

**MICHALE FEE:** So today, we're going to start a new topic. We're going to be talking about the propagation of signals in dendrites and axons. So the model that we've considered so far is just a soma. We basically had a kind of a spherical shell of insulator that we've been modeling that has different kinds of ion channels in it that allow the cell to do things like generate an action potential.

So the reason that we've been doing that is because in most vertebrate neurons, the soma is the sight in the neuron at which the decision to make an action potential is made. So all kinds of inputs come in, and then the soma integrates those inputs, accumulates charge, reaches some spiking threshold, and then generates an action potential. And so that's where the decision is about whether a neuron is going to spike or not.

Now, in real neurons, relatively few of the inputs actually come onto the soma. Most of the synaptic inputs, most of the inputs arrive onto the dendrites, which are these branching cylinders of cell membrane. And most of the synapses actually form onto the dendrite at some distance from the soma. There are synapses that form onto the soma.

But the vast majority of synapses form onto these dendrites. And sometimes, those synapses can be as far away as 1 or 2 millimeters for very large neurons in cortex. So there's a population of neurons in deep layer V some of you may have heard about that have dendrites that reach all the way up into layer I. And those cells can be-- those dendrites can be as long as a couple of millimeters.

So we really have to think about what this means, how signals get from out here in the dendrite down to the soma. And that's what we're going to talk about today. So the most important thing that we're going to do is to simplify this-- by the way, anybody know what kind of cell this is?

**AUDIENCE:** [INAUDIBLE]

**MICHALE FEE:** Good. It's a Purkinje cell. And it was one of the-- this is one of the cells that Ramon Cajal drew back in the late 1800s. So the most important thing we're going to do is to simplify this very complex dendritic arborization. And we're going to basically

think of it as a single cylinder.

Now mathematically, there are reasons why this is not actually unreasonable. You can write down-- if you analyze the structure of dendritic trees, there is something about the way the ratio of the diameters of the different dendrites as they converge to form thicker branches as you get closer and closer to the soma that mathematically makes this not a bad approximation for an extended dendritic arbor like this.

So we're going to think about the problem of having a synapse out here on this cylindrical approximation to a dendrite. And we're going to imagine that we're measuring the voltage down here at the soma or at different positions along the dendrite. And we're going to ask, how does synaptic input out here on this cylinder affect the membrane potential in the dendrite and down here at the soma?

And the basic conceptual picture that you should have is that those signals propagate some distance down the soma but gradually leak out. And there's a very simple kind of intuitive picture, which is that the dendrite you can think of this as a leaky pipe or a leaky hose. So imagine you took a piece of garden hose and you poked holes in the side of it or so that they're kind of close together.

And when you hook this up to the water faucet, you turn the water on, that some of that water flows down the hose. But some of it also leaks out through the holes that you drilled. And you can see that eventually the water is all going to leak out through the sides, and it's not going to go all the way down to the other end to get to your hydrangeas or whatever it is that you're watering. And so you can see that that signal isn't going to get very far if the holes you drilled are big enough.

And the general kind of analogy here is that current is like the flow of the water. Electrical current here is like water current flowing down the pipe. And voltage is like pressure. So the higher the pressure here, the higher the current flow you'll get.

And we're going to develop an electrical circuit model for a dendrite like this that's going to look like a set of resistors going down the axis of the dendrite and a set of resistors that go across the membrane. And you can see that each little piece of membrane here, a little piece of the dendrite is going to look like a resistor divider,

where you have a resistor along the axial direction and a resistance across the membrane.

And as you make a longer and longer piece of dendrite, you're going to get additional voltage dividers. Each voltage divider divides the voltage by some constant factor. And as you stack those things up, the voltage drops by some constant factor per unit length of the dendrite. And so you can see-- anybody want to just take a guess of what kind of functional form that would give you if you divide the voltage by some constant factor each unit length of the dendrite?

**AUDIENCE:** Exponential.

**MICHAEL FEE:** Exponential. That's right. And that's where this exponential falloff comes from. So today, we're going to do the following things. And we're going to basically draw a circuit diagram, an electrical equivalent circuit of a piece of dendrite. And I would like you to be able to make that drawing if you're asked to. We're going to be able to plot the voltage in a piece of dendrite as a function of distance for the case of a dendrite that has leaky walls and for the case of a dendrite that has non-leaky walls.

And we're going to describe the concept of a length constant, which I'll tell you right now is just the 1 over the distance at which the voltage falls by 1 over e as a function of length. So it's some length over which the voltage falls by some amount 1 over e. We're going to go over how that length constant depends on the radius of the dendrite. It's a function of the size. And also, we're going to describe the concept of an electrotonic length.

And then finally, we're going to go to some sort of extreme simplifications, even beyond taking that very complex dendrite, simplifying it as a cylinder. We're going to go to an even simpler case where we can just treat the cell as a soma connected to a resistor connected by a resistor to a separate compartment. And that's sort of the most extreme simplification of a dendrite. But, in fact, it's an extremely powerful one from which you can get a lot of intuition about how signals are integrated in dendrites.

