Neural Science for Engineers
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Lecture - 15
Analog and Digital Processing in the Neuron – II

Hi. So, in our previous classes, we have discussed something about how analog and digital in the physical terms which we understand have been replicated in neurological terms for thousands of years back.

And there seems to be some purpose in the reason of doing so; maybe the biological system did have an understanding of the necessity of keeping binary architecture in information transfer, which is why all axons transfer information in terms of action potentials which are yes or no and 0 1 equivalence.

So, you have a zero and there is no signal and one in which there is a single signal, which in itself does not have any attribute other than its timing; timing in the sense that you can have a phase component attached with the onset of the signal. So, when we look at trains of signals within the axon.

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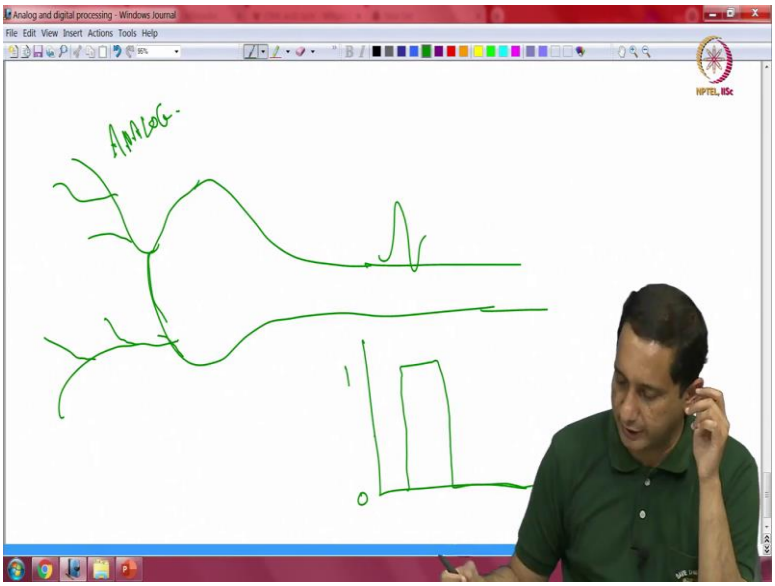

So, we know that you can have an action potential and then that produces a signal. So, you have 0 and if you have a 1, you have a single signal at this point and then there is no signal for extended duration, meaning until the next stimulus comes through.

So, this is a very distinct representation of how digital or the binary system of implementation has been looked upon by evolution and maybe the nervous system for whatever particular reason. But having said that for fans of analog computing, it is heartening to suggest that the rest of the neuron, which is the dendrites does not like this method of computation and is completely analog.

Now, it should not be thought of that the neuron is just a device which connects the analog part of computing to the digital part of computing. So, we will look at it in a little more detail; because I felt that some concepts may be misunderstood, because these are not conventionally taught in medical curriculum or biological curriculum.

Because there is no need to, meaning in medicine or biology in general we describe a process; we describe the attributes of the process, we describe the functions of the process and the pathologies where there are defects in the system, diseases in the system.

But if you look at it from a pure computing standpoint, we like to complete; one important thing which I had highlighted earlier is that you should not think of a neuron as something in which you know stimuli impinge from random places, no it just does not happen it. So, every neuron has thousands or maybe sometimes lakhs of synapses and it is through these synapses that signals get from the input into the next neuron.

So, we will highlight the analog digital story further, I think I will highlight this, because I thought that was necessary. And it is also to highlight that there are various places in the nervous system, where this switch happens.

So, switch happens between what I would say is analog processing and then it switches on to digital kind of processing and it switches back and forth at various levels. Now, it is in this place I would like to highlight the progress which you have made in learning.

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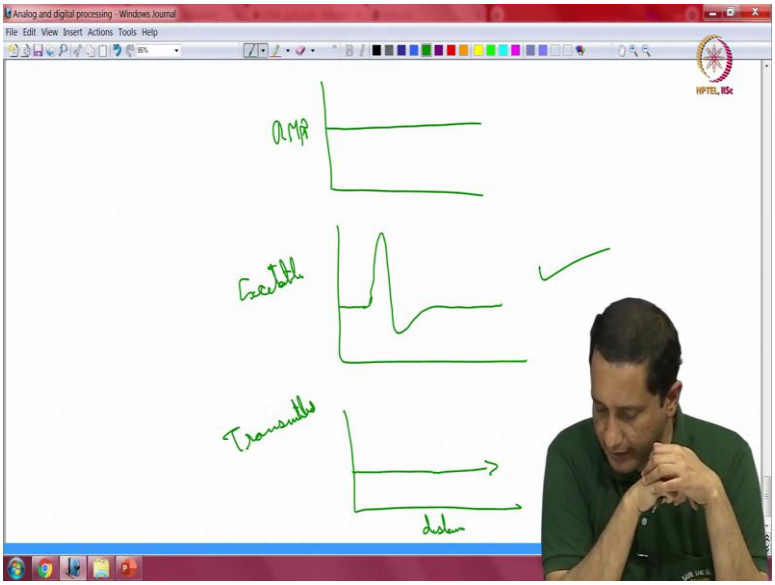

So, we started with the Gibbs dynamic equilibrium, in which we said that there is a resting membrane potential. And we progressed on to excitable cells, in which it is not just that the potential exists, but it can change and then it can revert back to normal.

Now, we also came to know that it is transmitted, so starting with distance. So, a signal can get propagated along the length of an axon. So, this is where we stopped. Now, if you notice that all of these are linear entities, you know linear entities in the sense that resting membrane. I have explained how the voltage is generated across the membrane, why it is active and the voltage is kept stagnant, meaning and it is kept constant.

