Chapter 1

Introduction

1.1 What is this book about?

This book is about how to construct and use computational models of specific parts of the nervous system, such as a neuron, a part of a neuron or a network of neurons. It is designed to be read by people from a wide range of backgrounds from the biological, physical and computational sciences. The word 'model' can mean different things in different disciplines, and even researchers in the same field may disagree on the nuances of its meaning. For example, to biologists, the term 'model' can mean 'animal model'; to physicists, the standard model is a step towards a complete theory of fundamental particles and interactions. We therefore start this chapter by attempting to clarify what we mean by computational models and modelling in the context of neuroscience. Before giving a brief chapter-by-chapter overview of the book, we also discuss what might be called the philosophy of modelling: general issues in computational modelling that recur throughout the book.

1.1.1 Theories and mathematical models

In our attempts to understand the natural world, we all come up with theories. Theories are possible explanations for how the phenomena under investigation arise, and from theories we can derive predictions about the results of new experiments. If the experimental results disagree with the **predictions**, the theory can be rejected, and if the results agree, the theory is validated – for the time being. Typically, the theory will contain **assumptions** which are about the properties of elements or mechanisms which have not yet been quantified, or even observed. In this case, a full test of the theory will also involve trying to find out if the assumptions are really correct.

Mendel's Laws of Inheritance form a good example of a theory formulated on the basis of the interactions of elements whose existence was not known at the time. These elements are now known as genes.

In the first instance, a theory is described in words, or perhaps with a diagram. To derive predictions from the theory we can deploy verbal reasoning and further diagrams. Verbal reasoning and diagrams are crucial tools for theorising. However, as the following example from ecology demonstrates, it can be risky to rely on them alone.

Suppose we want to understand how populations of a species in an ecosystem grow or decline through time. We might theorise that 'the larger the population, the more likely it will grow and therefore the faster it will

increase in size'. From this theory we can derive the prediction, as did Malthus (1798), that the population will grow infinitely large, which is incorrect. The reasoning from theory to prediction is correct, but the prediction is wrong and so logic dictates that the theory is wrong. Clearly, in the real world, the resources consumed by members of the species are only replenished at a finite rate. We could add to the theory the stipulation that for large populations, the rate of growth slows down, being limited by finite resources. From this, we can make the reasonable prediction that the population will stabilise at a certain level at which there is zero growth.

We might go on to think about what would happen if there are two species, one of which is a predator and one of which is the predator's prey. Our theory might now state that: (1) the prey population grows in proportion to its size but declines as the predator population grows and eats it; and (2) the predator population grows in proportion to its size and the amount of the prey, but declines in the absence of prey. From this theory we would predict that the prey population grows initially. As the prey population grows, the predator population can grow faster. As the predator population grows, this limits the rate at which the prey population can grow. At some point, an equilibrium is reached when both predator and prey sizes are in balance.

Thinking about this a bit more, we might wonder whether there is a second possible prediction from the theory. Perhaps the predator population grows so quickly that it is able to make the prey population extinct. Once the prey has gone, the predator is also doomed to extinction. Now we are faced with the problem that there is one theory but two possible conclusions; the theory is logically inconsistent.

The problem has arisen for two reasons. Firstly, the theory was not clearly specified to start with. Exactly how does the rate of increase of the predator population depend on its size and the size of the prey population? How fast is the decline of the predator population? Secondly, the theory is now too complex for qualitative verbal reasoning to be able to turn it into a prediction.

The solution to this problem is to specify the theory more precisely, in the language of mathematics. In the equations corresponding to the theory, the relationships between predator and prey are made precisely and unambiguously. The equations can then be solved to produce one prediction. We call a theory that has been specified by sets of equations a **mathematical model**.

It so happens that all three of our verbal theories about population growth have been formalised in mathematical models, as shown in Box 1.1. Each model can be represented as one or more differential equations. To predict the time evolution of a quantity under particular circumstances, the equations of the model need to be solved. In the relatively simple cases of unlimited growth, and limited growth of one species, it is possible to solve these equations analytically to give equations for the solutions. These are shown in Figure 1.1a and Figure 1.1b, and validate the conclusions we came to verbally.

