

NOTES TO SUPPLEMENT BIOS 414/514 LECTURES ON CABLE THEORY

Figure and equation numbers refer to the text. Large bold numbers refer to overheads in the handouts.

TERMS: V_m R_N τ , λ , R_m R_a C_m L morphology diam len
<http://cneuro.zool.ohiou.edu/holmes/Cablelecture.pdf>

1 Today I will talk about electrical signaling in nerve cells. As I am sure most of you know by now, in most neurons, information reaches the cell at synapses located on the dendrites or the cell body (RECEPTION). Synaptic input produces a voltage change at the synapse and this leads to a voltage change at the soma. If enough synapses are activated in a short time interval then inputs INTEGRATE. Integration will depend on morphology and as shown here above, neuron morphology can vary widely. The voltage change seen at the soma may cross a threshold, and GENERATE an action potential. The action potential travels down the cell's axon to send a signal to other neurons (OUTPUT). The signal can be ENCODED by the output pattern or frequency of action potentials or in non-spiking neurons, by the graded potential (Fig. 4.1)

In some neurons, maybe an action potential is produced for every synaptic input. In others, action potentials occur only if several hundred synaptic inputs occur in a short period of time. How fast is transmission of the signal down an axon? In some axons, transmission is fast (i.e. **100 meters/sec**). When your hand happens to touch something hot, you want your neurons to sense that and have your hand move quickly and then you appreciate having fast axonal transmission. In other axons, transmission is 100 times slower (**1 meter/sec**). Why do these differences exist? To appreciate why these differences exist, we need to understand some of the basic properties of neurons, particularly their passive cable properties.

OMIT HERE, MENTION LATER (In BIOS 171 you were taught that dendrites are passive, and axons have special channels for producing APs. Today we know that these special channels exist on dendrites too, although at lower densities, so dendrites are not entirely passive, but to a first approximation, they are.)

2 One of the first basic properties of a neuron that is easily measured is the resting membrane potential. There is a voltage difference across the membrane of nerve cells. Why? Because membranes are differentially permeable to different ions. The ionic basis of the resting membrane potential will be discussed later. For now all we need to know is that at rest, the potential inside the cell is negative relative to the outside of the cell. We know this because we can put an electrode into a cell and measure the difference in voltage between the inside and the outside of the cell. The resting membrane potential is usually between -40 and -90 mV depending on cell type.

Now for some TERMINOLOGY. When we say that the cell is hyperpolarized what do we mean? We mean that the membrane potential is more negative than the resting

potential. Conversely, when we say a cell is depolarized then the potential is more positive than the resting potential.

3 Not only can we put a recording electrode into a cell to measure voltage, we can also insert a stimulating electrode so that current can be injected into the cell. When small currents are injected into the cell, we see small voltage deflections. **(OH 3) top** (Why doesn't the voltage follow the current exactly? We will return to this point later) For example, consider the hyperpolarizing current: This would produce a voltage deflection that looks like this as on the overhead:

If a constant current is injected for a long time the voltage eventually reaches a steady-state. The amount of current necessary to produce a given voltage change characterizes another important property of the neuron, the INPUT RESISTANCE or R_N .

The input resistance can be calculated from Ohm's law. Do you remember your physics? What is Ohm's law? $V=IR$ or the voltage equals the product of current times the resistance. Rearranging this we see that $R=V/I$. So one can compute the input resistance of a neuron by injecting small currents and noting the steady-state voltage change. In practice this is done for several different hyperpolarizing currents and a few small depolarizing currents. Traditionally, I is plotted against V and $1/R$ is the slope of the line that best fits the data:

(OH 3 bottom)

You can't use large depolarizing currents. Why? You would get an action potential. Often you see curvature with small depolarizing currents. Why? not purely ohmic

4 QUIZ TIME. Suppose a -0.1 nA current causes the voltage to change from a resting potential of -65 mV to -70 mV. What is R_N ? Normally we do this for several current steps and fit a line as indicated above. Answer: R_N is V/I or 50 M Ω . R_N is about 1-5 M Ω for large motoneurons, although values of 50-200 M Ω are typical for most cells. Note R_N is always positive. $(-70)-(-65)\text{mV}/-0.1$ nA = 50 M Ω (be careful with units)

