**HAZEL SIVE:** Some good questions. Let's zip through quickly. Why can't an initial depolarization travel along the length of the axon? Last time, we went through in detail how a signal is transmitted from the outside to the inside of the cell by ion flux across the membrane, and then how that ion flux is transmitted down the neuron. Remember that the ions entering the cell are just ions. They'll diffuse away.

And so the depolarization kind of dissipates. And it then needs to be regenerated. The action potential, each small depolarization or the whole signal, each small depolarization with a specific magnitude, the reversal of membrane potential going from about minus 60 millivolts, negative inside, to plus 55 or 60 millivolts, positive inside. Each of those is an action potential.

And here is an interesting one. Why doesn't the membrane potential stop at zero when sodium rushes into the cell during an action potential, which is what you'd expect if sodium was just moving along its concentration radian? Because the potential's not only governed by sodium influx. There are chloride ions outside the cell and potassium ions inside over the duration of the potential. And as we'll discuss briefly in a moment, it's during the rectification process that you go back to zero, and then you reverse membrane potential again.

Well, let's move on to Nervous System 2. And I want to cover two things today, both of which connect with last lecture, and then move on to our topic today. We've drawn the analogy of the nervous system as a communication system through the body where there are wires, there are connections between the wires, and there are circuits that need to be laid down.

Today, we're mostly going to talk about the connections. But I want to talk a little more about pumps and channels. And then we're going to talk about the connections between neurons, which is also called synapses. Let's begin with a little more about pumps and channels. And I want to briefly summarize where we were with talking about an action potential, and introduce one last kind of pump-- of channel, excuse me-- that we didn't quite get to at the end of last lecture. And then we'll talk about the pumps and channels involved in synapses.

So in an action potential-- and the sequence of an action potential-- we define three phases, along the length of the axon with regard to the membrane potential that was involved in transmitting the signal, along the very long axon, intracellular signaling those with arresting

potential, the threshold or the action potential of the threshold leading to the action potential, and then the question of repolarization, resetting the membrane potential, which is pivotal. Otherwise, the cell can't fire again.

And we talked about one pump, which is really pivotal for life-- we study it in my own laboratory-- but one pump which is on all the time and which is involved primarily in the resting potential and the repolarization. This is the sodium potassium pump. It pumps sodium out and potassium in, but less sodium out and potassium in. And it is on all the time.

There are other channels that are open all the time. The key one are potassium channels, but there are also open chloride and sodium channels. And those are open all the time. And depending on the concentration of the ions, and also electrostatic repulsion, which will counter sometimes movement along a concentration gradient, those are involved in everything. But primarily-- they're open all the time-- but they are primarily involved in setting up resting potential and repolarization.

So we'll put some dots. I'm going to dash the line in the action potential area, which indicates that those pumps and channel, that pump and channel are being used and active, but they're not pivotal in those processes. The one that's really pivotal in the action potential is the voltage gated sodium channel. We talked about this last time. You can look a bit more on the slides that I posted with regard to the ideas behind how the channel is closed at certain membrane potential, how if the membrane potential changes slightly, there's a conformational change in the protein. And a pore opens that allows sodium to rush in down its concentration gradient, over a very small area of membrane.

So the voltage gated sodium channel allows sodium in, and it is closed, if we look at this. It's open during an action potential. It is closed at resting, but is ready to be open. And then subsequently, it is closed during repolarization when the membrane potential is reset. And it's not openable-- it's not actually clear why-- there's some funny confirmation and that pump is not ready to be opened for some period of time until the protein structure resets itself.

And then it's openable. So it's closed and it's not ready to be opened. And this is really pivotal in making sure that an action potential traverses in one direction along the axon, and doesn't go backwards as the ions diffuse backwards.

And then finally, I want to mention-- or I want to tell you-- that there is a voltage gated potassium channel that opens up after the action potential. And that is one of the things that is

pivotal in resetting the membrane potential during repolarization. The other thing that is really pivotal is this sodium potassium pump. So the voltage gated potassium channel gets potassium out of the cell in the area where there has been depolarization.

