Advanced Neural Science for Engineers
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Lecture – 52
Computational Neuroscience Fundamentals

Hi, everyone. This is a last class in terms of the course. We have already exceeded more than 30 hours but since I promise that we will just touch upon one section which is on the computational neurobiology or you can say computational neuroscience.

Now we will just go through some of the topics and whatever we have learned can be useful when we talk about the computational neurobiology. So, in this way we will just understand some of the topics and going forward there will be a small component where you will be taught, how to understand the raw signals. How to extract those raw signals? Where are the spikes, where are the slow waves through the computational science using some computational methods.

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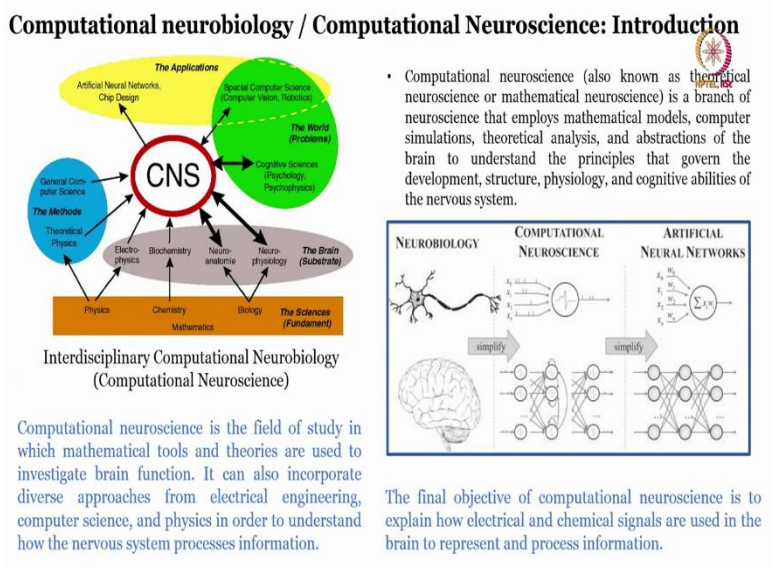

So, for that when you talk about computational neurobiology, if you see the applications, the applications are many. So, in the centre, if you say CNS which is computational neuroscience CNS, then if you talk about the fundamentals that is the basic science, that includes our physics, chemistry, math, biology and these are all the science of the fundamental science or the basic things.

Now this is very important because this forms a base for anything that we do. That means, if your biology is good then only you will understand the anatomy. How the cells looks like, what is within the cells, how the tissues are formed. How the organs are formed and many more things. Whether it is neurophysiology or neuro anatomy.

If you understand the chemistry then you understand how the different biochemistry things which are related to the brain works. For example, if you talk about the sodium channels or potential channels or chlorine, how exactly these forms. How the potentials are formed, these all forms under the chemicals which are used in the biology.

But the point is these chemicals or the chemistry of the brain is also very fundamental to understand before we actually use any devices that we have talked about. Same thing goes for physics, how the electro-physics works. How the potential difference arises?

So, my point that I am right now talking about is that if you really want to understand the details or how some of the structure of the brain actually works or you want to replicate few structures? For example, if you have heard about developing a wheel SI chip that will mimic a part of the brain. So, when you talk about neuromorphic computing that falls under the computational neurobiology or computational neuroscience.

But at the same time when we talk about physics, physics has other parameters as well. For example theoretical physics, the applied physics. And then all these things, and then math. So, math comes as a very important structure for applying all the formulas that we are looking around.

All the AI that we are right now talking about, the whole world is talking about. It requires you to have a very strong math background. So, this forms your base, this orange colour forms your base. The stronger the base better the understanding about the neural science.

So, next one. So, this all falls within the CNS. Now when you go for the cognitive sciences. So, whether it is a psychology or psychophysics. What are the wall problems, how the brain works. Why it is not working in a correct way. If somebody has a problem, you go through the cognitive sciences. Understanding that part of the brain which are related to either memory, depression. Sometimes people cannot remember, they cannot be attentive. So, a lot of other application can come within their computational neuroscience.

We are doing the computational of the structure. So, if you talk about the application, the BCI is one of the application of this CNS where you have a computer vision comes, robotics

comes, chip design comes, AI comes for understanding the part of the brain. Again, let me re-emphasize that it is at present we cannot completely mimic the brain, very difficult.

So, a part of the brain and a part of the brain where the… so, actually all of you know, nothing but a lot of neuron comes together to form your LFP's Local Field Potentials. But from each neuron how the signals are passing and can you replicate those things through our computational neuroscience models. So, can you simplify it, can you further work on the AI so that all falls under this computational biology or computational neuroscience.

So, it is a field study in which the mathematical tools and theories are used to investigate brain functions. It can also incorporate diverse approaches from electric engineering, computer science and physics in order to understand the nervous system process information. So, how exactly the information is processed, if you want to understand you need to go deep dive into the computational neuroscience and it also explained how the electrical and chemical signals are used in the brain to represent the process information.

Computational neuroscience also falls under the, also is known as theoretical neuroscience or mathematical neuroscience and is a separate branch of neuroscience that employs mathematical models, computer simulations, theoretical analysis and abstractions of the brain to understand the principles and government development, structure, physiology and cognitive abilities of the nervous system.

This is more how you read it but to understand it in a simpler way, I put it like cognitive abilities, attention, vision, hearing, cognition, psychology and how the structures are formed.

If you talk about cortical columns, each column is formed… however how many layers are there. How the ECOG signals are arising? At which part of the brain is related to what kind of function?

