Chapter 3

COMPARTMENTAL MODELS

INTRODUCTION

Chapter 2 introduced cable theory as a method of quantifying current flow in neurons. We saw that cable theory is adequate for dealing with current flow in some neurons, but suffers from a number of restrictions that make it inapplicable to most neurons. This chapter discusses an alternate approach in which a mathematical model of a neuron is constructed by dividing the neuron into small segments or *compartments* (Fig. 3-1). Each compartment is described by an ordinary differential equation so the model consists of a family of differential equations. Construction of such a compartmental model can be divided into three stages. First, the morphology of the neuron must be encoded by measuring the dimensions of each segment. Second, the biophysical parameters of the segments such as the specific membrane resistance and the specific capacitance must be estimated. Third, the family of differential equations that describe the model must be solved.

ENCODING THE MORPHOLOGY OF NEURONS

The anatomical data necessary to construct a compartmental model can be obtained from Golgi preparations or from neurons that have been injected with a substance, such as Procion yellow, biocytin, etc., that permits visualization of the neuron. If the neuron is present in a preparation that has been sectioned into a series of thin sections to permit microscopic study, it is possible to trace the individual processes of the neuron across adjacent sections. A drawing of the neuron is prepared, which gives a general idea of its morphology, and the dimensions of individual processes are measured and recorded. This can be done using a micrometer scale that is inserted into the ocular of the microscope. A difficulty, though, is that the image of the neuron collapses all three dimensions of the neuron onto an x,y-plane so the lengths of processes proceeding obliquely through the section are fore-shortened by the process of projecting them onto the plane. It is necessary to enter the x,y,z-coordinates of points at which the measurements are made. This can be done because research-grade microscopes usually have stage micrometers that measure the x,y-coordinates of points at the center of view and calibrations on the fine focus knob that allow measurements of the z-coordinate. This straightforward, but tedious, process can be speeded up using an automated reconstruction system that works by attaching sensors to the stage micrometer and fine focus knob so that the x,y,z-coordinates of points at the center of the field of the field of view are automatically measured. The three dimensional coordinates of the neuron are recorded as a cursor at the center of the view is moved over the neuron by the observer. This not only creates a file of x,y,z-coordinates, but also produces an image of the neuron that can be

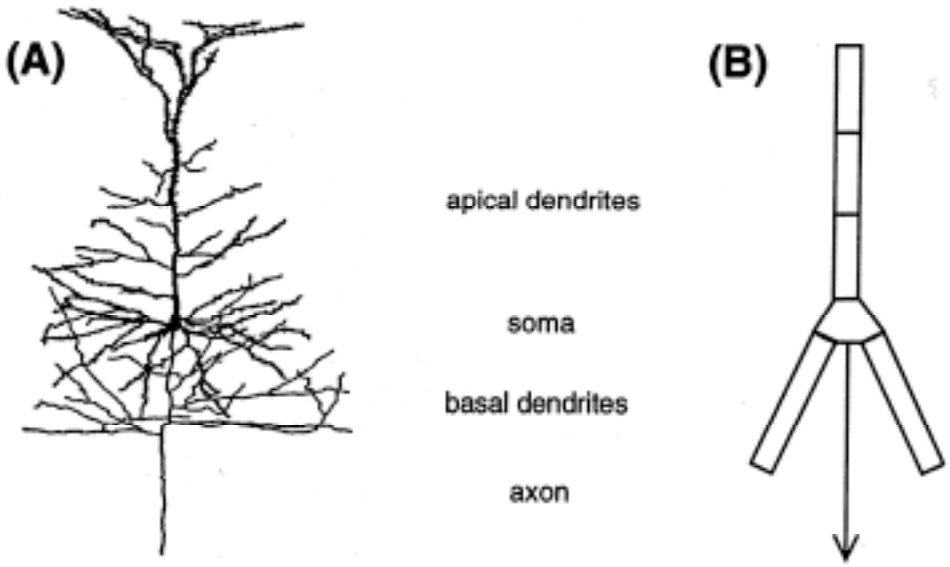

Figure 3-1. Compartmental model of a neuron. A. Drawing of a neocortical pyramidal cell. B. Compartmental model of same neuron. From (Bower and Beeman, 1995).

