

MICHALE FEE: OK, good morning, everyone. OK, so today we are going to continue the process of building our equivalent circuit model of a neuron. This model was actually developed in the late '40s and early '50s by Alan Hodgkin and Andrew Huxley, who started working on the problem of understanding how neurons make action potentials. And so they studied the squid giant axon, which is actually a very cool preparation, because that axon is actually about a millimeter across, and so you can stick wires inside of it. And they did a bunch of very cool experiments to figure out how these different ionic conductances and how these different components of the circuit work together to make an action potential.

So that's what we're going to continue doing, we're going to essentially continue describing and motivating the different components of this circuit. So today, we're going to get through the process of introducing a voltage-measuring device, a current source, a capacitor, a conductance, and we're going to start introducing a battery, OK?

OK. So here's what we want to accomplish today. So we want to understand how kind of at the simplest level how neurons respond to injected currents, we want to understand how membrane capacitance and membrane resistance allows neurons to integrate their inputs over time, and to filter their inputs or smooth their inputs over time-- and that particular model is called a resistor capacitor model or an RC model of a neuron.

We're going to go through how to derive the differential equations that describe that model-- it's actually quite simple, but some of you may not have been through that before, so I want to go through it step by step so we can really understand where that comes from. And we're going to learn to basically look at a current-- a pattern of current injection, and we should be able to intuitively see how the voltage of that neuron responds. And we're going to start working on where the batteries of a neuron actually come from, OK?

OK. So-- all right. So-- all right. So we're going to basically talk about the following sort of thought experiment, OK? The following conceptual idea. We're going to take

a neuron and we're going to put it in a bath of saline, OK? A saltwater solution that represents the extracellular solution that neurons-- extracellular solution in the brain. And we're going to put an electrode into that neuron so that we can inject current, and we're going to put another electrode into the neuron so that we can measure the voltage, and we're going to study how this neuron responds-- how the voltage of the neuron responds to current injections, OK?

Now why is it that we want to actually do that? Why is that an interesting or important experiment to do? Anybody have any idea why we would want to actually measure voltage and current for a neuron in the brain? Yes?

AUDIENCE: Be able to use the mathematical model [INAUDIBLE] provided for us?

MICHALE FEE: OK, but it's more than just so that we can describe it mathematically, right? It's because these things-- something about voltage and current are actually relevant to how a neuron functions. Yes?

AUDIENCE: Like the resistance inside?

MICHALE FEE: Yeah. So that's an important quantity, but we're looking for something more fundamental, like why is it actually important that we understand how voltage changes when a neuron has current injected into it? Habiba?

AUDIENCE: Equals [INAUDIBLE] different like ion channels, a different set of voltages [INAUDIBLE].

MICHALE FEE: Exactly. So ion channels are sensitive to voltage, and the way they function depends very critically on voltage. So many-- if not most-- ion channels are voltage sensitive and are controlled by voltage, OK? And that's exactly why. So nearly every aspect of what neurons do in the brain as you're walking around looking at things and doing things is controlled by voltage, and that goes through the voltage sensitivity of ion channels, OK? But what is it that changes the voltage in a neuron? Yes?

AUDIENCE: The action potential.

MICHALE FEE: That's on the output side. Yes?

AUDIENCE: Is it ion concentration?

MICHALE FEE: Good. That's correct. I'm looking for something a little bit different. Habiba?

AUDIENCE: Do you have pumps or [INAUDIBLE].

MICHALE FEE: Yeah, those are all good answers. Not quite what I'm looking for.

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Yes. So the answer is that the voltage of a neuron changes because-- the reason current is important is because the reason voltage changes in a neuron is because other cells are injecting current into our neuron. Sensory inputs are injecting current into our neuron, OK? Everything that a neuron receives, all the information that a neuron receives from other neurons in the network and from the outside world comes from currents being injected into that neuron, OK?

And so it's really important that we understand how the neuron transforms that current input from other cells and from the sensory periphery into voltage changes that then change the behavior of ion channels. Is that clear? That link of current inputs to voltage output is really crucial, and that's why we're doing this experiment, OK? OK, and that's this point right here.

OK, so one of the first things we're going to see when we go through this analysis is that neurons can perform analog integration. They can perform numerical integration over time, OK? That's pretty cool. Voltage is that integral over time of the injected current. To first order. It's the simplest behavior of a neuron. So if you measure the voltage of a neuron and you turn on current and you turn the current on, the voltage of a neuron will ramp up, integrating that input over time, OK? Pretty cool. So we're going to see how that happens, why that happens biophysically.

OK. So let's come back to our neuron in the dish. Let me just explain a little bit how you would actually do this experiment. So these electrodes are little pieces of glass tubing. So you take a fine glass tube about a millimeter across you heat it up in the middle over a flame, and you pull it apart when it melts in the middle, and it makes a very sharp point. You break off the fine little thread of glass that's left, and you have a tube that narrows down to a very sharp point, but it's still a tube, and you can literally just-- there are some cells, like in the old days people studied large neurons and in snails where the cells are a millimeter across, you can take an electrode and

literally just by hand poke it into the cell. And then you fill that electrode with a salt solution, and then you put a wire in the back of that electrode, and you hook it up to an amplifier.

Now we want to measure the voltage in the cell. Remember, voltage is always voltage difference. We're always measuring the difference between the voltage in one place and the voltage somewhere else. So this amplifier has two inputs. It's called a differential amplifier, and we're going to hook the electrode that's in the cell to the plus terminal, we're going to put a wire in the bath, hook it to the minus terminal, and this amplifier is measuring the difference between the voltage inside the cell and the voltage outside the cell, OK? Any questions about that?

So we're going to take the other half of that piece of glass that we pulled, fill it with salt solution, stick it in the cell, and we're going to hook it up to a current source. Now our current source is basically just a battery, OK? But it's got some fancy electronics such that the current that flows is equal to whatever value you set, OK? And of course, remember, that voltage is in units of volts and current is charge per second. Charge is coulombs, so coulombs per second, and that's equal to the unit of current, which is amperes.

