Principles of Computational Modelling in Neuroscience

The nervous system is made up of a large number of interacting elements. To understand how such a complex system functions requires the construction and analysis of computational models at many different levels.

This book provides a step-by-step account of how to model the neuron and neural circuitry to understand the nervous system at all levels, from ion channels to networks. Starting with a simple model of the neuron as an electrical circuit, gradually more details are added to include the effects of neuronal morphology, synapses, ion channels and intracellular signalling. The principle of abstraction is explained through chapters on simplifying models, and how simplified models can be used in networks. This theme is continued in a final chapter on modelling the development of the nervous system.

Requiring an elementary background in neuroscience and some high-school mathematics, this textbook is an ideal basis for a course on computational neuroscience.

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Principles of Computational Modelling in Neuroscience

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<td>globus pallidus internal segment</td>
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<td>HVA</td>
<td>high-voltage-activated</td>
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<td>IP$_3$</td>
<td>inositol 1,4,5-triphosphate</td>
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<td>IPSC</td>
<td>inhibitory postsynaptic current</td>
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<td>ISI</td>
<td>interspike interval</td>
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<td>IUPHAR</td>
<td>International Union of Pharmacology</td>
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<td>KDE</td>
<td>kernel density estimation</td>
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<td>LGN</td>
<td>Lateral Geniculate Nucleus</td>
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<td>LTD</td>
<td>long-term depression</td>
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<td>LTP</td>
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<td>LVA</td>
<td>low-voltage-activated</td>
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<td>MAP</td>
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<td>MEPP</td>
<td>miniature endplate potential</td>
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<td>mGluR</td>
<td>metabotropic glutamate receptor</td>
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<td>MLE</td>
<td>maximum likelihood estimation</td>
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<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
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<td>magnetic resonance imaging</td>
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<tr>
<td>mRNA</td>
<td>messenger RNA</td>
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<tr>
<td>NACH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<td>ODE</td>
<td>ordinary differential equation</td>
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<td>PIP2</td>
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<td>PMCA</td>
<td>plasma membrane Ca(^{2+})-ATPase</td>
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<td>PSC</td>
<td>postsynaptic current</td>
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<td>PSD</td>
<td>postsynaptic density</td>
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<td>RBA</td>
<td>rapid buffer approximation</td>
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<td>RC</td>
<td>resistor–capacitor</td>
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<td>RGC</td>
<td>retinal ganglion cell</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<tr>
<td>RRVP</td>
<td>readily-releasable vesicle pool</td>
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<tr>
<td>SERCA</td>
<td>sarcoplasmic reticulum Ca(^{2+})-ATPase</td>
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<tr>
<td>SSA</td>
<td>Stochastic Simulation Algorithm</td>
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<td>STDP</td>
<td>spike-timing-dependent plasticity</td>
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<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
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<td>TET</td>
<td>tetraethylammonium</td>
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<td>TPC</td>
<td>two-pore-channels family</td>
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<td>TRP</td>
<td>transient receptor potential channel family</td>
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<td>TTX</td>
<td>tetrodotoxin</td>
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<td>VSD</td>
<td>voltage-sensitive domain</td>
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To understand the nervous system of even the simplest of animals requires an understanding of the nervous system at many different levels, over a wide range of both spatial and temporal scales. We need to know at least the properties of the nerve cell itself, of its specialist structures such as synapses, and how nerve cells become connected together and what the properties of networks of nerve cells are.

The complexity of nervous systems make it very difficult to theorise cogently about how such systems are put together and how they function. To aid our thought processes we can represent our theory as a computational model, in the form of a set of mathematical equations. The variables of the equations represent specific neurobiological quantities, such as the rate at which impulses are propagated along an axon or the frequency of opening of a specific type of ion channel. The equations themselves represent how these quantities interact according to the theory being expressed in the model. Solving these equations by analytical or simulation techniques enables us to show the behaviour of the model under the given circumstances and thus addresses the questions that the theory was designed to answer. Models of this type can be used as explanatory or predictive tools.

This field of research is known by a number of largely synonymous names, principally computational neuroscience, theoretical neuroscience or computational neurobiology. Most attempts to analyse computational models of the nervous system involve using the powerful computers now available to find numerical solutions to the complex sets of equations needed to construct an appropriate model.

To develop a computational model in neuroscience the researcher has to decide how to construct and apply a model that will link the neurobiological reality with a more abstract formulation that is analytical or computationally tractable. Guided by the neurobiology, decisions have to be taken about the level at which the model should be constructed, the nature and properties of the elements in the model and their number, and the ways in which these elements interact. Having done all this, the performance of the model has to be assessed in the context of the scientific question being addressed.

This book describes how to construct computational models of this type. It arose out of our experiences in teaching Masters-level courses to students with backgrounds from the physical, mathematical and computer sciences, as well as the biological sciences. In addition, we have given short computational modelling courses to biologists and to people trained in the quantitative sciences, at all levels from postgraduate to faculty members. Our students wanted to know the principles involved in designing computational models of the nervous system and its components, to enable them to develop their own models; and the mathematical basis of the models, but only in as far as it describes neurobiological processes. They wanted to have more than the basic recipes for running the simulation programs which now exist for modelling the nervous system at the various different levels.
This book is intended for anyone interested in how to design and use computational models of the nervous system. It is aimed at the postgraduate level and beyond. We have assumed a knowledge of basic concepts such as neurons, axons and synapses. The mathematics given in the book is necessary to understand the concepts introduced in mathematical terms. Therefore we have assumed some knowledge of mathematics, principally of functions such as logarithms and exponentials and of the techniques of differentiation and integration. The more technical mathematics have been put in text boxes and smaller points are given in the margins. For non-specialists, we have given verbal descriptions of the mathematical concepts we use.

Many of the models we discuss exist as open source simulation packages and we give links to these simulators. In many cases the original code is available.

We hope that several different types of people will be attracted to read this book and that these will include:

*The experimental neuroscientist.* We hope that the experimental neuroscientist will be interested in the computational approach to neuroscience.

*A teacher of computational neuroscience.* This book can be used as the basis of a hands-on course on computational neuroscience.

*An interested student from the physical sciences.* We hope that the book will motivate graduate students, post doctoral researchers or faculty members in other fields of the physical, mathematical or information sciences to enter the field of computational neuroscience.
Acknowledgements

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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.

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
# 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 \( P \):

\[
\frac{dP}{dt} = \frac{P}{\tau}
\]

where the proportionality constant is expressed in terms of the time constant, \( \tau \), 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 \( \frac{dP}{dt} \) depends on the Verhulst, or **logistic function** of the population \( P \):

\[
\frac{dP}{dt} = P(1 - P/K)/\tau.
\]

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 with population size \( N(t) \) and a predator with population 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:

\[
\frac{dN}{dt} = N(a - bP) \quad \frac{dP}{dt} = P(cN - d).
\]

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), predators are 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 reliably predict 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.
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):

\[
P(x) = \frac{(m^x/x!)}{e^m} \exp(-m).
\]

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, \( m \equiv \frac{V_e}{q} \), 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:

\[
m \equiv \frac{V_e}{q} = \frac{\ln \text{trials}}{\text{failures}}.
\]

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.

**Fig. 1.2**

(a) Quantal hypothesis of synaptic transmission.
(b) Example Poisson distribution of 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.
1.1 WHAT IS THIS BOOK ABOUT?

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.

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.

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.

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 (Chapter 8). 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 $-80\text{mV}$ 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 important 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 did 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
diffusion and electrodiffusion is included. We then review models for other intracellular signalling pathways which involve more complex enzymatic reactions and cascades. We introduce the well-mixed approach to modelling these pathways and explore its limitations. The elements of more complex stochastic and spatial techniques for modelling protein interactions are given, including use of the Monte Carlo scheme.

Chapter 7, The synapse, examines a range of models of chemical synapses. Different types of model are described, with different degrees of complexity. These range from electrical circuit-based schemes designed to replicate the change in electrical potential in response to synapse stimulation to more detailed kinetic schemes and to complex Monte Carlo models including vesicle recycling and release. Models with more complex dynamics are then considered. Simple static models that produce the same postsynaptic response for every presynaptic action potential are compared with more realistic models incorporating short-term dynamics producing facilitation and depression of the postsynaptic response. Different types of excitatory and inhibitory chemical synapses, including AMPA and NMDA, are considered. Models of electrical synapses are discussed.

Chapter 8, Simplified models of neurons, signals a change in emphasis. We examine the issues surrounding the construction of models of single neurons that are simpler than those described already. These simplified models are particularly useful for incorporating in networks since they are computationally more efficient, and in some cases they can be analysed mathematically. A spectrum of models is considered, including reduced compartmental models and models with a reduced number of gating variables. These simplifications make it easier to analyse the function of the model using the dynamical systems analysis approach. In the even simpler integrate-and-fire model, there are no gating variables, with action potentials being produced when the membrane potential crosses a threshold. At the simplest end of the spectrum, rate-based models communicate via firing rates rather than individual spikes. Various applications of these simplified models are given and parallels between these models and those developed in the field of neural networks are drawn.

Chapter 9, Networks of neurons. In order to construct models of networks of neurons, many simplifications will have to be made. How many neurons are to be in the modelled network? Should all the modelled neurons be of the same or different functional type? How should they be positioned and interconnected? These are some of the questions to be asked in this important process of simplification. To illustrate approaches to answering these questions, various example models are discussed, ranging from models where an individual neuron is represented as a two-state device to models in which model neurons of the complexity of detail discussed in Chapters 2–7 are coupled together. The advantages and disadvantages of these different types of model are discussed.

Chapter 10, The development of the nervous system. The emphasis in Chapters 2–9 has been on how to model the electrical and chemical properties of nerve cells and the distribution of these properties over the complex structures that make up the individual neurons of the nervous system and their connections. The existence of the correct neuroanatomy is
essential for the proper functioning of the nervous system, and here we discuss computational modelling work that addresses the development of this anatomy. There are many stages of neural development and computational models for each stage have been constructed. Amongst the issues that have been addressed are: how the nerve cells become positioned in 3D space; how they develop their characteristic physiology and morphology; and how they make the connections with each other. Models for development often contain fundamental assumptions that are as yet untested, such as that nerve connections are formed through correlated neural activity. This means that the main use of such models is in testing out the theory for neural development embodied in the model, rather than using an agreed theory as a springboard to test out other phenomena. To illustrate the approaches used in modelling neural development, we describe examples of models for the development of individual nerve cells and for the development of nerve connections. In this latter category we discuss the development of patterns of ocular dominance in visual cortex, the development of retinotopic maps of connections in the vertebrate visual system and a series of models for the development of connections between nerve and muscle.

Chapter 11, Farewell, summarises our views on the current state of computational neuroscience and its future as a major tool within neuroscience research. Major efforts to standardise and improve both experimental data and model specifications and dissemination are progressing. These will ensure a rich and expanding future for computational modelling within neuroscience.

The appendices contain overviews and links to computational and mathematical resources. Appendix A provides information about neural simulators, databases and tools, most of which are open source. Links to these resources can be found on our website: compneuroprinciples.org. Appendix B provides a brief introduction to mathematical methods, including numerical integration of differential equations, dynamical systems analysis, common probability distributions and techniques for parameter estimation.

Some readers may find the material in Chapters 2 and 3 familiar to them already. In this case, at a first reading they may be skipped or just skinned. However, for others, these chapters will provide a firm foundation for what follows. The remaining chapters, from Chapter 4 onwards, each deal with a specific topic and can be read individually. For example, a reader interested in developing a new ion channel model based on their experimental data can go straight to Chapter 5, or someone interested in simplified models can go to Chapter 8.
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 $-65$ 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.
The second part of this chapter explores basic properties of the 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** 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

<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, Ω)</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 <em>onto</em> (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
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.

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:

$$q = C \cdot V.$$  \hfill (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 concentration gradient \( \frac{d[X]}{dx} \) (here in one dimension):

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

(2.2)

where \( D_X \) is defined as the 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 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:

\[
J_{X, \text{drift}} = -\frac{D_X F}{R T} z_X [X] \frac{dV}{dx}
\]

(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.

![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.](image_url)
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):

$$J_X = J_{X, \text{diff}} + J_{X, \text{drift}} = -D_X \left( \frac{d[X]}{dx} + \frac{z_X F}{RT} [X] \frac{dV}{dx} \right). \quad (2.4)$$

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

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:

$$I_X = F z_X J_X \quad (2.5)$$

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 $Na^+$ 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:

$$I = I_{Na} + I_{K} + I_{Cl} = F z_{Na} J_{Na} + F z_{K} J_{K} + F z_{Cl} J_{Cl}. \quad (2.6)$$
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 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
Fig. 2.8 Setup of a thought experiment to explore the effects of diffusion across the membrane. In this experiment a container is divided by a membrane that is permeable to both K\(^+\), a cation, and anions, A\(^-\). The grey arrows indicate the diffusion flux of both types of ion. (a) Initially, the concentrations of both K\(^+\) and A\(^-\) are greater than their concentrations on the right-hand side. Both molecules start to diffuse through the membrane down their concentration gradient to the right. (b) Eventually the system reaches an equilibrium.

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 electric 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:

$$E_X = \frac{RT}{z_X F} \ln \left( \frac{[X]_{\text{out}}}{[X]_{\text{in}}} \right)$$  (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:

$$E_{K} = \frac{RT}{z_{K} F} \ln \left( \frac{[K^+]_{\text{out}}}{[K^+]_{\text{in}}} \right) = \frac{(8.314)(279.3)}{(+1)(9.648 \times 10^4)} \ln \frac{20}{400} = -72.1 \text{ mV}. \quad (2.8)$$

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.
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 throughout, so from Equation (2.4), the Nernst–Planck equation:

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

Integrating, we obtain:

\[
\int_0^X \frac{dV}{R} = \int_{X_{\text{in}}}^{X_{\text{out}}} \frac{RT}{zF[X]} d[X].
\]

Evaluating the integrals gives:

\[
E_m = \frac{RT}{zF} \ln \left( \frac{X_{\text{out}}}{X_{\text{in}}} \right)
\]

which is the Nernst equation, Equation (2.7).

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 \( \mu \)F cm\(^{-2} \) and 1.3 \( \mu \)F cm\(^{-2} \), and the specific capacitance can be treated as a ‘biological constant’ of 0.9 \( \mu \)F cm\(^{-2} \) (Gentet et al., 2000), which is often rounded up to 1 \( \mu \)F 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 fraction. The intracellular and extracellular concentrations can therefore be treated as constants.

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 Ca\(^{2+}\) 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
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>

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...
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 $500\pi \mu m^2$, and so its total capacitance is $500\pi \times 10^{-8} \mu F$ ($1 \mu F cm^{-2}$ is the same as $10^{-8} \mu F \mu m^{-2}$). As charge is the product of voltage and capacitance (Equation (2.1)), the charge on the membrane is therefore $500\pi \times 10^{-8} \times 70 \times 10^{-3} \mu C$. Dividing by Faraday’s constant gives the number of moles of monovalent ions that charge the membrane: $1.139 \times 10^{-17}$. The volume of the axonal section is $\pi(500/2)^2 \mu m^3$, which is the same as $\pi(500/2)^2 \times 10^{-15}$ litres. Therefore, if the concentration of potassium ions in the volume is 400 mM (Table 2.2), the number of moles of potassium ions is $\pi(500/2)^2 \times 10^{-15} \times 400 \times 10^{-3} = 7.85 \times 10^{-11}$. Thus, there are roughly 6.9 x $10^8$ times as many ions in the cytoplasm than on the membrane, and so in this case the potassium ions charging and discharging the membrane have a negligible effect on the concentration of ions in the cytoplasm. 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 0.08$\pi \mu m^2$ and its total capacitance is $C = 0.08\pi \times 10^{-8} \mu F = 0.08\pi \times 10^{-18} F$. The number of moles of calcium ions required to change the membrane potential by $\Delta V$ is $\Delta V = \frac{\Delta C}{\epsilon F}$, where $z = 2$ since calcium ions are doubly charged. If $\Delta V = 10$ mV, this is $10 \times 10^{-3} \times 0.08\pi \times 10^{-18}/(2 \times 9.468 \times 10^{10}) = 1.3 \times 10^{-22}$ moles. Multiplying by Avogadro’s number (6.0221 x $10^{23}$ 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 $\pi(0.4/2)^2 \times 0.2 \times 10^{-15} \times 70 \times 10^{-9} = 1.8 \times 10^{-24}$ 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.

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.
2.4 MEMBRANE IONIC CURRENTS NOT AT EQUILIBRIUM

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 $-72 \text{ mV}$, and the equilibrium potential of calcium is $+139 \text{ mV}$.

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 reverse 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 Na$^+$, K$^+$ and Cl$^-$, it reads:

$$E_m = \frac{RT}{F} \ln \left( \frac{P_{K}[K^{+}]_{out} + P_{Na}[Na^{+}]_{out} + P_{Cl}[Cl^{-}]_{in}}{P_{K}[K^{+}]_{in} + P_{Na}[Na^{+}]_{in} + P_{Cl}[Cl^{-}]_{out}} \right)$$  \hspace{1cm} (2.9)$$

where $P_{K}$, $P_{Na}$, and $P_{Cl}$ are the membrane permeabilities to K$^+$, Na$^+$ and 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 K$^+$, Na$^+$ and 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):

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

This equation predicts the net flow \( I_X \) per unit area of membrane, measured in \( \text{cm}^{-2} \) of an arbitrary ion type \( X \) with valency \( z_X \). \( P_X \) is the permeability of the membrane to ion \( X \), with units of \( \text{cm s}^{-1} \). 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 \( \text{mS cm}^{-2} \). 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.
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 $I$:

$$\frac{dV}{dt} = \frac{I}{C} = \frac{1}{C} \frac{dq}{dt}. \quad (2.11)$$

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 simple 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:

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

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

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

---

**Thévenin’s theorem** states that any combination of voltage sources and resistances across two terminals can be replaced by a single voltage source and a single series resistor. The voltage is the open circuit voltage $E$ at the terminals and the resistance is $E$ divided by the current with the terminals short circuited.

**An intensive quantity** is a physical quantity whose value does not depend on the amount or dimensions of the property being measured. An example of an intensive quantity is the specific membrane capacitance, the capacitance per unit area of membrane.
Kirchhoff’s current law is based on the principle of conservation of electrical charge. It states that at any point in an electrical circuit, the sum of currents flowing toward that point is equal to the sum of currents flowing away from that point.

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 $I_c$ and the ionic current $I_i$:

$$I_a + I_e = I_c + I_i$$

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

$$I_i = \frac{V - E_m}{R_m/a}$$

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

$$I_c = C_m \frac{dV}{dt}$$

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:

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

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:

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

This is an inverted decaying exponential that approaches the steady state value $E_m + R_m I_e/a$ 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:

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

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 $R_m C_m$. 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 $R_m C_m$ 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.
Table 2.3  Passive quantities

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Description</th>
<th>Typical units</th>
<th>Relationships</th>
</tr>
</thead>
<tbody>
<tr>
<td>(d)</td>
<td>Diameter of neurite</td>
<td>µm</td>
<td></td>
</tr>
<tr>
<td>(l)</td>
<td>Length of compartment</td>
<td>µm</td>
<td></td>
</tr>
<tr>
<td>(R_m)</td>
<td>Specific membrane resistance</td>
<td>Ω cm(^2)</td>
<td>(r_m = \frac{d}{\pi l})</td>
</tr>
<tr>
<td>(C_m)</td>
<td>Specific membrane capacitance</td>
<td>µF cm(^{-2})</td>
<td>(c_m = \frac{C_m}{\pi d})</td>
</tr>
<tr>
<td>(R_a)</td>
<td>Specific axial resistance (resistivity)</td>
<td>Ω cm</td>
<td></td>
</tr>
<tr>
<td>(r_m)</td>
<td>Membrane resistance per inverse unit length</td>
<td>Ω cm</td>
<td></td>
</tr>
<tr>
<td>(c_m)</td>
<td>Membrane capacitance per unit length</td>
<td>µF cm(^{-1})</td>
<td></td>
</tr>
<tr>
<td>(r_a)</td>
<td>Axial resistance per unit length</td>
<td>Ω/cm</td>
<td>(r_a = \frac{4d}{\pi a})</td>
</tr>
<tr>
<td>(V)</td>
<td>Membrane potential</td>
<td>mV</td>
<td></td>
</tr>
<tr>
<td>(E_m)</td>
<td>Leakage reversal potential due to different ions</td>
<td>mV</td>
<td></td>
</tr>
<tr>
<td>(I)</td>
<td>Membrane current density</td>
<td>µA cm(^{-2})</td>
<td></td>
</tr>
<tr>
<td>(I_e)</td>
<td>Injected current</td>
<td>nA</td>
<td></td>
</tr>
<tr>
<td>(I_c)</td>
<td>Capacitive current</td>
<td>nA</td>
<td></td>
</tr>
<tr>
<td>(I_i)</td>
<td>Ionic current</td>
<td>nA</td>
<td></td>
</tr>
</tbody>
</table>

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 cm\(^{-2}\) and S 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.