viewed at any desired orientation on a monitor. A recent improvement is the development of software packages for confocal microscopes that automate much of the process of measuring neurons. The confocal microscope creates a stack of digital images through the neuron. The software facilitates calculations using this stored data. It can automatically measure the lengths, diameters and surface areas of segments of the neuron.

The information obtained through this process is used to divide the neuron into compartments. The number of compartments used to create the model is determined by the investigator and is subject to a tradeoff. The basic requirement is that each compartment be small enough to insure that it is *isopotential*. That is, a voltage fluctuation within any part of the compartment must spread through the entire compartment fast enough to be essentially instantaneous. The membrane voltage at any point on the surface of the compartment will be the same at any point in time. If the

compartment is too large, it will not be isopotential and errors will be introduced into the model. A good rule of thumb is that individual compartments should have lengths of 0.2λ or less. The first inclination is to create a large number of small compartments to assure the accuracy of the model. The difficulty, though, is that each compartment will be represented in the model by a differential equation and increasing the number of compartments increases the number of simultaneous differential equations that must be solved. It is possible to divide a CA1 pyramidal cell into 1,000 compartments, but there are then 1,000 differential equations to be solved simultaneously for every instant in time for which information about the neuron is required. The equations are solved by computer and increasing the number of compartments increases the time required to run a simulation of the behavior of the neuron from seconds to hours or even days, depending upon the speed of the computer. The decision about how many compartments to use is made based on the specific problem being addressed. Some problems can be examined accurately using models with a few, or even one, compartment while other problems require a large number of compartments.

Measurements from the neuron do not appear explicitly in the model, but are used to calculate the total membrane resistance, axial resistance and membrane capacitance of the individual compartments. The calculations are the ones that we carried out earlier. The surface area of a segment of a neuron cannot be calculated exactly because the neuronal membrane has many surface irregularities. It is necessary, instead, to model the individual segments as geometric objects such as cylinders, spheres or ellipsoids and to estimate the surface area of the segment by using standard formulae. It

is important when estimating the surface area of the soma of the neuron to remember to subtract off the area of those regions of the soma occupied by the dendrites and axon. Thus, the surface area of a soma could be estimated by using the major and minor diameters of an ellipsoid to calculate its surface area and subtracting off circular patches of membrane with diameters corresponding to each dendrite that originates from the soma.

Dendritic spines pose particular problems due to the irregularity of their shapes and their numbers. Their shapes are usually only a small difficulty in that individual spines can also be divided into two or more compartments. Spines often have a neck and a head so they can be modeled as a cylindrical compartment and a spherical or ellipsoidal compartment (with the surface area occupied by the neck being subtracted from the surface area of the sphere or ellipsoid). Spines lie near the resolution of the light microscope (about 1 μm), but they can be measured accurately with the electron microscope using series of ultrathin sections or high voltage electron microscopy (Wilson, 1987; Hama et al., 1989; Harris and Stevens, 1989; Harris et al., 1992).