All right. Now let's take a closer look at our little spherical neuron, our little neuron. We've chopped all the dendrites and axons off, so it's just a little sphere, and you can basically model a neuron just like any other cell as a spherical shell of insulating material, OK? In this case, a lipid bilayer. This is a phospholipid bilayer. Phospholipids are just little fat molecules that have a polar head on one side-- that means they're soluble in water on this side, and they have a non-polar tail, so they don't like to be in contact with water, and the two polar tails go end to end-- sorry, the non-polar tails go end to end, the polar heads face out into the water. Does that makes sense?

And they are very closely packed together so that ions can't pass through that membrane, so it's insulating. It's very thin, it's only about 23 angstroms across, OK? An angstrom is about the size of a hydrogen atom. They're very thin, OK? OK, we have saline inside. What is saline? What is it in our model? Remember on Tuesday what--

AUDIENCE: A wire.

MICHALE FEE: Good. It's a wire and we have saline outside, which is also a wire. So we have two wires separated by an insulator, what is that? That's a capacitor, because it's two conductors separated by an insulator, OK? So an electrical component that behaves like a capacitor-- like if you were to build one of those, you would take like a piece of aluminum foil, put a piece of paper on it, put another piece of aluminum foil next to it, and attach wires to that, and you would squeeze the stack of aluminum foil paper and aluminum foil together, and that becomes a capacitor, OK?

And it has a symbol that looks like this electrically. So this is now our equivalent circuit of this model neuron, OK? It's very simple. It's a capacitor with one wire here that represents the inside of the cell, another wire that represents the outside of the cell. We have a current source that connects the outside of the cell to the inside of the cell. When we turn on the current source, it takes charges from inside of here and sticks them through the electrode and pumps them into the cell. Does that makes sense?

This is our-- this is sort of a simplified symbol for a voltage-measuring device. The voltage difference between the inside of the cell and the outside of the cell is what we're measuring here, and that difference is called the membrane potential. It's the voltage difference between the inside and the outside of the membrane, all right? Any questions about that? Yes?

AUDIENCE: There's a narrow resistance for [INAUDIBLE].

MICHALE FEE: What's that?

AUDIENCE: The resistance for--

MICHALE FEE: Yes, but we're going to do it one piece at a time. So we're going to start with a capacitor. The resistor will come in a few slides. Yes?

AUDIENCE: So the [INAUDIBLE].

MICHALE FEE: Exactly. So we've simplified our neurons so that it's just an insulating shell, OK? No ion channels, no current anywhere else. If we want to inject current into this simple model neuron, we have to inject it through this electrode here, OK? So we're just

going down to the very simplest case, because this is already kind of interesting enough to understand just by itself. Yes?

AUDIENCE: So if the cell's acting as a capacitor, is their energy stored in their myelin?

MICHALE FEE: The energy is stored in the electric field that crosses the bilayer, and I'll get to that in a second. Any other questions? OK, great questions. All right, so what happens when we inject current into our neuron? As I said, the current source is pulling charges from the outside and pumping them into the inside, all right?

So what happens when goes on? So what we're doing is we are injecting current-- let's say this is our capacitor. There are charges, there are ions on the inside that are just up against the inside of the cell membrane. There are charges on the outside, OK? And when we inject a charge from the outside to the inside-- let's put one of those charges right here. And we're going to push it into this cell, when you inject a charge, you get an excessive charge on the inside of the cell membrane, OK?

And what does that do? You now have more positive charges inside than outside, like-charges repel-- so it pushes one of those charges away from the outside of the membrane. Does that makes sense? OK, that's kind of interesting. We took a charge, we pushed it in, and a charge comes out. Right? We have a current flowing. We have charges coming in and charges leaving. We have a current flowing through an insulator. How is that possible? It's a capacitive current, OK? No charges are actually passing through the insulator, but it looks like you have a current flowing. That's called a capacitive current.

And we represent that in our diagram by a current $I_{\text{sub C}}$, capacitive current that flows through the capacitor. Pretty cool, right? You have a current flowing through an insulator. That's what a capacitor is. OK. Now notice that you have a charge imbalance. You have three positive charges here and only one positive charge here. So there is an excess of two positive charges on the inside. That's because we added a positive charge to the inside and took away a positive charge from the outside, so that leaves a charge imbalance of 2, OK?

What do you get between positive charge and negative charge if you hold them next to each other? What is there in between?

AUDIENCE: It's attraction.

MICHALE FEE: Good, it's attraction, but what is it that causes that attraction? Remember yesterday, we talked about a something on a charge produces a force, what is it?

AUDIENCE: Electric field.

MICHALE FEE: Good. So there's an electric field between the positive-- the excess positive charges here and the excess negative charges here, OK? That's an electric field, all right? And that electric field stores energy. How do you know there's energy in this system, though? What could you do to demonstrate that there is energy stored in that system? Any ideas? You have two plates, two metal plates, let's say, in the metal version of this. Separated by an insulator. What would happen if you pulled away the insulator? Those two things would do that again, but louder-- boom. What does that take to make that sound? Energy, OK?

So there's energy stored in that electric field. So there's a charge imbalance, there's an electric field. What does an electric field over some distance correspond to?

AUDIENCE: A voltage difference.

MICHALE FEE: A voltage difference, OK? Now, there's a charge imbalance and a voltage difference, and they're proportional to each other. So there's a proportionality constant that's called the capacitance, all right? If you can put a lot of charge and have a small voltage difference, that's a big capacitor. Now you can get a big capacitor just by having a big area. You can see, you can have a lot of charges with a small voltage difference if you have big plates on your capacitor, OK? So the capacitance is actually proportional to the area of the plates, and it's inversely proportional to the distance between them. It's a very thin membrane, which means you can get a lot of capacitance in a tiny area, OK? That's pretty cool. All right, any questions?

So charge is coulombs, and there are 6×10^{18} charges in a coulomb, the elemental charges, electron or monovalent ion charges. Voltage is in units of volts, and the capacitance is in units of farads. Any questions? All right. So we have our relation between voltage difference and charge difference. And what we're going to do is we're going to calculate this capacitive current. How do you think we would

calculate the capacitive current?

