Appendix B

Mathematical methods

B.1 Numerical integration methods

Most of the mathematical models presented in this book involve differential equations describing the evolution in time and space of quantities such as membrane potential or calcium concentration. The differential equations are usually too complex to allow an analytical solution that would enable the explicit calculation of a value of, say, voltage at any particular time point or spatial position. The alternative is to derive algebraic expressions that approximate the differential equations and allow the calculation of quantities at specific, predefined points in time and space. This is known as numerical integration. Methods for defining temporal and spatial grid points and formulating algebraic expressions involving these grid points from the continuous (in time and space) differential equations are known as **finite difference** and **finite element methods**.

It is not our intention here to provide full details of these numerical integration methods. Instead, we will outline some of the simplest methods to illustrate how they work. This includes the Crank–Nicholson method (Crank and Nicholson, 1947), which is widely used as a basis for solving the cable equation. Further details on these methods as applied to neural models can be found in Carnevale and Hines (2006) and Mascagni and Sherman (1998).

B.1.1 Ordinary differential equations

We consider an ODE for the rate of change of membrane voltage:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = f(V,t) \tag{B.1}$$

for some function f of voltage and time. A particular example is the equation that describes the response of a patch of passive membrane to an injected current (Equation 2.16):

$$C_\mathrm{m}\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{E_\mathrm{m}-V}{R_\mathrm{m}} + \frac{I_\mathrm{e}}{a}. \tag{B.2}$$

As we saw in Chapter 2, if we assume that at time 0 that $V = E_m$ and I_e is switched from 0 to a finite value at this time and then held constant, this equation has an analytical solution:

$$V = E_m + (R_m I_e/a)[1 - \exp(-t/R_m C_m)]. \tag{B.3}$$

In general, an ODE cannot be solved analytically. We now consider how numerical approximations can be derived and solved for ODEs. We compute numerical solutions to Equation B.2 to illustrate how approximate and exact solutions can differ.

These numerical solutions are derived from algebraic equations that approximate the time derivative of the voltage. In combination with the function f, this enables the approximate calculation of the voltage at predefined time points. The **forward Euler method** estimates the time derivative at time t as the slope of the straight line passing through the points $(t, V(t))$ and $(t + \Delta t, V(t + \Delta t))$, for some small time-step Δt:

$$\frac{dV}{dt} \approx \frac{V(t + \Delta t) - V(t)}{\Delta t}. \tag{B.4}$$

This is known as a **finite difference method**, because it is estimating a quantity, the rate of change of voltage, that changes continually with time, using a measured change over a small but finite time interval Δt. How accurate this estimation is depends on how fast the rate of change of V is at that time. It becomes more accurate the smaller Δt is. For practical purposes in which we wish to calculate V at very many time points over a long total period of time, we want to make Δt as large as possible without sacrificing too much accuracy. Substituting this expression into our original Equation B.1 gives:

$$\frac{V(t + \Delta t) - V(t)}{\Delta t} = f(V(t), t). \tag{B.5}$$

Rearranging, we arrive at an expression that enables us to calculate the voltage at time point $t + \Delta t$, given the value of the voltage at time t:

$$V(t + \Delta t) = V(t) + f(V(t), t)\Delta t. \tag{B.6}$$

Suppose we start at time 0 with a known voltage $V(0) \equiv V^0$. We can use this formula to calculate iteratively the voltage at future time points Δt, $2\Delta t$, $3\Delta t$ and so on. If $t = n\Delta t$ and we use the notation $V^n \equiv V(t)$ and $V^{n+1} \equiv V(t + \Delta t)$, then:

$$V^{n+1} = V^n + f(V^n, n\Delta t)\Delta t. \tag{B.7}$$

For our example of the patch of passive membrane, this approximation is:

$$V^{n+1} = V^n + \frac{\Delta t}{C_m}\left(\frac{E_m - V^n}{R_m} + \frac{I_e^n}{a}\right). \tag{B.8}$$

This approximation has first order accuracy in time, because the local error between the calculated value of V and its true value is proportional to the size of the time-step Δt. A comparison of this method with the exact solution for the voltage response to an injected current is shown in Figure B.1. A rather large value of 5 ms for Δt is used to illustrate that this is only an

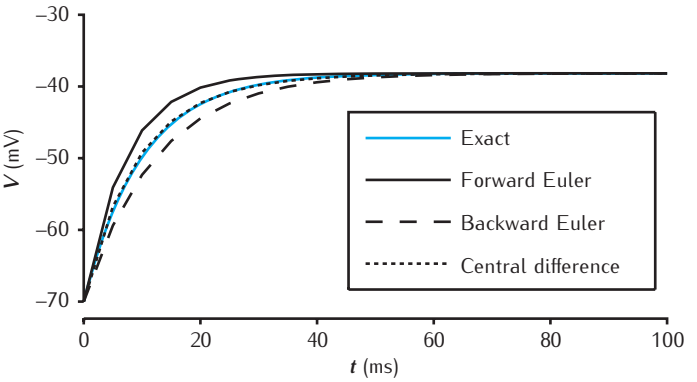

Fig. B.1 Comparison of finite difference approximations with the exact solution to current injection in passive membrane. The exact solution is plotted every 0.1 ms; the approximations use $\Delta t = 5$ ms.

approximation. If a time-step of less than 1 ms is used, then the approximation is virtually indistinguishable from the exact solution.