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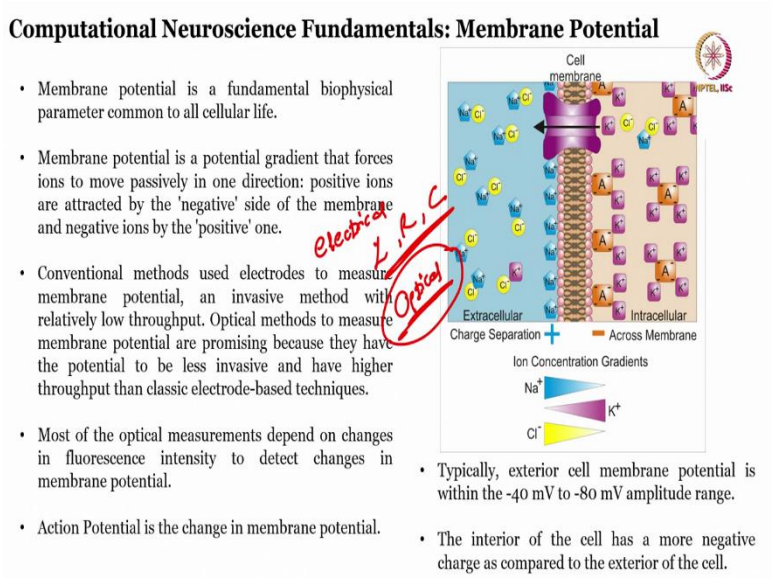

So, all these things are very important for us to understand but if you still go into the detail, then you can understand that there is something called membrane potential. And if you see here, you see the cell membrane, right? Then there is a extracellular charge separation layer, generally iron concentration gradients are formed between sodium, potassium and calcium. So, Na plus K plus and CL minus.

If you see the intracellular, you will see that there are again the across membrane how the ionic concentration gradients are there. And as you very well know that, the potential gradient that occurs, forces ions to move passively in one direction. Positive ions are attracted, whatever positives ions are there, they are attracted towards the negative side of the membrane and negative ions are attracted towards the positive side of the membrane. So, it is nothing but fundamental biophysical parameter common to all cellular life. Sodium, potential channels if you just write down that much in google you will understand lot of things about how the membrane potential works.

The conventional methods that are used to measure these membrane potentials are the electrodes that are invasive in nature and I have told you difference between the invasive and non-invasive or let me just again tell you non-invasive is something that you are not penetrating inside the body. Invasive, you are placing inside the body. Minimally invasive like a glucometer, the needle that goes is minimally invasive. Then there are terms like in-vitro, in-vitro is something in the laboratory that you grow the cells and study.

Then there is something called ex vivo, ex vivo is when you take out the tissues and you study those tissues, ex vivo. If you say in vivo, in vivo is within the body. So, these are some

of the terms. So, in this case were the membrane potential to measure membrane potential, people use different electrode.

Fundamentally you just take a tetrode, there is a fusion of four different electrodes and then this tip will be able to, if I see like this, it will be four tips like this and this all things are fused together these are called tetrodes, that are used to measure the action potentials or the biophysical parameters. The invasive method has a low throughput, optical methods to measure membrane potential are promising because they have the potential to be less invasive and have higher throughput than classical electrode based techniques. We will see some of the electrodes that are used to measure these membrane potentials.

Now, in terms of designing an electrode or resigning a system. The electrical signals, the electrical systems like for example, you measure the impedance or measure the resistance or measure the capacitance, these are very easy to develop. Optical techniques, optical technologies are comparatively complex to develop but the optical technique has several advantage like it can be used in a non-invasive way.

It is much more accurate, so depending on what kind of applications you can either go for the electrical parameter or optical parameter. Most of these current optical parameters depends on the fluorescence intensity to detect the changes in the membrane potential. So, the difficulty with optical thing is it is always a labelled method. What is labelled technique? Label technique is when we use a secondary antibody which will give a fluorescence effect in the in the presence of certain light of certain wavelength.

So, action potential is a change in the membrane potentials, so when the membrane potential is changing of the cell membrane, we call something call action potential that we measure and the value generally is between minus 40 millivolts to minus 80 millivolts. Where the interior of the cell has more negative charge as compared to the exterior of the cells.

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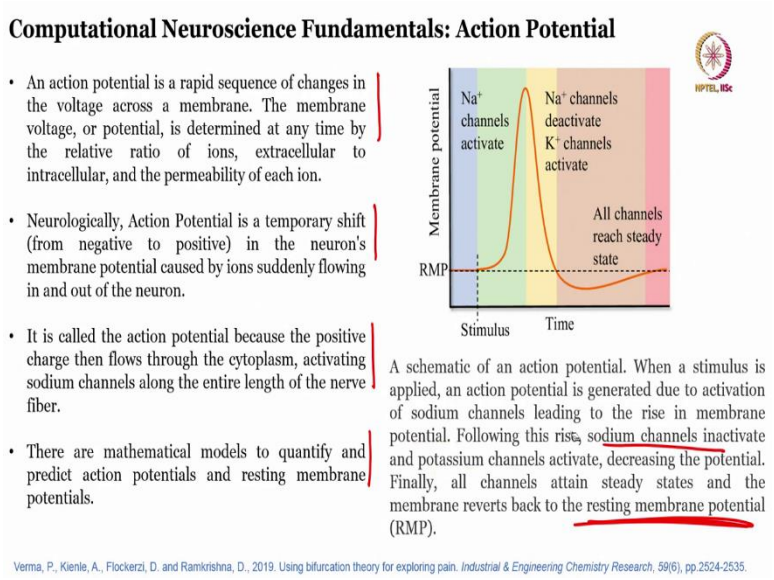

So, these charges are due to the sodium channels and potassium channels that are activated depending on the stimulus. So, if you see the left side let us read three paragraphs or four paragraphs. The first one says that an action potential is a rapid sequence of changes in voltage across the membrane. We have just see that there is a change in the potential, the negative ions goes towards the positive, positive goes to negative and the membrane voltage or potentially determined at any time by the relative ratio of ions or extracellular to intercellular and the permeability of each and ion.