So, why measure input resistance? Input resistance will tell you, in a general way, how excitable a neuron is. For example if the threshold for action potential generation is 10 mV from rest (i.e. threshold is -55 mV when resting potential is -65 mV), the input resistance tells you whether a little or a lot of current must be injected to reach threshold (or alternatively, whether a little or a lot of synaptic input is needed to reach threshold). Suppose a cell has an R_N of 11 M Ω . With a 1 nA current, will it fire an action potential (if threshold is 10 mV from rest)?

$V=IR$ $V= 1 \text{ nA} \times 11 \text{ M}\Omega = 11 \text{ mV}$. Yes.

4b QUIZ TIME: Is a cell with a small input resistance more, or less excitable than a cell with a large input resistance? Small R_N means a small voltage change for a given current (by Ohm's law $V=IR$). **Q2.** Is a small cell (small membrane area or volume) more or less excitable than a large cell? A small cell has a larger input resistance and therefore is more excitable. This is important, for example, in the sequence of recruitment of motoneurons when doing a task (size principle) or if a projection makes synapses on inhibitory interneurons as well as on excitatory principal cells. Inhibition can be feed-forward if inhibitory cells (usually smaller than principal cells) are more excitable or have a larger input resistance.

Notice that when we injected current into the cell, the voltage change was not instantaneous. Although the current injection was a square pulse, the voltage rise and fall were gradual. Why is this so? To understand this, we need a conceptual model of the membrane. Since we have been talking about voltages, currents and resistances, it is natural to set up an electric circuit to describe a patch of membrane.

5 We know that the membrane of the neuron is a lipid bilayer studded with proteins that have various functions. (**see also Fig. 4.6**) Some are ion channels, some are ionic pumps, and others have more esoteric functions that you have already learned or will learn about more later in the course. This membrane provides a resistance to the flow of ions so that the resting potential is maintained. If the membrane were a pure lipid bilayer, the resistance would be 10-100 Mohms-cm² or greater because there would be no holes for ions to get through. But it is not a pure lipid bilayer and so the resistance is much lower and ions leak out. We think that membrane resistivity is 5,000 to 100,000 Ωcm^2 or at least 1000 times smaller.

Besides providing a resistance, the membrane has the ability to separate and store charge. **What is this called?** We say it has a capacitance. Because the membrane potential is negative inside relative to the outside, what happens is that + and - charges line up on the sides of the membrane, attracted to each other. We say that charge is stored on the membrane.

So this leads us to the following electrical circuit to describe a patch of membrane:
We have a resistance in parallel with a capacitance. This is our conceptual model.

Now when we inject a current, what happens? Initially, you discharge the capacitance. As positive charge is injected the inside voltage becomes less negative, negative charges move away from the membrane and positive charges move away from the outside.

It is much easier to move charge this way than to force an ion through the membrane. However the capacitance is discharged quickly, and then current flows through the membrane.

6 If you were able to separate the current flow into its capacitive and resistive components, they would look like this:
Note that the sum of these currents equals the current that is injected, as it should.

To explain why the rise in voltage is as slow as it is, we must analyze these two forms of the current more closely. The bottom of this overhead describes the rise in terms of exponential functions, which foreshadows where we are going to go.

7 To describe what happens quantitatively, we need to go from the **conceptual model to a mathematical model**. I am going to ask you to try to remember a little bit of calculus and physics. If you wondered why biology majors need calculus and physics, you will see why now! First let's consider the capacitance. From your physics you, of course, remember how to determine how much charge is stored on a capacitor, don't you? Do you remember the simple formula? The amount of charge stored on a capacitor is equal to the capacitance of the material multiplied by the voltage change across the capacitor, or **$Q=CV$** . Is this familiar? Q is charge, C is the characteristic capacitance of membrane. For a neuron membrane **C_m is about $1.0 \mu F/cm^2$** as measured by K.C. Cole many years ago.