Your very positive inside ions go out along their concentration gradient, or along an electrostatic gradient. And so potassium goes out, both in this case. And so it is open during repolarization, and it is closed for the rest of the time. OK. The thing you're going to have to do with these channels, that you will do in section and with your problem set, is to really work through the kind of logic behind what pump and channel is doing what at what stage of the action potential. And then it will start to make sense. OK.

So we're going to move on in a moment and talk about the synapse. But I'm going to talk about the pumps and channels during a synapse, and point out to you that these pumps and channels are being used, but there are others, which are really crucial. One of them is the voltage gated-- VG for voltage gated-- calcium channel. And the other are a series of ligand gated, or second messenger gated. Second messenger regulated, let's say, not gated, ion channels. And these ligand gated, or voltage gated second messenger regulated channels, these things are specific to the synapse, and are specific to the connections between cells.

So let's move on to the major topic today, which is this question of the synapse, the connection between cells. And let me throw out some facts. And then I'll show you kind of a cool picture. Neurons connect with one another to make circuits. That's the deal. That's the wiring. So how complex is this wiring? I showed you a very cool 3D reconstruction of the brain that showed you the packing of the neurons in the brain. But quantitatively, what does that mean?

One neuron can connect with, can synapse with up to 100,000 other neurons. In the brain alone, there are at least 10 to the 10th neurons. It's not clear really, to anyone, how you put those two numbers together, whether you can multiply them, and whether that's fair. But whatever you come out with, that's a lot of connections, just in the brain. OK? The number of synapses, therefore, is huge.

So what kinds of connections are there? Let's just write this. I'm not going to try to-- huge number of synapses. There you go. That's quantitative. What are these connections? We've talked a lot about an electrical signal moving down the axon. But now I'm going to tell you that most connections between cells are not electrical, they're chemical.

And I told you last time when we explored the reason that you have these long axons and

intracellular signaling rather than cells all piled up next to one another doing intracellular signaling, that's slow. I told you that last time. And that's still true in a synapse. The connections between the cells is the slow point of neural transmission.

There are electrical synapses. And they are used sometimes, but rarely. They are fact because they are connected by gap junctions, one neuron to another. And that allows ion flow. But the thing about electrical synapses is that they're always open. The cells are always connected. They're unregulated.

And the thing about the nervous system is that it is exquisitely regulated. It is fine-tuned to respond to the smallest stimuli, both from within your body and from without. And unregulated synapses will not do that for you. So the flip of those are chemicals synapses. They are slow, their diffusion limited, and they're diffusion limited of chemicals that we'll discuss in detail, that are called neurotransmitters. But they have the wonderful property of being highly regulatable. And so the majority of synapses in higher animals are these chemical synapses. And that's what we'll talk about today.

This is a picture which I really like. It's a neuron where-- and these are the dendrites. And here's the cell body and the axon coming out. And each of these dots represents a synapse. Well, it doesn't represent a synapse. It is, it's stained for a protein that's only found in synapses. And you can see this tremendous studding of the dendrites with synapses, which gives you a sense of the complexity. OK.

It's really pivotal, when we talk about the connections, that we get some of the principles correct. So I want to spend a board going through some of the principles that we have to bear in mind in thinking about the connections. So let's think about this. Here are neurons-- well, let's have Neuron 1. But we could actually have Neuron 1 to n. It doesn't matter. It could be a whole bunch of Neuron 1. And along that one neuron, or those bunches of neurons, is coming an action potential.

And over here is Neuron 2. And between them is a connection, is a synapse. And the thing that Neuron 2 has to decide when it connects with Neuron 1 is whether it's going to make an action potential, whether it's going to send a signal. That is the big decision that this neuron has to make. So Neuron 2 must decide to make an action potential, and it is a yes/no decision. It's not a sort of an action potential or a half an action potential.

And so we need to remember action potential facts, all or none. You either get an action potential or you don't. That means you get complete depolarization or nothing. And if you have a lot of action potentials coming along Neuron 1, the way Neuron 2 can respond is not to make a big action potential, obviously. But it can make a lot of action potentials.