Other finite difference schemes can be more accurate for a given time-step and also more stable; the error grows but remains within finite bounds as the step size is increased. The **backward Euler method** is an example of a so-called implicit method that is also first order accurate in time, but is more stable than the forward Euler method. It results from using a past time point, rather than a future time point, in the approximation of the time derivative:

$$\frac{\mathrm{d}V}{\mathrm{d}t} \approx \frac{V(t) - V(t - \Delta t)}{\Delta t}. \tag{B.9}$$

The full ODE is thus approximated as:

$$\frac{V(t) - V(t - \Delta t)}{\Delta t} = f(V(t), t). \tag{B.10}$$

Shifting this to the same time points as the forward Euler method yields:

$$\frac{V(t + \Delta t) - V(t)}{\Delta t} = f(V(t + \Delta t), t + \Delta t). \tag{B.11}$$

Now both left- and right-hand sides involve the unknown voltage at the time point $t + \Delta t$. Using the notation for iterative time points, for our example we have:

$$C_\mathrm{m} \frac{V^{n+1} - V^n}{\Delta t} = \frac{E_\mathrm{m} - V^{n+1}}{R_\mathrm{m}} + \frac{I_\mathrm{e}^{n+1}}{a}. \tag{B.12}$$

Fortunately, as for the forward Euler expression, this can be rearranged to give an explicit, but now slightly different, equation for V^{n+1}:

$$V^{n+1} = \left[V^n + \frac{\Delta t}{C_\mathrm{m}} \left(\frac{E_\mathrm{m}}{R_\mathrm{m}} + \frac{I_\mathrm{e}^{n+1}}{a} \right) \right] \Big/ \left(1 + \frac{\Delta t}{R_\mathrm{m} C_\mathrm{m}} \right). \tag{B.13}$$

For the same time-step, this method tends to underestimate the rate of change in voltage in our example (Figure B.1), whereas the forward Euler approximation overestimates it. Consequently, the backward Euler method produces an approximation that smoothly approaches and never overshoots the final steady state value of V. For large step sizes, the forward Euler method may produce values of V that are greater than the steady state,

leading to oscillations in V around this value. Such oscillations are not seen in the exact solution and are not desirable in a good approximation.

Note that in more complex models in which several related variables are being solved for, the backward Euler method will result in a set of equations that need to be solved simultaneously. Consequently, the backward Euler method is known as an **implicit method**. We will see this below for approximations to the cable equation. In contrast, with the forward Euler method, values at future time points of all variables can be calculated directly from values at known time points. The forward Euler method is an example of an **explicit method**.

A third method, which is both more accurate and stable than these Euler methods, is the **central difference** method, in which the time derivative is estimated from a future and a past value of the voltage:

$$\frac{dV}{dt} \approx \frac{V(t+\Delta t)-V(t-\Delta t)}{2\Delta t}. \tag{B.14}$$

By examining the equations for the Euler methods, it should be clear that this method results by taking the average of the forward and backward Euler approximations. If we use the expression for the backward Euler method involving the future voltage, $V(t+\Delta t)$, then the ODE is approximated by:

$$\frac{V(t+\Delta t)-V(t)}{\Delta t} = \frac{1}{2}\left[f(V(t+\Delta t), t+\Delta t)+f(V(t),t)\right]. \tag{B.15}$$

That is, we now take an average of the forward and backward Euler right-hand sides. For our example this leads to the expression:

$$C_m \frac{V^{n+1}-V^n}{\Delta t} = \frac{1}{2}\left(\frac{E_m - V^n}{R_m} + \frac{I_e^n}{a} + \frac{E_m - V^{n+1}}{R_m} + \frac{I_e^{n+1}}{a}\right). \tag{B.16}$$

This can be rearranged to give an explicit expression for V^{n+1}. This approximation is accurate, even for the rather large time-step of 5 ms (Figure B.1). The central difference method is **second order** accurate in time because the error is proportional to the square of the step size Δt.

The choice of time-step depends critically on how rapidly the quantity of interest, such as membrane voltage, is changing. When simulating action potentials, a small time-step is required, on the order of 10–100 μs, to capture accurately the rapid rise and fall of the action potential. In between action potentials, however, a neuron may sit near its resting potential for a long period. During this time the small time-step is unnecessary. Variable time-step integration methods have been developed to account for just this sort of situation. The time-step is automatically increased when a variable is only changing slowly, and decreased when rapid changes begin. These methods can drastically decrease the computation time required and are available in certain neural simulators, such as NEURON (Carnevale and Hines, 2006).