Well, we want the current across the capacitor. **What is current?** What is the relationship between current and charge? Current is charge moving in time--right? $\Delta q/\Delta t$. So current equals **dq/dt** . To determine the current across the capacitor we take the derivative of $Q=CV$ with respect to time and

$$i_c = dq/dt = c dv/dt$$

and this is the current across the capacitor.

We get the current across the resistor with Ohm's law, $V=IR$ or rearranged, $I=V/R$. Then **$i_r = V/r_m$**

So the total current through the membrane **$I_m = c_m dV/dt + V/r_m$** (eq. 4.5). Now when we inject a given current the voltage rises to a steady-state voltage which I will call V_∞ . The mathematical solution of eq. 4.5 to describe the voltage change is

$$V(t) = V_\infty - (V_\infty - V_0) e^{-t/\tau}$$

where τ (or τ) = $r_m \cdot c_m$ or $R_m \cdot C_m$ for units expressed for a unit area of membrane instead of unit length. The book uses $I_{\text{pulse}}R$ instead of V_∞ but they mean the new steady-state value. I think it is better notation to say V_∞ . This is the general form of the equation. This simplifies to

$$V(t) = V_\infty (1 - e^{-t/\tau}) \text{ when } V_0 = 0 \text{ (eq. 4.7 in your book).}$$

8 Now when we shut the current off, the voltage decays back to its initial value. When we shut the current off, we have $c_m dV/dt + V/r_m = 0$. This is a differential equation. We can rearrange it to $dV/dt = -V/(r_m \cdot c_m)$. As an exercise you might try to see if you remember enough calculus to solve this. When you do solve it the answer is:

$$V_0 e^{-t/\tau} \text{ which is the most commonly seen form (eq. 4.8)}$$

(note this comes from the general form above when V_∞ or the final voltage value = 0)

9 So what is this τ and what do these equations mean? The equations tell us that the time course of the voltage decay is exponential, and is determined by the parameter τ which we call the time constant. The time constant is another important characteristic of a neuron. It is a measure of the rate of voltage decay (or charging) and determines how synaptic inputs are integrated.

We define the time constant as the time it takes for the voltage to decay to 1/e or 37% of its initial value in an isopotential cell. In most texts, this last prepositional phrase is ignored, but it is very important and I'll explain why in a moment. In your text, the importance of this distinction is apparent in the discussion of the two compartment model.

(e is a number. On your calculator you will find that $e^1 = 2.7128$, so $\exp(-1) = e^{-1} = 1/e = 0.37$. So if $\tau = 10$ ms, then as the voltage decays back to rest according to $V_0 e^{-t/\tau}$ the voltage at time = 10 ms will be $V_0 \exp(-10/10) = V_0 \exp(-1) = 0.37 V_0$).

Let's interpret our equations.

QUIZ TIME. If the time constant is large, then what happens to voltage decay? V decays slowly. If tau is small then V decays quickly. Why is this important for synaptic integration?

Let's take a simple example. Suppose two synaptic inputs are represented, for now, by current steps. The voltage change from the second current step will sum with that of the first current step, if delivered within a short time interval after the end of the first current. If tau is small, then the voltage decay following the first step is quick, and it will be difficult for the two inputs to add. If tau is large, the voltage changes are more likely to add and maybe the voltage reaches threshold for an action potential.

The summation we see has a name. It is called temporal summation.

We defined the time constant as the time it takes for the voltage to decay to 1/e or 37% of its initial value in an isopotential cell. I noted that this last prepositional phrase is often ignored but that it is important. Would anyone like to hazard a guess as to why the decay is described by this equation only in an isopotential cell?

10 Let's look at two cases--a simple sphere and a long cylinder. If your cell is a simple small sphere that polarizes uniformly, then current can only go out of the membrane. In cells with dendrites, the current can go through the membrane, but it also can go down the cable. Going down the cable is the preferred route because the resistance down the cable is smaller than through the membrane.

