Chapter 3

Expressing conceptual models in mathematical terms

Computational neuronal modeling usually focusses on voltage and current in excitable cells, but it is often necessary to represent other processes such as chemical reactions, diffusion, and the behavior of electronic instrumentation. These phenomena seem quite different from each other, and each has evolved its own distinct "notational shorthand." Because these specialized notations have particular advantages for addressing domain-specific problems, NEURON has provisions that allow users to employ each of them as appropriate (see **Chapter 9: How to expand NEURON's library of mechanisms**). Apparent differences notwithstanding, there are fundamental parallels among these notations that can be exploited at the computational level: all are equivalent to sets of algebraic and differential equations. In this chapter, we will explore these parallels by examining the mathematical representations of chemical reactions, electrical circuits, and cables.

Chemical reactions

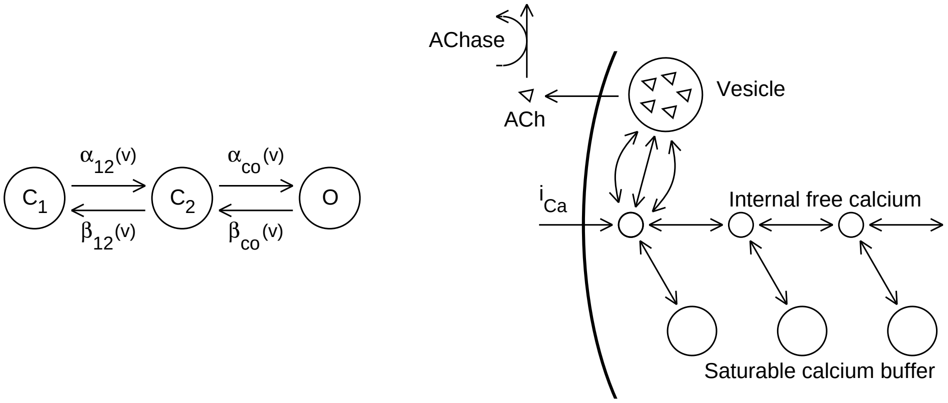


Fig. 3.1. Left: a voltage-gated channel modeled as a three-state kinetic scheme with voltage-dependent rate constants. Right: cartoon of a model of acetylcholine (ACh) release that involves the influx, buffering, and diffusion of calcium, exocytosis requiring binding of three calcium ions per vesicle, and enzymatic breakdown of ACh (rate constants omitted for clarity).

A natural first step in thinking about voltage-dependent or ligand-gated channel models or elaborate cartoons of dynamic processes is to express them with chemical reaction notation, i.e. kinetic schemes (Fig. 3.1). Kinetic schemes focus attention on conservation of material (in a closed set of reactions, material is neither created or destroyed) and flow of material from one state to another.

The notion of "state" is context-dependent: it may mean actual material quantity of a molecular species (sometimes moles, sometimes mass), the well-stirred molar concentration in a volume or the density on a surface, or the probability of a particle being in a particular state. Thus when we refer to "the value of state *A*" we mean a value expressed in the dimensions of *A*. When *A* is in units of concentration or density, "the material in state *A*" is the product of *A* and the size of the compartment (volume or surface) in which *A* is distributed.

Flux and conservation in kinetic schemes

In a kinetic scheme, arrows that point toward or away from a state represent paths along which material enters or leaves the state. For each state there is a differential equation that expresses how the amount of material in the state is affected by fluxes that enter and leave it. These differential equations are specified by the states in the kinetic scheme and the paths along which material can move between them.

Thus

$$A \xrightarrow{k} B \qquad \text{Eq. 3.1}$$

means that material leaves state *A* at a rate that is proportional to the product of the value of *A* and a rate constant *k*, where *A* and *k* are understood to be nonnegative. From the standpoint of state *A*, the flux along this path is $-kA$, and this defines a term in the differential equation for this state.

$$\frac{dA}{dt} = -k\,A \qquad \text{Eq. 3.2a}$$

But the flux that leaves *A* in Eq. 3.1 is just the flux that enters *B*, so

$$\frac{dB}{dt} = k\,A \qquad \text{Eq. 3.2b}$$

Suppose we have a closed system in which Eq. 3.1 is the only chemical reaction that can occur. Adding Eqns. 3.2a and b together, we have

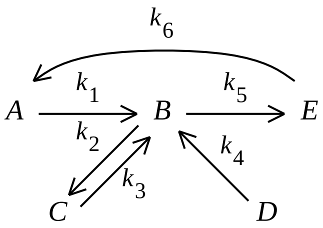
$$\frac{dA}{dt} + \frac{dB}{dt} = 0 \qquad \text{Eq. 3.3}$$

which we can integrate to get

$$A + B = \text{a constant} \qquad \text{Eq. 3.4}$$

Equation 3.4 is a statement of the principle of conservation of material: in a closed system with the reaction described by Eq. 3.1, the sum of *A* and *B* is conserved.