Neurologically, if you want to see action potential is nothing but a temporary shift from negative to positive in the neurons membranes potential caused by ion suddenly flowing in and out of neuron, that shift will cause the action potentials that we can measure and because… why it is called action potential? Why the term action potential because the positive charge then flows through the cytoplasm activating sodium channels along the entire length of the nerve.

So, that is why the action that creates a potential and you can see in this particular case, when you apply the stimulus the sodium channels gets activated and sodium that gets deactivated and the potassium channel gets activated and then all channels this is the steady state. So, this is the action potential that occurs or you can say membrane potential that we can see in this particular image.

So, when this happens the entire length of the nerve fibre get activated along when the action potential occurs. So, there are many mathematical models to quantify and predict action potential resting membrane potentials, we will not go into detail of this models.

I just want to touch upon the base of what are the action potentials and in this case again if you want to read what exactly schematic shapes, then schematic is action potential, when a stimulus is applied action potential is generated due to the activation of sodium channels leading to the rise in membrane potential. Following the rise, sodium channels are inactivated and the potential channels are activated decreasing the potential finally all generations are steady state and the membrane refers back to resting membrane potential or RMP. This is your resting membrane potential.

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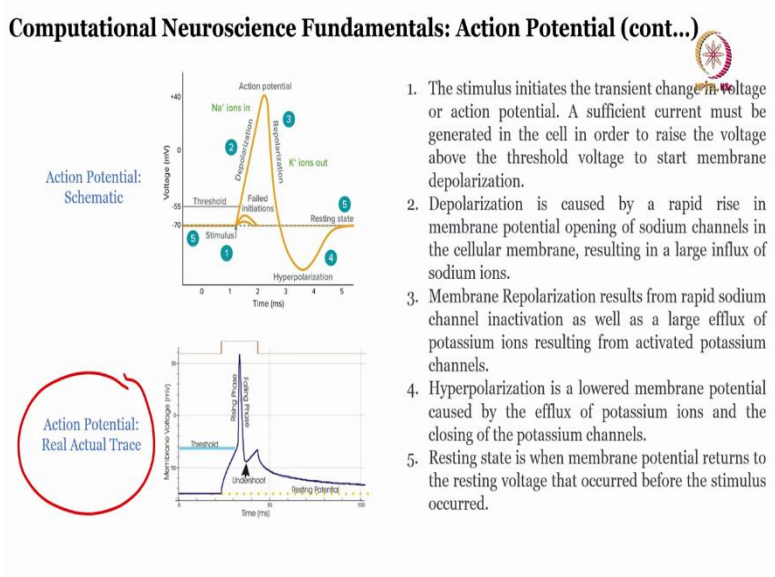

So, now if you further see in this particular schematics, there is an action potential schematic and there is action potential real actual trace. So, what you see here is that there is a RMP and then there is a stimulus. When stimulus applied not every time you have the action potential, there may be some failed iterations and if the stimulus is enough then the depolarization is occurring or sodium channels will get activated.

Then in this case the solar channel gets deactivated and the potassium gets activated and then finally it comes back to its resting state. So, it goes from stimulus to depolarization to polarization back to hyper polarization and back to resting state. So, this is the case of action potentials. The stimulus initiates the transient change in a voltage or action potential which is the stimulus that we are applying right over here.

Sufficient current must be generated in the cell in order to raise the voltage above the threshold voltage, threshold voltage is right over here. If the sufficient current is not there we will have field iterations and if the current is sufficient then the threshold voltage, it will cross the threshold voltage to start the membrane depolarization. Depolarization is caused by rapid

rise in membrane potential opening of sodium channels in the cellular membrane resulting in a large influx of sodium ions. And then when that happens, membrane repolarization occurs from depolarization to repolarization.

So, in that case the rapid sodium channel inactivation as well as large efflux of potassium ions resulting from activated position channels, efflux is throwing out. So, you know that, influx is how much time it spends within the cell. So, the hyperpolarization is a state with a lower membrane potential caused by the efflux of potential ions and the closing of the potassium channels. Finally the resting state is when the membrane potential returns to the resting voltage that occurred before the stimulus has occurred.

