Introductory Neuroscience & Neuro-Instrumentation
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Lecture No. 13
Axonology, Neuronal Biophysics (1)

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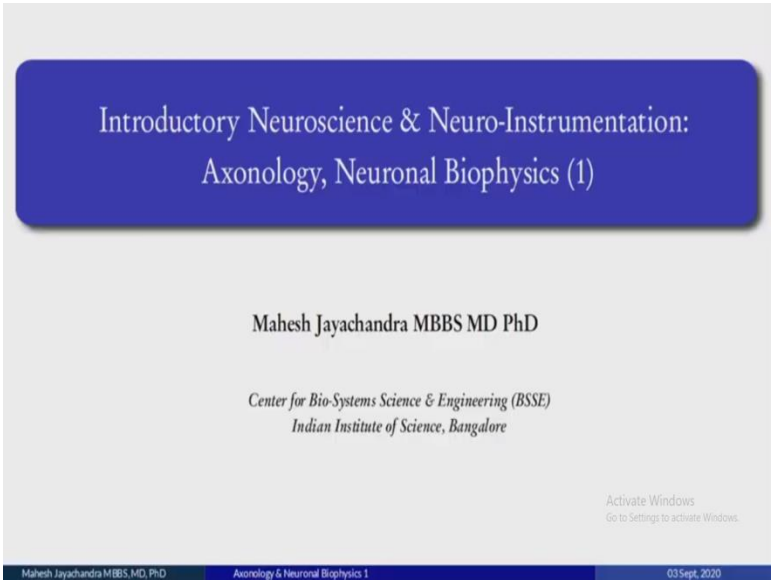

Introductory Neuroscience and Neuro-Instrumentation: Axonology, and Neuronal Biophysics.

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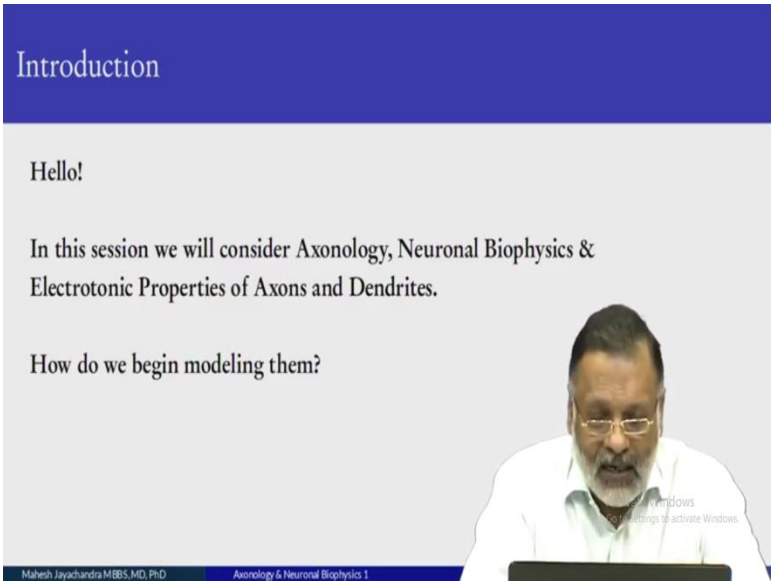

So, here, in this session, this is going to be a little complicated, I am warning you right now. But if you go through it slowly and if you take breaks and try and understand each slide, you will

have a fairly good knowledge of it. So, here we are going to consider the properties of axons. , so far we have considered action potentials, resting membrane potentials, and how axon potentials are formed and how they spread, and so forth. But what about the passive properties of the axon?

The neuronal-biophysics, the electrotonic properties of axon dendrites. Why should we model them? We model them because using modeling, we can have a pretty good idea and a realistic idea of how it works. And to do that, we need to know the different properties which are involved, which cause electrical transmission in axons.

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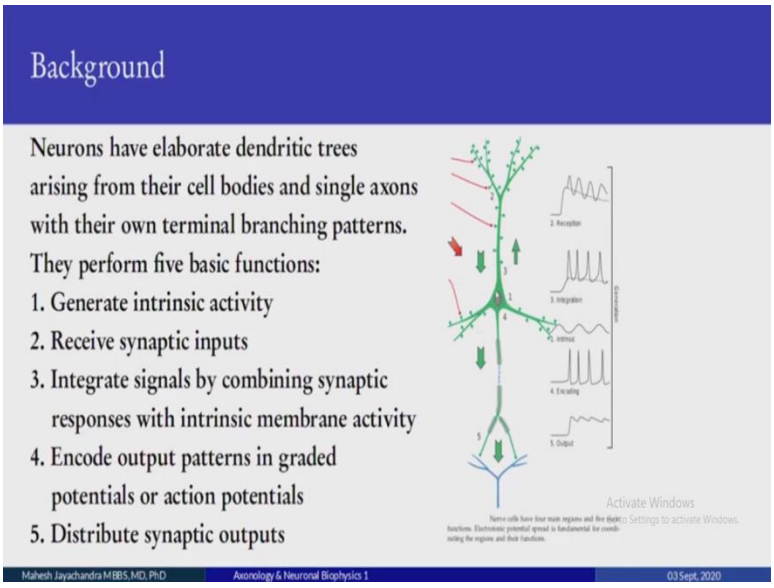

So, some background. So, as we saw in the earlier lecture on the microscopic anatomy of the central nervous system, neurons have elaborate dendritic trees, like regular trees, arising from their cell bodies and single axons with their own terminal branching patterns. So, you have your dendritic trees on top and then you have your axons going down transmitting information and they also have their own trees where they transmit information.