So we're going to analyze a piece of dendrite using a technique called finite element analysis. We're going to imagine-- we're going to approximate our piece of dendrite as a cylinder of constant radius  $a$ , an axial dimension that we're going to

label  $x$ . We're going to break up this cylinder into little slices. So imagine we just took a little knife, and we cut little slices of this dendrite. And they're going to be very small slices.

And we're going to model each one of those slices with a separate little circuit. And then we're going to connect them together. And we're going to let the length of that slice be  $\Delta x$ . And then eventually, we're going to let  $\Delta x$  go to 0. We're going to get some differential equations that describe that relationship between the voltage and the current in this piece of dendrite.

So let's start with a model for the inside of this cylinder. So remember, in a cell, we had the inside of the cell modeled by a wire. In a dendrite, we can't just use a wire. And the reason is that current is going to flow along the inside of the dendrite. It's going to flow, and it's going to experience voltage drops. So we have to actually model the resistance of the inside of the dendrite. And we're going to model it like the resistance between each one of those slices with a resistor value little  $r$ .

We're going to model the outside of the axon or the dendrite as a wire. And the reason we're going to put resistors inside and just a wire outside is because the resistance-- remember the axon or dendrite is very small. In the brain, dendrites might be about 2 microns across. So the current is constrained to a very small space.

When currents then flow outside, they're flowing in a much larger volume, and so the effective resistance is much smaller. And we're going to essentially ignore that resistance and treat the outside as just a wire. Now we have to model the membrane. Anybody want to take a guess how we're going to model the membrane?

**AUDIENCE:** [INAUDIBLE]

**MICHAEL FEE:** What's that? I heard two correct answers. What did you say Jasmine?

**AUDIENCE:** The capacitor.

**MICHAEL FEE:** Capacitor. And?

**AUDIENCE:** [INAUDIBLE]

**MICHALE FEE:** Excellent. Whoops. I wasn't quite there. Let's put that up. Good. So we're going to have a capacitance. We're going to imagine that this membrane might have an ion selective ion channel with some conductance  $G_{sub I}$  and an equilibrium or reversal potential  $E_{sub I}$ .

Now coming back to these terms here, we're going to model. We're going to write down the voltage in each one of our little slices of the dendrite. So let's do that. Let's just pick one of them as  $V$ , the voltage, at position,  $x$ , and time  $t$ . The voltage in the next slides over is going to be  $V$  at  $x$  plus  $\Delta x$  of  $t$ . And the voltage in this slice over here is  $V$  of  $x$  minus  $\Delta x$  and  $t$ .

So now, we can also write down the current that goes axially through that piece of-- that slice of our dendrite. We're going to call that  $I$  of  $x$  and  $t$ . And we can write down also the current in every other time-- in every other slice of the dendrite,  $I$  of  $x$  minus  $\Delta x$  and  $t$ . And we're going to model this piece of membrane in each one of those slices as well. Any questions about that? That's the basic setup. That's the basic finite element model of a dendrite. No questions?

Now we also have to model the current through the membrane. That's going to be  $I_{sub m}$ ,  $m$  for membrane. And it's going to be a current per unit length of the dendrite. We're going to imagine that there's current flowing from the inside to the outside through the membrane.

And there's going to be some current per unit length of the dendrite. And we can also imagine that we have current being injected, let's say, through a synapse or through an electrode that we can also model as coming in at any position  $x$ . And this is, again, current per unit length times  $\Delta x$ . Does that make sense?

So the first thing we're going to do is we're going to write down the relation between  $V$  in each node and the current going through that node. So let's do that. We're going to use Ohm's law. So the voltage difference between here and here is just going to be the current times that resistance. Does that make sense? We're just going to use Ohm's law-- very simple.

So  $V$  of  $x$  and  $t$  minus  $V$  of  $x$  plus  $\Delta x$ ,  $t$  is just equal to little  $r$  times that current. And now we're going to rewrite this. Let's divide both sides of this equation by  $\Delta x$

x. So you see  $1$  over  $\Delta x$  times  $V$  of  $x$  minus  $V$  of  $x$  plus  $\Delta x$  is equal to  $r$  over  $\Delta x$  times the current. And can anyone tell me what that thing is as  $\Delta x$  goes to  $0$ ?

**AUDIENCE:** [INAUDIBLE]

**MICHAEL FEE:** Good. It's the derivative of-- it's the spatial derivative of the voltage. That's just the definition of derivative when  $\Delta x$  goes to  $0$ . So let's write that out. Notice that it's the negative of the derivative because the derivative would have  $V$  of  $x$  plus  $\Delta x$  minus  $V$  of  $x$ . So it's a negative of the derivative. So negative  $dv/dx$  is equal to some resistance times the current. And notice that this capital  $R$  sub  $a$  is called the axial resistance per unit length. It's this resistance per unit length of the dendrite.

