Chapter 2

The basis of electrical activity in the neuron

The purpose of this chapter is to introduce the physical principles underlying models of the electrical activity of neurons. Starting with the neuronal cell membrane, we explore how its permeability to different ions and the maintenance by ionic pumps of concentration gradients across the membrane underpin the resting membrane potential. We show how the electrical activity of a small neuron can be represented by equivalent electrical circuits, and discuss the insights this approach gives into the time-dependent aspects of the membrane potential, as well as its limitations. It is shown that spatially extended neurons can be modelled approximately by joining together multiple compartments, each of which contains an equivalent electrical circuit. To model neurons with uniform properties, the cable equation is introduced. This gives insights into how the membrane potential varies over the spatial extent of a neuron.

A nerve cell, or neuron, can be studied at many different levels of analysis, but much of the computational modelling work in neuroscience is at the level of the electrical properties of neurons. In neurons, as in other cells, a measurement of the voltage across the membrane using an intracellular electrode (Figure 2.1) shows that there is an electrical potential difference across the cell membrane, called the membrane potential. In neurons the membrane potential is used to transmit and integrate signals, sometimes over large distances. The resting membrane potential is typically around $-65\,\text{mV}$, meaning that the potential inside the cell is more negative than that outside.

For the purpose of understanding their electrical activity, neurons can be represented as an electrical circuit. The first part of this chapter explains why this is so in terms of basic physical processes such as diffusion and electric fields. Some of the material in this chapter does not appear directly in computational models of neurons, but the knowledge is useful for informing the decisions about what needs to be modelled and the way in which it is modelled. For example, changes in the concentrations of ions sometimes alter the electrical and signalling properties of the cell significantly, but sometimes they are so small that they can be ignored. This chapter will give the information necessary to make this decision.
Fig. 2.1 Differences in the intracellular and extracellular ion compositions and their separation by the cell membrane is the starting point for understanding the electrical properties of the neuron. The inset shows that for a typical neuron in the CNS, the concentration of sodium ions is greater outside the cell than inside it, and that the concentration of potassium ions is greater inside the cell than outside. Inserting an electrode into the cell allows the membrane potential to be measured.

The second part of this chapter explores basic properties of electrical circuit models of neurons, starting with very small neurons and going on to (electrically) large neurons. Although these models are missing many of the details which are added in later chapters, they provide a number of useful concepts, and can be used to model some aspects of the electrical activity of neurons.

2.1 The neuronal membrane

The electrical properties which underlie the membrane potential arise from the separation of intracellular and extracellular space by a cell membrane. The intracellular medium, cytoplasm, and the extracellular medium contain differing concentrations of various ions. Some key inorganic ions in nerve cells are positively charged cations, including sodium (Na$^+$), potassium (K$^+$), calcium (Ca$^{2+}$) and magnesium (Mg$^{2+}$), and negatively charged anions such as chloride (Cl$^-$). Within the cell, the charge carried by anions and cations is usually almost balanced, and the same is true of the extracellular space. Typically, there is a greater concentration of extracellular sodium than intracellular sodium, and conversely for potassium, as shown in Figure 2.1.

The key components of the membrane are shown in Figure 2.2. The bulk of the membrane is composed of the 5 nm thick lipid bilayer. It is made up of two layers of lipids, which have their hydrophilic ends pointing outwards and their hydrophobic ends pointing inwards. It is virtually impermeable to water molecules and ions. This impermeability can cause a net build-up of positive ions on one side of the membrane and negative ions on the other. This leads to an electrical field across the membrane, similar to that found between the plates of an ideal electrical capacitor (Table 2.1).
Ion channels are pores in the lipid bilayer, made of proteins, which can allow certain ions to flow through the membrane. A large body of biophysical work, starting with the work of Hodgkin and Huxley (1952d) described in Chapter 3 and summarised in Chapter 5, has shown that many types of ion channels, referred to as active channels, can exist in open states, where it is possible for ions to pass through the channel, and closed states, in which ions cannot permeate through the channel. Whether an active channel is in an open or closed state may depend on the membrane potential, ionic concentrations or the presence of bound ligands, such as neurotransmitters. In contrast, passive channels do not change their permeability in response to changes in the membrane potential. Sometimes a channel’s dependence on the membrane potential is so mild as to be virtually passive.

Both passive channels and active channels in the open state exhibit selective permeability to different types of ion. Channels are often labelled by the ion to which they are most permeable. For example, potassium channels

### Table 2.1

<table>
<thead>
<tr>
<th>Component</th>
<th>Symbols and units</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battery</td>
<td>$E$ (volts, V)</td>
<td>Pumps charge around a circuit</td>
</tr>
<tr>
<td>Current source</td>
<td>$I$ (amps, A)</td>
<td>Provides a specified current (which may vary with time)</td>
</tr>
<tr>
<td>Resistor</td>
<td>$R$ (ohms, $\Omega$)</td>
<td>Resists the flow of current in a circuit</td>
</tr>
<tr>
<td>Capacitor</td>
<td>$C$ (farad, F)</td>
<td>Stores charge. Current flows onto (not through) a capacitor</td>
</tr>
</tbody>
</table>
primarily allow potassium ions to pass through. There are many types of ion channel, each of which has a different permeability to each type of ion.

In this chapter, how to model the flow of ions through passive channels is considered. The opening and closing of active channels is a separate topic, which is covered in detail in Chapters 3 and 5; the concepts presented in this chapter are fundamental to describing the flow of ions through active channels in the open state. It will be shown how the combination of the selective permeability of ion channels and ionic concentration gradients lead to the membrane having properties that can be approximated by ideal resistors and batteries (Table 2.1). This approximation and a fuller account of the electrical properties arising from the permeable and impermeable aspects of the membrane are explored in Sections 2.3–2.5.

**Ionic pumps** are membrane-spanning protein structures that actively pump specific ions and molecules in and out of the cell. Particles moving freely in a region of space always move so that their concentration is uniform throughout the space. Thus, on the high concentration side of the membrane, ions tend to flow to the side with low concentration, thus diminishing the concentration gradient. Pumps counteract this by pumping ions against the concentration gradient. Each type of pump moves a different combination of ions. The sodium–potassium exchanger pushes $K^+$ into the cell and $Na^+$ out of the cell. For every two $K^+$ ions pumped into the cell, three $Na^+$ ions are pumped out. This requires energy, which is provided by the hydrolysis of one molecule of adenosine triphosphate (ATP), a molecule able to store and transport chemical energy within cells. In this case, there is a net loss of charge in the neuron, and the pump is said to be **electrogenic**. An example of a pump which is not electrogenic is the sodium–hydrogen exchanger, which pumps one $H^+$ ion out of the cell against its concentration gradient for every $Na^+$ ion it pumps in. In this pump, $Na^+$ flows down its concentration gradient, supplying the energy required to extrude the $H^+$ ion; there is no consumption of ATP. Other pumps, such as the sodium–calcium exchanger, are also driven by the $Na^+$ concentration gradient (Blaustein and Hodgkin, 1969). These pumps consume ATP indirectly as they increase the intracellular $Na^+$ concentration, giving the sodium–potassium exchanger more work to do.

In this chapter, ionic pumps are not considered explicitly; rather we assume steady concentration gradients of each ion type. The effects of ionic pumps are considered in more detail in Chapter 6.

### 2.2 Physical basis of ion movement in neurons

The basis of electrical activity in neurons is movement of ions within the cytoplasm and through ion channels in the cell membrane. Before proceeding to fully fledged models of electrical activity, it is important to understand the physical principles which govern the movement of ions through channels and within **neurites**, the term we use for parts of axons or dendrites.

Firstly, the electric force on ions is introduced. We then look at how to describe the diffusion of ions in solution from regions of high to low
2.2 PHYSICAL BASIS OF ION MOVEMENT IN NEURONS

2.2.1 The electric force on ions

As ions are electrically charged they exert forces on and experience forces from other ions. The force acting on an ion is proportional to the ion’s charge, \(q\). The electric field at any point in space is defined as the force experienced by an object with a unit of positive charge. A positively charged ion in an electric field experiences a force acting in the direction of the electric field; a negatively charged ion experiences a force acting in exactly the opposite direction to the electric field (Figure 2.3). At any point in an electric field a charge has an electrical potential energy. The difference in the potential energy per unit charge between any two points in the field is called the potential difference, denoted \(V\) and measured in volts.

A simple example of an electric field is the one that can be created in a parallel plate capacitor (Figure 2.4). Two flat metal plates are arranged so they are facing each other, separated by an electrical insulator. One of the plates is connected to the positive terminal of a battery and the other to the negative terminal. The battery attracts electrons (which are negatively charged) into its positive terminal and pushes them out through its negative terminal. The plate connected to the negative terminal therefore has an excess of negative charge on it, and the plate connected to the positive terminal has an excess of positive charge. The separation of charges sets up an electric field between the plates of the capacitor.

Because of the relationship between electric field and potential, there is also a potential difference across the charged capacitor. The potential difference is equal to the electromotive force of the battery. For example, a battery with an electromotive force of 1.5 V creates a potential difference of 1.5 V between the plates of the capacitor.

The strength of the electric field set up through the separation of ions between the plates of the capacitor is proportional to the magnitude of the excess charge \(q\) on the plates. As the potential difference is proportional to the electric field, this means that the charge is proportional to the potential difference. The constant of proportionality is called the capacitance and is measured in farads. It is usually denoted by \(C\) and indicates how much charge can be stored on a particular capacitor for a given potential difference across it:

\[ q = CV. \]  (2.1)

Capacitance depends on the electrical properties of the insulator and size and distance between the plates.
Box 2.1 Voltage and current conventions in cells

By convention, the membrane potential, the potential difference across a cell membrane, is defined as the potential inside the cell minus the potential outside the cell. The convention for current flowing through the membrane is that it is defined to be positive when there is a flow of positive charge out of the cell, and to be negative when there is a net flow of positive charge into the cell.

According to these conventions, when the inside of the cell is more positively charged than the outside, the membrane potential is positive. Positive charges in the cell will be repelled by the other positive charges in the cell, and will therefore have a propensity to move out of the cell. Any movement of positive charge out of the cell is regarded as a positive current. It follows that a positive membrane potential tends to lead to a positive current flowing across the membrane. Thus, the voltage and current conventions fit with the notion that current flows from higher to lower voltages.

It is also possible to define the membrane potential as the potential outside minus the potential inside. This is an older convention and is not used in this book.

2.2.2 Diffusion

Individual freely moving particles, such as dissociated ions, suspended in a liquid or gas appear to move randomly, a phenomenon known as Brownian motion. However, in the behaviour of large groups of particles, statistical regularities can be observed. Diffusion is the net movement of particles from regions in which they are highly concentrated to regions in which they have low concentration. For example, when ink drips into a glass of water, initially a region of highly concentrated ink will form, but over time this will spread out until the water is uniformly coloured. As shown by Einstein (1905), diffusion, a phenomenon exhibited by groups of particles, actually arises from the random movement of individual particles. The rate of diffusion depends on characteristics of the diffusing particle and the medium in which it is diffusing. It also depends on temperature; the higher the temperature, the more vigorous the Brownian motion and the faster the diffusion.

In the ink example molecules diffuse in three dimensions, and the concentration of the molecule in a small region changes with time until the final steady state of uniform concentration is reached. In this chapter, we need to understand how molecules diffuse from one side of the membrane to the other through channels. The channels are barely wider than the diffusing molecules, and so can be thought of as being one-dimensional.

The concentration of an arbitrary molecule or ion X is denoted [X]. When [X] is different on the two sides of the membrane, molecules will diffuse through the channels down the concentration gradient, from the side with higher concentration to the side with lower concentration (Figure 2.5). Flux is the amount of X that flows through a cross-section of unit area per unit time. Typical units for flux are mol cm$^{-2}$ s$^{-1}$, and its sign
depends on the direction in which the molecules are flowing. To fit in with our convention for current (Box 2.1), we define the flux as positive when the flow of molecules is out of the cell, and negative when the flow is inward. Fick (1855) provided an empirical description relating the molar flux, \( J_{X,\text{diff}} \), arising from the diffusion of a molecule X, to its \textbf{concentration gradient} \( \frac{d[X]}{dx} \) (here in one dimension):

\[
J_{X,\text{diff}} = -D_X \frac{d[X]}{dx} \tag{2.2}
\]

where \( D_X \) is defined as the \textbf{diffusion coefficient} of molecule X. The diffusion coefficient has units of cm\(^2\) s\(^{-1}\). This equation captures the notion that larger concentration gradients lead to larger fluxes. The negative sign indicates that the flux is in the opposite direction to that in which the concentration gradient increases; that is, molecules flow from high to low concentrations.

### 2.2.3 Electrical drift

Although they experience a force due to being in an electric field, ions on the surface of a membrane are not free to move across the insulator which separates them. In contrast, ions in the cytoplasm and within channels are able to move. Our starting point for thinking about how electric fields affect ion mobility is to consider a narrow cylindrical tube in which there is a solution containing positively and negatively charged ions such as \( \text{K}^+ \) and \( \text{Cl}^- \). The concentration of both ions in the tube is assumed to be uniform, so there is no concentration gradient to drive diffusion of ions along the tube. Apart from lacking intracellular structures such as microtubules, the endoplasmic reticulum and mitochondria, this tube is analogous to a section of neurite.

Now suppose that electrodes connected to a battery are placed in the ends of the tube to give one end of the tube a higher electrical potential than the other, as shown in Figure 2.6. The \( \text{K}^+ \) ions will experience an electrical force pushing them down the potential gradient, and the \( \text{Cl}^- \) ions, because of their negative charge, will experience an electrical force in the opposite direction. If there were no other molecules present, both types of ion would accelerate up or down the neurite. But the presence of other molecules causes frequent collisions with the \( \text{K}^+ \) and \( \text{Cl}^- \) ions, preventing them from accelerating. The result is that both \( \text{K}^+ \) and \( \text{Cl}^- \) molecules travel at an average speed (\textbf{drift velocity}) that depends on the strength of the field. Assuming there is no concentration gradient of potassium or chloride, the flux is:

\[
J_{X,\text{drift}} = - \frac{D_X F}{RT} z_X [X] \frac{dV}{dx} \tag{2.3}
\]

where \( z_X \) is the ion’s signed \textbf{valency} (the charge of the ion measured as a multiple of the elementary charge). The other constants are: \( R \), the gas constant; \( T \), the temperature in kelvins; and \( F \), Faraday’s constant, which is the charge per mole of monovalent ions.
2.2.4 Electrodiffusion

Diffusion describes the movement of ions due to a concentration gradient alone, and electrical drift describes the movement of ions in response to a potential gradient alone. To complete the picture, we consider electrodiffusion, in which both voltage and concentration gradients are present, as is usually the case in ion channels. The total flux of an ion \( X \), \( J_X \), is simply the sum of the diffusion and drift fluxes from Equations 2.2 and 2.3:

\[
J_X = J_{X, \text{diff}} + J_{X, \text{drift}} = -D_X \left( \frac{d[X]}{dx} + \frac{z_X F}{RT} [X] \frac{dV}{dx} \right).
\]  

This equation, developed by Nernst (1888) and Planck (1890), is called the Nernst–Planck equation and is a general description of how charged ions move in solution in electric fields. It is used to derive the expected relationships between the membrane potential and ionic current flowing through channels (Section 2.4).