So, what is -70 millivolt continues to be in -70 millivolts until something drastic happens and in an excitable cell that is basically a input signal. So, in a dendrite, there is some input signal and at a synapse, there is an input signal and based on the synapse, whether it is at the dendrite level, at the axonal level, whether it is at the cell body level some further information gets processed. Now, so that is what is happening so far and we have seen that that signal gets from point a to point b.

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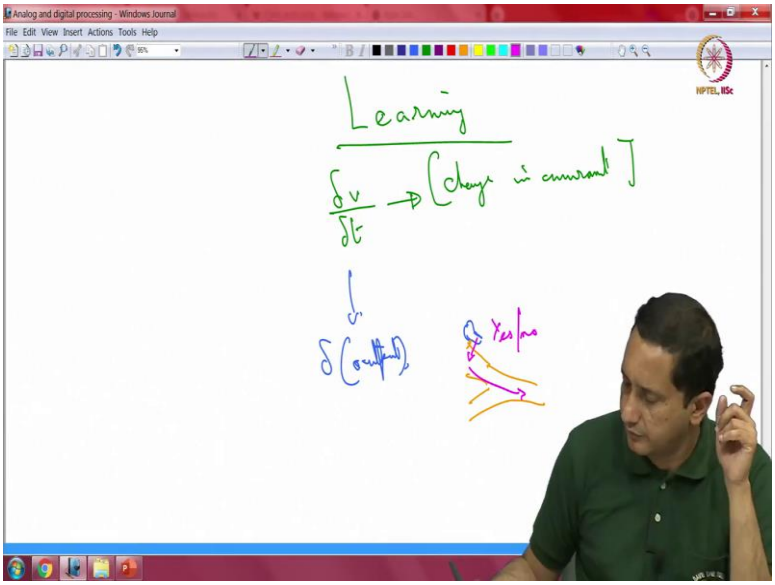

Now, if we look at the concept of learning or unlearning, so there should be a change. So, there should be I think that is a double differential. So, there should be a change in voltage with some point of time and that change in voltage with time has to reflect some change in environment, which is basically the input and that should actually result in a difference in output.

So, we need to find out where does the change happen, I have told you already that the action potential remains the same. Now, if you look at the dendritic part of the story, the synapses are fixed. So, there is a synapse which is ending on a particular area of the neuron, and we will draw that here. So, whatever signal comes through, it is a yes or no and the same signal goes through across that.

So, there is option of processing, but there is no option of change; this signal whether it is given today or whether the input comes sometime later today or tomorrow or any other point in future, continues to be the same signal. So, where is it that changes can happen? So, if we look at ANNs, the key change in an ANN; or why ANN is robust is because of the principle of back propagation.

So, back propagation is, there is an output and then that output causes some change back across the network and that is propagated across the entire network and that is how learning happens within ANN. And we have seen robust results of ANN technology as we see in so many fields.

So, it is with these two backgrounds I think I will continue with that; I will be dealing with learning at a much later stage in a greater detail, but that learning actually refers to what we understand of biological learning. So, the principles are what are going to be explained are biological principles of learning.

Back propagation happens in a very different way in biological systems; I will be dealing with that in very abstract fashion sometime later, not very concrete, not as a change in differential equations which happen with time.

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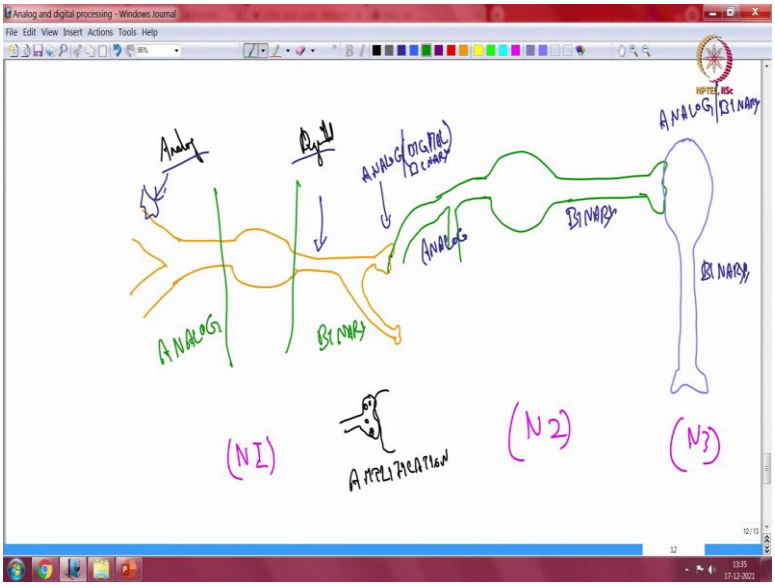

So, I wanted to draw a circuit, when in which we look at the issues of how information actually gets transferred across, and we will try to look at how information transfer is very different in different places. So, first neuron N1; then you have another synapse and then that is neuron N2 and for simplicity's sake I will make it simple, make it a single neuron at the end of this.

So, if you look at biological textbooks, you will find limitations in which we do not look at the entire story in a single frame. So, that is the idea of making it explicit over here. So, we have noticed that signals just cannot; in fact major large part of the nervous system activities and ensure that, this fidelity of signals is maintained throughout the network.

So, you know you just cannot have random signals coming from outside. To give you the opposite example; suppose you have injuries to the brain, you know direct injuries, traumatic injuries to the brain, one of the things which happens is seizures. So, but everybody who falls does not have a seizure.

So, you know there is an injury which is basically stimulus to this excitable tissue and then the excitable tissue propagates uncontrolled across the network and that is what is manifested as a seizure.