Now notice that if you pass current down that dendrite, the voltage drop is going to keep increasing. The resistance is going to keep increasing the longer that piece of dendrite is. So you can think about resistance in a piece of dendrite more appropriately as resistance per unit length. So there's Ohm's law--  $-dv/dx$  equals axial resistance per unit length times the current. Any questions?

And notice that according to this, current flow to the right, positive  $I$  is defined as current to the right here produces a negative gradient in the voltage. So the voltage is high on this side and low on that side. So the slope is negative.

So now let's take this, and let's analyze this for some simple cases where we have no membrane current. So we're going to just ignore those. And we're just going to include these axial resistances. And we're going to analyze what this equation tells us about the voltage inside of the dendrite. Does that make sense? So let's do that.

So if we take that equation, we can write down the current at, let's say, these two different nodes--  $I$  of  $x$  minus  $\Delta x$  and  $I$  of  $x$ . And because there are no membrane currents, you can see that those two currents have to be equal to each other. Kirchoff's Current Law says that the current into this node has to equal the current out of that node. So if there are no membrane currents, there's nothing leaking out here, then those two currents have to equal each other. And we can call that  $I_0$ .

So now,  $dv/dx$  is minus axial resistance times  $I_0$ . And what does that tell us about

how the voltage changes in a piece of dendrite if there's no membrane current, if there's no leaky membrane? There's no leakage in the membrane. If  $dv/dx$  is a constant, what does it tell us?

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** Yeah. But decreases how? What functional form?

**AUDIENCE:** [INAUDIBLE]

**MICHALE FEE:** Good. It changes linearly. So if there are no membrane conductances, then the membrane potential changes linearly. So you can see that the voltage as a function of position-- sorry I forgot to label that voltage-- just changes linearly from some initial voltage to some final voltage over some length  $l$ . We're considering a case of a piece of dendrite of length  $l$ . Yes?

**AUDIENCE:** [INAUDIBLE]

**MICHALE FEE:** Yep. So I just rewrote this equation. Sorry, I just rewrote this equation moving the minus sign to that side. Yep. Good. Now you can see that the  $\Delta V$  that the voltage difference from the left side to the right side is just the total resistance times the current-- just Ohm's law again.

And the total resistance is the axial resistance per unit length times the length. Really simple. Voltage changes linearly. If you don't have any membrane conductances, and you can just write down the relation between the voltage difference on the two sides and the current.

So, in general, let's think a little bit more about this problem of being able to what you need to write down the solution to this equation. It's a very simple equation. If you integrate this over  $x$ , you can see that the voltage as a function of position is some initial voltage minus a resistance times the current times  $x$ . And that, again, just looks like this. That's where that solution came from. It's just integrating this over  $x$ .

And you can see that in order to write down the solution to this equation, we need a couple of things. We need to either know the voltages at the beginning and end, or we need to know the current. We need to know some combination of those three

things. So let's write down the voltage here. Let's call it  $V_0$ . Let's write down the voltage there,  $V_{sub\ I}$ , and plug those in.

And you can see that-- there's  $V_0$ . There's  $V_{sub\ I}$ . You can see that if you know any two of those quantities--  $V_0$ ,  $V_{sub\ I}$ , or  $I_0$ -- you can calculate the third. So if you know  $V_0$  and  $V_{sub\ I}$ , you can calculate the current. If you know  $V_0$  and the current, you can calculate  $V_{sub\ I}$ . That is the concept of boundary conditions. You can write down the voltages or the currents at some positions on the dendrite and figure out the total solution to the voltage [AUDIO OUT] of position.

Does that make sense? If you don't know some of those quantities, you can't write down the solution to the equation. It's just the simple idea that when you integrate a differential equation, you need to have an initial condition in order to actually solve the equation. Any questions about that?

So let's think about a couple of different kinds of boundary conditions that you might encounter. So this boundary condition right here-- so let's say that we inject a  $x$  amount of current  $I_0$  into a piece of dendrite. And we take that piece of dendrite and we inject current on one end, and we cut the other end so that it's open. What does that produce at the other end? So we have a wire that describes the inside of the dendrite. We have a wire that describes the outside of the dendrite.

And if you cut the end of the dendrite off so that they're-- it's leaky-- so it's an open end-- what does that look like electrically? Like what's the word for-- like those two wires are touching each other. What's that called? They're shorts. If you cut the end of a dendrite off, you've created a short circuit. The inside is connected to the outside. So that's called an open end boundary condition.

And what can you say about the voltage at this end? If the outside is [AUDIO OUT] what can you say about the voltage inside the dendrite at that end?

**AUDIENCE:** [INAUDIBLE]

**MICHALE FEE:** It's 0. Good. So we have injected current. We have  $V_0$ , the voltage at this end. And we know, if we have an open end, that the voltage here is 0.