2.2.5 Flux and current density

So far, movement of ions has been quantified using flux, the number of moles of an ion flowing through a cross-section of unit area. However, often we are interested in the flow of the charge carried by molecules rather than the flow of the molecules themselves. The amount of positive charge flowing per unit of time past a point in a conductor, such as an ion channel or neurite, is called current and is measured in amperes (denoted A). The current density is the amount of charge flowing per unit of time per unit of cross-sectional area. In this book, we denote current density with the symbol \( I \), with typical units \( \mu A \ cm^{-2} \).

The current density \( I_X \) due to a particular ion \( X \) is proportional to the molar flux of that ion and the charge that it carries. We can express this as:

\[
I_X = F z_X J_X
\]

where \( F \) is Faraday’s constant and \( z_X \) is the ion’s signed valency. As with the flux of an ion, the sign of the current depends on the direction in which the charged particles are flowing. As defined earlier, the flux of molecules or ions through channels is positive when they are flowing out of the cell. Thus, the current due to positively charged ions, such as Na\(^+\) and K\(^+\), will be positive when they are flowing out of the cell, and negative when they flow into the cell, since \( z_X \) is positive for these ions. However, for negatively charged ions, such as Cl\(^-\), when their flux is positive the current they carry is negative, and vice versa. A negative ion flowing into the cell has the same effect on the net charge balance as a positive ion flowing out of it.

The total current density flowing in a neurite or through a channel is the sum of the contributions from the individual ions. For example, the total ion flow due to sodium, potassium and chloride ions is:

\[
I = I_{\text{Na}} + I_{\text{K}} + I_{\text{Cl}} = F z_{\text{Na}} J_{\text{Na}} + F z_{\text{K}} J_{\text{K}} + F z_{\text{Cl}} J_{\text{Cl}}.
\]
2.2 PHYSICAL BASIS OF ION MOVEMENT IN NEURONS

2.2.6 I–V characteristics

Returning to the case of electrodiffusion along a neurite (Section 2.2.4), Equations 2.3 and 2.6 show that the current flowing along the neurite, referred to as the axial current, should be proportional to the voltage between the ends of the neurite. Thus the axial current is expected to obey Ohm’s law (Figure 2.7a), which states that, at a fixed temperature, the current $I$ flowing through a conductor is proportional to the potential difference $V$ between the ends of the conductor. The constant of proportionality $G$ is the conductance of the conductor in question, and its reciprocal $R$ is known as the resistance. In electronics, an ideal resistor obeys Ohm’s law, so we can use the symbol for a resistor to represent the electrical properties along a section of neurite.

It is worth emphasising that Ohm’s law does not apply to all conductors. Conductors that obey Ohm’s law are called ohmic, whereas those that do not are non-ohmic. Determining whether an electrical component is ohmic or not can be done by applying a range of known potential differences across it and measuring the current flowing through it in each case. The resulting plot of current versus potential is known as an $I$–$V$ characteristic. The $I$–$V$ characteristic of a component that obeys Ohm’s law is a straight line passing through the origin, as demonstrated by the $I$–$V$ characteristic of a wire shown in Figure 2.7a. The $I$–$V$ characteristic of a filament light bulb, shown in Figure 2.7b, demonstrates that in some components, the current is not proportional to the voltage, with the resistance going up as the voltage increases. The filament may in fact be an ohmic conductor, but this could be masked in this experiment by the increase in the filament’s temperature as the amount of current flowing through it increases.

An example of a truly non-ohmic electrical component is the diode, where, in the range tested, current can flow in one direction only (Figure 2.7c). This is an example of rectification, the property of allowing current to flow more freely in one direction than another.

While the flow of current along a neurite is approximately ohmic, the flow of ions through channels in the membrane is not. The reason for this difference is that there is a diffusive flow of ions across the membrane due to...
2.3 The resting membrane potential: the Nernst equation

The ion channels which span the lipid bilayer confer upon the neuronal cell membrane the property of permeability to multiple types of ion. The first step towards understanding the origin of the resting membrane potential is to consider diffusion and electrical drift of ions through the membrane in a sequence of thought experiments.

The initial setup of the first thought experiment, shown in Figure 2.8a, is a container divided into two compartments by a membrane. The left-hand half represents the inside of a cell and the right-hand half the outside. Into the left (intracellular) half we place a high concentration of a potassium solution, consisting of equal numbers of potassium ions, K\(^+\), and anions, A\(^-\). Into the right (extracellular) half we place a low concentration of the same solution. If the membrane is permeable to both types of ions, both populations of ions will diffuse from the half with a high concentration to the half with a low concentration. This will continue until both halves have the same concentration, as seen in Figure 2.8b. This diffusion is driven by the concentration gradient; as we have seen, where there is a concentration gradient, particles or ions move down the gradient.

In the second thought experiment, we suppose that the membrane is permeable only to K\(^+\) ions and not to the anions (Figure 2.9a). In this situation only K\(^+\) ions can diffuse down their concentration gradient (from left to right in this figure). Once this begins to happen, it creates an excess of positively charged ions on the right-hand surface of the membrane and an excess of negatively charged anions on the left-hand surface. As when the plates of a capacitor are charged, this creates an electric field, and hence a potential difference across the membrane (Figure 2.9b).

The electric field influences the potassium ions, causing an electrical drift of the ions back across the membrane opposite to their direction of diffusion (from right to left in the figure). The potential difference across the
membrane grows until it provides an electric field that generates a net electrical drift that is equal and opposite to the net flux resulting from diffusion. Potassium ions will flow across the membrane either by diffusion in one direction or by electrical drift in the other direction until there is no net movement of ions. The system is then at equilibrium, with equal numbers of positive ions flowing rightwards due to diffusion and leftwards due to the electrical drift. At equilibrium, we can measure a stable potential difference across the membrane (Figure 2.9c). This potential difference, called the equilibrium potential for that ion, depends on the concentrations on either side of the membrane. Larger concentration gradients lead to larger diffusion fluxes (Fick’s first law, Equation 2.2).

In the late nineteenth century, Nernst (1888) formulated the Nernst equation to calculate the equilibrium potential resulting from permeability to a single ion:

$$E_X = \frac{RT}{z_X F} \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}}$$

(2.7)

where $X$ is the membrane-permeable ion and $[X]_{\text{in}}, [X]_{\text{out}}$ are the intracellular and extracellular concentrations of $X$, and $E_X$ is the equilibrium potential, also called the Nernst potential, for that ion. As shown in Box 2.2, the Nernst equation can be derived from the Nernst–Planck equation.

As an example, consider the equilibrium potential for K$^+$. Suppose the intracellular and extracellular concentrations are similar to that of the squid giant axon (400 mM and 20 mM, respectively) and the recording temperature is 6.3 °C (279.3 K). Substituting these values into the Nernst equation:

$$E_K = \frac{RT}{z_k F} \ln \frac{[K^+]_{\text{out}}}{[K^+]_{\text{in}}} = \frac{(8.314)(279.3)}{(+1)(9.648 \times 10^4)} \ln \frac{20}{400} \approx -72.1 \text{ mV.}$$

(2.8)

Table 2.2 shows the intracellular and extracellular concentrations of various important ions in the squid giant axon and the equilibrium potentials calculated for them at a temperature of 6.3 °C.

Since Na$^+$ ions are positively charged, and their concentration is greater outside than inside, the sodium equilibrium potential is positive. On the other hand, K$^+$ ions have a greater concentration inside than outside and so have a negative equilibrium potential. Like Na$^+$, Cl$^-$ ions are more concentrated outside than inside, but because they are negatively charged their equilibrium potential is negative.
Table 2.2  The concentrations of various ions in the squid giant axon and outside the axon, in the animal’s blood (Hodgkin, 1964). Equilibrium potentials are derived from these values using the Nernst equation, assuming a temperature of 6.3 °C. For calcium, the amount of free intracellular calcium is shown (Baker et al., 1971). There is actually a much greater total concentration of intracellular calcium (0.4 mM), but the vast bulk of it is bound to other molecules.

<table>
<thead>
<tr>
<th>Ion</th>
<th>K⁺</th>
<th>Na⁺</th>
<th>Cl⁻</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration inside (mM)</td>
<td>400</td>
<td>50</td>
<td>40</td>
<td>10⁻⁴</td>
</tr>
<tr>
<td>Concentration outside (mM)</td>
<td>20</td>
<td>440</td>
<td>560</td>
<td>10</td>
</tr>
<tr>
<td>Equilibrium potential (mV)</td>
<td>-72</td>
<td>52</td>
<td>-64</td>
<td>139</td>
</tr>
</tbody>
</table>

This thought experiment demonstrates that the lipid bilayer forming the cell membrane acts as a capacitor, with the surfaces of the thin insulating membrane being the plates of the capacitor. Direct measurements of the specific membrane capacitance of various types of neurons range between 0.7 μF cm⁻² and 1.3 μF cm⁻², and the specific capacitance can be treated as a ‘biological constant’ of 0.9 μF cm⁻² (Gentet et al., 2000), which is often rounded up to 1 μF cm⁻².

So far, we have neglected the fact that in the final resting state of our second thought experiment, the concentration of K⁺ ions on either side will differ from the initial concentration, as some ions have passed through the membrane. We might ask if this change in concentration is significant in neurons. We can use the definition of capacitance, \( q = CV \) (Equation 2.1), to compute the number of ions required to charge the membrane to its resting potential. This computation, carried out in Box 2.3, shows that in large neurites, the total number of ions required to charge the membrane is usually a tiny fraction of the total number of ions in the cytoplasm, and therefore changes the concentration by a very small amount. The intracellular and extracellular concentrations can therefore be treated as constants.

**Box 2.2 Derivation of the Nernst equation**

The Nernst equation is derived by assuming diffusion in one dimension along a line that starts at \( x = 0 \) and ends at \( x = X \). For there to be no flow of current, the flux is zero throughout, so from Equation 2.4, the Nernst–Planck equation, it follows that:

\[
\frac{1}{X} \frac{d[X]}{dx} = -\frac{zF}{RT} \frac{dV}{dx}.
\]

Integrating, we obtain:

\[
\int_{E_m}^{0} -dV = \int_{[X]_{in}}^{[X]_{out}} \frac{RT}{zF[X]} d[X].
\]

Evaluating the integrals gives:

\[
E_m = \frac{RT}{zF} \ln \frac{[X]_{out}}{[X]_{in}}
\]

which is the Nernst equation, Equation 2.7.
Box 2.3 | How many ions charge the membrane?
We consider a cylindrical section of squid giant axon 500 μm in diameter and 1 μm long at a resting potential of −70 mV. Its surface area is 500πμm², and so its total capacitance is 500π × 10⁻⁸ μF (1 μF cm⁻² is the same as 10⁻⁸ μF μm⁻²). As charge is the product of voltage and capacitance (Equation 2.1), the charge on the membrane is therefore 500π × 10⁻⁸ × 70 × 10⁻³ μC. Dividing by Faraday’s constant gives the number of moles of monovalent ions that charge the membrane: 1.139 × 10⁻¹⁷.

In contrast, the head of a dendritic spine on a hippocampal CA1 cell can be modelled as a cylinder with a diameter of around 0.4 μm and a length of 0.2 μm. Therefore its surface area is 0.08πμm² and its total capacitance is C = 0.08π × 10⁻⁸ μF = 0.08π × 10⁻¹⁴ F. The number of moles of calcium ions required to change the membrane potential by ΔV is ΔV C/(zF)
where z = 2 since calcium ions are doubly charged. If ΔV = 10 mV, this is 10 × 10⁻³ × 0.08π × 10⁻¹⁴/(2 × 9.468 × 10⁴) = 1.3 × 10⁻²² moles. Multiplying by Avogadro’s number (6.0221 × 10²³ molecules per mole), this is 80 ions. The resting concentration of calcium ions in a spine head is around 70 nM (Sabatini et al., 2002), so the number of moles of calcium in the spine head is π(0.4/2)² × 0.2 × 10⁻¹⁵ × 70 × 10⁻⁹ = 1.8 × 10⁻二十四 moles. Multiplying by Avogadro’s number the product is just about 1 ion. Thus the influx of calcium ions required to change the membrane potential by 10 mV increases the number of ions in the spine head from around 1 to around 80. This change in concentration cannot be neglected.

However, in small neurites, such as the spines found on dendrites of many neurons, the number of ions required to change the membrane potential by a few millivolts can change the intracellular concentration of the ion significantly. This is particularly true of calcium ions, which have a very low free intracellular concentration. In such situations, ionic concentrations cannot be treated as constants, and have to be modelled explicitly. Another reason for modelling Ca²⁺ is its critical role in intracellular signalling pathways. Modelling ionic concentrations and signalling pathways will be dealt with in Chapter 6.

What is the physiological significance of equilibrium potentials? In squid, the resting membrane potential is −65 mV, approximately the same as the potassium and chloride equilibrium potentials. Although originally it was thought that the resting membrane potential might be due to potassium, precise intracellular recordings of the resting membrane potential show that the two potentials differ. This suggests that other ions also contribute towards
the resting membrane potential. In order to predict the resting membrane potential, a membrane permeable to more than one type of ion must be considered.

### 2.4 Membrane ionic currents not at equilibrium: the Goldman–Hodgkin–Katz equations

To understand the situation when a membrane is permeable to more than one type of ion, we continue our thought experiment using a container divided by a semipermeable membrane (Figure 2.10a). The solutions on either side of the membrane now contain two types of membrane-permeable ions, K\(^+\) and Na\(^+\), as well as membrane-impermeable anions, which are omitted from the diagram for clarity. Initially, there is a high concentration of K\(^+\) and a very low concentration of Na\(^+\) on the left, similar to the situation inside a typical neuron. On the right (outside) there are low concentrations of K\(^+\) and Na\(^+\) (Figure 2.10a).

In this example the concentrations have been arranged so the concentration difference of K\(^+\) is greater than the concentration difference of Na\(^+\). Thus, according to Fick’s first law, the flux of K\(^+\) flowing from left to right down the K\(^+\) concentration gradient is bigger than the flux of Na\(^+\) from right to left flowing down its concentration gradient. This causes a net movement of positive charge from left to right, and positive charge builds up on the right-hand side of the membrane (Figure 2.10b). This in turn creates an electric field which causes electrical drift of both Na\(^+\) and K\(^+\) to the left. This reduces the net K\(^+\) flux to the right and increases the net Na\(^+\) flux to the left. Eventually, the membrane potential grows enough to make the K\(^+\) flux and the Na\(^+\) flux equal in magnitude but opposite in direction. When the net flow of charge is zero, the charge on either side of the membrane is constant, so the membrane potential is steady.