Some neurons have hundreds or thousands of spines, so modeling individual spines greatly increases the number of compartments in the model and escalates the amount of computer time needed to run simulations of the neuron. However, spines cannot be ignored because they often account for a significant percentage of the total membrane area of the cell. Ignoring them would greatly underestimate the total capacitance and resistance of the cell and create unacceptable errors in the simulations. A useful trick is to explicitly model only those spines that are receiving synapses and to

incorporate the surface membrane of all of the spines into the membrane bounding individual compartments (Stratford et al., 1989). This preserves the surface membrane that the spines contribute to the cell so that the model will have the correct total capacitance and resistance. Such a model can provide individual synapses that have compartments with the correct capacitance and resistance, but eliminate hundreds or thousands of compartments from the model. To carry out the calculations needed to construct the model it is necessary to know the number of spines that occur on each compartment and also to know something about their sizes. Estimating the number of spines present on a dendritic segment is actually more difficult than it appears at first glance because not all of the spines are visible. Spines present on the side of the dendrite facing the viewer in the microsope and counting them is a simple, but time-consuming, process. However, spines also originate from the surface of the dendrite facing away from the viewer. The numbers of *hidden spines* can be estimated from the number of visible spines and the dimensions of the spines and dendritic shaft by assuming that hidden spines occupy the same fraction of the volume of space behind the dendrite as the visible spines occupy on the sides and in front of the dendrites. The surface area of all of the spines on a segment can then be estimated by multiplying the number of spines times the average surface area of a spine. The surface area is calculated by modeling the spine as one or more geometrical objects and using the spine dimensions to estimate the surface area. The spine area is "folded" into the shaft area (Stratford et al., 1989). This calculation assigns the correct surface area to the dendritic compartment so it will have approximately the correct total capacitance and resistance. If the compartment has a spine that receives a synapse to be included in the model, the individual spine can be modeled as

two additional compartments, one for the neck and one for the head. The current flowing from the active synapse on the spine into the dendritic shaft will be correct because the spine neck will create a region of high resistance while the dendritic shaft will be a region of low resistance. This happens because small diameter elements have higher resistances than do large diameter elements. By contrast, current will not flow smoothly from the shaft into the spine due to the high resistance at the spine neck. Models in which the spines have been folded into the shaft membrane, thus, cannot be used to model currents flowing from the shaft into the spines.

ESTIMATING BIOPHYSICAL PARAMETERS

The morphological data needed to construct a compartmental model can be obtained from anatomical preparations as discussed above. Obtaining the biophysical parameters needed from experimental sources can be much more difficult, and impossible, in some cases (see Rall et al. (1992) and Borg-Graham (1999) for reviews). It is not possible with existing physiological techniques to measure local values of resistance and capacitance at specific points on a neuron. Capacitance can be measured quite accurately, but it is very difficult to obtain measurements of the area of membrane involved to the same degree of accuracy, so values of specific capacitance are not generally available for elements of neurons. It is necessary in most cases to use average values of biophysical parameters or to attempt to estimate the values of parameters from the voltage transients recorded in real neurons.

This process is a specific example of a general class of problems known as *inverse problems*. For example, if the diameter and length of a cylinder are known, the surface area or volume of the cylinder can be calculated to whatever degree of precision is required by substituting the known values into the equations for the surface area or volume of a cylinder. If the surface area of the cylinder is known, however, it is not possible to effect the inverse calculation and obtain unique values for the diameter and length of the cylinder because an infinite number of combinations of diameters and lengths can produce the same surface area. Methods for approaching inverse problems are available in the applied mathematics literature and some attempts have been made to use them in constructing compartmental models (Holmes and Rall, 1992b).

Estimates of the biophysical properties will in most cases rely upon comparisons of the performance of the model neuron to physiological data. The optimal situation is to have both anatomical and physiological data from the same individual neuron. This can often be achieved by recording from a neuron, filling the neuron with a marker substance and taking morphological data from the neuron after the physiological experiment is completed. However, it is also often possible to collect physiological and anatomical data from populations of neurons and use average values. The result is a model of a specific neuron in the first case and a model of a representative neuron in the second case.

Some estimate of the specific membrane resistance can be obtained from the voltage response recorded from a cell following a square current pulse. We have seen that the magnitude of the steady-state voltage is

determined by the surface area of the neuron and the specific membrane resistance. The value of R_m used in the model can then be systematically varied until the steady state voltage of the model neuron matches the steady-state voltage of the real neuron (e.g. Shelton, 1985). Additional information can be obtained from the value of the membrane time constant. If an initial estimate of R_m is incorrect, it will lead to a voltage transient with an incorrect waveform in the model neuron.