Now we can write down. We know that the initial voltage is  $V_0$ . The voltage at position  $L$  is 0. And now you can-- you know that the current here is equal to the

current there, and you can write down the equation and solve  $V_0$ . So  $V_0$  is just the resistance, the total resistance of the dendrite times the injected current. And that  $R_{in}$  is known as input impedance. It's just the resistance of the dendrite. It tells you how much voltage change you will get if you inject a given amount of current. All right. Any questions about that?

Let's consider another case. Rather than having an open end, let's leave [? the end of ?] the dendrite closed so that it's sealed closed. So we're going to consider a piece of dendrite that, one end, we're injecting current in, and the other end is closed. So what do you think that's going to look like? It's called a closed end. What does that look like here? It's an open circuit. Those two wires are not connected to each other. There's no resistance between them.

Let's say we define the voltage here as  $V_0$ . What can you say-- well, what you can say about the current there is that the current is 0, because it's an open circuit. There's no current flowing. And so the current flowing through this at this end is 0. Does that make sense? So what can you say about the current everywhere?

**AUDIENCE:** 0.

**MICHALE FEE:** It's 0. And what can you say about the voltage everywhere? It's  $V_0$ . Exactly. So the voltage everywhere becomes  $V_0$ . And the input impedance? Anybody want to guess what the input impedance is? How much-- what's the ratio of the voltage at this end and the current at this end?

**AUDIENCE:** Infinite?

**MICHALE FEE:** It's infinite. That's right. So we're just trying to build some intuition about how voltage looks [AUDIO OUT] of distance for one special case, which is a piece of dendrite of some finite length for which you have no membrane currents. And you can see that the voltage profile you get is linear, and the slope of it depends on the boundary conditions, depends on whether the piece of dendrite has a sealed end, whether it's open.

All right. So now we're going to come back to the case where we have membrane currents, and we're going to derive the general solution to the voltage in a piece of dendrite for the case where we have membrane capacitance and membrane

currents. All right. And I don't expect you to be able to reproduce this, but we're going to derive what's called the cable equation, which is the general mathematical description, the most general mathematical description for the voltage in a cylindrical tube, of which-- that's what dendrites look like. So we're going to write down that differential equation, and I want you to just see what it looks like and where it comes from, but I don't expect you to be able to derive it.

All right. So let's come back to this simple model that we started. We're going to put our model for the membrane back in. Remember, that's a capacitor and a conductance in parallel. We're going to-- we can write down the membrane current, and we're going to have an injected current per unit length. So Kirchoff's current law tells us the sum of all of those currents into each node has to be 0. So let's just write down-- let's just write down an equation that sums together all of those and sets them to 0.

So the membrane current leaking out minus that injected current coming in. They have positive signs because one is defined as positive going into the dendrite, and the other one is defined as positive going out. So those two, the membrane currents, plus the current going out this way minus the current coming in that way is 0.

So we're going to do the same trick we did last time. We're going to divide by  $\Delta x$ . So, again, membrane current per unit length times the length of this finite element. We're going to divide by  $\Delta x$ . So this thing right here,  $i_{\text{membrane}}$  minus  $i_{\text{electrode}}$ , I guess, equals minus  $1$  over  $\Delta x$   $I$  of  $x$  minus  $I$  of  $x$  minus  $\Delta x$ .

So what is this? You've seen something like that before. It's just a derivative. First derivative of  $I$  with respect to position. So now what you see is that the membrane current minus the injected current is just the first derivative of  $I$ . So hang in there. We're going to substitute that with something that depends on voltage. So how do we do that?

We're going to take Ohm's law. There's Ohm's law. Let's take the derivative of that with respect to position. So now we get the second derivative of voltage with respect to position is just equal to minus  $R_a$  times the first derivative of current. And you can see we can just take this and substitute it there. So here's what we get, that

the second derivative of voltage with respect to position is just equal to the membrane or injected current coming into the dendrite at any position.

So the curvature of the voltage, how curved it is, just depends on what's coming in through the membrane. Remember, in the case where we had no membrane current and no injected current, the curvature was 0,  $d^2V/dx^2$  is 0, which, if the curvature is 0, then what do you have? A straight line.

Now, we're going to plug in the right equation for our membrane current. What is that? That we know. It's just a sum of two terms. What is it? It's the sum of-- remember, this is going to be the same as our soma model. What was that? We had two terms. What were they? The current through the membrane in the model, in the Hodgkin-Huxley model is? What's that?

**AUDIENCE:** [INAUDIBLE].

**MICHAEL FEE:** Good. It's a capacitive current and a membrane ionic current. So let's just plug that in. We're just going to substitute into here the current through the capacitor and the current through this conductance. That's just  $C dV/dt + G(V - E_L)$ . It's a capacitive part and a resistive part.

