

Compartmental Models

6-1. Up to this point we have represented the cylinder as an electric circuit with axial resistances and membrane resistance and capacitance. We derived the cable equation by analyzing this circuit and letting Δx go to zero in the limit to produce the derivatives.

Another approach is to divide a cylinder into a number of segments or compartments where each compartment is isopotential and these isopotential compartments are connected with coupling resistances, as shown on this overhead.

We define the coupling resistance $r_{j,j+1} = r_j/2 + r_{j+1}/2$ or the axial resistance from the middle of compartment j to its end + the axial resistance from the start of compartment $j+1$ to its middle.

These compartments do not have to have the same diameter or length. In this case the coupling resistance is $r_{j,j+1} = \frac{R_a 4 \ell_j}{\pi d_j^2 2} + \frac{R_a 4 \ell_{j+1}}{\pi d_{j+1}^2 2}$ where the coupling resistance in ohms is the sum of

the resistances through a cross-sectional area for length $\ell/2$ for each of the two connected compartments.

6-2. We compare the characterized neuron with a cable model and a compartmental model here. The cable model models voltage continuously over a section of constant diameter and sections are matched at their boundaries with suitable boundary conditions. In the compartmental representation, the individual sections are isopotential and coupled together with coupling resistances.

6-3. NEURON distinguishes between Sections and Segments. A Section is typically a cylinder (although it can be a cable with taper or flare as well) of a given length (from measured morphology typically). These Sections are divided up into Segments in NEURON to provide numerical accuracy in the numerical solution.

For example, suppose we have a Section with $nseg=3$, or 3 segments. Then in NEURON, the voltage is computed for the middle of each segment. In NEURON the position within a section is given relative to $[0,1]$ where 0 is the start and 1 is the end of a section.

If $nseg = 3$, then voltage will be calculated at $x=0.16$, $x=0.5$, and $x=0.83$.

Voltage is also computed at the start of the first segment $x=0$.

At terminations, the boundary condition is a sealed end, so the voltage at the end will equal the voltage in the last segment. BC implies that $\Delta V/\Delta x = 0$ so $V(1)-V(.83) = 0$ or $V(1)=V(.83)$.

At branch points, voltage is calculated and is different from the voltages in the segments immediately before or after the branch point.

What this means is that $V(0)$ is a unique value, $V(x>0 \text{ and } x<0.33)=V(0.16)$, $V(x>0.33 \text{ and } x<0.67)=V(0.5)$, and $V(x>.67) = V(0.83)$ and $V(1) = V(0.83)$ at terminations or a unique value if at a branch point.

Currents or synapses applied in a segment are applied in the middle of the segment.

Currents or synapses can also be applied at the 0 or 1 ends of a section.

A current at $x=0.1$ will actually be applied at $x=0.16$ in the present example. You need to be aware of this when assigning locations for currents or synapses.

6-4. The equations for a compartmental approach are a bit different than for the cable approach. Compartments do not have their length go to zero in the limit. The length is finite. Consequently we will not see a derivative with respect to x in this approach.

Our membrane circuit is illustrated here on this overhead. The capacitance and resistance are for a compartment and are labeled c_{mj} and r_{mj} to indicate that they apply to compartment j . Similarly we have subscripts on the axial resistance terms to indicate compartment. Finally the axial current is expressed as $i_{j-1,j}$ or $i_{j,j+1}$ to indicate the current from compartment $j-1$ to compartment j or from compartment j to compartment $j+1$.

To develop the equations we need to apply Kirchoff's law and Ohm's law.

Kirchoff's law implies that $i_{j-1,j} = i_{mj} + i_{j,j+1}$ or that the current entering compartment j from compartment $j-1$ equals the current that leaves compartment j through the membrane plus the current that continues to compartment $j+1$ from compartment j . Expressed in terms of membrane current we have $i_{mj} = i_{j-1,j} - i_{j,j+1}$.

Applying Ohm's law we get $i_{j-1,j} = (V_j - V_{j-1})/r_{j-1,j}$ where the denominator is the coupling resistance and the numerator is the voltage drop from compartment $j-1$ to compartment j . Similarly $i_{j,j+1} = (V_{j+1} - V_j)/r_{j,j+1}$. Substituting into the expression for membrane current above we get

$$i_{mj} = \frac{V_j - V_{j-1}}{r_{j-1,j}} - \frac{V_{j+1} - V_j}{r_{j,j+1}}. \text{ But then we know from previous analysis } i_{mj} = c_{mj} \frac{dV_j}{dt} + \frac{V_j}{r_{mj}}.$$

Equating these two expressions and multiplying by r_{mj} and letting $\tau_{mj} = r_{mj}c_{mj}$ we get

$$\tau_{mj} \frac{dV_j}{dt} + V_j = r_{mj} \left(\frac{V_j - V_{j-1}}{r_{j-1,j}} - \frac{V_{j+1} - V_j}{r_{j,j+1}} \right). \text{ The term in the large parentheses replaces the}$$

second derivative term from before and looking at it you can almost see the definition of the second derivative in it.