So, why it does not happen is because the system is so robust that it prevents any kind of electrical leakage across this entire network. So, we look at the signal transmission from one side to the other side.

So, this is analog that we have discussed so far; this is so called digital and what actually happens over here is the synapse and it produces these vesicles. Now, vesicles are one method of amplification.

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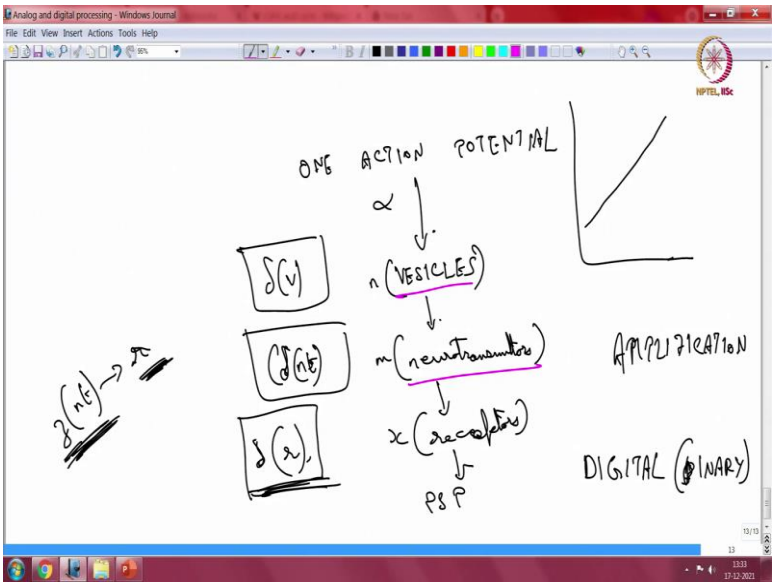

So, what I mean by amplification is, one action potential can produce multiple vesicles, which in turn act with multiple receptors; n vesicles that releases m transmitters, which activate x receptors, which reduces in a postsynaptic potential, it can be inhibitory or exhibitory.

So, the one single signal results in an amplification across a synapse. So, you can look at the synapses as an amplifier; amplifier can work in both ways, you know because if it is resulting in an IPSP or looking at post neuron decrease in activity, which in turn reduces the excitability and thereby signal transmission across the postsynaptic neuron.

So, how similar are these things to electrical systems, electronic systems? So, we have described, fidelity of transmission, we have described analog versus digital transmission, now we come to amplification. So, this is one of the techniques of amplification; I will be dealing with a little more detail with the other amplification systems in this.

It also incorporates some way by which you know how neuronal modifications happen when you learn or unlearn certain things or forget certain things and that is what is the discussion all about. So, one action potential can result in the release of a number of vesicles. Now, the number of vesicles again it is actually proportional to the number of action potentials which reach to the synaptic end.

So, you have one action potential, a certain amount of vesicles released and if you get 10 action potentials, it would be 10 times vesicles get released; internal regulations ensure the number of vesicles which can be released and each vesicle contains a fixed quantity of neurotransmitter, as an amount of molecular concentration of neurotransmitter, which in turn acts upon receptors.

Now, what of these can be changed? The neuron has the capacity of changing the vesicles, it also has a capacity of changing the neurotransmitters; it also has a capacity of changing receptors, now some background on from the biological side. So, you would have heard of myasthenia gravis, a disease which affects the receptors and how people with myasthenia gravis have increased tiredness, drooping of eyes and several muscular manifestations.

Basically, indicating muscle activity is not proportional to the input neuronal activity and that happens because basically there is a damage to the receptors. So, whatever be the input signal, the muscles which are the part of the postsynaptic pathway at the neuromuscular junction; the activity in the muscles is not sufficient enough to produce the relevant action.

And so, so these are the ways in which you can have changes; they do not happen signal to signal, that is you know one action potential comes and there is a fixed quanta of vesicles which changes, but you know repeated signaling causes changes in the number of vesicles, action amount of vesicles which release neurotransmitters and neurotransmitters which can act on receptors.

Post synaptic sensitivity can be changed, if you have a binding frequency of say z for the neurotransmitter to bind to receptors; that function can be changed by increasing or decreasing the number of receptors in the postsynaptic. So, these are some of the methods by which, changes happen over a period of time. Now, my point of discussion was not that actually.

So, we have said that amplification happens; amplification happens from the neuron across the synapse. And when you are looking at each individual neuron having multitudes of synapses, you are looking at several folds of amplification of one signal, which the neuron has decided. The cell body decides that a signal goes through, a cell body decides what is the output frequency of the signal, the cell body decides what is the phase of the signal.

So, these are the three parameters which the neuronal cell body has decided and based on that the signals have gone through; but the signals are hardwired, you know the neuron does not change it is synapses. So, the neuron has fixed synapses, multitudes of synapses, may be thousands of synapses and across the synapses, the signals are amplified.

So, each signal gets amplified into multiple neurons; not only means spatial amplification, but also temporal amplification and signal amplification in terms of EPSPs and IPSPs post synaptic.

So, what actually I was trying to say is the whole process is sort of a mix of analog and digital; I would like to still call it digital in the sense binary, I am using the terms, because binary vesicle can be released or not be released. If there is no signal, it does not get released and if a vesicle is released, there is only a fixed amount of neurotransmitter within the vesicle. So, it is a fixed quanta; of course, it does amplification, but a single action potential releases a fixed vesicle.