Now, the capacitance is a little funny. It's capacitance per unit length times the length of the element plus-- and the [AUDIO OUT] is conductance per unit length times the length of our finite element. Capacitance per unit length and ionic conductance per unit length. And we're going to plug that into there. We're first going to notice that this  $E_L$  is just an offset, so we can just ignore it. We can just set it to 0. We can always add it back later if we want.

We divide both sides by the membrane conductance per unit length to get this equation. And that's called the cable equation. It's got a term with the second derivative of voltage with respect to position, and it's got a term that's the first derivative of voltage with respect to time. That's because of the capacitor. And then it's got a term that just depends on [AUDIO OUT].

Now, that's the most general equation. It describes how the voltage changes in a dendrite if you inject a pulse of current, how that current will propagate down the dendrite or down an axon. We're going to take a simplifying case. Next, we're going

to study the case just of the steady state solution to this. But I want you to see this and to see how it was derived just using finite element analysis, deriving Ohm's law in a one-dimensional continuous medium. And by plugging in the equation for the membrane that includes the capacitive and resistive parts, you can derive this full equation for how the voltage changes in a piece of dendrite.

Now, there are a couple of interesting constants here that are important--  $\lambda$  and  $\tau$ . So  $\lambda$  has units of length. Notice that all of the denominators here have units of voltage. So this is voltage per distance squared. So in order to have the right units, you have to multiply by something that's distance squared. This is voltage per unit time, so you have to multiply by something that has units of time.

So that is the length constant right there, and that is a time constant. And the length constant is defined as  $1$  over membrane conductance. That's the conductance of the membrane, through the membrane, and this is the axial resistance down the dendrite. So this is conductance per unit length, and this is resistance per unit length. And when you multiply those things together, you get two per unit length down in the denominator. So when you put those in the numerator, you get length squared. And then you take the square root, and that gives you units of length.

The time constant is just the capacitance per unit length divided by the conductance per unit length. And that is the membrane time constant, and that's exactly the same as the membrane time constant that we had for our cell. It's a property of the membrane, not the geometry. So any questions about that? It was-- it's a lot. I just wanted you to see it. Yes, [INAUDIBLE].

**AUDIENCE:** Like, two slides ago [INAUDIBLE]

**MICHALE FEE:** This one, or--

**AUDIENCE:** One more slide [INAUDIBLE].

**MICHALE FEE:** Yes, here.

**AUDIENCE:** So when you plug that in for the derivative of  $V$ , were we not assuming that there was no membrane [INAUDIBLE]?

**MICHALE FEE:** No. That equation is still correct.

**AUDIENCE:** OK.

**MICHALE FEE:** It's-- voltage is the derivative with respect to position as a function of the axial current.

**AUDIENCE:** OK.

**MICHALE FEE:** OK? Remember, going back up to here, notice that when we derive this equation right here, we didn't even have to include these membrane. They don't change anything. It's just Ohm's law. It's the voltage here minus the voltage there has to equal the current flowing through that resistor. Doesn't matter what other currents-- whether current is flowing in other directions here.

**AUDIENCE:** OK.

**MICHALE FEE:** Does that make sense? The current through that resistor is just given by the voltage difference on either side of it. That's Ohm's law. So now we're going to take a simple example. We're going to solve that equation for the case of steady state. How are we going to take the steady state? How are we going to find the steady state version of this equation? Any idea?

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** Good. We just set  $dV/dt$  to 0, and we're left with this equals that. So we're going to take a piece of our cable, and we're going to imagine that we take a piece of dendrite that's infinitely long in either direction. And somewhere here in the middle of it, we're going to inject-- we're going to put an electrode, and we're going to inject current at one position. So it's injecting current at position 0.

How many of you have heard of a delta function, a Dirac delta function? OK. So we're going to define the current as a function of position as just a current times a Dirac delta function of  $x$ , that just says that all the current is going in at position 0, and no current is going in anywhere else. So the Dirac delta function is just-- it's a peaky thing that is very narrow and very tall, such that when you integrate over it, you get a 1.

So we're going to go to the steady state solution. And now let's write down that. So there's the steady state cable equation. And we're going to inject current at a single

point. So that's what it looks like. Does anyone know the solution to this? Notice, what this says is we have a function. It's equal to the second derivative of that function. Anybody know? There's only one function that does this. It's an exponential. That's right.

So the solution to this equation is an exponential.  $V$  of position is  $V_0$ , some voltage in the middle,  $e$  to the minus  $x$  over  $\lambda$ . Why do I have an absolute value? What is the voltage going to look like if I inject current right here? You're going to have current flowing. Where's the current going to go? If I inject current into the middle of a piece of dendrite, is it all going to go this way? No. What's it going to do?

It's going to go both ways. And the current-- the voltage is going to be high here, and it's going to fall as you go in both directions. That's why we have an absolute value here. So the voltage is going to start at some  $V_0$  that depends on how much current we're injecting, and it's going to drop exponentially on both sides.