While there is no net flow of charge across the membrane in this state, there is net flow of Na\(^+\) and K\(^+\), and over time this would cause the concentration gradients to run down. As it is the concentration differences that are responsible for the potential difference across the membrane, the membrane potential would reduce to zero. In living cells, ionic pumps counteract this effect. In this chapter pumps are modelled implicitly by assuming that they maintain the concentrations through time. It is also possible to model pumps explicitly (Section 6.4).

From the thought experiment, we can deduce qualitatively that the resting membrane potential should lie between the sodium and potassium equilibrium potentials calculated using Equation 2.7, the Nernst equation, from their intracellular and extracellular concentrations. Because there is not enough positive charge on the right to prevent the flow of K\(^+\) from left to right, the resting potential must be greater than the potassium equilibrium potential. Likewise, because there is not enough positive charge on the left to prevent the flow of sodium from right to left, the resting potential must be less than the sodium equilibrium potential.
To make a quantitative prediction of the resting membrane potential, we make use of the theory of current flow through the membrane devised by Goldman (1943) and Hodgkin and Katz (1949). By making a number of assumptions, they were able to derive a formula, referred to as the Goldman–Hodgkin–Katz (GHK) current equation, which predicts the current $I_X$ mediated by a single ionic species $X$ flowing across a membrane when the membrane potential is $V$. The GHK current equation and the assumptions from which it was derived are shown in Box 2.4, and the corresponding $I$–$V$ curves are shown in Figure 2.11.

There are a number of properties worth noting from these curves.

1. No current flows when the voltage is equal to the equilibrium potential for the ion. This is because at this potential, current flow due to electrical drift and diffusion are equal and opposite. For the concentrations of ions shown in Table 2.2, the equilibrium potential of potassium is $-72$ mV, and the equilibrium potential of calcium is $+139$ mV.

2. The current changes direction (reverses) at the equilibrium potential. The current is negative (positive charge inwards) when the membrane voltage is below the equilibrium potential and positive above it. For this reason, the equilibrium potential of an ion is also known as its **reversal potential**.

3. The individual ions do not obey Ohm’s law since the current is not proportional to the voltage.

4. A consequence of this is that the $I$–$V$ characteristics display rectification, defined in Section 2.2.6. The potassium characteristic favours outward currents, and is described as **outward rectifying** (Figure 2.11a). The calcium characteristic favours inward currents and is described as **inward rectifying** (Figure 2.11b). The rectification effect for calcium is particularly pronounced. The GHK current equation shows that when the extracellular concentration is greater than the intracellular concentration, the characteristic is inward rectifying, and when the converse is true, it is outward rectifying.

We can now calculate the $I$–$V$ characteristic of a membrane permeable to more than one ion type. Assuming that ions flow through the membrane independently, the total current flowing across the membrane is the sum of the ionic currents (Equation 2.6) predicted by the GHK current equations.
We can therefore calculate the total current flowing across the membrane for a given value of the membrane potential. The resulting characteristic is broadly similar to the characteristics for the individual ions, in that the current is negative at low potentials and then increases as the membrane potential is raised. We recall that the reversal potential is defined as the membrane potential at which the current reverses direction. The reversal potential for more than one ion type lies between the equilibrium potentials of the individual ions.

The GHK current equation can be used to calculate the reversal potential. As we have seen, there is one GHK current equation for every ion to which the membrane is permeable. By setting the membrane current \( I \) to zero and solving this equation for voltage, we obtain the Goldman–Hodgkin–Katz voltage equation for the reversal potential when there is more than one type of ion. For a membrane permeable to \( \text{Na}^+ \), \( \text{K}^+ \) and \( \text{Cl}^- \), it reads:

\[
E_m = \frac{RT}{F} \ln \frac{P_K[K^+]_{\text{out}} + P_{\text{Na}}[\text{Na}^+]_{\text{out}} + P_{\text{Cl}}[\text{Cl}^-]_{\text{in}}}{P_K[K^+]_{\text{in}} + P_{\text{Na}}[\text{Na}^+]_{\text{in}} + P_{\text{Cl}}[\text{Cl}^-]_{\text{out}}} \quad (2.9)
\]

where \( P_K \), \( P_{\text{Na}} \), and \( P_{\text{Cl}} \) are the membrane permeabilities to \( \text{K}^+ \), \( \text{Na}^+ \) and \( \text{Cl}^- \) respectively (membrane permeability is described in Box 2.4). The pattern of this equation is followed for other sets of monovalent ions, with the numerator containing the external concentrations of the positively charged ions and the internal concentrations of the negatively charged ions.

As the permeabilities occur in the numerator and the denominator, it is sufficient to know only relative permeabilities to compute the voltage at equilibrium. The relative permeabilities of the membrane of the squid giant axon to \( \text{K}^+ \), \( \text{Na}^+ \) and \( \text{Cl}^- \) ions are 1.0, 0.03 and 0.1 respectively. With these values, and the concentrations from Table 2.2, the resting membrane potential of the squid giant axon predicted by the GHK voltage equation is \(-60 \text{ mV}\) at \(6.3 \,^\circ\text{C}\).

Equation 2.9, the GHK voltage equation, looks similar to the Nernst equation. Indeed, it reduces to the equivalent Nernst equation when the permeability of two of the ions is zero. However, this equation also demonstrates that the membrane potential with two ion types is not the sum of the individual equilibrium potentials.
Box 2.4  The GHK equations
Goldman (1943) and Hodgkin and Katz (1949) developed a formalism for describing the currents through and voltages across semipermeable membranes. This formalism models the diffusion of ions through a uniformly permeable membrane, predating the notion of channels or pores through the membrane. It is assumed that ions cross the membrane independently (the independence principle) and that the electric field within the membrane is constant. The flux or movement of ions within the membrane is governed by the internal concentration gradient and the electric field arising from the potential difference, calculated by the Nernst–Plank equation.

From these assumptions, the Goldman–Hodgkin–Katz current equation can be derived (Johnston and Wu, 1995):

\[
I_X = P_X z_X F V \left( \frac{[X]_{in} - [X]_{out}}{1 - e^{-z_X F V / RT}} \right).
\]

This equation predicts the net flow \( I_X \) per unit area of membrane, measured in cm\(^{-2}\) of an arbitrary ion type \( X \) with valency \( z_X \). \( P_X \) is the permeability of the membrane to ion \( X \), with units of cm s\(^{-1}\). It characterises the ability of an ion \( X \) to diffuse through the membrane and is defined by the empirical relationship between molar flux \( J \) and the concentration difference across the membrane:

\[
J_X = -P_X ([X]_{in} - [X]_{out}).
\]

In the GHK model of the membrane, permeability is proportional to the diffusion coefficient, \( D_X \), defined in Fick's first law (Equation 2.2). Hille (2001) discusses the relationship in more detail.

The GHK equation predates the notion of membrane channels and treats the membrane as homogeneous. In active membranes we can interpret the diffusion coefficient, \( D_X \), as variable – an increase in the number of open channels in the membrane will increase the membrane permeability. Because of the assumption of a constant electric field in the membrane, the GHK equations are sometimes referred to as the constant-field equations.

2.4.1  An electrical circuit approximation of the GHK current equation
It is often sufficient to use a simpler equation in place of the GHK current equation. In the potassium characteristic shown in Figure 2.11a, the straight line that gives zero current at the equilibrium potential (−72 mV) is a close approximation of the \( I-V \) characteristic for membrane potentials between about −100 mV and 50 mV, the voltage range within which cells normally operate. The equation describing this line is:

\[
I_X = g_X (V - E_X)
\]

(2.10)

where \( X \) is the ion of interest, \( E_X \) its equilibrium potential, and \( g_X \) is the gradient of the line with the units of conductance per unit area, often mS cm\(^{-2}\). The term in brackets \((V - E_X)\) is called the driving force. When the membrane potential is at the equilibrium potential for \( X \), the driving force is zero.
The basis of electrical activity in the neuron

Fig. 2.12  Interpretation of the approximation of the GHK current equation. (a) The approximation can be viewed as a resistor, or conductance, in series with a battery. (b) The graph shows three different I–V characteristics from this circuit given different conductances and battery voltages.

(1) \( g_X = 5.5 \text{ mS cm}^{-2}, \)
\( E_X = -72 \text{ mV}; \) this line is the same as the K\(^+\) approximation in Figure 2.11a;

(2) \( g_X = 11.0 \text{ mS cm}^{-2}, \)
\( E_X = -72 \text{ mV}; \)

(3) \( g_X = 5.5 \text{ mS cm}^{-2}, \)
\( E_X = 28 \text{ mV}. \)

In some cases, such as for calcium in Figure 2.11b, the GHK \( I–V \) characteristic rectifies too much for a linear approximation to be valid.

Making this linear approximation is similar to assuming Ohm’s law, \( I = GV, \) where conductance \( G \) is a constant. Since the straight line does not necessarily pass through the origin, the correspondence is not exact and this form of linear \( I–V \) relation is called quasi-ohmic. There is still a useful interpretation of this approximation in terms of electrical components. The \( I–V \) characteristic is the same as for a battery with electromotive force equal to the equilibrium potential in series with a resistor of resistance \( 1/g_X \) (Figure 2.12).

2.5  The capacitive current

We now have equations that describe how the net flow of current \( I \) through the different types of channels depends on the membrane potential \( V. \) In order to complete the description of the system, we need to know how the current affects the voltage.

All the current passing through the membrane either charges or discharges the membrane capacitance. So the rate of change of charge on the membrane \( dq/dt \) is the same as the net current flowing through the membrane: \( I = dq/dt. \) By differentiating Equation 2.1 for the charge stored on a capacitor with respect to time, we obtain a differential equation that links \( V \) and \( I: \)

\[
\frac{dV}{dt} = \frac{1}{C} \frac{dq}{dt}.
\]

(2.11)

This shows that the rate of change of the membrane potential is proportional to the current flowing across the membrane. The change in voltage over time, during the charging or discharging of the membrane, is inversely proportional to the capacitance – it takes longer to charge up a bigger capacitor.

2.6  The equivalent electrical circuit of a patch of membrane

We have seen how we can represent the permeable and impermeable properties of the membrane as electrical components. Figure 2.13 shows how these
components fit together to form an equivalent electrical circuit of a small patch of membrane. It comprises the membrane capacitance in parallel with one resistor and battery in series for each type of ion channel. There is also a current source that represents an electrode that is delivering a constant amount of current. It is said to be in current clamp mode. The amount of current injected is denoted by $I_e$, and in electrophysiological applications is usually measured in nanoamps (nA).

For the remainder of this chapter, we consider a membrane that contains passive ion channels, with constant permeability or conductance. In general, ion channels are active, so their permeability changes in response to changes in membrane potential. It is useful to consider passive membranes as a first step towards understanding the behaviour of active membranes. In addition, for small deviations of the membrane potential from the resting potential, active channels can be treated as passive channels.

### 2.6.1 Simplification of the equivalent electrical circuit

We can simplify the electrical circuit representing a patch of passive membrane, such as the circuit shown in Figure 2.13, by lumping together all of the channel properties. Figure 2.14a shows this simplified circuit. In place of the two resistor/battery pairs in Figure 2.13, there is one pair with a resistance, which we call the specific membrane resistance $R_m$, measured in $\Omega \text{ cm}^2$, and a membrane battery with an electromotive force of $E_m$.

We can derive these values from the conductances and reversal potentials of the individual ions using Thévenin’s theorem. For channels X, Y and Z combined, the equivalent electromotive force and membrane resistance are:

$$E_m = \frac{g_X E_X + g_Y E_Y + g_Z E_Z}{g_X + g_Y + g_Z}$$  \hspace{1cm} (2.12)

$$\frac{1}{R_m} = g_m = g_X + g_Y + g_Z.$$

Note that Equation 2.12 is the ohmic equivalent of the GHK voltage equation Equation 2.9.

A summary of key passive quantities and their typical units is given in Table 2.3. It is usual to quote the parameters of the membrane as intensive quantities. To avoid adding extra symbols, we use intensive quantities in our electrical circuits and equations. Supposing that the area of our patch of membrane is $a$, its membrane resistance is proportional to the specific...
membrane resistance divided by the area: $R_m/a$. Since conductance is the inverse of resistance, the membrane conductance of the patch is proportional to area: $g_m a$; its membrane capacitance is proportional to the specific membrane capacitance: $C_m a$. Current (for example, current crossing the membrane) is given by the current density $I$ which has units $\mu A \text{cm}^{-2}$ multiplied by the area: $I a$.

### 2.6.2 The RC circuit

The simplified circuit shown in Figure 2.14a is well known in electronics, where it is called an RC circuit, since its main elements are a resistor R and a capacitor C. In order to find out how the membrane potential changes when current is injected into the circuit, we need to know how current varies with voltage. By Kirchhoff’s current law, the sum of the current $I_a$ flowing through the membrane and the injected current $I_e$ is equal to the sum of the capacitive current $I_c a$ and the ionic current $I_i a$:

$$I_a + I_e = I_c a + I_i a$$

$$I + \frac{I_e}{a} = I_c + I_i.$$  (2.13)

The ionic current flowing through the resistor and battery is given by the quasi-ohmic relation in Equation 2.10:

$$I_i = \frac{V - E_m}{R_m}.$$  (2.14)

Finally, the capacitive current is given by the membrane capacitance multiplied by the rate of change of voltage (Section 2.5):

$$I_c = C_m \frac{dV}{dt}.$$  (2.15)

If this circuit is isolated, i.e. the membrane current $I_a$ is zero, substituting for $I_i$, and $I_c$ in Equation 2.13 for this RC circuit gives:

$$C_m \frac{dV}{dt} = E_m - \frac{V}{R_m} + \frac{I_e}{a}.$$  (2.16)

This is a first order **ordinary differential equation** (ODE) for the membrane potential $V$. It specifies how, at every instant in time, the rate of
change of the membrane potential is related to the membrane potential itself and the current injected. For any particular form of injected current pulse and initial membrane potential, it determines the time course of the membrane potential.

### 2.6.3 Behaviour of the RC circuit

Solving the differential equation is the process of using this equation to calculate how the membrane potential varies over time. We can solve Equation 2.16 using numerical methods. Appropriate numerical methods are programmed into neural simulation computer software, such as **NEURON** or **GENESIS**, so it is not strictly necessary to know the numerical methods in depth. However, a basic understanding of numerical methods is useful and we present an overview in Appendix B. Figure 2.14b shows the result of solving the equation numerically when the injected current is a square pulse of magnitude $I_e$ and duration $t_e$. On the rising edge of the pulse the membrane potential starts to rise steeply. This rise away from the resting potential is referred to as **depolarisation**, because the amount of positive and negative charge on the membrane is reducing. As the pulse continues, the rise in voltage becomes less steep and the voltage gets closer and closer to a limiting value. On the falling edge of the pulse the membrane potential starts to fall quite steeply. The rate of fall decreases as the membrane potential gets close to its original value. As the charge on the membrane is building back up to resting levels, this phase is called **repolarisation**. By injecting negative current, it is possible to reduce the membrane potential below its resting level, which is referred to as **hyperpolarisation**.