1 and 20 ms. It is possible to measure the membrane time constant for use in a model RC type circuit. The assumptions that are made when doing this and the effects of measurement accuracy are discussed in Chapter 4.

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:

\[
R_{in} = \frac{V_\infty - E_m}{I_e}.
\]  

(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 \(R_{in} = R_m/a\). 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
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 \( \Omega \cdot cm \) 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 \( I_{a,j} \) 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:

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

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

\[
I_{c,j} + I_{e,j} = I_{a,j} + I_{c,j}
\]

\[
I_{c,j} + I_{e,j} = \frac{V_{j+1} - V_j}{4R_a l/\pi d^2} + \frac{V_{j-1} - V_j}{4R_a l/\pi d^2} + I_{e,j}.
\] (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 \( j + 1 \):

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

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

\[
C_m \frac{dV_j}{dt} = \frac{E_m - V_j}{R_m} + \frac{d}{4R_a} \left( \frac{V_{j+1} - V_j}{l^2} + \frac{V_{j-1} - V_j}{l^2} \right) + I_{e,j}.
\] (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
membrane potential is now going to vary over space and time, the spatial variations being from compartment to compartment.

Before looking at examples of the spatiotemporal evolution of the membrane potential, consider the steady state behaviour. If current is injected for long enough, the membrane potential in each compartment will stabilise. Figure 2.17a shows the simulated steady state membrane potential along a cable in response to continuous current injection at a point ($x = 0 \mu m$). The membrane potential is highest nearest to the point of current injection. The injected current flows down the cable, gradually leaking out through the membrane resistances. This results in the membrane potential decaying further away from the site of injection.

An example of the time-dependent behaviour of the membrane potential is shown in Figure 2.17b. To simulate synaptic input, a pulse of current is injected at time zero at a ‘synapse’ at one end of the cable, and the membrane potential is measured at different points along the cable. The membrane potential close to the point of injection peaks quickly and has greater amplitude than the membrane potential measured further away from the synapse. After about 2 ms, the membrane potential measured at the different points converges and decays slowly. This example demonstrates that the further away a synaptic input is from some point on a neuron, the lower the amplitude of the EPSP measured at that point is expected to be. Thus, in less idealised neurons, synaptic inputs to distal parts of the dendritic tree are expected to be attenuated more on their way to the soma, or cell body, than inputs to the proximal dendritic tree.

### 2.9 The cable equation

We saw in Section 2.6 that it is possible to analytically solve the equation representing a single membrane compartment. This gave us an equation from which it is easy to see the basis for the time course of the membrane

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**Fig. 2.17** (a) Steady state membrane potential as a function of distance in a semi-infinite cable in response to current injection at one end ($x = 0 \mu m$). The parameters are $d = 1 \mu m$, $R_a = 35.4 \Omega \text{cm}$, $R_m = 10 k\Omega \text{cm}^2$, which, from Equation (2.26), gives the length constant $\lambda = 840 \mu m$. (b) Top: a simulated excitatory postsynaptic current (EPSC). Below: the membrane potential measured at different points along a cable in response to the EPSC evoked at one end of the cable (site indicated by triangle). The colour of each trace corresponds to the locations of the electrodes. The neurite is 500 $\mu m$ long and other parameters are the same as the semi-infinite cable shown in (a).
potential, and the important concept of the membrane time constant. In
the preceding section, extra compartments were added to allow spatially ex-
tended neurites to be described, but this has come at the expense of being
able to solve the equations analytically. Although modern computers can nu-
merically integrate the equations of the compartmental model at very high
spatial resolutions by using many compartments, looking at analytical solu-
tions can give a deeper understanding of the behaviour of the system.

In this section, we introduce the cable equation, which allows the spa-
tiotemporal 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 split-
ting a neurite into an infinite number of infinitesimally small compartments.
The cable equation is a partial differential equation (PDE) with the form:

\[ C_m \frac{\partial V}{\partial t} = E_m - \frac{V}{R_m} + \frac{d}{4R_a} \frac{\partial^2 V}{\partial x^2} + \frac{I_e}{\pi d}. \] (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 compart-
ment (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 approxi-
mately 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 analyt-
ical solution to Equation (2.24), along with the sealed end boundary condi-
tions (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:

\[ V(x) = E_m + R_{\infty} I_e e^{-x/\lambda}. \] (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.
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:

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

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:

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

(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 curly 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:

\[
\frac{d}{4R_a} \frac{V_1 - V_0}{\pi d \delta x} = \frac{l_e(0, t)}{\pi d} + \frac{E_m - V_1}{\pi d R_L}.
\]

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:

\[
R_\infty = \frac{R_m}{\pi d \lambda} = \sqrt{\frac{4R_m R_a}{\pi^3 d^3}} = \sqrt{r_m r_a}.
\]  

(2.27)

This tells us that we should expect the input resistance of smaller neurites to be higher than that of larger ones. This means that a given injection current will have a greater effect on the membrane potential of a smaller 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 \( I \) 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 THE CABLE EQUATION

The cable equation is a mathematical model that describes the distribution of electrical potential along a cable, such as a neuron, as a function of distance and time. The equation is given by

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

---

The two blue lines show what happens under a killed end condition. The membrane potential at the far end of the cable is equal to the extracellular membrane potential (0 mV). This is because the circuit is effectively 'short circuited' by a zero end resistance.

The two dotted grey lines show what happens when there is a leaky end to the cable. Here, there is a finite resistance \( R_L \) at the cable end. The upper dotted line shows the situation when \( R_L \) is greater than \( R_\infty \) and the lower line shows \( R_L \) being less than \( R_\infty \). The importance of this situation will become apparent in Chapter 4, where we consider simplifying branched dendrites.

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:

\[ V(x, t) = C_0(x)e^{-t/\tau_2} + C_1(x)e^{-t/\tau_1} + C_2(x)e^{-t/\tau_2} + \ldots \] (2.28)
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 $R_\ell$ at the end of a leaky cable and injection current $I_e$, the membrane potential as a function of length $X$ is given by:

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

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:

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

In the case of a sealed end, where $R_\ell = \infty$, 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:

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

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

$$\coth x = \frac{\cosh x}{\sinh x} = \frac{e^x + e^{-x}}{e^x - e^{-x}}.$$
**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). This 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 $V/V_0 = \frac{1}{6}(1 - \exp(-t/\tau)) + \frac{5}{6} \text{erf}\sqrt{T/\tau}$, 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 erf $x$ is the area under the Gaussian $\frac{1}{\sqrt{\pi}} \exp(u^2)$ 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,
The basis of electrical activity in the neuron

**Fig. 2.19** Membrane charging curves in three models. The thick black line shows the original data of Coombs et al. (1956). The solid black curve shows the membrane charging curve of a point neuron with a membrane time constant of 5 ms. The blue curve shows the charging curve of a ‘ball and stick’ neuron in which the membrane time constant is 5 ms. The dashed black curve shows the charging curve of a point neuron which has a membrane time constant of 2.5 ms. It can be seen that the charging curve of the ball and stick neuron is similar to the curve of the point neuron with a membrane time constant a factor of two smaller. All membrane potentials are shown relative to the resting potential, and as a fraction of the steady state displacement of the membrane potential from rest $V_0$.

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 $\text{Ca}^{2+}$. 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 $R_a$, have on the membrane potential over the length of the cable.
Chapter 3

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 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.
Box 3.1 The voltage clamp

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 remains at the desired steady value or time-varying profile waveform.

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 capacitative and an ionic current (Equation (3.1)). When the voltage clamp is used to set the membrane potential to a constant value, no capacitative 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:

$$I = I_c + C_m \frac{dV}{dt} + I_i, \quad (3.1)$$

where the membrane current $I$ and the capacitative 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:

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

$$I_K = g_K(V - E_K), \quad (3.4)$$

$$I_L = \overline{g}_L(V - E_L), \quad (3.5)$$

where the sodium, potassium and leak conductances are $g_{Na}$, $g_K$ and $\overline{g}_L$ respectively, and $E_{Na}$, $E_K$ and $E_L$ are the corresponding equilibrium potentials. The bar on the leakage conductance $\overline{g}_L$ indicates that it is a constant, in contrast with the sodium and potassium conductances which depend on the recent history of the membrane potential.

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**Fig. 3.2** The Hodgkin–Huxley equivalent electrical circuit.
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 3.1 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 depolarisation, 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
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 (Section 3.2.1).

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, $n^4$.

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:

$$g_K = g_K n^4.$$  \hfill (3.6)

If each potassium gate were dependent solely on a single theoretical gating particle, the conductance would be $g_K n$. 

---

**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 (Section 3.2.1).

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).
Fig. 3.5 A family of curves showing the time course of $n$ raised to various powers. From top to bottom curves with $n$ raised to the power 1, 2, 3 and 4 are shown. The parameters are as in Figure 3.4: $\tau_n(V_0) = 1.1$ ms, $\tau_n(V_1) = 0.75$ ms, $g_{K\infty}(V_0) = 0.09$ mS cm$^{-2}$ and $g_{K\infty}(V_1) = 7.06$ mS cm$^{-2}$. To compare the curves, the time course of $n$ raised to the powers 2, 3 and 4 have initial and final values of $g_{K\infty}$ given by $(g_{K\infty}/g_{K\infty})^{1/2}$, $(g_{K\infty}/g_{K\infty})^{1/3}$, and $(g_{K\infty}/g_{K\infty})^{1/4}$. The circular data points shown are the same as in Figure 3.4. Adapted from Hodgkin and Huxley (1952d), with permission from John Wiley & Sons Ltd.

The movement of a gating particle between its closed (C) and open (O) positions can be expressed as a reversible chemical reaction:

$$C \xrightleftharpoons{\beta_n}{\alpha_n} O.$$ (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:

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \quad \text{and} \quad \tau_n = \frac{1}{\alpha_n + \beta_n},$$ (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:

\[
n_{\infty}(V) = \left( \frac{g_{K,\infty}(V)}{g_K} \right)^{\frac{1}{2}}.
\] (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
$n_\infty$ and $\tau_n$ plots. The equations for the functions $\alpha_n(V)$ and $\beta_n(V)$ are given in the summary of the entire set of equations describing the potassium ionic current through the membrane:

$$I_K = g_K n^4 (V - E_K)$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\alpha_n = 0.01 \frac{V + 55}{1 - \exp(-(V + 55)/10)}$$

$$\beta_n = 0.125 \exp(-(V + 65)/80)$$

### 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 $n$:

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h.$$
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 \( \beta_m \):

\[
\frac{dm}{dt} = \alpha_m(1 - m) - \beta_mm.
\]  
(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:

\[
g_{Na} = g_{Na}m^3h
\]  
(3.17)

This enabled a good fit to be made to experimental recordings by adjusting \( m_\infty \), \( \tau_m \) for different holding potentials and \( g_{Na} \) 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 \((\alpha_m, \beta_m, \alpha_h, \beta_h)\) 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:

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

\[
\frac{dm}{dt} = \alpha_m(1 - m) - \beta_mm,
\]

\[
\frac{dh}{dt} = \alpha_h(1 - h) - \beta_hh,
\]

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

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

$$I_L = \frac{g_L}{V}(V - E_L). \quad (3.19)$$

Although the leak conductance $g_L$ 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:

$$C_m \frac{dV}{dt} = -\frac{g_L}{V}(V - E_L) - \frac{g_{Na}}{V}m^3h(V - E_{Na}) - \frac{g_K}{V}n^4(V - E_K) + I, \quad (3.20)$$

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 2.6. 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 $-41 \text{ mV}$ above resting potential, there is virtually no response to the test pulse. Conversely, when the membrane is hyperpolarised to beyond $-116 \text{ mV}$ 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 (i.e. including spatial spread of current from local circuits):

\[ C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{Na}m^3h(V - E_{Na}) - g_Kn^4(V - E_K) + \frac{d}{4R_a} \frac{d^2V}{dx^2}. \]

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

\[ C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{Na}m^3h(V - E_{Na}) - g_Kn^4(V - E_K). \]

Sodium activation and inactivation gating variables:

\[
\begin{align*}
\frac{dm}{dt} &= \alpha_m(1 - m) - \beta_m m, \\
\frac{dh}{dt} &= \alpha_h(1 - h) - \beta_h h,
\end{align*}
\]

\[
\begin{align*}
\alpha_m &= 0.1 \frac{V + 40}{1 - \exp(-(V + 40)/10)}, \\
\beta_m &= 4 \exp(-(V + 65)/18), \\
\alpha_h &= 0.07 \exp(-(V + 65)/20), \\
\beta_h &= \frac{1}{\exp(-(V + 35)/10) + 1}.
\end{align*}
\]

Potassium activation gating variable:

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

\[
\begin{align*}
\alpha_n &= 0.01 \frac{V + 55}{1 - \exp(-(V + 55)/10)}, \\
\beta_n &= 0.125 \exp(-(V + 65)/80).
\end{align*}
\]

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

\[
\begin{align*}
C_m &= 1.0 \mu F \text{ cm}^{-2} \\
E_{Na} &= 50 \text{ mV} \\
E_K &= -77 \text{ mV} \\
E_L &= -54.4 \text{ mV} \\
\sigma_{Na} &= 120 \text{ mS cm}^{-2} \\
\sigma_K &= 36 \text{ mS cm}^{-2} \\
\sigma_L &= 0.3 \text{ mS cm}^{-2}
\end{align*}
\]

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 (Figure 3.10). Secondly, the prolonged activation of the potassium conductance means that any inward sodium current has to counteract a more considerable outward potassium current than in the resting state. Hodgkin and Huxley’s simulations (Figure 3.13) confirmed this view, and were in broad agreement with their experiments.

### 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 m s\(^{-1}\), close to the experimental value of 21.2 m s\(^{-1}\) at 18.5°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
Fig. 3.13 Refractory properties of the HH model. Upper curves are calculated membrane action potentials at 6.3°C. Curve a is the response to a fast current pulse that delivers 15 nC cm$^{-2}$. Curves b to d are the responses to a charge of 90 nC cm$^{-2}$ delivered at different times after the initial pulse. Adapted from Hodgkin and Huxley (1952d), with permission from John Wiley & Sons Ltd.

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:

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

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:

$$\alpha(V, T_2) = \alpha(V, T_1)Q_{10}^{T_2-T_1} \quad \text{and} \quad \beta(V, T_2) = \beta(V, T_1)Q_{10}^{T_2-T_1}. \quad (3.22)$$
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 $Q_{10}^{(T_2-T_1)/10}$ 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 of $Q_{10}$ 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 $g_X(T_1)$ at temperature $T_1$, at temperature $T_2$ it will be given by:

$$g_X(T_2) = g_X(T_1)Q_{10}^{T_2-T_1}/10.$$  \hspace{1cm} (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

**Fig. 3.14** Calculated and recorded propagating action potentials. (a) Time course of action potential calculated from the Hodgkin–Huxley equations. The conduction velocity was 18.8 m s$^{-1}$ and the temperature 18.5°C. (b) Same action potential at a slower timescale. (c) Action potential recorded from squid giant axon at 18.5°C on same time scale as simulation in (a). (d) Action potential recorded from a different squid giant axon at 19.2°C at a slower timescale. Adapted from Hodgkin and Huxley (1952d), with permission from John Wiley & Sons Ltd.
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 through 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:

\[ I_{Na}(t) = \rho_{Na}(t) \frac{F^2V(t)}{RT} \left( \frac{[Na^+]_{in} - [Na^+]_{out}e^{-FV(t)/RT}}{1 - e^{-FV(t)/RT}} \right), \quad (3.24) \]

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 \( \rho_{Na} = \bar{\rho}_{Na}m^2h \)) 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; namely, 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
3.5 BUILDING MODELS USING THE HH FORMALISM

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 capacitative surge.

that it took 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 (to be discussed in Section 5.3.2), or expression in oocytes (to be discussed in 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 piece-wise 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 branch points, varicosities, axon tapering and so on 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.
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Quantitative Neurophysiology

Joseph V. Tranquillo
Bucknell University

SYNTHESIS LECTURES ON BIOMEDICAL ENGINEERING #21
ABSTRACT
Quantitative Neurophysiology is supplementary text for a junior or senior level course in neuroengineering. It may also serve as a quick-start for graduate students in engineering, physics or neuroscience as well as for faculty interested in becoming familiar with the basics of quantitative neuroscience. The first chapter is a review of the structure of the neuron and anatomy of the brain. Chapters 2–6 derive the theory of active and passive membranes, electrical propagation in axons and dendrites and the dynamics of the synapse. Chapter 7 is an introduction to modeling networks of neurons and artificial neural networks. Chapter 8 and 9 address the recording and decoding of extracellular potentials. The final chapter has descriptions of a number of more advanced or new topics in neuroengineering. Throughout the text, vocabulary is introduced which will enable students to read more advanced literature and communicate with other scientists and engineers working in the neurosciences. Numerical methods are outlined so students with programming knowledge can implement the models presented in the text. Analogies are used to clarify topics and reinforce key concepts. Finally, homework and simulation problems are available at the end of each chapter.

KEYWORDS
Neurophysiology, neuroengineering, neuroscience, electrophysiology, biomedical engineering, neuron, neural signal processing, neural anatomy, brain, CNS
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The function of the brain and connection to the mind is perhaps one of the most enigmatic pursuits in all of science. Some have even dubbed the study of the brain the final frontier. Others claim that we will never know exactly how our brain works. We do, however, understand a great deal about the brain, as evidenced by nearly 100 years of Nobel Prizes.

