Bioelectricity
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Lecture - 6

Welcome back to the NPTEL lecture series on Bioelectricity. So as of now, we have finished five lectures three of the introductory sections and two for the annual electricity. So, talking about the annual electricity, as of now we talked about the structure of the membrane, the positions of the membrane proteins, which can be a ion channel could be other receptors and other functional proteins on the membrane. We talked about the position on the glycol proteins. From there, we talked about the Nernst equations, where basically we described how charges which are ionic charges which present on the either side of the membrane inside and outside. How there is a balance being established between the chemical gradient and the electrical gradient. There should be a electrical neutrality as well as there should be a concentration dependant neutrality. So, what is the governing dynamics for those kinds of situations?

So, what I will do from here is this, we will be move to the ionic channels and action potentials. So initially, I thought that I will be starting with the ionic channels and then I will come to the action potentials, but historically if we look at it that is the discovery of action potential, which eventually pace way for the discovery of the ion channels. When action potential was discovered, there was absolutely no idea about the presence of ion channels, this is back in 1940s during the time of ((Refer Time: 02:08)). They came up with the (( )) formalism for which they were award with the Nobel prize. At that time, there was hardly any idea because protein chemistry was just kind of starting people were not really very clear about the membrane structure and what hutch kane and hughs lee precisely mentioned in there seminal manuscript is that these are basically some kind of ports through which ions are moving inside the cell or exiting from the cell. And assuming that those are ports, they did the whole formalism which is famously known as hutch kane hughs lee formalism.

After that ion channels were discovered nineteen seventies and eighties tremendous progress in the field by the discovery of batch clamp electrophysiology and that credit goes to Irvin Nihar and Bird Sackman the two german physiologists, biophysists who

discovered a technique by which you could study the dynamics or flow of ions through ion channels or through a port. And that of course, for that discovery they were awarded a Nobel prize. And soon after that, there was a huge rush to understanding ionic channels, and after that the molecular valency techniques were really coming in the forefront with the discovery of PCR, and other molecular valency techniques and sequencing new mah. It was new mar who did the first sequencing of different channels of the I think it is the sodium of channels likewise.

And then came 1997 that was the time when the first channel structure was deciphered that was ((Refer Time: 04:26)) and in between there was one more structure which was discovered before that, but that was not purely a channel that is the battery reduction membrane protein. So, if you look at the history of the ion channels and the action potentials and bioelectrical phenomena across animal kingdom, you will see there is always a gap and there is quantum jump and there is a gap and there is a quantum jump. And the field has progressively developed for the last century nineteen hundreds; it is started with or even might before that is started with intracellular, extracellular recording electrons.

People had absolutely no idea about ion channels or anything or even membrane as were a fact then came as I was telling you nineteen forties and nineteen thirties and nineteen, I should say thirties and forties and hutch kane and hughs lee formalism. Then with the discovery of action potentials, then came the discovery of batch clamp, and now the whole trust area is on understanding membrane protein structures especially the ion channels. It is a very very tough job. So, once we will be talking about the techniques of measurement I will tell you why it is so tough; and till date, we hardly have hardly have one may be for which we have at least one angstrom resolution or slightly more than one extra resolution image. So, most of these ion channels are still people are hunting trying to hunt down the exact structure at the easy crystallography techniques using cryogen techniques cryo electron microscopic techniques and several other techniques.

So, what I will do instead of moving to the ion channels first, I will give you the feel about action potentials, I will just go with historical prospective. So, action potential is observed in all the excitable cells of the body, and what are the excitable cells of the body, and why we call them excitable cell first. So, the excitable cells of the body differs from the other cell types in term of the presence of high proportion of voltage gated

sodium potassium channels, and it is the shared numbers which differs them from the other cell type which do not have that. And it is developmentally programmed that some specific cell types in our body have this interesting structural features, as they have a lot more significantly high number of voltage gated sodium, potassium, calcium channels and that makes them very I should susceptible or that give them to respond to any kind of signal from outside.

So, what are those cells, which are called excitable cells of the body. So, there are three kind of excitable cells in our body - the nerve cells, the muscle cells or muscle tissue, and the neuroendocrine cells. Nerve cells constitute that whole nervous system pretty much all the neurons in the nervous system, their functional hallmark is that they are electrically active. Having said this let me highlight one point, which many time we got miss we see there is currently a lot of progress in developing neurons from skin cells developing neurons from stem cells. So, let me point out here neuron can only be called a neuron when it is functionally active in terms of its expression of voltage gated sodium potassium and other ion channels. And it should be able to functionally shoot an action potential. If it is not an excitable electrically active serve in spite of the fact it expresses all different kind of marker or proteins, it cannot be called as excitable cells or a neuron or any other excitable cells.