Say if we imagine in the simplistic scenario one action potential producing one vesicle release, which produces so much moles of a neurotransmitter; 1 mole of neurotransmitter, it is to 1 nanomole of neurotransmitter, and that 1 nanomole attaches to a fraction of the receptors on the postsynaptic surface.

So, we are looking at a digital part. But at the synapse what happens is; because of the relative disproportion, there are more number of receptors than vesicles. So, given the input, the ratio between the vesicles and the postsynaptic receptors, we are still again looking at an analog transmission. So, affinity of different neurotransmitters to their receptors can be changed, can be tweaked. And so, you are looking at regulatory methods by which that change happens.

So, we have covered analog over here, digital in the axon, analog at the synapse; then again we are back at the next synapse. So, there is an analog digital pathway over here, I think I should use only binary as a term. So, then again, we are going to analog here, then binary and then an analog, binary, back to a binary.

So, processing is not you know the brain, or the nervous system does not like to differentiate between analog computing and digital computing; it seamlessly integrates the two systems and continuously for some evolutionary reason.

See logically if you look at the power of analog computing, in fact I have always been impressed with the analog computing power of the dendrites. So, when we look at the analog power of the dendrites, you would feel that, that much computing capacity is all that is required; but for whatever reason the evolution ensure that there is a there is a distinct split between one half of the neuron and the other half of the neuron, where the output is binary and input is analog.

So, that is something remarkable and it is per neuron. So, you have entire systems networks of neurons which do this analog digital analog computing and whatever outputs we see are in terms of this. Now, somewhere prior I had hinted about the possibility of what actually happens within the cell.

Now, the cell is a huge computing structure; you know I have told you about the power of computing in my introductory classes, in which we have said that DNA to RNA

proteins and the regulatory mechanisms for proteins and DNA are responsible for a lot of computing power, but how is it reflected.

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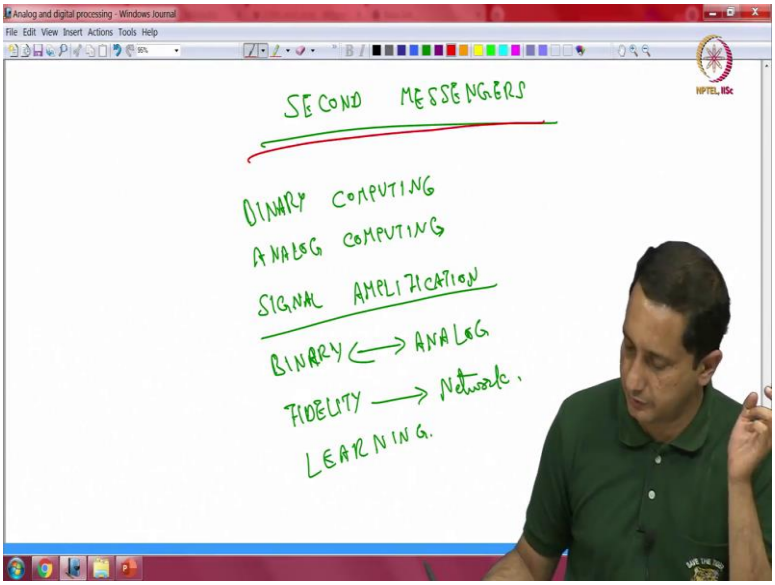

So, that leads to our next discussion of second messengers. So, second messengers are important; because we are jumping into learning territory, you know we are gradually jumping into learning territory. So, I started with today's discussion with amplification, which is one of the electronic techniques which is very important for core fundamental electronics. Now, we look at; we looked at processing in which you can have gates within the various places.

So, we have so far discussed binary computing, analog computing, signal amplification, then how binary and analog changes from one to another and it goes on continuously within the network. And I also spoke in some fashion about fidelity of the signal, how fidelity is maintained across the network.

Now, so signal amplification is here. Now, learning I have started to explain a little bit of learning and how it occurs within biological systems. So, second messengers is the basic discussion we are having here right now. So, how does second messengers work or what are the functions of second messengers?

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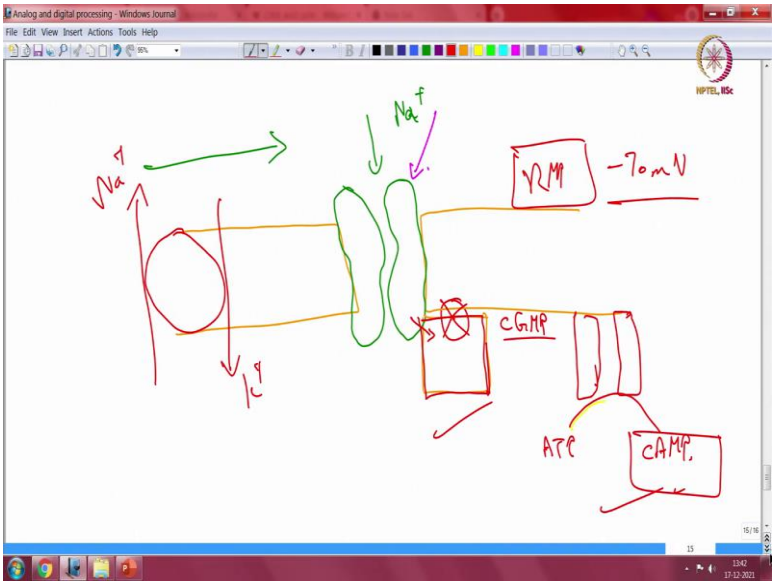

We go back to our original discussion of the cell membrane. So, cell membrane is a lipid bilayer and we have discussed that in various terms. So, in the discussion, we also decided that we had this membrane receptors which go across this one and these are sensitive to a particular kind of ion. Now, what needs to be coupled is, you need to couple the ionic part of the story to the protein part of the story.

