GERALD SCHNEIDER: OK, these are what I call the primitive cellular mechanisms-- irritability, that is, response to something in the environment, conduction to other parts of the cell, movement of the cell, secretion. We should probably add-- that's exocytosis. We should probably add endocytosis and define those terms, taking in as well as secreting. And we'll talk about membrane specializations, transduction mechanisms, and a little bit about endogenous activity before we go to the multicellular structures.

Now, movement of cells. What cells are we usually talking about when we talk about movement? What cells move the most? Muscle cells. And what does it require? It requires contractile proteins and energy.

Now, are there any contractile proteins in neurons? Well, especially in development, there's a lot of actin. There are many actin filaments, OK? Especially in the part of the neuron changing the most during development.

And that occurs in migration of the whole cell as well as in the growth of the processes. "Process" is used in anatomy to mean the little extensions of neurons. It's not the way you usually use the term "process." So cellular processes are the little extensions of the neurons, OK? I'll try to stop myself and define terms. If I don't, you should stop me and ask me.

You also, of course, get movement in regeneration. And I'm going to talk a little bit about regeneration, which is a topic I do research on, when we talk about development a little bit later. More generally, there's various kinds of plasticity, not only in developing but even in adult brains. Yes, even your brain is changing in its structure and its connections.

Today, we're more concerned with how activity spreads within a cell. Some of it's mechanical. If the cell is mechanically moved, you get changes that are communicated to the rest of the cell through the cytoskeleton. That's been a particular topic of research of Don Ingber at Harvard. But usually, we're dealing with these other things-- diffusion of molecules, chains of reactions, molecular cascades within the cell.

We also have in neurons specialized mechanisms that we call active transport mechanisms involving these molecules, kinesin and dynein, for moving organelles and molecules from one part of the cell to another, usually from the cell body down to the endings of the axon or back from the axon ending, back to the cell body. OK, and we'll mention this again.

And then the topic we'll talk most about today, electrical changes in the membrane. So a mechanical stimulus or a chemical stimulus or an electrical stimulus to the cell membrane will lead to a depolarization of the membrane. In some cases, hyperpolarization.

But if it's a mechanical nudge, it's always depolarization. And then that change is conducted away from the point of origin, OK? So that's how activity spreads within a cell.

And when we talk about irritability and conduction in neurons, these are the terms at the left. We're usually talking about polarization of the membrane, either a graded or an all-or-none response.

Conduction. That can be decremental or nondecremental depending on whether we're talking about action potentials or not and afterpotentials. OK, and the terms on the right refer to synaptic action. We'll talk about that afterwards.

This is-- I'm not sure. I can't remember now which version of the text-- whether this picture is in your text or not. But it was in an earlier version. And I haven't changed the pictures.

I just want to note that these-- he puts these up as classification of neurons into three principal types. He actually means only three principal types of long axon neuron, OK? In fact, there's probably more short axon neurons in the nervous system than there are long axon neurons.

But these are-- when you see people talking about neurons, they usually draw something that looks like that one on the left. That would be like a motor neuron in the spinal cord with the cell body in the central nervous system and the axon going to a muscle.

The middle cell type is like the cell with its axon coming in through a dorsal root, so the cell bodies outside the CNS. And what we call a dorsal root ganglion, that would be the cell type furthest to the right, whereas the middle one, that would be like a cell connected to your vestibular or auditory apparatus, the cochlea in the inner ear.

These are bipolar neurons-- a little bit more primitive in nature because all the neurons in lower creatures look like that. So these are the types of long axon neurons.

In any neuron, we can divide up the neuron into functional divisions-- an input area or input zone in the picture here, a zone of transmission or conduction, just mostly the axon, and then finally, an output area where the activity affects other cells, the axon terminals.

Now, say we're going to record from a cell. And I'm just indicating the cell here with a circle, which is the lipid bilayer. And I've indicated there that if we take an electrode here, shown here in red, OK?