So, this is something I wish to very pin point, because many people get confused that all there are neuron and markers; that means, it a neuron. Essentially, unless they are functionally a neuron, you really cannot call them a neuron. It is just another cell which has expression of some of the characteristic of a neuron, but you cannot called them a neuron, so nervous system, the major excitable tissue of the body. Muscular system, muscle system which includes your skeleton muscle, the bulk of your body which is electrically excitable. You have cardiac, which is electrically excitable all your life, the very moment it loses its electrical excitability most likely you are in deep trouble. Third the smooth muscles, which lines your g i tract. These are the three muscle component excitable muscle component of the body, which has the ability to shoot an action potential.

Then there is another specialized group of cells up in the deeper regions of the brain, those are called neuro endocrine cells. These neuro endocrine cells are the one which has dual functions they have a endocrine functions as well as a neuronal functions. So, these

cell essentially receives neuronal signals and shoot an action potentials and thereby secrete the hormones or pro hormones, so these cells are also excitable cells. So, these all these three cells or all these three tissues share the common hallmark of shooting action potentials and more specialized are the ones which are muscle they have ability to translate that electrical signals into mechanical signal using excitation contraction coupling a barraters. We will come to all those things which is a hallmark of cardiac cells cardiac tissues and a skeleton cell.

Whereas, all the different kind of neurons, which includes a motor neuron, sensor neurons, higher brain neurons they have different pattern of action potentials and that what distinguishes them from one to another. There is another supporting cell within a nervous system called glean cells, though they are part of the nervous system, but they do not shoot an action potential. They do have some percentage of voltage gated sodium channels, but not in high numbers. They shoot something like action potentials, but it never overshoots you. So, the only cells in the nervous system, a nervous tissue which shoots action potential are the neuron this is another thing which need to be understood very clearly.

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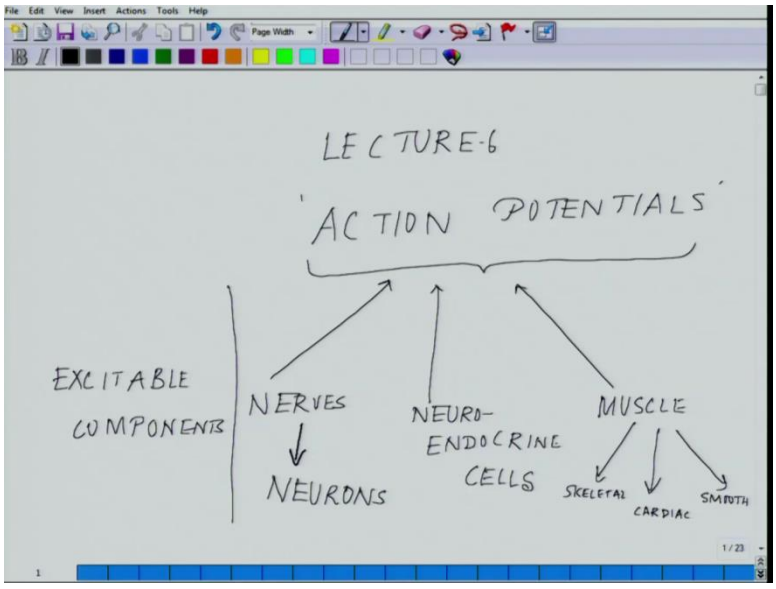

So, enumerating them in the slide, so we are into lecture 6 now. So the action potential, so the excitable components, nerves and here mostly the neurons, which are involved in it, and the other neuro endocrine cells and then you have the muscle. And within the

muscle, you have skeleton, cardiac and we have smooth. Within cardiac, if I had to do another classification on that within the cardiac tissue, there are again two kinds of cells the pacemaker cells and…

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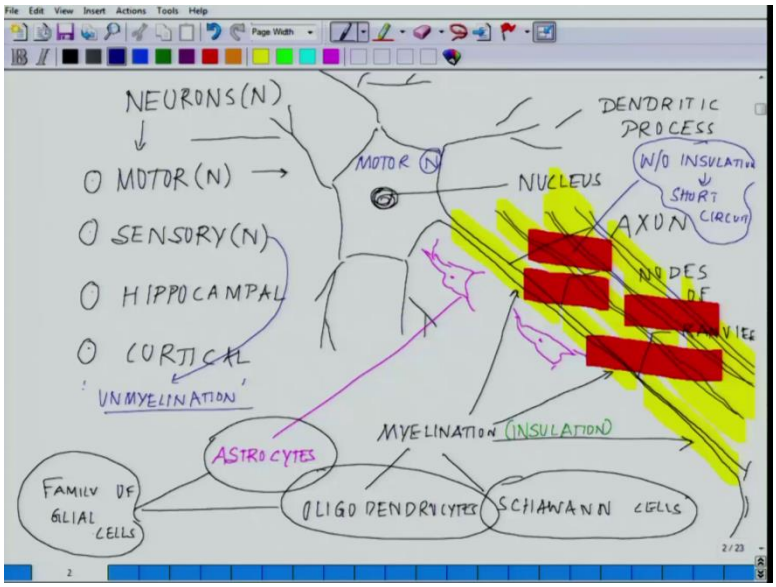

So, let us see the examples of these excitable tissues. So, the neurons, the neurons you have motor neurons, I will just putting N for neurons, sensory neurons, you have hippo campal, cortical. And here it is what mentioning that these action potential and the pattern of action potentials shoot while different kind of cells and the kind of competition they do is function of their morphology too. So, if you look at the morphology of these different neurons as such talking about the motor neurons, these are the largest neuron in our body, and they are the one which are formed earliest among all of them.