Generally, it is difficult, and often not possible, to solve differential equations analytically. However, Equation 2.16 is sufficiently simple to allow an analytical solution. We assume that the membrane is initially at rest, so that $V = E_m$ at time $t = 0$. We then integrate Equation 2.16 to predict the response of the membrane potential during the current pulse, giving:

$$V = E_m + \frac{R_mC_m}{a} \left( 1 - \exp \left( -\frac{t}{R_mC_m} \right) \right).$$

This is an inverted decaying exponential that approaches the steady state value $E_m + \frac{R_mC_m}{a}$ as time $t$ gets very large. Defining $V_0$ as the value the membrane potential has reached at the end of the current pulse at $t = t_e$, the response of the membrane is given by:

$$V = E_m + (V_0 - E_m) \exp \left( -\frac{t-t_e}{R_mC_m} \right),$$

which is a decaying exponential.

In both rising and falling responses, the denominator inside the exponential is the product of the membrane resistance and membrane capacitance $R_mC_m$. This factor has the units of time, and it characterises the length of time taken for the membrane potential to get to $1/e$ (about one-third) of the way from the final value. For this reason the product $R_mC_m$ is defined as the **membrane time constant** $\tau$. It is a measure of how long the membrane ‘remembers’ its original value. Typical values of $\tau$ for neurons range between

---

**NEURON** and **GENESIS** are two well known open source neural simulators which allow numerical solutions to the differential equations describing the spatiotemporal variation in the neuron membrane potential to be obtained. These simulators can be applied to a single neuron or a network of interconnected neurons. Appendix A.1 contains a comprehensive list of neural simulators.
The units of $R_m$ and $r_a$ can often seem counter-intuitive. It can sometimes be more convenient to consider their inverse quantities, specific membrane conductance and specific intracellular conductance. These have units of $S \text{ cm}^{-2}$ and $S \text{ cm}^{-1}$ respectively. The quantities $r_m$, $r_a$, and $c_m$ are useful alternatives to their specific counterparts. They express key electrical properties of a neurite of specific diameter and can clarify the equations representing a specific cable or neurite of arbitrary length.

Another important quantity that characterises the response of neurons to injected current is the input resistance, defined as the change in the steady state membrane potential divided by the injected current causing it (Koch, 1999). To determine the input resistance of any cell in which current is injected, the resting membrane potential is first measured. Next, a small amount of current $I_e$ is injected, and the membrane potential is allowed to reach a steady state $V_\infty$. The input resistance is then given by:

$$R_{\text{in}} = \frac{V_\infty - E_m}{I_e}.\quad (2.19)$$

For a single RC circuit representation of a cell, the input resistance can be calculated from the properties of the cell. From Equation 2.16, by setting $dV/dt = 0$ the steady state membrane potential can be shown to be $V_\infty = E_m + (R_m/a)I_e$. By substituting this value of $V_\infty$ into Equation 2.19, it can be seen that the input resistance $R_{\text{in}} = R_m/a$. This is a quasi-ohmic current–voltage relation where the constant of proportionality is the input resistance, given by $R_m/a$.

The input resistance measures the response to a steady state input. A more general concept is the input impedance, which measures the amplitude and phase lag of the membrane potential in response to a sinusoidal
injection current of a particular frequency. The input impedance of the RC circuit can be computed, and shows that the RC circuit acts as a low-pass filter, reducing the amplitude of high-frequency components of the input signal. The topic of input impedance and the frequency-response of neurons is covered in depth by Koch (1999).

2.7 Modelling permeable properties in practice

Both the approximations expressed by the GHK current equations and quasi-ohmic electrical circuit approximation are used in models. However, neither should be considered a perfect representation of currents through the membrane. The GHK equations were originally used to describe ion permeability through a uniform membrane, whereas today they are used primarily to describe the movement of ions through channels. Assumptions on which the equations are based, such as the independence of movement of ions through the membrane (the independence principle; Box 2.4 and Chapter 5) and of constant electric fields, are generally not valid within the restricted space of a single channel. It is therefore not surprising that experiments reveal that the flux through channels saturates at large ionic concentrations, rather than increasing without limit as the GHK equations would predict (Hille, 2001).

There are a number of models of the passage of ions through ion channels, which are more detailed than the GHK and quasi-ohmic descriptions (Hille, 2001), but these more detailed descriptions are not generally used in computational models of the electrical activity of neurons. We might ask how we can justify using a more inaccurate description when more accurate ones exist. In answer, modelling itself is the process of making approximations or simplifications in order to understand particular aspects of the system under investigation. A theme that will be visited many times in this book is: what simplifications or approximations are appropriate? The answer depends on the question that the model is designed to address. For certain questions, the level of abstraction offered by the quasi-ohmic approximation has proved extremely valuable, as we see in Chapter 3. Similarly, the GHK equation is used in many modelling and theoretical approaches to membrane permeability.

When choosing which of these approximations is most appropriate, there are a number of issues to consider. Most ion types do not have a strongly rectifying $I$–$V$ characteristic in the region of typical membrane potentials, and so the quasi-ohmic approximation can be useful. However, if the $I$–$V$ characteristic is very strongly rectifying (as in the example of calcium), the GHK current equation may give a better fit. Even with fairly weak rectification, the GHK can fit the data better than the quasi-ohmic approximation (Sah et al., 1988).

We might want to model how changes in intracellular concentration affect the $I$–$V$ characteristic. In this case, the GHK equations may be a more useful tool. This often applies to calcium, since its intracellular concentration is so low that relatively small influxes can change its concentration by an order of magnitude. Moreover, we may need to consider modelling imperfect
(and more realistic) ion selective channels which have permeabilities to more than one ion. All ion selective channels allow some level of permeability to certain other ions, and so the GHK voltage equation can be used to calculate the reversal potential of these channels.

2.8 The equivalent electrical circuit of a length of passive membrane

So far, we have looked at the properties of a patch of membrane or small neuron. This is appropriate when considering an area of membrane over which the membrane potential is effectively constant, or isopotential. However, most neurons cannot be considered isopotential throughout, which leads to axial current flowing along the neurites. For example, during the propagation of action potentials, different parts of the axon are at different potentials. Similarly, dendrites cannot generally be treated as isopotential. This is evident from changes in the form of the excitatory postsynaptic potentials (EPSPs) as they move down a dendrite.

Fortunately, it is quite easy to extend the model of a patch of membrane to spatially extended neurites. In this chapter, we consider only an unbranched neurite, and in Chapter 4 we look at branched structures. Because of the similarity to an electrical cable, we often refer to this unbranched neurite as a cable.

2.8.1 The compartmental model

The basic concept is to split up the neurite into cylindrical compartments (Figure 2.15). Each compartment has a length $l$ and a diameter $d$, making its surface area $a = \pi dl$. Within each compartment, current can flow onto the membrane capacitance or through the membrane resistance. This is described by the RC circuit for a patch of membrane, encountered in the last section. Additionally, current can flow longitudinally through the cytoplasm and the extracellular media. This is modelled by axial resistances that link the compartments.

Since it is usually assumed that the intracellular resistance is much greater than the extracellular resistance, it may be acceptable to consider the extracellular component of this resistance to be effectively zero (implying that the main longitudinal contribution is intracellular resistivity). We may then
model the extracellular medium as electrical ground, and it acts in an isopotential manner (as shown in Figure 2.15). For many research questions, such as modelling intracellular potentials, this assumption is valid. However, in any case it is straightforward to incorporate the non-zero extracellular resistance. In Chapter 9 the approach is extended to networks of resistances to model the field potentials in extended regions of extracellular space (Box 9.1).

We assume here a circuit as given in Figure 2.15, with the extracellular medium modelled as ground. The axial resistance of a compartment is proportional to its length $l$ and inversely proportional to the cylinder’s cross-sectional area $\pi d^2/4$. The axial resistivity, also known as the specific axial resistance, $R_a$, has units $\Omega \text{ cm}$ and gives the resistivity properties of the intracellular medium. The axial resistance of the cylindrical compartment is then $4R_a l/\pi d^2$. Compartments with longer lengths have larger axial resistance and those with larger cross-sectional areas have reduced resistances.

We can describe the electrical circuit representing the cable with one equation per compartment. We number the compartments in sequence using the subscript $j$. For example, $V_j$ denotes the membrane potential in the $j$th compartment and $I_{e,j}$ is the current injected into the $j$th compartment. Following the procedure used in the previous section, we can use Kirchhoff’s current law, the quasi-ohmic relation and the equation for the capacitive current (Equations 2.13 to 2.16) to derive our circuit equations. The main difference from the previous treatment is that, rather than the compartment being isolated, the membrane current $I_{j,a}$ is now able to spread both leftwards and rightwards within the cytoplasm, i.e. the membrane current is equal to the sum of the leftwards and rightwards axial currents, each given by Ohm’s law:

$$I_{j,a} = \frac{V_{j+1} - V_j}{4R_a l/\pi d^2} + \frac{V_{j-1} - V_j}{4R_a l/\pi d^2}.$$ (2.20)

In this case, we are assuming all compartments have the same cylindrical dimensions. Substituting for this membrane current into Equation 2.13:

$$I_{c,j,a} + I_{i,j,a} = I_{j,a} + I_{e,j}$$

$$I_{c,j,a} + I_{i,j,a} = \frac{V_{j+1} - V_j}{4R_a l/\pi d^2} + \frac{V_{j-1} - V_j}{4R_a l/\pi d^2} + I_{e,j}.$$ (2.21)

This leads to an equation that is similar to Equation 2.16 for a patch of membrane, but now has two extra terms, describing the current flowing along the axial resistances into the two neighbouring compartments $j - 1$ and $j + 1$:

$$\pi dl C_m \frac{dV_j}{dt} = \frac{E_m - V_j}{R_m l/\pi d} + \frac{V_{j+1} - V_j}{4R_a l/\pi d^2} + \frac{V_{j-1} - V_j}{4R_a l/\pi d^2} + I_{e,j}.$$ (2.22)

We have used the surface area of the cylinder $\pi dl$ as the area $a$. Dividing through by this area gives a somewhat less complicated-looking equation:

$$C_m \frac{dV_j}{dt} = \frac{E_m - V_j}{R_m} + \frac{d}{4R_a} \left(\frac{V_{j+1} - V_j}{l^2} + \frac{V_{j-1} - V_j}{l^2}\right) + \frac{I_{e,j}}{\pi dl}.$$ (2.23)

This equation is the fundamental equation of a compartmental model.
2.8.2 Boundary conditions

The equations above assume that each compartment \( j \) has two neighbouring compartments \( j - 1 \) and \( j + 1 \), but this is not true in the compartments corresponding to the ends of neurites. Special treatment is needed for these compartments, which depends on the condition of the end of the neurite being modelled.

The simplest case is that of a **killed end**, in which the end of the neurite has been cut. This can arise in some preparations such as dissociated cells, and it means that the intracellular and extracellular media are directly connected at the end of the neurite. Thus the membrane potential at the end of the neurite is equal to the extracellular potential. To model this, in the equation for the membrane potential, \( V_0 \) in the first compartment is set to 0, as illustrated in Figure 2.16a. This allows Equation 2.23 to be used. The condition \( V_0 = 0 \) is called a **boundary condition** as it specifies the behaviour of the system at one of its edges. This type of boundary condition, where the value of a quantity at the boundary is specified, is called a **Dirichlet** boundary condition.

If the end of the neurite is intact, a different boundary condition is required. Here, because the membrane surface area at the tip of the neurite is very small, its resistance is very high. In this **sealed end** boundary condition, illustrated in electric circuit form in Figure 2.16b, we assume that the resistance is so high that a negligible amount of current flows out through the end. Since the axial current is proportional to the gradient of the membrane potential along the neurite, zero current flowing through the end implies that the gradient of the membrane potential at the end is zero. For reasons made clear in Appendix B.1 in the compartmental framework, this boundary condition is modelled by setting \( V_{-1} = V_1 \). This leads to a modified version of Equation 2.23 for compartment 0. This type of boundary condition, where the spatial derivative of a quantity at the boundary is specified, is called a **Neumann** boundary condition.

It can also be assumed that there is a **leaky end**; in other words, that the resistance at the end of the cable has a finite absolute value \( R_L \) (Figure 2.16c). In this case, the boundary condition is derived by equating the axial current, which depends on the spatial gradient of the membrane potential, to the current flowing through the end, \((V - E_m)/R_L\).

2.8.3 Behaviour of the membrane potential in a compartmental model

As with the patch of membrane, we can use a simulation software package, such as NEURON or GENESIS, to solve these equations numerically. The
2.9 THE CABLE EQUATION

(a) 

(b) 

$\frac{d}{dx} \frac{V}{I} = \frac{V}{I} (x) \frac{d}{dt} \frac{T}{\mu m}$

$V_{(mV)}$

$I_{(nA)}$

$t_{(ms)}$

$V_{(mV)}$

$x_{(\mu m)}$

$d_{-}$

$k_{0}$
potential, and the important concept of the membrane time constant. In the preceding section, extra compartments were added to allow spatially extended neurites to be described, but this has come at the expense of being able to solve the equations analytically. Although modern computers can numerically integrate the equations of the compartmental model at very high spatial resolutions by using many compartments, looking at analytical solutions can give a deeper understanding of the behaviour of the system.

In this section, we introduce the cable equation, which allows the spatiotemporal evolution of the membrane potential to be solved analytically. As shown in more detail in Box 2.5, the cable equation is derived from the equations of a compartmental model (Equation 2.23) by effectively splitting a neurite into an infinite number of infinitesimally small compartments. The cable equation is a partial differential equation (PDE) with the form:

$$C_m \frac{\partial V}{\partial t} = \frac{E_m - V}{R_m} + \frac{d}{4R_a} \frac{\partial^2 V}{\partial x^2} + \frac{I_e}{\pi d}. \quad (2.24)$$

In the cable equation the membrane potential is a function of distance $x$ along a continuous cable, and time $V(x, t)$, and $I_e(x, t)$ is the current injected per unit length at position $x$.

The cable equation is very similar to the equation of a single compartment (Equation 2.16), except that the derivative $dV/dt$ has been replaced by the partial derivative $\partial V/\partial t$ and there is an extra term $d/4R_a \partial^2 V/\partial x^2$. The extra term is the net density of current flowing along the length of the cable into point $x$.

### 2.9.1 Steady state behaviour of the membrane potential

The simplest situation to examine is the steady state case, in which a constant current is injected into the cable; this situation often arises in experiments. In the steady state, when the system has settled and the voltage no longer changes through time, the derivative $\partial V/\partial t$ in Equation 2.24 is zero. This equation then turns into a second order, ordinary differential equation, which is considerably easier to solve.

**Semi-infinite cable**

We start by considering a semi-infinite cable which was simulated approximately in Figure 2.17. It has one sealed end from which it extends an infinite distance, and current with an absolute value of $I_e$ is injected into the cable at the sealed end. Although this is unrealistic, it gives us an initial feel for how voltage changes over large distances from a single injection site. The analytical solution to Equation 2.24, along with the sealed end boundary conditions (Box 2.5), shows that, in agreement with the numerical solution of the discrete cable equation shown in Figure 2.17a, the steady state membrane potential is a decaying exponential function of distance along the neurite:

$$V(x) = E_m + R_\infty I_e e^{-x/\lambda}. \quad (2.25)$$

The quantity $\lambda$ is called the length constant of the cable and $R_\infty$ is the input resistance (defined in Section 2.6.3) of a semi-infinite cable.
2.9 THE CABLE EQUATION

Box 2.5 Derivation of the cable equation

To derive the cable equation from the discrete equations for the compartmental model (Equation 2.23) we set the compartment length \( l \) to the small quantity \( \delta x \). A compartment indexed by \( j \) is at a position \( x = j \delta x \) along the cable, and therefore the membrane potentials in compartments \( j-1 \), \( j \) and \( j+1 \) can be written:

\[
V_j = V(x, t) \quad V_{j-1} = V(x - \delta x, t) \quad V_{j+1} = V(x + \delta x, t).
\]

Also, we define the current injected per unit length as \( I_e(x, t) = I_e/j \delta x \). This allows Equation 2.23 to be rewritten as:

\[
C_m \frac{\partial V(x, t)}{\partial t} = \frac{E_m - V(x, t)}{R_m} + \frac{d}{4R_a} \left[ \frac{1}{\delta x} \left( \frac{V(x + \delta x, t) - V(x, t)}{\delta x} \right) - \frac{V(x, t) - V(x - \delta x, t)}{\delta x} \right] + \frac{l_e(x, t)}{\pi d}.
\] (a)

The derivative of \( V \) with respect to \( t \) is now a partial derivative to signify that the membrane potential is a function of more than one variable.

The length \( \delta x \) of each compartment can be made arbitrarily small, so that eventually there is an infinite number of infinitesimally short compartments. In the limit as \( \delta x \) goes to 0, the term in square brackets in the equation above becomes the same as the definition of the second partial derivative of distance:

\[
\frac{\partial^2 V(x, t)}{\partial x^2} = \lim_{\delta x \to 0} \frac{1}{\delta x} \left( \frac{V(x + \delta x, t) - V(x, t)}{\delta x} - \frac{V(x, t) - V(x - \delta x, t)}{\delta x} \right).
\]

Substituting this definition into Equation (a) leads to Equation 2.24, the cable equation.

In the case of discrete cables, the sealed end boundary condition is that:

\[
\frac{d}{4R_a} \left( \frac{l_e}{\delta x} \right) = \frac{E_m - V_1}{\pi d R_L} + \frac{l_e}{\pi d \delta x R_L}.
\]

In the limit of \( \delta x \to 0 \), at the \( x = 0 \) end of the cable, this is:

\[
- \frac{d}{4R_a} \frac{\partial V}{\partial x} = \frac{l_e(0, t)}{\pi d} + \frac{E_m - V(0, t)}{\pi d R_L}.
\]

At the \( x = l \) end of the cable, this is

\[
\frac{d}{4R_a} \frac{\partial V}{\partial x} = \frac{l_e(l, t)}{\pi d} + \frac{E_m - V(l, t)}{\pi d R_L},
\]

assuming a sealed end means that the axial current at the sealed end is zero, and therefore that the gradient of the voltage at the end is also zero.

The value of \( \lambda \) determines the shape of the exponential voltage decay along the length of the cable. It is determined by the specific membrane resistance, the axial resistivity and the diameter of the cable:

\[
\lambda = \sqrt{\frac{R_m d}{4R_a}} = \sqrt{\frac{r_m}{r_a}}.
\] (2.26)
This equation shows that the smaller the membrane resistance is relative to the axial resistance, the smaller the length constant will be. The leakier the membrane is (smaller $r_m$), the more current is lost earlier in its journey along the neurite. Just as the membrane time constant sets the temporal scale of a neurite, so the length constant sets the spatial scale.

The input resistance of a semi-infinite cable $R_\infty$ is determined by the specific membrane resistance, the axial resistivity, and the diameter:

$$R_\infty = \frac{R_m}{\pi d} \sqrt{\frac{4R_m R_a}{\pi^2 d^3}} = \frac{r_m}{r_a}. \quad (2.27)$$

This tells us that we should expect the input resistance of thinner neurites to be higher than that of thicker ones. This means that a given injection current will have a greater effect on the membrane potential of a thinner neurite. As we will see, this general idea also applies with time-varying input and in branching dendrites.

**Finite cable**

The situation of a cable of finite length is more complicated than the infinite cable as the boundary conditions of the cable at the far end (sealed, killed or leaky) come into play. It is possible to solve the cable equation analytically with a constant current injection applied to a finite cable. This will give an expression for the membrane potential as a function of distance along the cable that also depends on the injection current $I_e$ and the type of end condition of the cable. The end condition is represented by a resistance $R_L$ at the end of the cable. For a sealed end, the end resistance is considered to be so large that $R_L$ is effectively infinite. For leaky end conditions, $R_L$ is assumed to be finite. A killed end is a short circuit where the intracellular and extracellular media meet and there is zero potential difference at the end of the axon. The analytical solution to the finite cable equation in these cases is given in Box 2.6.

Examples of how different end conditions alter the change in voltage over the length of the axon are plotted in Figure 2.18. The solid black line shows the membrane potential in a semi-infinite cable, and serves as a reference. The two solid grey lines show the membrane potential in two cables with sealed ends but of different lengths, one of length $l = 1000\, \mu m$ and the other $l = 2000\, \mu m$. Given that the displacement of the membrane potential from its resting value of $-70$ mV is proportional to the input resistance, Figure 2.18 shows that the shorter cable has a higher input resistance than both the longer one and the semi-infinite cable. This makes sense since the shorter cable offers fewer paths to the extracellular medium than the longer one. The membrane potential of the longer cable is quite close to that of the semi-infinite cable. As the cable gets longer, the difference between the two will become negligible. Note that the gradient of the membrane potential at the end of a sealed end cable is zero. Since the gradient of the curve is proportional to the current flowing along the axon, a zero gradient means that there is no axial current flowing at the end of the cable, which has an infinitely large resistance.
2.9.2 Time-dependent behaviour of the membrane potential

So far we have ignored time in our study of the cable equation. It is possible to solve the cable equation to give mathematical expressions for the time course of the membrane potential at different points along a passive cable in response to pulses of current or continuous input. At any point along the dendrite, the time course of the membrane potential will be given by:

\[ V(x, t) = C_0(x)e^{-t/\tau_0} + C_1(x)e^{-t/\tau_1} + C_2(x)e^{-t/\tau_2} + \ldots \]  \hspace{1cm} \text{(2.28)}

where the coefficients \( C_n(x) \) depend on distance along the cable, \( \tau_0 \) is the membrane time constant and \( \tau_1, \tau_2, \) and so on, are time constants with successively smaller values (Rall, 1969). A method for determining multiple time constants experimentally is described in Chapter 4.

Figure 2.17b shows the simulation of the membrane potential at different points along a cable following synaptic input at one end. After about 2 ms, in this simulation, the membrane potential at all points has equalised, and the membrane potential decays exponentially to its resting value. The time constant of this final decay is the membrane time constant, \( \tau_0 \), as this is the
Box 2.6 Solutions to the cable equation

It is often useful to express the length along the neurite or cable in relation to the length constant. We denote this normalised length as $X$, defined as $X = x/\lambda$. The quantity $X$ is dimensionless and it leads to clearer formulae.

For example, the steady state membrane potential along a semi-infinite cable (compare with Equation 2.25) becomes:

$$V(X) = E_m + R_{\infty}I_e e^{-X}$$

For clarity, we look at the finite cable solutions for the sealed end and leaky end boundary conditions. As we are not dealing with the killed end case, we do not present it here.

Given a resistance $R_L$ at the end of a leaky cable and injection current $I_e$, the membrane potential as a function of length $X$ is given by:

$$V(X) = E_m + \frac{R_L}{R_{\infty}} \cdot \frac{R_{\infty} \cosh(L - X) + \sinh(L - X)}{R_L/R_{\infty} \sinh L + \cosh L}, \quad (a)$$

where $R_{\infty}$ is the input resistance of a semi-infinite cable with the same diameter, membrane resistance and cytoplasmic resistivity (Equation 2.27) and $L$ is the length of the cable measured in terms of the length constant $\lambda$, the true length of the cable being $l = L\lambda$. The hyperbolic functions $\sinh$ and $\cosh$ are the hyperbolic sine and hyperbolic cosine, defined as:

$$\sinh x = \frac{e^x - e^{-x}}{2}, \quad \cosh x = \frac{e^x + e^{-x}}{2}.$$

According to the definition of input resistance (Equation 2.19), the input resistance of the leaky cable is:

$$R_{in} = \frac{V(0) - E_m}{I_e} = \frac{R_L}{R_{\infty}} \cdot \frac{R_{\infty} \cosh L + \sinh L}{R_L/R_{\infty} \sinh L + \cosh L}.$$

In the case of a sealed end, where $R_L = \infty$, the membrane potential as a function of length in Equation (a) simplifies to:

$$V(X) = E_m + R_{\infty}I_e \frac{\cosh(L - X)}{\sinh L} \quad (b)$$

and the input resistance simplifies to:

$$R_{in} = R_{\infty} \frac{\cosh L}{\sinh L} = R_{\infty} \coth L,$$

where the function $\coth$ is the hyperbolic cotangent, defined as:

$$\coth x = \frac{\cosh x}{\sinh x} = \frac{e^x + e^{-x}}{e^x - e^{-x}}.$$

longest time constant ($\tau_0 > \tau_1$, etc.). The contributions of the faster time constants, $\tau_1$, $\tau_2$, etc., become smaller as $t$ becomes large.

The solutions of the time-dependent cable equation are not just of descriptive value, but have also been decisive in resolving interpretations of data (Box 2.7). In Chapter 4, we see how the smaller time constants can be used to infer the length constant of a dendrite.
Box 2.7 Eccles, Rall and the charging time constant of motor neurons

A dispute between Eccles and Rall – described in detail in Segev et al. (1995) – over how to interpret the charging curves of motor neurons demonstrates the importance of time-dependent solutions to the cable equation. Recall that when a current is injected into a small passive neuron, the membrane potential responds by shifting to a new steady state value. The time course of the approach to the new potential varies exponentially with the membrane time constant. Coombs et al. (1956) injected current into motor neurons and recorded the membrane potential as a function of time (thick black line in Figure 2.19). These data could be fitted by an exponential function with a time constant of 2.5 ms (Figure 2.19, dashed curve). Under the implicit assumption that a spatially extended motor neuron has the equivalent electrical behaviour to a neuron composed of a soma only, Coombs et al. concluded that the membrane time constant was 2.5 ms.

Rall showed that this method of analysing the data gives an answer for the membrane time constant that is too small by a factor of two (Rall, 1957). In Figure 2.19, the blue line shows Rall’s solution of the full time-dependent cable equation for a ‘ball and stick’ model of the motor neuron, a soma with a single dendrite attached to it, in which the membrane time constant is 5 ms. This solution can be seen to be very similar to the charging curve of a lone soma with a membrane time constant of 2.5 ms. For comparison, the charging curve of a lone soma with a membrane time constant of 5 ms is shown in black.

The Eccles group was effectively using the lone soma model to analyse data from a soma and dendrites. They therefore had to fit the experimental data (dashed line) with a curve with a shorter time constant instead of fitting the curve generated from the ball and stick model with a longer time constant (black line); this procedure therefore gave the wrong result.

The expression for the charging curve of the ball and stick model is \[ \frac{V}{V_0} = \frac{1}{6}(1 - \exp(-t/\tau)) + \frac{5}{6}\text{erf}\sqrt{\frac{t}{\tau}}, \] where the function ‘erf’ is the error function, defined below. The factors \( \frac{1}{6} \) and \( \frac{5}{6} \) derive from Rall’s assumption that in the steady state, one-sixth of the current injected flows out through the soma and the remaining five-sixths through the dendrites.

The error function \( \text{erf} x \) is the area under the Gaussian \( \frac{2}{\sqrt{\pi}} \exp(u^2) \) between 0 and \( x \):

\[ \text{erf} x = \frac{2}{\sqrt{\pi}} \int_0^x \exp(u^2)du. \]

2.10 Summary

This chapter has touched on some of the primary electrical properties of neurons that provide a basis for the development of neuronal models. The physical properties of certain cell components, such as lipid membranes,
intracellular and extracellular solutions and passive membrane channels, are drawn together to build an electrical circuit model of the neurite. This RC circuit model is an approximation of the passive electrical properties and is based on assumptions such as linear $I$–$V$ characteristics for ions traversing the membrane, i.e. passive membrane channels acting as electrical resistors. The Goldman–Hodgkin–Katz theory of current flow through the membrane provides an alternative model that demonstrates that the linear assumptions made in the electrical model are inappropriate for ions such as Ca$^{2+}$. Models of multiple channel types will generally involve combinations of these approaches (Chapter 5).

Modelling the membrane potential along a length of a neurite can be achieved by connecting together individual electrical circuits, or compartments. This is a fundamental modelling approach used for simulating the electrical properties over complex neuronal morphologies (Chapter 4). Treating a length of neurite as a cable also provides a useful analogy for understanding the influence that specific passive properties, such as $R_m$ and $R_s$, have on the membrane potential over the length of the cable.
The Hodgkin–Huxley model of the action potential

This chapter presents the first quantitative model of active membrane properties, the Hodgkin–Huxley model. This was used to calculate the form of the action potentials in the squid giant axon. Our step-by-step account of the construction of the model shows how Hodgkin and Huxley used the voltage clamp to produce the experimental data required to construct mathematical descriptions of how the sodium, potassium and leak currents depend on the membrane potential. Simulations of the model produce action potentials similar to experimentally recorded ones and account for the threshold and refractory effects observed experimentally. While subsequent experiments have uncovered limitations in the Hodgkin–Huxley model descriptions of the currents carried by different ions, the Hodgkin–Huxley formalism is a useful and popular technique for modelling channel types.

3.1 The action potential

In the previous chapter we described the basis of the membrane resting potential and the propagation of signals down a passive neurite. We now explain a widespread feature of signalling in the nervous system: the action potential.

Intracellular recordings (Figure 3.1) demonstrate that action potentials are characterised by a sharp increase in the membrane potential (depolarisation of the membrane) followed by a somewhat less sharp decrease towards the resting potential (repolarisation). This may be followed by an afterhyperpolarisation phase in which the membrane potential falls below the resting potential before recovering gradually to the resting potential. The main difference between the propagation of action potentials and passive propagation of signals is that action potentials are regenerative, so their magnitude does not decay during propagation.

Hodgkin and Huxley (partly in collaboration with Katz) were the first to describe the active mechanisms quantitatively (Hodgkin et al., 1952; Hodgkin and Huxley, 1952a, b, c, d). Their work proceeded in three main stages:
They recorded intracellularly from the squid giant axon. They used a voltage clamp amplifier in space clamp configuration (Box 3.1) to look at how current flow depends on voltage. By changing the extracellular concentration of sodium, they were able to infer how much of the current was carried by sodium ions and how much by other ions, principally potassium.

They fitted these results to a mathematical model. Part of the model is the theoretically motivated framework developed in Chapter 2. Another part is based on the idea of ion-selective voltage-dependent gates controlled by multiple gating particles. The remainder of the model is determined by fitting curves to experimental data. The model is expressed in terms of a set of equations which are collectively called the Hodgkin–Huxley model, or HH model for short.

They solved the equations defining the model to describe the behaviour of the membrane potential under various conditions. This involved solving the equations numerically. The simulated action potentials were very similar to the recorded ones. The threshold, propagation speed and refractory properties of the simulated action potentials also matched those of the recorded action potentials.

Their work earned them a Nobel prize in 1963, shared with Eccles for his work on synaptic transmission.

Hodgkin and Huxley were not able to deduce the molecular mechanisms underlying the active properties of the membrane, which was what they had set out to do (Box 3.3). Nevertheless, their ideas were the starting point for the biophysical understanding of the structures now known as ion channels, the basics of which are outlined in Chapter 5. Hille (2001) provides a comprehensive treatment of the structure and function of ion channels.

The HH model characterises two types of active channel present in the squid giant axon, namely a sodium channel and a potassium channel belonging to the family of potassium delayed rectifier channels. Work since 1952 in preparations from many different species has uncovered a large number of other types of active channel. Despite the age and limited scope of the HH model, a whole chapter of this book is devoted to it as a good deal of Hodgkin and Huxley’s methodology is still used today:

(1) Voltage clamp experiments are carried out to determine the kinetics of a particular type of channel, though now the methods of recording and isolating currents flowing through particular channel types are more advanced.

(2) A model of a channel type is constructed by fitting equations, often of the same mathematical form, to the recordings. Modern methods of fitting equation parameters to data are covered later on, in Section 4.5.

(3) Models of axons, dendrites or entire neurons are constructed by incorporating models of individual channel types in the compartmental models introduced in Chapter 2. Once the equations for the models are solved, albeit using fast computers rather than by hand, action potentials and other behaviours of the membrane potential can be simulated.
The next great experimental advance after intracellular recording was the voltage clamp. This was developed by Cole and Marmont in the 1940s at the University of Chicago (Marmont, 1949; Cole, 1968). Hodgkin, who was already working on a similar idea, learnt about the technique from Cole in 1947. The basic idea is to clamp the membrane potential to a steady value or to a time-varying profile, determined by the experimenter (see figure above). As with a current clamp (Chapter 2), an electrode is used to inject current \( I_e \) into the cell. At the same time, a voltage electrode records the membrane potential. The apparatus adjusts the injected current continually so that it is just enough to counteract deviations of the recorded membrane potential from the desired voltage value. This ensures that the membrane potential remains at the desired steady value or follows the required time-varying profile.

Hodgkin and Huxley used a space clamp configuration, where the electrodes are long, thin wires that short circuit the electrical resistance of the cytoplasm and the extracellular space. This ensures that the potential is uniform over a large region of membrane and that therefore there is no axial current in the region. There is no contribution to the membrane current from the axial current. In this configuration, the membrane current is identical to the electrode current, so the membrane current can be measured exactly as the amount of electrode current to be supplied to keep the membrane at the desired value.

To understand the utility of the voltage clamp, we recall that the membrane current \( I \) comprises a capacitive and an ionic current (Equation 3.1). When the voltage clamp is used to set the membrane potential to a constant value, no capacitive current flows as the rate of change in membrane potential, \( dV/dt \), is zero. The voltage clamp current is then equal to the ionic current. Therefore, measuring the voltage clamp current means that the ionic current is being measured directly.

In this chapter, we focus on the second (modelling) and third (simulation) parts of the procedure. In Section 3.2, we begin with a step-by-step description of how Hodgkin and Huxley used a mixture of physical intuition and curve-fitting to produce their mathematical model. In Section 3.3, we look
at simulations of nerve action potentials using the model, and compare these with the experimental recordings. In Section 3.4 we consider how Hodgkin and Huxley corrected for temperature. Finally, in Section 3.5, we consider the simplifications inherent in the HH model and how to use the Hodgkin–Huxley formalism to build models of ion channels.

3.2 The development of the model

The starting point of the HH model is the equivalent electrical circuit of a compartment shown in Figure 3.2. There are three types of ionic current in the circuit: a sodium current, $I_{Na}$, a potassium current, $I_{K}$, and a current that Hodgkin and Huxley dubbed the leak current, $I_{L}$, which is mostly made up of chloride ions. The key difference between this circuit and the one presented in Chapter 2 is that the sodium and potassium conductances depend on voltage, as indicated by the arrow through their resistors. Since their properties change with the voltage across them, they are active rather than passive elements.

The equation that corresponds to the equivalent electrical circuit is:

$$I = I_c + I_i = C_m \frac{dV}{dt} + I_i,$$

where the membrane current $I$ and the capacitive current $I_c$ are as defined in Chapter 2. The total ionic current $I_i$ is the sum of sodium, potassium and leak currents:

$$I_i = I_{Na} + I_{K} + I_{L}. \quad (3.2)$$

The magnitude of each type of ionic current is calculated from the product of the ion’s driving force and the membrane conductance for that ion:

$$I_{Na} = g_{Na}(V - E_{Na}), \quad (3.3)$$
$$I_{K} = g_{K}(V - E_{K}), \quad (3.4)$$
$$I_{L} = g_{L}(V - E_{L}), \quad (3.5)$$

where the sodium, potassium and leak conductances are $g_{Na}$, $g_{K}$ and $g_{L}$ respectively, and $E_{Na}$, $E_{K}$ and $E_{L}$ are the corresponding equilibrium potentials.

The bar on the leakage conductance $g_{L}$ indicates that it is a constant, in contrast with the sodium and potassium conductances which depend on the recent history of the membrane potential.

As defined in Section 2.4.1, the driving force of an ion is the difference between the membrane potential and the equilibrium potential of that ion. Hence, the sodium driving force is $V - E_{Na}$.
3.2 The development of the model

3.2.1 The potassium current

Hodgkin and Huxley measured the potassium conductance for a number of voltage clamp holding potentials. After first isolating the potassium current (Box 3.2 and Figure 3.3), they calculated the conductance using Equation 3.4. The form of the curves at each holding potential is similar to the example of the response to a holding potential of 25 mV above rest, shown in Figure 3.4a. Upon depolatisation, the conductance rises to a constant value. This rise in conductance is referred to as activation. The conductance stays at this peak value until the voltage is stepped back down to rest, where the conductance then decays exponentially (Figure 3.4b). The fall in conductance is called deactivation.

Box 3.2 The ion substitution method

In order to fit the parameters of their model, Hodgkin and Huxley needed to isolate the current carried by each type of ion. To do this they used the ion substitution method. They lowered the extracellular sodium concentration by replacing a proportion of the sodium ions in the standard extracellular solution (sea water) with impermeant choline ions. The currents recorded under voltage clamp conditions in sea water and in choline water were carried by sodium ions, potassium ions and other ions. On the assumption that the independence principle holds (Box 2.4), the currents carried by sodium ions in sea water and choline water differ, but the other ionic flows will remain the same. Therefore, the difference between currents recorded in sodium water and choline water can be used to infer the sodium current (Figure 3.3). Having isolated the sodium current and calculated the leak current by other methods, the potassium current can be deduced by subtracting the sodium and leak currents from the total current.
The family of conductance activation curves (Figure 3.4c) show that there are two features of the curve that depend on the level of the voltage clamp holding potential:

1. The value that the conductance reaches over time, \( g_{K\infty} \), increases as the holding potential is increased. It approaches a maximum at high holding potentials. This implied that there was a maximum potassium conductance per unit area of membrane, which Hodgkin and Huxley denoted \( g_K \) and were able to estimate.

2. The speed at which the limiting conductance is approached becomes faster at higher depolarising holding potentials.

The conductance curves show that the limiting conductance and the rate at which this limit is approached depends on the membrane voltage. Hodgkin and Huxley considered a number of models for describing this voltage dependence (Box 3.3). They settled on the idea of the membrane containing a number of gates which can be either closed to the passage of all ions or open to the passage of potassium ions. Each gate is controlled by a number of independent gating particles, each of which can be in either an open or closed position. For potassium ions to flow through a gate, all of the gating particles in the gate have to be in the open position.

The movement of gating particles between their closed and open positions is controlled by the membrane potential. The gating variable \( n \) is the probability of a single potassium gating particle being in the open state. As the gating particles are assumed to act independently of each other, the probability of the entire gate being open is equal to \( n^x \), where \( x \) is the number...
Box 3.3 | Gating particles

Hodgkin and Huxley’s goal had been to deduce the molecular mechanisms underlying the permeability changes evident in their experimental data. Reflecting on this later, Hodgkin (1976) wrote:

> although we had obtained much new information the overall conclusion was basically a disappointment… As soon as we began to think about molecular mechanisms it became clear that the electrical data would by itself yield only very general information about the class of system likely to be involved. So we settled for the more pedestrian aim of finding a simple set of mathematical equations which might plausibly represent the movement of electrically charged gating particles.

Their initial hypothesis was that sodium ions were carried across the membrane by negatively charged carrier particles or dipoles. At rest these would be held by electrostatic forces. Consequently, they would not carry sodium ions in this state and, on depolarisation, they could carry sodium into the membrane. However, Hodgkin and Huxley’s data pointed to a voltage-dependent gate. They settled on deriving a set of equations that would represent the theoretical movement of charged gating particles acting independently in a voltage-dependent manner.

In the contemporary view, the idea of gating particles can be taken to imply the notion of gated channels, but the hypothesis of ion pores or channels was not established at that time. Thus, though Hodgkin and Huxley proposed charged gating particles, it is perhaps tenuous to suggest that they predicted the structure of gated channels. Nevertheless, there is a correspondence between the choice of the fourth power for potassium conductance and the four subunits of the tetrameric potassium channel (Section 5.1).

of gating particles in the gate. Although, as described in Chapter 5, gating particles do not act independently, this assumption serves reasonably well in the case of potassium conductance in the squid giant axon. When there are large numbers of particles present, the large numbers ensure the proportion of particles being in the open position is very close to the probability \( n \) of an individual channel being in the open position, and the expected proportion of gates open is also the same as the probability of an individual gate being open, \( n^x \).

The conductance of the membrane is given by the maximum conductance multiplied by the probability of a gate being open. For example, if each gate is controlled by four gating particles, as Hodgkin and Huxley’s experiments suggested, the relationship between the potassium conductance \( g_K \) and gating particle open probability \( n \) is:

\[
g_K = \bar{g}_K n^4. \tag{3.6}
\]

If each potassium gate were dependent solely on a single theoretical gating particle, the conductance would be \( \bar{g}_K n \).
The movement of a gating particle between its closed (C) and open (O) positions can be expressed as a reversible chemical reaction:

\[ C \xrightarrow{\alpha_n} O, \]

(3.7)

The fraction of gating particles that are in the O state is \( n \), and the fraction in the C state is \( 1 - n \). The variables \( \alpha_n \) and \( \beta_n \) are rate coefficients which depend on the membrane potential; sometimes they are written \( \alpha_n(V) \) and \( \beta_n(V) \) to highlight their dependence on voltage. Just as rate laws govern the evolution of concentrations in chemical reactions, there is a rate law or first order kinetic equation corresponding to Equation 3.7, which specifies how the gating variable \( n \) changes over time:

\[ \frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n. \]

(3.8)

The time course of the response of the gating variable \( n \) to a step change in membrane potential to a particular voltage \( V_1 \) can be determined by integrating Equation 3.8. A solution for the response of \( n \) to a voltage step is shown in Figure 3.5, along with the time courses of \( n \) raised to various powers. The curve for \( n \) looks roughly like the conductance curve shown in Figure 3.4. The main difference is that the theoretical time course of \( n \) is not S-shaped like the experimental curve; it has no initial inflection. As Figure 3.5 shows, when the time course of \( n \) in response to a positive voltage step is squared, cubed or raised to the power four, the resulting rising curve does have an inflection. The decaying part of the curve retains its decaying exponential shape. Hodgkin and Huxley found that raising \( n \) to the power four could give a better fit than cubing or squaring, suggesting that each gate contains four gating particles.

The general form of the time course for \( n(t) \) in response to a voltage step is:

\[ n(t) = n_{\infty}(V_1) - (n_{\infty}(V_1) - n_0) \exp(-t / \tau_n(V_1)), \]

(3.9)

where \( n_0 \) is the value of \( n \) at the start of the step, defined to be at time zero; the variables \( n_{\infty}(V) \) and \( \tau_n(V) \) are related to the rate coefficients \( \alpha_n(V) \) and \( \beta_n(V) \) by:

\[ n_{\infty} = \frac{\alpha_n}{\alpha_n + \beta_n} \text{ and } \tau_n = \frac{1}{\alpha_n + \beta_n}, \]

(3.10)
where \( n_\infty \) is the limiting probability of a gating particle being open if the membrane potential is steady as \( t \) approaches infinity and \( \tau_n \) is a time constant. When the membrane potential is clamped to \( V_1 \), the rate coefficients will immediately move to new values \( \alpha_n(V_1) \) and \( \beta_n(V_1) \). This means that, with the membrane potential set at \( V_1 \), over time \( n \) will approach the limiting value \( n_\infty(V_1) \) at a rate determined by \( \tau_n(V_1) \). The variables \( n_\infty \) and \( \tau_n \) allow Equation 3.8 to be rewritten as:

\[
\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}.
\] (3.11)

The final step in modelling the potassium current is to determine how the rate coefficients \( \alpha_n \) and \( \beta_n \) in the kinetic equation of \( n \) (Equation 3.8) depend on the membrane potential. In using experimental data to determine these parameters, it is convenient to use the alternative quantities \( n_\infty \) and \( \tau_n \) (Equation 3.10). The value of \( n_\infty \) at a specific voltage \( V \) may be determined experimentally by recording the maximum conductance attained at that voltage step, called \( g_{K\infty}(V) \). Using Equation 3.6, the value of \( n_\infty \) at voltage \( V \) is then given by:

\[
n_\infty(V) = \left( \frac{g_{K\infty}(V)}{\bar{g}_K} \right)^{1/4}.
\] (3.12)

The value for \( \tau_n \) at a particular membrane potential is obtained by adjusting it so as to give the best match predicted time course of \( n \) given in Equation 3.9 and the data (Figure 3.4).