There are five basic functions. One is the neuron generates intrinsic activity. Second, they receive synaptic inputs from other neurons, axons, cells. So, then they integrate all this, they combine the synaptic activity with intrinsic membrane activity, so it is integrating stuff. Then they encode output patterns in the form of graded action potentials or graded electrotonic potentials, sub-threshold potentials. And finally, they distribute the synaptic inputs. So, here you see inputs coming in and they get integrated in the somatic area. Then you have the intrinsic

activity of the cell and then it is encoded and then you have output in the form of an action potential or graded electrotonic potentials.

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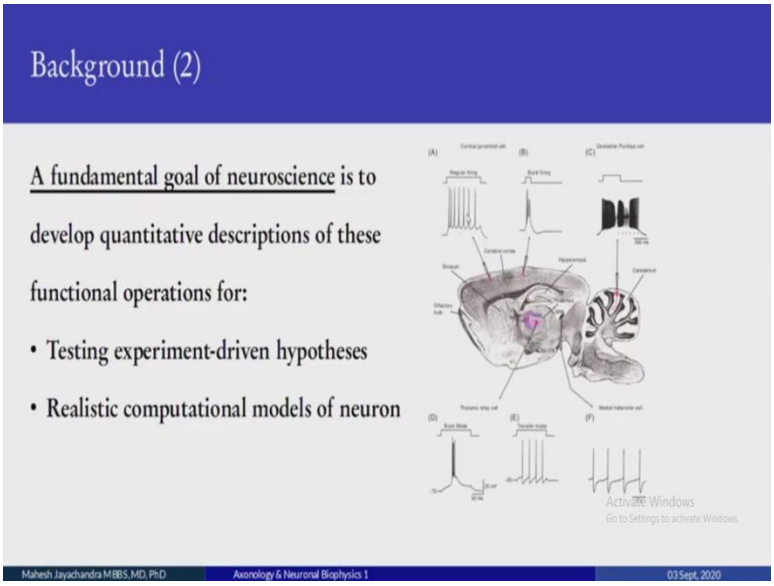

So, a fundamental goal of neuroscience is to develop quantitative descriptions of all these functional operations. One, we can test the experiment-driven hypothesis, and two, we can do realistic computational models of neurons. When I say realistic, this is compared and contrasted with a very simple form of computational depiction where you have a neuron that integrates everything coming inside and produces a spike.

So, these are called spike and integrate neurons, these were earlier ways of modeling neurons. But now we put in details of the dendritic trees, different conductances, the actual shape of the branches and their diameter so that computationally it requires more resources, but it is more realistic.

For example, you have the rat brain on the right and you have electrodes going into different parts of the brain and it shows different kinds of activity of neurons or neuronal cells. So, here you have regular firing, here you have burst firing, then you have intermittent bursts happening in the cerebellum, which we have not talked about much. And in the mid-brain, the thalamus, you have burst modes or fast spikes happening. So, all these different kinds of neuronal activity can all be modeled.

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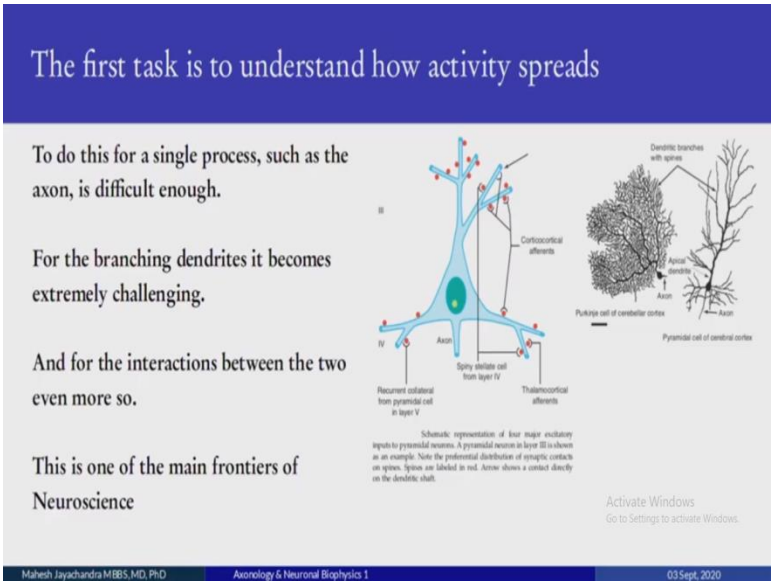

The first task is to understand how the activity spreads. So, to do this for a single process such as an axon is difficult, to begin with. Now, when you have branching dendritic trees, it becomes very complicated and challenging. And then you have interactions between two of these trees, it becomes even more complex, and this is one of the main frontiers of neuro-science how to figure out all the details of what happens in single cells, in cortical columns and neuron (05:00).