So a change in input where we can call this action potential from Neuron 1, the input, a change in input results in an increase or change, let's just say, a change in the number of action potentials per time, or the frequency of action potentials in Neuron 2.

Other facts, other really key facts. Resting potential can change. Threshold potential and the action potential, as I've been belaboring, do not change. And you can see that nicely in the slide, where here's a neuron firing, and this is a different way of showing the neuron firing. Here is the action potential showing as a spike of depolarization. And then there's a time, another spike, another action potential, wait, another spike, and so on.

Here is a neuron that's gotten a lot of input. And look at it. It's spike, spike, spike, spike, spike. But if you look at the height of that spike, that is the depolarization height. It's the same within the sensitivity of the recording device for each of these action potentials. So I really like that slide to exemplify these principles that I've just put on this board. OK.

There are the principles. How does it work? Very cool. This is really amazing. Let's again have Axon 1. We're going to have Axon 1 here. OK? Axon, oh, let's have axon derived from Neuron 1. And now we've got to distinguish two different parts of the axon. And I'm going to draw this on the board and then I'm going to go through it with you on a hand out, because it's important.

There's an electrical signal coming along Axon 1. And you know that it involves an action potential via the voltage gated sodium channels. As that signal nears the end of the axon, the axon kind of bulges out into a terminal, and the voltage gated channels change from sodium to calcium. So here's the end of the axon. And here you change to voltage gated calcium channels that are activated. OK.

These voltage gated calcium channels, this is called-- actually, let's put some terminology. This is called the pre-synaptic neuron. And the voltage gated calcium channels are at the pre-synaptic terminus. Now the thing about calcium that we've mentioned before is that it is a mediator of exocytosis, of having little vesicles containing proteins or other molecules released from the cell.

These voltage gated calcium channels increase intracellular calcium and lead to the exocytosis, the release of chemicals that are contained in vesicles at the end, at the pre-synaptic terminus. So the pre-synaptic terminus contains vesicles with neurotransmitter. We'll talk about this in detail. The voltage gated calcium channels, which increase intracellular calcium, lead to exocytosis release of the neurotransmitter, which is released outside the cell.

And that neurotransmitter diffuses across the space between Neuron 1 and Neuron 2. It's about 30 nanometers. And it diffuses across the space. And when it gets to the other side to-- here's Neuron 2, called the post-synaptic neuron-- when it gets to the other side, and it'll get to either the dendrites or the cell body, this neurotransmitter binds to things that we've talked about a lot, it binds to receptors. Those receptors plus ligand do all the things we've talked about in many lectures.

They do something. In this case, they can do one of two things, as we'll talk about. But it all culminates in changing ion flux across the post-synaptic membrane. So the neurotransmitter diffuses. It hits the dendrites, or cell body. It binds receptors to change ion flux, or ion movement. And this eventually gets turned into the action potential decision. OK.

So let's put some more on here. Here's an electrical signal from Neuron 1. Here, this neurotransmitter diffusion is a chemical signal across what is called the synaptic cleft, which is the space between neurons. And the signal in Neuron 2 becomes electrical again. So there's a conversion device, which converts electrical to chemical to electrical signals. All right.

Let's look at your first handout and we'll hammer this in in more detail. Here's the action potential. So let me stand here in case you're-- they don't like me doing it. OK. Let me stand here. Here's the action potential coming along Neuron 1. Voltage gated sodium channels until you get near the end, when you switch to these voltage gated calcium channels. Calcium flows in, leads to exocytosis of vesicles containing neurotransmitter. The neurotransmitter diffuses across the synaptic cleft, binds to receptors on either side, which changes the ion flux into Neuron 2.

And there is an action potential decision-- it's on your sheet-- an action potential decision that eventually, as we'll discuss, involves voltage gated sodium channels so that the cell decides whether or not it's going to fire an action potential. OK. We'll talk about the neurotransmitters and the receptors in more detail in a moment. But I want to introduce you to three concepts of the synapse, which are really very important.