Well, the capacitive current is just the rate at which the charge imbalance is changing, right? Current is just charge per unit of time. OK? So we're going to calculate the capacitive current as the time rate of change of the charge-- and I've dropped the deltas here. So capacitive current is dQ/dt , all right? And remember that Q is just CV , so the capacitive current is just $C dV/dt$, and the V_m here represents the membrane potential, OK? So the capacitive current through a membrane is just the capacitance times the time rate of change of the membrane potential. Any questions? OK. Pretty straightforward.

Now what we're going to do now is we're going to relate the injected charge to the-- sorry, the injected current to the capacitor. And what does Kirchhoff's current law tell us? It tells us that the amount of current going into this wire has to be equal to the amount of current leaving that wire. OK? So we can write that down as follows. The difference in sign here is because the electrode current is defined as positive inward, the capacitive current is defined as positive outward. OK?

So you can see that we just calculated the capacitive current, it's $C dV/dt$, so we can just plug that in here, and now we see this very simple relation between the injected current and the voltage. And again, the current has unit of amperes, which is coulombs per second. OK, so we have that. Now we have a differential equation that describes the relation between current and voltage, we can just integrate it to get the solution. So that membrane potential will just be some initial membrane potential at time 0 plus $1/C$ integral over time of the injected current. Just integrate both sides. You get V here, you get integral of I there, and divide both sides by C . Any questions? It's either really confusing or really obvious. Yeah? Everybody OK?

All right, good. Now what is this? What is the integral of current over time?

AUDIENCE: It's charge [INAUDIBLE]

MICHALE FEE: Good. It's the amount of charge you injected between time 0 and time t , right? And what is the amount of charge you inject-- if I tell you that I injected an amount of charge ΔQ , how much did I change the voltage? ΔV is ΔQ over C , and that's exactly. So the voltage is just the starting voltage plus ΔV . Does that

makes sense? This integral here is just-- that part is just the amount of charge you injected divided by C gives you the change in the voltage. So the voltage is just the starting voltage plus delta V, OK? Yes?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: What's that?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Oh. Because this equation here just came from here. That was our charge-- our relation between charge balance and voltage difference. Yeah? If it's not clear, just please ask, thank you. OK. There we go. So what is the interval constant? It's just some constant times time, right? So our voltage is just some initial voltage plus the injected current over C times time. And so you can see where this comes from, right? When you turn the current on, the voltage just increases linearly over time with a slope that's given by the current divided by the capacitance. OK? All right, any questions? You guys are being very quiet. This is the point where I start feeling nervous, I went too fast. Yes?

AUDIENCE: You continually draw the curve for a while--

MICHALE FEE: Yep.

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Yes, it does. And it breaks at about a volt or so. Because the electric field gets so strong, it literally just rips the atoms apart in the molecules of the lipid bilayer. Yes?

AUDIENCE: Why do you [INAUDIBLE]

MICHALE FEE: Sorry, I shouldn't say-- it doesn't rip the atoms apart, it rips the molecules apart. You need much higher electric fields to do that. Yes?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Oh. Because we're integrating from time 0 to time t. We want to know the voltage at time t, OK? We're starting at 0, we're integrating the current from time 0 to time t, which is where we're wanting to know the voltage, right? So you have to integrate

the current from 0 to t . We can't use t in here. t is the endpoint. Yeah. Does that makes sense? Good question, thank you.

OK, everybody all right? I'm going to stand here until I hear one more question. Yes?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Oh, here. Because it's a current of value I_0 . Great question. Yes?

AUDIENCE: So to maintain this constant current [INAUDIBLE] the amount of [INAUDIBLE] you're pumping it and--

MICHALE FEE: Yes. That's right. This-- OK, I should have maybe been more clear. This current source has a knob on it that I get to set. I get to like-- there would be an app now, and I'd pull out my current source app and I type in 10 milliamps, boom. And this thing-- because there's a Bluetooth connection to this thing, and it like sets this thing to 10 milliamps, and it just keeps pumping 10 milliamps until you tell it to do something else, OK? Yes?

AUDIENCE: [INAUDIBLE] make the right direction instead of it being constant current state that usually--

MICHALE FEE: Oh, OK.

AUDIENCE: --that would create some weird kind of--

MICHALE FEE: Sure. Yeah. What would that be, actually? If you put in a linear ramp in current? It would be a parabolic voltage profile. Yeah, very good. That's exactly it. This current profile that you-- this voltage profile is literally just the numerical integral of this function. So all you have to do is look at this and integrate it in your head, and you can see what the voltage does, OK? Great. That's exactly right. So let's do another example. Let's put in a current pulse. So we start at zero current, we step it up to I_0 , we hold it there for τ , then we turn the current off.

So let's start our neuron right here. What's going to happen? What's your name? I'm going to ask you to do this problem. What-- yeah.

AUDIENCE: Sammy.

MICHALE FEE: Sammy. What's this voltage going to do?

AUDIENCE: So I'd say constant.

MICHALE FEE: Good. Because it's zero current. Then what's going to happen?

AUDIENCE: And it's going to [INAUDIBLE]

MICHALE FEE: Good.

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Good.

AUDIENCE: And then the [INAUDIBLE] go back to constant at that point.

MICHALE FEE: Awesome. That's it. It's that simple. OK? Good. All right. Now somebody brought up resistors. Who brought up ion conductances? Somebody mentioned that. So that's the next thing we're going to add. This is sort of the zero order model of a neuron. It has the simplest view and it's often not so bad, OK? For short periods of time. But neurons actually have ion channels, all right? Allow current to flow through the membrane. So we're going to start today by analyzing the case of the simplest kind of ion channel which is the kind of ion channel you get when you take a needle and you poke a hole in the membrane, OK? It's called the leak or a hole, all right? And we're going to analyze what our neuron does when you do that.