So, here you have four possible excitatory inputs that come to the pyramidal cell. This is a cell in layer three of the cortex and you have cortical afferents that are inputs coming from other cortical cells. You have spiny stellate layers cells - these are cells in layer four which give inputs to layer three.

Then you have other inputs coming from layer five. And then you have inputs coming from the thalamus - typical, this is a typical sensory pyramidal cell in layer three. And the cells as mentioned can have very different dendritic trees. This is the dendritic tree of a Purkinje cell which is a pyramidal cell in the cerebella cortex. And this in the cerebral cortex, a pyramidal cell. Very very different, like a banyan tree versus a pine tree.

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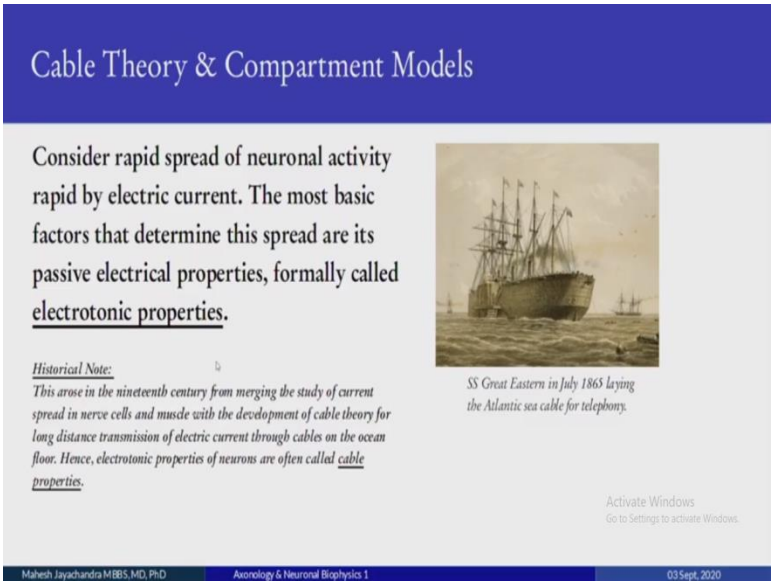

So, to model this, we borrowed an electrical theory from the engineers and this is called cable theory and compartment models. So, in the 19th century, cables were laid between Europe, England, and America to transmit telegraphic signals. Now, a cable is like a co-axial cable. So, you have a central conductor and then there is insulation and then it is surrounded by sea-water. So, the theory of cables can be easily applied to neurons. Very similar maths are involved. And on the right is a famous cabling ship, the Great Eastern. And that laid the first Atlantic sea cable for a telephoning between England and America.

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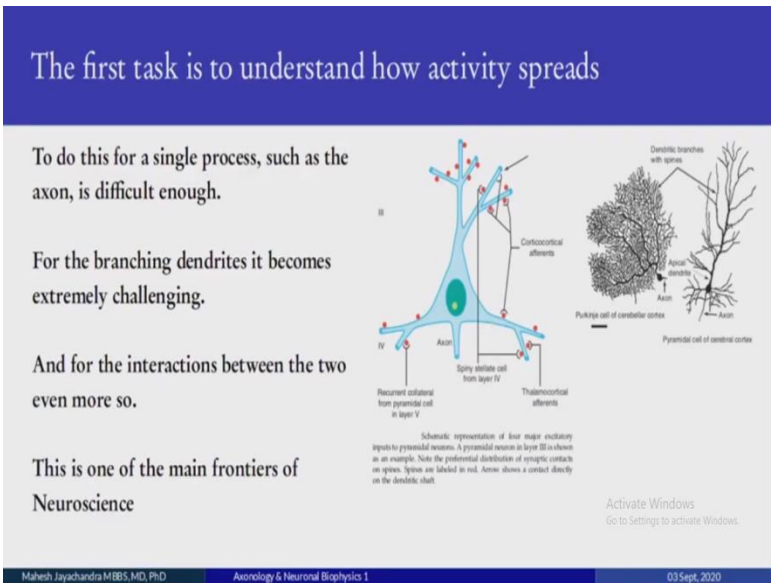

Just consider this tree.