B.1.2 Partial differential equations

These same methods can be used for the temporal discretisation of PDEs, but now the spatial dimension must also be discretised. Let us consider the cable equation (Section 2.9) for voltage spread along a neurite of uniform diameter d:

$$C_m \frac{\partial V}{\partial t} = \frac{E_m - V}{R_m} + \frac{d}{4R_a}\frac{\partial^2 V}{\partial x^2} + \frac{I_e(x)}{\pi d}. \tag{B.17}$$

This involves the first derivative of V with respect to time, but the second derivative of V with respect to space. Consequently, a second order central difference method involving values at three different spatial grid points is required to discretise the spatial dimension:

$$\frac{\partial^2 V}{\partial x^2} \approx \frac{V(x+\Delta x)-2V(x)+V(x-\Delta x)}{(\Delta x)^2} \tag{B.18}$$

for a small spatial step Δx. If we use the notation that position x is the midpoint of compartment j, $x+\Delta x$ corresponds to compartment $j+1$, $x-\Delta x$ to $j-1$, and the length of each compartment is $l=\Delta x$, then this is identical to the compartmental structure introduced in Chapter 2. Using this notation and the above spatial discretisation, the forward Euler numerical approximation to the full cable equation is:

$$C_{\mathrm{m}}\frac{V_j^{n+1}-V_j^n}{\Delta t}=\frac{E_{\mathrm{m}}-V_j^n}{R_{\mathrm{m}}}+\frac{d}{4R_{\mathrm{a}}}\frac{V_{j+1}^n-2V_j^n+V_{j-1}^n}{l^2}+\frac{I_{\mathrm{e},j}^n}{\pi d l}. \tag{B.19}$$

To make clear the compartmental structure and enable all our equations to fit on one line so they are easy to read, now we will assume that the injected current is zero in compartment j, $I_{\mathrm{e},j}^n=0$, so we can remove this term. We can rewrite Equation B.19 to indicate explicitly the current flow between compartments:

$$C_{\mathrm{m}}\frac{V_j^{n+1}-V_j^n}{\Delta t}=\frac{E_{\mathrm{m}}-V_j^n}{R_{\mathrm{m}}}+\frac{c}{R_{\mathrm{a}}}\left(V_{j+1}^n-V_j^n\right)+\frac{c}{R_{\mathrm{a}}}\left(V_{j-1}^n-V_j^n\right), \tag{B.20}$$

where we define a coupling coefficient c between compartments as the cross-sectional area between compartments divided by the surface area of a compartment multiplied by the length l between compartments:

$$c\equiv\frac{\pi d^2}{4}\frac{1}{\pi d l}=\frac{d}{4l^2}. \tag{B.21}$$

Rearranging Equation B.20, we arrive at an expression for the voltage V_j^{n+1} in compartment j at time-step $n+1$ as a function of the values of the voltage at the previous time-step n in compartment j and in its two neighbours, $j-1$ and $j+1$:

$$V_j^{n+1}=V_j^n+\frac{\Delta t}{C_{\mathrm{m}}}\left(\frac{E_{\mathrm{m}}-V_j^n}{R_{\mathrm{m}}}+\frac{c}{R_{\mathrm{a}}}\left(V_{j+1}^n-V_j^n\right)+\frac{c}{R_{\mathrm{a}}}\left(V_{j-1}^n-V_j^n\right)\right). \tag{B.22}$$

The backward Euler method uses the same spatial discretisation, but with values of V at time point $n+1$ on the right-hand side:

$$C_{\mathrm{m}}\frac{V_j^{n+1}-V_j^n}{\Delta t}=\frac{E_{\mathrm{m}}-V_j^{n+1}}{R_{\mathrm{m}}}+\frac{c}{R_{\mathrm{a}}}\left(V_{j+1}^{n+1}-V_j^{n+1}\right)+\frac{c}{R_{\mathrm{a}}}\left(V_{j-1}^{n+1}-V_j^{n+1}\right). \tag{B.23}$$

To solve this, we rearrange it so that all unknown quantities are on the left-hand side and all known quantities are on the right:

$$-aV_{j-1}^{n+1}+bV_j^{n+1}-aV_{j-1}^{n+1}=V_j^n+\frac{\Delta t E_{\mathrm{m}}}{C_{\mathrm{m}}R_{\mathrm{m}}}, \tag{B.24}$$

where $a=\Delta t c/C_{\mathrm{m}}R_{\mathrm{a}}$ and $b=1+2a+\Delta t/C_{\mathrm{m}}R_{\mathrm{m}}$. This gives a set of equations involving values of V at the new time $n+1$, but at different spatial points along a cable, that must be solved simultaneously: