Cognition and Its Computation
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Lecture - 15
Short Term Plasticity and STDP

Welcome. So, we have been talking about Synaptic Plasticity, and we ended the last lecture with introduction of short Spike Timing Dependent Plasticity or STDP. Before we go into STDP, we would have a relook at the short term plasticity, and how that usually manifests itself that procedure or mechanism is what we will discuss first and then go into the spike timing dependent plasticity.

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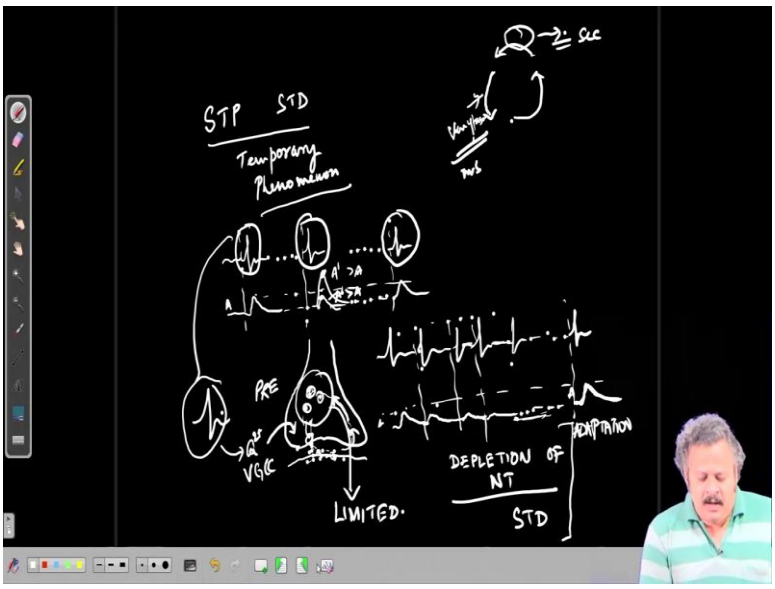

So, as we were saying that the short term plasticity, short term potentiation or short term depression, these are temporary phenomena. And they usually occur because of pre-synaptic properties, changes in pre-synaptic properties, like the amount of neurotransmitter or the amount of calcium in the pre-synaptic site. So, we see short term depression as a general phenomena in most cortical synapses, and some of course also show short term potentiation.

So, what we mean by short term depression, if we recollect is that we have a spike and we have post-synaptic potential in response to that spike excitatory post-synaptic potential let us say, amplitude A. And then after some time we have another spike and

we measured the post-synaptic potential and we have a decrease or an increase in the post-synaptic potentials amplitude. So, A prime greater than A, or A prime less than A.

And if we let the system sit for a while at rest may be few seconds to minutes and we measure we have a pre-synaptic spike again and measure the post-synaptic spike post-synaptic potential we see that it goes back to its original amplitude A. And so, this temporary phenomena as we have mentioned is what is short term plasticity; short term potentiation in this case and short term depression in this case.

What; the reason behind the short term potentiation, short term depression is very simple, in the sense that we have in the pre-synaptic site, if we look at the pre-synaptic terminal, pre-synaptic site we have vesicles with the neurotransmitters in them. And they are docked here and they release neurotransmitter when calcium goes in, which happens due to the pre-synaptic action potential which is this, but these events. So, these events cause this calcium to go in through the VGCCs and the neurotransmitter gets released on to the synaptic cleft and then the neurotransmission happens.

Now, if we have sequential spikes occurring in within 50 milliseconds or so, over and over again, in the pre-synaptic site what happens is that due to the limited amount of resources, that is the limited amount of neurotransmitter present, this is limited in amount. So, finally, the amount of neurotransmitter released actually in every step gets smaller and smaller. So, this is the A, then at this spike we have A prime, then at this spike we have even smaller A double prime, then at this spike and even smaller and so on.

And if we let it go the neurotransmitter gets replenished and we regain the original A. So, it is really the depletion of the neurotransmitter in the pre-synaptic site, depletion of NT that causes this long short term depression or synaptic depression. So, essentially this is the basis of what we will call adaptation later on, adaptation. So, given an input that is occurring continuously, neurons tend to adapt to that input. That is this, they gradually stop responding to it, as if nothing is happening anymore. This we will talk about in our sensory circuits, when we discuss sensory circuits.

And also we will be talking about these in attention and other phenomena in terms of cognition. So, that is the short term depression side of it. And actually to fully understand it, we can actually model this process of this neurotransmitter available amount being

limited at a fixed amount. Then some of it is getting released, some of it is binding to the post-synaptic neurons receptors and some of it is getting re-up taken into the or into the back into the pre-synaptic site. And then they are getting packaged into vesicles and this cycle goes on.

So, the time constant of the different steps in this cycle from the release to the re-uptake to the packaging, these three steps, this releases extremely fast, very fast. And this uptake and packaging to replenish, this is extremely so. This is, this process is in the scale of millisecond and this process is in the scale of seconds. And so, this difference in time constant with activity, continuous activity causes the neurotransmitter release to decrease gradually and actually basically no effect even of the pre-synaptic spike is seen in the post-synaptic neuron after a while.

And this replenishment taking seconds time scale. Then finally, you need the system or the synapse to be at rest for some time to actually get back to the normal state and produce post-synaptic potential of the original size to a pre-synaptic spike. This is the basis of the short term depression and is a very common phenomena.

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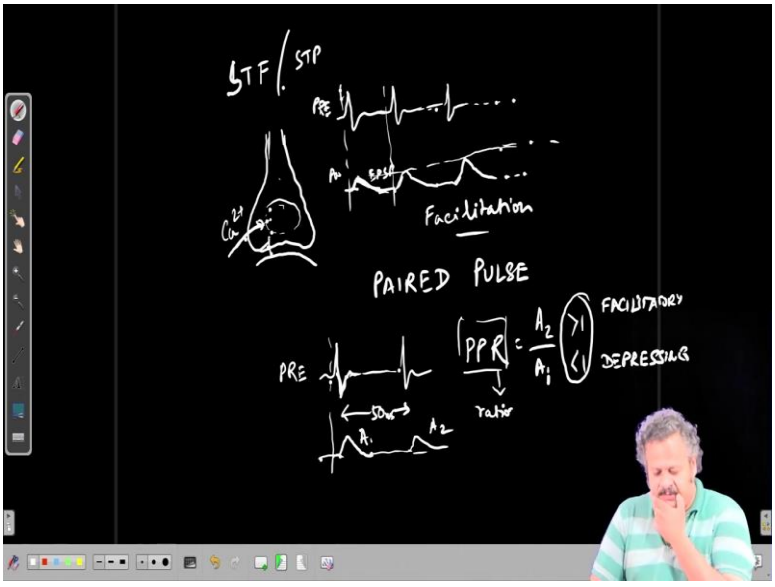

And the opposite of this which is our long short term facilitation or short term potentiation, it can be explained in a different way. The, it usually happens in very small synapses. And the as you can as if we think about it that we have sufficient neurotransmitter there, but the calcium that comes in, if that gets that builds up because

the release of the neurotransmitter is a calcium concentration dependent process. The building up of calcium due to every spike in the synapse causes more and more neurotransmitter to be released in every spike.

So, what happens in this case is that let us say this is the pre-synaptic spike, and let us say this is the post side, we have a small EPSP, and given that the post-synaptic potential is small, very little neurotransmitter is required in every step. The building up of calcium in subsequent spikes causes more neurotransmitter to be released in every step. So, this gradually increases and of course, it has to saturate at some point.

And this is what is called facilitation or short term facilitation or short term potentiation. So, it is the build-up of calcium in the intracellular, in the pre-synaptic intracellular region that causes this long short term facilitation. So, all of these phenomena can actually be modeled and are quite well understood, barring some specific things which are topics of research. Some of these will be discussed at the end in open questions of this course.

So, the effects of both of these, the whether a particular synapse is either facilitatory or is it depressing that is usually studied with what is known as a paired pulse phenomena, paired pulse procedure, paired pulse. That is usually two pre-synaptic spikes are produced, that is through stimulation of the pre-synaptic neuron by currents in a gap of about 50 millisecond. This is varied in order to study the effect of different gaps.

But typically, with a gap of 50 milliseconds, if the pre-synaptic neuron is made to fire two action potentials and if we measure the post-synaptic potentials amplitude in the two cases. That is, this amplitude is A 1 and this amplitude is A 2, what is known as the PPR or paired pulse ratio which is A 2 by A 1, this being greater than 1 or less than 1 that determines whether it is facilitatory or depressing.

So, this paired pulse ratio will also come up later in our discussions in order to understand how adaptation is happening in neurons and in certain phenomena when we try to understand certain aspects of attention and so on in our following lectures. So, this sort of ends the discussion on the short term aspects and long term aspects of plasticity that has been studied for a long while.

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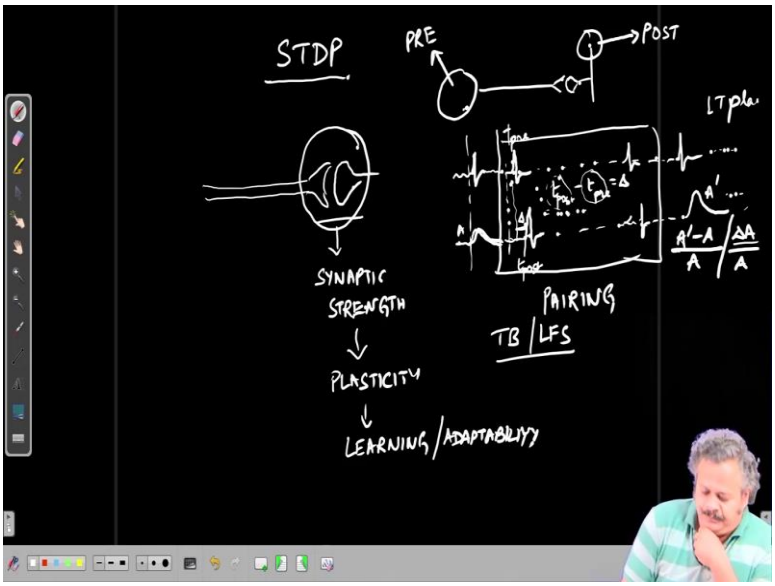

So, now we will go on to the discussion of the spike timing dependent plasticity, which is a form of long term plasticity which is studied through stimulation of both the pre-synaptic and post-synaptic neurons. So, if you think about synapse or two neurons connected by a synapse, we have been talking about this synaptic strength being changed. That is sort of the basis of plasticity and hence the basis of learning or even memory and many many or a rather in fact, all sort of higher level functions involve this process of plasticity. So, let us keep it at learning here or even adaptability.

So, we must ask this question is to what actually tells this synapse to change its strength, what tells this synapse, ok you should increase your strength or you should decrease your strength. There is actually nothing from outside that is going to tell each particular synapse, how to change its strength in order to learn something or in order to behave in a particular way or how it should change.

So, the whole process is dependent on actually the information available at the synapse itself. That is, the pre-synaptic activity and what is happening post-synaptically, that is the pre-synaptic activity and post-synaptic activity. These two things themselves tell the synapse what to do. I mean I am talking in a very abstract loose way. All of these are studied very precisely. And this telling means that there is some molecular signal that gets activated with certain kind of pre-synaptic and post-synaptic activity or some kind of relative pre-synaptic and post-synaptic activity.

And the and that is the basic idea behind the spike timing dependent plasticity. So, what we are saying is that the timing of the spikes in the pre-synapse and the post synapse or rather the activity of the pre-synapse and the post synapse and its timing. These are together helping the system self organize or adapt to different situations. I mean depending on the requirement of the organism.

So, it is simply not possible for external signals to manipulate thousands of synapses together which is what is happening in a particular learning. Let us say, when a baby learns to write or even we when I was learning to write on this particular kind of way of teaching. All these require learning. And this process involves changes in synaptic strength. So, it is the activity itself in the pre-synaptic side and post-synaptic side that modulates the synaptic strength.

So, the way it can be studied is by being able to have control over the neurons both the pre-synaptic neuron and the post-synaptic neuron. So, this is the synapse and this is the post-synaptic neuron. And let us say we have a means of controlling the spiking behavior in the post-synaptic neuron and separately on the pre-synaptic neuron. So, these are done by specific experimental methods that involve patch clamp recordings which we will not go into.