A difficult issue to resolve experimentally is whether or not the specific membrane resistance is constant over the entire neuron. Burke et al. (1991) carried out careful simulations of cat spinal motoneurons and found that they could not accurately recreate the measured voltage transients if they assumed a constant value for specific membrane resistance. It was necessary to assign smaller values of R_m to the soma compartment than were used for dendritic compartments. The precise distribution of membrane resistances over the neuron did not have a major impact on the behavior of the model neuron. The important feature seemed to be the inclusion of a somatic "shunt" into the soma compartment. The idea is that the cells membrane does not seal completely to the electrode so that some current can leak around the electrode and escape the cell. The amount of current that is actually injected into the cell is, thus, less than the amount that is injected.

The smaller specific membrane resistance of the soma membrane could result from two factors, neither of which is exclusive of the other. The first is that there could be real variations in the specific membrane resistance in the composition of the bilipid layer of the membrane or in the

density of non-voltage gated channels that are often called *leak channels*. These are ion channels whose behavior does not depend upon the membrane potential of the neuron. They lead to a constant leak of current through the membrane. Increases in the density of leak channels in the soma would result in a larger conductance and smaller resistance for the soma membrane. A second possibility is that the somatic shunt is an artifact of impaling the soma with a microelectrode. The membrane of the cell must adhere to the shaft of the electrode in order to obtain a viable recording situation, but there remains the real possibility that the seal is imperfect and current can leak around the electrode resulting in a decreased resistance. The general finding that recordings made with whole-cell patch clamp methods yield larger membrane time constants are consistent with this interpretation. The membrane time constant depends upon both the specific membrane resistance and capacitance. The capacitance of the membrane can vary only by a factor of, perhaps, two while the membrane time constants obtained with patch-clamp methods can be an order of magnitude, or more, larger than those obtained with sharp electrodes for a given type of neuron. Most of the increase in measured values of membrane time constants results from higher values of specific membrane resistance. Current estimates of specific membrane resistance for adult mammalian neurons are on the order of 100 $k\Omega \cdot cm^2$, or more.

The total capacitance of a cell can be measured with substantial precision, so the factor limiting accurate measurements of specific capacitance is the difficulty of obtaining a precise measurement of the surface area of the membrane being studied. Patch-clamp methods permit careful measurements of either a whole cell or a small patch of membrane.

In both cases, however, it is difficult to obtain an equally accurate measurement of the total surface area of the cell or of the patch of membrane that adheres to the tip of the electrode. It is not difficult to measure the diameter of the electrode, but it is difficult to assure that the patch of cell membrane has exactly the equivalent surface area. Early estimates of the specific capacitance of cell membranes have provided values of about 1 $\mu F/cm^2$, and this value is generally accepted as a default value. Recent attempts to match the behavior of model neurons to physiological data often tend towards higher values of specific capacitance so that estimates of up to 2 $\mu F/cm^2$ are common. We have virtually no information on whether or not membrane capacitance varies for different parts of neurons and the same value of specific membrane capacitance is generally assigned to all of the compartments in a model.

Estimates of both the total membrane resistance and capacitance depend on knowledge of how much shrinkage has occurred during the preparation of the cell for morphological analysis. Shrinkage occurs because water must be removed from the preparation to embed the tissue in a material that permits serial sectioning of the tissue and also to obtain a preparation that is optically clear. Water is removed by passing the tissue through a series of water-alcohol mixtures of increasing alcohol concentration until it is in 100 % alcohol. The tissue is then moved into a clearing agent such as xylene so that it can be placed into a mounting medium and sectioned for either light or electron microscopy. Preparing tissue for electron microscopy normally results in less shrinkage than does preparation for light microscopy because more effective fixing agents are needed to stabilize the membrane of the cell to the extent that is needed for