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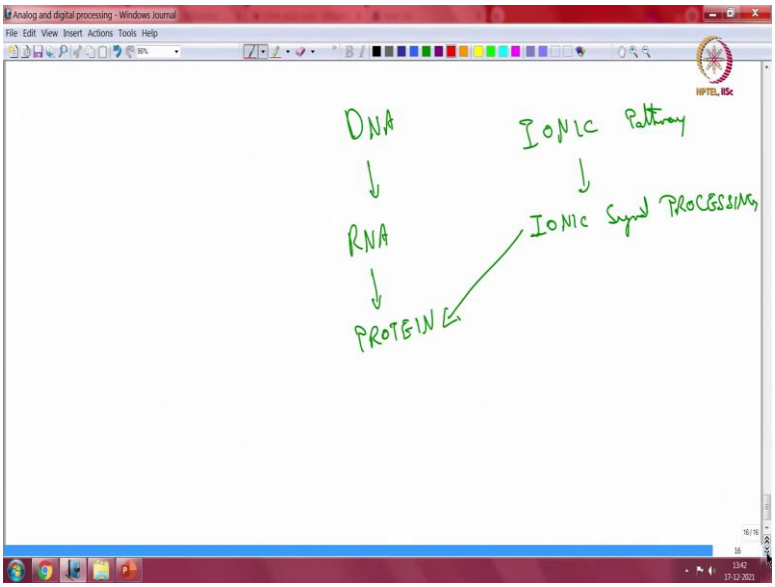

So, the protein part of the story is the DNA to RNA to protein. How do you couple an ionic pathway which does ionic signal processing to this protein pathway? So, that is the basic question which I am trying to highlight. And so, we look at we look at this particular methodology.

So, there are proteins which when the sodium channel opens due to whatever reason, you know you can have the signal which is coming from somewhere and then it opens or you can have a stimulus which is impinging on the particular sodium channel or this channel for having electrical change in the local environment or the transmitting signal through the axon.

So, in such a case what happens is, there are downstream proteins. So, you can have a downstream protein which is called as cyclic GMP, guanosine monophosphate; I think I will try to avoid all these bigger names and make it simple cyclic GMP. So, you can look at this diagram in the textbooks. So, there is a conformational change by which cyclic GMP gets released, it further causes binding to distal proteins on the cell membrane, which in turn converts an important molecule, ATP into cyclic AMP.

So, cyclic AMP is an important messenger. And now what happens is, these are not linear functions; it is not that one signal is equivalent to a single output. So, there is amplification happening at various stages and you have a larger amount of cycle AMP which can act for a longer duration of time. Signal is transitory, because as soon as the sodium potassium pump goes back into action, your signal is lost.

So, if you look back into the original discussion, we had the action potential which in turn activates the sodium potassium pump and that brings back the resting membrane potential to normal, RMP is restored. So, though RMP is restored -70 millivolts; cyclic GMP which is a protein, which acts on further set of downstream proteins and produces this cyclic AMP.

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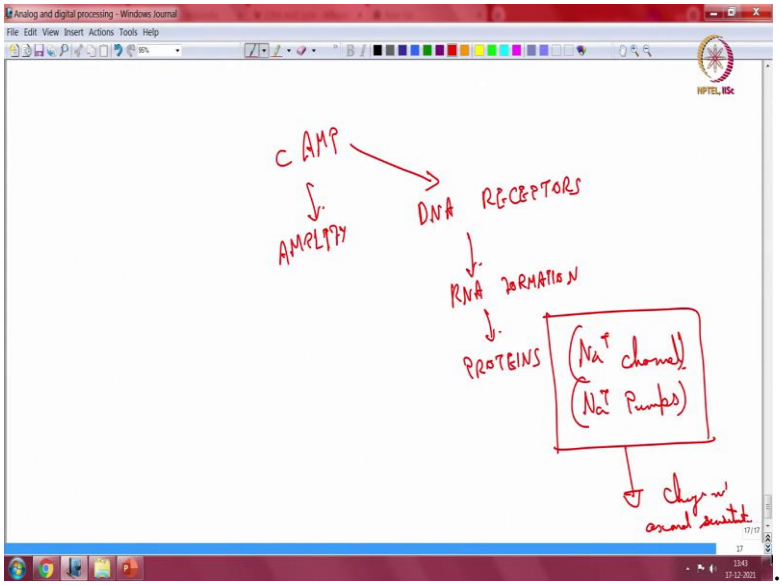

So, cyclic AMP in turn can do multiple functions; they again can amplify, they can actually intervene and attach to DNA receptors, which in turn results in RNA formation, which in turn results in proteins. To give an example of how to link up the whole thing.

Now, basically a sodium channel is a protein. So, you can have a sodium channel protein which is generated, and it can also produce sodium pumps. So, by this mechanism you can ensure that, this in turn causes change in axonal sensitivity, axonal sensitivity in the sense a smaller amount of.