This process provides values for \( n_\infty \) and \( \tau_n \) at various voltages. Hodgkin and Huxley converted them to the values for \( \alpha_n \) and \( \beta_n \) using the inverse formulae to Equation 3.10:

\[
\alpha_n = \frac{n_\infty}{\tau_n} \quad \text{and} \quad \beta_n = \frac{1 - n_\infty}{\tau_n}.
\] (3.13)

These experimental data points are shown in Figure 3.6, along with plots of the final fitted functions for \( \alpha_n \) and \( \beta_n \); see also Figure 3.10 for the equivalent
3.2.2 The sodium ionic current

In a similar manner to the procedure used for potassium conductance, Hodgkin and Huxley isolated the sodium current and calculated the sodium conductance curves over a range of voltage clamp steps. The time course of the sodium conductance is illustrated in Figure 3.7. The most notable difference from the potassium conductance is that the sodium conductance reaches a peak and then decays back to rest, even while the clamped voltage remains in a sustained depolarising step. This reduction in conductance is termed inactivation, in contrast to deactivation (Section 3.2.1) when the reduction in conductance is due to termination of a voltage step. The time course of the conductance during inactivation differs from the time course during deactivation, and this suggested that two distinct processes can act to reduce the conductance.

The inactivation of the sodium conductance meant that Hodgkin and Huxley could not use the description they used for potassium, where there was just one gating variable, \( n \). In order to quantify the inactivation process, Hodgkin and Huxley applied a range of voltage clamp experiments and protocols (Box 3.4 and Figures 3.8 and 3.9). They introduced a gating type variable, called \( h \), to represent the level of inactivation. It could either be in the state of ‘not inactivated’ or the state of ‘inactivated’. The rate of transition between these states is voltage dependent and governed by a first order kinetic equation similar to \( n \):
As with the $n$ gating particle, the voltage-dependent rate coefficients $\alpha_h$ and $\beta_h$ can be reexpressed in terms of a limiting value $h_\infty$ and a time constant $\tau_h$. Hodgkin and Huxley’s experiments suggested that sodium conductance was proportional to the inactivation variable $h$.

Hodgkin and Huxley completed their model of sodium conductance by introducing another gating particle which, like $n$, may be viewed as the proportion of theoretical gating particles that are in an open state, determining sodium conductance activation. They called this sodium activation particle $m$. As with $n$ and $h$, the time course of $m$ was governed by a first order kinetic equation with voltage-dependent forward and backward rates $\alpha_m$ and $\beta_m$:

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_mm. \quad (3.16)$$

As with potassium (Figure 3.5), the activation curve of the sodium conductance is inflected. The inflection was modelled satisfactorily by using three independent $m$ gating particles, making the sodium conductance:

$$g_{Na} = g_{Na}^\infty m^3h. \quad (3.17)$$

This enabled a good fit to be made to experimental recordings by adjusting $m_\infty$ and $\tau_m$ for different holding potentials and $g_{Na}^\infty$ for all holding potentials. As with the gating variable $n$, Hodgkin and Huxley converted the limiting values and time constants of the $m$ and $h$ variables into rate coefficients ($\alpha_m$, $\beta_m$ and $\alpha_h$, $\beta_h$) and plotted each as a function of voltage. They then found a fit to each rate coefficient that matched their experimental data. The final model of the sodium current is given by the following set of equations:

$$I_{Na} = g_{Na}^\infty m^3h(V - E_{Na}),$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_mm, \quad \frac{dh}{dt} = \alpha_h(1-h) - \beta_hh,$$

$$\alpha_m = 0.1 \frac{V + 40}{1 - \exp(-(V + 40)/10)}, \quad \alpha_h = 0.07 \exp(-(V + 65)/20),$$

$$\beta_m = 4 \exp(-(V + 65)/18), \quad \beta_h = \frac{1}{\exp(-(V + 35)/10) + 1}. \quad (3.18)$$

### 3.2.3 The leak current

Hodgkin and Huxley’s evidence suggested that while potassium is a major part of the non-sodium ionic current, other ions besides sodium might carry current across the membrane. At the potassium equilibrium potential, they found that some non-sodium current still flows. This current could not be due to potassium ions since the driving force $V - E_K$ was zero. Hodgkin and Huxley proposed that it was due to a mixture of ions, and they dubbed it the leak current $I_L$. They assumed this was a resting background current that was not dependent on voltage. Using a quasi-ohmic current–voltage relationship they derived $E_L$ and $g_L$, from their experimental results. Both the leakage conductance and equilibrium potential are due largely to the permeability
of the membrane to chloride ions. The leak current is modelled by:

\[ I_L = \bar{g}_L (V - E_L). \] (3.19)

Although the leak conductance \( \bar{g}_L \) in the Hodgkin–Huxley circuit and the membrane resistance \( R_m \) in the passive circuit (Chapter 2) appear similar, they have different meanings. In the HH model, the resting membrane potential differs from the electromotive force of the leak battery and the resting membrane resistance is not equal to the inverse of the leak conductance. Instead, the resting membrane potential and the resting membrane resistance are determined by the sodium, potassium and leak resting conductances. We return to this difference in Section 4.4.

### 3.2.4 The complete model

In the final paper of the series, Hodgkin and Huxley (1952d) inserted their expressions for the three ionic currents (Equations 3.3–3.5) into the membrane equation (Equation 3.1) to give a description of how the membrane potential in a small region of squid giant axon changes over time:

\[ C_m \frac{dV}{dt} = -\bar{g}_L (V - E_L) - \bar{g}_Na m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K) + I, \] (3.20)

where \( I \) is the local circuit current, the net contribution of the axial current from neighbouring regions of the axon. In a continuous cable model of the axon, this contribution is the second derivative of the membrane potential with respect to space (Equation 2.24). When Equation 3.20 is put together with the differential equations for the gating variables \( n, m \) and \( h \) and the expressions for the rate coefficients (Equations 3.14 and 3.18), the resulting set of four differential equations forms the HH model. It is summarised in Box 3.5.

Equation 3.20 could equally well relate to a compartment in a compartmental model, as described in Section 2.8. In this case, the local circuit current depends on the membrane potential in the neighbouring compartments (Equations 2.20).

The system can be simplified by imposing the space clamp condition (Box 3.1) so that the membrane potential is constant over the membrane.
This means that there is no local current and the system reduces to a much simpler first order ordinary differential equation (Box 3.5).

**Box 3.4 | Fitting inactivation kinetics**

In order to quantify inactivation, Hodgkin and Huxley applied a voltage clamp protocol using two pulses. The first pulse was a long (30 ms) **conditioning pulse**. This was set to a range of different voltages, and its purpose was to give the sodium conductance enough time to inactivate fully at that holding potential. The second pulse was a **test pulse**, which was set to the same value each time. Figure 3.8a shows that the response to the conditioning pulse was similar to the response to a prolonged pulse: the sodium conductance rises to a peak with a height that increases with membrane depolarisation and then decays. The response to the test pulse is similar, but the height of the test pulse depends on the level of the conditioning pulse. The higher the conditioning pulse, the smaller the current amplitude at the test pulse. At a conditioning pulse depolarisation of \(-41\) mV above resting potential, there is virtually no response to the test pulse. Conversely, when the membrane is hyperpolarised to beyond \(-116\) mV below resting potential, the amplitude of the current at the pulse reaches a limiting value. This allowed Hodgkin and Huxley to isolate the amount of inactivated conductance at different voltages. By performing a large number of these experiments over a range of conditioning voltages, they were able to fit the data to produce the voltage-dependent inactivation function \(h_\infty\) (Figure 3.8b).

To measure the time constant \(\tau_h\) of inactivation, a different form of the two-pulse experiment was used (Figure 3.9b). A short depolarising pulse is followed by an interval in which the membrane is clamped to a **recovery potential** and then by a depolarising pulse identical to the first. The peak sodium conductance in both test pulses is measured. The ratio gives a measure of how much the sodium conductance has recovered from inactivation during the time the membrane has been held at the recovery potential. Plotting the ratio against the time of the recovery pulse gives the exponential curve shown in Figure 3.9b, from which the time constant of recovery from inactivation \(\tau_h\) can be obtained at that particular recovery potential. Over a range of recovery potentials, the voltage dependence of \(\tau_h\) can be assessed.
3.3 Simulating action potentials

In order to predict how the membrane potential changes over time, the complete system of coupled non-linear differential equations comprising the HH model (Box 3.5) have to be solved. Hodgkin and Huxley used numerical integration methods (Appendix B.1). It took them three weeks’ work on a hand-operated calculator. Nowadays, it takes a matter of milliseconds for fast computers to solve the many coupled differential equations in a compartmental formulation of the HH model.

In this section we look at the action potentials that these equations predict, both under space clamp conditions and under free propagation conditions. This will lead us to comparisons with experimental recordings and a brief review of the insights that this model provided. It is worth noting that the recordings in this section were all made at 6.3 °C, and the equations and simulations all apply to this temperature. Hodgkin and Huxley discovered that temperature has a strong influence on the rate coefficients of the gating variables, but were able to correct for this, as will be discussed in Section 3.4.

3.3.1 Space clamped action potentials

In one set of experiments under space clamp (but not voltage clamp) conditions, Hodgkin and Huxley depolarised the membrane potential to varying levels by charging the membrane quickly with a brief current clamp pulse. Small depolarisations led to the membrane potential decaying back to its resting value, but when the membrane was depolarised above a threshold of around 10 mV above resting potential, action potentials were initiated.
Box 3.5 Summary of the Hodgkin–Huxley model

The equation for the membrane current is derived by summing up the various currents in the membrane, including spatial spread of current from local circuits:

\[
C_m \frac{\partial V}{\partial t} = -\bar{g}_L(V - E_L) - \bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K) + \frac{d}{dx} \frac{\partial^2 V}{\partial x^2}.
\]

Under space clamp conditions, i.e. no axial current:

\[
C_m \frac{dV}{dt} = -\bar{g}_L (V - E_L) - \bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K).
\]

Sodium activation and inactivation gating variables:

\[
dm = \alpha_m (1 - m) - \beta_m m, \quad dh = \alpha_h (1 - h) - \beta_h h,
\]

\[
\alpha_m = 0.1 \frac{V + 40}{1 - \exp\left(-\frac{(V + 40)}{10}\right)}, \quad \alpha_h = 0.07 \exp\left(-\frac{(V + 65)}{20}\right),
\]

\[
\beta_m = 4 \exp\left(-\frac{(V + 65)}{18}\right), \quad \beta_h = \frac{1}{\exp\left(-\frac{(V + 35)}{10}\right) + 1}.
\]

Potassium activation gating variable:

\[
dn = \alpha_n (1 - n) - \beta_n n,
\]

\[
\alpha_n = 0.01 \frac{V + 55}{1 - \exp\left(-\frac{(V + 55)}{10}\right)}, \quad \beta_n = 0.125 \exp\left(-\frac{(V + 65)}{80}\right).
\]

Parameter values (from Hodgkin and Huxley, 1952d):

\[
C_m = 1.0 \ \mu F \ cm^{-2}
\]

\[
E_{Na} = 50 \ mV \quad \bar{g}_{Na} = 120 \ mS \ cm^{-2}
\]

\[
E_K = -77 \ mV \quad \bar{g}_K = 36 \ mS \ cm^{-2}
\]

\[
E_L = -54.4 \ mV \quad \bar{g}_L = 0.3 \ mS \ cm^{-2}
\]

See Figure 3.10 for plots of the voltage dependence of the gating particle rate coefficients.

(Figure 3.11). Hodgkin and Huxley referred to these action potentials induced under space clamp conditions as **membrane action potentials**.

To simulate the different depolarisations in experiments, they integrated the equations of their space clamped model with different initial conditions for the membrane potential. Because the current pulse that caused the initial depolarisation was short, it was safe to assume that initially \( n, m \) and \( h \) were at their resting levels.

The numerical solutions were remarkably similar to the experimental results (Figure 3.11). Just as in the experimental recordings, super-threshold depolarisations led to action potentials and sub-threshold ones did not, though the threshold depolarisation was about 6 mV above rest instead of 10 mV. The time courses of the observed and calculated action potentials were very similar, although the peaks of the calculated action potentials were too sharp and there was a kink in the falling part of the action potential curve.
Besides reproducing the action potential, the HH model offers insights into the mechanisms underlying it, which experiments alone were not able to do. Figure 3.12 shows how the sodium and potassium conductances and the gating variables change during a membrane action potential. At the start of the recording, the membrane has been depolarised to above the threshold. This causes activation of the sodium current, as reflected in the increase in $m$ and $g_{Na}$. Recall that the dependence of $m$ on the membrane potential is roughly sigmoidal (Figure 3.10). As the membrane potential reaches the sharply rising part of this sigmoid curve, the $g_{Na}$ activation increases greatly. As the sodium reversal potential is much higher than the resting potential, the voltage increases further, causing the sodium conductance to increase still further. This snowball effect produces a sharp rise in the membrane potential.

The slower potassium conductance $g_{K}$, the $n$ gating variable, starts to activate soon after the sharp depolarisation of the membrane. The potassium conductance allows current to flow out of the neuron because of the low potassium reversal potential. The outward current flow starts to repolarise the cell, taking the membrane potential back down towards rest. It is the delay in its activation and repolarising action that leads to this type of potassium current being referred to as the delayed rectifier current.

The repolarisation of the membrane is also assisted by the inactivating sodium variable $h$, which decreases as the membrane depolarises, causing the inactivation of $g_{Na}$ and reduction of the sodium current flow into the cell. The membrane potential quickly swoops back down to its resting level, overshooting somewhat to hyperpolarise the neuron. This causes the rapid deactivation of the sodium current ($m$ reduces) and its deinactivation,
whereby the inactivation is released (h increases). In this phase, the potassium conductance also deactivates. Eventually all the state variables return to their resting states and the membrane potential returns to its resting level.

The HH model also explains the refractory period of the axon. During the **absolute refractory period** after an action potential, it is impossible to generate a new action potential by injecting current. Thereafter, during the **relative refractory period**, the threshold is higher than when the membrane is at rest, and action potentials initiated in this period have a lower peak voltage. From Figure 3.12, the gating variables take a long time, relative to the duration of an action potential, to recover to their resting values. It should be harder to generate an action potential during this period for two reasons. Firstly, the inactivation of the sodium conductance (low value of h) means that any increase in m due to increasing voltage will not increase the sodium conductance as much as it would when h is at its higher resting value.
3.3.2 Propagating action potentials

The propagated action potential calculated by Hodgkin and Huxley was also remarkably similar to the experimentally recorded action potential (Figure 3.14). The value of the velocity they calculated was $18.8 \text{ m s}^{-1}$, close to the experimental value of $21.2 \text{ m s}^{-1}$ at $18.5^\circ \text{C}$.

