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.

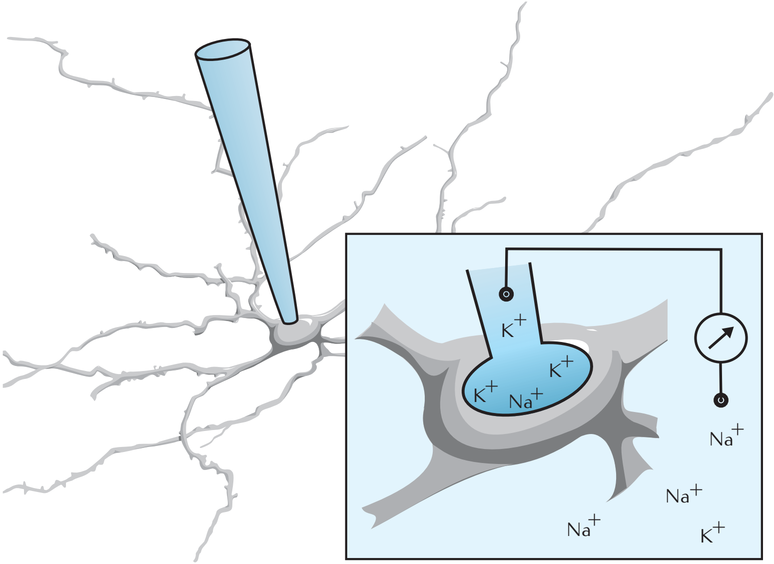

Fig. 2.1 Differences in the intracellular and extracellular ion compositions and their separation by the cell membrane is the starting point for understanding the electrical properties of the neuron. The inset shows that for a typical neuron in the CNS, the concentration of sodium ions is greater outside 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).

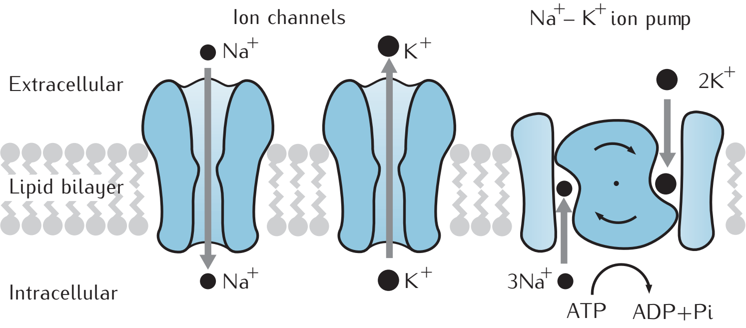

Fig. 2.2 Constituents of the membrane. Three types of component play important electrical roles in a neuron's membrane. The lipid bilayer forms a virtually impermeable barrier for inorganic ions. The ion channel is a protein or cluster of proteins that form a pore through the membrane, allowing certain ions to pass through. The ionic pump, or ion exchanger, pumps or exchanges certain ion types across the membrane. This example shows the Na^+–K^+ pump which exchanges three Na^+ ions from inside with two K^+ ions from outside using the energy from the hydrolysis of ATP into ADP and a phosphate ion.

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 Review of electrical circuit components. For each component, the circuit symbol, the mathematical symbol, the SI unit, and the abbreviated form of the SI unit are shown

Component	Symbols and units	Function
Battery	 *E* (volts, V)	Pumps charge around a circuit
Current source	 *I* (amps, A)	Provides a specified current (which may vary with time)
Resistor	 *R* (ohms, Ω)	Resists the flow of current in a circuit
Capacitor	 *C* (farad, F)	Stores charge. Current flows *onto* (not through) a capacitor

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 concentration in the absence of an electric field. This is a first step to understanding movement of ions through channels. We go on to look at electrical drift, caused by electric fields acting on ions which are concentrated uniformly within a region. This can be used to model the movement of ions longitudinally through the cytoplasm. When there are both electric fields and non-uniform ion concentrations, the movement of the ions is described by a combination of electrical drift and diffusion, termed **electrodiffusion**. This is the final step required to understand the passage of ions through channels. Finally, the relationship between the movement of ions and electrical current is described.

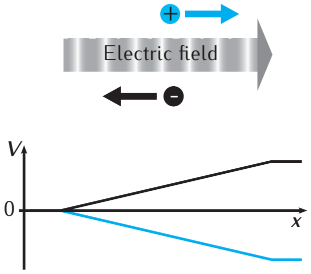

Fig. 2.3 The forces acting on both positively and negatively charged ions placed within an electric field. The potential difference V between the left-hand side of the field and points along the x axis is shown for the positively charged ion (in blue) and the negatively charged ion (in black).

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.