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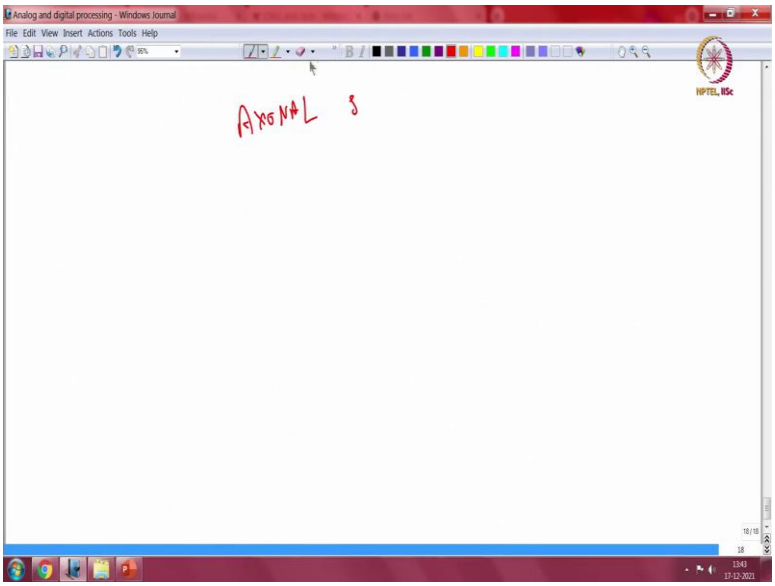

I think I should not confuse at this stage. So, axonal sensitivity or sorry not axonal that is sensitivity.

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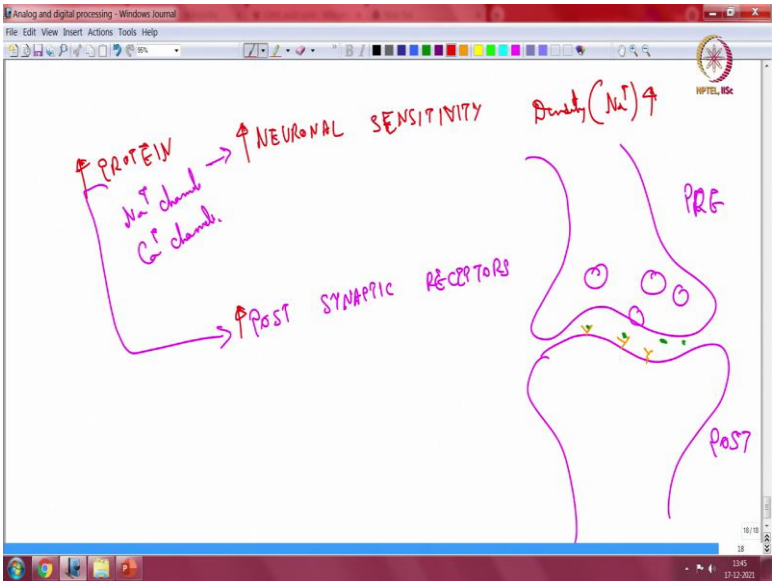

So, increase in proteins and therein I mean this sodium channels, also calcium channels. So, produces an increase in the neuronal sensitivity and that is one of the mechanisms, what I mean is the density of channels is increased.

You can also look at a very more interesting phenomenon that, protein also could refer to post synaptic receptors. Again, recollect that synapse is like this; pre and post vesicles over here, vesicles fusing and neurotransmitters released, and binding on to this one. So, what happens is, you can increase the amount of postsynaptic receptors and thereby the signal gets changed.

So, you have a method of amplification. Now, we have looked at only at the positive part of the story, in which a single action potential causes a release of cyclic GMP; cyclic GMP is another intracellular activating amplification system. So, cyclic GMP goes and results in the formation of more cyclic AMP.

And cyclic AMP has multitudes of functions, it has receptors across the cell which are connected to various biological mechanisms; one of the key biological mechanisms is within the nucleus, where the DNA has receptors for cycle AMP.

So, when the cyclic AMP binds on to the binds onto the DNA receptors, that causes an amplification of results in the production of proteins; the example of a protein so produced are receptors, sodium channels or post synaptic receptors and that increases the density of this one.

So, we have a method of by which you have amplification of a signal over a period of time; one signal produces a certain change in cyclic AMP and cyclic GMP and cyclic AMP and that produces the increase in synapse.

Now, you also can have the other way around; you should not look at the second messenger system as an activation function, you look at it as a steady state function, in which there is a certain amount of time cyclic AMP.

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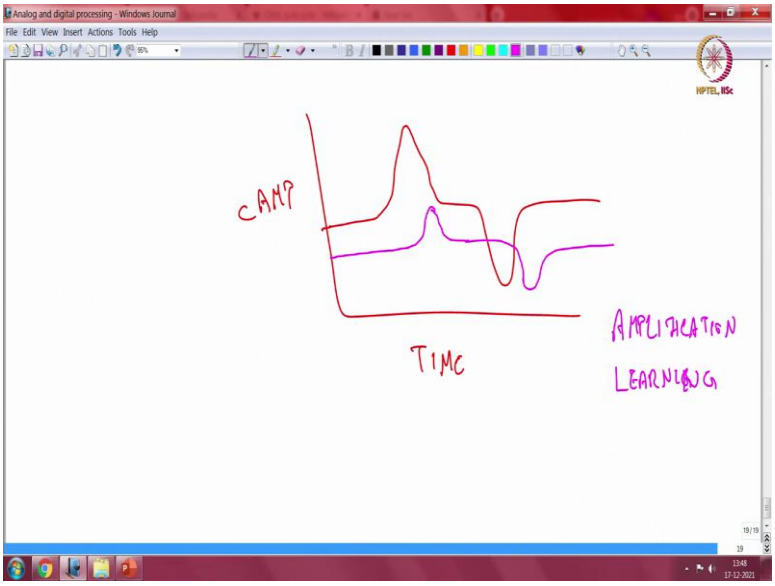

And so, what happens is you have an increase in cyclic AMP or a decrease subsequently in cyclic AMP. Now, what happens with that is if you look at protein production would somewhat be associated with that. So, you would have steady states protein production, which after lag in the increase of cyclic AMP, results in increased cyclic protein production and then that causes it comes back to steady state after some time.