electron microscopic visualization of the membrane. The percentage of shrinkage that occurs in an individual neuron within a block of tissue is difficult to measure and cannot be assumed to equal the shrinkage of the block of tissue as a whole because different tissue elements within the block probably shrink at different rates. Better estimates of shrinkage can be obtained in some circumstances using *confocal microscopy* which allows visualization of filled neurons before during and after histological processing. In general, shrinkage factors are probably at least 30 % and 50 % of the linear dimensions of a neuron.

Once a shrinkage factor has been assigned to a compartmental model, the choices of specific membrane capacitance and resistance are partially constrained by the physiological data. This happens because the total resistance and capacitance of each compartment depend upon the surface area of the compartment in opposite ways. Increasing surface area increases total capacitance but decreases total resistance. Also, capacitance and resistance have their primary effects upon different regions of the voltage response to a square current pulse. Small changes in capacitance have major changes on the initial phase of the response, while changes in resistance have effects principally on the steady-state voltage, which is determined by the total input resistance of the cell.

The final biophysical parameter to be assigned is the axial resistance (Foster et al., 1976; Gilbert, 1975; Scharme, 1969). Total axial resistance can be measured in large neural structures (such as squid giant axons) by impaling the structure with two electrodes and measuring the current that flows between electrodes separated by a known distance. Values of about

100 Ω·cm have been usually reported. However, several recent modeling studies have employed values of up to 400 Ω·cm to match physiological data. There is no indication that axial resistance varies dramatically between different regions of the cell and models universally assign uniform values of axial resistance to each of the compartments.

DERIVING AND SOLVING THE MEMBRANE EQUATION

The process of encoding the morphology of a neuron produces a series of compartments with known lengths and surface areas. This information is used to formulate an ordinary differential equation that describes the voltage behavior of each individual compartment. This equation is the *membrane equation* (Hodgkin and Huxley, 1952; Stratford et al., 1989; Segev et al., 1990; Clairborne et al., 1992; Segev and Burke, 1998). The membrane equation contains the biophysical parameters discussed above. The geometry and biophysical properties of each compartment in the neuron are, thus, brought together in the membrane equation for that compartment. The membrane of each compartment is represented in the corresponding equation by a resistor, a capacitor and a battery. The resistor represents the resistance of the bilipid membrane and non-voltage gated ion channels that make up the membrane. The non-voltage gated channels are involved in establishing the resting membrane potential of the neuron, which is represented as a battery that tends to hold the membrane at the resting membrane potential. The capacitor represents the capacitance of the membrane. Current is flowing through the membrane and we represent it as flowing in parallel across the capacitor (the capacitive

element of the circuit) and the resistor (the resistive element) and battery. The battery is in series with the resistor.

We take advantage of one of the laws of electrical circuits introduced by Kirchoff (*Kirchoff's law*) which says that the algebraic sum of all of the currents flowing through the membrane must equal zero. It requires in our case that

(3-1) $$i_c + i_r + I_s = 0$$

where i_c is the capacitive current, i_r is the current flowing through the resistor and battery and I_S is a stimulating current that we apply through an electrode. We have already derived an expression for the current flowing through a capacitor in Equation 2-8, so we know that $i_c = CdV/dt$, where C is the total capacitance of the compartment. Similarly, we know that the current flowing through the resistor is given by Ohm's law as either $V = i_r R$ or $i_r = GV$, depending on which expression is most convenient for a particular purpose. R and G are the total membrane resistance and conductance, respectively, of the compartment. Since we want an expression for i_r, we choose to use $i_r = GV$. The only issue is to determine how to include the battery into the circuit. This is done by introducing a factor created by the non-voltage gated conductances in the membrane. This factor is called the *driving potential* and is given by $\left[V - E_r\right]$ where E_r is the resting membrane potential. The factor becomes zero when the membrane is at the resting membrane potential, where $V = E_r$. It has a positive sign when V is greater than E_r and a negative sign when V is less than E_r. The magnitude and sign of the force driving the membrane back towards rest will depend on the

value of at any point in time. The battery is incorporated into the circuit by writing $i_r = G\left[V - E_r\right]$. The equivalent circuit for a patch of membrane follows easily from Equation 3-1