And notice what's right here. The  $\lambda$  tells us the  $1/e$  point, how far away the  $1/e$  point of the voltage is. What that means is that the voltage is going to fall to  $1/e$  of  $V_0$  at a distance  $\lambda$  from the side at which the current is injected. Does that make sense? That is the steady state space constant. It has units of length. It's how far away do you have to go so that the voltage falls to  $1/e$ -- falls to  $1/2.7$  of the initial voltage. Any questions? It's pretty simple.

We took an unusually complicated route to get there, but that's the-- the nice thing about that is you've seen the most general solution to how a cable-- a dendrite will behave when you inject current into it. So now we can calculate the current as a function of position. Any idea how to do that? What-- if you know voltage, what do you use to calculate current? Which law?

**AUDIENCE:** Ohm's.

**MICHALE FEE:** Ohm's law. Anybody remember what Ohm's law looks like here?

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** Yes. And we have to do something else. The-- remember, the current is what? Ohm's law in a continuous medium, the current is just going to be what of the voltage, the

blank of the voltage?

**AUDIENCE:** Derivative?

**MICHALE FEE:** The derivative of the voltage. So we're just going to take this and take the derivative. That's it.  $dV/dx$  is just equal to minus  $R$  times  $I$ . So the current is proportional to the derivative of this. What's the derivative of an exponential? Just another exponential. So there we go. The current, and then there's some-- you have to bring the  $\lambda$  down when you take the derivative. So the current is now just minus 1 over the axial resistance per unit length times minus  $V_0$  over  $\lambda$ --  $\lambda$  comes down when you take the derivative-- times  $e$  to the minus  $x$  over  $\lambda$ .

Notice, the current is to the right on this side, so the current is positive it's flowing to the left on that side, so the current is negative. So to do this properly, you'd have-- this is the solution on the right side. You'd have to write another version of this for the current on the left side, but I haven't put that in there.

And, again, the current starts out at  $I_0$ , and drops exponentially, and it falls to 1 over  $e$  at a distance  $\lambda$ . Why is that? Because the current is leaking out through the holes in our garden hose. So as you go further down, less and less of the current is still going down the dendrite. I don't expect you to be able to derive this, but, again, just know where it comes from. Comes from Ohm's law.

So I want to show you one really cool thing about the space constant. It has a really important dependence on the size of the dendrite. And we're going to learn something really interesting about why the brain has action potentials. So let's take a closer look at the space constant, and how you calculate it, and how it depends on the size, this diameter, this radius of the dendrite.

So we're going to take a little cylinder of dendrite of radius  $a$  length little  $l$ .  $G_{sub m}$  is the membrane conductance per unit length. Let's just derive what that would look like. The total membrane conductance of this little cylinder of dendrite, little cylinder of cell membrane, is just the surface area of that cylinder times the conductance per unit area. Remember, this is the same idea that we've talked about when we were talking about the area of our soma. We have a conductance per unit area that just depends on the number of ion channels and how open they

are on that piece of membrane.

So the total conductance is just going to be the conductance per unit area times the area. And the area of that cylinder is  $2\pi a$ — that gives us the circumference— times the length,  $2\pi a l$ . And the conductance per unit length is just that total conductance divided by the length. So it's  $2\pi a$  times  $g$  sub  $l$ , the conductance per unit area. So that's membrane conductance per unit length.

The axial resistance per unit length along this piece, this little cylinder of dendrite, we can calculate in a similar way. The total axial resistance along that dendrite is— can be calculated using this equation that we developed on the very first day, the resistance of a wire in the brain, the resistance of a chunk of extracellular or intracellular solution. The resistance is just the resistivity times the length divided by the area. The longer— for a given medium of some resistivity, the longer you have to run your current through, the bigger the resistance is going to be. And the bigger the area, the lower the resistance is going to be.

So that total resistance is— it has units of ohm-millimeters. So it's the resistivity times  $l$  divided by  $A$ . In intracellular space, that's around 2,000 ohm-millimeters. And the cross-sectional area is just  $\pi$  times  $a$  squared. So now we can calculate the axial resistance per unit length. That's the total resistance divided by  $l$ . So that's just resistivity divided by  $A$ , which is resistivity divided by  $\pi$  radius squared, just the cross-sectional area, and that has units of ohms per millimeter.

So now we can calculate the steady state space constant. Conductance per unit length and axial resistance for unit length— the space constant is just  $1$  over the product of those two, square root. We're just going to notice that that's siemens per millimeter, ohms per millimeter, inverse ohms. So those cancel, and you're left with millimeter squared, square root, which is just millimeters. So, again, that has the right units, units of length.

But now let's plug these two things into this equation for the space constant and calculate how it depends on  $a$ . So let's do that. Actually, the first thing I wanted to do is just show you what a typical  $\lambda$  is for a piece of dendrite. So let's do that. Conductance per area is around  $5 \times 10^{-7}$ , typically. So the conductance per unit length of a dendrite, 6 nanosiemens per millimeter. You don't

have to remember that. We're just calculating the length constant.