<table>
<thead>
<tr>
<th>Year</th>
<th>Winners</th>
<th>For</th>
</tr>
</thead>
<tbody>
<tr>
<td>1906</td>
<td>Golgi and Cajal</td>
<td>Structure of the nervous system</td>
</tr>
<tr>
<td>1920</td>
<td>Nernst</td>
<td>Membrane potentials</td>
</tr>
<tr>
<td>1932</td>
<td>Sherrington and Adrian</td>
<td>The synapse</td>
</tr>
<tr>
<td>1936</td>
<td>Dale and Loewi</td>
<td>Chemical propagation across a synapse</td>
</tr>
<tr>
<td>1944</td>
<td>Erlanger and Gasser</td>
<td>Differentiation of nerve fibers</td>
</tr>
<tr>
<td>1949</td>
<td>Hess</td>
<td>Role of interbrain in regulation</td>
</tr>
<tr>
<td>1950</td>
<td>Kendall, Reichstein and Hench</td>
<td>Hormones in the adrenal cortex</td>
</tr>
<tr>
<td>1963</td>
<td>Eccles, Hodgkin and Huxley</td>
<td>Ionic mechanisms of action potentials</td>
</tr>
<tr>
<td>1970</td>
<td>Katz, Euler and Axelrod</td>
<td>Function of neurotransmitters</td>
</tr>
<tr>
<td>1977</td>
<td>Guillemin and Schally</td>
<td>Neurohormones in the brain</td>
</tr>
<tr>
<td>1981</td>
<td>Sperry, Hubel and Wiesel</td>
<td>Specialization of cerebral hemispheres</td>
</tr>
<tr>
<td>1991</td>
<td>Neher and Sakmann</td>
<td>Function of single ion channels</td>
</tr>
<tr>
<td>1994</td>
<td>Gilman and Rodbell</td>
<td>G-proteins in signal transduction</td>
</tr>
<tr>
<td>1997</td>
<td>Prusiner</td>
<td>Prions as a principle for infection</td>
</tr>
<tr>
<td>2000</td>
<td>Carlsson, Greengard and Kandel</td>
<td>Dopamine signal transduction</td>
</tr>
<tr>
<td>2003</td>
<td>Lauterbur and Mansfield</td>
<td>Magnetic Resonance Imaging (MRI)</td>
</tr>
<tr>
<td>2003</td>
<td>Agre and MacKinnon</td>
<td>Ion channel selectivity</td>
</tr>
</tbody>
</table>

The objective of "Quantitative Neurophysiology" is to provide an overview of the theory underlying electrical impulses in the neuron. The material presented is purposely distinct from a traditional neuroscience text in that it is geared toward engineers and applied scientists. As such the focus will be place more on neurons in the central nervous system, where a deep quantitative understanding has been developed, and less on the large-scale functions of the brain. Despite this narrow focus you will find some classic neuroscience woven into the text.

For the student, it is hoped that you will see concrete applications of fundamental engineering and science concepts in the description of a real biological system. It will be most helpful if you have already taken differential equations as well as a basic circuits course. The philosophy of the text is that by understanding the mathematical models of neuronal function (Chapters 2-6), you will gain a deeper understanding of how neurons work together to create complex behavior (Chapter 7) and how we might listen in on the chatter of neurons to unravel their language (Chapters 8-9). Finally, the theory presented...
should prepare you to read the latest neuroengineering literature and move on to more advanced topics (Chapter 10).

For the instructor, it is hoped that this text will provide a resource that can aid you in your instruction. I have found that students are capable of digesting one chapter each week (≈3 hours of class time, supplemented by homework problems). At the end of each chapter are homework and simulation problems which can be assigned as is, or modified to better suit the abilities of the students. This schedule leaves ample time to cover more advanced topics at the instructor’s discretion.

This text would not be possible without the support of two important groups. First, I wish to thank the Bucknell students who have taken my Neural Signals and System course. Second, I wish to thank my family for their patience and keeping me focused on what is really important in life.

Joseph V. Tranquillo
Lewisburg, Pennsylvania
The brain may be studied at many scales, ranging from molecular to gross anatomy. In this text, the focus will be primarily on quantifying cellular behavior for two reasons. First, much more is known about the function of individual neurons. Second, an underlying assumption of neuroscience is that a complete understanding of brain function will require deep insights at the cell and molecular level. In this chapter, the anatomy of the neuron is explored to the depth needed to understand future chapters. It is very important, however, to not lose sight of the goal of understanding the brain at the larger scales. Therefore, this chapter also outlines some of the gross level structures of the brain.

1.1 THE NEURON

The human brain is composed of more than $10^{12}$ neurons. The table below is a summary of some types of neurons.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar</td>
<td>Found in eye, transduction of light to neural impulse</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>Found in skin, tactile senses of pain and proprioception</td>
</tr>
<tr>
<td>Motor</td>
<td>Found in spinal cord, projects to muscles</td>
</tr>
<tr>
<td>Pyramidal cell</td>
<td>Found in cortex, relay information within brain</td>
</tr>
<tr>
<td>Purkinje Cell</td>
<td>Found in cerebellum, motor skills</td>
</tr>
<tr>
<td>Association cell</td>
<td>Found in thalamus, connect neurons together</td>
</tr>
</tbody>
</table>

Although the anatomy and function of the individual neuron can vary throughout the brain, Fig. 1.1 shows the features of a generic neuron. Like other cells, the neuron separates space inside from space outside by a $5 \text{nm}$ bi-lipid membrane that acts as an electrical insulator. Typically, the neuron is divided into the dendritic tree, soma, and axon.

The dendritic tree is a complex web of branching structures that range in diameter from $1-20 \mu m$. One interesting feature of some dendrites is the presence of spines that play a somewhat unclear electrical or chemical role in neuronal function.

The soma, or cell body, is approximately $20 \mu m$ in diameter and contains most of the organelles, including the nucleus, Golgi apparatus, mitochondria, microtubules, and endoplasmic reticulum. It is here that the cell generates ATP, packages neurotransmitters, houses the genetic material, and assembles proteins for the cell.

The axon branches off of the soma at the axon hillock. Axons can vary greatly in length ($1 \text{mm} - 1 \text{m}$) and diameter ($1-25 \mu m$). The intracellular space of the axons are covered in small specialized proteins called legs kinesin which mechanically transport ATP, vesicles filled with neurotransmitter and enzymes to and from the soma. Some axons have offshoots called axon collaterals.

The synapse is the site where the dendrite of one neuron interfaces with the axon of another neuron. It was first described in 1897 by Sherrington who coined the term from the Greek, Syn (together) +
Haptin (to fasten). There are approximately $10^{15}$ synapses in the brain, so each neuron has on average 1,000 synapses. The number of synapses in an individual neuron, however, can vary greatly. It is important to note that the synapse is not a singular structure, but rather the combination of three structures. The pre-synapse is the very end of an axon and houses vesicles, or small spheres of membrane, that contain neurotransmitters. The post-synapse is on the very end of a dendrite. The 20nm space between the pre-synapse and post-synapse is called the synaptic cleft and is technically outside of both neurons.

Neurotransmitters are specialized molecules that are packaged into vesicles in the soma, transported to the end of the pre-synaptic axon by the legs kinesin, and released into the synaptic cleft in response to an electric impulse. Neurotransmitters diffuse across the synaptic cleft and reach the post-synapse where they either excite or inhibit electrical impulses in the dendrite of a new neuron. There is enormous diversity in the molecules that function as neurotransmitters as well as the mechanisms by which they affect the post-synapse.
To indicate the direction of ionic or molecular movement in a neuron, two sets of terms have been defined. When discussing motion within the axon, **anterograde** is movement from the soma to the end of the axons and **retrograde** is movement from the axon to the soma. To discuss movement in the entire neuron, **orthodromic** is in the direction from the axon to the dendrites, while **antidromic** is from the dendrites to the axon.

### 1.2 GLIAL CELLS

Although often overlooked, *glial cells* in the brain outnumber neurons nearly two to one. Historically, glial cells were thought to only impact electrical properties indirectly by maintaining extracellular ion concentrations and by speeding electrically propagation through the growth of the *myelin sheath*. Recent evidence, however, suggests that glial cells may play a more direct role in the propagation of impulses. Some of the more common types of glial cells are listed in the table below.

<table>
<thead>
<tr>
<th>Table 1.2:</th>
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</thead>
<tbody>
<tr>
<td><strong>Astroglia</strong></td>
</tr>
<tr>
<td><strong>Oligodendroglia</strong></td>
</tr>
<tr>
<td><strong>Schwann Cells</strong></td>
</tr>
<tr>
<td><strong>Microglia</strong></td>
</tr>
<tr>
<td><strong>Ependymal cells</strong></td>
</tr>
</tbody>
</table>

### 1.3 THE BRAIN

While our primary focus will be on quantifying the function of nerve cells, it is important not to lose sight of the fact that our brain regulates nearly all voluntary and involuntary actions. It is often reported that we only use 10% of our brain, with the implication that there is 90% of the brain that we do not understand. The 10% number is the percentage of the brain that is active *at any one time*. Each structure of the brain is known to perform some function. What is not clear is how these structures use neurons to perform their functions. Below is a brief overview of the structure and function of the most significant regions of the brain.

### 1.3.1 From Neuron to Nuclei

Typically, cells that are close to one another are more densely connected by synapses and perform similar functions. These groupings of cells form a *nucleus*. In histological slices, the dense tangle of cell bodies, dendrites, and capillaries have a grayish color and so have been given the name *grey matter*. Several nuclei may be connected together to form larger structures in the brain. The connections between nuclei are made by bundles of long axons, called *tracts*, that may carry large amounts of information. Long axons require fast propagation and so are covered in a fatty coating of myelin. In histological slices, these dense regions of axons have a white color and so have been given the name *white matter*. 
1.3.2 Brain Systems
The gross anatomy of the brain consists of both tissue (neurons and glia) as well as chambers called ventricles that are filled with cerebral-spinal fluid. The tissue is organized into three regions based upon embryonic development.

The hindbrain, or Rhombencephalon, is an offshoot of the spinal cord and was inherited from the reptile brain. It is primarily involved in involuntary control of basic functions such as breathing and heart rate. In addition to forming the lower portion of the brain stem, it also includes the cerebellum, a relatively large outcropping at the base of the brain that controls motor movements and relays signals to the spinal cord.

<table>
<thead>
<tr>
<th>Table 1.3:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelencephalon</td>
</tr>
<tr>
<td>Metencephalon</td>
</tr>
<tr>
<td>Pons</td>
</tr>
<tr>
<td>Cerebellum</td>
</tr>
<tr>
<td>Reticular Formation</td>
</tr>
</tbody>
</table>

The midbrain, or Mesencephalon, forms the upper part of the brain stem. Its primary function is to connect the lower brain stem with higher-level brain structures. In size, it is much smaller than the other two embryonic regions. It is involved in involuntary motor control and sensation.
The forebrain, or Prosencephalon, forms the bulk of the brain tissue in mammals. It contains the limbic system that regulates drives, hunger, hormones, emotions, and memory, as well as the cerebral cortex. The regions of the forebrain are tightly connected together by tracts in complex feedback networks.

### Table 1.4:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Location</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diencephalon</td>
<td>Lateral and 3rd ventricles, limbic system</td>
<td></td>
</tr>
<tr>
<td>Epithalamus</td>
<td>Pineal body, wake/sleep patterns</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Relay information to cerebral cortex</td>
<td></td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Link to endocrine system, metabolism, hunger</td>
<td></td>
</tr>
<tr>
<td>Pituitary Gland</td>
<td>Master endocrine gland</td>
<td></td>
</tr>
<tr>
<td>Telencephalon</td>
<td>Also called the cerebrum</td>
<td></td>
</tr>
<tr>
<td>White Matter</td>
<td>Axons that connect cortex to other structures</td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>Process memory and emotions</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Process memory and spatial navigation</td>
<td></td>
</tr>
<tr>
<td>Rhinencephalon</td>
<td>Olfaction (smell)</td>
<td></td>
</tr>
<tr>
<td>Cerebral Cortex</td>
<td>Higher level tasks</td>
<td></td>
</tr>
</tbody>
</table>

The cerebral cortex occupies the top 2–4 mm of the forebrain and is composed of grey matter organized into six layers. The cortex is split into a number of lobes which are roughly mirrored on left and right hemispheres of the brain.

### Table 1.5:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Location</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Lobe</td>
<td>Behind forehead</td>
<td>Impulse control, language</td>
</tr>
<tr>
<td>Parietal Lobe</td>
<td>Crown of head</td>
<td>Sensory, numbers</td>
</tr>
<tr>
<td>Temporal Lobe</td>
<td>Behind temples</td>
<td>Auditory, speech, and vision</td>
</tr>
<tr>
<td>Occipital Lobe</td>
<td>Back of head</td>
<td>Primary visual center</td>
</tr>
<tr>
<td>Insula</td>
<td>Between temporal and parietal</td>
<td>Emotions, pain, addition</td>
</tr>
<tr>
<td>Cingulate Cortex</td>
<td>Surrounds the corpus callosum</td>
<td>Emotions</td>
</tr>
<tr>
<td>Corpus Collosum</td>
<td>Connection between hemispheres</td>
<td>Millions of axons</td>
</tr>
</tbody>
</table>

### 1.3.3 Blood Brain Barrier

In the body, capillaries are lined with endothelial cells that contain small gaps, allowing for easy diffusion of chemicals and gasses to and from the blood. In the brain, a similar membrane, called the blood brain barrier, is present but the cells are more packed tightly so that most chemicals can not diffuse through. The only chemicals that can pass are either lipid soluble (e.g., O₂, CO₂, ethanol, steroid hormones) or carried by a specific channel (e.g., sugars, amino acids). The result is that the brain is able to maintain a high rate of metabolism but is protected from potentially dangerous chemicals and infections. In addition, glial cells surround capillaries in the brain, forming a second barrier. There are, however, a few entry points...
that allow the brain to sense the concentrations of hormones in the blood. The downside of the blood brain barrier is that it is difficult to design drugs that will work directly on the brain.

1.3.4 Directions in the Brain
Directions in the brain are the same as in the body. Anterior refers to the front of the brain while posterior is toward the back. Medial is toward the center of the brain while lateral is away from the center. Superior (also dorsal) is toward the top of the brain while interior (also ventral) is toward the base of the brain.

Two additional terms are used in the brain that trace a curved line from the bottom of the spinal cord to the nose (or frontal lobe). Moving in a rostral direction is moving toward the nose. Moving in a caudal direction is moving toward the bottom of the spinal cord.

1.3.5 Inputs and Outputs
The focus of the text is on neurons in the central nervous system. The mathematical models, however, apply equally well to neurons in the peripheral nervous system. We therefore briefly mention that the brain interacts with neurons in the body. Neural inputs to the brain typically originate from sensory systems. Neurons that carry impulses to the brain are called afferent, sensory or receptor nerves. Typically, these nerves originate in a sensory system such as the eyes or nose. Neurons that carry impulses away from the brain are called efferent, motor or effector nerves. Typically, they will innervate muscles or glands.
Electrophysiology is the study of the electrical properties of biological materials from the molecules to the entire body. Although all materials in the body can be characterized by their electrical properties, the nervous and muscular system in particular use electrical impulses to communicate information between cells. In this chapter, we will lay down the basic principles of cellular electrophysiology which may be applied to any cell in the body. In Ch. 3, we will consider the more specialized electrical properties of neurons.

### 2.1 CELLULAR ELECTROPHYSIOLOGY

As we are primarily concerned with electrical properties, we must first define what voltages (difference in potential) and currents (flow of charged particles) mean in the context of a cell. All of the normal principles of electricity apply, however, most electrical texts consider the movement of negatively charged electrons. In biological systems, currents are a flow of ions (e.g., $Na^+$, $Cl^-$) and voltages are differences in potential created by different ionic concentrations.

#### 2.1.1 Cellular Voltages

The transmembrane voltage, $V_m$, is defined as the difference in potential across the cell membrane (Fig. 2.1) and is typically measured in $mV$.

$$V_m = \phi_i - \phi_e = -\Delta \phi$$  \hspace{1cm} \text{(2.1)}

where $\phi_i$ is the potential inside the cell and $\phi_e$ is the potential outside the cell. Surprisingly, the transmembrane voltage will reach a steady state called the resting membrane voltage, $V_{rest}$, that is not zero. In most neurons $V_{rest} \approx -60mV$, meaning that at rest the inside of the cell has a more negative potential than the outside. Any positive change in $V_m$ is called a depolarization (Fig. 2.2) and may occur because
the inside has become more positive or the outside of the cell has become more negative. Any negative change in $V_m$ is called a repolarization. Any time the membrane voltage drops below $V^\text{rest}$ is known as hyperpolarization.

![Diagram of Depolarization, Repolarization, and Hyperpolarization](image)

**Figure 2.2:** Depolarization, repolarization, and hyperpolarization of $V_m$.

### 2.1.2 Cellular Currents

The transmembrane current, $I_m$, is a measure of the movement of ions across the membrane and is typically measured in units of $\mu A/cm^2$. By definition, a positive $I_m$ is positive charge leaving the cell. Therefore, a positive $I_m$ will repolarize the cell membrane voltage. The transmembrane current is the sum of four currents

$$I_m = I_{cm} + I_{\text{ion}} + I_{\text{syn}} - I_{\text{stim}} \quad (2.2)$$

The capacitive current, $I_{cm}$, is a result of the natural capacitance of the cell membrane. Recall that a capacitor is nothing more than an insulator sandwiched between two conductors. The cell membrane is composed of lipids which are a natural isolator. The intra and extracellular solutions are nothing more than salty water and therefore are good conductors. We will examine the role of the membrane capacitance, $C_m$, in more detail in Sec. 2.1.4.

The ionic current, $I_{\text{ion}}$, is the primary way for ions to cross the membrane. $I_{\text{ion}}$ may be composed of many different currents (carrying different ions) summed together. We will consider $I_{\text{ion}}$ in greater detail in Ch. 3.

The synaptic current, $I_{\text{syn}}$, is any one of hundreds of specialized currents that allow neurons to communicate chemically across a synapse. We will consider $I_{\text{syn}}$ in Ch. 6.

The stimulus current, $I_{\text{stim}}$, is an externally applied current and will be considered in more detail in Sec. 2.2. Note that the sign of $I_{\text{stim}}$ is opposite of the other currents.

### 2.1.3 Membrane Circuit Analog

It is customary to use circuit analogies to describe the relationship between voltages and currents. In Fig. 2.3, the top node represents the inside of the cell and the bottom node represents outside of the cell.
2.1. CELLULAR ELECTROPHYSIOLOGY

All currents are represented by a unique parallel pathway through which current may cross the membrane. In the literature, this circuit is therefore known as the parallel conductance model. By conservation of current, the total membrane current, $I_m$, must sum to zero, so

$$0 = I_{cm} + I_{ion} + I_{syn} - I_{stim}.$$  \hfill (2.3)

Figure 2.3: Parallel conductance model.

Substituting the known relationship between voltage and current for a capacitor,

$$0 = C_m \frac{dV_m}{dt} + I_{ion} + I_{syn} - I_{stim}$$  \hfill (2.4)

$$\frac{dV_m}{dt} = \frac{1}{C_m} \left[ I_{ion} + I_{syn} - I_{stim} \right].$$  \hfill (2.5)

Equation (2.5) is a differential equation that describes how $V_m$ evolves over time based upon the currents that flow across the cell membrane.