It also when there is a decrease in the cyclic AMP production, causes a decrease in the channel generation. So, that is a mechanism by which you can produce changes within the membrane, we can change the function of various pathways within the neuronal cell.

So, these second messenger systems are powerful systems, they have multitudes of roles. A simple implication is amplification of signal, signal amplification is what is stored. But you also looking at learning as a method; we will be looking at reflexive pathways, in which increased number of signals produces increased amount of downstream signaling, decreased number of input signals causes decreased number of output signaling.

So, this is one of the fundamental principles by which learning also happens. So, amplification, learning are the important results of this mechanism and that is something which we need to look at.

So, through this class I have discussed the various ways in which analog and digital signals have switched between various parts of the neuronal network; neural network indicating that the multitudes of numerous cells in connected in series and how signaling happens across cells and how a part of the cell also changes the cell itself.

So, there are multiples of input signals coming to the cell, that signal itself causes internal changes within the cell and that modulates the further signal which comes through. So, either the neuron can have increased sensitivity, or a neuron can have decreased sensitivity. I think I should discuss over here very interesting concept and that sort of summarizes the stuff which we have dealt with so far. What constitutes recording from a cell?

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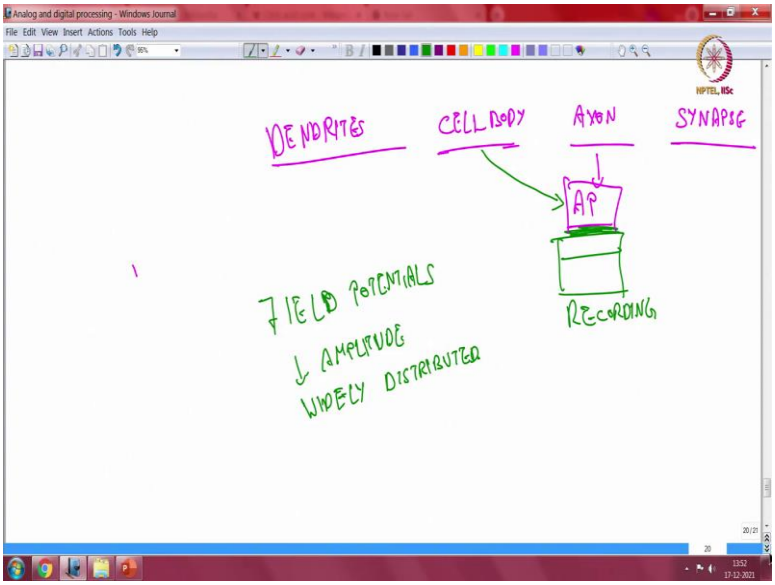

So, we have dendrites, cell body, axon, synapse. So, there are four different entities within a cell. So, if we look at what we call as combined action potential; we are looking only at the axonal function, which is where the action potential is generated. So, action potential is a function of the axon.

And if you look at what we call what is called as single cell recordings; we are looking only at action potential outputs of the neuron and how those things change with time, it sort of reflects the cell body function also. But dendrites on the other hand have graded potentials across the tree.

So, that is a huge tree and within the tree at any given point of time the voltages are very different at each junction and maybe at each synapse and along the length of a dendrite based upon various outputs in its earlier part of the tree. So, if we want to study a neuron; so we are so far capable only of generating an action potential based recording.

Now, these produce something which is I think called as field potentials and field potentials are very difficult, because they are much smaller in amplitude and widely distributed because the dendritic tree is so big when compared to the axonal part of the story.

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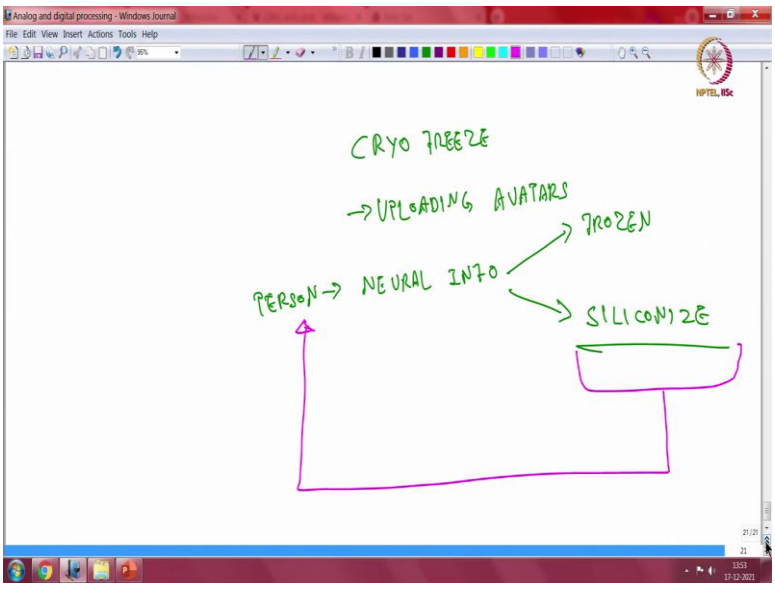

Thought experiment, we are aware that you know I must have seen I think may be movies and there are very rich people who go into I think the term is called cryo freeze

or you know it is also about uploading avatars and I think I will take this opportunity to poke fun at the concept.

I would not say that it is impossible, the term impossible is a very dangerous term; but let us look at the practical implications of how much information which you need to capture the state. So, the principle of all of this is, there is a person whose neural information is either frozen in the first instance or is digitized as in siliconized, I think digitize is a very wrong term in the with the discussion we have had so far. So, we siliconized.