In the case of the predator and prey model, analytical solution of its differential equations is not possible and so the equations have to be solved

Box 1.1 Mathematical models

Mathematical models of population growth are classic examples of describing how particular variables in the system under investigation change over space and time according to the given theory.

According to the Malthusian, or exponential, growth model (Malthus, 1798), a population of size $P(t)$ grows in direct proportion to this size. This is expressed by an **ordinary differential equation** that describes the rate of change of P:

$$\mathrm{d}P/\mathrm{d}t = P/\tau$$

where the proportionality constant is expressed in terms of the time constant, τ, which determines how quickly the population grows. Integration of this equation with respect to time shows that at time t a population with initial size P_0 will have size $P(t)$, given as:

$$P(t) = P_0 \exp(t/\tau).$$

This model is unrealistic as it predicts unlimited growth (Figure 1.1a). A more complex model, commonly used in ecology, that does not have this defect (Verhulst, 1845), is one where the population growth rate $\mathrm{d}P/\mathrm{d}t$ depends on the Verhulst, or **logistic function** of the population P:

$$\mathrm{d}P/\mathrm{d}t = P(1 - P/K)/\tau.$$

Here K is the maximum allowable size of the population. The solution to this equation (Figure 1.1b) is:

$$P(t) = \frac{KP_0 \exp(t/\tau)}{K + P_0(\exp(t/\tau) - 1)}.$$

A more complicated situation is where there are two types of species and one is a predator of the other. For a prey population with size $N(t)$ and a predator population with size $P(t)$, it is assumed that (1) the prey population grows in a Malthusian fashion and declines in proportion to the rate at which predator and prey meet (assumed to be the product of the two population sizes, NP); (2) conversely, there is an increase in predator size in proportion to NP and an exponential decline in the absence of prey. This gives the following mathematical model:

$$\mathrm{d}N/\mathrm{d}t = N(a - bP) \qquad \mathrm{d}P/\mathrm{d}t = P(cN - d).$$

The parameters a, b, c and d are constants. As shown in Figure 1.1c, these equations have periodic solutions in time, depending on the values of these parameters. The two population sizes are out of phase with each other, large prey populations co-occurring with small predator populations, and vice versa. In this model, proposed independently by Lotka (1925) and by Volterra (1926), predation is the only factor that limits growth of the prey population, but the equations can be modified to incorporate other factors. These types of models are used widely in the mathematical modelling of competitive systems found in, for example, ecology and epidemiology.

As can be seen in these three examples, even the simplest models contain parameters whose values are required if the model is to be understood; the number of these parameters can be large and the problem of how to specify their values has to be addressed.