(3-2) $$C\,\frac{dV}{dt} + G\left[V - E_r\right] + I_S = 0$$

or

(3-3) $$\frac{dV}{dt} = \frac{-1}{C}\left[G\left(V - E_r\right) + I_S\right] = -\frac{1}{C}\left[\frac{1}{R}(V - E_r) + I_s\right]$$

Because the ion channels are not voltage-gated, G depends on neither time nor voltage. Each compartment is described by a membrane equation analogous to Equation 3-3.

The last step in formulating the differential equations that describe a compartmental model of a neuron is to hook the individual compartments up to each other (Fig. 3-2). This is done by considering the compartments as linked to each other by resistors that determine the current flow from one compartment to another. It means that a term has to be added to the equation for each compartment to which the compartment under consideration is connected. The current flow between two compartments will be determined in part by the axial resistance between the compartments, but will also be affected by the relative potentials of the two compartments. If the potential in compartment 1 is greater than that of compartment 2, current will flow from 1 to 2 until the two voltages are equalized.

Conversely, current will flow into 2 if $V_2 < V_1$. A common way to characterize the terms for current flow between compartments is, therefore,

(3-4) $$\frac{[V_2 - V_1]}{R_c}, \quad R_c = \frac{1}{2}[R_{a1} + R_{a2}]$$

Where R_{a1} and R_{a2} are the total axial resistances of the two compartments. If two compartments are linked together in series, the membrane equation for each compartment will have one additional term. If a dendrite branches into two daughter branches, the equation for the parent compartment will have two additional terms, one for each daughter compartment, etc.

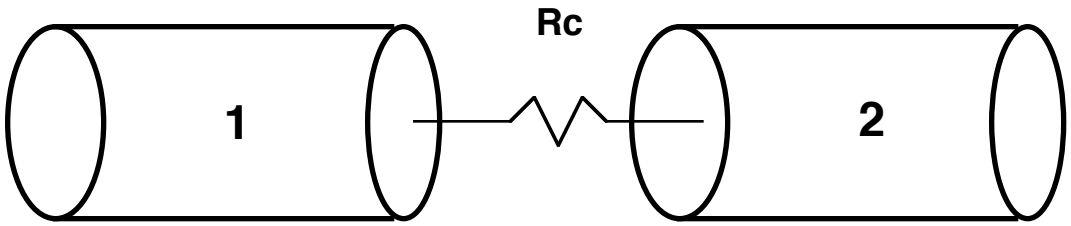

Figure 3-2. Two linked compartments. Two identical, isopotential compartments are linked by a coupling resistance.

A model of a neuron with two identical compartments with a depolarizing, stimulating current injected into compartment 1 is consequently specified by a pair of ordinary differential equations:

$$\frac{dV_1}{dt} = \frac{-1}{C}\left[\frac{1}{R}(V_1 - E_r) + \frac{[V_1 - V_2]}{R_c} - I_S\right]$$

(3-5)

$$\frac{dV_2}{dt} = \frac{-1}{C}\left[\frac{1}{R}\left(V_2 - E_r\right) + \frac{[V_2 - V_1]}{R_c}\right] \quad .$$

When the current is turned on, current flows into compartment 1, charging the capacitance of the membrane bounding the compartment and leading to a steady state membrane voltage determined by the specific membrane resistance and surface area of the membrane. As the membrane voltage begins to change, a difference in voltage develops between the two compartments and current flows from compartment 1 into compartment 2. This process depends upon the axial resistances. When the voltage of compartment 2 reaches that of compartment 1, there will be no net current flow between the two compartments.