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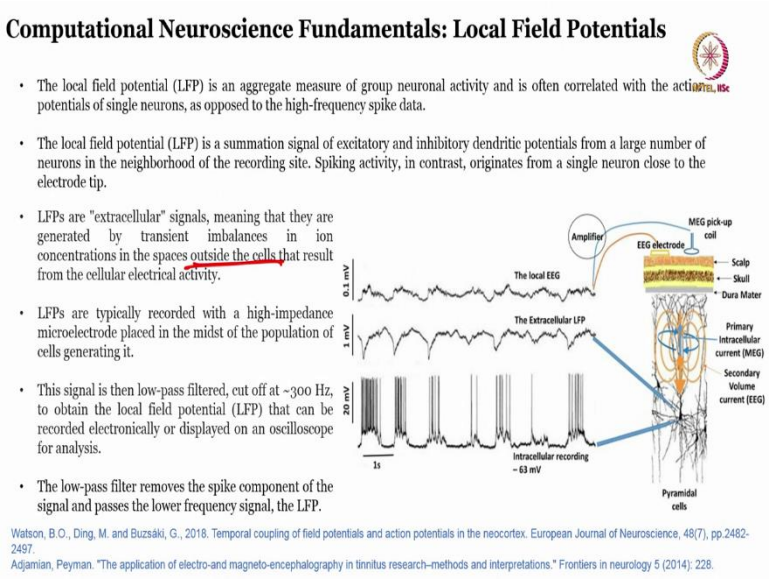

So, until now we are looking at action potential but what about local field potential. So, now you can see that there are pyramidal cells secondary volume current which is your EEG. Primary inter cellular current which we call MEG, there is a durometer scalp and then this has scalp electrode whether you want to come to capture the MEG or you want to capture the EEG and finally you apply whatever the signal is there you have to amplify it and then you can present it.

So, this entire thing we will be looking at as a Matlab, we will have a 15 to 20 minutes of lecture where you will be shown how these channels… how these voltages are picked up. What are the processing techniques to understand where are the noise, where is the signal. How to understand where are the peaks and so and so forth.

So, the extracellular LFP nothing but Local Fill Potentials and the local EEG as you can see in this particular case, so the local build potentials are about 0.1 millivolt. The local temperature is nothing but then aggregate measurement of the group neuronal activity and often correlated with the action potential of the single neuron as opposed to high frequency spec data.

The LFP is nothing but a summation, summation of excitatory and inhibitory dendrictic potentials from a large number of neurons in the neighbourhood of recording site. I told you that one single neuron, if you just measure the action potential but if a group of neurons that contributes to a signal, that is where we have the summation of the signals from the neurons, then we call this as LFP.

This packing activity in contrast original from a single neuron close to electrode tip. LFP's are excess cellular signals measuring and generally until now whatever we have seen, whether it is ECOG signal for epilepsy or we have seen ECOG signal for Parkinson. Those are all LFP's, okay? We have not fabricated or we have not shown how to fabricate electrode that can be used to measure the action potentials. But you can very easily change the dimension and you can go for the action potential as well.

So, in case of the LFP's, they are extra cellular where we say extra cellular, what does that mean? Extra cellular means that the signals are generated by the transient imbalances in ion concentration in the space outside the cells that result from the cellular electric activity, extracellular.

But when you go about LFP's further then they are recorded with a high impedance micro electrode plays in the midst of population of cells generating it. The signal is then low pass filter cut-off frequency is returned to obtain the LFP and then recorded electronically or displayed on our DSO. The low pass filter removes a spike component of the signals and passes the lower frequency signals the LFP.

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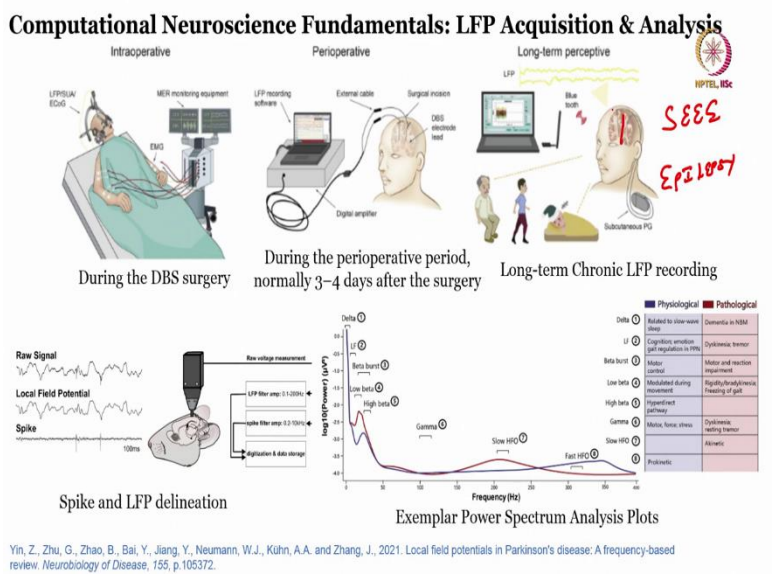

So, we will see how this… we can we can have this low pass filter in the Matlab programming. So, you can see here that if you measure the raw voltages from a rat's brain and you have this LFP, spike filter amplifier and digitization and data storage then with that we can take the raw signals, we can understand where are the spikes whether local wind potentials and so on so forth. And we have seen in the earlier examples where we were taking the LFP's how the signals looks like when it is a baseline, if it is a epileptic signals and when you recover the baseline how the things were looking at.

But when you take the signals from human brain using the non-invasive techniques that using the scalp electrodes then we are talking about the spikes and slow waves and the combination of both to understand how or what kind of seizures were there. So, in the interpreted environment there is a DBS surgery, DBS stands for the De-transposition electrodes.

During the pre-operative period normal 3-4 days after the surgery…I am sorry it is called peri-operative which is after the surgery not pre-operative, perioperative. The measurement can be still, we can we can measure using the DBS and DBS particularly are used only when the drugs does not work. DBS is nothing but your Deep Brain Stimulation electrodes.

If you have any kind of like if a person has any kind of episodes like for example Parkinson or so…automatically the subcutaneous PG is there and there are signals that that goes through the DBS will reach to particular region to counteract the electrical signals or in a way to stop the Parkinson.