But it is feasible to do this kind of a study where we control the spiking behavior of the pre-synaptic and the post-synaptic neuron. And also be able to measure the effect of the pre-synaptic neuron on the post-synaptic neuron in terms of its IPSC or EPSC or EPSP, whatever is required in order to study the synapse in terms of it is, its functionality and how it is changing. So, the experiment goes in this way that we ourselves find these kind of two neurons. There are ways to do that in let us say a brain slice and make the pre-synaptic neuron fire and action potential ourselves.

And we measure the strength of the post-synaptic potential, that is A just like we have been doing earlier. Now, we can do a manipulation a kind of pairing, just like we had the titanic burst or the low frequency stimulation that we talked about earlier for Hebbian plasticity. Here in terms of studying spike timing dependent plasticity, we manipulate the activity of the pre-synaptic neuron and the post-synaptic neuron in a particular way. And that is what is called pairing. So, this period of time is what we call the pairing period.

And let us say in this period, we make the pre-synaptic neuron fire and action potential, and after a delay delta we make the post-synaptic neuron fire an action potential. So, remember we are in control of the spiking activity of the pre-synaptic and the post-synaptic neuron. So, they, they it is not allowing the normal kind of communication or the normal kind of flow information, flow of information happen because we ourselves are making the pre and post-synaptic neuron fire.

Let us say with a time gap of delta, so let us say this is t pre and this is t post. And the t pre, t post minus t pre is delta. That is if delta is positive my post-synaptic potential, post-synaptic spike is occurring delta time after the pre-synaptic action potential. And we do this kind of pairing may be a 100 times, it depends on the type of synapse, let us say a number of times. And this is sort of the end of the pairing protocol.

And after that we again do the initial measurement where we produce an action potential in the pre-synaptic neuron and measure the amplitude of the EPSP in the post-synaptic neuron.

And here let us say the amplitude is A prime. And what we see is that this also induces long term plasticity, in the sense that if we keep on measuring for minutes to a scale of tens of minutes to even an hour, this amplitude is maintained. So, it is a long term plasticity protocol, long term plasticity. So, it is not temporary, it is more permanent as we have discussed. So, the thing is the key player in this whole issue, in this whole scheme of things is the parameter or time delay delta.

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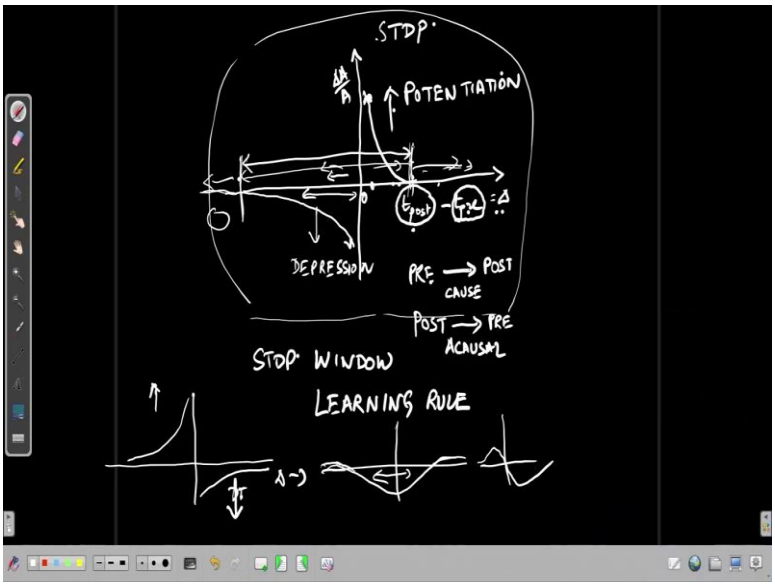

So, if we think about this axis as t post minus t pre, that is this is our axis as delta and on this axis we are measuring, we will be plotting let us say this A prime minus A by A, so A prime minus A by A. That is our delta A by A, delta being the change in A. So, in plotting that and so, for a particular delta that we used let us say we got an delta A by A or change in A by A about by some amount, let us say 1 percent or 2 percent or 3 percent whatever. And we repeat the experiment for different deltas, both positive and negative. So, this is 0 delta and we do it for positive delta as well as negative delta.

A typical Hebbian synapse shows the profile that this delta A by A follows is something like this. Asymmetric first of all and we have that is usually the negative side is depressing. There is depression when we have delta as a negative and there is facilitation our potentiation when we have delta as positive. This is the typical Hebbian synapse in terms of how it manifest itself in spike timing dependent plasticity.