2.1.4 The Membrane Capacitance

The value of the membrane capacitance can be directly computed by

$$C_m = \frac{k\epsilon_0}{d}$$  \hfill (2.6)

where $k$ is the dielectric constant of the insulator, $\epsilon_0$ is the permittivity of free space ($1 \times 10^{-9}$/$36\pi F/m^2$), and $d$ is the membrane thickness. Using $k = 3$ (value for oil) and $d = 3$ nm:

$$C_m = \frac{3 \times 10^{-9}}{36\pi(3 \times 10^{-9})} = 0.009 \frac{F}{m^2} = 0.9 \frac{\mu F}{cm^2}. $$  \hfill (2.7)

For simplicity, $1 \mu F/cm^2$ is often used as an approximation for $C_m$. As our estimate for $C_m$ is measured per unit area, it is independent of the size of the cell.
2.2 STIMULATING THE PASSIVE MEMBRANE

If an external current \( (I_{\text{stim}}) \) is applied to the membrane of a cell such that positive ions are forced into the cell, the membrane voltage will depolarize. For now we will assume that there are no synapses \( (I_{\text{syn}} = 0) \), so

\[
\frac{dV_m}{dt} = \frac{1}{C_m} \left[ -I_{\text{ion}} + I_{\text{stim}} \right].
\]  
(2.8)

The membrane, although composed primarily of lipids, has “leaky” channels that will allow some current to pass. Experimentally, it has been observed that when \( V_m \) is close to \( V_{\text{rest}} \), the leakage of ions is proportional to \( V_m \). Therefore, we can approximate \( I_{\text{ion}} \) using Ohm's Law:

\[
I_{\text{ion}} = \frac{\phi_i - \phi_e}{R_m} = \frac{V_m}{R_m}
\]  
(2.9)

where \( R_m \) is the specific membrane resistivity \( (k\Omega \text{cm}^2) \) to current flow and measures the “leakiness” of the membrane. Given our assumption of linear \( R_m \),

\[
\frac{dV_m}{dt} = \frac{1}{C_m} \left[ -\frac{V_m}{R_m} + I_{\text{stim}} \right].
\]  
(2.10)

Rearranging Eq. (2.10)

\[
R_mC_m \frac{dV_m}{dt} + V_m = R_m I_{\text{stim}}.
\]  
(2.11)

It has become customary rewrite Eq. (2.11) as:

\[
\tau_m \frac{dV_m}{dt} + V_m = V_{\infty}
\]  
(2.12)

where

\[
\tau_m = R_m C_m
\]  
(2.13)

is the subthreshold membrane time constant measured in \( \text{msec} \) and

\[
V_{\infty} = R_m I_{\text{stim}}
\]  
(2.14)

is the steady-state voltage as time \( \rightarrow \infty \).

When \( I_{\text{stim}} \) is applied, \( V_m \) will charge up the capacitor to \( V_{\infty} \) at a rate governed by \( \tau_m \). If the current remains on, the voltage will remain at \( V_{\infty} \). Solving Eq. (2.12) during stimulation,
2.2. STIMULATING THE PASSIVE MEMBRANE

\[ V_m(t) = V_\infty (1 - e^{-t/\tau_m}) \]  \hspace{1cm} (2.15)

where \( t \) is the time after applying \( I_{\text{stim}} \).

When \( I_{\text{stim}} \) is turned off, \( V_m \) will be at some initial voltage \( V_0 \) due to charging. From this initial value, \( V_m \) will return to \( V_{m}^\text{rest} \), again at a rate governed by \( \tau_m \)

\[ V_m(t) = V_0 e^{-t/\tau_m} . \]  \hspace{1cm} (2.16)

2.2.1 Finding Membrane Properties from \( V_m(t) \)

The left-hand side of Fig. 2.5 is a plot of \( V_m(t) \) over time as a current pulse is applied and then removed. The rising phase is governed by Eq. (2.15) while the falling phase is governed by Eq. (2.16). The rising or falling phase can be used to determine the membrane properties, \( R_m, C_m, \) and \( \tau_m \). The right-hand side of Fig. 2.5 shows a stimulus that is applied only for a short time, so \( V_m \) does not have time to reach \( V_\infty \) before the stimulus is turned off.

2.2.2 The Passive Membrane

To perform the analysis above, we assumed that the current flowing through the membrane was linearly proportional to the membrane voltage. It turns out that this assumption is a good approximation as long as \( V_m \) is below some threshold voltage, \( V_{m}^{th} \). When \( V_m < V_{m}^{th} \), the membrane is called passive, \( R_m \) is a constant and the membrane can be represented as the RC circuit in Fig. 2.4. In a real neuron, \( V_{m}^{th} \) is typically between 5mV and 10mV higher than \( V_{m}^\text{rest} \). When \( V_m \) depolarizes above the threshold, however, the membrane will become active and \( R_m \) will no longer be a constant. In Ch. 3 we will consider the nonlinear relationship between \( R_m \) and \( V_m \) above the threshold.
To perform our analysis of the passive membrane we assumed that $V_m < V_{th}^m$. It would therefore be helpful to know in what situations our assumption is valid. Examining Eq. (2.15), $V_m(t)$ during the stimulus is dependent on $V_{\infty} = I_{stim}R_m$ and $\tau_m = R_mC_m$. Consider that $I_{stim}$ may be small such that $V_{\infty} < V_{th}^m$. In this case, the stimulus may remain on forever and $V_m$ will charge up to a steady state value below $V_{th}$. In other words, the membrane will remain passive. If $I_{stim}$ is steadily increased, eventually $V_{\infty}$ will be equal to $V_{th}^m$. In this case, the steady state will level out exactly at the threshold but it may take a very long time for $V_m$ to reach threshold. If $I_{stim}$ is increased further, $V_{\infty}$ will clearly be greater than $V_{th}^m$. As the right side of Fig. 2.5 indicates, however, even if $V_{\infty} > V_{th}^m$ the stimulus may be on for such a short time that the membrane does not have time to charge to the threshold. It follows that there is an interplay between the strength of $I_{stim}$ and the duration of $I_{stim}$, which can be represented graphically in a strength-duration plot. Given a constant value for $V_{th}^m$, Fig. 2.6 shows the combinations of strength and duration that exactly charge the membrane to the threshold. Mathematically, we can set $V_m = V_{th}^m$ and substitute into Eq. (2.15)

$$V_{th}^m = I_{stim}R_m(1 - e^{-D/\tau_m}) \quad (2.17)$$

where $D$ is the duration of the stimulus. One interesting limit is to find the minimum current that can bring the membrane to $V_{th}^m$. If $D \to \infty$

$$V_{th}^m = I_{stim}R_m \quad (2.18)$$

$$I_{stim} = I_{rhe} = \frac{V_{th}^m}{R_m} \quad (2.19)$$

which explains the value of asymptote in Fig. 2.6. This value is called \textit{rheobase}, $I_{rhe}$, and is a measure of current. Another important measure can be derived by assuming that we apply two times the rheobase current to find the corresponding time to charge the membrane to $V_{th}^m$.

$$V_{th}^m = 2I_{rhe}R_m(1 - e^{-D/\tau_m}) \quad (2.20)$$
and solving for $D$

$$D = -\tau_m \cdot \ln \left[ 1 - \frac{V_{th}^m}{2I_{rhe} R_m} \right]$$  \hfill (2.21)

but we know that $I_{rhe} R_m = V_{th}^m$ so

$$D = -\tau_m \cdot \ln \left[ 1 - \frac{1}{2} \right]$$  \hfill (2.22)

$$T_c = D = 0.693 \tau_m.$$  \hfill (2.23)

The time $T_c$ is known as chronaxie. Therefore, given a strength duration curve, and Eqs. (2.19) and (2.23) one could find the passive membrane properties.

### 2.3.1 A Fluid Analogy

An alternative way to think about the passive membrane is as a cup with a hole in the bottom and a line painted half way up the side. In the analogy, the volume of the cup is similar to the capacitance in that it can store the quantity of interest (water instead of charge). The size of the hole is similar to the resistance in that it tends to leak out the quantity of interest (water instead of charge). The line on the cup represents the threshold voltage. As long as the water level remains below the threshold, the water will leak from the hole at a constant rate. A stimulus (a flow rate of charges) in our analogy would be the steady poring of water into the cup.

Using our analogy we can gain some intuition about charging and discharging in response to a stimulus. For example, if water is poured in slower than the rate at which it leaks out of the hole, then the threshold line will never be reached. This is analogous to being below $I_{rhe}$. You could imagine, however,
that more aggressive pouring would eventually result in the threshold being reached but only very slowly. It may also be possible to pour water in only for some short period of time. If this is the case, then the rate at which you pour and the duration of your pour will determine if the water will reach the threshold. You could in fact create a strength-duration plot for this cup-water system. Furthermore, if you assume that the cup already has water in it, you may ask how long it will take for the cup to drain. The two parameters of interest will be the size of the cup (capacity) and the size of the hole (resistance). The combination of the two, as in the circuit analogy, can be used to define the time constant of the filling or draining of the cup.

2.4 THE MEMBRANE AT REST
A careful examination of Fig. 2.4 will reveal that $V_{rest}$ must be $0mV$, which biologically is not true. In this section we will examine how a cell can maintain a nonzero resting potential.

2.4.1 The Forces Driving Ion Movement
Consider Fig. 2.7 where circles and dots represent two types of positively charged ions but the membrane will only allow dots to pass through. The special property of the membrane to easily pass some ions but not others is called selective permeability and results in a nonzero resting potential.

![Figure 2.7: Concentrations and electrical potentials in a cell.](image)

There are two forces driving the motion of an ion. The electric force, $F_{\phi}$, is due to any difference in potential ($\Delta \phi$) between the inside and outside of the cell. Remember that potential differences arise because there are different amounts of charge on either side of the membrane. The potential is therefore due to all of the charges, whether they are able to cross the membrane or not. The chemical force, $F_C$, is due differences in specific ionic concentrations ($\Delta C$) across the membrane and will act only on a single type of ion (e.g., dot or circle in Fig. 2.7). It is because $F_{\phi}$ is a function of all charges and $F_C$ is a function of only a specific ion that the membrane can support a nonzero rest potential.

2.4.2 A Helium Balloon Analogy
An alternative way to think of the balance of two forces is using an analogy to a Helium balloon. There are always two forces acting on the balloon: gravity pulling the balloon downward and, because Helium gas is less dense than air, an upward buoyant force. When the balloon is first bought it is full of Helium gas that will not easily pass through the balloon and the buoyant force is much stronger than the pull of gravity. Therefore, the balloon will tend to sail into the air. As the balloon sails higher, however, the air
becomes less dense, and so the buoyant force begins to decrease. At some elevation, the buoyant force and gravitational forces will exactly cancel out and the balloon will no longer move up or down. The height of the balloon is the point at which two forces balance and is similar to the resting membrane voltage. As the balloon slowly leaks Helium, however, the buoyant force will decrease. The partially deflated balloon will sink to reestablish the balance of buoyant gravitational forces. Eventually, the balloon will have leaked so much Helium that it can no longer overcome the force of gravity.

2.4.3 Definition of Resting Membrane Voltage
Although we have an intuitive feel for $V_{\text{rest}}^m$, we can now derive a more formal mathematical definition. At rest the membrane voltage is not changing so $\frac{dV_m}{dt} = 0$. If no stimulus is being applied, then Eq. (2.8) reveals that $I_{\text{ion}}$ must equal zero. The meaning is that there is no net current crossing the membrane. We can only say net current because in general, $I_{\text{ion}}$ may be composed of many currents which may balance one another.

As $F_\phi$ and $F_C$ are the driving forces behind ion movement, if $F_C \neq F_\phi$ then charged particles will cross the membrane, i.e., $I_{\text{ion}} \neq 0$). For $I_{\text{ion}} = 0$ this means that $F_C = F_\phi$, or alternatively, the current due to the potential gradient, $I_\phi$, is equal to the current due to the concentration gradient, $I_c$. In the next sections we will use Fick’s Law and Ohm’s law to define $I_\phi$ and $I_c$.

2.4.4 Fick’s Law and Chemical Gradients
Fick’s Law describes the flux (mol$\cdot$m$^{-2}\cdot$s$^{-1}$) of ions through an area of membrane with a thickness of $dx$ due to a concentration gradient.

$$I_c = -D \frac{dC}{dx} \quad (2.24)$$

where the diffusion coefficient, $D$ (m$^2$)$^{-s}$, is a material property of the membrane and is a measure of how easily ions can pass. $C$ is a concentration in mol$^{-m^3}$.

2.4.5 Ohm’s Law and Electrical Gradients
As stated earlier, Ohm’s Law for a passive membrane is

$$V_m = I_\phi R_m \quad (2.25)$$

$$I_\phi = \frac{V_m}{R_m} = \frac{\phi_i - \phi_e}{R_m}. \quad (2.26)$$

The specific membrane resistivity, $R_m$, may be thought of as the ability of some ion to pass across the thickness ($dx$) of the membrane

$$R_m = \frac{dx}{\mu_p C} \cdot \frac{|Z|}{Z} \quad (2.27)$$

where $\mu_p$ is the ion mobility. $Z$ is the ion valence, so $Z/|Z|$ is the charge sign (+ or -). $C$ is the ionic concentration.
In 1905 Einstein recognized that mobility ($\mu_p$) and the diffusion coefficient ($D$) are related by

$$\mu_p = \frac{D|Z|F}{RT}$$  \hspace{1cm} (2.28)

where $R$ is the ideal gas constant, $T$ is the temperature, and $F$ is Faraday’s constant. We can therefore, rewrite the equation for $R_m$ as

$$R_m = \frac{dx \cdot RT}{DCFZ}.$$  \hspace{1cm} (2.29)

Substitution back into Eq. (2.26) yields

$$I_\phi = \frac{[\phi_i - \phi_e] DCFZ}{dx \cdot RT}.$$  \hspace{1cm} (2.30)

$$I_\phi = \frac{DCFZ}{RT} \frac{d\phi}{dx}.$$  \hspace{1cm} (2.31)

### 2.4.6 The Nernst Equation

Using Eqs. (2.24) and (2.31)

$$I_{\text{ion}} = I_c + I_\phi$$  \hspace{1cm} (2.32)

$$I_{\text{ion}} = -D \left[ \frac{dC}{dx} + \frac{ZF \cdot d\phi}{RT} \frac{dx}{dx} \right].$$  \hspace{1cm} (2.33)

At rest we know that $I_{\text{ion}} = 0$

$$0 = -D \left[ \frac{dC}{dx} + \frac{ZF \cdot d\phi}{RT} \frac{dx}{dx} \right]$$  \hspace{1cm} (2.34)

and after some rearranging

$$V_{\text{rest}} = E_{\text{rest}} = \frac{RT}{ZF} \ln \left[ \frac{C_e}{C_i} \right].$$  \hspace{1cm} (2.35)

Equation (2.35) is the Nernst equation that relates $V_{\text{rest}}$ to the difference in intracellular and extracellular concentrations. In our derivation we assumed that $C$ was a positive ion. The only different in Eq. (2.35) for negative ions is that $C_e$ and $C_i$ are switched in the numerator and denominator. Figure 2.8 is the circuit analog for the passive membrane where the Nernst potential is represented by a battery, $E_{\text{rest}}$.

The ionic current that flows through the resistor is described by

$$I_{\text{ion}} = \frac{1}{R_m} \left[ V_m - E_{\text{rest}} \right].$$  \hspace{1cm} (2.36)

It can now be understood why the membrane settles to $V_{\text{rest}} = E_{\text{rest}}$. If $V_m > V_{\text{rest}}$, then $I_{\text{ion}}$ will be positive. If $V_m < V_{\text{rest}}$ then $I_{\text{ion}}$ is negative. Therefore, $E_{\text{rest}}$ is sometimes also referred to as the reversal potential.
2.4.7 The Goldman-Hodgkin-Katz Equation

In reality, there are many ions with different abilities to cross the membrane. There are also some large charged particles (e.g., proteins) that cannot cross the membrane. The result is that achieving $I_{\text{ion}} = 0$ to calculate $V_m^{\text{rest}}$ is somewhat more difficult. We will not provide a derivation here but as the major ions involved are Sodium, Potassium, and Chloride, $V_m^{\text{rest}}$ can be approximated by the Goldman-Hodgkin-Katz equation:

$$E_m = \frac{RT}{F} \ln \left[ \frac{P_K[K^+]_e + P_Na[Na^+]_e + P_Cl[Cl^-]_l}{P_K[K^+]_l + P_Na[Na^+]_l + P_Cl[Cl^-]_e} \right]$$

(2.37)

where the $P$-terms are the relative permeabilities (unitless) of the respective ions.

\[
\begin{align*}
\text{Na}^+ &= 14\text{mM} \\
\text{K}^+ &= 140\text{mM} \\
\text{Na}^+ &= 142\text{mM} \\
\text{K}^+ &= 4\text{mM}
\end{align*}
\]

Figure 2.9: Multiple ions species and the Goldman-Hodgkin-Katz equation.

Figure 2.9 shows a simple example for only $Na^+$ and $K^+$ ions when the cell is at rest. Given that $P_K = 1$, $P_Na = 0.002$, $R = 8.316 \frac{J}{K\text{mol}}$, $T = 300K$, and $F = 96487 \frac{C}{\text{mol}}$,

$$\frac{RT}{F} = 0.0258 \frac{J}{C} = 25.8mV$$

(2.38)
The individual Nernst potentials for $K$ and $Na$ may be found using Eq. (2.35). Perhaps surprisingly the computations show that $E_{Na} = 59.8mV$ and $E_K = -91.7mV$, neither of which are exactly at -90mV. It is worth noting that $V_{rest}$ is much closer to $E_K$ than $E_{Na}$ at rest. It is also important to consider that $Na^+$ and $K^+$ may still be able to cross the membrane as long as the total current, $I_{ion}$, sums to zero. The direction of current flow may also be found by comparing $V_{rest}$ and the reversal potential for an ion. In general, a particular ion will flow in the direction that will send $V_m$ closer to its own Nernst potential. Remember that the definition of positive current is positive charge leaving the cell.

2.5 NUMERICAL METHODS: THE EULER METHOD

In this chapter we have defined a differential equation to relate $V_m$ to membrane currents. Analytical solutions were possible because we assumed that all terms were linear. Once terms such as $I_{ion}$ become nonlinear (as they will in Ch. 3), analytical solutions are no longer possible. In these situations we can turn to numerically simulations using a computer. Perhaps the simplest and most used method of finding $V_m(t)$ given $\frac{dV_m}{dt}$ is the Euler method. The general strategy is to use the current value, $V_m(t)$, and the current slope, $\frac{dV_m}{dt}$ to predict what the new membrane potential ($V_m(t + \Delta t)$ will be forward in time (see Fig. 2.10). Mathematically,

$$ \frac{dV_m}{dt} = \frac{1}{C_m}[-I_{ion} - I_{syn} + I_{stim}] \quad (2.40) $$

$$ \frac{\Delta V_m}{\Delta t} = \frac{1}{C_m}[-I_{ion} - I_{syn} + I_{stim}] \quad (2.41) $$

$$ \Delta V_m = \frac{\Delta t}{C_m}[-I_{ion} - I_{syn} + I_{stim}] \quad (2.42) $$

$$ V_{new} = \Delta V_m + V_{old} \quad (2.43) $$

Therefore, to solve a coupled set of nonlinear differential equations, we can apply Eq. (2.40) over and over again to march forward in time. One word of warning is that if $\Delta t$ is large, you may overshoot the real solution.

Homework Problems

(1) Assuming that $V_{rest} = -70mV$ and the initial voltage is $V_m = -60mV$, draw a $V_m$ trace that repolarizes from $t = 0msec$ to $t = 30msec$, then hyperpolarizes from $t = 30msec$ to $t=35msec$, depolarizes from $t = 35msec$ to $t = 50msec$, and then repolarizes to rest from $t = 50msec$ to $t = 70msec$. The exact values of the peaks and valleys are not important.

(2) A negative stimulus of $-15.7pA$ was applied to a membrane at $t = 1msec$ and produced the following trace. Note that hyperpolarizing pulses are always considered to be subthreshold.
a) What is the resting membrane potential?
b) Compute the total $R_m$ in $M\Omega$. Explain your reasoning.
c) Compute $\tau_m$ in $msec$. Explain your reasoning.
d) Compute the total cellular $C_m$ in $pF$.
e) Given that the specific $C_m$ is $1\mu F/cm^2$, find the cell surface area.

(3) The following data were obtained from a neuron at 300K (see Table 2.1).
<table>
<thead>
<tr>
<th>Ion</th>
<th>Intracellular (mM)</th>
<th>Extracellular (mM)</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[K^+]$</td>
<td>280</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>$[Na^+]$</td>
<td>51</td>
<td>485</td>
<td>1</td>
</tr>
<tr>
<td>$[Cl^-]$</td>
<td>46</td>
<td>340</td>
<td>0.5</td>
</tr>
</tbody>
</table>

a) Report the Nernst potential for each ion.
b) Compute the resting potential.
c) Report the direction that each ionic current moves at rest.