And if you look at the morphology, it is something like this, huge cell body like this, and as a long long long process - the hexagonal process. Here is the nucleus and these are the dendritic processes likewise. So, these are the dendrites dendritic process. This is axon, here is the nucleus and this axon could be either insulated or non-insulated. If it is a insulated, it is called milinated. So, the insulation is just like you see this cables on which there is a plastic covering almost exactly similar to that here something like this, you have something like this. So, there is a slight discontinuity you will observe out here, you see out here, out here, these are called nodes of Ranviee, and these are the myelination sheet. And these myelination sheets is either, they are myelinated by a oligo dendrocytes

or they are myelinated by schawann cells. These are the two myelinating cells and these are the ones which I was trying to tell you these are the supporting cells or the glial cells apart from it there is two more glial cells out there which is the astrocytes. So, these are the myelination ones, which are involved in myelination and apart from it there are supporting cells which are kind of you know present in the proximity of these neurons likewise all over the place and which are called astrocytes.

So, here it is what mentioning that these ones, these ones, these ones are the family of glial cells, this is the family of glial cells, which are present. These are supporting cells and essentially what you see this myelination, which I am just for your understanding putting another word here is called insulation. The idea is that if simultaneously there is another neuron which is moving like this, say for example, in blue I am showing another neuron. Unless these two cables, another neuron another axon moving and that is how exactly the real life it is they are like that, and unless there is myelination or there is separation by this insulator, there will be enormous short circuit taking place out here. So, this is short circuiting what I am trying you show in red.

So, without insulation, there will be a short circuit. These are some of the basic understanding, which is very essential to understand how these are propagated. Yet there are so this is what we talked about a motor neuron. Yet there are cells in the sensory neurons which are unmyelinated, they have no wrapping. The way I showed the wrapping out here that is partly related to the fact that there are certain neuron, where you want the signal to be lost and those neurons do not have any myelination. So, this is another structural features which helps them in the electrical conduction.

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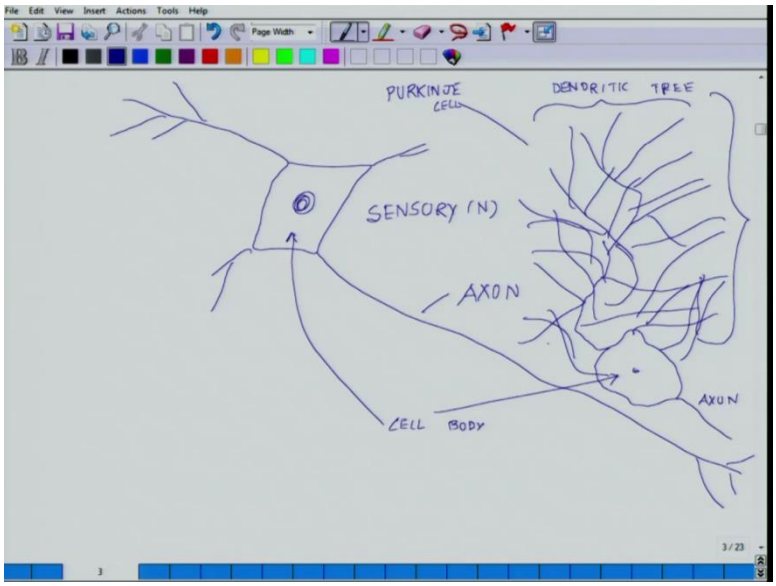

Many of these cells look like this. Some of these sensory neurons are like this. They could be unipolar, they could be bipolar. So, here is the axon, they have a long dendrite. So, this is the sensory neuron, if there are cells which are very dense, dendritic armor something like this. Cell is a smaller than their dendritic harbor something like this. If it has an axon, here is axon, here is the dendritic tree, and here is the cell body, here the cell body out here. So, these are some of the cells which are called these are the cells which are present in higher center of the brain called purkinje or the hallmark is there is enormous amount of dendritic armorisation along it. And the way it works is this, the electrical signal first of all reaches the dendrite from the dendrite there is an summation of the electrical signals then it travels along the axon and communicated to the next to the dendrite of the next neuron. And likewise the information flows in one direction and we will talk about why the information cannot flow in the reverse direction, there is some reasons.