So, what we mean here is that on the right side that is when delta is positive, t post that is the post-synaptic spike is followed by the pre-synaptic spike. That is it occurs after the pre-synaptic spike. It is as if the pre-synaptic spike is causing the post-synaptic spike, and like a cause and effect kind of situation. And the closer it is to 0, the more immediate the effect the stronger is the potentiation.

And there is a window within which there is a change. Outside that window the two spikes, if we are pairing the spikes, let us say with t pre-and t post being very negative or

very positive larger than these values then there is no effect on the synapse. That is the spikes pre-synaptic and post-synaptic spikes do not influence the change in influence or cause a change in the synapse. That is they are not following any causational phenomena or they do not cause any; their dependence is not there anymore.

I mean rather the plasticity does not have any dependence on the pre-and post-synaptic spikes that are very far apart. On the other hand, if we have a small negative delta that is the post-synaptic spike precedes the pre-synaptic spike that is my post-synaptic neuron is occurring even before or rather before just before the pre-synaptic spike occurs, then there is actually depression. So, it is almost as a acausal that is the post neuron should be; since it comes later in the pathway, it should be that the behavior of the post-synaptic neuron should be caused by the pre-synaptic neuron.

And deltas in this range or rather in the negative side are actually almost acausal in the sense, as if the post-synaptic neuron is causing the pre-synaptic neuron fire. Actually it is not causing that, but it appears in that way. So, the mechanisms by which these deltas can influence the synaptic strength is a lot of it is known. And for Hebbian synapses, this is sort of the learning window or the window; STDP window or the learning rule that the synapse follows.

And this is not necessary that all synapses will follow this kind of a learning rule. Different synapses have different kinds of learning rule in the STDP window. Typical numbers for this window is about 50 to 100 milliseconds, that is on the positive side about 40 to 50 milliseconds, on the negative side about 80 to 100 milliseconds. But that can also be different. And the shape of the learning rule can also be different.

So, there are synapses that are not totally anti-Hebbian that is they are actually positive when it is acausal and depressive. So, potentiation on this side, so this axis is delta potentiation on the negative delta side and depression on the positive delta side. So, that is it is going down, exactly opposite behavior of that. So, that is anti-Hebbian. There are also synapses that we know about that are primarily depressive in nature in a small window around 0 that is whenever the pre-synaptic and post-synaptic spikes are close to each other, the synapse has a depression.

Only far away do they have a little bit of excitation. There are synapses also with much more complicated learning rules like this and so on. So, these are area, these are it is

things that have to be determined experimentally. And different kinds of synapses that is different input type of neuron and the different output type or the post-synaptic neuron can have a very different kind, the particular types determine the kind of STDP learning rule that is associated with such synapses.

So, there can be a variety of those, and that produces the different kinds of adaptability in synapses or aids in the learning process. With this kind of variety of number of things can happen. So, this kind of a learning rule or STDP learning rule is used to model many phenomena that we will be talking about throughout the course. And is often associated with excitatory to excitatory synapses, inhibitory to excitatory synapses, excitatory inhibitory synapses with different kinds of learning rules in this STDP process.

So, with this we can see that it is really over time the nature of the pre-synaptic and post-synaptic spiking, the behavior or rather the relationship between the pre-synaptic spike and the post-synaptic spike over a long period of time can modulate a synaptic strength depending on this learning rule, the particular learning rule that a synapse has. So, with this we will be concluding our discussion on STDP.

Small thing that remains another some types of plasticity, that is homeostatic plasticity and some other modulations of plasticity that we have not talked about. But they will come up in our discussion. So, I will briefly introduce you to homeostatic plasticity and that is basically a form of scaling of synapses or that is all the synapses on the neuron are scaled in such a way, so that the overall activity of the neuron remains more or less same.

And this is, this happens over a very long time scale, and is there to sort of a control phenomena to not have runaway excitation or runaway inhibition in synapses. That is as you can see if a synapse continues to potentiate the post-synaptic neuron will keep on increasing its activity given the inputs. And so, there is a need to control this and that is what we mean by homeostatic plasticity which maintains an average overall level of activity. So, with this we will come to the conclusion of this lecture. And we will continue later with more topics on Neuroplasticity.

Thank you.