This is a system of ODEs of the form $V' = AV + b$ in matrix form. It provides a straight-forward computation, but its accuracy will depend on how finely we divide up the dendrites into compartments.

6-5. Compartmental models essentially approximate the 2nd derivative term from the cable equation. Now how many compartments do we need to divide our cables into to give appropriate accuracy? What criteria should we use? You explored this a bit in the last computer lab and you will explore this further in the next problem set. A rule of thumb is to have no compartment longer than 0.05λ . However for fast changing inputs or action potentials we might want to consider length in terms of the AC space constant (at some frequency). This is where NEURON's d_lambda function and you can use this function, as we saw in lab, to set the number of segments in a section.

What are some complications for the cable or compartmental equations?

1. R_m often has a fixed (or leak) component and a component dependent on voltage. That is $R_m(V)$ or R_m is a function of V . This occurs for the voltage dependent conductances.
2. The equations so far do not allow for synaptic inputs.

These complications are easily fixed as we shall show. We need a more general cable equation. Hodgkin and Huxley used a parallel conductance and we will modify our conceptual circuit model and our equations to follow this paradigm.

General Cable Equation

7-1. In reality r_m is not just the resistance to one ion, but to many different ions and ions enter through many different selective and not so selective channels which may or may not have a voltage dependence for their opening.

To account for this, we let $i_{m(res)} = i_{Na} + i_K + i_{Cl} + i_{Ca} + i_{leak} + \dots$ and replace the single resistive part of the membrane circuit with multiple resistive paths, one for each type of ionic conductance. We have done this here. The battery refers to the reversal potential of the particular resistive path, which in many cases is the Nernst potential for a single ion.

In this parallel conductance circuit $i_{Na} = g_{Na}(V_m - E_{Na}) = g_{Na}(V - V_{Na})$. Recall that $V = V_m - E_r$. Also $V_{Na} = E_{Na} - E_r$.

We develop similar expressions for i_K , i_{Cl} , etc.

Now E_{Na} , E_K and E_{Cl} are the Nernst potentials from the Nernst equation which is

$$E_x = \frac{RT}{zF} \ln \left(\frac{[X]_{out}}{[X]_{in}} \right)$$

where R is the gas constant, T is temperature in degrees Kelvin, z is the

valence of the ion, F is Faraday's constant and the terms in the parentheses are the concentration of the ion outside and inside the cell. Basically what this says is that the voltage needed to balance a concentration gradient is E_x .

7-2. As mentioned above we define $V_{Na} = E_{Na} - E_r$ which means that $V_m - E_{Na} = V - V_{Na}$. This redefines V as displacement from 0. So $V_{Na} = 115$ mV when $E_{Na} = 45$ mV and $E_r = -70$ mV

With this parallel conductance model instead of $i_m = c_m dV/dt + V/r_m$ we have

$$i_m = c_m dV/dt + g_{Na}(V - V_{Na}) + g_K(V - V_K) + g_{Cl}(V - V_{Cl}) + \dots + g_{leak}(V - V_{leak})$$

where we have substituted in for all of the currents and g_{leak} is the passive portion of r_m which NEURON calls g_{pas} .

7-3. Some remarks.

1. At rest the net membrane current is 0, or $i_m=0$ or $i_{Na} + i_K + \dots = 0$. This means that $g_{Na}(V - V_{Na}) + g_K(V - V_K) + g_{Cl}(V - V_{Cl}) = 0$ or rearranging

$$V(g_{Na} + g_K + g_{Cl}) = g_{Na}V_{Na} + g_K V_K + g_{Cl}V_{Cl} \text{ or}$$

$$V = \frac{g_{Na}V_{Na} + g_K V_K + g_{Cl}V_{Cl}}{g_{Na} + g_K + g_{Cl}}. \text{ This should look familiar to those who took the course last}$$

quarter. This defines the resting potential in terms of the conductances of the ions present. In our notation we have $V=0$. (You could just as well define the terms with resting potential equal to some value, say -70 mV if you wanted to).

If $V=0$ then $g_{Na}V_{Na} + g_K V_K + g_{Cl}V_{Cl} = 0$. If your model has a stable resting potential then this condition must hold. Some times modelers manipulate the reversal potential of the leak conductance to make the resting potential stable.

2. With multiple non-uniformly distributed voltage dependent conductances, it may be a good idea to run the simulation for some time period to get the resting voltage to become stable before you do your computational experiment. NEURON has a trick to get stability. The trick is to start in the past and use large time steps. This is given in the NEURON book p. 197.