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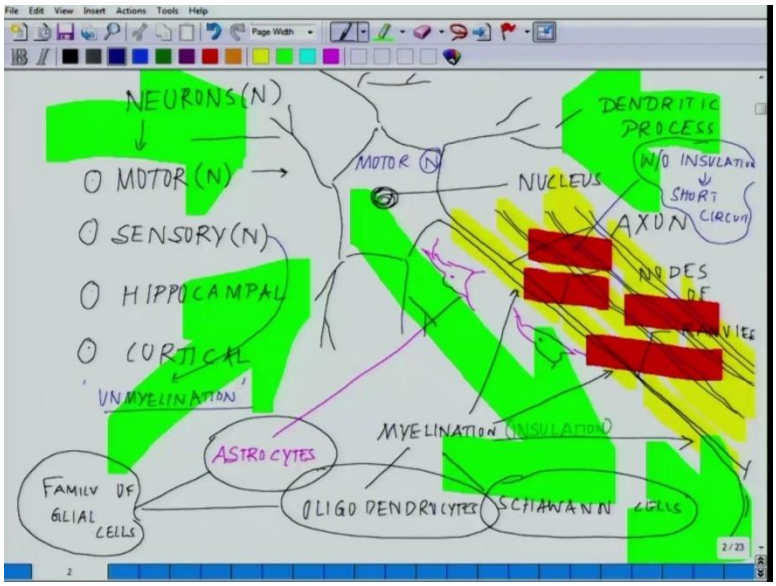

So, the information transfer is pretty much like this. So, the information are coming to the different dendrites likewise, and this information is travelling like this, why is it so. And here it is so what help in this is again to do with the ion channels how it is happening and there is a special and temporal summation. So, what I meant by that this is something at this stage itself we need to highlight.

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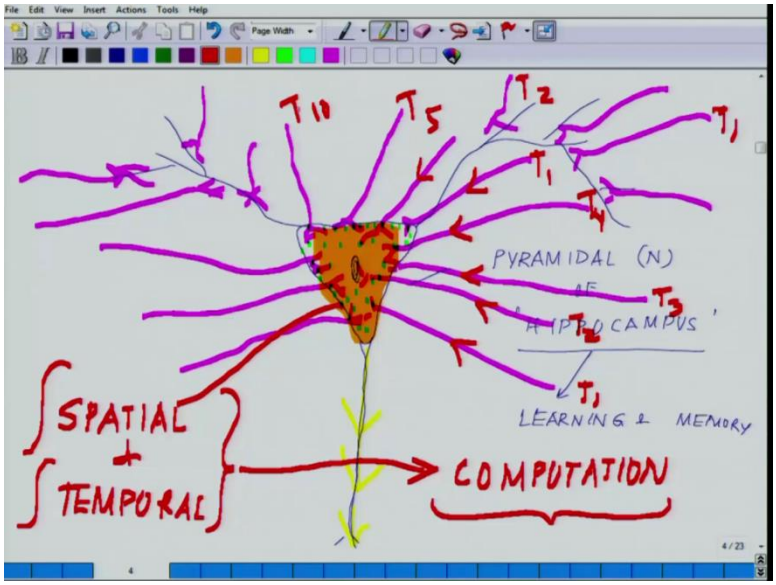

So, for example, let me draw a pyramidal neuron. So, I took this purkinje cells, purkinje neurons and this is a sensory. Now I drew a hippocampus neuron which is mostly the cell

body is more like a pyramidal shape, something like this. We have a dendritic tree which is and here is the axon which is moving along. So, these are the classic pyramidal neuron of hippocampus or the center for learning and memory. So, what I meant by special and temporal summation. So, within the certain numbers of system, each one of these neurons receives at one point of time, they are connected physically connected with ten thousand other connections. So, even if we at one point of time, they receive hundreds signals or two hundred signals which they do, it is an enormous amount of calculation. So, what I meant by this ten thousands, so it is something like this.

So, imagine these are the connections, these are the different sources from different other sources the axons are form synapses that form synapses on it. These are ((Refer Time: 24:48)) on the other neuron, which are making connection on the body of it from different other sources they are making connections. So, this is an imaginary drawing I wanted to show you. So, imagine at one point of time, there are such ten thousands physical connections on neuron, this is kind of a lower side. There are ten thousands connections means there are ten thousand synapses. So imagine that at the one point, it can receive ten thousands such signals with slight delay of time or at the same spot.

So, at this zone the amount of calculation it needs to do is enormous and the summation of this calculation what you see is transmitted along this. So, what essentially is happening out there is at this zone there is two sets of things which are happening. There is an spatial and there is an temporal computation, spatial and temporal computation. So, all the different signal which are reaching like this. They may be at time T 1 at time T 2 time T 3 time T 4 time T 1 time T 2 time T 5 time T 10 likewise with little staggering.