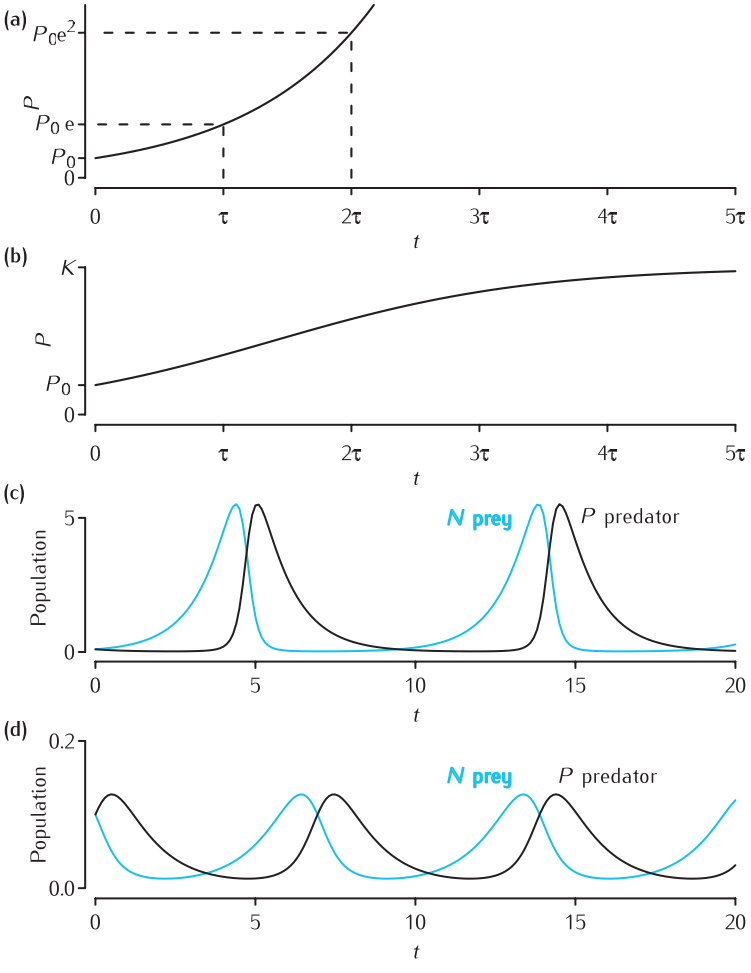


Fig. 1.1 Behaviour of the mathematical models described in Box 1.1. **(a)** Malthusian, or exponential growth: with increasing time, t, the population size, P, grows increasingly rapidly and without bounds. **(b)** Logistic growth: the population increases with time, up to a maximum value of K. **(c)** Behaviour of the Lotka–Volterra model of predator–prey interactions, with parameters $a = b = c = d = 1$. The prey population is shown by the blue line and the predator population by the black line. Since the predator population is dependent on the supply of prey, the predator population size always lags behind the prey size, in a repeating fashion. **(d)** Behaviour of the Lotka–Volterra model with a second set of parameters: $a = 1$, $b = 20$, $c = 20$ and $d = 1$.

using numerical integration (Appendix B.1). In the past this would have been carried out laboriously by hand and brain, but nowadays, the computer is used. The resulting sizes of predator and prey populations over time are shown in Figure 1.1c. It turns out that neither of our guesses was correct. Instead of both species surviving in equilibrium or going extinct, the predator and prey populations oscillate over time. At the start of each cycle, the prey population grows. After a lag, the predator population starts to grow, due to the abundance of prey. This causes a sharp decrease in prey, which almost causes its extinction, but not quite. Thereafter, the predator population declines and the cycle repeats. In fact, this behaviour is observed approximately in some systems of predators and prey in ecosystems (Edelstein-Keshet, 1988).

In the restatement of the model's behaviour in words, it might now seem obvious that oscillations would be predicted by the model. However, the step of putting the theory into equations was required in order to reach this understanding. We might disagree with the assumptions encoded in the mathematical model. However, this type of disagreement is better than the inconsistencies between predictions from a verbal theory.

The process of modelling described in this book almost always ends with the calculation of the numerical solution for quantities, such as neuronal membrane potentials. This we refer to as **computational modelling**. A particular mathematical model may have an analytical solution that allows exact calculation of quantities, or may require a numerical solution that approximates the true, unobtainable values.

1.1.2 Why do computational modelling?

As the predator–prey model shows, a well-constructed and useful model is one that can be used to increase our understanding of the phenomena under investigation and to predict reliably the behaviour of the system under the given circumstances. An excellent use of a computational model in neuroscience is Hodgkin and Huxley's simulation of the propagation of a nerve impulse (action potential) along an axon (Chapter 3).

Whilst ultimately a theory will be validated or rejected by experiment, computational modelling is now regarded widely as an essential part of the neuroscientist's toolbox. The reasons for this are:

(1) Modelling is used as an aid to reasoning. Often the consequences derived from hypotheses involving a large number of interacting elements forming the neural subsystem under consideration can only be found by constructing a computational model. Also, experiments often only provide indirect measurements of the quantities of interest, and models are used to infer the behaviour of the interesting variables. An example of this is given in Box 1.2.

(2) Modelling removes ambiguity from theories. Verbal theories can mean different things to different people, but formalising them in a mathematical model removes that ambiguity. Use of a mathematical model ensures that the assumptions of the model are explicit and logically consistent. The predictions of what behaviour results from a fully specified mathematical model are unambiguous and can be checked by solving again the equations representing the model.

(3) The models that have been developed for many neurobiological systems, particularly at the cellular level, have reached a degree of sophistication such that they are accepted as being adequate representations of the neurobiology. Detailed compartmental models of neurons are one example (Chapter 4).