Figure 3.15 shows the capacitive, local and ionic currents flowing at different points on the membrane at a particular instant when an action potential is propagating from left to right. At the far right, local circuit currents are flowing in from the left because of the greater membrane potential there. These local circuit currents charge the membrane capacitance, leading to a rise in the membrane potential. Further to the left, the membrane is sufficiently depolarised to open sodium channels, allowing sodium ions to flow into the cell. Further left still, the sodium ionic current makes a dominant contribution to charging the membrane, leading to the opening of more sodium channels and the rapid rise in the membrane potential that characterises the initial phase of the action potential. To the left of this, the potassium conductance is activated, due to the prolonged depolarisation. Although sodium ions are flowing into the cell here, the net ionic current is outward. This outward current, along with a small local circuit contribution, discharges the membrane capacitance, leading to a decrease in the membrane potential. At the far left, in the falling part of the action potential, only potassium flows as sodium channels have inactivated. The final afterhyperpolarisation potential is not shown fully for reasons of space and because the current is very small. In this part, sodium is deinactivating and potassium is deactivating. This leads to a small inward current that brings the membrane potential back up to its resting potential.
3.4 The effect of temperature

Hodgkin et al. (1952) found that the temperature of the preparation affects the time course of voltage clamp recordings strongly: the rates of activation and inactivation increase with increasing temperature. In common with many biological and chemical processes, the rates increase roughly exponentially with the temperature. The $Q_{10}$ temperature coefficient, a measure of the increase in rate for a 10°C temperature change, is used to quantify this temperature dependence:

$$Q_{10} = \frac{\text{rate at } T + 10^\circ C}{\text{rate at } T}.$$  \hspace{1cm} (3.21)

If the values of the HH voltage-dependent rate coefficients $\alpha$ and $\beta$ at a temperature $T_1$ are $\alpha(V,T_1)$ and $\beta(V,T_1)$, then their values at a second temperature $T_2$ are:

$$\alpha(V,T_2) = \alpha(V,T_1)Q_{10}^{T_2-T_1}$$ and $$\beta(V,T_2) = \beta(V,T_1)Q_{10}^{T_2-T_1}.$$  \hspace{1cm} (3.22)

In the alternative form of the kinetic equations for the gating variables (see, for example, Equation 3.11), this adjustment due to temperature can
be achieved by decreasing the time constants $\tau_n$, $\tau_m$ and $\tau_h$ by a factor of $Q^{(T_2-T_1)/10}$ and leaving the steady state values of the gating variables $n_\infty$, $m_\infty$ and $h_\infty$ unchanged.

Hodgkin et al. (1952) estimated, from recordings, a $Q_{10}$ of about 3 for the time constants of the ionic currents. This is typical for the rate coefficients of ion channels (Hille, 2001). In fact, the principles of transition state theory, outlined in Section 5.8.1, show that the $Q_{10}$ itself is expected to depend on temperature: the $Q_{10}$ at 6°C is not expected to be the same as the $Q_{10}$ measured at 36°C. Transition state theory also allows temperature to be incorporated into the equations for the rate coefficients explicitly, rather than as a correction factor.

As well as the rate coefficients, the maximum channel conductances also increase with temperature, albeit not as strongly. If the maximum conductance for an ion type $X$ is $\bar{g}_X(T_1)$ at temperature $T_1$, at temperature $T_2$ it will be given by:

$$\bar{g}_X(T_2) = \bar{g}_X(T_1) Q_{10}^{(T_2-T_1)/10}.$$  

(3.23)

The $Q_{10}$ is typically around 1.2 to 1.5 for conductances (Hodgkin et al., 1952; Rodriguez et al., 1998; Hille, 2001).

3.5 Building models using the Hodgkin–Huxley formalism

The set of equations that make up the HH model (Box 3.5) were constructed to explain the generation and propagation of action potentials specifically in the squid giant axon. How relevant is the HH model to other preparations? While the parameters and equations for the rate coefficients present in the HH model are particular to squid giant axon, the general idea of gates comprising independent gating particles is used widely to describe other types of channel. In this section, we explore the model assumptions and highlight the constraints imposed by the Hodgkin–Huxley formalism. Moreover, we outline the types of experimental data that are required in order to construct this type of model of ion channels.

3.5.1 Model approximations

The HH model contains a number of approximations of what is now known about the behaviour of channels. Each of these will induce an error in the model, but the approximations are not so gross as to destroy the explanatory power of the model.

Each channel type is permeable to only one type of ion

Implicit in the HH model is the notion that channels are selective for only one type of ion. In fact, all ion channels are somewhat permeable to ions other than the dominant permeant ion (Section 2.1). Voltage-gated sodium channels in squid giant axon are about 8% as permeable to potassium as they are to sodium, and potassium channels are typically around 1% as permeable to sodium as they are to potassium (Hille, 2001).
The independence principle
As it is assumed that each type of current does not depend on the concentrations of other types of ion, these equations imply that the independence principle holds (Box 2.4). Hodgkin and Huxley (1952a) verified, to the limit of the resolving power of their experiments, that the independence principle holds for the sodium current. However, improved experimental techniques have revealed that this principle of independence does not hold exactly in general (Section 2.7).

The linear instantaneous \( I-V \) characteristic
One of the key elements of the HH model is that all the ionic currents that flow though open gates have a linear, quasi-ohmic dependence on the membrane potential (Equations 3.3–3.5), for example:

\[
I_{Na} = g_{Na}(V - E_{Na}).
\]  

(3.3)

As described in Chapter 2, this relation is an approximation of the non-linear Goldman–Hodgkin–Katz current equation, which itself is derived theoretically from assumptions such as there being a constant electric field in the membrane.

Hodgkin and Huxley (1952b) did not take these assumptions for granted, and carried out experiments to check the validity of Equation 3.3, and the corresponding equation for potassium. Testing this relation appears to be a matter of measuring an \( I-V \) characteristic, but in fact it is more complicated, since, as seen earlier in the chapter, the conductance \( g_{Na} \) changes over time, and the desired measurements are values of current and voltage at a fixed value of the conductance. It was not possible for Hodgkin and Huxley to fix the conductance, but they made use of their observation that it is rate of change of an ionic conductance that depends directly on voltage, not the ionic conductance itself. Therefore, in a voltage clamp experiment, if the voltage is changed quickly, the conductance has little chance to change, and the values of current and voltage just before and after the voltage step can be used to acquire two pairs of current and voltage measurements. If this procedure is repeated with the same starting voltage level and a range of second voltages, an \( I-V \) characteristic can be obtained.

As explained in more detail in Box 3.6, Hodgkin and Huxley obtained such \( I-V \) characteristics in squid giant axon and found that the quasi-ohmic \( I-V \) characteristics given in Equations 3.3–3.5 were appropriate for this membrane. They referred to this type of \( I-V \) characteristic as the instantaneous \( I-V \) characteristic, since the conductance is given no time to change between the voltage steps. In contrast, if the voltage clamp current is allowed time to reach a steady state after setting the voltage clamp holding potential, the \( I-V \) characteristic measured is called the steady state \( I-V \) characteristic.

In contrast to the instantaneous \( I-V \) characteristic, this is non-linear in the squid giant axon. With the advent of single channel recording (Chapter 5), it is possible to measure the \( I-V \) characteristic of an open channel directly in the open and closed states, as for example do Schrempf et al. (1995).

A potentially more accurate way to model the \( I-V \) characteristics would be to use the GHK current equation (Box 2.4). For example, the sodium
current would be given by:

\[ I_{Na}(t) = \rho_{Na}(t) \frac{F^2 V(t)}{RT} \left( \frac{[Na^+]_{in} - \left[Na^+_\text{out}\right] e^{-FV(t)/RT}}{1 - e^{-FV(t)/RT}} \right) , \]  

(3.24)

where \( \rho_{Na}(t) \) is the permeability to sodium at time \( t \). This equation could be rearranged to determine the permeability over time from voltage clamp recordings, and then a gating particle model for the permeability (for example, of the form \( \rho_{Na} = \bar{\rho}_{Na} m^3 h \)) could be derived. Sometimes it is desirable to use this form of the model, particularly where the \( I-V \) characteristic is non-linear and better fitted by the GHK equation. This is particularly the case for ions whose concentration differences across the membrane are large, such as in the case of calcium (Figure 2.11b).

**The independence of gating particles**

Alternative interpretations and fits of the voltage clamp data have been proposed. For example, Hoyt (1963, 1968) suggested that activation and inactivation are coupled. This was later confirmed through experiments that removed the inactivation in squid giant axon using the enzyme pronase (Bezanilla and Armstrong, 1977). Subsequent isolation of the inactivation time course revealed a lag in its onset that did not conform to the independent particle hypothesis. Inactivation now appears to be voltage independent and coupled to sodium activation. Consequently, more accurate models of sodium activation and inactivation require a more complex set of coupled equations (Goldman and Schauf, 1972). Unrestricted kinetic schemes, described in Section 5.5.3, provide a way to model dependencies such as this.

**Gating current is not considered**

In the HH model, the only currents supposed to flow across the membrane are the ionic currents. However, there is another source of current across the membrane, the movement of charges in channel proteins as they open and close. This gating current, described in more detail in Section 5.3.4, is very small in comparison to the ionic currents, so small in fact that it took
Box 3.6 Verifying the quasi-ohmic $I-V$ characteristic

To verify that the instantaneous $I-V$ characteristics of the sodium and potassium currents were quasi-ohmic, Hodgkin and Huxley (1952a) made a series of recordings using a two-step voltage clamp protocol. In every recording, the first step was of the same duration, and depolarised the membrane to the same level. This caused sodium and potassium channels to open. The second step was to a different voltage in each experiment in the series. The ion substitution method allowed the sodium and potassium currents to be separated.

Figure 3.16c shows one such recording of the sodium current. At the end of the step, the current increases discontinuously and then decays to zero. There is a small gap due to the capacitive surge. The current just after the discontinuous leap ($I_2$) depends on the voltage of the second step ($V_2$). When $I_2$ was plotted against $V_2$, a linear relationship passing through the sodium equilibrium potential $E_{Na}$ was seen. The gradient of the straight line was the conductance at the time of the start of the second voltage step.

This justified the calculation of the conductance from the current and driving force according to Equation 3.3. Figure 3.16d shows the conductance so calculated. In contrast to the current, it is continuous at the end of the voltage step, apart from the gap due to the capacitive surge.

many years to be able to measure it in isolation from the ionic currents. Adding it to the HH model would make very little difference to the model's behaviour, and would not change the explanation provided by the model for the action potential. However, the gating current can be used to probe the detailed kinetics of ion channels. Thus, ignoring the gating current is a good example of a kind of simplification that is appropriate for one question, but if asking a different question, may be something to model with great accuracy.

3.5.2 Fitting the Hodgkin–Huxley formalism to data

The Hodgkin–Huxley formalism for a channel comprises

1. an instantaneous $I-V$ characteristic, e.g. quasi-ohmic or GHK equation;
2. one or more gating variables (such as $m$ and $h$) and the powers to which those gating variables are raised;
3. expressions for the forward and backward rate coefficients for these variables as a function of voltage.

The data required for all the quantities are voltage clamp recordings using various protocols of holding potential of the current passing through the channel type in question. This requires that the channel be isolated by some method, such as the ion substitution method (Box 3.2), channel blockers, Section 5.3.2, or expression in oocytes, Section 5.3.3. The data required for each is now discussed.
Linear $I-V$ characteristic
For greatest accuracy, the instantaneous $I-V$ characteristic should be measured. Even the GHK equation might not be able to capture some features of the characteristic. Also, the reversal potential may differ significantly from the equilibrium potential of the dominant permeant ion if there are other ions to which the channel is significantly permeable. However, in practice, the quasi-ohmic approximation is often used with a measured reversal potential as equilibrium potential. When the intracellular and extracellular concentration differences are great, such as in the case of calcium, the GHK equation may be used.

Gating variables
If the channel displays no inactivation, only one gating variable is required, but if there is inactivation, an extra variable will be needed. The gating variable is raised to the power of the number of activation particles needed to capture the inflection in conductance activation, which then determines the voltage-dependent rate coefficient functions $\alpha_n$, $\beta_n$ of Equation 3.7.

Coefficients for each gating variable
The voltage dependence of the forward and backward reaction coefficients $\alpha$ and $\beta$ for each gating particle need to be determined. The basis for this is the data from voltage clamp experiments with different holding potentials.

These can be obtained using the types of methods described in this chapter to determine plots of steady state activation and inactivation and time constants against voltage. With modern parameter estimation techniques (Section 4.5), it is sometimes possible to short circuit these methods. Instead, the parameters of a model can be adjusted to make the behaviour of the model as similar as possible to recordings under voltage clamp conditions.

The steady state variables, for instance $n_\infty$ and $\tau_n$ in the case of potassium, need not be converted into rate coefficients such as $\alpha_n$ and $\beta_n$, since the kinetics of the gating variable can be specified using $n_\infty$ and $\tau_n$ (Equation 3.11). This approach is taken, for example, by Connor et al. (1977) in their model of the A-type potassium current (Box 5.2). Hodgkin and Huxley fit smooth functions to their data points, but some modellers (Connor and Stevens, 1971c) connect their data points with straight lines in order to make a piecewise linear approximation of the underlying function.

If functions are to be fitted, the question arises of what form they should take. The functions used by Hodgkin and Huxley (1952d) took three different forms, each of which corresponds to a model of how the gating particles moved in the membrane (Section 5.8.3). From the point of view of modelling the behaviour of the membrane potential at a particular temperature, it does not really matter which two quantities are fitted to data or what functional forms are used, as long as they describe the data well. However, from the point of view of understanding the biophysics of channels, more physically principled fitting functions (Section 5.8) are better than arbitrary functions. This can include temperature dependence, rather than having to bolt this on using the value of $Q_{10}$.
3.6 Summary

In their model, Hodgkin and Huxley introduced active elements into the passive membrane equation. These active currents are specified through the concept of membrane-bound gated channels, or gates, each gate comprising a number of independent gating particles. While the Hodgkin–Huxley formalism does not relate directly to the physical structure of channels, it does provide a framework within which to describe experimental data. In particular, the use of kinetic reaction equations allows the system to be fitted to voltage-dependent characteristics of the active membrane currents through the voltage dependence of the kinetic rate coefficients. Putative functions for the kinetic rate coefficients are fitted to experimental voltage clamp data. The resulting quantitative model not only replicates the voltage clamp experiments to which it is tuned, but also reproduces the main features of the action potential.

In this chapter we have been considering the squid giant axon only. Furthermore, we have focused on single stretches of axon and have not included features such as branch points, varicosities and axon tapering in the model. These extensions may be added to the models using the multi-compartmental model approach. As seen previously, a single equivalent electrical circuit representing an isopotential patch of membrane can be connected to other membrane circuits in various ways to form an approximation of membrane area and discontinuities. This approach is introduced and discussed in Chapter 4.

Representing more complex neurons requires a model to contain more than sodium and potassium conductances. This can be achieved by including in the equivalent electrical circuit any number of transmembrane conductances in series with a voltage source representing new ionic currents. The voltage dependence of conductances may be characterised by the Hodgkin–Huxley formalism if the independent gating particle approach is deemed accurate enough. However, as will be seen in Chapter 5, the Hodgkin–Huxley formalism cannot explain some behaviours of ion channels, and more complex models are required. Conductances may also exhibit more than voltage dependence; for example, ligand-gated channels and channels dependent on ionic concentrations. These variations are discussed in Chapters 5 and 7.