Any kinetic scheme is easily translated into a corresponding set of differential equations. Each differential equation expresses the rate of change of each state as the difference between the flux entering the state and the flux leaving the state. For example the kinetic scheme



Eq. 3.5

has five states, and is equivalent to five differential equations. Focussing on *B*, we see that the flux entering is the sum of $k_1 A$, $k_3 C$, and $k_4 D$, while the flux leaving is the sum of $k_2 B$ and $k_5 B$, so the corresponding differential equation is

$$\frac{dB}{dt} = k_1 A - (k_2 + k_5) B + k_3 C + k_4 D \qquad \text{Eq. 3.6a}$$

The differential equations for the other states are

$$\frac{dA}{dt} = -k_1 A + k_6 E \qquad \text{Eq. 3.6b-e}$$

$$\frac{dC}{dt} = k_2 B - k_3 C$$

$$\frac{dD}{dt} = -k_4 D$$

$$\frac{dE}{dt} = k_5 B - k_6 E$$

To derive the conservation rules for a kinetic scheme, we just find linear combinations of these equations that add up to 0, and then integrate them. For the example of Eq. 3.6, we see that adding all of the equations together gives

$$\frac{dA}{dt} + \frac{dB}{dt} + \frac{dC}{dt} + \frac{dD}{dt} + \frac{dE}{dt} = 0 \qquad \text{Eq. 3.7}$$

which we integrate to obtain the conservation rule

$$A + B + C + D + E = \text{a constant} \qquad \text{Eq. 3.8}$$

i.e. the sum of the five states is conserved.

Stoichiometry, flux, and mole equivalents

In the reaction

$$A + B \underset{k_b}{\overset{k_f}{\rightleftarrows}} C \qquad \text{Eq. 3.9}$$

we see that producing one mole of *C* requires consumption of two moles: one mole of *A*, and one mole of *B*. That is, a change of *C* implies equal (but opposite) changes of *A* and B. The forward flux is $k_f\ A\ B$ and the backward flux is $k_b\ C$, so this reaction translates to the differential equations

$$\begin{aligned}\frac{dA}{dt} &= -\,k_f\ A\,B + k_b\ C \\ \frac{dB}{dt} &= -\,k_f\ A\,B + k_b\ C \\ \frac{dC}{dt} &= k_f\ A\,B - k_b\ C\end{aligned} \qquad \text{Eq. 3.10}$$

from which we can generate several different linear combinations that add up to zero. Two obvious combinations are

$$\frac{dA}{dt} + \frac{dC}{dt} = 0 \qquad \text{Eq. 3.11a}$$

and

$$\frac{dB}{dt} + \frac{dC}{dt} = 0 \qquad \text{Eq. 3.11b}$$

from which we conclude that both $A + C$ and $B + C$ are conserved. Note that A, B, and C must have the same units (otherwise Eqns. 3.11a and b would involve the addition of dimensionally inconsistent values), while k_b has units of 1/time and k_f is in units of 1/time × units of A.

Confusion may occur with reactions like

$$A + A\ \underset{k_b}{\overset{k_f}{\rightleftarrows}}\ B \qquad \text{Eq. 3.12}$$

or the equivalent

$$2\,A\ \underset{k_b}{\overset{k_f}{\rightleftarrows}}\ B \qquad \text{Eq. 3.13}$$

if the underlying principle of conservation is overlooked. There is certainly no question that the equation for B is

$$\frac{dB}{dt} = k_f\ A^2 - k_b\ B \qquad \text{Eq. 3.14}$$

but what can we say about dA/dt?

To answer this question, we reexamine Eq. 3.13 and realize that it means that two moles of A produce one mole of B. So an increase of B implies twice as large a decrease of A, i.e.

$$\frac{dA}{dt} = 2\left(-k_f\, A^2 + k_b\, B\right) \qquad \text{Eq. 3.15}$$

From Eqns. 3.14 and 15 we see that, in a closed system described by Eq. 3.13,

$$\frac{dA}{dt} + 2\frac{dB}{dt} = 0 \qquad \text{Eq. 3.16}$$

and the conservation rule is that $A + 2B$ is constant.

Compartment size

Textbook treatments of kinetic schemes generally begin with the explicit assumptions that all states use identical dimensions (usually concentration) and are distributed in the same volume. Up to this point, we have tacitly made the same assumptions, because they allow kinetic schemes to be translated into differential equations without having to take compartment size into account.

However, in neuronal modeling this is often too restrictive. Consider a model of the role of diffusion and active transport in regulating the amount of calcium in a thin shell adjacent to the cell membrane (Fig. 3.2). Some of the calcium is pumped out, and some diffuses between the shell and a bulk internal compartment ("core") at a rate that is proportional to a constant k_d.