So, it is a way to look at it but in certain cases we need to also see by putting the SEG electrode, stereo easy electrodes and see the or record the signals for long time to understand the source localization in case of the epilepsy signal. In case of epilepsy, in order to understand the source localization we need to use the SEG electrodes that is placed deeper inside the brain and so that the source of that epilepsy can be identified. This is commonly used in the current scenarios.

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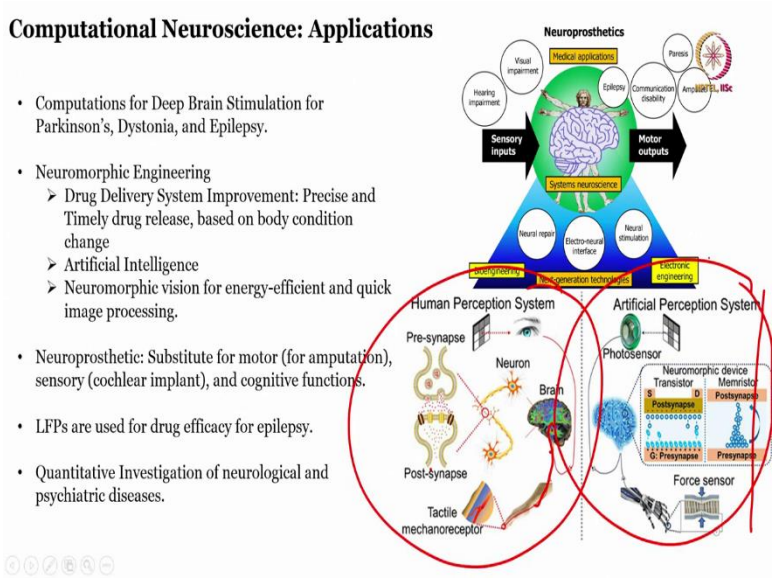

Now when you talk about the applications, so what are the computational neuroscience applications? Applications are many, when you see in this particular neural prosthetics these are one of the very important area where we can understand the sensory inputs that is your visual impairment or hearing impairment and then the motor outputs can be epilepsy, communication disability, can be amputee and the way to… from bioengineering to electron engineering, everything comes together to form either neural repair or electro neural interface or neural stimulation.

Either you stimulate certain area to activate it or you need to replace the area with a core processor or you can do the repairing of the area by using different bioengineering tools. In fact a lot of biomaterials are also used to regenerate the nerves. So, that is a very different topic than what we are right now focus on in this particular lecture but if you really understand is called the electro active polymers.

Electro active polymers, these are some of the materials that are used in bioengineering application. In general called tissue regeneration or tissue engineering. So, tissue engineering is divided into several sub-domains or one is for ocular studies, one is for the osteogenesis or

bone studies. One is for cardiovascular, one is for nerve generation, one is for skin applications, one is to heal the wounds.

So, many applications but not only biomaterials can be sufficient in those cases. If you apply electric assimilation along with biomaterials then the recovery is faster, the wound healing is faster, the bone that is cracked can regenerate itself faster. So, there is a positive impact of applying electrical stimulation along with the biomaterials.

In any case, when you talk about the nerve and conduction of the nerve, it falls under the neuroscience perspective and that is why I talked about little bit about the materials. So, competitions for deep brain simulation for Parkinson, dystonia and epilepsy, this is a fundamental studies that people are working on and in fact neuromorphic engineering that is understanding the part of the brain and replicating using the chip has several applications including a co-processor development or in the AI or for vision, for energy efficient and quick image processing.

We talked about neuro-prostatic suspend, we have to substitute for the motor area. Motor area can be for amputations or for cochlear implant and cognitive functions. So, visual people are trying and then for amputations and sensory. NFP's are used for drug efficacy for epilepsy. We have seen that if you want to study the efficacy of the drugs there is an anti-appropriate drug you can use the local field potentials and quantitative investigation of the neurological and psychiatric diseases you can again use the LFP's.

Here is a human perception system versus AI perception system. So, you can see that pre-synapse to post synapse, how the signals are transferred. When you visualize something and how the brain is activated, from that brain activation how the tactile mechanoreceptor works. How are hand is moving, the motor area in the brain region, how the signals are transmitted.

But the same thing if you want to replicate in terms of a chip then you have a photo sensor. We are looking at this particular thing, same thing this this photo sensor will work as an eye. It looks at it and it gives the feedback to the neuromorphic device. It can be a transistor from pre-synapse to pro-synapse and then there is a memory star from pro-synapse to pre-synapse.

So, how the signals are transferred. When it is transferred can you activate a robotic hand and the robotic hand can be indicated with the force sensor and you can also look at the haptics. So, the point is can you replicate the similar system using the artificial perception and that is another area of study.