On this overhead we compare the two cases of a small sphere and an infinite cylinder. For an infinite cylinder the decay (or rise time here) is much faster, and at one time constant the voltage has come 84% of the way. If the length of the cable is finite, then the rise time (or decay time) will lie between these two extremes. This occurs because the solution for the finite cable contains an infinite number of exponential terms representing fast time constants. You will have a chance to play with this on the computer. I should mention that the final decay time is the same in these cases. Once charge has equalized in the dendrites, and the faster decay governed by the faster time constants has finished, all decay is according to the time constant tau.

Despite these caveats, tau is quite useful as a measure of the rate of voltage decay or charging and as an indicator of the degree of temporal summation that can take place.

11 In the last overhead, I did not explain why the cylinder has time constants that differ from tau. The reason is that the membrane circuit I drew previously represents only at an isolated patch of membrane. However, neurons are not isopotential patches of membrane. They have one or more processes that are more or less cylindrical in shape, so the simple membrane circuit above should not be used as a conceptual model of the whole neuron. What we need to do is to connect the patches of membrane as follows

membrane picture (Fig 4.6):

Current flows down the longitudinal axis of the cable and can exit the membrane at any one of these patches of membrane. The current flowing inside the cell faces a resistance governed by the composition of the intracellular media.

There is also a resistance outside the cell due to the extracellular media. We often neglect this resistance, but it is there. Why do we know that it is there? If it weren't present we couldn't do extracellular recordings.

We can analyze the current flows in this circuit, but I won't go into the details here. That is covered in Bios 418/518 which I will teach in winter quarter. For now I will just say that the equation we get from analyzing the electrical circuit is the **cable equation** or:

$$\lambda^2 d^2V/dx^2 - V = \tau dV/dt$$

This equation is called the cable equation because Lord Kelvin used it in calculations needed to lay the first transatlantic telegraph cable. It wasn't long after that that this equation was applied to neuroscience back in the late 1800s and the cable equation was a key element in the pioneering studies of Hodgkin, Huxley and Rushton in the late 1940s and early 1950s. A more complicated version of this equation played a role in Hodgkin and Huxley winning the Nobel Prize.

Note that this equation is the same as the equation for the patch except that it has this $\lambda^2 d^2V/dx^2$ term. This is what distinguishes the cable from the patch.

Now what is this lamda? Lamda is called the space constant. Lamda is the square root of the ratio of the membrane resistance to the sum of the intracellular and extracellular resistances or $\sqrt{r_m/(r_a+r_e)}$ where r_m is the resistance of a unit length of membrane Ωcm and r_a and r_e are resistances per unit length Ω/cm . We usually ignore the r_e and say that lamda = $\sqrt{r_m/r_a}$. Note, your book uses r_i instead of r_a .

What is the significance of the space constant? What does it mean? **(OH 11 bottom)**. Suppose we inject a current into a cell and wait for the voltage to reach steady-state. Then if we were to measure the voltage at different locations along the cable we would see that voltage decays as a function of distance. How can we describe this decay quantitatively?

We can look at the steady-state cable equation. In the steady-state there is no capacitive current and so we have only $\lambda^2 d^2V/dx^2 - V = 0$. This differential equation is easily solved--you might try this as an exercise. We want a function whose second derivative gives back the original function times a constant. One possible solution to this is $V(x) = V(0) \exp(-x/\lambda)$. This particular solution is for a semi-infinite cable.

We can graph this function as on the bottom of this overhead

12 This leads to the following definition of the space constant: The space constant is the distance over which the voltage decays to 1/e or 37% of its value at the origin in a semi-infinite cable. As with the time constant, we have this short prepositional phrase at the end of the definition that is not included in most texts. For axons this is not that serious of an omission because axons tend to be very long, but dendrites tend to be about a space constant long. You may read that the dendritic tree of a neuron has an

electrotonic length of 1.0. Electrotonic length = physical length/ λ . The abbreviation is $L = 1.0$.

What happens is that for a finite cable, the voltage decay at one space constant from the origin is much smaller than would be predicted from $1/e$ on the overhead.