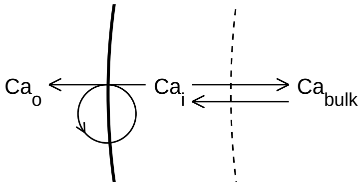


Fig. 3.2. In this model, [Ca^{2+}] in a thin shell just inside the cell membrane is regulated by a pump in the cell membrane and by diffusional exchange with bulk stores of calcium in the core of the cell.

A kinetic scheme formulation of this model is

$$Ca_i \underset{k_d}{\overset{k_d}{\rightleftarrows}} Ca_{bulk} \qquad \text{Eq. 3.17a-c}$$

$$Ca_i + Pump \underset{k_2}{\overset{k_1}{\rightleftarrows}} Ca\,Pump$$

$$Ca\,Pump \underset{k_4}{\overset{k_3}{\rightleftarrows}} Ca_o + Pump$$

Here the active transport of calcium is represented by a pair of first order reactions between calcium ions in solution on either side of cell membrane, and a calcium pump that is restricted to the membrane. The states of this model are the amounts of calcium in the extracellular fluid (Ca_o), the shell (Ca_i), and the core of the cell (Ca_{bulk}), and the membrane-associated pump in its "free" and "calcium-bound" forms (*Pump* and *CaPump*, respectively). We want to translate these reactions into a corresponding set of differential equations, but the reactants occupy four regions, each of which has a different size. If the volume of the core (vol_{bulk}) is much larger than that of the shell (vol_{shell}), then a small amount of calcium could move from the core to the shell and have a significant effect on the concentration Ca_i while there is almost no change in the concentration Ca_{bulk}. And how do we deal with Eq. 3.17b and c, in which some reactants are described in terms of concentration, i.e. material/volume, while others are material densities, i.e. material/area?

In such situations, it is useful to realize that what we're trying to do is to write an equation for each state variable that expresses the rate of change of material as the difference between fluxes (material/time) into and out of the state. We start by defining the quantity of material as the product of the state variable and the size of its compartment, and then ensure that each term in the equation has the same units.

To see how this works, let's translate Eq. 3.17a-c into the corresponding differential equations. In order to avoid the distraction of scale factors, we start by assuming that areas and volumes and are in [cm^2] and [cm^3], respectively, while material densities (*Pump* and *CaPump*) are in micromoles per cm^2 [µmole/cm^2] and concentrations (Ca_o, Ca_i, and Ca_{bulk}) are in [µmole/cm^3]. Later we will relax this assumption to see how scale factors enter into the picture.

We start with Ca_{bulk}, which has the simplest equation.

$$vol_{bulk} \frac{d\,Ca_{bulk}}{dt} = k_d Ca_i - k_d Ca_{bulk} \qquad \text{Eq. 3.18}$$

The total material in this state is $vol_{bulk}\, Ca_{bulk}$, the flux that enters it is $k_d\, Ca_i$, and the flux that leaves it is $k_d\, Ca_{bulk}$. The left hand side of Eq. 3.18 is the rate of change of material in this state, and it has units of [µmole/ms]. Since every term in this equation must have the same units, it is clear that k_d must be in [cm^3/ms].

The equation for Ca_o is

$$vol_o \frac{d\,Ca_o}{dt} = k_3 CaPump - k_4 Ca_o\, Pump \qquad \text{Eq. 3.19}$$

which, like Eq. 3.18, has units of [µmole/ms] on the left hand side. Since *CaPump* is in [µmole/cm^2], it follows that k_3 must have units of [cm^2/ms], and k_4 must be in [cm^5/ms µmole].

The state *CaPump* appears in two reactions, so its differential equation has more terms.

$$area_{pump} \frac{d\, CaPump}{dt} = k_1 Ca_i Pump + k_4 Ca_o Pump - (k_2 + k_3) CaPump \qquad \text{Eq. 3.20}$$

Once again the left hand side is in [µmole/ms], and it is clear that k_1 must have the same units as k_4, i.e. [cm^5/ms µmole], while the units of k_2 must be [cm^2/ms], identical to those of k_3.

The equation for *Pump* is

$$area_{pump} \frac{d\, Pump}{dt} = (k_2 + k_3) CaPump - (k_1 Ca_i Pump + k_4 Ca_o Pump) \qquad \text{Eq. 3.21}$$

The terms on the right hand side of this equation are the same as those in Eq. 3.20 but with opposite signs, and units are obviously consistent throughout.

For Ca_i the equation is

$$vol_{shell} \frac{d\, Ca_i}{dt} = k_d Ca_{bulk} - k_d Ca_i - k_1 Ca_i Pump + k_2 CaPump \qquad \text{Eq. 3.22}$$

and the units of all terms are consistent.