So what we're going to find is that the ion channel-- a leak conductance, it can be represented in our model simply by a resistor, OK? And we're going to have our capacitive current, membrane capacitive current, and a membrane ionic current that's due to ions flowing through ion channels in the membrane, OK? And that current will be-- we're going to call that our leak resistance, and that current will be our leak current, OK?

So now, Kirchhoff's current law tells us what? That the leak current plus the capacitive current has to equal the injected current, all right? We know the capacitive current is just $C \, dV/dt$, so we just plug that in, and now we have $I_{\text{leak}} + C \, dV/dt$ equals the injected electrode current. That is called membrane ionic current, that is called membrane capacitive current, and that is our electrode

current.

There's a sign convention in neuroscience, which is that membrane ionic currents that are outward from the inside of the cell to the outside of the cell membrane are positive in sign. Positive charges leaving the cell have a positive sign. It's just convention, it could have been the other way. But you have to choose something, so that's what-- I think it was Hodgkin and Huxley, actually, who decided that. Inward currents, positive charges entering the cell through the membrane going this way from extracellular to intracellular, are defined as negative. Electrode currents, the other way. Electrode current-- inward current is-- into the cell is positive.

OK, so we're going to poke a hole in our membrane and we're going to model that ion channel using Ohm's law. So the leak current is just membrane potential divided by resistance, leak resistance. So what do we get if we plug this into our-- I leak plus I capacitance? Capacitive equals injected current. We get V membrane potential, V_m over R_L plus C dV/dt equals injected current, OK? We multiply both sides by resistance, we get V plus RC -- that's why it's called an RC model-- dV/dt equals leak resistance times the injected current, all right?

Now that's looking a little complicated, but we're going to simplify things now. Tau-- I'm sorry, RC is resistance times capacitance, and it turns out, that has units of time. And so we're going to call that tau-- got a little ahead of myself. That's called tau, we're going to make that substitution in a minute. But first we're going to calculate the steady state solution to that little equation, OK? So bear with me, hang on, it's all going to make sense in a minute.

Does anyone know how to calculate the steady state solution of a differential equation? Yes?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Good. What's your name?

AUDIENCE: Rebecca.

MICHALE FEE: Rebecca. So you said the derivative-- so let's do that. Set dV/dt equal to 0. And what do you find? Sorry, we flashed the answer up there. What do you get if you said dV/dt equals 0?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Good. So you inject some current, we're going to hold the current constant, let's say, OK? We've put some current in and we hold it constant. The voltage will change, and eventually things will settle down and the dV/dt will go to 0. At that point, we know the voltage. It's just RL times I_e . What is the voltage equals resistance times current? What is that?

AUDIENCE: Ohm's law.

MICHALE FEE: Ohm's law. It's just when we inject current, a bunch of stuff happens, and when the dust settles, the voltage difference is just the injected current divided by the resistance. Does that makes sense? Yes?

AUDIENCE: Where is [INAUDIBLE]

MICHALE FEE: Well, right now we just took a needle and poked a hole in our cell. So--

AUDIENCE: How big the hole is?

MICHALE FEE: Yep, exactly. It's how big the hole is. Now cells-- real cells do have leak channels. They're actually ion channels that leak kind of any ion that's in there. It's not very common. And you'll see why in a minute. Actually, that's not quite true. There are ion channels that look essentially like leaks, and it turns out that the ion channels that many neurotransmitter receptors like glutamate and acetylcholine, the ion channels actually look like little leaks. They pass multiple ions that makes them look like leaks.

OK. So in steady state, the membrane potential goes to RL times I_e , and we call that voltage something special, V_{∞} , because it's the voltage that the system reaches at time equals infinity, OK? Any questions about that? OK. So we're going to just rewrite this equation as V_m plus τ dV/dt equals V_{∞} . And that equation we're going to see over and over and over again in this class in many different contexts, all right? It's a first order linear differential equation and it's very powerful, so I want you to get used to it.

So what does this mean? So let's rewrite this equation a little bit. Let's move this

term to the other side and divide both sides by tau, and here's what you get. dV/dt equals minus 1 over tau V minus-- times V minus V infinity. OK? Now let's take a look at what the derivative dV/dt looks like as a function of voltage. Yes?

AUDIENCE: So why couldn't we have said we didn't mean to [INAUDIBLE].

MICHALE FEE: V infinity is defined as RL times I_e .

AUDIENCE: Oh, so that's a [INAUDIBLE].

MICHALE FEE: It's a definition. Sorry, I should have put like three lines there to indicate that it's the definition.

AUDIENCE: OK.

MICHALE FEE: Yeah. Sorry, that's a very important question. What's your name?

AUDIENCE: Rishi.

MICHALE FEE: Rishi. OK. I'm going to make an attempt to remember names. So is everyone clear about that? V infinity is defined as the resistance times this injected current. So the injected current, when we inject current into our neuron, you're changing V infinity, OK? You're controlling it. Does that makes sense? OK. So let's look at how the derivative changes as a function of voltage, it's very simple. Bear with me. All of this is going to crystallize in your mind in one beautiful construct very shortly. Yes?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Yep. Resistance times capacitance has units time, OK? And so we call it tau. Tau is just a constant, OK? So hang on, bear with me. The derivative is a function of voltage. And at V equals V infinity, the derivative is 0, right? That's the definition of the infinity, it's the voltage at which the derivative is 0. Yeah?

And the voltage is less than V infinity, the derivative is positive, right? When the voltage is below the infinity, the derivative of voltage is positive. So what is the voltage doing? It's approaching V infinity. If the voltage is above V infinity, voltage greater than V infinity, the derivative is negative. So voltage does what?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Yes, but it's--

AUDIENCE: Approaches--

MICHALE FEE: It approaches V infinity. So no matter where voltage is, it's always approaching V infinity. If it's below V infinity, the slope is positive, and it approaches V infinity. If it's above V infinity, the slope is negative, and it approaches V infinity from above. Pretty cool, right? So V is always just relaxing toward V infinity. And how does it get there? Does it go linearly? Well, you can see that the slope-- the rate at which it approaches V infinity is proportional to how far away it is from V infinity. And so it doesn't just go vroom, boom, crash into V infinity, it kind of slowly approaches V infinity, OK?