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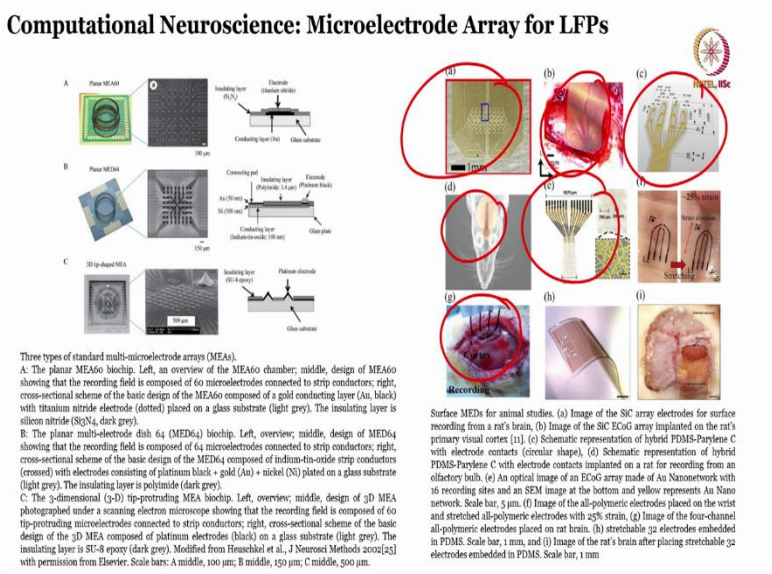

So, when you talk about the different kind of electrodes that are used in computational neuroscience, then this is one of the example where the electrode is formed on the glass substrate and there is a gold conductive layer on which there is an insulating layer of silicon nitrate on which there is an electrode which is titanium nitride and you can see here…these are the electrodes here and you can cover these electrodes and you can put it within the well to study.

Same thing goes for the platinum base electrodes, same thing goes for the different devices that you can see here and we have seen this as an example how to create one… let us take, if you really want to again see the example, we can take any one example to see how it is fabricated but I am sure that now you know exactly how the device is fabricated.

Now this is one of the examples of the migrator arrays and the right side shows nothing but the surface MED's for animal studies. Image of the silicon carbide array, electron for surface according from red sprain which is here, image of silicon carbide ECOG array which is here you can see and then you have schematic measurement of the hybrid PDMS, Perylene C with electrode context right now here and then we have schematic representation of the hybrid Perylene C contact which is right over here and then we have an optical image of ECoG made of AU network and olfactory bulb, it is right over here. Then we have F, image of all polymeric electrodes placed on the wrist and stretched all polymer electrodes with 25 percent of strain you can see here.

Next one is your image of four channel all polymer electrons placed under its brain, you can see here. Next one is touchable 32 electrodes embedded in PDMS you can see here. The

PDMS is used as a substrate and finally what you see in I is your stretchable 32 electrodes again in PDMS, so using PDMS as a material. PDMS is a silicone and it is also exclusively used when you look at the soft lithography.

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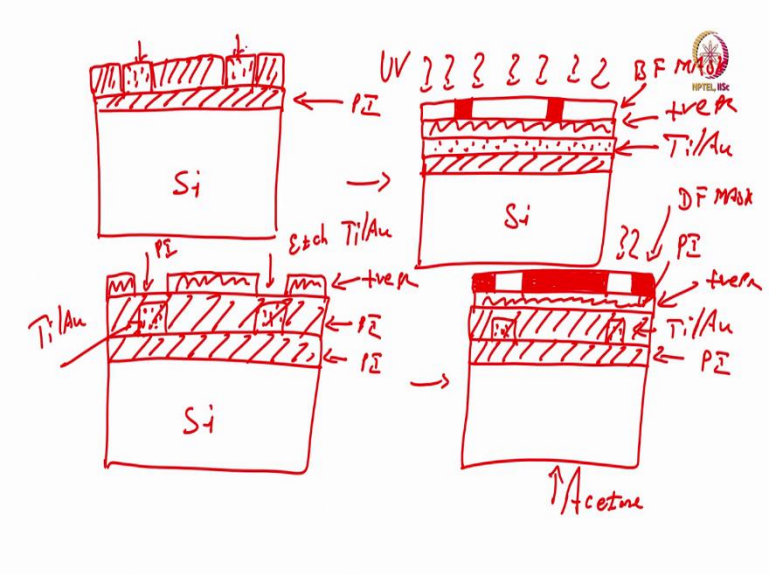

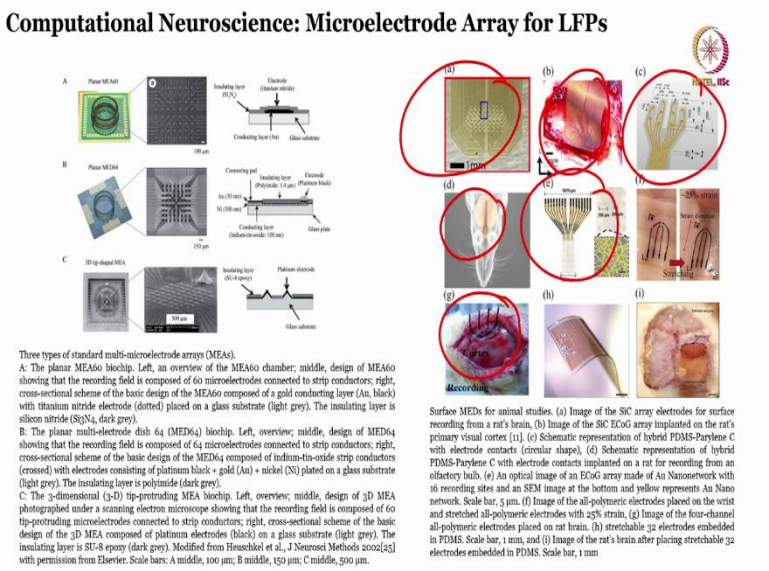

Now if you want to just take an example so you know, you can take a substrate can be anything and then on substrate you can spin code your polymer. It can be PDMS or it can be your PI and cure it. So, once you cure it, the next step is that you take the same substrate and on that you deposit a material a metal let us say, so we can deposit a metal… this metal is your titanium gold.