Scale factors

Up to this point we have used the same units for all calcium concentrations: [µmole/cm^3]. What if we prefer a more customary measure for Ca_o, e.g. [millimole/liter]? No problem--1 µmole/cm^3 is equivalent to 1 millimole/liter, i.e. the values are numerically equal, so we can use the same rate constants and equations as before, without having to insert scale factors into our equations.

Now suppose we decide that [cm^3] is too large a unit for intracellular volumes, and that we would prefer to use [µm^3] instead for vol_{bulk} and vol_{shell}? At first this seems perplexing, because the units of the left hand side of Eq. 3.18 would be [µm^3 µmole/ms cm^3], while the right hand side is still in [µmole/ms]. We are rescued from confusion by recalling that 1 µm = 10^{-4} cm, so [µm^3 µmole/ms cm^3] is equivalent to 10^{-12} [µmole/ms], and we have

$$vol_{bulk} \frac{d\, Ca_{bulk}}{dt} = 10^{12} \, (k_d Ca_i - k_d Ca_{bulk}) \qquad \text{Eq. 3.23}$$

The 10^{12} on the right hand side of Eq. 3.23 is a scale, or "conversion," factor, and if we wanted to be pedantic we would point out that it has units of [$\text{cm}^3/\mu\text{m}^3$]. In any case, its numeric value makes sense, because a small net movement of calcium will have a much larger effect on the concentration Ca_{bulk} if vol_{bulk} is 1 μm^3 rather than 1 cm^3.

Of course we also have to apply a scale factor in Eq. 3.22, the other equation that involves an intracellular volume. By identical reasoning we obtain

$$vol_{shell} \frac{d\, Ca_i}{dt} = 10^{12} \Big(k_d \, Ca_{bulk} - k_d \, Ca_i - k_1 \, Ca_i \, Pump + k_2 \, CaPump \Big) \qquad \text{Eq. 3.24}$$

Electrical circuits

An electrical circuit (Fig. 3.3) can be translated to an equivalent set of equations by combining Kirchhoff's current and voltage laws with the characteristics of the individual devices in the circuit. Here we present a brief heuristic approach to how this can be done. Space and time preclude discussion of related topics such as graph theory; for a more thorough development of circuit analysis, motivated readers are referred elsewhere (e.g. (Nilsson and Riedel 1996)).

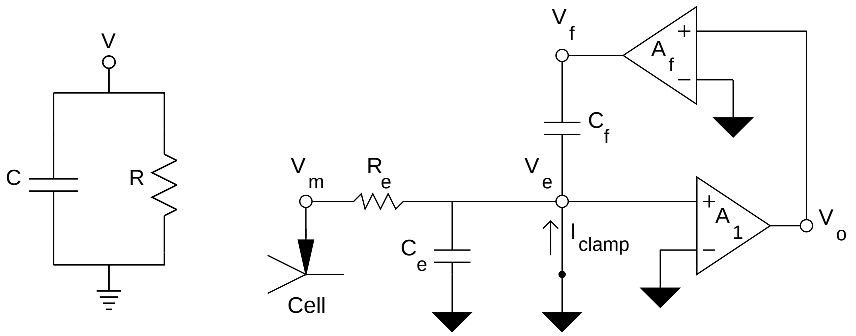


Fig. 3.3. Left: A simple parallel RC circuit. Right: Circuit for recording from a cell while passing current through the same electrode. Amplifier A_f and capacitor C_f are used to compensate for the electrode capacitance C_e.

To develop the equations that describe a circuit, we will employ Kirchhoff's current law which states that the algebraic sum of all currents entering a node (a connection between two or more device terminals) is always zero. Every node in a circuit has a voltage, and every connection between nodes ("branch" or "edge") has a current. In order for voltage throughout a circuit to be determined unambiguously, each node must be on a path that ultimately leads to ground. We can then write the current balance equation for each node (the "node equations"), and solve these equations to find the potential at each node and the current through each element in the circuit.

Table 3.1 lists common circuit elements with their characteristic equations and schematic representations. The arrows in the figures of the resistor and capacitor indicate the direction of current flow when *i* given by the characteristic equation is positive. For the voltage source we have adopted the usual convention for the direction of positive current flow (away from the "positive" terminal, which is symbolized by the longer of the two transverse lines).