Anybody know what that function is called?

AUDIENCE: Exponential.

MICHALE FEE: It's an exponential, good. And it approaches with a timescale of τ . So if τ is small, it approaches quickly. If τ is long, it approaches slow. You can see that if τ is big, the derivatives are small. If τ is small, the derivatives are bigger, all right? Any questions about that? Yes?

AUDIENCE: So a τ usually is a--

MICHALE FEE: Sorry, say it again?

AUDIENCE: --times equals to τ --

MICHALE FEE: Yes.

AUDIENCE: --is V infinity plus 1 over e .

MICHALE FEE: At time τ , the--

AUDIENCE: Times V_0 .

MICHALE FEE: At time τ -- at time 0 , the difference between V infinity-- sorry, V and V infinity is V_0 minus V infinity. At time τ , that initial difference drops by about a third.

AUDIENCE: OK.

MICHALE FEE: About $1/e$, which I think is 2.7-something, OK? So in 1τ , this voltage difference falls by about a-- drops by about a third. And in another τ , it drops by another third, it keeps going, OK? All right. So let's just write down the general solution. The general solution for the case where you have constant current, that voltage difference from the voltage at time t to V_{∞} is just equal to the initial voltage difference times $e^{-t/\tau}$, OK? So if t is equal to τ , then this is e^{-1} , so the voltage difference will be $1/3$ of the original voltage difference. Is that clear? OK.

So now let's see what this looks like in our neuron. We have our neuron, we have a current pulse, we have zero current, we turn the current on to I_0 at this time, we hold the current constant, and we turn current off at this time right here, OK? So what does the voltage do? Let's go step by step. The first thing is that voltage-- sorry-- the current controls what in that equation? The current controls V_{∞} . So we can plot V_{∞} immediately, because V_{∞} is just the resistance times the injected current. So what does V_{∞} look like? It's constant here, and then what happens to V_{∞} ?

AUDIENCE: Increases.

MICHALE FEE: It increases, that's correct, but--

AUDIENCE: It'll just be [INAUDIBLE].

MICHALE FEE: Good. It will just be the resistance times the current. Resistance is a constant, so V_{∞} will just go up here, right? Good. It'll go up, and then it stays constant at R times I . And then at this point, the current goes back to 0, so V_{∞} is resistance times 0, so V_{∞} drops back to 0. Does that make sense? That's V_{∞} , that's not the voltage of the cell. That's the steady state voltage of the cell.

So now what does voltage of the cell actually do? So let's start our voltage here at 0. What happens? Good. What is it doing?

AUDIENCE: Approaching from infinity.

MICHALE FEE: Good. It approaches. So V at every point is relaxing toward V_{∞} exponentially, right? And that looks like-- at some time constant, and that looks like this, all right?

Now what happens here?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Good. Because V_{∞} suddenly change to 0, and so V relaxes toward V_{∞} exponentially with some time constant. OK? Any questions? OK. Now this-- that is our RC model neuron, OK? Resistance times capacitance-- they got a resistor and a capacitor, but the solutions are just exponential decays toward some steady state solution.

Now it turns out that an RC system, a first order linear system acts like a filter, OK? So remember, our neuron that just has a capacitor is an integrator, it integrates over time. When you add a resistor, this thing-- it's kind of integrating here, but then it gets tired and stops integrating, OK? It relaxes to some steady state.

So this actually looks like a filter. It takes time to respond to something. So that system responds well to things that are changing slowly in time, and it responds very weakly to things that are changing rapidly in time. So here's an example-- I'll put together this demonstration. In red is the injected current. So if you have long pulses of injected current, the time constant of this garners about 10 milliseconds-- I think this is probably a-- what is that, a 50 or 100-millisecond pulse? 80--

AUDIENCE: Nanofarads.

MICHALE FEE: Yeah. You can see that in blue is the voltage, it relaxes toward V_{∞} . And then the current goes off, it relaxes back. And you can see that the voltage is responding very well to the current injection. But now let's make really short pulses that are much shorter than τ . You can see that the voltage starts relaxing toward V_{∞} , but it doesn't get very far, and all of a sudden the current's turned off and it relaxes back.

And so you can plot the peak voltage response as a function of the width of these pulses, and you can see that for long pulses, it responds very well, but for short pulses-- really responds at all. And that's called a low pass filter, OK? It responds well to slowly-changing things, but barely responds to rapidly-changing things. So it's passing low frequencies, low pass filter, OK? All right. Any questions? That was a lot of stuff all at once. Yes?

AUDIENCE: I'm just curious, like on what order is the capacitance for nanofarads?

MICHALE FEE: OK. It's 10 nanofarads per-- 1 microfarads per square centimeter. 10 nanofarads per square millimeter, OK? We're going to get to that in a second, that's a great question. We're going to get to what the actual numbers look like for real neurons, OK? I think you had a question.

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Sorry, say it again?

AUDIENCE: Past [INAUDIBLE]? Is that [INAUDIBLE] reacts to [INAUDIBLE]?

MICHALE FEE: What happens is it reacts to it, but because it's changing kind of linearly at these short times, it doesn't get very far. If the current stays on for a long time, you can see it has exactly the same profile here, but it just has time to reach V_{∞} . Here, it doesn't have time to reach V_{∞} , it just gets a little bit away from 0 and then it decays back. Yes?

AUDIENCE: Are there other sorts of filters for non-responses like [INAUDIBLE]?

MICHALE FEE: You can build different kinds of filters from circuits of neurons, but neurons themselves tend to be high pass filters. You can-- sorry, low pass filters. You can make-- so you can put in different kinds of ion channels that change the properties of neurons, but sort of to first order, you should think of neurons as low pass filters. Yeah?

AUDIENCE: Can you show the [INAUDIBLE]

MICHALE FEE: I wrote it like this-- you can write it as $V = V_{\infty} + \text{this other stuff}$, but I wrote it like this because what you should really be seeing here is that the voltage difference from-- time between the voltage and V_{∞} decays exponentially. So the distance you are from V_{∞} decays exponentially, OK? It makes it more obvious that you're decaying toward V_{∞} , OK? Yes?