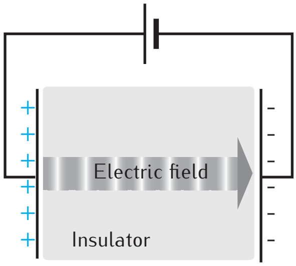

Fig. 2.4 A charged capacitor creates an electric field.

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:

$$q = CV. \tag{2.1}$$

Capacitance depends on the electrical properties of the insulator and size and distance between the plates.

The capacitance of an ideal parallel plate capacitor is proportional to the area a of the plates and inversely proportional to the distance d between the plates:

$$C = \frac{a}{\epsilon d}$$

where ϵ is the permitivity of the insulator, a measure of how hard it is to form an electric field in the material.

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.

Concentration is typically measured in moles per unit volume. One mole contains Avogadro's number (approximately 6.02×10^{23}) atoms or molecules. **Molarity** denotes the number of moles of a given substance per litre of solution (the units are $\mathrm{mol\,L^{-1}}$, often shortened to M).

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.

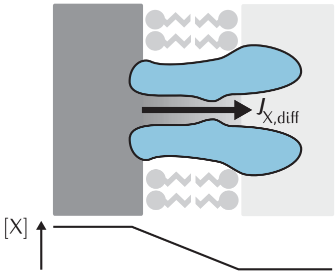

Fig. 2.5 Fick's first law in the context of an ion channel spanning a neuronal membrane.

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 $\mathrm{mol\,cm^{-2}\,s^{-1}}$, 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, $J_{\mathrm{X,diff}}$, arising from the diffusion of a molecule X, to its **concentration gradient** $\mathrm{d}[\mathrm{X}]/\mathrm{d}x$ (here in one dimension):

$$J_{\mathrm{X,diff}} = -D_{\mathrm{X}} \frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}x} \tag{2.2}$$

where D_{X} is defined as the **diffusion coefficient** of molecule X. The diffusion coefficient has units of $\mathrm{cm}^2\,\mathrm{s}^{-1}$. 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.

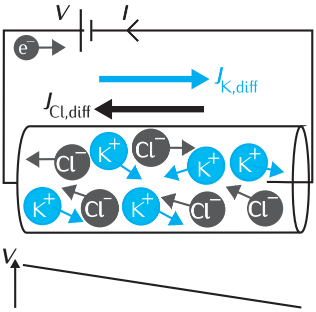

Fig. 2.6 Electrical drift. The cylinder represents a section of neurite containing positively charged potassium ions and negatively charged chloride ions. Under the influence of a potential difference between the ends, the potassium ions tend to drift towards the positive terminal and the chloride ions towards the negative terminal. In the wire the current is transported by electrons.

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 K^+ and 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 K^+ ions will experience an electrical force pushing them down the potential gradient, and the 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 K^+ and Cl^- ions, preventing them from accelerating. The result is that both K^+ and Cl^- molecules travel at an average speed (**drift velocity**) that depends on the strength of the field. Assuming there is no concentration gradient of potassium or chloride, the flux is:

$$J_{\mathrm{X,drift}} = -\frac{D_{\mathrm{X}} F}{RT} z_{\mathrm{X}} [\mathrm{X}] \frac{\mathrm{d}V}{\mathrm{d}x} \tag{2.3}$$

where z_{X} is the ion's signed **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.

z_{X} is +2 for calcium ions, +1 for potassium ions and −1 for chloride ions.

$R = 8.314\,\mathrm{J\,K^{-1}mol^{-1}}$
$F = 9.648 \times 10^4\,\mathrm{C\,mol^{-1}}$

The universal convention is to use the symbol R to denote both the gas constant and electrical resistance. However, what R is referring to is usually obvious from the context: when R refers to the universal gas constant, it is very often next to temperature T.

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:

$$J_\mathrm{X} = J_\mathrm{X,diff} + J_\mathrm{X,drift} = -D_\mathrm{X}\left(\frac{\mathrm{d}[\mathrm{X}]}{\mathrm{d}x} + \frac{z_\mathrm{X}F}{RT}[\mathrm{X}]\frac{\mathrm{d}V}{\mathrm{d}x}\right). \tag{2.4}$$

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 $\mu\mathrm{A\,cm^{-2}}$.

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:

$$I_\mathrm{X} = F\,z_\mathrm{X}J_\mathrm{X} \tag{2.5}$$

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 $\mathrm{Na^+}$ and $\mathrm{K^+}$, 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 $\mathrm{Cl^-}$, 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:

$$I = I_\mathrm{Na} + I_\mathrm{K} + I_\mathrm{Cl} = F\,z_\mathrm{Na}J_\mathrm{Na} + F\,z_\mathrm{K}J_\mathrm{K} + F\,z_\mathrm{Cl}J_\mathrm{Cl}. \tag{2.6}$$