Table 3.1. Common circuit elements

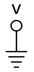
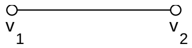
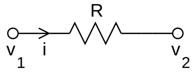
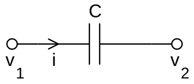
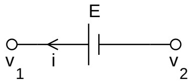
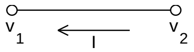
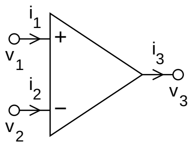
Type of element	**Characteristic equation**	**Schematic representation**
Ground	$v = 0$	
Wire	$v_1 = v_2$	
Linear resistor	$i = (v_1 - v_2)/R$	
Linear capacitor	$i = C\ d(v_1 - v_2)/dt$	
Voltage source	$v_1 - v_2 = E(t)$	
Current source	$i = I(t)$	
Ideal amplifier	$v_3 = G(v_1 - v_2)$ $i_1 = i_2 = 0$	

Figure 3.4 illustrates the application of Kirchhoff's current law to a circuit consisting of a capacitor in parallel with a resistor. There are two nodes, but one is grounded so its potential is 0. Since only one node has a potential that is unknown, this circuit can be described by a single node equation.

The current flow along all branches attached to the ungrounded node is indicated by the diagram on the right side of Fig. 3.4. To apply Kirchhoff's current law to this node, we must assume a positive direction for current flow along every edge that attaches to the node. We want to emphasize that these assumed directions are completely arbitrary, and no matter what we decide, the final equations will be the same. Here we have chosen the convention that current away from a node *adds* to the current balance equation, which gives us

$$I_C + I_R = 0 \qquad \text{Eq. 3.25}$$

Referring to Table 3.1 for the device properties of capacitors and resistors, we obtain the ordinary differential equation

$$C\frac{dV}{dt} + \frac{V}{R} = 0 \qquad \text{Eq. 3.26}$$

whose solution is

$$V(t) = V_0 e^{-t/RC} \qquad \text{Eq. 3.27}$$

where V_0 is the initial voltage on C.

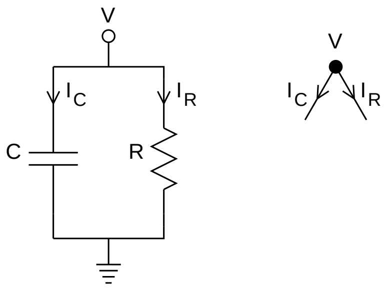


Fig. 3.4. Left: Schematic diagram of a simple parallel RC circuit, which has only one node at which potential is unknown. Right: Node diagram indicating the flow of current away from this single node.

The slightly more complex circuit of Fig. 3.5 has four nodes. There are only two nontrivial equations for the voltages at these nodes, since we already know that the grounded nodes have a voltage of 0. The potentials at the two ungrounded nodes are unknown, and we need to formulate the node equations for them. Once again, we can assign the directions of all currents arbitrarily, but once we have chosen the positive direction of current flow through R_3, we have committed ourselves to the positive direction of I_{R_3} relative to both node 1 and node 2. So if we assume that positive current in C_1, R_1, and R_3 flows away from node 1, and apply the convention that "current away from a node adds to the current balance equation," we have

$$I_{C_1} + I_{R_1} + I_{R_3} = 0 \qquad \text{Eq. 3.28a}$$

which is the current balance equation for node 1.

To get the other current balance equation, we will assume that the positive direction for current in C_2 and R_2 are away from node 2, so these currents add to its current balance equation. However, we have already chosen a direction for positive current flow in R_3, and it happens to be *toward* node 2. The current flow diagrams for nodes 1 and 2 (Fig. 3.5 bottom right) underscores the fact that resistor R_3 makes equal but opposite contributions to current balance at nodes 1 and 2. Consequently the current I_{R_3} is subtracted from the current balance equation for node 2.

$$I_{C_2} + I_{R_2} - I_{R_3} = 0 \qquad \text{Eq. 3.28b}$$

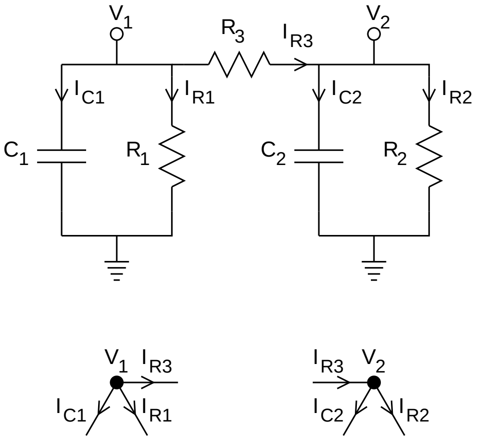


Fig. 3.5. Top: A circuit with three nodes. Bottom: Current flow diagram at each of the two nodes where potential is unknown. Note the direction of current flow in R_3.