(4) Perform the derivation from Eqs. (2.34) and (2.35).

(5) Below is a strength-duration curve for a membrane with a threshold $7mV$ above rest.

Given the figure, answer the following questions.

a) If a stimulus is above the curve, will the membrane behave linearly or nonlinearly?
b) What is $I_{the}$?
c) What is $R_m$ in $k\Omega cm^2$?
d) What is $T_c$ in msec?
e) What is $\tau_m$ in msec?
f) What is $C_m$ in $\mu F/cm^2$?

(6) Draw Strength Duration curve given $C_m = 1\mu F/cm^2$, $R_m = 3k\Omega cm^2$, $V_{rest} = -60mV$ and $V^{th} = -50mV$. Be sure to label $I_{the}$ and $T_c$ and report numerical values for each.

(7) Given that a negative stimulus of $-15.7pA$ applied at t=1msec produced the following:

---

Table 2.1:
2.5. NUMERICAL METHODS: THE EULER METHOD

a) What is the resting membrane potential?
b) Compute total cellular $R_m$ in $M\Omega$. Explain your reasoning.
c) Compute $\tau_m$ in msec. Explain your reasoning.
d) Compute the total cellular $C_m$ in pF. Explain your reasoning.

(8) Demonstrate that the units in Eq. (2.11) are the same on the left- and right-hand side of the equation.

(9) Cellular currents are often measured in units of $\mu A/pF$. Explain why this may be a good measure to use and explain how you would convert Eq. (2.11) to the proper form.

Simulation Problems

(1) Program a passive membrane with input variables of $R_m$, $C_m$, $dt$, endtime, Stim start, Stim End, and Stim Strength.

(2) Program a passive membrane with input variables of $R_m$, $C_m$, $dt$, endtime, Stim start, Stim End, and Stim Strength.
In the previous chapter we considered the response of a membrane to a small stimulus. In these situations the resistance of the membrane was linear and $I_{\text{ion}}$ was modeled as a simple resistor and battery in series. In this chapter, we consider what happens when a stimulus causes $V_m$ to reach threshold. The result is that $R_m$ no longer behaves linearly a property that may be represented in a circuit model as the variable resistance in Fig. 3.1.

![Figure 3.1: A nonlinear resistive membrane.](image)

### 3.1 THE HODGKIN-HUXLEY MODEL

The first physiologically accurate nonlinear model of $I_{\text{ion}}$ was published in 1952 by Hodgkin and Huxley. To create the model, Hodgkin and Huxley combined a brilliant experiment a number of assumptions were about the biophysics of ion channels. Despite its relative simplicity, it remains the gold-standard of ionic membrane models.

#### 3.1.1 The Parallel Conductance Model

The first assumption was that $I_{\text{ion}}$ was composed of three currents that acted independently of one another. These currents were Sodium ($I_{Na}$), Potassium ($I_K$), and a generic leakage current ($I_L$). Mathematically,

$$I_m = C_m \frac{dV_m}{dt} + I_{Na} + I_K + I_L .$$

(3.1)

Experimental data showed that $I_L$ was a linear current, while $I_{Na}$ and $I_K$ were nonlinear. Therefore, the circuit analog, taking into account the independence assumption and nonlinear ionic currents, can...
be represented as in Fig. 3.2. The resistors have been replace by $G$-terms that represent conductances. Conductance is simply the inverse of resistance ($G = \frac{1}{R}$) and is measured in units of siemens, abbreviated with a capital 'S'. Therefore, as resistance is increased, conductance is decreased. For biological membranes the most commonly used unit for conductance is $mS/cm^2$.

\[ I_L = G_L[V_m - E_L] \]  

(3.2)

where $G_L$ is the leakage conductance and $E_L$ is the leakage Nernst potential. The nature of the leakage current was not fully known to Hodgkin and Huxley but they guessed (again correctly) that it was some combination of other ionic currents.

3.1.3 Nonlinear Currents and the Voltage Clamp
Characterization of the two nonlinear currents ($I_{Na}$ and $I_K$) is nontrivial because there is a natural feedback loop between $I_{ion}$ and $V_m$. Consider the following generic nonlinear current

\[ I_{nl} = G_{nl}(V_m)[V_m - E_{nl}] \]  

(3.3)

Notice that the conductance, $G_{nl}$, is a function of $V_m$. Therefore, a change in $V_m$ causes a change in $G_{nl}$ which has an impact on $I_{nl}$. As $I_{nl}$ is a component of $I_{ion}$, any nonzero value for $I_{nl}$ may in fact lead to a further change in $V_m$. Untangling this interdependence in an experiment was a monumental step first taken by Cole and later used by Hodgkin and Huxley.

The voltage clamp is a method of forcing $V_m$ to be constant at any desired holding voltage, $V_h$, using an external circuit (Fig. 3.3). In this way, the feedback loop between $V_m$ and $I_m$ is effectively cut.
3.1. THE HODGKIN–HUXLEY MODEL

If the circuit can react faster than the membrane, an exactly counterbalancing current, $I_{in}$, may be sent into the cell to maintain a specific voltage level. The transient of this counterbalancing current can be used to determine how fast the membrane can react to changes when $V_m = V_h$, while the steady-state current can be used to determine the maximum current at the clamped $V_m$. The combination of these two parameters, reaction time and maximum current, as a function of $V_h$, enabled Hodgkin and Huxley to develop the first mathematical model of an excitable cell.

It is clear from Fig. 3.3 that at least one electrode must have access to the inside of a cell. At the time of Hodgkin and Huxley, electrodes were relatively large compared to mammalian neurons. To create their model, Hodgkin and Huxley chose to study the large axon (up to 1 mm in diameter) of the giant squid. Since 1952, the size of electrodes has drastically shrunk, allowing for many types of neurons to be studied. The electronic feedback loop of the voltage clamp, however, has remained largely unchanged.

\[ I_{Na} = G_{Na}(V_m)[V_m - E_{Na}] \]  

3.1.4 The Sodium Current

The Sodium current is formulated in the same way as the leakage current.

but now the leakage term $G_{Na}$ is a nonlinear function of $V_m$. To begin, Hodgkin and Huxley assumed (again correctly) that the nonlinear nature of the flow of Sodium ions was due to the opening and closing of proteins that spanned the membrane. These proteins could somehow change their shape to be either open or closed in response to pH, intra and extracellular concentrations of ions and molecules, temperature, or even $V_m$. Hodgkin and Huxley focused on the impact of changes in the membrane voltage. Yet another assumption was that each ion channel would be either entirely open or entirely closed. In other words, there would be no in between states. To create their model, however, they assumed that there were thousands or millions of Sodium channels embedded in a small patch of membrane. Therefore, the model would be based on the probability that any individual channel would be open. So, although each ion channel would be either open or closed, 30% of the channels may be open and 70% are closed. To capture the aggregate behavior, Hodgkin and Huxley defined a variable, $O$, that would be 0.3, or the
probability of randomly picking an open channel. Next they next assumed that the rate at which channels opened (on average) was not necessarily the same as the rate at which channels closed. This situation can be represented kinematically by

\[ O \rightleftharpoons \alpha(V_m)\beta(V_m)C \]

where rate constants, \( \alpha(V_m) \) and \( \beta(V_m) \), would be functions of \( V_m \). Using this formulation they could write down a differential equation to describe the dynamics of the \( O \) variable.

\[
\frac{dO}{dt} = \alpha(V_m)(1 - O) - \beta(V_m)O_m .
\]

(3.5)

Given the variable \( O \), they defined the Sodium current as:

\[
I_{Na} = g_{Na} \times O(V_m)[V_m - E_{Na}]
\]

(3.6)

where \( g_{Na} \) is the maximum conductance. The meaning of \( g_{Na} \) is that if \( O = 1 \), i.e., every sodium channel is open), the maximum possible current will flow. \( O \), on the other hand, can vary between a probability of 0 and 1. When Hodgkin and Huxley fit parameters for \( \alpha \) and \( \beta \) using the voltage clamp, they found that the channel was more complicated than the simple \( O \) variable could capture. They assumed that the Sodium channel was composed of four parts (Fig. 3.4) and for the channel to be fully open, all four parts needed to be in the right configuration. They therefore assumed \( I_{Na} \) to take the form of:

\[
I_{Na} = g_{Na}O_1(V_m)O_2(V_m)O_3(V_m)O_4(V_m)[V_m - E_{Na}]
\]

(3.7)
where \( O_{1,2,3,4} \) were the four parts. Further analysis showed that three of the parts functioned in the same way, i.e., \( \alpha \) and \( \beta \) functions were identical. These channel parts were each called \( m \) and the remaining part was called \( h \). Their model of the Sodium current was described by

\[
I_{Na} = g_{Na} m^3 h (V_m - E_{Na})
\]  
(3.8)

\[
\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m
\]  
(3.9)

\[
\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h
\]  
(3.10)

where \( m \) and \( h \) are known as gating variable because they control how ions are gated through the channel. The only difference between the \( h \) and \( m \) variables is that the functions of \( \alpha \) and \( \beta \) are different.

Using their experimental data and some curve fitting, Hodgkin Huxley found the following fits for the \( \alpha \)’s an \( \beta \)’s:

\[
\alpha_m = 0.1 \frac{25 - v_m}{e^{(25 - v_m)/10} + 1}
\]  
(3.11)

\[
\beta_m = 4e^{-v_m/18}
\]  
(3.12)

\[
\alpha_h = 0.07e^{v_m/20}
\]  
(3.13)

\[
\beta_h = \frac{1}{e^{(30 - v_m)/10} + 1}
\]  
(3.14)

where \( v_m \) is scaled by the resting potential such that \( v_m = V_m - V_m^{rest} \).

3.1.5 The Potassium Current

The Potassium current may be assumed to be of the nonlinear form

\[
I_K = g_K O(V_m)[V_m - E_K].
\]  
(3.15)

Recall, however, that the first assumption was that each current was independent of the other currents present. So, simply performing the voltage clamp as described above would yield data on \( I_K + I_{Na} \). To separate the two currents, Hodgkin and Huxley used tetrodotoxin (TTX), a Sodium channel blocker, to isolate \( I_K \). They then performed the same experiment without TTX to yield \( I_K + I_{Na} \) and by simple subtraction they isolated \( I_{Na} \). Using this two-step procedure, they found that \( O(V_m) \) for \( I_K \) was the product of four gating variables that were all identical:

\[
I_K = g_K n^4 [V_m - E_K].
\]  
(3.16)

\[
\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n.
\]  
(3.17)

Experimental data for the \( n \) gating variable was fit to the following \( \alpha \) and \( \beta \) functions:

\[
\alpha_n = 0.01 \frac{10 - v_m}{e^{(10 - v_m)/10} + 1}
\]  
(3.18)

\[
\beta_n = 0.125e^{-v_m/30}.
\]  
(3.19)
3.1.6 Steady-State and Time Constants

An alternative, and possibly more intuitive, way of writing the gating differential equations is

\[
\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m},
\]

(3.20)

\[
m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m},
\]

(3.21)

\[
\tau_m = \frac{1}{\alpha_m + \beta_m},
\]

(3.22)

Figure 3.5: Steady-state and time constant for Hodgkin-Huxley gates.

with similar equations to describe the h and n variables. Plots of the steady-state and time constant curves for m (red), h (blue), and n (green) are shown in Fig. 3.5. The reason for writing the equations this way is that the steady state (\( \infty \)-terms) and time constants (\( \tau \)-terms) have a physical interpretation. The solution to Eq. (3.20) is

\[
m(t) = m_\infty - (m_\infty - m_0)e^{-t/\tau_m}
\]

(3.23)

where \( m_0 \) is the initial value of m. In the context of the voltage clamp, consider that \( V_m \) is equal to a value A and has been there for a long time, i.e., \( t \to \infty \). Therefore, \( m \to m_\infty(A) \) which could be read directly from Fig. 3.5. Next, consider that the membrane potential is suddenly changed to \( V'_m = B \). Since the gating variable, m, cannot change instantaneously, the initial condition \( m_0 \) is equal to \( m_\infty(A) \). The steady-state and time constants, however, do change instantaneously. Therefore, to compute \( m(t) \) at any point after \( V_m \) is clamped to B
\[ m(t) = m_\infty(B) - (m_\infty(B) - m_0) e^{-t/\tau_m(B)} \]  
\[ m(t) = m_\infty(B) - (m_\infty(B) - m_\infty(A)) e^{-t/\tau_m(B)}. \]  

**Figure 3.6:** \( m \)-gate changes over time for changes in holding potential.

The intuitive interpretation is that \( m_\infty \) is the target for \( m \) and \( \tau_m \) is the rate at which this new target is reached. To demonstrate this idea, Fig. 3.6 shows three changes in \( V_h \) with the corresponding change in \( m \). It may be helpful to think about how Figs. 3.5 and 3.6 are related.

### 3.1.7 A Game of Tag

An analogy to the steady-states and time constants may be thought of as a game on an obstacle course. You and 100 of your friends all have the goal of reaching a diamond that will be set somewhere on the course. You can imagine that if the diamond stays in one location, you would simply navigate through water, hoops, sand, and gravel to get to it. Although this may take time, eventually you would all reach the diamond. The location of the diamond therefore is analogous to the steady state. If the location of the diamond, however, suddenly changed, you and your friends would again set out across the course to reach it. The type of obstacles in your way (not necessarily the distance) would determine how long it takes to reach the diamond. The way that your time to reach the diamond is dependent upon the obstacles in your way is analogous to the time constant. Now imagine that the diamond is moving around the course, suddenly appearing in one location and then quickly moving to a new location, faster than you and your friends can keep up.

Next imagine that at the same time that you and your friends are chasing a diamond, another group of 101 people are also chasing a ruby, and a third set of 101 people are chasing an emerald. Here, the analogy is at the diamond is the \( m \)-gate, the ruby is the \( h \)-gate, and the emerald is the \( n \)-gate. Although our game is not a perfect analogy to the dynamics of gates, it may help understand the next section where the Hodgkin-Huxley action potential is examined.
3.2 THE HODGKIN-HUXLEY ACTION POTENTIAL

When stimulated, the Hodgkin-Huxley model generates a rapid depolarization followed by a slower depolarization back to rest. This cycle is known as an action potential and is the basic functional measure of all excitable cells. Below we discuss the four phases of the action potential as summarized in Fig. 3.7.

3.2.1 Phase 0 - Rest

When $V_m$ is at rest, $m = m_\infty \approx 0.05$ and $h = h_\infty \approx 0.6$ and therefore $g_{Na} m^3 h$ is small. On the other hand, $V_m$ is close to $E_K$, so the driving force for $I_K$ is small. For these different reasons, both $I_{Na}$ and $I_K$ are small. The result is that at rest the linear leakage current, $I_L$, will dominate and the membrane behaves linearly.

3.2.2 Phase 1 - Activation

If a stimulus is applied, $V_m$ will depolarize. As $V_m$ changes, the $\alpha$, $\beta$, time constants and steady-state values will also change. Consider the following:

1. The driving force for $I_{Na}$ (e.g., $V_m - E_{Na}$) at rest is large and negative because $V_m$ is much smaller than $E_{Na}$. If given the chance, $Na^+$ ions would therefore move into the cell.
2. $Na^+$ ions are prevented from crossing the membrane because $m$ is small.
3. Although the $m_\infty$ curve is flat at $V_{m,rest}$, if the membrane is depolarized slightly, $m_\infty$ will become relatively large. This is because of the steep slope of the $m_\infty$ curve.
4. $\tau_m$ is small so any change to $m_\infty$ will result in a fast change in $m$.
5. The driving force for $I_K$ at rest is small because $V_m$ is close to $E_K$. Given these properties, consider that a small depolarizing change in $V_m$ would cause $m_\infty$, and therefore $m$, to increase quickly. The result is that $g_{Na} m^3 h$ and $I_{Na}$ increase and $Na^+$ will rush into the cell. The fast rise in the membrane potential is called activation or upstroke and the $m$ gate is therefore called the activation gate. The origin of a threshold voltage can now be understood. Below $V_{m,th}$, $m_\infty$ and $m$ are not large enough to create a large $I_{Na}$. But, when $V_m$ reaches $V_{m,th}$, $m$ is on the steep part the $m_\infty$ curve. So, a small depolarizing $I_{Na}$ current pushes $V_m$ and $m$ to larger and larger values. This runaway effect is counterbalanced by repolarization.

3.2.3 Phase 2 - Repolarization

As the $I_{Na}$ current attempts to drive $V_m \rightarrow E_{Na}$, two other players become important. First, during the upstroke $h_\infty$ changes from $\approx 0.6$ to $\approx 0$, but does so slowly, i.e., $\tau_h$ is relatively large compared to $\tau_m$). Over time, however, $h$ becomes small enough that the $m^3 h$ term, and therefore $I_{Na}$, is reduced. The $h$ gating variable is therefore called the inactivation gate because it turns the Sodium current off after activation. Second, after depolarization, $V_m$ is no longer close to $E_K$ and the driving force for $I_K$ is increased. Due to the sign of $E_K$, $I_K$ will be a positive current, i.e., $K^+$ flows out of the cell). Positive charge exiting the cell causes $V_m$ to decrease or repolarize.
3.2.4 Phase 3 - Hyperpolarization
In the Hodgkin-Huxley model, the n-gate does not return the membrane directly to rest. Instead, $V_m$ drops slightly below $V_{m\text{rest}}$, a hyperpolarization, and then depolarizes back to rest.

![Figure 3.7: Hodgkin-Huxley action potential and currents.](image)

3.3 PROPERTIES OF NEURONAL ACTION POTENTIALS

The Hodgkin-Huxley model was successful largely because it explained the origin of four of the most important features of an action potential. We review these properties below and related them to the relevant parts of the model.
3.3.1 All Or None
When a stimulus of a small amplitude is applied to an active membrane, the membrane will act in the same way as a passive membrane. We argued in Ch. 2 that at some combination of strength and duration (recall Fig. 2.6) the membrane will reach a threshold, $V_{th}$, after which the membrane becomes nonlinear. Furthermore, the Hodgkin–Huxley model correctly predicts that once the membrane is above threshold, the Sodium current begins the positive feedback cycle that results in the upstroke of the action potential. Therefore, once the Sodium current is activated, an action potential is inevitable. This abrupt all or none response of a neuron also highlights the importance of the strength-duration curve because any stimulus above the curve will result in an action potential.

3.3.2 Refractory Periods
After $I_{Na}$ has caused the upstroke of the action potential and repolarization has begun, $m$ will remain relatively high. The $h$-gate, however, will slowly drop to a value forcing $I_{Na}$ to become small. But remember that $\tau_h$ is large so any changes in $h$ occur slowly. Therefore, $h$ will remain small for some time while the repolarization of the action potential is occurring. During this time, no additional change in $m$ will cause a second large influx of $I_{Na}$. The time when no second action potential is possible is called the absolute refractory period (see Fig. 3.8). Following the absolute refractory period is the relative refractory period. During the relative refractory period a second action potential is possible, but requires a greater depolarization (e.g., larger $I_{stim}$) than the first action potential.

![Figure 3.8: Demonstration of action potential refractory period.](image-url)
3.3.3 Anode Break

An interesting phenomenon can occur if a hyperpolarizing current is applied to the membrane for a long time. In this case, \( m \) is forced low and because the current is on for a long time, \( h \) is forced high. When the stimulus is turned off, \( m \) will respond quickly and increase. \( h \), on the other hand, will respond slowly and stay at approximately 1. The combination of these two factors can cause \( g_{Na}m^3h \) to reach a level high enough for \( I_{Na} \) to increase in magnitude. As in a normal activation, the increase in \( I_{Na} \) can lead to the run-away process that causes the upstroke. The firing of an action potential using a long duration hyperpolarizing current is known as anode break and is shown in Fig. 3.9.