7-4. To initialize to the steady state. NEURON's default numerical method is the backward Euler method and with this method you can find the steady-state of a linear system in a single large time step, where the time step is large compared to the longest system time constant.

With non-linear systems, it is useful to try several iterations with large dt . This often works, but sometimes you might just miss oscillations in voltage. Anyhow the code here is copied from the NEURON book. Please note the caveats on p. 198 for using this routine.

7-5. So how do we modify the cable equation to take into account these other conductances? In the cable equation we had $\frac{\partial^2 V}{\partial x^2} = (r_e + r_i) \left(c_m \frac{\partial V}{\partial t} + \frac{V}{r_m} \right)$ and all ionic currents were grouped into

the $i_{ion} = V/r_m$ term in this equation. We can replace the V/r_m according to the parallel conductance model and get

$$\frac{\partial^2 V}{\partial x^2} = (r_e + r_i) \left(c_m \frac{\partial V}{\partial t} + g_{Na}(V - V_{Na}) + g_K(V - V_K) + g_{Cl}(V - V_{Cl}) \right)$$

To show the equivalence with the cable equation we can rearrange this and get

$$\frac{\partial^2 V}{\partial x^2} = (r_e + r_i) \left(c_m \frac{\partial V}{\partial t} + V(g_{Na} + g_K + g_{Cl}) - g_{Na}V_{Na} - g_KV_K - g_{Cl}V_{Cl} \right)$$

If we let $g_m = g_{Na} + g_K + g_{Cl}$ and let $r_m = 1/g_m$ we get

$$\frac{r_m}{r_e + r_i} \frac{\partial^2 V}{\partial x^2} = r_m c_m \frac{\partial V}{\partial t} + V - \frac{(g_{Na}V_{Na} + g_KV_K + g_{Cl}V_{Cl})}{g_m}$$

The $r_m/(r_e + r_i)$ is just λ^2 and $r_m c_m$ is just τ and the fraction on the right is 0 at rest (see OH 7-3) and this returns us to the cable equation.

With this modification, we note that if g_{Na} , g_K , and g_{Cl} are functions of time and voltage, then λ and τ are also functions of time and voltage. Instead of being constants, these parameters will be dynamic variables. A conductance increase will reduce both λ and τ .

7-6. NOTE: g_{Na} , g_K , and g_{Cl} are conductances per unit length. Just as we normally deal with R_m , R_a , and C_m instead of r_m , r_i and c_m to use parameters related to area, we convert to conductances per unit length to conductances per unit area. For example $G_{Na} = g_{Na}/\pi d$ in units of S/cm². This is similar to $1/R_m = g_m/\pi d = G_m$

Conductance densities can then be compared among cells. In the literature there is less consistency in the use of capital G_{Na} vs. small g_{Na} so it is best to determine the units that the author is using.

So conceptually we think of

$$\frac{1}{r_i} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + g_{Na}(V - V_{Na}) + g_K(V - V_K) + \dots + g_{leak}(V - V_{leak})$$

or in different units

$$\frac{1}{\pi d} \left(\frac{\pi d^2}{4R_a} \right) \frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V}{\partial t} + G_{Na}(V - V_{Na}) + G_K(V - V_K) + \dots + G_{leak}(V - V_{leak})$$

where the terms are currents

Computationally we think of $\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V - R_m (G_{Na} V_{Na} + G_K V_K + \dots + G_{leak} V_{leak})$

where the terms have units of voltage, and where λ , τ , R_m , G_{Na} , G_K , ..., G_{leak} are functions of time and possible voltage.

Membrane with ion channels with a known conductance description can be modeled with this general cable equation, i.e., the Hodgkin-Huxley axon.

7-7. Synapses and applied currents. How do we get these into the equations? There are two ways.

First you can include synaptic currents and applied currents in the parallel conductance model for the membrane, as shown on this OH. Here we have included synaptic currents of the form $i_{syn} = g_{syn}(V - V_{syn})$ where $g_{syn}=g_e$ for excitation and $g_{syn}=g_{gi}$ for inhibition and $V_{syn}=E_{ex}$ or E_{in} where these are the synaptic reversal potentials for excitation and inhibition (strictly speaking we should use V_{ex} and V_{in}) in our notation. These act like any other ion current conceptually.

Similarly an applied current is the dial in the figure.

Applied currents and synaptic conductances modeled in this way are modeled as densities, i.e., current densities in A/cm^2 and conductance densities G_{syn} in S/cm^2 . The current or synaptic conductance is applied to a whole section of the dendrite and not just at a point. A simulator may convert an applied current in A to a current density in A/cm^2 or a synaptic conductance into a conductance density by taking into consideration the dimensions of the compartment or segment.

Note that synaptic conductances modeled this way contribute directly to λ and τ when they are activated because they add to the conductance of the membrane directly.