Substituting device properties into these equations gives

$$C_1 \frac{dV_1}{dt} + \frac{V_1}{R_1} + \frac{(V_1 - V_2)}{R_3} = 0 \qquad \text{Eq. 3.29a}$$

$$C_2 \frac{dV_2}{dt} + \frac{V_2}{R_2} - \frac{(V_1 - V_2)}{R_3} = 0 \qquad \text{Eq. 3.29b}$$

Again note the - sign applied to the current in R_3 in the second node equation. This pair of coupled first order differential equations constitutes a second order initial value problem, which has a solution of the form

$$V_1(t) = A_1 e^{-t/\tau_a} + B_1 e^{-t/\tau_b} \qquad \text{Eq. 3.30a-b}$$

$$V_2(t) = A_2 e^{-t/\tau_a} + B_2 e^{-t/\tau_b}$$

where A_1, B_1, A_2, and B_2 are determined by the values of V_1 and V_2 at t = 0, and the time constants τ_a and τ_b are the eigenvalues of the matrix

$$\begin{bmatrix} -\frac{1}{C_1}\left(\frac{1}{R_1} + \frac{1}{R_3}\right) & \frac{1}{C_1 R_3} \\ \frac{1}{C_2 R_3} & -\frac{1}{C_2}\left(\frac{1}{R_2} + \frac{1}{R_3}\right) \end{bmatrix} \qquad \text{Eq. 3.31}$$

As a final example of the equivalence between an electrical circuit and a set of equations, let us consider a circuit that could be used to compensate for electrode capacitance. Anyone who has ever recorded from a cell with a microelectrode knows that electrode resistance and capacitance can interfere with experimental measurements. Figure 3.6 shows a simplified circuit of a common method used to compensate for electrode capacitance when recording with a sharp microelectrode under current clamp. This circuit includes a cell, a microelectrode whose electrical properties are represented by an equivalent circuit consisting of a series resistance R_e and a single lumped capacitance C_e located at the "amplifier" end of the electrode, a current source I_{clamp} for injecting current into the cell, and a "headstage amplifier" A_1. It also has an amplifier A_f and capacitor C_f that provide positive feedback to compensate for the electrode capacitance.

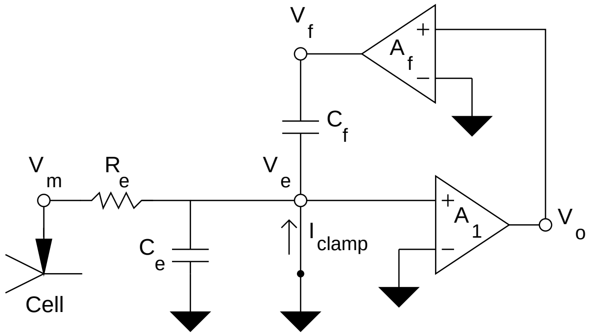


Fig. 3.6. Capacitance compensation under current clamp. The capacitance C_e of the microelectrode distorts recordings by slowing and attenuating the response of V_e to changes in V_m and I_{clamp}. Amplifier A_f and capacitor C_f compensate for this by supplying charging current to C_e.

The open circles mark the nodes that are not grounded. The first node is the site at which the electrode is attached to the cell, and the voltage at this node is V_m, the local membrane potential of the cell. As Fig. 3.7 suggests, the current balance equation for this node is

$$i_{inj} - i_{R_e} = 0 \qquad \text{Eq. 3.32}$$

i.e. the current i_{R_e} that flows through the electrode resistance equals the current i_{inj} that is injected into the cell.

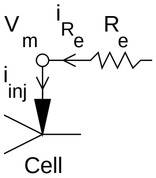


Fig. 3.7. The first node of the circuit in Fig. 3.6. The current injected into the cell equals the current that passes through the electrode resistance R_e.

The voltages at the remaining three nodes are unknown, so we will need three equations. Taking advantage of the characteristic equations for an amplifier (Table 3.1), we see immediately that the nodes at the outputs of the feedback and headstage amplifiers have voltages that are given by

$$V_f = G_f V_o \qquad \text{Eq. 3.33}$$

and

$$V_o = G_1 V_e \qquad \text{Eq. 3.34}$$

where G_f and G_1 are the "gains" or amplification factors of the feedback and headstage amplifiers, respectively. For the third equation, we apply Kirchhoff's current law to the remaining node, which is diagrammed in Fig. 3.8. The current balance equation for this node is

$$i_{R_e} + i_{C_e} - I_{clamp} - i_{C_f} + i_+ = 0 \qquad \text{Eq. 3.35}$$

Each device attached to this node contributes a term to Eq. 3.35, e.g. i_{C_e} is the current that charges the electrode capacitance, and i_{C_f} is the current supplied by the feedback capacitor C_f. Referring to Fig. 3.6 and Table 3.1, we replace each term in Eq. 3.35 by the corresponding characteristic equation to get

$$\frac{V_e - V_m}{R_e} + C_e \frac{d V_e}{dt} - I_{clamp} - C_f \frac{d\left(V_f - V_e\right)}{dt} + 0 = 0 \qquad \text{Eq. 3.36}$$

which rearranges to

$$\left(C_e + C_f\right) \frac{d V_e}{dt} - C_f \frac{d V_f}{dt} = \frac{V_m - V_e}{R_e} + I_{clamp} \qquad \text{Eq. 3.37}$$

Interested readers may wish to combine Eqns. 3.33, 34, and 37 to derive a single differential equation that relates the "output" voltage V_o to the "input" voltage V_m.