I'm taking a little microelectrode. And I'm advancing it toward the cell, OK? And I'm recording against the extracellular fluid. Now, as soon as I poke through the membrane, the potential changes to about minus 70 millivolts, OK? Negative on the inside of the cell with respect to the outside, OK?

Because the membrane of neurons, like the membrane of many other cells too, is polarized, OK? There's an electrical potential across the membrane. It's not only true of neurons. It's even true of leaf cells, OK?

But the neuron is specialized in several ways. And if we nudge neuron around a little bit, as I'm showing there, I poke the neuron a little bit, there's a depolarization in the membrane. That's the response, primary response of that neuronal membrane to being stimulated, even mechanically, OK?

Now, I've indicated here that there's a differential distribution of ions on either side of the membrane. First of all, there are negatively charged anions inside the cell. Very few on the outside. And the membrane is impermeable to them, OK? So they can't get through.

We call this membrane of the neuron a semipermeable membrane because it's impermeable to some things. It's permeable to other ions. And it's semipermeable to others.

So for example, when the neuron's in the resting state, it's pretty impermeable to sodium ions. There's many more sodium ions on the outside than there are on the inside. There's also many more chloride ions on the outside.

On the inside, besides those negatively charged anions, you have the potassium ions. Now, the membrane does have some potassium channels that are open, others that are closed. So the permeability of potassium can change depending on how many channels are open, OK?

So the membrane potential, then, is a result of this distribution of ions on either side of the membrane as well as, of course, on electrostatic forces and one other thing I've indicated there at the bottom.

That's a little, active protein engine in the membrane we call the sodium pump, OK? Using a little energy, it moves three sodiums out and brings two potassiums with every cycle, OK? And that's important in order to maintain the high concentration of sodium on the outside.

But why would you have to maintain it? What's happening to it? Well, whenever you get an action potential, there's an implosion of sodium ions. And we will talk about that.

Now, I'll first say a little bit about the factors determining a resting potential. If you look at this picture, it shows a picture of the lipid bilayer with proteins embedded in it, proteins, transmembrane proteins. And these are the ion channels. And it's showing potassium channels that are open, so potassium can move in either direction. But the sodium channels are closed.

Well, then why would potassium end up distributed differently on the two sides of the membrane if the channels are open? Anybody?

Well, remember, you've got those big anions inside. You've got the sodium ions on the outside. So the way the other ions distribute, even if they can get through the membrane, will depend on what two kinds of forces-- electrostatic forces and concentration gradients, OK? Diffusion forces. OK.

Let's talk a little more now about what happens if we poke an electrode inside the axon of the cell. You see over there at the left, they show a neuron in a Petri dish. And there's a recording electrode in the axon here and a stimulating electrode.

OK, and it's showing two kinds of stimulation here-- a hyperpolarizing stimulus that's making the axon more negative on the inside, OK? And depolarizing stimuli, which reduce that membrane polarity, OK? And this shows what you will record just a little ways down the membrane because those little changes in polarity are being conducted.

The hyperpolarization, you can see here. It's a little weaker than at the point of stimulation. It would be weaker yet if you were further away, OK? And here, same thing, but for depolarization. But when the stimulus reaches a certain threshold-- and here, they're indicating the threshold, depolarization-- you trigger a much larger response.

That's called the action potential. It's due to a sudden opening of voltage-gated ion channels. The sodium channels are voltage-gated, so when they reach a certain threshold level of depolarization, they will open up. Sodium ions will rush in. So there's an implosion of sodium ions.

And that's what causes the action potential. And it's overshoot. The membrane actually becomes positive on the inside very briefly. And then there's a recovery of the membrane as the channels change.

OK, so now we've talked about different kinds of responses, different regions of the cell. Let's just review that, relating the structural parts to the functional parts of a neuron to structural parts of the neuron. Then we'll look more carefully at a couple of neurons.

First of all, the receptive region. That's the dendrites and the cell body primarily. And when those areas are stimulated, whether it be mechanically or with an electrode or physiologically with a synaptic input, you get a graded response.