AUDIENCE: If you were to arrange like the physical properties of the neuron itself, you [INAUDIBLE]

MICHALE FEE: Not-- not really. Not simply. You can put in certain ion channels that could make a

neuron less responsive at low frequencies, OK? So you can make them kind of responsive to some middle range of frequencies that won't respond to very high frequencies and they won't respond much to very low frequencies, but for the most part, again, just you should-- at this point, let's just think of them as low pass filters.

We're going to start adding fancy stuff to our neuron that's going to make it more complicated. So don't get too hung up on this. All right, let me just make this point. This one right here, V equals τ -- V plus τ dV/dt equals V infinity appears everywhere, it's ubiquitous in physics, chemistry, biology, we'll be using it in multiple different contexts in different parts of the class, and in-- computation, OK?

And even slightly more complicated versions of this, like the Michaelis-Menten equations in chemistry, you can kind of understand them in simple terms. If you like have a handle on this, other slightly more complicated things become much more intuitive, OK? All right, so try to really make sure that you understand this equation and how we derived it, OK?

OK, let's talk about the origin of this-- the timescale of a neuron. So the tau of a neuron-- of most neurons is about 100 milliseconds to-- sorry, 10 milliseconds to 100 milliseconds, kind of in that range. And it comes from the values of resistance and capacitance of a neuron. So a resistor-- the resistance of a neuron-- range of 100 million ohms, OK? And the capacitance is about 10 to the minus 10 ohms or about 100 picofarads. And you multiply those two things together and you get a time constant of about 10 milliseconds, OK? So what that means is if you inject current into a neuron, it takes about 10 to 100 milliseconds for it to fully respond to that step of current. The voltage will jump up and relax to the new V infinity in about 10 to 100 milliseconds, OK?

So let's take a little bit closer look at the resistance-- what this resistance in capacitance looks like in a neuron. So we've described the relation between leak current and voltage as current equals voltage over resistance, but rather than using resistance to think about currents flowing through a membrane, it's much more useful, usually, to think about something called conductance, and conductance is just 1 over resistance, OK?

So conductance, G -- and we use the simple G for conductance-- it's equal to 1 over

resistance. So now we can write Ohm's law as I equals G times V . Resistance has units of ohms, G -- conductance has units of inverse ohms or siemens is the SI unit for conductance. So if we have conductances, if we have two-- let's say two ion channels in the membrane, they operate in parallel. Current flows through them separately, right? They're not in series, like it flows through one and then flows through the other, right? They are in parallel-- the current can flow through both like this up in parallel. And we can write down the current using Kirchhoff's law, the total current is just the sum of the current through those two separate conductances, right?

Now the total current is-- we can just expand this in terms of the conductance of each one of those. So the total current is G_1 times the voltage difference plus G_2 times the voltage difference for this conductance. So the total current is just-- you factor out the V , the total current is just G_1 plus G_2 , so we can write down the total conductance as just G_1 plus G_2 . Does that make sense?

So conductances in parallel add together. So if we have a piece of membrane that's got some ion channels in it-- or holes, and we add another piece of membrane that kind of has the same density of ion channels, you have twice the holes, twice the current, and twice the conductance. So we can write the current as conductance times membrane potential, but we can rewrite that conductance as the area times that conductance per unit area, and that's called specific membrane conductance-- in this case, it's a leak, so we call it specific leak conductance, and it has units of conductance per area. We multiply that by the area and we get that total conductance. Any questions about this? No?

So you can see that we can now plot the current through the membrane as a function of voltage. This is called a I - V current plotted as a function of voltage. You can see that the current is linear as a function of voltage, right? That's just Ohm's law. And you can see that for a low conductance, G is small, so the slope is small. For a high conductance, you get a lot of current for a little bit of voltage, and so the-- deeper, OK? So if you plot current versus voltage, you get a curve, and the slope of that curve is just equal to the conductance, all right?

OK. Now let's look at capacitance. The total current through these two capacitors in parallel is just the current through one capacitor plus the current through the other.

We can write the current through each capacitor separately. I_{total} equals $C_1 dV/dt$ plus $C_2 dV/dt$. Factor out the dV/dt and you get that the total current is just C_1 plus $C_2 dV/dt$. So the total capacitance is the sum of the capacitances.

So if you have a patch of membrane, you measure the capacitance, if you put another one next to it, you'll get the sum of those two capacitances. So the capacitance also scales with area. So we can write down the total membrane capacitance as capacitance per unit area times the area of the cell, right? And the area of a cell is like the-- if it's a sphere, it's $4\pi r^2$ where r is the radius, OK? All right. And here's the-- this C_m is called this specific membrane capacitance, and it's 10 nanofarads per square millimeter, all right?

OK, now, I want to show you something really cool. We have a cell that has a membrane with some-- this cell has some time constant-- remember, 10 milliseconds. Now you might think, oh, the capacitance of the cell depends on how big it is, right? And so the time constant will change depending on how big the cell is, you might think. But let's actually calculate the time constant from this capacitance and this conductance, OK? So here we go.

Time constant $C \cdot R$ is just 1 over the conductance, right? So the time constant is capacitance divided by conductance-- total capacitance divided by total conductance. But you can rewrite this capacitance as capacitance per unit area times area, you can rewrite that conductance as conductance per unit area times the area of the cell, and the areas cancel. And so the time constant is just that capacitance per unit area of the membrane divided by the conductance per unit area of the membrane. And what that means is that the time constant of a cell-- nothing to do with the cell. The time constant is the membrane time constant, and it's a property only of the membrane. That's pretty cool, right? Any questions about that?

Now in a more complicated neuron where you have a soma and dendrites and axons, different parts of the cell can have different conductance per unit area-- like more ion channels out here on the dendrite and maybe fewer on the soma. And so one part of a cell can have a different membrane time constant than some other part of the cell, OK? But again, it's a property of the membrane. Any questions about that? Yes?