Axial resistance is-- plugging in the numbers for a piece of dendrite that's about 2 microns in radius, the axial resistance per unit length is about 60 megaohms per millimeter. And so when you plug those two things to calculate lambda, you find that lambda for a typical piece of dendrite is about a millimeter.

So that's a number that I would hope that you would remember. That's a typical space constant. So if you inject a signal into a piece of dendrite, it's gone-- it's mostly gone or about 2/3 gone in a millimeter.

And that's how you can have dendrites that are up in the range of close to a millimeter, and they still are able to conduct a signal from synaptic inputs out onto the dendrite down to the soma. So a millimeter is a typical length scale for how far signals propagate.

So now let's plug in those-- the expressions that we derived for conductance per unit length and axial resistance for unit length of a into this equation for the space constant. And what you find is that the space constant is a divided by 2 times the resistivity times the membrane conductance per unit area, per area to the 1/2. It goes as the square root. The space constant, the length, goes as the square root of the radius.

And notice that the space constant gets bigger as you increase the size of the dendrite. As you make a dendrite bigger, what happens is the resistance down the middle gets smaller. And so the current can go further down the dendrite before it leaks out. Does that make sense?

But the resistance [AUDIO OUT] is dropping as the square of the area, but the surface area is only increasing linearly. And so the resistance down the middle is dropping as the square. The conductance out the side is growing more slowly. And so the signal can propagate further the bigger the dendrite is.

So that's why-- it's very closely related to why the squid giant axon is big. Because the current has more access to propagate down the axon the bigger the cylinder is. But there are limits to this. So you know that, in our brains, neurons need to be able to send signals from one side of our head to the other side of our head, which is

about how big? How far is that? Not in Homer, but in [AUDIO OUT] seen the cartoon with little-- OK, never mind.

How big across is the brain? How many millimeters, about? Yes. Order of magnitude, let's call it 100. So a piece of dendrite 2 microns across has a length constant of a millimeter. How-- what diameter dendrite would we need if we needed to send a signal across the brain passively through a piece of-- a cylindrical piece of dendrite like this?

So  $\lambda$  scales with radius. 2 microns diameter, radius, gives you 1 millimeter. Now you want to go to-- you want to go 100 times further. How-- by what factor larger does the radius have to be?

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** 10,000. Good. And so how big does our 2-micron radius piece of dendrite have to be to send a signal 100 millimeters? 10,000 times 2 microns, what is that? Anybody?

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** 2 centimeters. So if you want to make a piece of dendrite that sends a signal from one side of your brain to the other 100 millimeters away, you need 2 centimeters across. Actually, that's the radius. It needs to be 4 centimeters. across. Doesn't work, does it?

So you can make things-- you can make signals propagate further by making dendrites bigger, but it only goes as the square root. It's like diffusion. it's only-- it increases very slowly. So in order to get a signal from one side of your brain to the other with the same kind of membrane, your dendrite would have to be 4 centimeters in diameter. So that's why the brain doesn't use passive propagation of signals to get from one place to the other. It uses action potentials that actively propagate down axons. Pretty cool, right?

All right. So I want to just introduce you to the concept of electrotonic length. And the idea is very simple. If we have a piece of dendrite that has some physical length  $l$ , you can see that that length  $l$  might be very good at conducting signals to the soma if what? If-- what aspects of that dendrite would make it very good at conducting signals to the soma?

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** So it's big. Or what else?

**AUDIENCE:** Short.

**MICHALE FEE:** It's got a fixed physical length  $l$ , so let's think of something else.

**AUDIENCE:** [INAUDIBLE].

**MICHALE FEE:** Less leaky. Right. OK. So depending on the properties of that dendrite, that piece of dendrite of physical length  $l$  might be very good at sending signals to the soma, or it might be very bad if it's really thin, really leaky. So we have to compare the physical length to the space constant.

So in this case, there's very little decay. The signal is able to propagate from the site of the synapse to the soma. In this case, a slightly smaller piece of dendrite might have a shorter  $\lambda$ , and so there would be more decay by the time you get to the soma. And in this case, the  $\lambda$  is really short, and so the signal really decays away before you get to the soma.

So people often refer to a quantity as the-- referred to as the electrotonic length, which is simply the ratio of the physical length to the space constant. So you can see that in this case, the physical length is about the same as  $\lambda$ , and so the electrotonic length is 1. In this case, the physical length is twice as long as  $\lambda$ , and so the electrotonic length of that piece of dendrite is 2. And in this case, it's 4.

And you can see that the amount of signal it gets from this end to that end will go like what? Will depend how on the electrotonic length? It will depend something like  $e^{-L/\lambda}$ . So a piece of dendrite that has a low electrotonic length means that the synapse out here at the other end of it is effectively very close to the soma. It's very effective at transmitting that signal.