So, we can say it is titanium gold and how it is used to replicate something, on that you can spin code your photoresist. So, here is my photoresist and then on photoresist we can have a

mask… we can have a mask so let us have a mask and then using this mask we can have these two electrodes that we want to patent. We can have 32, 64, 128, 256 and so and so forth. And the resolution can also be improved by reducing size of electrode and having a dense micro electrode array.

So, this is your bright filled mask… bright filled mask and then you have to expose this photoresist using your ultraviolet rays. So, what will happen? When you unload the mask and develop the photoresist, you will have your PI on this you will have your metal and you will have your photoresist only in this region because the unexposed region becomes stronger. You go for hard bake and then you etch Au, so in this case we say Ti Au.

So, first you dip the wafer in Au followed by rinsing followed by the titanium match. If you do that what you will have? You will have PI with a Ti Au and then you will have the photoresist protecting that area, this is your positive photoresist and this is your gold on titanium, this is polymide. Then you dip this wafer in acetone, if we do that you will have this one, correct? Now what you can do?

You code it with another Pi and then you do again positive photoresist mask such that only the electrode contact area is opened. You got it what I am saying? So, we have coated with the Pi which is here on the top of the electrode and then we have coated a photoresist, so this is our photoresist and then we take a mask such that only the contact electrode, the windows can be open only on the contact electrodes.

So, we have done that you can see here. So, this will be your dark filled mask and then we expose using UV, what will happen? The unexposed region will be weaker. Exposed region will be stronger, so what will I have? I will have my photoresist everywhere except on the electrode, isn't it?

I will have my Pi then your gold electrodes then another Pi and photoresist in this region. Then we go for hard-bake and we etch the Pi from this region. When we do that, how it will look like? It will look like… like this… now the contact area is opened. So, you can take the recording electrode or surface electrode. You can see this contact areas, these are contact areas that are open also recording electrode is open. So, these are all the contacts are open for recording electrode and they contact electrodes also we can open the window so that you can take the contact out of the device.

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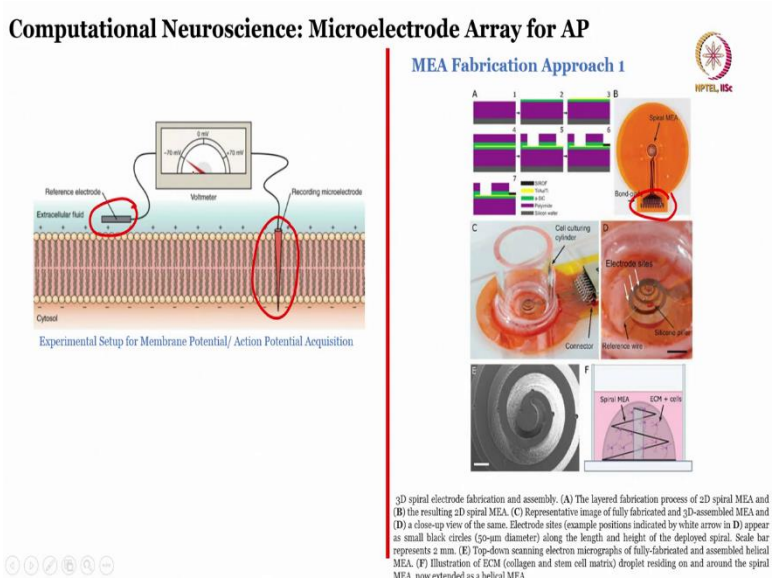

So, for action potentials here is an one example of how we can use silicon wafer and below is a polymide and then you have your silicon wafer followed by your titanium gold and again you form the insulating material and then finally you open the contact area, these are bonding pads, these are the spiral MEA that can be used for recording. You can see here electrode sites and you can use the circles or the cylinder in which you can put the neural cells to grow and you can measure the change in the action potentials.

So, this is another way of fabricating the device, the details are already given in the figure caption. So, please look into that and here is the example of how the experimental setup for membrane potential, extra potential is used. There is a recording electrode which goes deeper, there is a reference electrodes and then there is a voltmeter in which you can measure the changes. So, this is a traditional way of measuring the action potentials.

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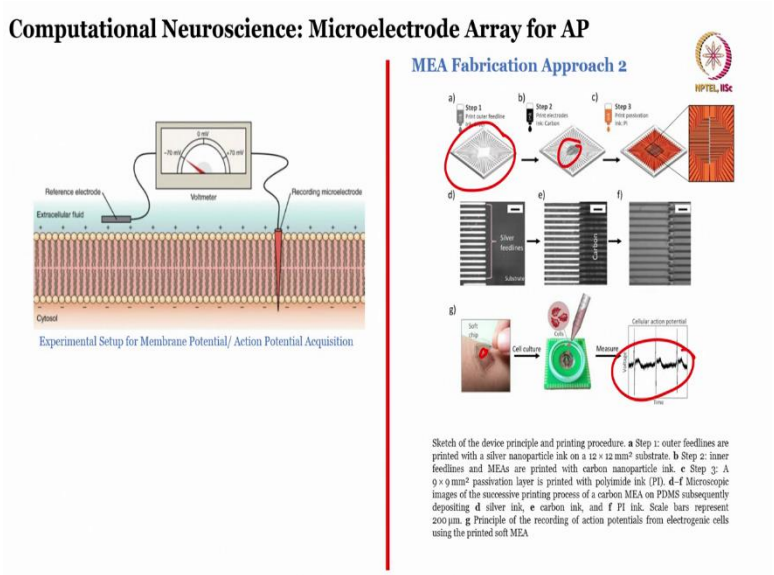

These are another example of the MEA that can be used to measure. It is nothing but outer feed lines are printed with the silver nanoparticle ink and then the inner field lines and MEA's have entered with carbon nanoparticles. You can see here, these are for the outer these are for the inner feed lines and then from D to F what you see is nothing but the images of successive printing process of carbon MEA on PDMS subsequently by deposing.