AUDIENCE: So in that case, like different time constants, do you have to like consider flow between different areas?

MICHAEL FEE: You sure do. Absolutely. That's one of the interesting things about-- when cells have multiple-- they have different properties, you have current flowing between them, but you have to understand this kind of basic stuff before you even get anywhere close to understanding a more complicated neuron, right? OK. So we're going to add a new component to our model. It's a battery, and it's going to solve one really fatal problem with this model. What's the problem with this model? Can anyone see-- I'm kind of showing it right here.

What happens to this neuron if I turn the current off? It goes back to zero. And in order to get the voltage to go different from zero, I have to inject current through my current source. Without me, the experimenter with an electrode in it injecting current, this neuron literally just sits at zero and stays there, all right? It's actually a good model of a dead neuron, OK?

So in order to change that, we need to add a battery here, OK? And that battery is going to power this thing up, so now it can change its own voltage. And then things start getting really interesting. So how can these batteries allow a neuron to change its own voltage? Well, the way a neuron controls its own voltage is it has ion channels-- conductances-- that have little knobs on them that the cell can control called voltage. So these conductances are voltage-dependent, and now the cell connects these batteries to its inside wire at different times in different ways.

So let's say we want to make an action potential. So we have a battery that's got a positive voltage, we have a battery that's got a negative voltage, and we make an action potential by connecting the back to the inside of the cell by turning on this conductance, and then we're going to connect the battery with a negative voltage to our cell, and we're going to do that one after the other. So watch this. We're going to connect the positive battery and the voltage is going to go up; we're going to turn off the positive battery, connect the negative battery, the voltage goes down; and then we're going to turn off both batteries, and the voltage just relaxes, OK? Cool, right? So now the neuron can control its own voltage. But before we do that, we need to put batteries in our neuron, OK?

All right. So anybody know what the-- yes?

AUDIENCE: [INAUDIBLE] What does that [INAUDIBLE]

MICHALE FEE: Good, we're going to get to that. That was-- exact next question. What is it that makes a battery in a neuron? Yeah?

AUDIENCE: Well I mean, like, you have like something, right? Even in like--

MICHALE FEE: Good.

AUDIENCE: --concentration gradient--

MICHALE FEE: Good.

AUDIENCE: --so that give us a [INAUDIBLE]

MICHALE FEE: Here. You give the rest of the lecture. That's exactly right. OK? Well concentration gradients. There's one more thing we need. Concentration gradients by themselves don't do it. We need ion channels that are permeable only to certain ions, OK? And that's what we're going to do now. So you need concentration gradients and ion-selective permeability, OK? So we're going to go through that.

So let's take a beaker, fill it with water, have a membrane, dividing it into two. We're going to have an electrode on one side, we measure the voltage difference-- sorry, we have an electron on both sides, we hook it up to our differential amplifier, and measure the voltage difference on the two sides, OK? Then we're going to put-- we're going to take a-- we're going to buy some potassium chloride from sigma, we're going to take a spoonful of it and dump it into this side of the beaker. Stir it up, and now you're going to have lots of potassium ions and chloride ions on this side of the beaker, right?

Now we're going to take a needle and poke a hole in that membrane. That becomes a leak, a leak channel. It's a non-specific-- a non-selective pore that passes any ion, OK? So what's going to happen?

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Good. The ions are going to diffuse. From where to where? Somebody else.

AUDIENCE: To the lower concentration.

MICHALE FEE: To the lower concentration, good. So some of those ions are going to diffuse from here to here. And we can plot the potassium-- let's focus on potassium now. We're going to plot-- we can plot the potassium concentration on this side over time and on this side over time. By the way, this side of the beaker is going to represent the inside of the neuron, which has lots of potassium, and this is going to represent the outside of our neuron, which has very little potassium, OK?

So if we plot that potassium concentration on this side, it's going to increase over time. It's going to take a long-- and the concentration here will decrease and eventually they'll meet in the middle somewhere. They'll become equal. And that's going to take a really long time, right? Because it takes a long time for this half of this spoonful of potassium chloride to diffuse to the other side. Yeah? OK.

Now let's get a different kind of needle, a very special needle. It's really small and poke a hole in the membrane that is only big enough to pass potassium ions but not chloride ions. So what's going to happen now? Yeah? Somebody-- yes?

AUDIENCE: Half of it flows to the other side--

MICHALE FEE: Good.

AUDIENCE: [INAUDIBLE]

MICHALE FEE: Good. So some potassium ions are going to diffuse through this pore and go to the other side. And what's going to happen is if we plot the potassium concentration here, it will decrease-- sorry-- over here it will increase a little bit, and the potassium concentration on this side will decrease a little bit, but then it will stop changing, and it will never come to equilibrium.

It will also take a very short time for that equilibrium to happen, because just a few potassium ions need to go to the other side before it stops. So why does the concentration stop changing here? Well, it's because the potassium current from this side to this side goes to zero, and it goes to zero very quickly. So why is that?

Well, one hint to the answer to that question comes if we look at the voltage

difference between the two sides. So what you see is that the voltage difference started at 0, and when we poked that hole, all of a sudden there was a rapidly-developing voltage difference across the two sides, OK? Why does that voltage go negative? Anybody? What happened when these positive charges started diffusing from this side to this side?

AUDIENCE: Didn't you say it can bond to the positive and negative charge [INAUDIBLE]

MICHAEL FEE: Basically this is like a capacitor, right? And some charges diffused from here to here, some positive charges diffused from here to here, that charges up this side, and so the voltage is positive. We put positive charge-- more positive charges here, the voltage here goes up, OK? So if the voltage here is higher than the voltage here-- we're plotting V_1 minus V_2 , the voltage here is lower than the voltage here, and so this is going negative, OK? And that voltage difference, that negative voltage here, positive voltage here, what does that do? It repels, it makes-- the positive side starts repelling which ions? It's repelling positive ions. So it keeps more potassium ions from diffusing through the hole. Does that makes sense? Blank stares. Are we OK? OK, good.