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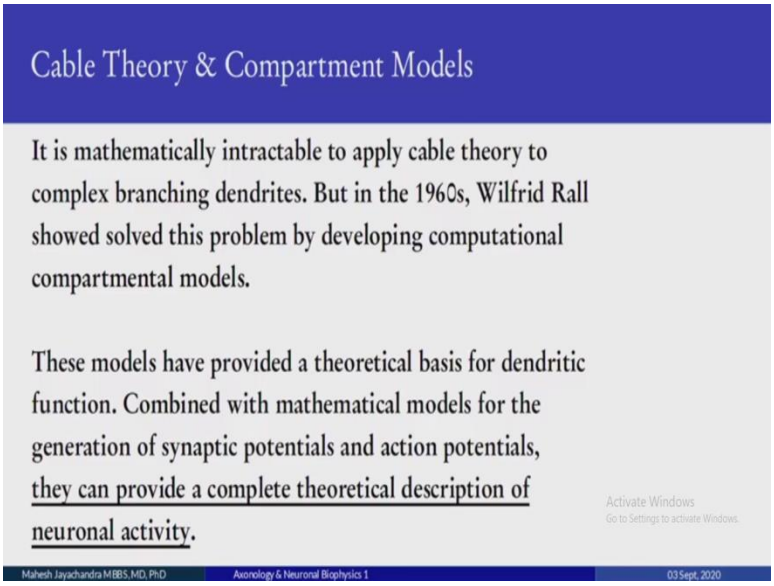

So, it is mathematically very difficult t apply cable theory to complex branching dendrites. But in the 1960s, a great computational neuro-physiologist, Wilfrid Rall from the United States, he solved this problem by developing computational compartmental models. And these models have provided a theoretical basis for dendritic function. So, combined with mathematical models for the generation of synaptic potentials and action potentials, they can provide a complete theoretical description of neuronal activity. And the more data your plug-in, the more realistic it and faithfully follows what we record from the brain.

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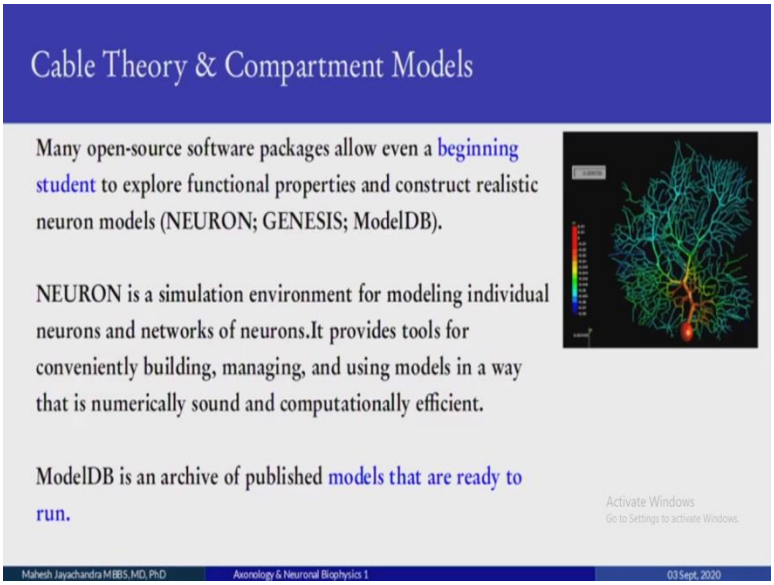

So, many open-source packages allow even a beginning student like you to explore functional properties and construct realistic neuronal models. There is a whole branch of neuroscience, computational neuroscience, where scientists only do this. And for this, you just need a computer and some theoretical background and you can start doing it at home. Of course, the more you model the more computation you need. But for starters, a laptop is more than enough to do this.

So, the program, there are many programs, genesis, neurons, etc which do this. So, you just have to learn one properly. So, I suggest neurons. I use Genesis but I suggest Neuron because there is a lot of documentation available on the internet and Neuron is from Yale, it is a simulation environment for modeling individual neurons and networks.

And it provides tools for building, managing and using models in a numerically sound and computationally efficient manner. ModelDB is an archive of published models. So, you do not have to have to do things from scratch, you can, for example, get a model of a pyramidal cell or a network of neurons from the somatosensory cortex, plug it into your neuron, and then start playing with it, modifying it, as you wish. So, you do not have to do it from scratch.

So, ModelDB is the database where all the neuron models are there. So, Neuron is free, it is an open-source program. You have to download it, go through the tutorials, and then use realistic published data from ModelDB and take off.

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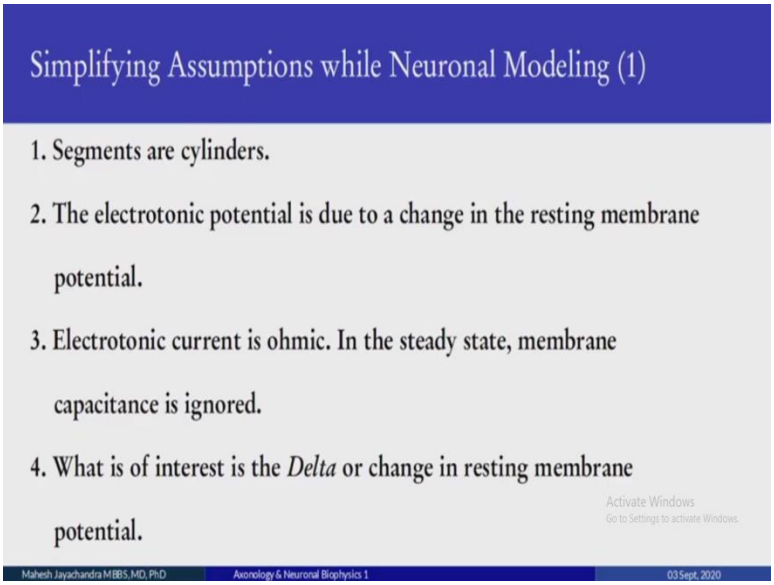

So, now we talk about actually how do you model and what are the assumptions involved. Now, regardless of which modeling software you use, you need to have these facts under your belt. So, first point - segments are cylinders, we treat them as cylinders. So, an axon segment is a cylinder, so the electrotonic potential or the local potential, which spreads, that is called an electrotonic potential as opposed to resting membrane or action potential.