"Graded" means the response depends on the strength of the stimulus. You get a greater response for a greater stimulus, OK? That's a graded response.

The conduction is decremental in most dendrites, cell bodies. There's a few exceptions to that. That just means that the further away from the point of stimulation you get, the weaker the effect is, OK? So if you've got very long dendrites, and the stimulus is way out at the end, the effects on the cell body will be a lot less than if you're much closer.

OK, then you have the region of rapid conduction. That's the axon. That's where the membrane is specialized to give you that all-or-none response. The action potential is nondecremental. It's like a row of dominoes going down. Once you tip the first one, the whole-- it goes right down the axon. There's a wave of depolarization reaching the axon terminals.

And then after certain afterpotentials, it recovers to the resting potential until you get another action potential. And finally, the region of transmission to other cells. These are the axon end-arbors.

Enlargements are called boutons. We always like the French term for some reason. It's actually boutons terminaux.

OK, at the end, this is at the axon telodendria. That means "the end branches." "Telo-" means "end." Teleology, the study of purposes and ends. OK, the end branches. Dendrites are the branches. That's where you have synaptic potentials and where we get neurotransmitters released. And we'll be talking about.

OK, now let's just take a look at two neurons. There's actually three neurons in the picture here. I want to talk about the two with long axons.

One is an axon that comes in through the dorsal root of the spinal cord, OK? The ending is in these endings out near the body surface. You have many axons that have endings like that on your skin, OK?

And then the axon begins about right there, OK? And notice, there's no cell body there. But that's where the axon begins. And the axon goes right by the cell body, which is off to the side here, and reaches terminals inside the central nervous system. This is peripheral nervous system. CNS there means Central Nervous System, OK?

DRG, dorsal root-- it's a Dorsal Root Ganglion cell. The ganglion is a collection of those cells, OK? So one cell isn't a dorsal root ganglion. It's a dorsal root ganglion cell, OK? It's also referred to sometimes as a primary sensory neuron. But I'll be defining that for you later.

OK, now functionally, we can look at the motor neuron in exactly the same way. We'll put the receptive region clear over on the right. And that's the cell body and dendrites inside the CNS, the Central Nervous System, and the motor neuron.

Then we have the axon. And the axon is starting right there. This one is starting right there. That region is called the axon hillock.

Nope. Go back to my pen. Axon hillock-- beginning point of the axon where that action potential normally begins, OK?

Now, in the case of the motor neuron, again, we can follow the axon to the axon telodendria, the endings, which, in the case of a motor neuron, is on a muscle cell, OK? But functionally, now we can look at those two neurons and describe the same kinds of processes happening in these three divisions, OK?

So now, let's take just a piece of one of those axons and look at it. Here, you see that we're dealing with a axis cylinder, sometimes called a tube formed by the axonal membrane.

I just sliced out a piece of it there. And I'm representing the distribution, route to distribution with the positive and negative charges, showing that it's normally positive on the outside unless an action potential is going by. And I've taken a piece of the axon right when an action potential is there, OK?

Now, first of all, on the right there, if we're recording from the axon when it's quiet, there's no action potentials. If we put two electrodes on the outside, of course, we'll get nothing in our recording. If we put two little probes on the inside, we'll get nothing. If we put one on the outside, one on the inside, we'll find that the inside is negative, about 70 millivolts, a little more, a little less depending on the cell, OK?

Now, if we trigger an action potential and we're recording from this type of arrangement, we can construct the picture that I've shown in the left. And I've graphed down below. That graph would show the recording you would get if you were, at one point, looking at the onrush of the action potential as it passed by. And you would be plotting potential against time.

But as I've shown it here, we're actually looking at the spatial distribution of potentials across the membrane as the action potential goes from right to left there, OK? So we're in front. Here, we're in front of the action potential. And there, we're at minus 70, OK?