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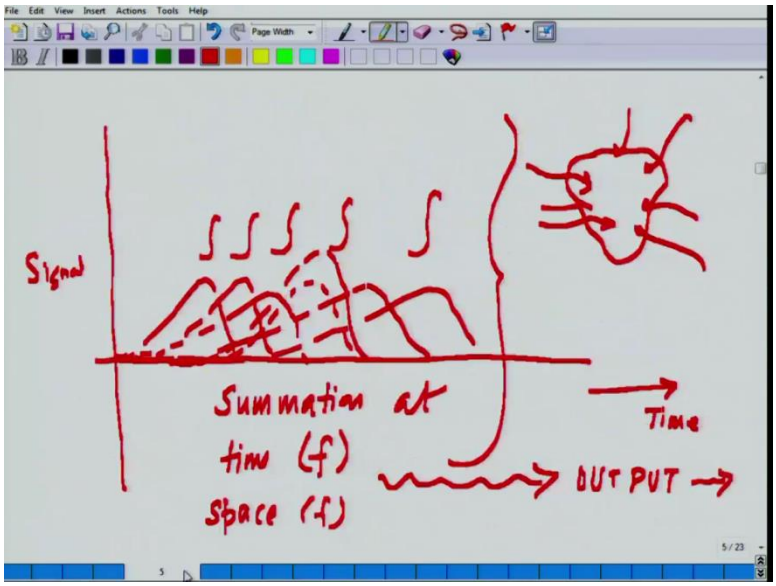

So, the ((Refer Time: 26:59)) imagine and if is just an temporal thing I am drawing. So, here comes the time axis, and here comes the signal. So, here is a signal reaching, followed by another signal coming, followed by another signal coming, followed by another signal coming, and simultaneously which is already come there, another signal before this likewise. So, there is a continues addition of these signals taking place and this hatch zone where you are seeing signal one is kind of you know of the previous one. These are the one also where the part of that signal is added to the previous signal and simultaneously if this with respect to the time, there is on the space. Say for example, if this is a cell body, one is added from here, one it added from here, one is added from here at the same time say for example, so overall what is happening?

There is an summation at time function and space function. And the output what you see is the one which is carried by the I was trying to show you on this picture carried by the axon now. And this is the level on complexity with which our signal is being processed which even the most simple chip cannot think of. It is probably the final frontier of human endeavor in terms of understanding the neural code, and all this codes all this coding lies in that seminal discovery. The last in the middle half way through the last century by hutch kane and hughs lee the action potentials, it is those which coded.

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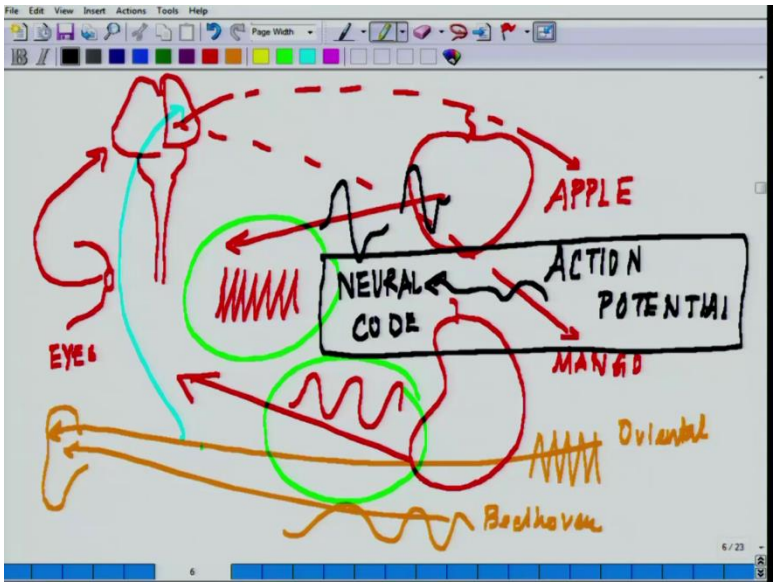

So, if tried to understand this see for example, I show you for example, an apple like. This is an apple and I show you say for example, mango what makes and apple and apple and what makes an mango and mango and your eyes are looking at it. So, these are the eyes, what distinguishes. So, stored information which is stored has a specific pattern whereas the information which is stored has a different pattern, and these pattern from here is are getting stored in your brain, as where you call something an apple and something a mango. So, in other word, what I am trying to highlight, if I know this signal and if I know this signal then technically I can feel that signal to make any blind person whose eyes are not functional to see an apple, when this person is actually not seeing an apple or when this person is actually not seeing a mango.

Same way by the same token comes the other side of the story which we say for an example hearing. So, you are hearing say for example, you are hearing something like Beethoven or you are hearing something like say oriental, music and different trends are coming and here different trends are coming. So, technically if these signals are put in the visual area which is processed by visualized transmission, we would be able see the music, this is something that you imagine. All this things are happening by that simple most ordinary event which you call the action potentials. All the cruxlize in action potential and the next frontier wave we are heading is basically the neural code.