![Figure 3.9: Demonstration of an action potential generated by anode break.](image)

3.3.4 Accommodation

Another interesting phenomenon can be observed if the membrane is very slowly depolarized. A slow depolarization can be accomplished by making \( I_{stim} \) a ramp with a small slope as in Fig. 3.10. If the depolarization is slow enough, the \( h \) gate will have time to reach \( h_\infty \) (unlike in a normal depolarization). Therefore, even though \( m \) increases, \( h \) will decrease such that \( g_{Na}m^3h \) will not be a large enough to initiate the run-away \( I_{Na} \) current. The effect is that \( V_m \) can become higher than \( V_{th} \) without causing an action potential to fire. This phenomenon is called accommodation because the \( h \) gate is impacting the value of the threshold. The meaning of both anode break and accommodation is that what we typically think of as the threshold voltage is not an exact number and depends on the path taken to cause the run-away \( I_{Na} \). Both are related to the time constant of \( h \).
3.4 COMPLEX IONIC MODELS

While Hodgkin and Huxley created the first physiologically based mathematical model of a neuron, there were many neuronal phenomenon that it could not reproduce. Below we review some of the ways researchers have extended the Hodgkin-Huxley model.

3.4.1 More Currents

As the electrodes used for the voltage clamp method have become smaller and smaller, and new channel blocking drugs were found, it became possible to isolate more than the three simple currents of the Hodgkin-Huxley model. The result has been that more recent models have many more currents included in $I_{\text{ion}}$. For example, the unspecified leakage current was found to be due to other ions such as $Ca^{2+}$, $Mg^{2+}$, and $Cl^-$. To include these currents we would simply add them to the parallel conductance $I_{\text{ion}}$ term.

\[ I_{\text{ion}} = I_{Na} + I_K + I_{Ca} + I_{Mg} + I_{Cl}. \]  

(3.26)

Here the leakage current has been replaced by $I_{Ca} + I_{Mg} + I_{Cl}$. It was also found that $I_K$ may in fact be the summation of many different types of Potassium ion channels.

\[ I_{\text{ion}} = I_{Na} + I_{K1} + I_{K2} + I_{K3} + I_{Ca} + I_{Mg} + I_{Cl}. \]  

(3.27)

where $I_K$ has been split into three different currents. Similarly, $I_{Ca}$ may be decomposed into many currents. For each current added, there will be new gating variables and new differential equations.

Figure 3.10: Demonstration of accommodation of threshold voltage.
It may be questioned why the addition of these currents is necessary. After all, the Hodgkin-Huxley model successfully reproduced the properties of the action potential. There are at least three reasons why the extra currents, and complexity, are important. First, the giant squid axon does not display all of the behavior of mammalian neurons. Second, it is often the case that a genetic mutation, drug, or hormone will only effect one type of ion channel. For example, Nifedipine specifically blocks a certain type of Calcium ion channel, while allowing other Calcium channels to remain functional. Third, when a single action potential fire, \( \text{Na}^+ \), \( \text{K}^+ \), and other ions cross the membrane. Surprisingly, it does not require many ions to cross the membrane to achieve the \( \approx 100mV \) change in \( V_m \) during the action potential. Therefore, the intracellular and extracellular concentrations do not change significantly during a single action potential. If many action potentials fire in rapid succession, however, the concentrations will eventually begin to change. Cells therefore have a variety of \textit{pumps} and \textit{exchangers} that slowly act in the background, transporting ions back across the membrane. As these pumps are typically working against a concentration gradient, they require ATP. Similar to other currents, they may be added to \( I_{ion} \).

We will consider how to incorporate changing concentrations in Sec. 3.4.5.

### 3.4.2 The Traub Model of the Pyramidal Neuron

A model with additional currents is the Traub model. We present the model here as an example of how extra currents lead to more realistic behavior and because it will be encountered again in Ch. 7.

\[
I_{ion} = I_{Na} + I_K + I_{Ca} + I_{kCa}
\]

\[
I_{Na} = g_{Na}m^3h(V_m - E_{Na})
\]

\[
I_K = g_Kn^4y(V_m - E_K)
\]

\[
I_{Ca} = g_{Ca}s^5r(V_m - E_{Ca})
\]

\[
I_{kCa} = g_{kCa}q(V_m - V_k)
\]

where the gates are defined in Table 3.1.

<table>
<thead>
<tr>
<th>gate</th>
<th>( \alpha )</th>
<th>( \beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( s )</td>
<td>( 0.03(60 - V_m) )</td>
<td>( 0.0001(V_m - 45) )</td>
</tr>
<tr>
<td>( m )</td>
<td>( 0.32(12 - V_m) )</td>
<td>( 0.28(V_m - 40) )</td>
</tr>
<tr>
<td>( h )</td>
<td>( 0.128 \exp \left( \frac{17 - V_m}{18} \right) )</td>
<td>( 4 \exp \left( \frac{20 - V_m}{5} \right) + 1 )</td>
</tr>
<tr>
<td>( n )</td>
<td>( 0.032(15 - V_m) )</td>
<td>( 0.5 \exp \left( \frac{10 - V_m}{40} \right) )</td>
</tr>
<tr>
<td>( y )</td>
<td>( 0.028 \exp \left( \frac{15 - V_m}{15} \right) + \frac{2}{\exp \left( \frac{25 - V_m}{20} \right) + 1} )</td>
<td>( 0.4 \exp \left( \frac{20 - V_m}{40} \right) + 1 )</td>
</tr>
<tr>
<td>( r )</td>
<td>( 0.005 )</td>
<td>( 0.025(200 - x) \exp \left( \frac{200 - x}{20} \right) - 1 )</td>
</tr>
<tr>
<td>( q )</td>
<td>( \frac{0.005(200 - x) \exp \left( \frac{V_m}{20} \right)}{\exp \left( \frac{200 - x}{20} \right) - 1} )</td>
<td>0.002</td>
</tr>
</tbody>
</table>
and the differential equations for each gate are of the form shown in Eq. (3.5). One additional $x$-gate is defined by

$$\frac{dx}{dt} - \frac{c \cdot I_{Ca}}{A \cdot d} - \beta_x \cdot x.$$  

The constants for the Traub model appear in Table 3.2.

| $\beta_x$ | 0.1 |
| $A$ | 3320 |
| $d$ | 0.0005 |
| $E_{Na}$ | 115 mV |
| $g_{Na}$ | 3.32 $\mu$S |
| $g_{Ca}$ | 6.64 $\mu$S |
| $c$ | 5.2 |
| $E_{Ca}$ | 140 mV |
| $E_k$ | -15 mV |
| $g_{kCa}$ | 0.1 $\mu$S |
| $g_K$ | 3.98 $\mu$S |

The additional phenomena the Traub model enables is a repeating cycle of depolarization and repolarization called **bursting**. Bursting is often modulated by the strength of a sustained input current and is shown in Fig. 3.11.

**Figure 3.11:** Bursting in the Traub membrane model.

### 3.4.3 Complex Gating

Hodgkin and Huxley assumed that ion gates could be either open or closed. But, the $h$ gate was a clue to the more complex nature of channels. In reality, some channels may be open in more than one way, closed in more than one way, and even inactivated in more than one way. The method of modeling the more complex dynamics of an ion channel is through a **Markov State** model. Figure 3.12 is an example of...
3.4. COMPLEX IONIC MODELS

the more complex dynamics of a Sodium channel. Each circle is a state that the channel may be in. The $\alpha$ and $\beta$ terms are the rates of transition from one state to another and typically do not depend upon $V_m$. To derive the differential equations for a state, we subtract the product of the state and all outflowing rates (exiting arrows) from the product of the entering states and inflow rates (entering arrows). For example, the equations for the model in Fig. 3.12 are:

$$\frac{dC_3}{dt} = \beta_{23}C_2 - \alpha_{32}C_3 \quad (3.28)$$
$$\frac{dC_2}{dt} = \beta_{12}C_1 + \alpha_{32}C_3 - (\alpha_{21} + \beta_{23})C_2 \quad (3.29)$$
$$\frac{dC_1}{dt} = \beta_{01}O + \alpha_{21}C_2 - (\alpha_{10} + \beta_{12})C_1 \quad (3.30)$$
$$\frac{dIF}{dt} = \beta_{45}IS + \alpha_{40}O - (\alpha_{54} + \beta_{40})IF \quad (3.31)$$
$$\frac{dIS}{dt} = \alpha_{54}IF - \beta_{45}IS \quad (3.32)$$
$$\frac{dO}{dt} = \beta_{40}IF + \alpha_{10}C_1 - (\alpha_{40} + \beta_{10})O \quad (3.33)$$

The advantage of this type of model is that it is a more direct link between the genetic code, expressed protein, structure of the channel, and electrophysiologic function. It is hoped that someday we will be able to engineer sections of genetic code and simulate their function before they are made. In this way, diseased channels could be repaired by making only the correction that is needed. Such a simulation of the function will require a Markov model.

Figure 3.12: Markov model of Sodium channel.

3.4.4 Gating Dependence on pH, Temperature and Concentrations

It was mentioned in Sec. 3.1.4 that ion channels are often gated by $V_m$ but could also be gated by $pH$, ionic or molecular concentrations, temperature, or some combination of all of these gating mechanisms. For example, the functions for $\alpha$ and $\beta$ in the Hodgkin-Huxely model were for a particular temperature. In general, these function may be much more complex, for example $\alpha(V_m, pH, [Mg^{2+}]_e, [Atropine], T)$. Although this may seem to be a daunting modeling task, there are some very important ion channels that are not gated by $V_m$ and are only sensitive to the concentration of some ion or molecule. These channels are said to be Ligand-gated and typically play an important role in mutations, the impact of drugs and the onset of diseases. In Ch. 6, the dynamics of the synapse will be modeled as gating by concentration of neurotransmitter.
3.4.5 Changes in Nernst Potentials

Earlier it was stated that a bursting neuron may begin to change the intra and/or extracellular concentrations. Even with pumps and exchangers, the cell may build up concentrations of some ions. Accompanying these concentration changes, will be a change in the Nernst potentials, and thus the driving forces behind the action potential. It is therefore important for some models to incorporate a way for concentrations to change. The most common technique is to write differential equations for the intra and extracellular ionic concentrations. For example, consider that there may be several $I_K$ outward currents that could potentially deplete the intracellular Potassium concentration, $[K^+]_i$. This change in $[K^+]_i$ would impact $E_K$ as well as $V_m$ through the Goldman-Hodgkin-Katz equation. A common formulation would be:

$$\frac{d[K^+]_i}{dt} = \frac{I_{K1} + I_{K2} + I_{K3}}{FV_i} \tag{3.34}$$
$$\frac{d[K^+]_e}{dt} = \frac{I_{K1} + I_{K2} + I_{K3}}{FV_s} \tag{3.35}$$

where $F$ is Faraday’s constant, $V_i$ is the volume of the intracellular space, and $V_s$ is the small shell of extracellular space surrounding the outside of the cell. In this formulation, any $K^+$ ions leaving the intracellular space must enter the extracellular space.

A situation where ionic concentrations may drastically change is during a disease. For example, during ischemia (e.g., lack of $O_2$) the concentration of ATP drops and the pumps that restore concentration gradients become less efficient and may even fail. The result is a buildup of ions. If this buildup continues, cells may die and lyse (e.g., pop) spilling their ions into the extracellular space and lead to a drastic change in concentrations.

3.4.6 Intracellular Compartments and Buffers

The intracellular space in a cell is populated by many smaller organelles. Some of these organelles have their own membranes, with their own ion channels, and are capable of transporting ions to and from the intracellular space to the intra-organelle space. When this transport occurs, the concentration of that ion will change in the intracellular space. Functionally, these organelles behave as a buffer. As in the previous section, these changes in concentration can impact the Nernst potential of that ion. Figure 3.13 is a schematic of a $Ca^{2+}$ buffer.

3.5 PHENOMENOLOGICAL MODELS

Although the Hodgkin-Huxley mathematical model is simple to solve using today’s computers, Hodgkin and Huxley performed all of their calculations using calculators. In particular, computing exponentials was difficult, so a number of simplified models were developed that captured the basic features of neuronal action potentials.

3.5.1 Fitzhugh-Nagumo Model

In 1961, Fitzhugh and Nagumo independently developed a model based upon simple polynomials. In the Fitzhugh-Nagumo model, the $m$, $h$, $n$, and $V_m$ variables were reduced to only two differential equations.
The model has a steady-state resting potential, fast all-or-none upstroke, and slower repolarization. Furthermore, the parameters $a$, $b$, and $c$ can be tuned to generate action potentials of different shapes and durations.

### 3.5.2 Hindmarsh-Rose Model

The Fitzhugh-Nagumo model does not generate bursting behavior. In 1984, Hindmarsh and Rose developed a set of three differential equations that would allow for the phenomenon of bursting:

\[
\frac{dV_m}{dt} = V_m - \frac{V_m^3}{3} - W + I_{\text{stim}} \tag{3.36}
\]

\[
\frac{dy}{dt} = -dV_m^2 - y + c \tag{3.39}
\]

\[
\frac{dz}{dt} = r s V_m - rz - rs V_{\text{rest}} \tag{3.40}
\]

where $a$, $b$, $c$, $d$, $r$, $s$, and $V_{\text{rest}}$ are constants and may be tuned to producing different bursting behavior.

### 3.5.3 Integrate and Fire Model

In 1907, long before Hodgkin and Huxley, Lapicque proposed that the firing of an action potential could be modeled simply as a spike in voltage. As $I_{\text{stim}}$ is applied, $V_m$ will depolarize according to the familiar passive model

\[
\frac{dV_m}{dt} = \frac{1}{C_m} \left[ -G_L(V_m - E_L) + I_{\text{stim}} \right] . \tag{3.41}
\]
When $V_m$ reaches some predefined $V_m^{th}$, however, all solving of differential equations is suspended. The simulation then abruptly jumps $V_m$ to some value, $V_m^{peak}$, to simulate the upstroke of the action potential. In some implementations, $V_m$ is clamped to $V_m^{peak}$ for some short time and then reset back to the resting value as in Fig. 3.14. In other implementations, the reset is not exactly back to rest but below $V_m^{th}$. This simple yet elegant model is called the integrate and fire model. It is still used in neural modeling because it requires no updating of gating variables.

![Figure 3.14: Integrate and fire action potential.](image)

### 3.6 NUMERICAL METHODS: TEMPLATE FOR AN ACTIVE MEMBRANE

In Sec. 2.5, a way of numerically solving a differential equation was outlined. In the active membrane models, we need to keep track of several differential equations as well as compute rate constants, steady-state values and currents. Below is a template for how to write a program to solve the active equations.

- Define constants (e.g., $G_L, g_{Na}, g_K, C_m, dt$)
- Compute initial $\alpha$s and $\beta$s
- Compute initial conditions for state variables (e.g., $V_m^{rest}, m, h, n$)

for (time=0 to time=end in increments of $dt$)

- Compute Currents (e.g., $I_L, I_{Na}, I_K$)
- Compute $\alpha$s and $\beta$s
- Update Differential Equations ($V_m, m, n, h$)
- Save values of interest into an array (e.g., $V_m$)
Homework Problems

(1) If a stimulus is above a strength duration curve and the membrane is active, will and action potential fire? Explain.

(2) The following data were recorded at the peak of a Hodgkin-Huxely action potential:

\[ I_K = 353.574 \frac{\mu A}{cm^2} \]
\[ I_{Na} = -394.59 \frac{\mu A}{cm^2} \]
\[ g_K = 3.36737 \frac{mS}{cm^2} \]
\[ g_{Na} = 130.7429 \frac{mS}{cm^2} \]
\[ m = 0.889 \]
\[ h = 0.288 \]
\[ E_K = -75.0 mV \]
\[ E_{Na} = 50 mV \]

a) What is the peak magnitude of the action potential in mV?
b) How does this compare to \( E_{Na} \)? What does this mean?
c) Compute the fraction of \( K^+ \) channels open.
d) What is the value of \( I_{leak} \)?

(2) In a voltage-clamp experiment, the transmembrane potential \( (V_m) \) was changed from rest (-60mV) to 0mV, kept at 0mV for 100ms, and then changed to -50mV. Relevant parameters are given in the table below (time constants in msec).

<table>
<thead>
<tr>
<th>( V_m )</th>
<th>( \alpha_m )</th>
<th>( \tau_m )</th>
<th>( \alpha_h )</th>
<th>( \tau_h )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60mV</td>
<td>0.225</td>
<td>0.238</td>
<td>0.0697</td>
<td>8.51</td>
</tr>
<tr>
<td>-50mV</td>
<td>0.433</td>
<td>0.368</td>
<td>0.0423</td>
<td>6.16</td>
</tr>
<tr>
<td>0mV</td>
<td>3.62</td>
<td>0.266</td>
<td>0.00347</td>
<td>1.05</td>
</tr>
</tbody>
</table>

a) Sketch the holding potential and label the times and voltage levels.
b) Compute the fraction of h gates open at \( t = 100msec \).
c) Compute the fraction of h gates that are open at \( t = 104msec \).
d) Compute the probability of an Na+ channel being open at \( t = 104msec \).

(3) Extend the Hodgkin-Huxely model to include Potassium buffering by an intracellular organelle. Be sure to write down differential equations for the concentrations of \( K^+ \) in the organelle, cell,
42 CHAPTER 3. ACTIVE MEMBRANES

and extracellular space. Include two additional currents, one between intra and extracellular space
and one between intracellular and organelle space.

(4) Write down the differential equations to describe the Markov Model of the $K^+$ channel shown
below.

Simulation Problems

(1) Program the Hodgkin-Huxley membrane model and reproduce one of the properties in Sec. 3.3.
Assume $G_L = 0.3 mS/cm^2$, $g_{na} = 120.0 mS/cm^2$, $g_K = 36.0 mS/cm^2$, $E_L = -50 mV$, $E_{Na} = 55 mV$, $E_K = -72.0 mV$ $C_m = 1 \mu F/cm^2$.

(2) Create a strength-duration curve for anode break of the Hodgkin-Huxley model.

(3) Program the Integrate and Fire membrane model with $R_m = 2 k\Omega cm^2$, $C_m = 1.0 \mu F/cm^2$, $V_{rest} = -70 mV$, $V_{th} = -60 mV$, and $V_{peak} = 20 mV$. Assume that the voltage is reset to rest after firing.

(4) Find $I_{the}$ for the Integrate and Fire model in problem 3. Then, proceed to problem 5.

(5) Program the Hindmarsh-Rose model with the parameters $a = 0.4$, $b = 2.4$, $c = 1.5$, $d = 1.0$, $s = 1.0, r = 0.001$. Show that by adding a short-duration $I_{stim}$ to the $dx/dt$ term, these parameters will cause periodic bursting.

(6) For the Hindmarsh-Rose model in problem 5, find a value for a continuous $I_{stim}$ that will turn the bursting into a model that fires periodically.

(7) Program the Traub Neuron model and determine if the properties in Sec. 3.3 apply.

(8) For the Traub model, determine if a continuously applied current can induce repeated bursting. If stimulus strength is changed how does the behavior of the model change?
Experimental studies have shown that a neuron does not fire all at once. Rather, there is a wave of electrical activity that is passed from one small patch of membrane to the next, and so on, around the cell. Likewise, electrical impulses spread down dendrites to the soma by moving from one patch to the next. A similar process is involved in the spread of electrical impulses from the axon hillock down the axon. These waves of electrical activity are called *propagation*. Not all propagation, however, is the same. As the dendrites are composed of passive patches of membrane, they will leak charge out of each patch as propagation moves forward. Therefore, the strength of the impulse will be decreased or *attenuated* down the dendrite. Attenuated propagation is often called *passive propagation*. The axon, on the other hand, is composed of active patches of membrane that can generate their own currents (e.g., an action potential). Therefore, an impulse that enters the axon hillock will propagate *unattenuated* to the end of the axon. Furthermore, because of the refractory period, *propagation* can proceed in only one direction. Unattenuated propagation is often called *active propagation*.