Then the action potential arrives. And you get the implosion of sodium, as I show there, and you get the depolarization, OK? And it goes more than 70 millivolt, OK? Usually goes up to about 30 millivolts positive. But then it quickly recovers, as you see there. And you get some afterpotentials until you get back to the resting potential.

Now, the main explanation for the rapid depolarization of the membrane, as I said, is the implosion of sodium ions. And well, it starts to recover. You get an opening of the potassium channels further than they already are and a closing of the sodium channels, OK? And it's that extra opening of potassium channels that results in the afterpotential there. So it becomes a little more than minus 70 initially, until you get a recovery of the resting state.

OK, and this just shows another picture of the action potential at these different stages. It's just showing you sodium and potassium channels and the distribution of these ions on either side of the membrane. So you see at the far left some potassium channels open, some closed. And you see the closed sodium channels.

And then the action potential is getting close. Just before it's triggered, the sodium channels start to open. And then at the peak, they're all open. You still have some potassium channels open, some closed. And then, in the fourth region there, you see more of the potassium channels open. And now the sodium channels are closed as the recovery occurs, until you get back to the initial state.

Explanation of the action potential in terms of changing conductance for sodium and potassium ions across this membrane was worked out by Hodgkin and Huxley. And this is a picture from Hodgkin in 1964 in which he's depicting the voltage potential difference across the membrane with a dashed line. And then he's showing sodium conductance and potassium conductance and how they're changing.

That was a very simple model that could completely account for the shape of the action potential. And you see the whole thing is occurring in a few milliseconds.

Now, what I've said so far can explain conduction in an unmyelinated axon. That's just a bare axon, OK? And here, you have a picture of that wave of depolarization that's going down the membrane, in this case, from left to right. And I'm showing a picture of the membrane at three different times.

This is a cartoon of an axon with a myelin sheath. And they've enlarged the axon and made it very short, OK? But right here, you see a cell as seen in cross-section.

That's a cell that has wrapped its membrane around and around the axon. The cell is called a glial cell, a particular type of glial cell. Depends on whether you're in the central nervous system or the peripheral nervous system, OK?

If we're dealing with a motor neuron, so we're in the PNS, we're dealing with Schwann cells. If we're dealing with the CNS, we're dealing with-- whoops. We're dealing with oligodendrocytes or oligodendroglia.

Now, these terms come from Greek and Latin-- in this case, Greek. "Oligo-" means "few." "Dendro," "few branches." "-Cyte" means "cell." OK, the cell with few branches because there are other glial cells in the CNS that have many more branches, OK?

The Schwann cell is named after Mr. Schwann. OK. It's a wonderful cell. It does a lot of interesting things. And we'll be talking about it a number of times in the class.

Now, what does that do for us? What do we need myelin for? We think of it as an insulator, and it is in many ways. Because when you have that tight wrapping of the Schwann cell membrane, you tremendously change the membrane capacitance, and you cannot get-- it blocks this ionic conduction, OK?

But it does another thing. With the change in capacitance of the membrane, you get much more rapid decremental conduction down the axon, OK? So what happens is that depolarization at the beginning there, the axon hillock, triggers the action potential in the axon hillock region.

That spreads very rapidly down the axon. Of course, it gets weaker because it's decremental. But it reaches the next node, which is close enough so it exceeds the threshold for firing an action potential. So the little, bare part of the membrane fires an action potential.

This only works if you have these little nodes where there's no myelin. So there's myelin, and then there's a little unmyelinated region. And then there's more myelin and then another unmyelinated region and so forth, all the way down the axon. And that's what they're showing here.

So basically, the action potential is jumping from node to node. And because the conduction is so rapid between nodes, the decremental conduction, the speed of action potential conduction is much greater than in the unmyelinated axon, OK? That jumping from node to node is called a saltatory conduction, OK? Saltations are jumps. Saltatory conduction.

Here's a picture of that. Well, sorry. First of all, dealing with why it's faster, you can draw an equivalent circuit for a patch of membrane in terms of resistance across the membrane, capacitance across the membrane and along the membrane, along the axial direction of the membrane. That's r sub a in that.