So, with this background what I needed two kind of highlight to I will move on. So, I one more thing which I forgot here which I realize because I told you in the beginning, I will show you that. So, regarding the cardiac cells I forgot, I will come back, I told you that there are two different classifications. As I start the cardiac, I will tell you what are the different cell type of course, we have highlighted the about the neurons. But I have not highlighted about the what are the different cell types in the cardiac cells which shoots action potentials this is something I have missed as of now, but we will come back with that. So, in the light of this, what I have taught you just now. So, understanding action potential is the most critical thing unless you understand this basic phenomena, it is really tough to appreciate what are the electrical events which are taking place.

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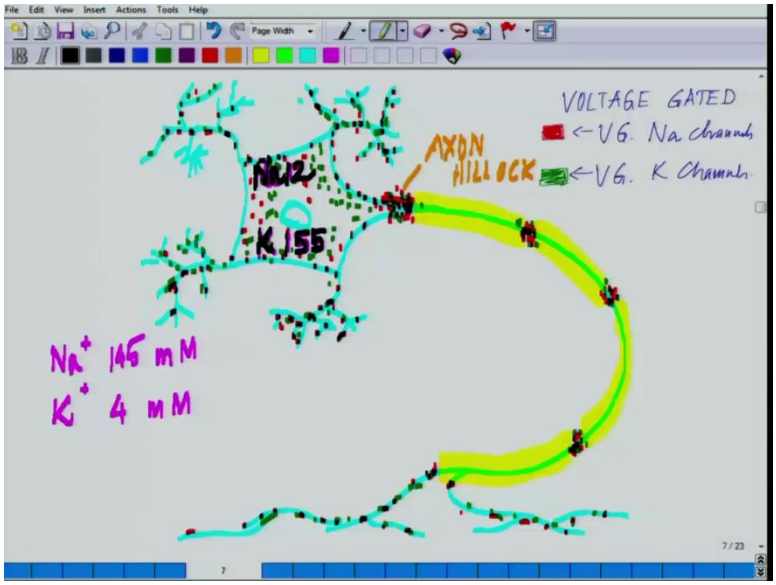

So, now, let us try to understand action potentials. So, for example, now here you have a cell sitting like this, and this is the axon and here are the dendritic trees, dendritic phase and dendritic armorisation, dendritic spines and all that that is the nucleus. Now I told you that these cells are rich in voltage gated, I will just abbreviate as an VG, voltage gated sodium channels and voltage gated potassium channels. Interestingly, the voltage gated represent this voltage gated sodium channel as in red, I will represent in red color and voltage gated potassium channels will be represented by green color. So, interestingly it has been observed that voltage gated sodium channels are concentrated at specific parts, initially when the neuron is forming they are scattered over the place, then

they migrated at specific spots and it has been observed for the cells which are myelinated we represent the cell of this kind which is a myelinated cells.

So, voltage gated sodium channel population is fairly high in this zone, fairly high here, again fairly high here, these are the nodes where they are high, and rest of the places they are scattered around like this. So, this anatomical understanding is very essential to appreciate. If you look at these zones, they are fairly fairly dense, where is the voltage gated potassium channels follows very similar trends, they are also scattered around all over the place, and they are fairly high in the cell body. And I will try to highlight these cells depending on the situations, they aggregate and they again dispersed and this is the zone which is called your axon hillock. So, now I have been drawn this.

So, we know outside the cell in this your sodium concentration is fairly high is around hundred and fifty mille molar. Whereas the potassium is fairly low which is around ten milli molar of these things are known to us. Even actually it is less than ten mille molar, it is around I think four mille molar and this is again from booked to booked in varies 145 milli molar. Whereas, inside we know sodium is 12 milli molar and your potassium is 155 milli molar; let me do it in black, so that you can read it properly. This is your sodium, this is your potassium. So, looking at the shared numbers, we can understand that if there is sodium, which is twelve inside and which is hundred and fifty five outside then most likelihood the sodium from outside will try to rush inside the cell, but this is being continuously prevented, this is not being allowed. Whereas, if you look at the potassium, which is around 144 or 155 inside and 4 outside, so all likelihood potassium will try to move from inside to outside.