The process of constructing a compartmental model of a neuron, thus, results in a family of coupled, ordinary differential equations, one for each compartment, that contain information on the geometry of the cell and the biophysical properties of each compartment. We have seen that a cable model of a neuron will be accurate only if the neuron meets a list of rather restrictive conditions. The compartmental model requires none of these restrictions and can accommodate any branching pattern and any set of local biophysical properties. Although we are concentrating on the passive behavior of neurons in this chapter, voltage-gated channels and ligand-gated receptors can easily be incorporated into compartmental models and we will have occasion to do this in subsequent chapters. The only requirement for a compartmental model is that the individual compartments be isopotential. This is -- for all practical purposes -- not a restriction because the

compartments can be made as small as is desired, subject only to the cost of increased computation time.

In principal, it is possible to obtain an analytic solution for the family of differential equations. That is, to find a family of equations that describes the time dependence for the membrane potential of each compartment. The process can be illustrated for a two compartment model. To start with, let's examine the situation in which the membrane potentials of the two compartments are different, but there is no stimulating current (i.e. $I_s = 0$ in Equation 3-4). Then, the two equations in Equation 2-84 become

$$\dot{V}_1 = \frac{dV_1}{dt} = \frac{-1}{C}\left[\frac{V_1}{R} + \frac{V_1}{R_a} - \frac{V_2}{R_a}\right]$$

(3-5)

$$\dot{V}_2 = \frac{dV_2}{dt} = \frac{-1}{C}\left[-\frac{V_1}{R_a} + \frac{V_2}{R} + \frac{V_2}{R_a}\right] \quad .$$

If we define the parameters $\alpha = \frac{1}{C}\left[\frac{1}{R} + \frac{1}{R_a}\right]$ and $\beta = 1/R_aC$, we can rearrange the equations and obtain

$$\dot{V}_1 = -\alpha V_1 + \beta V_2$$

(3-6)

$$\dot{V}_2 = \beta V_1 - \alpha V_2$$

The family of equations can now be written in matrix form

(3-7) $$\dot{\mathbf{V}} = \mathbf{AV}$$

where $\mathbf{V} = \begin{pmatrix} V_1 \\ V_2 \end{pmatrix}$

and $\mathbf{A} = \begin{pmatrix} -\alpha & \beta \\ \beta & -\alpha \end{pmatrix}$.

The solution to Equation 3-7 is $\mathbf{V}(t) = e^{\mathbf{A}t}$, and

(3-8)
$$V_1(t) = ae^{\lambda_1 t} + be^{\lambda_2 t}$$
$$V_2(t) = ce^{\lambda_1 t} + de^{\lambda_2 t}$$

where a, b c and d are constants determined by the initial conditions and λ_1 and λ_2 are the eigenvalues of the eigenvalue equation $(\mathbf{A} - \lambda\mathbf{I})\mathbf{V} = 0$. We obtain the eigenvalues by evaluating the determinant

(3-9) $$\det\begin{vmatrix} -\alpha & \beta \\ \beta & -\alpha \end{vmatrix} = 0$$.

This gives

(3-10) $(\alpha^2 - \lambda^2) - \beta^2 = 0$ and $\lambda^2 + 2\alpha\gamma + (\alpha^2 - \beta^2) = 0$

or

$$\lambda = \frac{-2\alpha \pm \sqrt{4\alpha^2 - 4(\alpha^2 - \beta^2)}}{2}$$

(3-11)
$$\lambda_1 = -\frac{1}{RC} \quad \text{and} \quad \lambda_2 = -\frac{1}{RC} - \frac{2}{R_a C} \quad .$$