The two critical ones here are the capacitance and the axial resistance. We just look at that in terms of these passive cable properties. It's showing a piece of membrane here, extracellular fluid at the top, and the cytoplasm inside the cell on the bottom. And they're representing resistance for current flow along the direction of the axon as r sub a.

The resistance is shown at the bottom. And then at any point along the membrane, the membrane is a certain resistance to current flow, but it also has a capacitance, OK? And when we add myelin, we're decreasing the capacitance, OK?

I won't go through the conduction of the potential here. It's a little model. But the rate of passive spread of the current down the axis cylinder is inversely proportional to the axial resistance and the membrane capacitance. So if CM decreases by itself, rate will increase, OK?

And there's an additional effect because when the axon diameter increases, the rate also increases. Now, that's true for unmyelinated axons, too. OK? The reason is axial resistance decreases when we increase the diameter but increases in proportion to d squared. And you have an opposite effect due to the change in membrane capacitance, but it's only in proportion to d.

There's two ways then to increase the rate of current flow down the axon. One is to increase the diameter. And the other is myelin. And the myelin only works with the nodes, OK?

This is a picture of current flow on a myelinated axon. And it's showing in the graph here a distance along the axon. And so you'll see the rate of the potential change there. And you see the very rapid conduction and then the slower conduction at the node, then very rapid conduction and the slower conduction of the node.

But remember, it works only because the threshold is exceeded at the nodes. And that's a large enough potential change to spread down to the next node and trigger the action potential. So it's basically jumping, producing saltations. That's what saltatory conduction is.

OK, now if we look at all these terms on the left, we should know what they mean. You know what membrane polarization is in terms of distribution of ions across the membrane. We can record it with an electrode. You know what a graded response is.

Decremental conduction or nondecremental. Nondecremental. And we get the all-or-none response of the action potential. And we've also looked at the afterpotentials.

OK, so now we can go to these terms used to talk about synaptic action. What happens when the potential reaches the axon endings where there are contacts with other cells, the synapse? OK. And to introduce that, we'll look at this cartoon showing recording from the big, yellow cell there and from two cells that are connected to it.

One cell, the pink one there, is connected with an excitatory synapse. And the little blue one there, they show connected with an inhibitory synapse, OK? In each case, we can stimulate the cell providing input. And we can record what happens postsynaptically, OK?

So if we get an action potential, it's not actually showing the stimulus. It's just recording the action potential from the blue or the pink cell, OK? So it's showing the recording of the action potential. And then it shows what happens in the cell on the other side of the synapse.

If it's a depolarization, the top one, we call it an Excitatory Postsynaptic Potential, an EPSP. Excitatory because it's bringing the membrane closer to the threshold for triggering an action potential. You say, but you can't get an action potential in the cell. You already said that they don't conduct action potentials.

Well, that's true. But you remember, that EPSP will get conducted. It will get conducted away from the point, the synapse. And what counts is how big the depolarization is at the axon hillock, which is right near the cell body, OK? This would be in the region of the-- all the way down the membrane.

It's about the same amplitude throughout. Thank you, Bob. It's about the same amplitude throughout. That's right. They're very important. That's why I said it's like a row of dominoes. Once you start the first one, it goes all the way down, OK?

OK, so here, we've got the same kind of action potential in the two input cells, the blue and the red. And it's shown in blue and the red there. But the effect in the postsynaptic cell is very different. Why?

Well, there's something different happening at those axon terminals, OK? There's different molecules being released in different receptors in the postsynaptic membrane. And that determines what's happening to the postsynaptic membrane, OK? That's why you get an excitatory postsynaptic potential moving the membrane of the cell closer at its axon hillock there, closer to the point of triggering an action potential.

But in the case of an Inhibitory Postsynaptic Potential, the IPSP, it's moving the cell away from the threshold, making it less likely to fire an action potential. So that's why we call it inhibitory postsynaptic potential.

