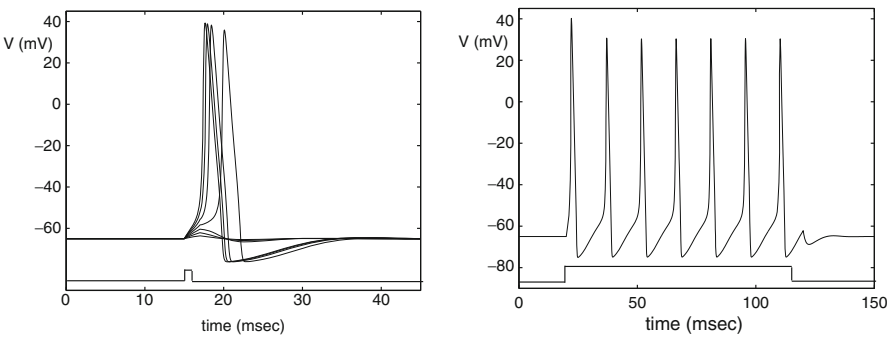

Fig. 1.13 Responses of the Hodgkin–Huxley model to applied currents. *Left* transient responses showing "all-or-none" behavior and *right* sustained periodic response

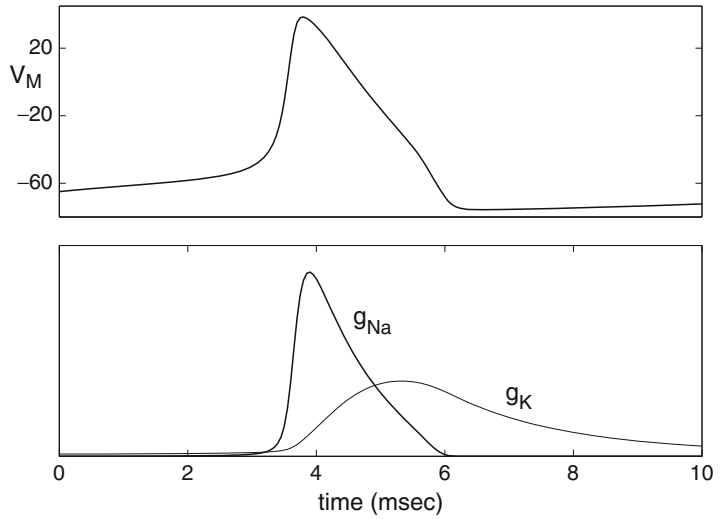

Fig. 1.14 Solution of the Hodgkin–Huxley equations showing an action potential. Also shown are the Na^+ and K^+ conductances

Figure 1.14 shows an action potential along with plots of the Na^+ and K^+ conductances, g_{Na} and g_K. Here, we start with the cell at rest and then depolarize the cell by 10 mV at $t = 0$. The cell then generates a single action potential. In Sect. 1.8, we described the events underlying the action potential in terms of the inward and outward flow of Na^+ and K^+ ions. Here, we give a more "mathematical" explanation in terms of the behavior of the dependent variables in the differential equations.

When we depolarize the cell, we change the values of the activation curves: $n_\infty(V)$ and $m_\infty(V)$ increase, whereas $h_\infty(V)$ decreases. Since n, m, and h tend toward their activation curves, it follows that n and m initially increase, whereas h decreases. That is, K^+ channels open, whereas Na^+ channels both activate and inactivate. However, τ_m is much smaller than both τ_h and τ_n. It follows that the Na^+ channels activate much faster than they inactivate or K^+ channels open. Therefore, the Na^+ conductance, $g_{Na} = \bar{g}_{Na} m^3 h$, increases faster than $g_K = \bar{g}_K n^4$.

The increase in the Na^+ conductance leads to a large increase in the Na^+ current, $I_{Na} = g_{Na}(V - E_{Na})$. As long as the cell is near rest, the driving force $V - E_{Na}$ is large (recall that $E_{Na} \approx +55$ mV). Hence, the Na^+ current will dominate the equation for the membrane potential and V will increase toward the Na^+ Nernst potential. As V increases, $m_\infty(V)$ increases further, leading to further increase in Na^+ activation.

As V increases toward E_{Na}, Na^+ channels inactivate. This is because $h \to h_\infty(V) \approx 0$. Moreover, the Na^+ driving force $V - E_{Na}$ decreases. For both reasons, the Na^+ current turns off. Meanwhile, the K^+ channel activates because $n \to n_\infty(V) \approx 1$. Moreover, the K^+ driving force $V - E_K$ becomes very large.

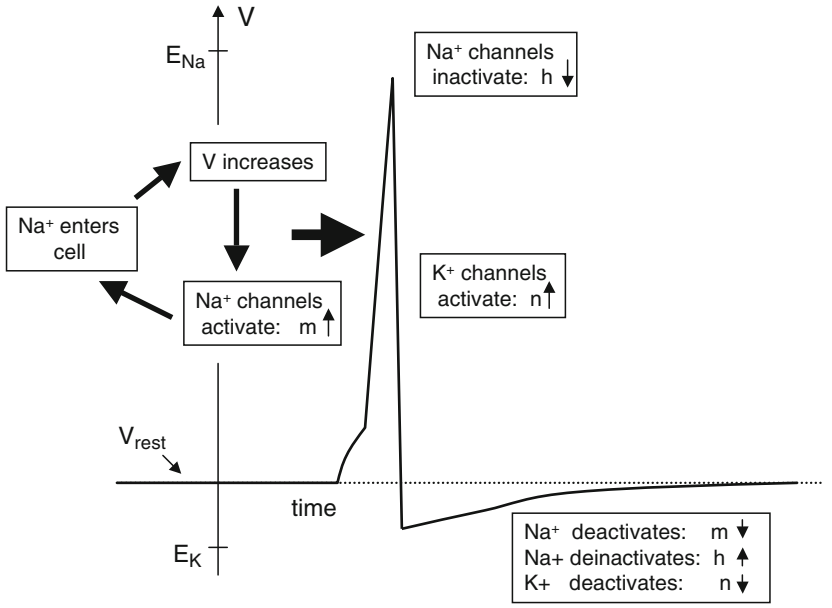

Fig. 1.15 Mechanisms underlying the action potential

It follows that eventually, the K^+ current dominates and the membrane potential must fall back toward the K^+ Nernst potential. This corresponds to the downstroke of the action potential.

After the action potential (Fig. 1.15), the cell is hyperpolarized with $m_\infty \approx 0$, $n_\infty \approx 0$, and $h_\infty \approx 1$. After some time, m, n, and h approach their steady-state values and the cell returns to rest.

1.11 Bibliography

There are many standard neuroscience textbooks that present the biological aspects covered in this chapter in much more detail. These textbooks include those by Kandel et al. [144], Hille [122], and Martin [192]. The reader is also highly recommended to look at Hodgkin and Huxley's original papers [124]. A review of these papers, along with a short review of the history leading up to them, is given in Rinzel [229]. Excellent textbooks which emphasize modeling and quantitative approaches are those of Johnston and Wu [139], Koch [156], Jack et al. [137], Izhikevich [136], and Dayan and Abbott [54]. Keener and Sneyd [148] and Fall et al. [83] give detailed introductions to mathematical aspects of cellular biophysics.

1.12 Exercises

1. Suppose the external potassium in a mammalian cell is increased by a factor of 10. What is the new value of E_K?
2. At 10°C a cell contains 80 mM sodium inside and has only 100 mM sodium outside. What is the equilibrium potential for sodium?
3. Compute the resting potential for the mammalian cell using the same permeabilities as were used for the squid axon and the ion concentrations listed in Table 1.1.
4. Derive the Nernst equation (1.2) from the Nernst–Planck equation by setting the current to zero and integrating with respect to x across the membrane.
5. Compute the calcium equilibrium potential for a mammalian cell assuming that the extracellular concentration is 5 mM and the intracellular concentration is 10^{-4} mM.
6. Complete the derivation the constant-field equation (1.3) from the linear Nernst–Planck equation.
7. Derive the GHK equation (1.4) from the constant-field equation.
8. Consider the GHK equation and plot the I–V relation for different values of the inside and outside concentrations. Show that for $[C]_{out} > [C]_{in}$ (respectively $[C]_{out} < [C]_{in}$) the I–V plot is concave down (respectively up).
9. Consider a passive, spherical cell with radius 0.003 cm^2, a resting membrane potential of −65 mV, a membrane capacitance of 1 $\mu F/cm^2$, and a membrane resistance of $R_M = 700\,\Omega\ cm^2$. Suppose the cell is injected with an applied current of 5 $nA/\mu m^2$ for 2 s and then the current is turned off. What is the membrane potential at $t = 1, t = 2$, and $t = 3$?
10. Suppose a passive axon has a diameter of 0.5 mm, a resting membrane resistance of $R_M = 700\,\Omega\ cm^2$, and a transmembrane resistance of $R_L = 30\,\Omega$ cm. Compute the space constant. If the axon is 5 cm long and one end of the axon is held at 120 mV above rest, then what is the potential at the other end?
11. (Johnston and Wu [139], page 12) The membrane capacitance of a typical cell is 1 $\mu F/cm^2$ and the concentration of ions inside and outside the cell is about 0.5 M. Calculate the fraction of uncompensated ions on each side of the membrane required to produce 100 mV in a spherical cell with a radius of 25 μm.
12. Numerically solve the Hodgkin–Huxley equations. Start the system at rest and, at some later time, inject an applied current to generate an action potential. Plot the time courses of the Na^+ and K^+ conductances, as well as the gating variables m, h and n.
13. Numerically perform space-clamp experiments. That is, start the Hodgkin–Huxley model at rest and, at some later time, change the membrane potential and keep it as some "clamped" level. Plot the Na^+ and K^+ conductances for when the membrane potential is stepped to different values.