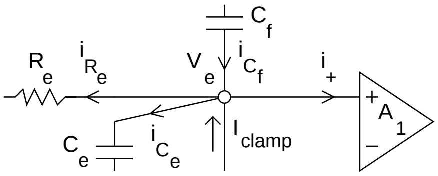


Fig. 3.8. The third node of the circuit in Fig. 3.6. Perfect compensation for electrode capacitance (which can never be achieved with real amplifiers and electrodes) requires that i_{C_f} balances i_{C_e} exactly.

Cables

The spread of electrical and chemical signals in a cable are described by equations that combine conservation laws with formulas that express how voltage and concentration gradients drive the movement of charge and mass. This discussion focusses on electrical signals, since the basic form of these equations is identical for chemical signals (Rall 1977; Crank 1979; Carslaw and Jaeger 1980; Jack et al. 1983), and similar considerations arise in connection with their numerical solution.

The propagation of electrical signals along an unbranched cable is governed by the one-dimensional cable equation

$$\frac{\partial V}{\partial T} + F(V) = \frac{\partial^2 V}{\partial X^2} \qquad \text{Eq. 3.38}$$

where V and F are continuous functions of space and time, which are represented by X and T (with appropriate scaling) (Rall 1977; Jack et al. 1983). The branched architecture typical of most neurons is dealt with by combining partial differential equations of this form with appropriate boundary conditions. This is the approach taken in NEURON, whose programming language `hoc` and graphical user interface have special features that allow us to avoid the task of writing families of cable equations and puzzling out their boundary conditions. Instead, we construct models by specifying the properties of individual neurites and how they are interconnected. NEURON then applies the standard strategy of spatial and temporal discretization to convert our specification into algebraic difference equations, which it solves numerically (Rall 1964; Crank 1979; Carslaw and Jaeger 1980) (see **Chapter 4: Essentials of numerical methods for neural modeling**).

We can derive the cable equation by combining the physical principle of conservation of charge with Ohm's law. Focussing on these separately provides insight into the process of spatial discretization and the meaning of boundary conditions. In addition we can easily handle issues of branching and spatially-varying diameter that were assumed away in the cable equation but are dominant physical features of real neurons.

Conservation of charge requires that the sum of currents flowing into any region from all sources must equal zero. For example, if Figure 3.9 represents part of a cell, conservation of charge means that

$$\sum i_a - \int_A i_m \, dA = 0 \qquad \text{Eq. 3.39}$$

where the first term is the sum of all axial currents i_a (in [mA]) flowing into the region through cross-section boundaries, and the second term is the total transmembrane current found by integrating the transmembrane current density i_m (in [mA/cm^2]) over the membrane area A (in [cm^2]) of the region. The usual sign convention is that outward transmembrane current is positive and axial current into a region is positive. If electrode current sources are present, they are treated exactly the same as membrane currents except for the sign convention, i.e. electrode current into a cell (depolarizing current) is positive. Including electrode current i_s in the conservation equation gives

$$\sum i_a - \int_A i_m \, dA + \int_A i_s \, dA = 0 \qquad \text{Eq. 3.40}$$

The physical size of electrode current sources is generally very small compared to the spatial extent of a region, so the mathematical form for i_s is usually a delta function of position i_s [mA] · $\delta(x-x_0, y-y_0, z-z_0)$ [cm^{-2}]. It becomes a matter of personal preference whether to keep electrode currents under an integral, analogous to distributed membrane currents, or merely to add i_s [mA] to the sum of i_a in whatever region the electrode happens to be. In either case, the extra terms add nothing to the conceptual analysis, so we will omit them from the following equations to reduce irrelevant clutter.

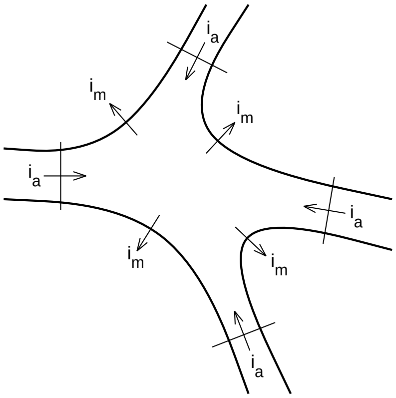


Fig. 3.9. The net current that flows into any region of a cell is 0. The arrows indicate the positive directions for transmembrane (i_m) and axial (i_a) currents.

A standard approach in computer simulation is to divide the neuron into regions or compartments small enough that the spatially-varying i_m in any compartment j is well approximated by its value at the center of the compartment. Equation 3.40 then becomes

$$i_{m_j} A_j = \sum_k i_{a_{kj}} \qquad \text{Eq. 3.41}$$

where A_j is the surface area of compartment j.