If the electrotonic length is large, it's telling you that some input out here at the end of it is very far away. The signal can't propagate to the soma. And the amount of signal that gets to the soma goes as  $e^{-L/\lambda}$ ,  $e^{-L/\lambda}$  [AUDIO OUT]. So if I told you that a signal is at the end of a piece of dendrite that has electrotonic

length 2, how much of that signal arrives at the soma. The answer is  $e^{-2}$ , about 10%, whatever that is.

So I want to tell you a little bit more about the way people model complex dendrites in-- sort of in real life. So most of the time, we're not integrating or solving the cable equation. The cable equation is really most powerful in terms of giving intuition about how cables respond. So you can write down exact solutions to things like pulses of current input at some position, how the voltage propagates down the dendrite, the functional form of the voltage as a function of distance. But when you actually want to sort of model a neuron, you're not usually integrating the cable equation.

And so people do different approximations to a very complex dendritic structure like this. And one common way that that's done is called multi-compartment model. So, basically, what you can do is you can model the soma with this capacitor-resistor combination. And then you can model the connection to another part of the dendrite through a resistor to another sort of finite element slice, but we're gonna let the slices go to 0 length. We're just going to model them as, like, chunks of dendrites, that are going to be modeled by a compartment like this.

And then that can branch to connect to other parts of the dendrite, and that can branch to connect to other parts of the model that model other pieces [AUDIO OUT] So you can basically take something like this and make it arbitrarily complicated and arbitrarily close to a representation of the physical structure of a real dendrite. And so there are labs that do this, that take a picture of a neuron like this and break it up into little chunks, and model each one of those little chunks, and model the branching structure of the real dendrite.

And you can put in real ionic conductances of different types out here in this model. And you get a gazillion differential equations. And you can [AUDIO OUT] those differential equations and actually compute, sort of predict the behavior of a complex piece of dendrite like this.

Now, that's not my favorite way of doing modeling. Any idea why that would be-- why there could be a better way of modeling a complex dendrite? I mean, what's the-- one of the problems here is that, in a sense, your model gets to be as

complicated as the real thing. So it would be-- it's a great way to simulate some behavior, but it's not a great way of getting an intuition about how something works.

So people take simplified versions of this, and they can take this very complex model and simplify it even more by doing something like this. So you take a soma and a dendrite. You can basically just break off the dendrite into a separate piece and connect it to the soma through a resistor.

Now, we can simplify this even more by just turning it into another little module, a little compartment, that's kind of like the soma. It just has a capacitor, and a membrane resistance, and whatever ion channels in it you want. And it's a dendritic compartment that's connected to the somatic compartment through a resistor.

And if you write that down, it just looks like this. So you have a somatic compartment that has a somatic membrane capacitance, somatic membrane conductances, a somatic voltage. You have a dendritic compartment that has all the same things-- dendritic membrane capacitance, conductances, and voltage, and they're just connected through a coupling resistor.

It turns out that that very simple model can explain a lot of complicated things about neurons. So there are some really beautiful studies showing that this kind of model can really explain very diverse kinds of electrophysiological [AUDIO OUT] neurons. So you can take, for example, a simple model of a layer 2/3 pyramidal cell that has a simple, compact dendrite. And you can write down a model like this where you have different conduct [AUDIO OUT] dendrite. You have Hodgkin-Huxley conductances in the soma. You connect them through this resistor.

And now, basically, what you can do is you can model that spiking behavior. And what you find is that if you have the same conductances in the dendrite and in the soma but you simply increase the area, the total area of this compartment, just increase the total capacitance and conductances, that you can see that-- and that would model a layer 5 neuron that has one of these very large dendrites-- you can see that the spiking behavior of that neuron just totally changes. And that's exactly what the spiking behavior of layer 5 neurons looks like.

And so you could imagine building a very complicated thousand-compartment

model to simulate this, but you wouldn't really understand much more about why it behaves that way. Whereas [AUDIO OUT] a simple two-compartment model and analyze it, and really understand what are the properties of a neuron that give this kind of behavior as opposed to some other kind of behavior.

It's very similar to the approach that David Corey took in modeling the effect of the T tubules on muscle fiber spiking in the case of sodium-- failures of the sodium channel to inactivate. That was also a two-compartment model. So you can get a lot of intuition about the properties of neurons [AUDIO OUT] simple extensions of an additional compartment onto the soma. And, next time, on Thursday, we're going to extend a model like this to include a model of a [AUDIO OUT]

So let me just remind you of what we learned about today. So you should be able to draw a circuit diagram of a dendrite, just that kind of finite element picture, with maybe three or four elements on it. Be able to plot the voltage in a dendrite as a function of distance in steady state for leaky and non-leaky dendrites, and understand the concept of a length constant.

Know how the length constant depends on dendritic radius. You should understand the idea of an electrotonic length and be able to say how much a signal will decay for a dendrite of a given electrotonic length. And be able to draw the circuit diagram of a two-compartment model. And we're going to spend more time on that on Thursday.