The first is the concept of summation. And now we go back to the notion that many neurons can give signals to another neuron, such that that other neuron is deciding yes, no, I'm going to fire an action potential and transmit the signal. The neuron that's receiving all of that signaling has to add up its inputs and say what's the sum of the inputs. Literally, it has to add up the inputs.

So summation is the addition of all synaptic input, which is change in membrane potential governed by change in ion movement on a recipient neuron. OK. So the addition of all synaptic input on a recipient neuron, or bio-recipient neuron, if you like. There's two kinds. There's spatial summation, which has to do where the signal is received.

And so those synapses that I showed you in that picture of the cell with all its dendrites and all of those little dots were all over the place? Each of those little dots is getting a signal on the dendrites, on the ends of the dendrites, near the cell body, in the cell body. All of those inputs have to be added up. So where the signal received, is received, cell body plus dendrites, that would be spatial summation.

And then temporal summation means over time, when the signal is received. Over a period of a millisecond or so, all of those inputs to the neuron are added up. And the addition is actually a simple one. The addition is how much has the membrane potential changed, and overall, have you brought the membrane potential of the recipient neuron up to threshold. If you have, that recipient neuron fires. And if you haven't, it doesn't.

So the total membrane potential-- so the answer of whether to fire or not, is the total membrane potential, which is the decision. And if it's threshold potential, out of that, an action potential results. The addition, the summation is done in the dendrites and the cell body. And the answer is read at the place where the axon comes off the cell body, which is called the axon hillock.

So the sum is calculated over all of the dendrites plus the cell body. But it is read at this thing called the axon hillock. And they only read the axon hillock is where the axon leaves the cell body, or originates from the cell body. And the reason that that is an important place is that that is where the voltage gated sodium channels are found. It's only there. They start at the axon hillock, and they are present all the way down the axon.

There are no-- and you can look at your diagram for this-- there are no voltage gated sodium

channels in the cell body or the dendrites. So they can't fire an action potential. They can add up how membrane potentials changed, but they can't do anything about it. So the hillock is where the axon leaves the cell body, and where the voltage gated sodium channels begin, begin, and where an action potential can therefore come out. That's a bunch of sentences. OK.

Couple more terms. Excitatory and inhibitory synapses, excitatory and inhibitory. It's kind of like a simple math problem where you're adding positive numbers or negative numbers. You know, you come out with something that's either 0, negative, or positive. Same idea here. When you add all these inputs that a neuron gets, it figures out what it's going to do.

And the inputs can be either pushing a neuron closer towards an action potential, closer towards threshold, or pushing a neuron away from being able to make an action potential, further away from threshold. Excitatory synapses bring the resting potential closer to threshold, whereas inhibitory bring the resting potential further from threshold.

All right. Here's where it gets even more complicated. One neuron can be making both excitatory and inhibitory synapses. And depending on which predominate, the recipient neuron will either be told to fire or not to fire, to make an action potential or not. So one neuron can make both excitatory and inhibitory synapses.

How does this work, you ask? Well, you have all the tools to know. It's all got to do with ion flux and which ions are flowing in and which ions are flowing out. And we can answer that by looking at your next handouts. In Number 2 of your handouts, I've shown you the synaptic cleft. Here's a synaptic cleft. And here are the voltage gated calcium channels opening to allow calcium in and neurotransmitter vesicle exocytosis.

Here is an excitatory synapse bringing the resting potential closer to threshold. Let's think about that. You want positive ions to come in from the outside. That would help bring your resting potential closer to threshold. So there is some sodium channels that can open, maybe calcium channels that can open-- not the voltage gated ones. And that would increase the resting potential. That would increase the potential inside the cell, bring it more positive, closer to threshold.

Conversely, in an inhibitory synapse, you'd get a net inflow of negative charges. The chloride ions might move from the outside in. That would take, make your inside of your cell more negative and further away from threshold. You could also get potassium out. And that would,

again, make the inside of the cell more negative and further from threshold. So you can see already I've got four different channels-- they're not the ones we've talked about before, they're different ones-- four different channels which can modulate the membrane potential on the recipient cell.