That electrotonic potential is due to a change in the resting membrane potential. Also, it is ohmic, and in the steady-state membrane, capacitance is ignored. What we are interested in is the delta or the change in the resting membrane potential.

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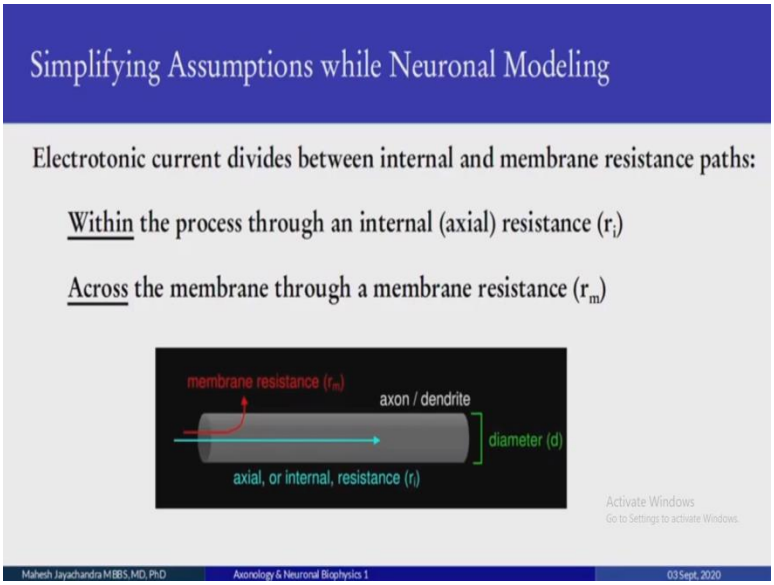

So, we have to make some simplifying assumptions. So, this local spread of current is also called electrotonic current. So, there are two pathways it can take. One is, it can go through the axon and the other is it can go out of the axon via the membrane. So, when it goes through the axon, it encounters resistance and this is internal resistance or r_i. And when it goes through the membrane out, its membrane resistance is r_m. And here, d is the diameter.

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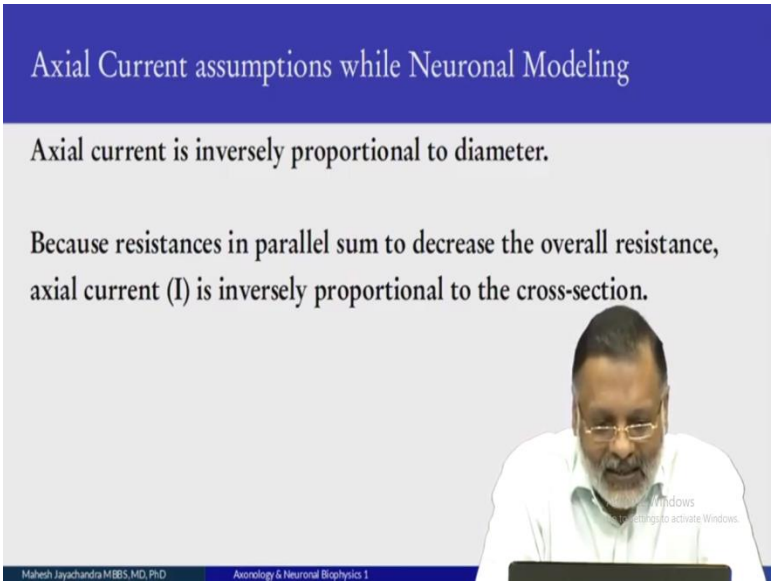

So, with more assumptions, the axial current is inversely proportional to the diameter. So, because the resistance is in parallel sum to decrease the overall resistance, so axial current is inversely proportional to the cross-sectional area. This is straight-forward geometry.