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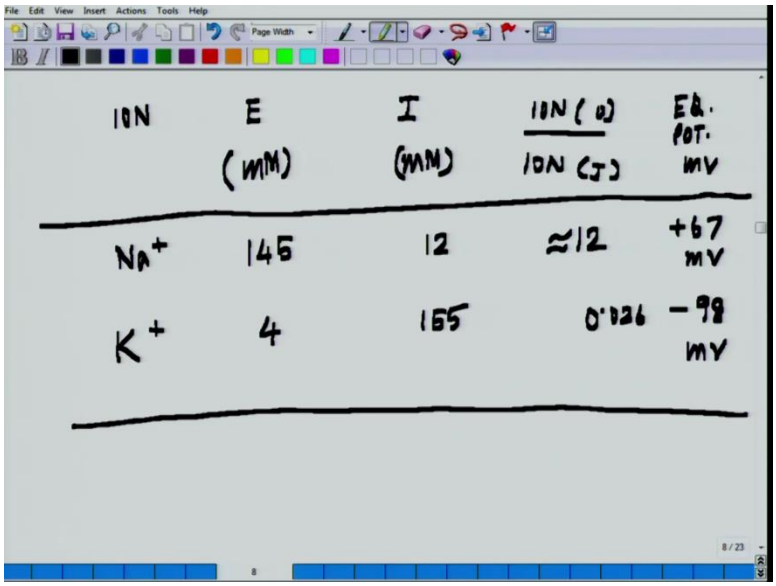

So, let do something, let do the calculation based on the Nernst equations, if you guys remember I was telling you that you know based on that you can do this simple calculation. This is extracellular, this is the intracellular and the ratio ion outside upon ion inside. And you just want do for two ions sodium and potassium; sodium outside is 145 and inside it is around 12, and this is all in mille molar, this is in mille molar. Whereas, potassium in 4 and outside it is 155. And if you see the ratio of these two, so this would be coming approximately twelve, whereas potassium will be coming around 0.026. And if you calculate the equilibrium potential in milli volt, these values will come for sodium it will be positive 67 milli volt, whereas for potassium it is minus 98 milli volt. Now this minus 98milli volt says you something, what it says?

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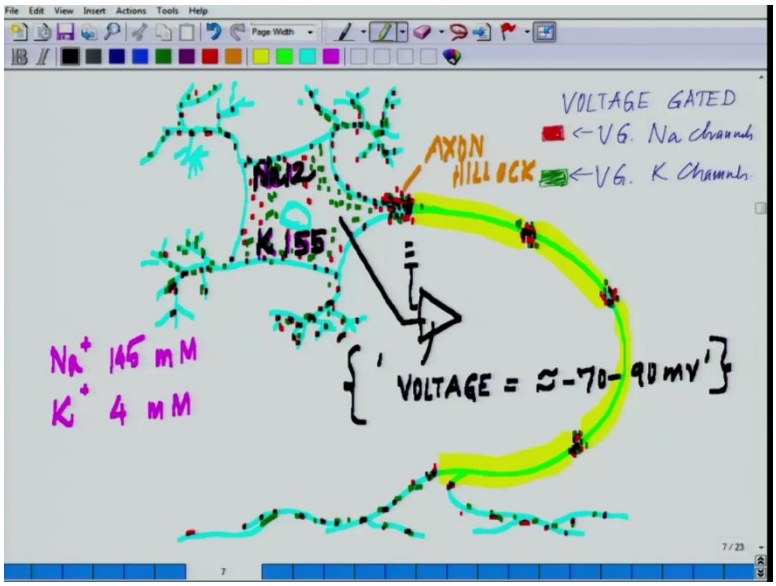

If you see this diagram, the diagram before out here, if you put an electrode outside the cell and inside for example, I have a electrode like this and have another electrode. So, I have the measuring device out here something like this, and I have another electrode outside and I am trying to measure the voltage. So, if I measure the voltage with inside with respect to outside, we see it approximately 70 to 90 milli volt. So, inside the cell, it is more negative as compared to outside, and the membrane potential is between minus 70 and minus 90 depending on the cell type.

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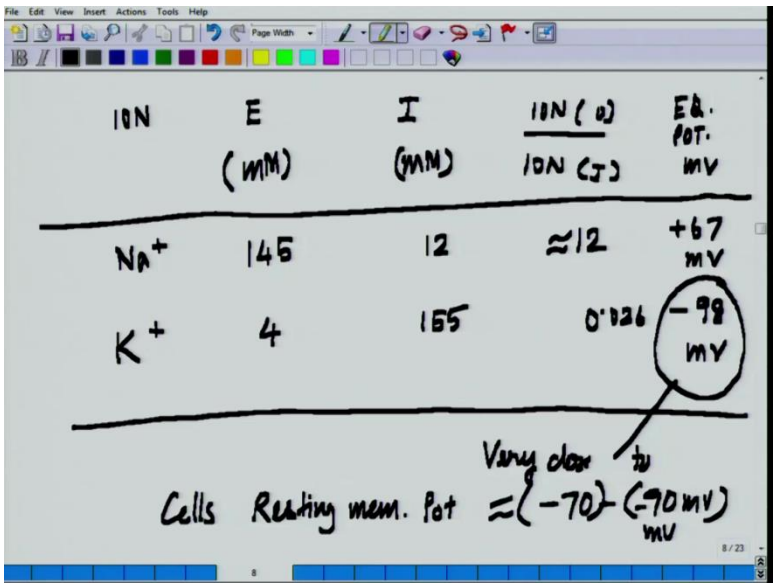

So, if you look at this value in the light of this, you will see that value of potassium equilibrium potential is very close to cells resting membrane potential, which is around minus 70 to minus 90-milli volt why is it so?