In this chapter, we will develop models to describe propagation. As passive propagation is considerably more simple than active propagation, we will begin by considering propagation in the dendrites. Active propagation in an axon will be explained as a special case of passive propagation.

### 4.1 PASSIVE PROPAGATION IN DENDRITES

#### 4.1.1 The Core Conductor Model

The dendrites of a neuron may be thought of as being composed of many small cylindrical patches of passive membrane connected together into a thin one-dimensional cable (Fig. 4.1). In fact, these assumptions are the same as those used by the pioneers of cable theory to describe propagation of electricity down a wire. Since the theory of propagation down a wire was developed before propagation in neurons was considered, the terms *cable theory* and *core conductor theory* have been adopted by electrophysiologists.

Consider the **discrete** cable in Fig. 4.2 where the passive elements are separated by \( dx \) and connected together in the intracellular and extracellular space by resistance per unit length, \( r_i \) and \( r_e \) (\( \Omega/cm \)). From Fig. 4.2, we can choose a node in the center of this cable in Fig. 4.3 and write down intra- and extracellular currents at nodes 1, 2, and 3 using Kirchhoff’s Current Law.

At Node 2,

\[
\frac{\phi_1^i - \phi_2^i}{r_i \cdot dx} - \frac{\phi_2^i - \phi_3^i}{r_i \cdot dx} - dx \cdot i_m = 0 \tag{4.1}
\]

\[
\frac{\phi_1^e - \phi_2^e}{r_e \cdot dx} - \frac{\phi_2^e - \phi_3^e}{r_e \cdot dx} + dx \cdot i_m = 0 \tag{4.2}
\]
or more compactly,

\[
\frac{\phi_1 - 2\phi_2 + \phi_3}{dx^2 \cdot r_i} = i_m
\]  

(4.3)

\[
\frac{\phi_e - 2\phi_2 + \phi_3}{dx^2 \cdot r_e} = -i_m
\]  

(4.4)

where \(i_m\) is defined as the passive circuit:

\[
i_m = c_m \frac{dV_m}{dt} - \frac{V_m}{r_m}
\]  

(4.5)

rearranging Eqs. (4.3) and (4.4)

\[
\frac{\phi_1 - 2\phi_2 + \phi_3}{dx^2} = r_i \cdot i_m
\]  

(4.6)

\[
\frac{\phi_e - 2\phi_2 + \phi_3}{dx^2} = -r_e \cdot i_m
\]  

(4.7)

and then subtracting Eq. (4.7) from Eq. (4.6)

\[
\frac{(\phi_1 - \phi_e) - 2(\phi_2 - \phi_2) + (\phi_3 - \phi_3)}{dx^2} = (r_i - r_e)i_m
\]  

(4.8)

\[
\frac{V_m^1 - 2V_m^2 + V_m^3}{dx^2} = (r_i - r_e)i_m
\]  

(4.9)
4.1. PASSIVE PROPAGATION IN DENDRITES

If we let \( dx \to 0 \), Eq. (4.10) becomes the continuous cable equation:

\[
\frac{V_m^1 - 2V_m^2 + V_m^3}{dx^2} = (r_i - r_e) \left[ c_m \frac{dV_m}{dt} + \frac{V_m}{r_m} \right].
\]  

(4.10)

If we let \( dx \to 0 \), Eq. (4.10) becomes the continuous cable equation:
\[ \frac{\partial^2 V_m}{\partial x^2} = (r_i - r_e) \left[ c_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m} \right] \] (4.11)

where we have replaced the \(d/dt\) terms by \(\partial/\partial t\) to indicate that this is a partial differential equation. A bit of algebra yields the following:

\[ \frac{1}{r_i - r_e} \frac{\partial^2 V_m}{\partial x^2} = c_m \frac{\partial V_m}{\partial t} + \frac{V_m}{r_m} \] (4.12)
\[ \frac{r_m}{r_i - r_e} \frac{\partial^2 V_m}{\partial x^2} = r_m c_m \frac{\partial V_m}{\partial t} + V_m \] (4.13)

or in the typical core-conductor form

\[ \lambda^2 \frac{\partial^2 V_m}{\partial x^2} = \tau_m \frac{\partial V_m}{\partial t} + V_m \] (4.14)

where \(\tau_m = r_m c_m\) is the membrane time constant in msec, as defined in Sec. 2.2 and

\[ \lambda = \sqrt{\frac{r_m}{r_i + r_e}} \] (4.15)

is the cable space constant in units of cm.

### 4.1.2 A Simplification

One very common simplification to the cable equation is achieved by assuming that the extracellular bath is much more conductive than the intracellular space. As a result, we can assume that \(r_e \approx 0\). As a result, all of the \(\phi_e\) potentials are equal and the extracellular bath acts as a ground. Therefore, \(V_m = \phi_i\) and \(\lambda = \sqrt{\frac{r_m}{r_i}}\).

### 4.1.3 Units and Relationships

The units of the variables in Eqs. (4.1)–(4.15) can be confusing because they are different than the units used in Ch. 2. The tables show the units used in parameters of the core conductor model and their relationship to the membrane parameters.

Given these relationships we can rewrite Eq. (4.14) as:

\[ \frac{1}{(R_i + R_e)} \frac{\partial^2 V_m}{\partial x^2} = \beta \left[ C_m \frac{\partial V_m}{\partial t} + \frac{V_m}{R_m} \right] \] (4.16)

where \(\beta = 2/a\).
4.1. PASSIVE PROPAGATION IN DENDRITES

Table 4.1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Name</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r_m )</td>
<td>Membrane Resistance</td>
<td>( \Omega/cm )</td>
</tr>
<tr>
<td>( r_i )</td>
<td>Axial Intracellular Resistance</td>
<td>( \Omega/cm )</td>
</tr>
<tr>
<td>( r_e )</td>
<td>Axial Extracellular Resistance</td>
<td>( \Omega/cm )</td>
</tr>
<tr>
<td>( c_m )</td>
<td>Axial Membrane Capacitance</td>
<td>( \mu F/cm )</td>
</tr>
<tr>
<td>( i_m )</td>
<td>Axial Membrane Current</td>
<td>( \mu A/cm )</td>
</tr>
<tr>
<td>( dx )</td>
<td>Spatial Step Size</td>
<td>( cm )</td>
</tr>
<tr>
<td>( a )</td>
<td>Cable radius</td>
<td>( cm )</td>
</tr>
</tbody>
</table>

Table 4.2:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Name</th>
<th>Unit</th>
<th>Equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_i )</td>
<td>Specific Intracellular Resistivity</td>
<td>( \Omega/cm )</td>
<td>( \pi a^2 r_i )</td>
</tr>
<tr>
<td>( R_e )</td>
<td>Specific Extracellular Resistivity</td>
<td>( \Omega/cm )</td>
<td>( \pi a^2 r_e )</td>
</tr>
<tr>
<td>( R_m )</td>
<td>Specific Membrane Resistivity</td>
<td>( \Omega/cm^2 )</td>
<td>( 2\pi a r_m )</td>
</tr>
<tr>
<td>( C_m )</td>
<td>Specific Membrane Capacitance</td>
<td>( \mu F/cm^2 )</td>
<td>( c_m / (2\pi a) )</td>
</tr>
<tr>
<td>( I_m )</td>
<td>Specific Membrane Current</td>
<td>( \mu A/cm^2 )</td>
<td>( i_m / (2\pi a) )</td>
</tr>
</tbody>
</table>

4.1.4 An Applied Stimulus

A stimulus, \( i_{\text{stim}} \), may be applied at a particular location on the cable for some particular duration. Mathematically, a stimulus applied to a point can be represented using the Dirac delta function, \( \delta(s) \). If the stimulus at this point is applied at \( t = 0 \) and remains on, the unit step function, \( u(t) \), may be used. For the simple case where a stimulus is applied to a point in the middle of an infinitely long cable beginning at \( t = 0 \),

\[
\lambda^2 \frac{\partial^2 V_m}{\partial x^2} = \tau_m \frac{\partial V_m}{\partial t} + V_m \pm r_m i_{\text{stim}} \delta(x) u(t)
\]  
(4.17)

where the \( \pm \) is to take into account either an intracellular or extracellular stimulus.

4.1.5 Steady-State Solution

We can consider the steady state solution to Eq. (4.17) by assuming \( \frac{\partial V_m}{\partial t} = 0 \):

\[
\lambda^2 \frac{d^2 V_m}{dx^2} - V_m = -r_m i_{\text{stim}} \delta(x)
\]  
(4.18)

where we have assumed the stimulus will depolarize the membrane. Equation (4.18) is an ordinary differential equation that no longer depends upon time. We can find the homogeneous solution by finding the solution to:
\[
\lambda^2 \frac{d^2 V_m}{dx^2} - V_m = 0 .
\] (4.19)

The solution to Eq. (4.19) is the Helmholtz equation:

\[
V_m(x) = Ae^{-|x|/\lambda} + Be^{|x|/\lambda} .
\] (4.20)

The second term does not make physical sense so

\[
V_m(x) = Ae^{-|x|/\lambda} .
\] (4.21)

To find \( A \) we will integrate Eq. (4.18) around the stimulus \((x = 0)\):

\[
\lambda^2 \int_{0-}^{0+} \frac{d^2 V_m}{dx^2} \, dx - \int_{0-}^{0+} V_m \, dx = -r_m i_{stim} \int_{0-}^{0+} \delta(x) \, dx .
\] (4.22)

Evaluation shows that \( A = \frac{r_m \cdot i_{stim}}{2\lambda} \) so the steady-state solution is

\[
V_m(x) = \frac{r_m \cdot i_{stim}}{2\lambda} e^{-|x|/\lambda} .
\] (4.23)

Note that the value of the constant \( A \) will be dependent upon the nature of the stimulus. For example, the solution would change if we applied the stimulus to one end of the cable rather than at the middle.

### 4.1.6 Finding The Length Constant

If a cable with unknown membrane properties is encountered, Eq. (4.23) is a way to find \( \lambda \) and \( r_m \). If a known stimulus is applied for a long time, the membrane will eventually reach steady-state. At the point of the stimulus, \( x = 0 \) so the exponential term becomes 1. Therefore, the voltage at the stimulus is \( \frac{r_m \cdot i_{stim}}{2\lambda} \).

Furthermore, this voltage level will fall off in space (in both directions because of \(|x|\)) at an exponential rate governed by \( \lambda \). Therefore, \( \lambda \) can be found as the rate of fall off in a similar way to finding \( \tau_m \) in Ch. 2.

Once \( \lambda \) is known, \( r_m \) can be found from \( \frac{r_m \cdot i_{stim}}{2\lambda} \).

### 4.1.7 Time and Space Dependent Solution

Although we will not show the solution here, it is possible to solve Eq. (4.17) for \( V_m \) as a function of both time and space:

\[
V_m(x, t) = \frac{r_m \cdot i_{stim}}{4\lambda} \left[ e^{-|x|/\lambda} \text{erfc} \left( \frac{|x|}{2\lambda} \sqrt{\frac{\tau_m}{t}} - \sqrt{\frac{t}{\tau_m}} \right) 
- e^{\frac{|x|}{\lambda}} \text{erfc} \left( \frac{|x|}{2\lambda} \sqrt{\frac{\tau_m}{t} + \sqrt{\frac{t}{\tau_m}}} \right) \right].
\] (4.24)
where \( \text{erfc} \) is the complimentary error function defined by

\[
erfc(y) = 1 - \text{erf}(y)
\]

and

\[
erf(y) = \frac{2}{\pi} \int_0^y e^{-z^2} dz
\]  

is defined as the error function (see Fig. 4.4). It is important to note that Eq. (4.24) is for an infinite cable with a negative \( i_{\text{stim}} \). The leading terms in Eqs. (4.23) and (4.24) will change if the nature of the stimulus is changed or the cable is not infinitely long.

Figure 4.4: Error and complimentary error functions.

Figure 4.5 shows the time and space solutions to Eq. (4.24) for different times (left panel) and different locations in space (right panel). Because the specific numbers may vary for any given cable, the plot is shown in terms of the general passive properties of the cable, i.e., \( \lambda \) and \( \tau_m \). It is important to note that the fall off in space is exponential only for the steady-state \( t \to \infty \). Likewise, the rise in time is exponential (as in an RC circuit) only at \( x = \lambda \).

### 4.2 ACTIVE PROPAGATION IN AXONS

In Sec. 4, we considered passive propagation down a cable as a model of dendritic propagation. The membrane of the axon, however, has many nonlinear ion channels that are capable of generating an action potential. The only modification needed to create an active cable is to replace the passive \( I_{\text{ion}} = V_m/r_m \) with a more complex model as outlined in Ch. 3. Whereas a stimulus applied to a passive cable will be attenuated, in an active cable the action potential will propagate unattenuated. In this way, a signal that reaches the axon hillock will be propagated unattenuated to the end of the axon. In all but the simplest cases, it is not possible to derive an analytic solution when propagation is active.

To demonstrate the concept of active propagation, Fig. 4.6 shows propagation down an active 3cm long axon. The superthreshold stimulus was delivered to the left end of the axon at \( t = 0 \text{msec} \). In
Figure 4.5: Time and space solution in a passive cable.

In the left panel, action potentials shown at $x = 1\text{cm}$ (black) and $x = 2\text{cm}$ (red). Notice that although the action potential shape does not change, there is a delay in timing of the upstroke. The right panel shows a snapshot of the voltage along the cable at $t = 40\text{msec}$. Notice that the when propagation is from left to right, the spatial plot has the shape of a reversed action potential. To understand why, consider the location at $x = 2\text{cm}$. In the right panel, at $40\text{msec}$, the point is at rest. The shape in the left panel, however, is moving to the right so eventually the sharp spike will reach $x = 2\text{cm}$. From the right panel we know that this occurs at approximately $t = 55\text{msec}$. In space, the reversed action potential shape will continue to move to the right causing the location at $x = 2\text{cm}$ to undergo all of the phases of an action potential.

Figure 4.6: Propagation down an active cable.

For uniform propagation down a cable and uniform $I_{\text{ion}}$ everywhere in the cable, we say that

$$V_m(x, t) = V_m(x - \theta(t)) \tag{4.26}$$
where $\theta$ is the *propagation velocity* and is a measure of the speed at which the action potential moves down the cable. The reason Eq. (4.26) works is because the shape of the action potential is the same at every point on the cable. The only parameter that changes is *when* the action potential occurs in time. Using the chain rule twice

$$\frac{\partial V_m}{\partial x} = \frac{1}{\theta} \frac{\partial V_m}{\partial t}$$  \hspace{1cm} (4.27)

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{1}{\theta^2} \frac{\partial^2 V_m}{\partial t}$$  \hspace{1cm} (4.28)

Substitution into Eq. (4.16) yields

$$I_m = \frac{a^2 R_i \theta^2}{d^2 V_m} dt.$$  \hspace{1cm} (4.29)

Upon careful inspection, Eq. (4.29) has a deeper meaning. As long as $I_{ion}$ does not change throughout the cable, a family of solution exists with the only requirement being:

$$\frac{a^2 R_i \theta^2}{d^2 V_m} = K$$  \hspace{1cm} (4.30)

$$\theta = \sqrt{\frac{a}{2R_i K}}$$  \hspace{1cm} (4.31)

where $K$ is a constant. The usefulness of Eqs. (4.30) and (4.31) are that only one set of $a$ and $\theta$ are needed to find $R_i K$. Once $R_i K$ is known, the effect of any change in $a$ on $\theta$ can be predicted.

### 4.2.1 Saltatory Conduction

A problem with using active propagation to transmit an impulse over long distances is that the signal will take time to traverse the axon. In fact, in some regions of the body an axon can be up to one meter long. To compensate, the nervous system has developed a clever solution to speed up propagation. Schwann cells (a type of glial cell) create a *myelin sheath* around the axon. The presence of this sheath makes it nearly impossible for current to cross the cell membrane. The impact is that membrane directly under the sheath has a much higher $R_m$ and the thicker membrane decreases $C_m$. Therefore, membrane covered in myelin is effectively *passive*.

As shown in Fig. 4.7, the sheath does leave small regions of the neuron cell membrane exposed, called *Nodes of Ranvier*, which may fire an action potential. If an active patch of membrane fires at a Node of Ranvier, current will flow to the right but will not be able to easily cross the cross the membrane because of the high $R_m$. Instead, most current will follow the path of least resistance and jump farther down the cable. So, in effect, the high resistance of the myelin creates a short circuit that skips quickly from one Node of Ranvier to the next. Multiple Sclerosis (MS) is a disease that causes inflammation and scaring of the myelin sheath leading to degradation of neural impulse propagation. The symptoms are changes in sensations, muscle spasms, a lack of coordination and balance, pain, and eventually cognitive and emotional impairment.
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Propagation occurs in many other systems, using chemical, mechanical, fluid, or bits of information as the medium of propagation. For an alternative perspective on propagation, consider arranging you and ten of your classmates in a line all shoulder to shoulder. To the right of the line is a large bag filled with shredded paper. The person on the far right end then grabs a large handful of shreds in their right-hand. The rules for each person will be to receive paper in their right-hand, pass it to their left-hand and then pass to the right-hand of the next person in the line. Using these simple rules, the shreds will propagate down the line from right to left. If your line tries to propagate shreds quickly, you will notice that most of the shreds are lost by the time propagation ends at the left end of the line. In the activity, the shreds are analogous to charges and the movement of shreds is a current flow. The size of each person’s hands are analogous to a capacitance and how much paper they lose is similar to a leakage resistance. You may also notice that much of the paper has fallen to the ground. In fact, this may the exact situation in the neuron as change that leaves the cell disappears into the extracellular space which acts as a large electrical ground. Next, consider that most of the shreds were lost in the first few transitions with much less being lost as propagation continued. Therefore, the way shreds are lost as propagation continues down the cable may be approximated by a decaying exponential.

As the shreds are lost during propagation, our analogy is to passive propagation. A small change, however, could turn passive propagation to active propagation. If everyone in the line has a handful of shreds in their left hand, and the propagation is reinitiated, you will discover that the person at the end of the line will have a considerable amount of shreds. Furthermore, the active propagation activity could be modified for saltatory conduction by simply skipping every other (or every three) people in the line.

Figure 4.7: Schematic of saltatory conduction.
4.4 NUMERICAL METHODS: THE FINITE AND DISCRETE CABLE

In all but the most simple situations, the continuous cable model can only be solved numerically using a computer. It is therefore required that the cable be of finite length and divided into small patches of membrane. Beginning with the continuous Eq. (4.11) the finite difference approximation may be made for the second derivative in space.

\[
\frac{V^{k-1}_m - 2V^k_m + V^{k+1}_m}{(r_i - r_e) \, dx^2} = (r_i - r_e) \left( c_m \frac{dV_m}{dt} + \frac{V_m}{r_m} \right) \tag{4.32}
\]

where \( k \) is a variable to represent any node in the middle of the cable. Note that the equation able is similar to Eq. (4.10). Rearranging

\[
\frac{dV_m}{dt} = \frac{1}{c_m} \left[ \frac{V^{k-1}_m - 2V^k_m + V^{k+1}_m}{(r_i - r_e) \, dx^2} - \frac{V_m}{r_m} \right] \tag{4.33}
\]

and using the Euler method of Sec. 2.5

\[
dV_m = \frac{dt}{c_m} \left[ \frac{V^{k-1}_m - 2V^k_m + V^{k+1}_m}{(r_i - r_e) \, dx^2} - \frac{V_m}{r_m} \right] \tag{4.34}
\]

\[
V_{\text{new}} = V_{\text{old}} + dV_m \tag{4.35}
\]

an every \( V_m \) is not discrete in both time and space. Note that in active propagation the gating variable must also be integrated in time, however, they do not require information from their neighbors. Therefore, the simple Euler method may be used.