All right. Let us move on now to those neurotransmitters and their receptors. Neurotransmitters and neurotransmitter receptors are very cool because they are probably what makes us who we are in terms of personality, in terms of ability, in terms of our interface with the world, in terms of whether we're an intrinsically happy or not so happy person, er cetera. Neurotransmitters, however, are a class of molecule we have previously encountered. They are ligands, but they're different ligands.

When we talked about ligands previously, we have largely been talking-- not entirely-- we've largely been talking about peptides or molecules that are sort of a reasonable size. Not always. The steroid, the steroid hormones are very tiny. Neurotransmitters are pretty much all very tiny. And the thing that you should know is that you can have one or many types of neurotransmitter per synapse.

Here's another complication. Neurotransmitters can be peptides sometimes, but they are very largely amino acids, the same amino acids that you build proteins with, nucleotides, or other small molecules, like the kinds of synapses. Synapses are excitatory or inhibitory because of the kinds of neurotransmitters that they're making. So there are excitatory neurotransmitters.

Glutamate, glutamate, glutamate, glutamic acid-- OK, the same one we've talked about before-- and adenine are both examples of excitatory, are examples of excitatory neurotransmitters. Glutamate is involved in being alert. Adenine is involved in being sleepy. And one of the things that caffeine does is to counteract the effects of adenine so that it's thought to competitively interact or competitively inhibit adenine function.

Inhibitory neurotransmitters, something called GABA, gamma-Aminobutyric acid, and glycine are the two major CNS, Central Nervous System neurotransmitters. GABA particularly is an anti-anxiety neurotransmitter. And things like Xanax, which I will get to today or Friday, are things which will be agonists of GABA function.

And sometimes, neurotransmitters can be both excitatory and inhibitory. Acetylcholine, for example, which is involved in connections between nerves and muscles. Neuromuscular

connections, and also found in the CNS, can be both excitatory and inhibitory. And serotonin-- and I'll put dopamine on the same line for space-- serotonin and dopamine, both of which are kind of feel good neurotransmitters, also involved in alertness and other things. For dopamine-- locomotor activity movement-- they can be either excitatory or inhibitory.

What do they look like? Let me go on and then I'll show you some pictures in a moment. All right. So how can something be excitatory and inhibitory? What's downstream of these neurotransmitters? The receptors. Good job. All right. Neurotransmitters, ligands bind receptors. And the way the neurotransmitters affect what they're going to do is by binding the appropriate receptor. So here are the receptors for the neurotransmitters. And like the neurotransmitters, there can be many different kinds per synapse.

There are two classes of receptors that you should know. One are ion channels. They're receptors which bind the neurotransmitter, and they open up. They're ligand gated ion channels. But the other kind are not ion channels. They bind the receptor and then they activate a second messenger system, as we talked about before. And it's the second messenger system that later on opens an iron channel.

They have names. So two classes, one are the iron channels. They're called ionotropic receptors. So they're ligand gated ion channels. And the thing about these is that their response is very rapid, in the millisecond range. There's another class of those receptors which activate ion channels.

They are called metabotropic. It's the concept that is more important than the term, but I'm giving you the term for completeness. And they act via a second messenger system that almost always involves G proteins. And these are slow. Their response is at least a second, often much greater than a second.

OK. And let me, as the last thing I'll tell you today, I'll show you-- if we have a moment I'll show you some pictures-- but I want to tell you that one neurotransmitter can activate different kinds of the receptor. So one neurotransmitter can activate greater than one type of receptor. And this was implicit in the notion that neurotransmitters could be both excitatory and inhibitory.

For example, serotonin binds to no fewer than 14 different receptors. And one neuron can express probably not all 14, but it could probably express five different serotonin receptors. And they do different things. One of them is a ligand gated sodium channel. Another type is G protein coupled, so including both metabotropic and ionotropic receptors.

And to throw out at you the last couple of slides, here are some of these amino acids and small molecules that are neurotransmitters. And this really exemplifies what I've said on the board. So I'm going to stop here now.