And it continues to drop until it reaches a constant voltage, and that's called the equilibrium potential, OK? The voltage changes until it comes to equilibrium, and that voltage difference is called the equilibrium potential. And that voltage difference is a battery, OK? And I'm going to-- we're going to explain a little bit-- I think it's in the next lecture, the one that's on tape that explains how you actually can justify representing that as a battery. But right now, I'm going to show you how to calculate what that voltage difference actually is-- what's the size of the battery, how big is the battery, OK?

So you can see that when ions-- positive ions diffuse to this side, this voltage goes up, you have a voltage gradient that corresponds to a field pointing in this direction. And that electric field pushes against the ions-- remember, we talked about drift in an electric field, so when those ions are trying to diffuse across, that electric field is literally dragging them back to this side, right?

So we have a current flowing this way from diffusion, and we have a current flowing that way from being dragged in the electric field. And so we can calculate that

voltage difference because at equilibrium, the current flowing this way from diffusion has to equal the current flowing that way from drift in an electric field, OK? So one way to calculate this is we're going to calculate the current due to drift, current due to diffusion, add those up, and that's equal to the total, and at equilibrium, that has to equal to 0, right?

So what I'm showing you now is just sort of the framework for how you would calculate this using this drift and diffusion equation. So we have Ohm's law that tells us how the voltage difference produces a current due to drift, and we have Fick's law that tells us how much current is due to diffusion, and you can set the sum of those two things to equal zero, all right? And so this is the way it would look. I don't expect you to follow anything on this slide just except to see that it can be done in this way, OK? So you don't even have to write this down, OK?

So the drift current is proportion-- it's some constant times voltage. Fick's law is some constant times that concentration gradient, remember that. And we just set those two things equal and solve for delta V, and that's what you find. What you find is the delta V is just some constant times the log of the difference in concentrations on the inside and outside, OK? Now it turns out, there's a way of calculating this that's much simpler and more elegant, and I'm going to show you that calculation, OK? Yes?

AUDIENCE: And so like the concentrations inside and outside, like at the [INAUDIBLE] beginning of the--

MICHAEL FEE: Yes, at the beginning. And the answer is that the concentrations don't change very much through this process, so you can even ignore that change, OK? All right, everybody got this? All right. So here's how we're going to calculate an alternative way of calculating this voltage difference, just really beautiful. We're going to use the Boltzmann equation. The Boltzmann equation tells the probability of a particle being in two states as a function of the energy difference between those two states. And one of those states is going to correspond to a particle being on the left side of the beaker or inside of our cell, and that particle being outside of our cell or on the other side of the beaker. And those two, left side and right side, have different energies, OK?

So our system has two states, a high-energy state and a low-energy state.

Boltzmann equation just says the probability of being in state 1 divided by the probability of being in state 2 is just e to the minus energy difference divided by kT . k is the Boltzmann constant, T is temperature-- this is the same kT that we talked about in the last lecture.

Now, you can see if the temperature is very low, all those particles are-- if the temperature is 0, they're not being jostled, they're just sitting there quietly. They can't move, they can't get into state 1, they just sit in state 2, OK? So the probability of being in state 1 divided by the probability of being in state 2 is 0, OK? If kT is 0, this is a very big number, e to the minus big number is 0.

Now let's say that we heat things up a bit so that now kT gets big. So the kT actually gets approximately the same size as the energy difference between our two states. So now some of those particles can get jostled over into state 1. And we can write down-- we can just calculate-- you can see now that the probability of being in state 1 is-- divided by the probability of being in state 2 is bigger than 0 now. You can actually just calculate it. If the energy difference is just twice kT , then energy difference, $2kT$ divided by kT , that ratio of probabilities is just e to the minus 2, OK?

If the energy difference is bigger, then you can see, that probability ratio is smaller. The probability of being a state 1 goes to 0 if you increase that energy. If you make that energy difference very small at temperature kT , you'd see that if the energy difference is about the same as kT , then the probability of being at state 1 is equal to the probability in state 2. Those particles just jostle back and forth between the two states.

OK, so we're ready to do this. Ratio of probabilities is e to the minus energy difference over kT . What's the energy of a particle here versus here? Well, that's a charged particle, the energy difference is just given by the voltage difference. So energy is charge times voltage where Q is the charge of an ion. The ratio of probabilities is e to the-- Q times voltage difference over kT . Take the log of both sides, solve for the voltage difference, $V_{in} - V_{out} = \frac{kT}{Q} \ln$ times the log of the probability ratio, but the probability is just this concentration.

And so we can write this as ΔV -- the voltage difference is equal to $\frac{kT}{Q} \ln$

which is 25 millivolts, times the log of the ratio of potassium concentration outside to potassium concentration inside. And that's exactly the same equation that we get if you do that much more complicated derivation based on Fick's law and Ohm's law, balancing Fick's law and Ohm's law, OK? And this is equilibrium potential here, not electric field.

OK, so let's take a look at potassium concentrations in a real cell. This is actually from squid giant axon. 400 millimolar inside. So 20 millimolar outside, so there's a lot of potassium inside of a cell, not very much outside. Plug those into our equation. kT over Q is 25,000 millimolar-- temperature at room temperature. The log of that concentration ratio is minus 3, so e_k is minus 75 millivolts. That means if we start with a lot of potassium inside of our cell, open up a potassium-selective channel, what happens? Potassium diffuses out through that channel and the voltage goes to minus 75 millivolts.

How do you know it's negative? Like, I always can't remember whether this is concentration inside or outside, outside over inside, I don't know. But the point is, you don't actually have to know, because you can just look at it and see the answer what sign it is. If you have positive ions-- a high concentration of positive ions inside, they diffuse out, the voltage inside of the cell when positive ions leave is going to do what? It's going to go down, so that's why it's minus, OK?

So-- the battery and in those video modules that I recorded for you, it's going to explain how you actually incorporate that into a battery in our circuit model. And so we've done all of these things, we've looked at how membrane capacitance and resistance allows neurons to integrate over time, we've learned how to write down the differential equations, we're now able to just look at a current input and figure out the voltage change, and we now understand where the batteries in a neuron come from.