So, how do you, how siliconize? So, what is the and not only that it is not sufficient to do that, because it would be a very useless exercise. The idea is that to bring back the person from the these entities. So, what is the state function?

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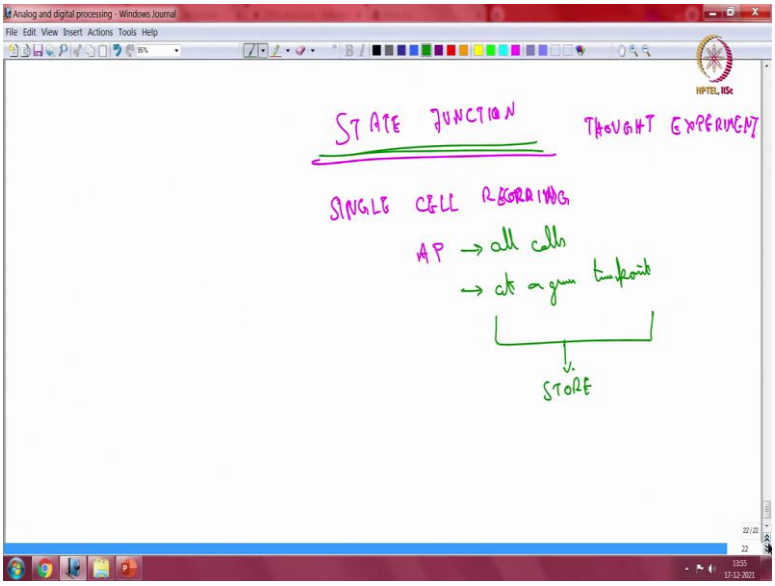

So, at the time of freezing or at the time of uploading, acquiring a digital avatar by whatever means, we know you do not have methods. So, what would constitute the state function is a very interesting thought experiment? Conventionally we have been told that you know single cell recording is the way head.

So, you are looking at action potentials from all cells; not only all cells, but it should also be at a given time point, single time point, because you need to know relative differences between signals that this one and then you have to store all of that. So that would constitute the state function.

So, we are looking at what is the amount of information which you need to look at the activity of a particular neuron. So, from the discussion so far, we understand that a neuron actually does not do just action potentials, it does a lot of computing upstream.

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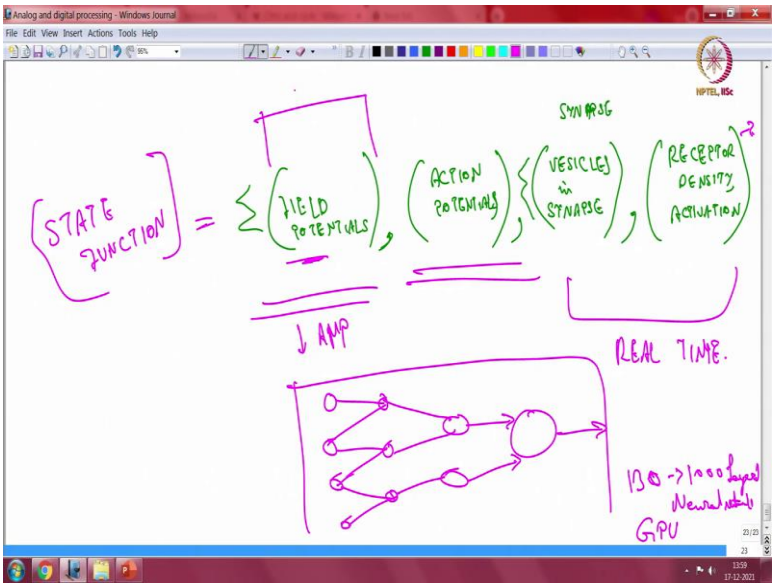

So, we are looking at the sum of all field potentials, then sum of all field potentials comma and sum of all action potentials, then sum of all the vesicles in the synapse; this is actually again sum for all synapses, you need to know the function value of every single vesicle in every single synapse and receptor density, not only density, but you are looking also at activation. And that I think is what would be the state function, which you need to develop before you start thinking of digital avatars.

So, the reason of doing this thought experiment is not to make fun or to boo a particular stream of study, it is definitely not the intention; it is just to say that the amount of information which needs to be captured even to understand the function of a single neuron, you know we have billions of neurons and even a single neuron, the amount of information which is required to be understood to replicate its functioning; forget about understanding its functioning, it is only to replicate the functioning is enormous.

So, you have dendritic potentials, you have action potentials, you have synaptic functions, chemical functions and each of these things need to be computed and stored and retrieved to achieve a state function of the functioning of a neuron. This has

important implications, because means of study; if you look at electrical recordings, we are looking at only the action potentials.

So, action potentials are the most prominent part of the neuronal activity, but there is a lot of other stuff which is happening; one is the signals are very low amplitude, the other thing is you do not have a method of measuring or quantifying vesicles function or synaptic function in real time. You can look at post synaptic function; so what is the current coming which is happening, which is the field potential is distal to that.

But we do not actually have methods by which we can capture functions of synaptic activity at every given point of time for all synapses of a single neuron. So, that is the complex amount of computing power which a single cell has and with that I think I will conclude this giving you a thought process.

When we look at ANN, you know we look at something like this; one layer and then there is two layer and then there is an output, and this is you know you have so many of these things resulting in outputs. So, that is how a neural network goes.

But this entire thing, even if you look at how much is that 130, 140, 200, 1000 layered neural network which you would use lots of GPU computing power to implement, design, do all the funny stuff, you would still be replicating only the field potentials of dendrites.

Thank you.