Up to this point we have relied entirely on the principle of conservation of charge. Ohm's law is invoked to resolve the axial currents between compartment j and its neighbors (right hand side of Eq. 3.41): each axial current is approximated by the voltage drop between the centers of the compartments divided by the resistance of the path between them (the "axial resistance")

$$i_{a_{kj}} = (v_k - v_j) / r_{jk} \qquad \text{Eq. 3.42}$$

This transforms Eq. 3.41 into

$$i_{m_j} A_j = \sum_k (v_k - v_j) / r_{jk} \qquad \text{Eq. 3.43}$$

This automatically takes care of the direction of axial current flow, since $v_j < v_k$ implies that current flows into compartment *j*.

The total membrane current is the sum of capacitive and ionic components

$$i_{m_j} A_j = c_j \frac{dv_j}{dt} + i_{ion_j}(v_j, t) \qquad \text{Eq. 3.44}$$

where c_j is the membrane capacitance of the compartment and $i_{ion_j}(v_j, t)$ includes the effects of varying ionic channel conductances. In summary, the spatial discretization of branched cables yields a set of ordinary differential equations of the form

$$c_j \frac{dv_j}{dt} + i_{ion_j}(v_j, t) = \sum_k (v_k - v_j) / r_{jk} \qquad \text{Eq. 3.45}$$

As mentioned above, injected source currents would be added to the right hand side of this equation.

Equation 3.45 involves two approximations. First, axial current is specified in terms of the voltage difference between the centers of adjacent compartments. The second approximation is that spatially-varying membrane current is represented by its value at the center of each compartment. This is much less drastic than the often heard statement that a compartment is assumed to be "isopotential." It is far better to picture the approximation in terms of voltage, membrane current, and axial current varying linearly between the centers of adjacent compartments. Indeed, the linear variation in voltage is implicit in the usual description of a cable in terms of discrete electrical equivalent circuits where all the membrane channels in a compartment have been pushed into a single point at the center of the compartment.

Two special cases of Eq. 3.45 deserve particular attention. The first of these allows us to recover the usual parabolic form of the cable equation. Consider the interior of an unbranched cable with constant diameter. The axial current consists of two terms involving compartments with indices *j*-1 and *j*+1, i.e.

$$c_j \frac{dv_j}{dt} + i_{ion_j}(v_j, t) = \frac{v_{j-1} - v_j}{r_{j-1,k}} + \frac{v_{j+1} - v_j}{r_{j+1,k}} \qquad \text{Eq. 3.46}$$

If each compartment has length Δx and diameter *d*, its capacitance is $C_m \pi d \Delta x$ and the axial resistance is $R_a \Delta x / \pi (d/2)^2$, where C_m is specific membrane capacitance and R_a is cytoplasmic resistivity. Equation 3.46 then becomes

$$C_m \frac{dv_j}{dt} + i_j(v_j, t) = \frac{d}{4 R_a} \frac{v_{j+1} - 2 v_j + v_{j-1}}{\Delta x^2} \qquad \text{Eq. 3.47}$$

where the total ionic current i_{ion_j} is replaced by the ionic current density i_j. As $\Delta x \to 0$, the right hand term becomes the second partial derivative of membrane potential with respect to distance at the location of the now infinitesimal compartment *j*, and we have

$$C_m \frac{\partial v}{\partial t} + i(v, t) = \frac{d}{4 R_a} \frac{\partial^2 v}{\partial x^2} \qquad \text{Eq. 3.48}$$

Multiplying both sides by R_m and recognizing that $i\,R_m = v$ gives

$$R_m C_m \frac{\partial v}{\partial t} + v = \frac{d\,R_m}{4 R_a} \frac{\partial^2 v}{\partial x^2} \qquad \text{Eq. 3.49}$$

Scaling t and x by the time and space constants $\tau_\mathrm{m} = R_m C_m$ and $\lambda = \frac{1}{2}\sqrt{\frac{d\,R_m}{R_a}}$ (i.e. substituting $T = t / \tau_\mathrm{m}$ and $X = x / \lambda$) transforms Eq. 3.49 into the form shown in Eq. 3.38.

The second special case of Eq. 3.45 allows us to recover the boundary conditions. This is an important issue since naive discretizations at the ends of the cable have destroyed the second order accuracy of many simulations. The boundary condition for the terminal end of a nerve fiber is that no axial current flows at the end of the cable, i.e. the end is sealed. This is implicit in Eq. 3.45, where the right hand side will consist only of the single term $(v_{j\text{-}1} - v_j) / r_{j\text{-}1,\,j}$ when compartment j lies at the end of an unbranched cable.

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Chapter 3 Index