OK, now think about putting this together with-- let's think about decremental conduction in the cell. Oops. OK. Let's draw a cell here and draw several inputs coming into it, OK?

And here's its axon going out. And let's say we have one action potential there, one action potential here, and one action potential here. I've just shown it in a moment in time. And they're all rushing down to the axon terminals.

OK, and they're all going to cause EPSPs. They're going to summate, OK? So if we're recording here at the axon hillock, just one of them might be a little blip in the membrane potential like that.

If two of them arrive, it'll be bigger. If three of them arrive, it'll be bigger still. And if this is the threshold, you see we might reach the threshold and trigger an action potential, OK? That effect is called spatial summation.

So multiple terminals contact in the cell. If you have enough inputs through these different axons coming in, they can summate at the axon hillock and result in the firing of an action potential when a single input would not have done that, OK?

Let's draw another cell here and show another kind of summation, temporal summation. Here, we have a series of action potentials in this axon, OK? And I'll graph that here.

So here, the first one arrives. Little EPSP. The next one arrives a little bit later, but the first one hasn't decayed all the way yet, OK? So it gets a little higher and a little higher and little higher. And then with enough summation, it might exceed the threshold and fire an action potential, OK?

That would be temporal summation because each little postsynaptic potential takes a little time to decay. So if another one arrives on top of the first one before the first one is decayed, you'll get a summation, OK? So spatial and temporal summation-- pretty critical events in the way the nervous system works because there's a tremendous amount of convergence of inputs on neurons.

Remember, I mentioned in the motor cortex-- remember how many synapses I said are found on one cell on the average in the monkey motor cortex? 60,000. OK, so spatial information is a major process.

OK, now why are some synapses excitatory? Others, inhibitory? Why are synapses different? It was difficult to explain them when it was argued that synapses just acted by electrical effects only. And that was believed for a long time in the early part of the 20th century, OK?

But then Otto Loewi, who was studying the innervation of the viscera and other organs, like the heart, using frogs as his subjects, had a dream. In it, he realized how he could demonstrate it was chemical transmission at the synapse. The only trouble was he forgot the dream. And he got up in the morning, and he couldn't remember.

So what did he do? Fortunately, he had the same dream the next night. He left paper by his bed so he would write it down. But he decided not to take the chance. He got up and went to the lab. That's the story.

He was studying the innervation of the frog heart. And the frog heart is innervated by two major nerves out of the peripheral nervous system. One is called the accelerator nerve because if you stimulate it electrically, it causes the heart to speed up. And the other, the decelerator nerve because you can slow the heart down. We now know that those are the connections of sympathetic and parasympathetic divisions of the autonomic nervous system. And we will describe those. And you'll read about it in your book.

So here's what he did. He put two frog hearts in separate Petri dishes, each attached to those two nerves, which are now severed from the nervous system. But they were still alive. And the hearts were beating, OK?

Now, if he caused one heart to speed up by stimulating the accelerator nerve-- and he did that for a while-- and then he took some of the fluid from around that heart and moved the fluid to the other Petri dish, the second heart would speed up without having its nerve stimulated, OK? So it had to be a chemical effect. He did the same thing for deceleration and showed a similar thing.

And he said that the material-- he named them just according to the function. And the first one, "acceleranstoff" in German, OK? The accelerator stuff from the accelerator nerve.

Where did he get this "vagusstoff"? The vagus nerve is the nerve that, when stimulated, slows the heart down, OK? And it wasn't known at his time, but not very long afterwards, it was discovered that "vay-gus-shtoff" or "vah-gus-shtoff" is what, that slows the heart down? Acetylcholine. The same neurotransmitter that acts at the neuromuscular junction of striated muscles also acts in the autonomic nervous system, OK?

Acceleranstoff. What causes the heart to speed up? A different neurotransmitter. Norepinephrine or noradrenaline, OK? Similar to adrenaline. Released by the adrenal medulla, OK? OK, and that's where we'll start next time.