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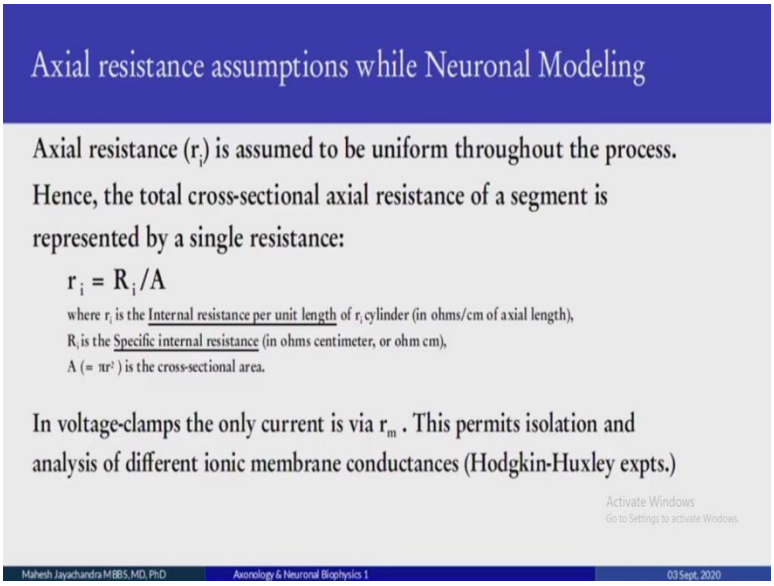

The other thing is axial resistance that is the resistance through the longitudinal axis of the axon, it is assumed to be uniform through its process. Hence, the total cross-sectional axial resistance of a segment is represented by a single resistance. So, $r_i = R_i / A$ which is a specific internal resistance divided by the cross-sectional area.

So, keep in mind that the units for internal resistance are different from the specific internal resistance. So, the units for resistance is in ohms per centimeter of axial length. While r_i is a specific internal resistance, it is ohm centimeter. It is the resistance of a patch. So, A is the cross-sectional area.

So, r_i is ohms per centimeter while R_i is a specific internal resistance ohm centimeter. In voltage-clamps, the only current is via r_m. So, that is going through the membrane. So, this permits the isolation and analysis of different ionic membranes conductances as shown in the Hodgkin–Huxley experiments earlier.

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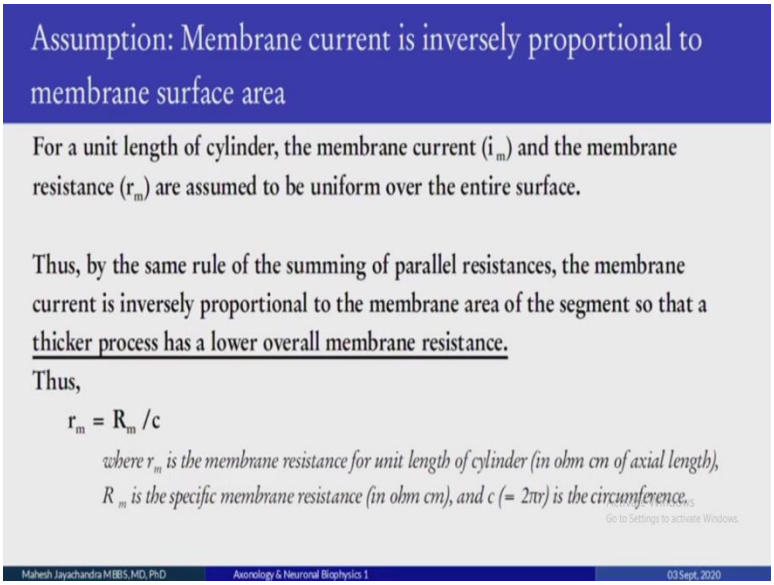

So, membrane current is inversely proportional to the membrane surface area. So, for a unit length of the cylinder, that is the axial cylinder, the membrane current i_m and the membrane resistance r_m they are assumed to be uniform over the entire surface. So, thus, by the same rule of summing parallel resistances, the membrane current is inversely proportional to the membrane area of the segment so that a thicker process has lower overall membrane resistance. Thus,

$r_m = R_m / c$ where R_m is the membrane resistance of a unit length of the cylinder again, ohm centimeter and R_m is a specific membrane resistance and $c = 2\pi r$, the circumference.

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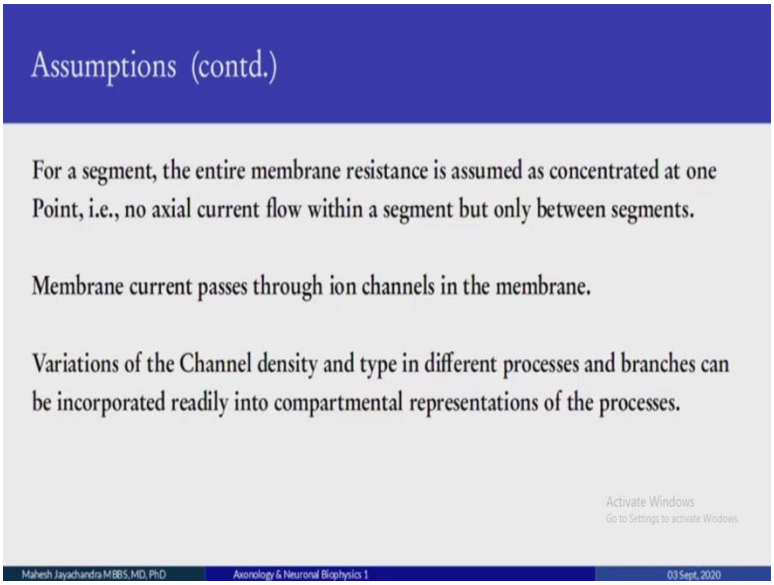

So, for a segment, the entire membrane resistance is assumed as concentrated at one point, that is no axial current flow within a segment but only between segments. Membrane current passes through the ionic channels in the membrane as shown earlier, the sodium channels, the potassium channels, the calcium channels, etc.