Second, synaptic and applied currents can be included in the boundary condition as illustrated here. If we consider the junction of two dendritic cables, the conservation of current condition at the boundary is $-\frac{1}{r_{i1}} \frac{\partial V_1}{\partial x} + g_{syn}(V - V_{syn}) + I_0 = -\frac{1}{r_{i2}} \frac{\partial V_2}{\partial x}$. In this case the currents are point processes, applied at a point and have units of A for the current and S for the conductance.

7-8. The compartmental equations can also be generalized in a similar manner. We go from

$$\tau_{mj} \frac{dV_j}{dt} + V_j = r_{mj} \left(\frac{V_j - V_{j-1}}{r_{j-1,j}} - \frac{V_{j+1} - V_j}{r_{j,j+1}} \right) \text{ (from OH 6-4) to}$$

$$c_{mj} \frac{dV_j}{dt} + (I_{ion} + I_{syn} + I_{stim}) = \left(\frac{V_j - V_{j-1}}{r_{j-1,j}} - \frac{V_{j+1} - V_j}{r_{j,j+1}} \right)$$

where $I_{ion} = \sum g_x (V - V_x)$ and $I_{syn} = \sum g_s (V - V_s)$ and I_{stim} is the applied current.

Now there are no boundary conditions in compartmental models, so currents and synapses are converted to current densities and conductance densities and are applied over the whole compartment.

Note, if there are multiple synapses of the same type on one compartment, the conductances add.

In NEURON, currents and synapses are defined as point processes, rather than as distributed mechanisms. As such, they are incorporated with the “Boundary Condition” shown above. The locations of these processes, however, depend on $nseg$.

Suppose we have a section with $nseg=5$. Then voltage is computed at $x=0, 0.1, 0.3, 0.5, 0.7, 0.9,$ and 1.0 of the relative length along the section. Currents and synapses get inserted at one of these locations regardless of your specification. If you want to apply a current at location 0.41 , it gets applied at location 0.5 .

Strange things can happen if you change $nseg$ in a simulation. Synapses and currents will not be where you think they are.

7-9. So what do we need to do models?

For passive models we need to know the

- lengths of processes,
- diameters of processes,
- their connectivity,
- R_m the membrane resistivity,
- R_a the axial resistivity, and
- C_m the membrane capacity.

For models with voltage dependent conductances, we additionally need to have knowledge of the types and densities of membrane ionic conductances in the cell. IN particular we need to know:

- location and densities of the conductances, the $G_{Na}(x)$
- time course of activation and inactivation, $G_{Na}(t)$
- the voltage dependence of activation and inactivation, $G_{Na}(V)$
- the reversal potential of the conductance, i.e., V_{Na}

If our models have synapses, we also need knowledge of the synaptic conductances

- location of the synapses
- kinetics or time course of the conductance activation, $g_{syn}(t)$
- voltage dependence of conductance activation (I.e., NMDA receptor channels)
- times of activation
- reversal potential

To match experiments we need to know the experimental manipulations

- applied currents
- voltage clamps

For network models we need to know the network connections as well as all of the above information for each cell in the network.

7-10. Strategies and typical values.

The lengths and diameters for use in a model can come from a reconstructed cell morphology or from some assumed simplification (equivalent cylinder or perhaps some reduced morphology that is more than a cylinder but less than full morphology)

C_m we typically assume this is $1.0 \mu\text{F}/\text{cm}^2$ Typical range is 0.6-1.2

R_a typically use 100 ohm-cm. range 50-400 in mammalian neurons (35.4 in squid)

R_m typically 8000-50000 ohm-cm². Range 2000-200,000

If the cell has spines, we need some means to include spines without having to represent every spine that may be present. A typical scheme is to increase C_m and reduce R_m according to the proportion of membrane area due to spine. Another scheme is to change the length and diameter of a process to account for the membrane area increase due to spines. We will discuss these methods further later in the course.

For membrane conductances, an increasing number of voltage dependent conductances are becoming characterized for a variety of different cell types. Hodgkin and Huxley developed a formalism to represent the Na and K conductances for the squid and their formalism is the most widely used means today to express voltage dependent conductances. When we say that we assume a conductance has Hodgkin-Huxley type kinetics, this means that the conductance is characterized in the manner H-H used. We will discuss this later in the course, perhaps next class. For these voltage dependent conductances we generally

- assume H-H type kinetics

- use activation and inactivation curves determined via experiment

- assume some maximum conductance values for each location or dendrite (S/cm^2)

For synaptic conductances we need to know something about the conductance time course $g(t)$

- peak conductance (usually less than 0.5 nS)

- kinetics—there are some standard kinetic forms that we will discuss

 - alpha function (AlphaSynapse in NEURON)

 - double exponential (Exp2Syn)

 - exponential decay (ExpSyn)

 - other custom forms that you can write.