A problem is encountered, however, with the above formulation. Consider evaluating the left most node on the cable (e.g., \( k = 1 \)). An update of the end node requires information at \( k = 0 \) which does not exist. The same problem occurs at the right most node of the cable. To overcome the problem at the endpoints, we must enforce a boundary condition. The most common assumption in neural propagation is that no current can leave either end of the cable. This is called a sealed-end boundary condition. Mathematically,

\[
\frac{d\phi_i}{dx} = -I_i r_i = 0 \tag{4.36}
\]

\[
\frac{d\phi_e}{dx} = -I_e r_e = 0 . \tag{4.37}
\]

The most straightforward way to enforce this boundary condition is to define a ghost node that extends past the end of the cable (see Fig. 4.8). Then, at the two cable ends

\[
\phi^{\text{left}}_{i,e} = \phi_{i,e}^2 \tag{4.38}
\]

\[
\phi^{\text{right}}_{i,e} = \phi_{i,e}^{n-1} \tag{4.39}
\]
and ensures that at the first and last node, Eqs. (4.36) and (4.37) are satisfied.

Combining Eq. (4.34) and the sealed-end, we can write the equation for node 1 as

\[
\frac{dV_m}{dt} = \frac{c_m}{cm} \left[ \frac{V_m^{left} - 2V_m^1 + V_m^2}{(r_i - r_e) dx^2} - \frac{V_m}{r_m} \right]
\]  \hspace{1cm} (4.40)

\[
\frac{dV_m}{dt} = \frac{c_m}{cm} \left[ \frac{2V_m^2 - 2V_m^1}{(r_i - r_e) dx^2} - \frac{V_m}{r_m} \right].
\]  \hspace{1cm} (4.41)

\[\begin{array}{c}
\Phi_i \\
r_i \\
c_m \\
r_e \\
\Phi_e
\end{array}\]

\[\begin{array}{c}
\Phi_i \\
r_i \\
c_m \\
r_e \\
\Phi_e
\end{array}\]

**Figure 4.8:** Sealed-end boundary condition.

Other possible boundary conditions for the end of the cable are to allow current to leave (*leaky end*) or to clamp the voltage (*clamped end*).

### 4.5 NUMERICAL METHODS: TEMPLATE FOR CABLE PROPAGATION

In Sec. 2.5, a way of numerically solving a differential equation was outlined. In the active membrane models, we need to keep track of several differential equations as well as compute rate constants, steady-state values and currents. Below is a template for how to write a program to solve the active equations.

1. Define constants (e.g., \(R_i, R_e, a, C_m\), other membrane variables)
2. Compute initial \(\alpha\)s and \(\beta\)s
3. Compute initial conditions for state variables (e.g., \(V_{rest}, m, h, n\))

   for (time=0 to time=end in increments of \(dt\))
   for (i=1 to i=Last Node in increments of (1))
Compute Currents at node \( i \)
Compute \( \alpha_s \) and \( \beta_s \) at node \( i \)

\[
\text{if (i=1)} \\
\quad \text{Update Differential Equations at left boundary} \\
\text{else if (i=last node)} \\
\quad \text{Update Differential Equations at right boundary} \\
\text{else} \\
\quad \text{Update Differential Equations at all middle nodes} \\
\text{end}
\]

Save values of interest into an array (e.g., \( V_m(i) \))

end

end

Store values of interest to a file

Homework Problems

(1) Work out the units for Eqs. (4.13)–(4.16).

(2) Show the steps between Eq. (4.22) and Eq. (4.23).

(3) Show how Eq. (4.24) becomes Eq. (4.23) as \( t \to \infty \).

(4) Using Eq. (4.24), show that at \( x = \lambda \), the time constant, \( \tau_m \), can be found as 63% of the steady-state value. Show that at \( x = 0 \), \( \tau_m \) can be found as 84% of the steady-state value.

(5) A passive nerve of radius 50\( \mu m \) is stimulated with a current pulse of 10nA in the middle \( (x = 0.0cm) \) of and cable. Using the plots below to answer the questions:
   a) Find \( \tau \) in msec.
   b) Find \( \lambda \) in cm. Start with the full solution to the cable equation.
   c) What is the \( R_m \) in \( \Omega cm^2 \)?

(6) In Fig. 4.6:
   a) What is the propagation velocity in \( cm/s \)?
   b) Explain what would happen to the spatial distribution if the propagation velocity was slower.
   c) Explain what would happen to the spatial distribution be is the propagation direction was reversed?
   d) Explain what would happen to the spatial distribution if the propagation was saltatory.

(7) In Fig. 4.6, assume \( a = 10\mu m \), and predict the propagation velocity if \( a \) is changed to \( a = 13\mu m \).
Simulation Problems

(1) Write code to simulation a passive 3cm cable with $R_m = 1k\Omega\,cm^2$, $C_m = 1\mu F/cm^2$, $dx = 100\mu m$, $a = 10\mu m$, $R_i = 100\Omega\,cm$ and assume that the extracellular space is large and acts as a ground and the boundaries are sealed-ends. Demonstrate that your problem is working by reproducing the left and right panels of Fig. 4.5.

(2) Modify the program from 1 above for active propagation of a Hodgkin-Huxely action potential. Stimulate the left end of the cable with a strength and duration sufficient to begin propagation. Demonstrate that your program works by creating a figure similar to 4.6.

(3) Use the code from 2 above to demonstrate the impact of changing the cable radius on propagation velocity.

(4) Use the code from 2 above to demonstrate the impact of changing $R_i$.

(5) Modify the program from 2 to demonstrate how saltatory conduction speeds propagation velocity. Let $R_m = 10k\Omega$ and $C_m = 0.01\mu F/cm^2$ for the sheath.
CHAPTER 5

Neural Branches

In Ch. 4, we considered propagation in uniform and straight cables. Figure 5.1 shows the complex web of dendrites that is collectively called the dendritic tree. It is clear that the tree contains branching cables, changes in diameter and curves. In this chapter we will generalize cable theory to handle changes in membrane properties and branching. We will first examine a method of simplifying the tree by lumping the dendrites into one large compartment. We will then turn to the more sophisticated method of multicompartment models.

Figure 5.1: Dendritic tree.

5.1 LUMPED MODELS

Lumped models were developed before computers became available as a way to simplify a complex neuron to a single unit. The goal was to make analytical predictions about the behavior of neurons.

5.1.1 The Rall Model

To model the complex dendritic tree, Rall recognized that the branching dendrite was simply acting as a receiver for many inputs and then attenuating the input. He therefore proposed that the dendritic tree could be collapsed down to one signal passive cable of varying diameter. This would mean that the dendritic tree could be represented by an equivalent cable as shown in Fig. 5.2. Likewise, the various
stimuli to the ends of the dendrites would be approximated by a single stimulus. The advantage of this idea is that computation would become fast and efficient and the actual geometry of the tree would not matter. It also enabled the analytical solution of attenuation down the dendritic tree. The disadvantage was that to achieve this collapse of the tree, Rall had to assume a relationship between the radii of all branches in relation to their main trunk

$$a_{\text{main}}^{3/2} = a_{\text{branch1}}^{3/2} + a_{\text{branch2}}^{3/2} + \ldots$$

(5.1)

This relationship was assumed to apply to every branch in the tree. Although Eq. (5.1) appears to be very restrictive, Rall showed that for many dendritic trees it was a reasonable approximation.

Figure 5.2: Rall’s equivalent cable.

5.1.2 The Ball and Stick Model

Another advantage of the collapsed dendritic tree is that the equivalent cable can be attached to a soma and axon to create a ball and stick model of a neuron. In Fig. 5.3, the dendrites have been collapsed using the method outlined by Rall and the soma is modeled as single compartment which may be either active or passive. The axon is in fact not present at all and is simulated by a time delay. As we found in Ch. 4, once an action potential has fired in the soma, it will propagate down the axon unattenuated to the axon terminal. So, the delay depends only upon the speed of propagation and length of the axon. All of these simplifications allow for the behavior of a neuron to solved numerically with a minimum of computing power.

Figure 5.3: Ball and stick model.
5.2 MULTICOMPARTMENT MODELS

It is clear from Fig. 5.1 that not all neurons will follow the assumption of Eq. (5.1). To lift the assumptions of the lumped models, we can consider that the dendrites and axons are made up of many small compartments. The general concept is shown in Fig. 5.4 and is a similar idea to when we derived the original cable equation using many small patches of membrane. Again, current is passed from one compartment to another in one direction only. At a branch, the current is simply split and passed into two (or more) compartments. Below we will derive equations to describe how this current split is achieved. Multicompartment models not only remove the Rall restriction but also allow for many different types of post-synapses to be incorporated into the model. The post-synapse will be considered in more detail in Ch. 6. The disadvantage of the multicompartment models is that compared to the Rall model, they must be solved numerically and required considerable greater computing power. Below we will introduce the basic elements of how to construct a dendritic tree of any complexity.

Figure 5.4: Schematic of dendritic compartments.

5.2.1 A Simple Compartment

To begin, we will make a slight change to the definition of a compartment by placing a node at the center of each patch as in Fig. 5.5. Each compartment will therefore have a length of $2dx$ and each half resistor in a compartment will be defined as

$$R = \frac{dx \cdot R_i}{\pi a^2}. \quad (5.2)$$

5.2.2 Change in Fiber Radius

Since the composition of the cytoplasm does not change drastically, the intracellular resistivity ($R_i$, a material property) does not change. Therefore, the determining factor of the half resistance with a radius, $a$, is

$$R(a) = \frac{dx \cdot R_i}{\pi a^2}. \quad (5.3)$$
Using the function $R(a)$, we can consider the impact of coupling a patch with a small radius $(a)$ to a patch with a larger radius $(b)$ as in Fig. 5.6. If we assume that all current flows from left to right and that extracellular space is conductive (e.g., $V_m = \phi_i$), then at Node 1

$$\frac{V_m^0 - V_m^1}{(R(a) + R(a))} - \frac{V_m^1 - V_m^2}{(R(a) + R(b))} - I_m = 0 \quad (5.4)$$

and at Node 2

$$\frac{V_m^1 - V_m^2}{(R(a) + R(b))} - \frac{V_m^2 - V_m^3}{(R(b) + R(b))} - I_m = 0. \quad (5.5)$$
Although these equations are not compact, they are easy to compute numerically. Because \( R \) is also dependent upon \( dx \), it is simple to extend our result to compartments of different lengths.

### 5.2.3 Branches

It is clear from Fig. 5.1 that we also must describe the points at which the dendrite branches. For simplicity, we will consider a single branch, as shown in Fig. 5.7, and assume that \( dx \) and \( a \) remain constant. The node labeled \( b \) is known as a *branch* node. There is no membrane at the branch node because it is not at the center of a compartment and is only used to make computation easier. At Node \( b \),

\[
\frac{V_{m}^{1} - V_{m}^{b}}{(R + R)} - \frac{V_{m}^{b} - V_{m}^{2}}{(R + R)} - \frac{V_{m}^{b} - V_{m}^{3}}{(R + R)} = 0 .
\]

(5.6)

To simplify, we can multiply through by the denominator:

\[
\frac{V_{m}^{1}}{3} - \frac{V_{m}^{b} + V_{m}^{2}}{3} + \frac{V_{m}^{3}}{3} = 0
\]

(5.7)

\[
V_{m}^{b} = \frac{V_{m}^{1} + V_{m}^{2} + V_{m}^{3}}{3} .
\]

(5.8)

Note that if \( dx \) or \( a \) were not the same everywhere, this equation would become much more complicated but still computable. We can now use \( V_{m}^{b} \) to derive equations for Nodes 1, 2, and 3:

\[
\frac{V_{m}^{0} - V_{m}^{1}}{2R} - \frac{V_{m}^{1} - V_{m}^{b}}{2R} - I_{m} = 0
\]

(5.9)

\[
\frac{V_{m}^{0} - 2V_{m}^{1} + V_{m}^{b}}{2R} = I_{m} .
\]

(5.10)

Similarly:

\[
\frac{V_{m}^{b} - 2V_{m}^{2} + V_{m}^{4}}{2R} = I_{m}
\]

(5.11)

\[
\frac{V_{m}^{b} - 2V_{m}^{3} + V_{m}^{5}}{2R} = I_{m} .
\]

(5.12)

The remainder of the extension of these branches (e.g., Nodes 4, 5, 6, . . .) can be formulated as uniform cables. Therefore, the key to writing the equations for a branch is the branch node.

### 5.2.4 The Soma

Although the Soma is considered to be the center of the neuron, it is often modeled as a single large passive compartment. The special role of the soma, however, is to integrate all impulses entering the dendritic tree. It is also directly connected to the axon hillock which is capable of generating an action potential. So, if the dendrites charge up the soma above threshold, the axon hillock will fire and send an action potential propagating down the axon. The soma therefore acts as a relay center between the dendrites and axon. Figure 5.8 shows a simple model of a neuron composed of two active axon compartments of...
radius \( a \), a passive soma of radius \( b \), a main dendritic trunk of radius \( c \), two branches of radius \( d \), and a third branch of radius \( e \).

By combining the ideas of active and passive cables with the ability to create branches and changes in diameter, we have all the concepts needed to create compartment models of any complexity. In fact, some researchers have created neuronal models, based upon the histology of real neurons that contain hundreds (or even thousands) of compartments. Although most of these models are two-dimensional,
the technology exists to create three-dimensional images of the branching structures of real dendrites. You may wish to think about how the analysis above needs to be changed to allow for a 3D structure.

5.2.5 Axon Collaterals and Semi-Active Dendrites
To simplify the discussion above we have made a number of assumptions that may not be true in a real neuron. First, some specialized neurons have either multiple axon projections or a single axon that branches many times. The geometry of a branching axon can be modeled in the same way as a branching dendrite with the exception that the ionic current, $I_{\text{ion}}$, will be more complex.

Recent data has also shown that dendrites are not simply passive cables. In other words, there are some ion channels embedded in the membrane that have nonlinear behavior so $I_m \neq \frac{V_m}{R_m}$. To model a semi-active dendrite we can simply replace the passive $I_{\text{ion}}$ term with the appropriate nonlinear currents. The presence of these channels allows currents and potentials to back propagate in the orthodromic direction. Back propagation may impact future pulses in the antidromic direction by changing the concentrations of ions (in particular $[Ca^{2+}]_i$) and transiently change $R_m$ of the dendrite.

Lastly, anatomical studies have shown that small protrusions, called spines, appear on some dendrites. Although it is not clear what role spines play, there have been a number of suggestions. One possibility is that spines increase the amount of membrane area for synaptic inputs from other neurons. Another view is that spines store $[Ca^{2+}]_i$ and other ions which modulate the strength of synaptic inputs. Lastly, some consider the spines to serve an electrical role by modulating the attenuation of a voltage headed toward the soma.

5.3 NUMERICAL METHODS: MATRIX FORMULATION
A typical node, $k$, in an unbranched cable of length $n$ with uniform membrane properties is connected to two neighbors. The governing equation for this node is therefore of the form:

$$\frac{V(k-1) - 2V(k) + V(k)}{R} = I_m(k). \quad (5.13)$$

At the ends of the cable we can assume seals ends as in Sec. 4.3

$$\frac{-2V(1) + 2V(2)}{R} = I_m(1) \quad (5.14)$$
$$\frac{2V(n-1) - 2V(n)}{R} = I_m(n). \quad (5.15)$$

Using matrices we can write this system of equations as

$$\begin{bmatrix}
\frac{-2}{R} & \frac{2}{R} & \cdots & \\
\frac{1}{R} & \frac{-2}{R} & \frac{1}{R} & \cdots \\
0 & \frac{1}{R} & \frac{-2}{R} & \frac{1}{R} & \cdots \\
\vdots & \vdots & \vdots & \ddots \phantom{\cdots} & \\
\cdots & \frac{1}{R} & \frac{-2}{R} & 0 & \frac{1}{R} & \frac{-2}{R} & \frac{1}{R} & \frac{-2}{R} & \frac{1}{R} & \cdots
\end{bmatrix}
\begin{bmatrix}
V(1) \\
V(2) \\
V(3) \\
\vdots \\
V(n-2) \\
V(n-1) \\
V(n)
\end{bmatrix}
= \begin{bmatrix}
I_m(1) \\
I_m(2) \\
I_m(3) \\
\vdots \\
I_m(n-2) \\
I_m(n-1) \\
I_m(n)
\end{bmatrix}$$
or including a more detailed representation for $I_m$

\[
\begin{bmatrix}
-\frac{2}{R} & \frac{2}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
0 & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \ddots \\
\cdots & \frac{1}{R} & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \ddots \\
\end{bmatrix}
\begin{bmatrix}
V(1) \\
V(2) \\
V(3) \\
\vdots \\
V(n-2) \\
V(n-1) \\
V(n) \\
\end{bmatrix}
\]

\[
\begin{bmatrix}
\frac{2}{R} & \frac{2}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
0 & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \ddots \\
\cdots & \frac{1}{R} & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & -\frac{2}{R} & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \frac{1}{R} & \cdots & \frac{1}{R} & \frac{1}{R} & \cdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \ddots \\
\end{bmatrix}
\begin{bmatrix}
I_{ion}(1) \\
I_{ion}(2) \\
I_{ion}(3) \\
\vdots \\
I_{ion}(n-2) \\
I_{ion}(n-1) \\
I_{ion}(n) \\
\end{bmatrix}
\]

or more compactly,

\[
AV = C_m \frac{dV}{dt} + I_{ion}
\]

(5.16)

where the bold text indicates a vector or matrix. $A$ is called a coupling matrix because the location of the entries show exactly how nodes are connected. Each row of $A$ corresponds to one node. Although we have assumed $R$ is constant, in reality we know that the resistance will depend upon $a$ and $dx$. In principle, $R$ could vary in the matrix $A$ and will indicate the strength of the connections.

To solve Eq. (5.16) we can perform the same rearrangement as in Sec. 2.5

\[
dV = \frac{dt}{C_m} [AV - I_{ion}]
\]

(5.17)

\[
V_{new} = V_{old} + dV.
\]

(5.18)

Besides being a compact way of writing the simultaneous equations of a cable, there is a practical reason for the vectorized form of Eq. (5.17). There exist many sophisticated methods of multiplying, adding, and factoring vectors and matrices that can drastically speedup the simulations.

Homework Problems

1. Create the $A$ coupling matrix for a cable where $R_i = 100 \Omega cm$.

2. How does the form of the matrix derived in problem 1 change if the cable branches?
(3) Create the coupling matrix for the simple neuron in Fig. 5.8. Assume sealed end boundaries.

(4) Explain how to create the matrix for the right side of Fig. 5.4 assuming all of the radii are equal.

(5) The Traub model of a Pyramidal neuron is shown in Fig. 7.1. Create the coupling matrix for this neuron assuming the diameter of all compartments is the same.

Simulation Problems

(1) Write a computer program to simulate the simple neuron in Fig. 5.8 where the passive properties are as given in Ch. 4, simulation problem 1, and the active properties are determined by HH parameters. Demonstrate that by stimulating one branch with a large enough current that an action potential is fired in the soma and propagates down the axon.

(2) In the program create above, does the stimulus threshold change if you stimulate the branch with radius $e$ versus stimulating one of the branches with radius $d$.

(3) There are two primary ways that the threshold at a soma could reach threshold. First, a single large current may depolarize one branch, which although attenuated, may still be above the threshold of the soma. Second, many smaller currents may enter many branches simultaneously and be integrated (added up) to bring the soma to threshold. Use the program in 1 to demonstrate both ways of firing the soma.