Why is this so? **(OH 12 bottom)** It happens because the current cannot flow through the end of the cylinder. The boundary there dams the current and more current flows out the membrane. Consequently, from Ohms law, $V=IR$, increasing current will increase the voltage, and so the decay is smaller. I hope to be able to have you explore this on the computer as well.

What is the significance of the space constant? The space constant is important for spatial summation in dendrites and for the spread of potential in axons as we shall see later on. **(OH 12 top)**

13 QUIZ TIME. If λ is large, then the spatial decay of an input with distance is (little or a lot) little and the effect of that input is felt at other locations in the cell. If λ is small, then decay with distance is (a little or a lot) sharp (a lot) and an input at one location may not be felt at some distance away from the input. (International students often do not describe this correctly even when they understand the concept because of language—need to be careful).

Although we have discussed resistances and capacitances of patches of membrane, knowing the total membrane resistance or capacitance of a cell is not very useful if one is going to compare different cell types. Consequently we express the membrane resistance in terms reflecting the resistance of a unit membrane area and the intracellular resistance in terms of resistance through a unit cross-sectional area having unit length. **(OH 13 middle)**

So in the literature you will see people measuring the specific membrane resistance or membrane resistivity of a cell or R_m . $R_m = r_m \pi d$ $R_a = r_a \pi d^2/4$ $C_m = c_m / \pi d$.

R_m is the specific membrane resistance or membrane resistivity Ωcm^2

R_a or R_i is the specific axial resistance or axial resistivity Ωcm

C_m is the specific membrane capacitance or membrane capacity $\mu\text{F}/\text{cm}^2$

In general R_m is 5,000-100,000 Ωcm^2 10-40 $\text{k}\Omega\text{cm}^2$ is most common

R_a is 50-200 Ωcm

C_m is 1.0 $\mu\text{F}/\text{cm}^2$

These are numbers I want you to know. These are numbers that you will find reported in the literature.

When resistance and capacitance are expressed in these terms, the definition of lamda assumes a slightly different form

(and so does tau; although for tau, $\tau=r_m*c_m=R_m*C_m$ so there is nothing very different).

For lamda, using capital R_m and R_a we get:

$$\lambda = \sqrt{R_m * d / (4 * R_a)} \quad (\text{Eq. 4.3})$$

(OH 13 bottom) This equation shows the explicit dependence of lamda on the diameter of the cell, R_m , and R_a . The dependence is a square root dependence. So if I double R_m , what happens to lamda? It increases by $\sqrt{2}$. Same with diameter. If I double R_a , I am in effect making it more difficult for current to travel down the cable, and this reduces lamda by $\sqrt{2}$.

We can see the effect of different diameter and R_m values on the passive decay in the next two overheads.

14 The voltages here are scaled. The cylinder with the small diameter has a large input resistance and for the same current the voltage would be much larger than in the other two cylinders. On this first overhead we see that multiplying the diameter by 4 increases lamda by 2 and consequently the decay with distance is much smaller. So from this, we see that transmission is more efficient in large diameter processes in that there is less decay.

15 Turning to the second example, if we multiply R_m by 4 we also double lamda and this makes the decay with distance much less for a fixed diameter. Please look at these examples carefully and make sure you understand what is going on.

16 Now let's put together what we have learned to see how we can explain electrical signaling.

Inputs come to the dendrites at synapses.
A synaptic current is injected into the dendrite.
Let's assume that it is a square pulse of some duration. **The amplitude of the voltage change depends on what cable property that we have discussed?** (there are other factors, such as the number of postsynaptic receptors, but let's keep to cable factors).

ANS: the input resistance at the synaptic site. If the input resistance at the site of the synapse is large, the amplitude of the voltage change will be large. We measure the

input resistance at the soma--the input resistance is likely to be higher in the thin dendrite.

What factors determine the decay of the voltage at the synaptic site? Again, let's consider cable factors and not kinetics of channel opening or closing.

ANS: The voltage change in the dendrite will increase and decrease according to the membrane time constant.

The voltage change that occurs at the synaptic site is then seen at neighboring areas as the synaptic current spreads, but the voltage change is smaller than at the synapse.