So, these are silver feed lines followed by the electrodes. So, you have the carbon based micro electrode array and the silvering carbon ink and Pi ink, you can get it. So, this is another way of doing the fabrication. Not every time you have to deposit a material but you can use a chemical to also fabricate the different kind of electrodes.

And finally, the advantage of using this kind of material is that, it is Pi. So, Pi is nothing but a polyamide and polyamide is flexible in nature, is bar compatible. So, finally if you drop some cells inside this well and which there are some electrodes then you can see or measure the voltage from the cells or cellular action potentials.

So, here we will stop and I am really sorry that I wanted to take each of this topic and go deeper and make you understand how the next part of this thing could work. For example, if you want to just do a better images or image processing, how you can have your neuromorphic chip for that or how can design those chip.

Also, similarly if you want to take a part of the AI and understand that can this traditional way of convolutional neural network and what are the feed forward network. What are the open loop circuits versus globe loop circuits that we can think of and we can design the

models accordingly. How we can design or think about getting the signals from the part of the brain and doing the encoding and decoding of this and in a way can you develop a chip that can be…can replace a part of the brain that is taken out during the surgery.

And this chip will work or will replace and perform the same action that part of the brain was supposed to. So, this is a very complex and interesting area but before that what are the different models that can be used to do the same study before we actually fabricate the device.

Anyhow does not matter, we tried whatever we can within that 30 hours of the dynamic. In fact, we have we will be crossing the 30 years more than that. So, what I will request is that if you want a certain notes or something I would see if we can provide through a forum so that you can look further into the neurobiology concepts. For now, we will stop here and I will still show as a part of the demonstration how the raw signals are taken and how we can do the Matlab programming to get the actual signals and remove the noise from the signals and how to identify different signatures in the EEG signals.

So, with this I will stop here and I wish you all the best for your complete exam and hope that you have understood a slightly better than if you already know about neural engineering neuroscience. How and where to apply the micro side the engineering side for neural science. So, can we now have chip or can we use the micro technology to fabricator chip for certain applications. If you have more questions before your exams please feel free to send it via your NPTEL Forum.

We will try to solve it, in certain case if you have any question and it is really like you do not understand then I will write down my email here, just make sure that you only ask the equations that you are really not understanding. So, in spite of we having a NPTEL forum, I will still give you my email ID, you can approach and me you can ask me something that you may or may not have understood. There is a live session for that but I saw that because of your time schedule, you may not be able to join the live session.

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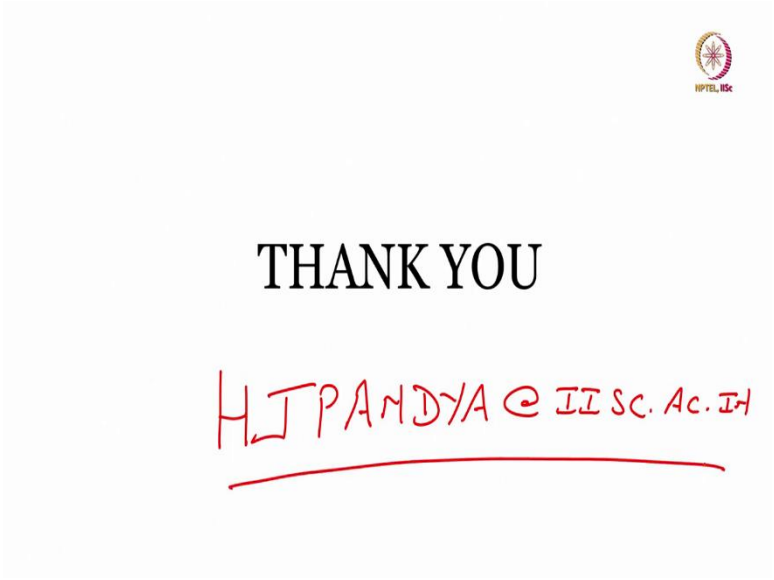

So, I am writing here my email ID you can note it down and you can send me an email. My email ID is hjpandya@iisc.ac.in. So, if you have any questions, feel free to send me an email. Again, it should be a really things that you cannot find it. So, just do not send me good morning, good evening. More than that is certain that you do not understand, some notes that you may not be able to get it. See, my point is we read lot of books so to get you to this level that you do not have to read many.

There are some textbooks that you need to anyway ready to clear the fundamentals but the lecture notes should be good enough for you to understand the concept and take it further. So, that is my approach of teaching you this particular course that you understand the application, you understand the gaps, you understand how can you feel those gaps by identifying certain solutions using the content what we have learned across these 30 hours.

With that I will stop here and hopefully sometime in life we will meet in person so that we can discuss further or take it further and learn from each other. Thank you, bye for now and I hope that I see you sometime in my lifetime and meet you somewhere. Discuss something interesting from your end as well. It is a online course so you may not be able to ask questions like in person class or an actual physical class but nevertheless it is better to have something than nothing. So, thank you very much once again and I will see you later. Bye.