So, variations in the channel density and type in different processes and branches can be easily incorporated into the compartment models. So, because when we model, we handle segment by segment, we can change, depending on if it is an initial segment, whether a more sodium channels or in the interneuron areas where less sodium channels. We can handle all these within our segment models.

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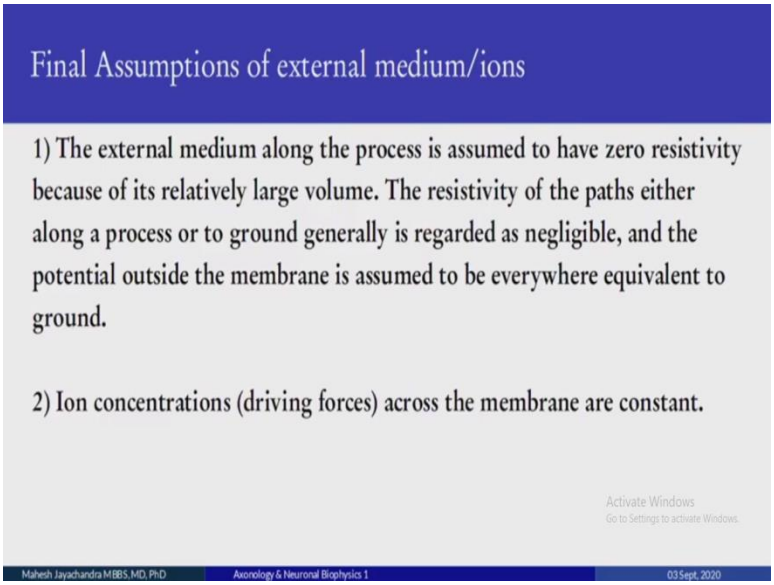

So, the final assumptions are the external mediums, the extracellular fluid fuel, it is assumed to have zero resistance, because of its large volume. And also the resistance of the parts either along a process to the ground or straight to the ground is regarded as negligible. And the potential outside the membrane is assumed to be everywhere equivalent to the ground. We also assume that the ionic concentrations, the driving force, the emf across the membrane are constant.

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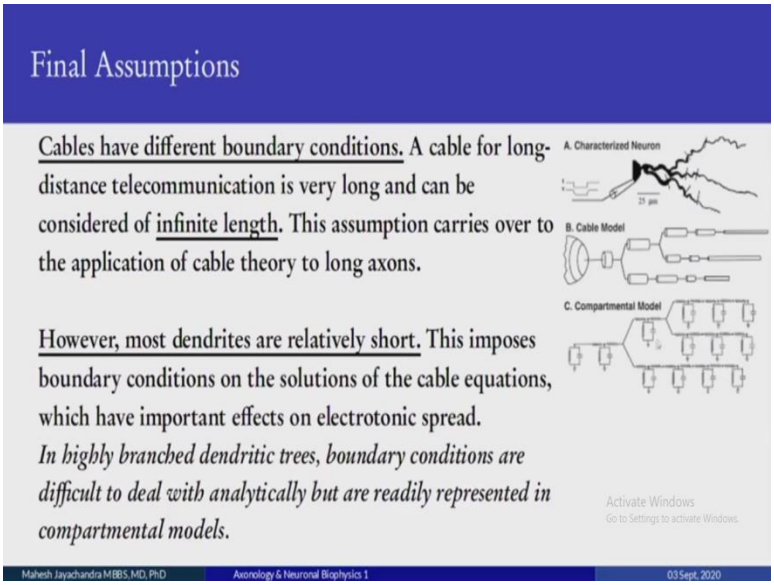

So, cables, a cable can have different boundary conditions. So, it can be infinite boundaries or it can be a particular length, it can be closed or open or partial. So, for long-distance

communication, like a cable in the sea, it is considered of infinite length and these kinds of assumptions carry over to the application of cable theory to long axons.

However, if you look at the dendrites, they are very short. So, this imposes boundary conditions as solutions of cable equations which have important effects on the electrotonic spread. So, suppose it is highly branched, boundary conditions are very difficult to deal with analytically like you see a neuron over here.

It is very very difficult to handle this on a computer. But if you use compartment models and divide this into, first use cable models, divide into different cables of different diameters and each of them is a particular compartment with different resistance and capacitances. Then it is tractable, this problem.