Since $R >> R_a$, $\lambda_2 \sim -2 / R_a C$ and

(3-12)
$$V_1(t) = ae^{-t/RC} + be^{-2t/R_aC}$$
$$V_2(t) = ce^{-t/RC} + de^{-2t/R_aC} \quad .$$

The time constant for the first exponential depends upon the membrane resistance and capacitance and describes how rapidly charge leaks through the membrane. The second time constant depends upon the axial resistance of the compartments and determines how rapidly charge equalizes between the two compartments. Putting the stimulating current back into the equations adds an extra term to the solution (you should make certain you understand what the resulting equations would be). This method of solving families of ordinary differentials equations is entirely general and can be extended to N compartments. The solutions will then be sums of N exponentials and require finding N eigenvalues. This quickly becomes prohibitively difficult to do by hand, but there are software packages for doing linear algebra that can be used to obtain analytic solutions for relatively large values of N.

However, analytic solutions to the families of ordinary differential equations that describe compartmental models are prohibitively time consuming, and work with compartmental models is usually done with solutions obtained using *numerical methods*. The use of numerical methods to solve families of equations is a large area in applied mathematics and a complete treatment of the subject is beyond the scope of this chapter. Interested readers are referred to standard textbooks on numerical methods such as the one by Gerald and Wheatley (1990) and to the

discussion by Mascagni and Sherman (1998) of numerical solutions of equations that occur in computational neurobiology. To get an idea for the process, though, we can consider a numerical solution to the equation $dV/dt = -t/\tau$ with the initial condition $V(0) = V_o$. (We already know that the solution is $V = V_o e^{-t/\tau}$). The simplest numerical method of solving the equation is called the *method of Euler* and involves replacing the differential equation with an equation involving finite differences

(3-14) $$\frac{\Delta V}{\Delta t} = \frac{V_{i+1} - V_i}{t_{i+1} - t_i} = -aV$$

where we have written $a = 1/\tau$ just to simplify the calculations. If we rearrange Equation (2-93), we find that

(3-15) $$V_{i+1} = V_i - a\Delta t$$

If we know the value of V at some initial time, t, then we can estimate the value of V at some later time $t + \Delta t$ using this equation. Numerical methods do not produce a solution to the membrane equations that can be written down, but create a list of values of V for discrete values of t that can be displayed graphically. The accuracy of the estimates will depend upon the magnitude of the time step, Δt. A small time step provides a more accurate estimate. The process can be continued so that the value of V can be estimated for as many subsequent times as is desired. The smallest time step is not always the best choice because the amount of time required to run a simulation depends directly on the size of the time step. Some compromise between the accuracy desired and reasonable simulation times

has to be reached. Choice of the time step becomes more complicated when voltage-gated channels or ligand-gated receptors are added to the compartments because inclusion of channels or receptors adds additional processes with different time constants to the solutions. Such equations are referred to as *stiff* and can cause simple numerical schemes such as the Euler method to fail and produce solutions that oscillate. Sophisticated methods of solving membrane equations often use variable time steps and change the size of the step used to match the rate at which the voltage is changing. They may use small time steps when the voltage is changing rapidly, such as during an action potential, and larger time steps when the voltage has reached steady state.

The Euler method is a simple method for solving families of differential equations, but is seldom used for scientific work. Several more accurate methods, such as the *Runge-Kutta* method, are available and in wide use. Readers interested in this topic can create their own programs for solving membrane equations using software such as *Mathematica* or *Matlab*. However, it is generally not worth the effort needed to construct a functioning software package *de novo* because several excellent packages are available either as freeware or for a nominal cost. Examples of such packages are *Nodus* (DeShutter, 1989), *Neuron* (Hines, 1984, 1989, 1993) and *Genesis* (Bower, 1995). They allow simulations of essentially unlimited numbers of compartments and very large scale network models. The details of working with these packages vary, but all of the programs free the investigator from having to worry about the numerical methods employed. The model is constructed by entering data on the morphology of the neuron being studied and specifying values of biophysical parameters.