(4) Advances in computer technology mean that the number of interacting elements, such as neurons, that can be simulated is very large and representative of the system being modelled.

(5) In principle, testing hypotheses by computational modelling could supplement experiments in some cases. Though experiments are vital in developing a model and setting initial parameter values, it might be possible to use modelling to extend the effective range of experimentation.

Building a computational model of a neural system is not a simple task. Major problems are: deciding what type of model to use; at what level to model; what aspects of the system to model; and how to deal with parameters that have not or cannot be measured experimentally. At each stage of this book we try to provide possible answers to these questions as a guide

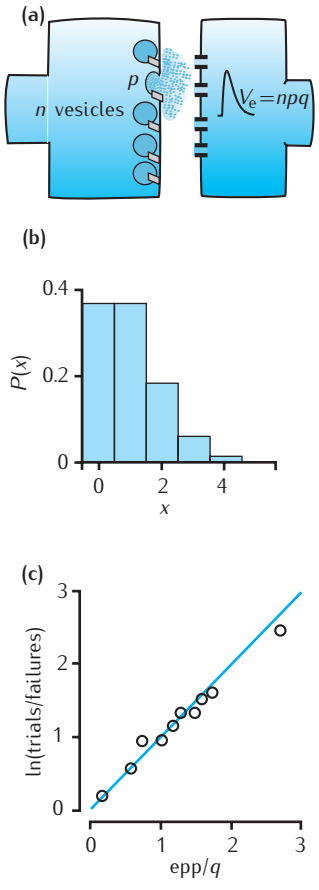


Fig. 1.2 **(a)** Quantal hypothesis of synaptic transmission. **(b)** Example Poisson distribution of the number of released quanta when $m = 1$. **(c)** Relationship between two estimates of the mean number of released quanta at a neuromuscular junction. Blue line shows where the estimates would be identical. Plotted from data in Table 1 of Del Castillo and Katz (1954a), following their Figure 6.

Box 1.2 Reasoning with models

An example in neuroscience where mathematical models have been key to reasoning about a system is chemical synaptic transmission. Though more direct experiments are becoming possible, much of what we know about the mechanisms underpinning synaptic transmission must be inferred from recordings of the postsynaptic response. Statistical models of neurotransmitter release are a vital tool.

In the 1950s, the **quantal hypothesis** was put forward by Del Castillo and Katz (1954a) as an aid to explaining data obtained from frog neuromuscular junctions. Release of acetylcholine at the nerve–muscle synapse results in an **endplate potential** (**EPP**) in the muscle. In the absence of presynaptic activity, spontaneous **miniature endplate potentials** (**MEPPs**) of relatively uniform size were recorded. The working hypothesis was that the EPPs evoked by a presynaptic action potential actually were made up by the sum of very many MEPPs, each of which contributed a discrete amount, or 'quantum', to the overall response. The proposed underlying model is that the mean amplitude of the evoked EPP, V_e, is given by:

$$V_e = npq,$$

where n quanta of acetylcholine are available to be released. Each can be released with a mean probability p, though individual release probabilities may vary across quanta, contributing an amount q, the **quantal amplitude**, to the evoked EPP (Figure 1.2a).

To test their hypothesis, Del Castillo and Katz (1954a) reduced synaptic transmission by lowering calcium and raising magnesium in their experimental preparation, allowing them to evoke and record small EPPs, putatively made up of only a few quanta. If the model is correct, then the mean number of quanta released per EPP, m, should be:

$$m = np.$$

Given that n is large and p is very small, the number released on a trial-by-trial basis should follow a Poisson distribution (Appendix B.3) such that the probability that x quanta are released on a given trial is (Figure 1.2b):

$$P(x) = (m^x/x!)exp(-m).$$

This leads to two different ways of obtaining a value for m from the experimental data. Firstly, m is the mean amplitude of the evoked EPPs divided by the quantal amplitude, $m \equiv \overline{V}_e/q$, where q is the mean amplitude of recorded miniature EPPs. Secondly, the recording conditions result in many complete failures of release, due to the low release probability. In the Poisson model the probability of no release, $P(0)$, is $P(0) = \exp(-m)$, leading to $m = -\ln(P(0))$. $P(0)$ can be estimated as (number of failures)/(number of trials). If the model is correct, then these two ways of determining m should agree with each other:

$$m \equiv \overline{V}_e/q = \ln \frac{\text{trials}}{\text{failures}}.$$

Plots of the experimental data confirmed that this was the case (Figure 1.2c), lending strong support for the quantal hypothesis.

Such **quantal analysis** is still a major tool in analysing synaptic responses, particularly for identifying the pre- and postsynaptic loci of biophysical changes underpinning short- and long-term synaptic plasticity (Ran *et al.*, 2009; Redman, 1990). More complex and dynamic models are explored in Chapter 7.

to the modelling process. Often, there is no single correct answer, but is a matter of skilled and informed judgement.

1.1.3 Levels of analysis

To understand the nervous system requires analysis at many different levels (Figure 1.3), from molecules to behaviour, and computational models exist at all levels. The nature of the scientific question that drives the modelling work will largely determine the level at which the model is to be constructed. For example, to model how ion channels open and close requires a model in which ion channels and their dynamics are represented; to model how information is stored in the cerebellar cortex through changes in synaptic strengths requires a model of the cerebellar circuitry involving interactions between nerve cells through modifiable synapses.

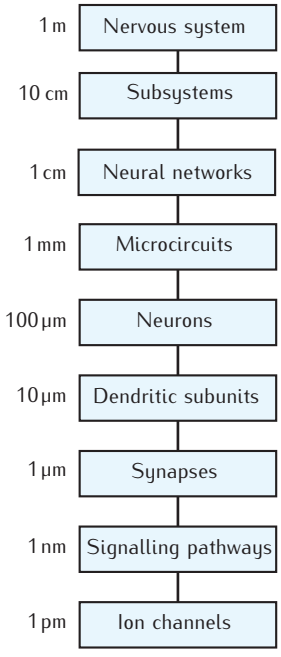


Fig. 1.3 To understand the nervous system requires an understanding at many different levels, at spatial scales ranging from metres to nanometres or smaller. At each of these levels there are detailed computational models for how the elements at that level function and interact, be they, for example, neurons, networks of neurons, synapses or molecules involved in signalling pathways.

1.1.4 Levels of detail

Models that are constructed at the same level of analysis may be constructed to different levels of detail. For example, some models of the propagation of electrical activity along the axon assume that the electrical impulse can be represented as a square pulse train; in some others the form of the impulse is modelled more precisely as the voltage waveform generated by the opening and closing of sodium and potassium channels. The level of detail adopted also depends on the question being asked. An investigation into how the relative timing of the synaptic impulses arriving along different axons affects the excitability of a target neuron may only require knowledge of the impulse arrival times, and not the actual impulse waveform.

Whatever the level of detail represented in a given model, there is always a more detailed model that can be constructed, and so ultimately how detailed the model should be is a matter of judgement. The modeller is faced perpetually with the choice between a more realistic model with a large number of parameter values that have to be assigned by experiment or by other means, and a less realistic but more tractable model with few undetermined parameters. The choice of what level of detail is appropriate for the model is also a question of practical necessity when running the model on the computer; the more details there are in the model, the more computationally expensive the model is. More complicated models also require more effort, and lines of computer code, to construct.

As with experimental results, it should be possible to reproduce computational results from a model. The ultimate test of reproducibility is to read the description of a model in a scientific paper, and then redo the calculations, possibly by writing a new version of the computer code, to produce the same results. A weaker test is to download the original computer code of the model, and check that the code is correct, i.e. that it does what is described of it in the paper. The difficulty of both tests of reproducibility increases with the complexity of the model. Thus, a more detailed model is not necessarily a better model. Complicating the model needs to be justified as much as simplifying it, because it can sometimes come at the cost of understandability.

In deciding how much detail to include in a model we could take guidance from Albert Einstein, who is reported as saying 'Make everything as simple as possible, but not simpler.'

1.1.5 Parameters

A key aspect of computational modelling is in determining values for model parameters. Often these will be estimates at best, or even complete guesses. Using the model to show how sensitive a solution is to the varying parameter values is a crucial use of the model.

Returning to the predator–prey model, Figure 1.1c shows the behaviour of only one of an infinitely large range of models described by the final equation in Box 1.1. This equation contains four **parameters**, a, b, c and d. A parameter is a constant in a mathematical model which takes a particular value when producing a numerical solution of the equations, and which can be adjusted between solutions. We might argue that this model only produced oscillations because of the set of parameter values used, and try to find a different set of parameter values that gives steady state behaviour. In Figure 1.1d the behaviour of the model with a different set of parameter values is shown; there are still oscillations in the predator and prey populations, though they are at a different frequency.

In order to determine whether or not there are parameter values for which there are no oscillations, we could try to search the **parameter space**, which in this case is made up of all possible values of a, b, c and d in combination. As each value can be any real number, there are an infinite number of combinations. To restrict the search, we could vary each parameter between, say, 0.1 and 10 in steps of 0.1, which gives 100 different values for each parameter. To search all possible combinations of the four parameters would therefore require 100^4 (100 million) numerical solutions to the equations. This is clearly a formidable task, even with the aid of computers.

In the case of this particular simple model, the mathematical method of stability analysis can be applied (Appendix B.2). This analysis shows that there are oscillations for *all* parameter settings.

Often the models we devise in neuroscience are considerably more complex than this one, and mathematical analysis is of less help. Furthermore, the equations in a mathematical model often contain a large number of parameters. While some of the values can be specified (for example, from experimental data), usually not all parameter values are known. In some cases, additional experiments can be run to determine some values, but many parameters will remain **free parameters** (i.e. not known in advance).

How to determine the values of free parameters is a general modelling issue, not exclusive to neuroscience. An essential part of the modeller's toolkit is a set of techniques that enable free parameter values to be estimated. Amongst these techniques are:

Optimisation techniques: automatic methods for finding the set of parameter values for which the model's output best fits known experimental data. This assumes that such data is available and that suitable measures of goodness of fit exist. Optimisation involves changing parameter values systematically so as to improve the fit between simulation and experiment. Issues such as the uniqueness of the fitted parameter values then also arise.

Sensitivity analysis: finding the parameter values that give stable solutions to the equations; that is, values that do not change rapidly as the parameter values are changed very slightly.

Constraint satisfaction: use of additional equations which express global constraints (such as, that the total amount of some quantity is conserved). This comes at the cost of introducing more assumptions into the model.

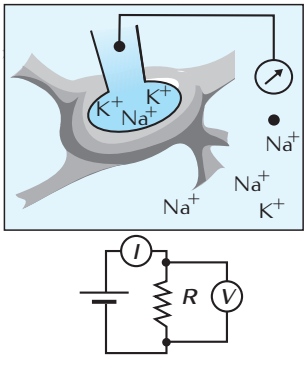
Educated guesswork: use of knowledge of likely values. For example, it is likely that the reversal potential of potassium is around −80 mV in many neurons in the central nervous system (CNS). In any case, results of any automatic parameter search should always be subject to a 'sanity test'. For example, we ought to be suspicious if an optimisation procedure suggested that the reversal potential of potassium was hundreds of millivolts.

1.2 Overview of the book

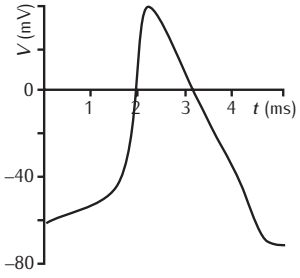
Most of this book is concerned with models designed to understand the electrophysiology of the nervous system in terms of the propagation of electrical activity in nerve cells. We describe a series of computational models, constructed at different levels of analysis and detail.

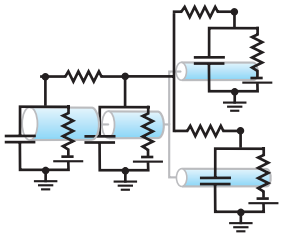
The level of analysis considered ranges from ion channels to networks of neurons, grouped around models of the nerve cell. Starting from a basic description of membrane biophysics (Chapter 2), a well-established model of the nerve cell is introduced (Chapter 3). In Chapters 4–7 the modelling of the nerve cell in more and more detail is described: modelling approaches in which neuronal morphology can be represented (Chapter 4); the modelling of ion channels (Chapter 5); or intracellular mechanisms (Chapter 6); and of the synapse (Chapter 7). We then look at issues surrounding the construction of simpler neuron models (Chapter 8). One of the reasons for simplifying is to enable networks of neurons to be modelled, which is the subject of Chapter 9.

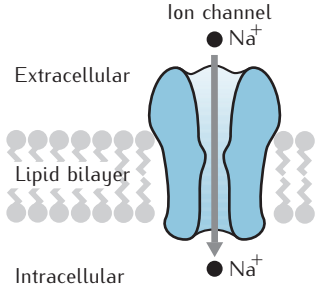
Whilst all these models embody assumptions, the premises on which they are built (such as that electrical signalling is involved in the exchange of information between nerve cells) are largely accepted. This is not the case for mathematical models of the developing nervous system. In Chapter 10 we give a selective review of some models of neural development, to highlight the diversity of models and assumptions in this field of modelling.

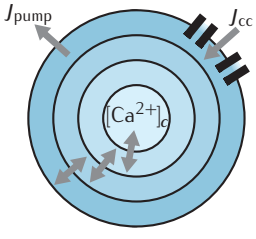


Chapter 2, The basis of electrical activity in the neuron, describes the physical basis for the concepts used in modelling neural electrical activity. A semipermeable membrane, along with ionic pumps which maintain different concentrations of ions inside and outside the cell, results in an electrical potential across the membrane. This membrane can be modelled as an electrical circuit comprising a resistor, a capacitor and a battery in parallel. It is assumed that the resistance does not change; this is called a passive model. Whilst it is now known that the passive model is too simple a mathematical description of real neurons, this approach is useful in assessing how specific









passive properties, such as those associated with membrane resistance, can affect the membrane potential over an extended piece of membrane.

Chapter 3, The Hodgkin–Huxley model of the action potential, describes in detail this landmark model for the generation of the nerve impulse in nerve membranes with active properties; i.e. the effects on membrane potential of the voltage-gated ion channels are now included in the model. This model is widely heralded as the first successful example of combining experimental and computational studies in neuroscience. In the late 1940s the newly invented voltage clamp technique was used by Hodgkin and Huxley to produce the experimental data required to construct a set of mathematical equations representing the movement of independent gating particles across the membrane thought to control the opening and closing of sodium and potassium channels. The efficacy of these particles was assumed to depend on the local membrane potential. These equations were then used to calculate the form of the action potentials in the squid giant axon. Whilst subsequent work has revealed complexities that Hodgkin and Huxley could not consider, today their formalism remains a useful and popular technique for modelling channel types.

Chapter 4, Compartmental models, shows how to model complex dendritic and axonal morphology using the multi-compartmental approach. The emphasis is on deriving the passive properties of neurons, although some of the issues surrounding active channels are discussed, in anticipation of a fuller treatment in Chapter 5. We discuss how to construct a compartmental model from a given morphology and how to deal with measurement errors in experimentally determined morphologies. Close attention is paid to modelling incomplete data, parameter fitting and parameter value searching.

Chapter 5, Models of active ion channels, examines the consequences of introducing into a model of the neuron the many types of active ion channel known in addition to the sodium and potassium voltage-gated ion channels studied in Chapter 3. There are two types of channel, those gated by voltage and those gated by ligands, such as calcium. In this chapter we present methods for modelling the kinetics of both types of channel. We do this by extending the formulation used by Hodgkin and Huxley of an ion channel in terms of independent gating particles. This formulation is the basis for the thermodynamic models, which provide functional forms for the rate coefficients determining the opening and closing of ion channels that are derived from basic physical principles. To improve on the fits to data offered by models with independent gating particles, the more flexible Markov model is then introduced, where it is assumed that a channel can exist in a number of different states ranging from fully open to fully closed.

Chapter 6, Intracellular mechanisms. Ion channel dynamics are influenced heavily by intracellular ionic signalling. Calcium plays a particularly important role and models for several different ways in which calcium is known to have an effect have been developed. We investigate models of signalling involving calcium: via the influx of calcium ions through voltage-gated channels; their release from second messenger and calcium-activated stores; intracellular diffusion; and buffering and extrusion by calcium pumps. Essential background material on the mathematics of