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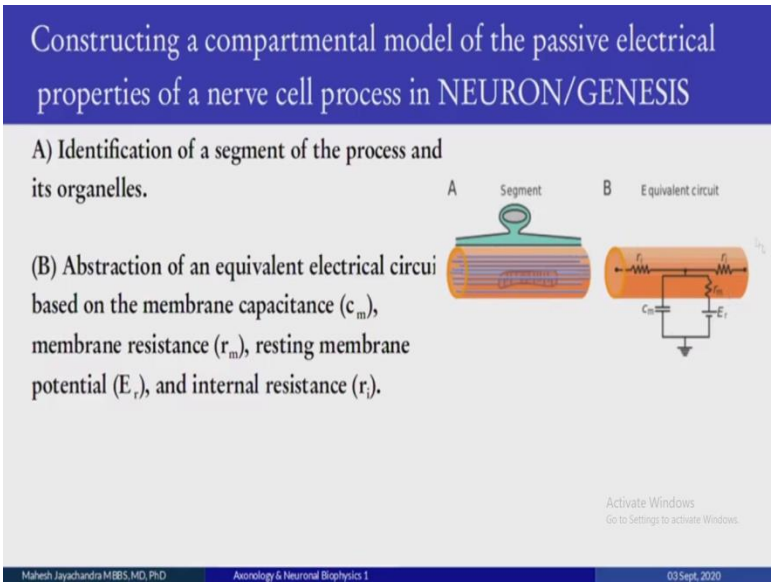

So, how do you do it? How do you construct a compartment model of passive electrical properties of a nerve cell either Neuron or Genesis? So, there are discreet steps. The first step is, you identify which part of the axon you want to model, which is the segment, what is in there, stuff. Based on this, you abstract this into an electrical equivalent circuit. So, you have c_m, which is the membrane capacitance. You have internal resistance, r_i and then you have, of course, the resting membrane potential, here it is E_r. And then you also have r m. So, we abstract this whole thing into this and it works pretty well, surprisingly.

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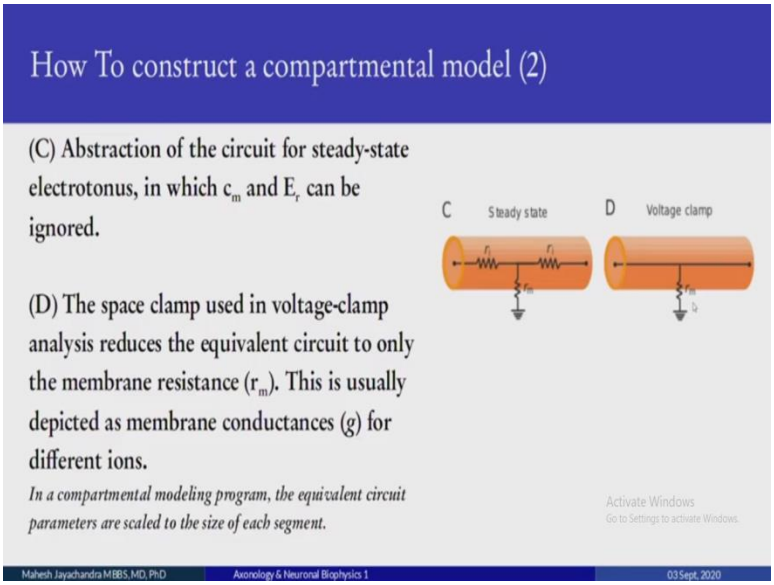

So, suppose you want to do a study state spread. So, if it is a steady-state spread, you can ignore the capacitance and the electromotive force because it is a steady-state spread. And if you use the voltage clamp, then even it can be further reduced to only the membrane resistance because everything else is held constant. And instead of r_m, you call it g because you call it conductance which is the inverse of resistance.

And finally, the equivalent circuit parameters can be scaled to the size of each segment. One segment may be big so you can scale that and the next segment may be small so we can adjust to the size.

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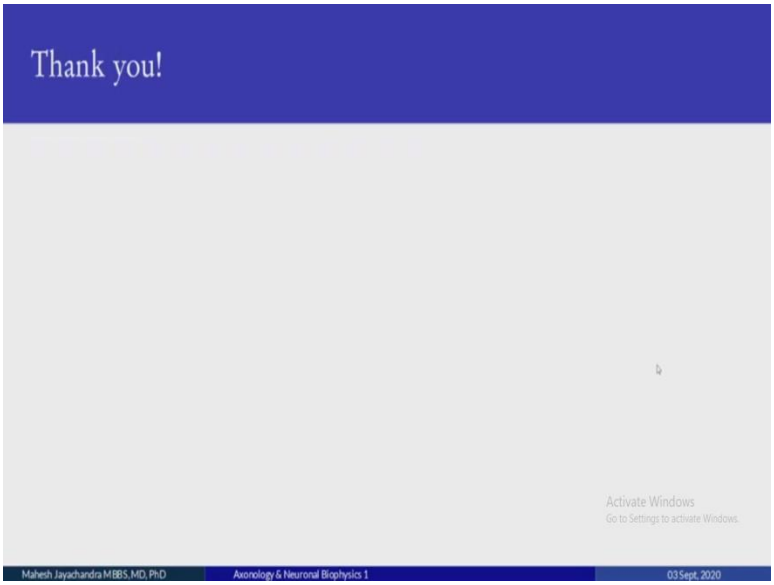

So, thank you and in the next session, we will get into details of neuronal biophysics.