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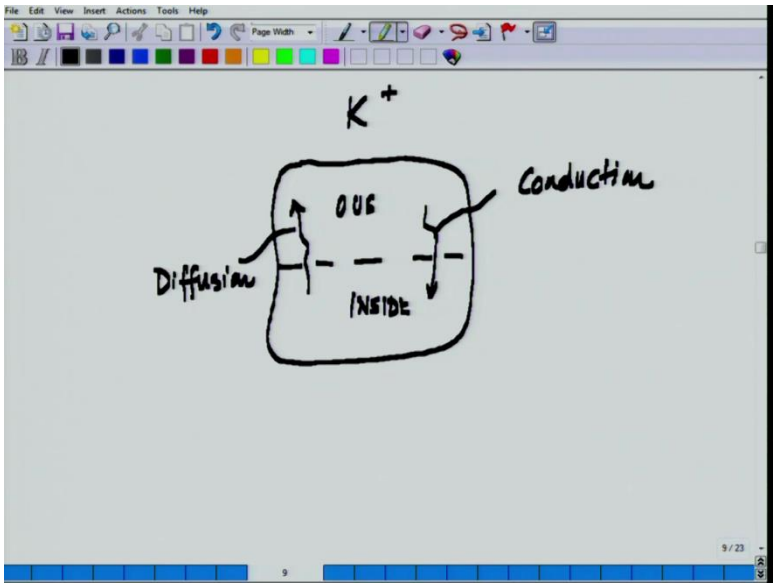

The first question, this is so because potassium is fairly leaking and as a matter of fact across the membrane, if we try to draw something like this if this is the situation of the potassium, and this is say for example outside and this is the semi permeable membrane and this is inside the cell. Then you will see potassium is kind of you know always the potassium is, there is the slight degree of diffusion which takes place outside the cell, and of course, the entry is because of the conduction. So, always there is potassium which diffuses out.

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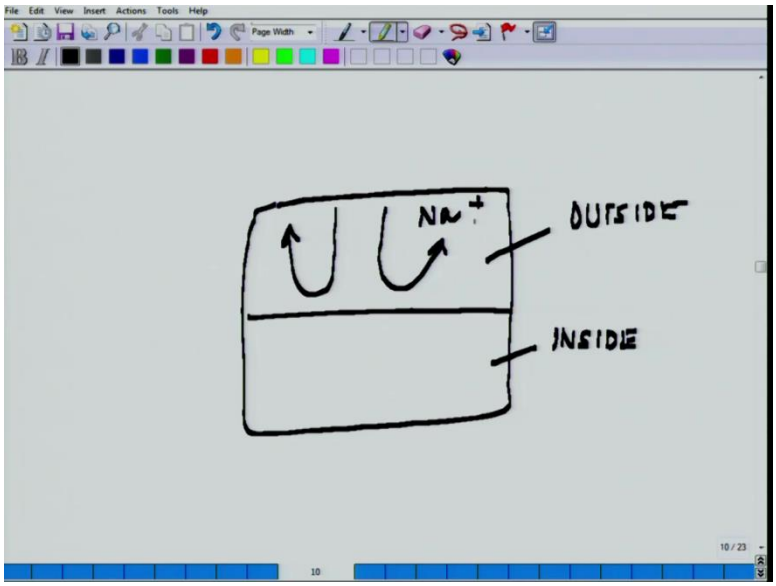

Whereas, in the case of sodium if you see if I again draw the same thing for sodium, so this is inside the cell and this is outside the cell. If you look at it, sodium could never get an entry neither it leaks out nor it moves in. So, sodium that is why if you look at it these value if you compare. So, if you compare these two value minus 98 and these, they are fairly close. They are close, because this reason that sodium diffuses out it is much more leaky actually as compared to sodium, potassium is leaky; whereas, sodium very tightly it cannot really passed through there is hardly any way that sodium can pass through unless otherwise there is specific channels which opens up an allows the entry of sodium inside the cell. So, this is the the hallmark of beginning of understanding of action potential. So, essentially what is needed is that somewhere other in order to create disturbance in this structure.

So, I go back in order to create the disturbance in this structure, you have to have some way by which these channels what you see out here these channels have to be opened. Without opening these channels, you cannot create any kind of movement in them. They will remain static, this is the very basic fundamental understanding. All this background is needed to understand action potential. You do not understand this and the rest would not make sense. What I will do, I close in here, and in the next class we will see when these channels opens what it leads to and the series of events which takes place and will explain the whole action potential in that process. Then will one of the propagation and

we will come back to the structure of the ion channels and how those structures are helping in this kind of conduction processes.

Thanks a lot.