What determines the decay of the voltage signal as it propagates to the soma?

ANS: How much smaller the voltage change is at the soma is determined by the space constant (along with other factors such as current time course).

Inputs from different synapses sum at the soma in a process called what?

ANS: Spatial summation

As the voltage changes at the soma, will an action potential be fired?

ANS: It depends if the voltage crosses threshold or not. If threshold is crossed, an active response, all-or-none, is generated called the action potential.

The action potential propagates down the axon. **What determines the voltage decay between nodes of Ranvier in the axon?**

ANS: The voltage decays between nodes according to the space constant.

If the space constant is not extremely short, then this depolarization is sufficient to exceed threshold in the neighboring node and the AP is propagated down the axon.

Many CNS neurons have a myelin sheath to increase propagation speed. What the myelin does is reduce the capacitance and increase the membrane resistance so that there is no current flow through the membrane. Consequently all current flows ahead to the next node of Ranvier and the signal jumps from node to node. This is called saltatory conduction.

How fast does the AP go down the axon? What is the definition of velocity or speed? Velocity in the simplest terms is distance per time. What basic properties of the cell that we have studied can be related to distance and time? The space constant and the time constant, right. So consider velocity as being related to the space constant λ divided by the time constant τ . If we incorporate our definitions of λ and τ we can see how

propagation speed is affected by the cable properties of the neuron. Try this on your own. In particular, conduction velocity is proportional to \sqrt{d} and inversely proportional to \sqrt{Ra} . So larger diameter fibers have a greater propagation speed.

17 Let's put some numbers on an example. Suppose there is a synaptic input lasting 10 msec with amplitude of 0.1 nA. Let the resting potential be -65 mV. If the input resistance at the synapse is 300 M Ω and the membrane time constant, tau, is 10 msec, **what does the potential change at the synapse look like?**

ANS: If the input were a steady state input the voltage would reach $IR = 30$ mV. However, the current lasts 10 msec. In this time the voltage rises to 63% of its final value or 18.9 mV. (Actually higher because we have a cable and not a sphere, so at least 18.9 mV)

Suppose the synapse is one space constant from the soma. **What decay should the synaptic potential (EPSP—excitatory postsynaptic potential) experience going to the soma?**

ANS: At one space constant away, a steady state input would be reduced to 37% of its starting value or to about 7 mV in the present case. The decay will actually be more (voltage will be smaller) because brief transient inputs decay more than steady state ones, but we will use this approximation.

18 **If threshold is 10 mV from rest, will an action potential be produced? If not, how many identical inputs are needed to produce an action potential?**

If each input produces a 7 mV change at the soma, we will need 2 of these inputs to get an AP assuming spatial summation is linear.

If a myelinated segment is 2λ long, will the action potential make it to the next node (will the voltage at the next node exceed threshold)?

ANS: As the AP goes down the axon it will decay, but not much because of the myelin. At a distance of two space constants an AP that peaks 100 mV above rest will decay to 13.5 mV above rest which, with a threshold 10 mV from rest, is big enough to give another AP at the next node.

DROP THIS PART

19 (If time permits, it usually doesn't) Lastly I want to talk about how different information is coded in the nervous system. The action potential propagates in what we call an all-or-none fashion in that once depolarization passed threshold, you will get an action potential that is virtually identical regardless of the strength of the original stimulus. So information cannot be coded in the amplitude of the action potential because it is independent of stimulus intensity.

So, how can different strength inputs be differentiated? One factor that is different for different strength inputs is latency or the time delay between the onset of the stimulus to the peak of the action potential. The stronger the stimulus, the shorter the delay between stimulus and action potential. A second means different strength inputs can be coded is by the frequency of action potentials. A third means is through different patterns of action potentials. Information may be coded in the pattern.

Neurons differ in their firing patterns.

Some are silent unless there is input

Others fire regularly with input just modifying the frequency

Still others fire in bursts

The differences are due to different ion channel densities in the soma and dendrites. Furthermore a single cell can undergo transitions between firing regularly and firing in bursts depending on the pattern of input received.