Advanced Neural Science for Engineers
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Lecture - 43
Flexible MEA for Electrocorticography Signal Acquisition

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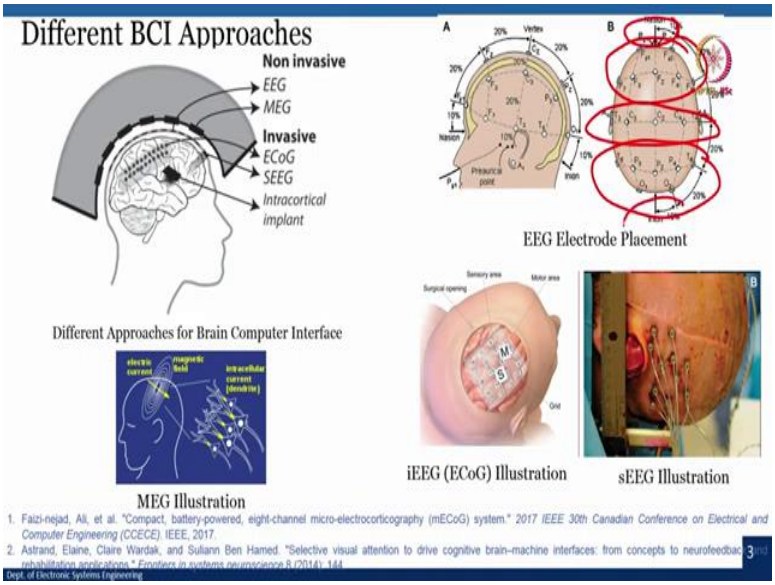

Hi everyone. Welcome to this class and in the last class what we have seen is about the epilepsy and what are the different BCI approaches whether it is your EEG, it is your MEG which are the non invasive techniques or invasive techniques like ECoG and about SEEG which is the stereo EEG or electrocorticography which is ECoG which are invasive technique and then we have also have a little bit understanding about intracortical implant.

And if you recall we have this 10, 20 system which is standard system used across the globe and at different region we had to place the electrodes that is when it comes to the non invasive technique about capturing the EEG signals from different part of the brain. Now, we have also seen over a period of time how these electrodes are given the name or the numbers. For example, if we say that what is P that P letter stands for parietal if it says for T; T stands for temporal, if we say for F; F stands for frontal, if we say O; O stands for occipital and so on.

Also numbers letter P comes with 4 that it is a P 4 there is a region which is near by the inion, if it is at CZ it is at the central exactly here, if it is OZ or OZ it is by occipital backwards towards the nasion OZ so it is towards this inion and if it is F4 also it is near by the inion earlier I said F 4 is near by the nasion.

P 4, P 3, T 6 these are all nearby your inion while all this P 1, F 3 it goes towards the front; front is frontal so F always goes towards nasion. P and O always goes towards your inion. In another way if you want to just remember what I said is F frontal P and O is on the back side, C is in the center in that way you can remember it is easier. So, in the front side we say nasion, in the back side we say inion.

Now, once you have learn that we have seen that these electrodes are placed by performing the craniotomy that is opening the skull removing the dura and placing the electrodes on to the brain surface and then we also have this sEEG illustration here where the electrodes are placed inside the brain.

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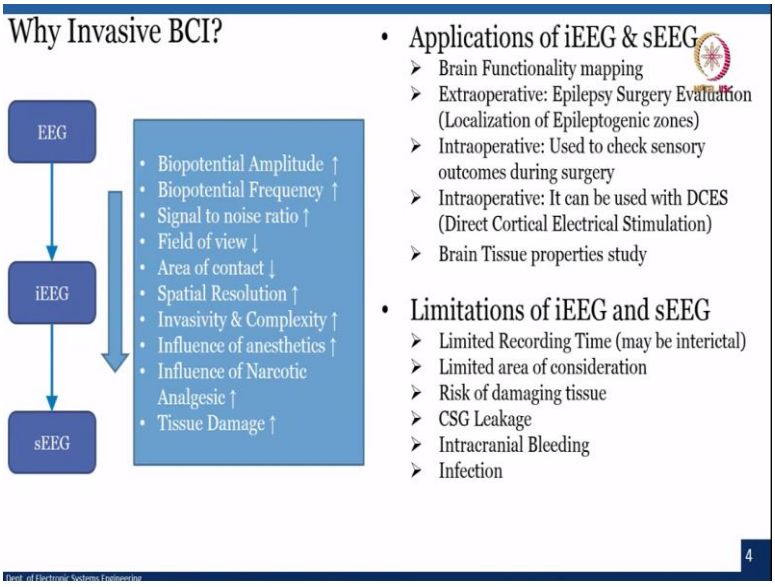

We have also seen how these EEG, iEEG and sEEG differs and what are the applications of the iEEG and sEEG and what are the corresponding limitations as well.

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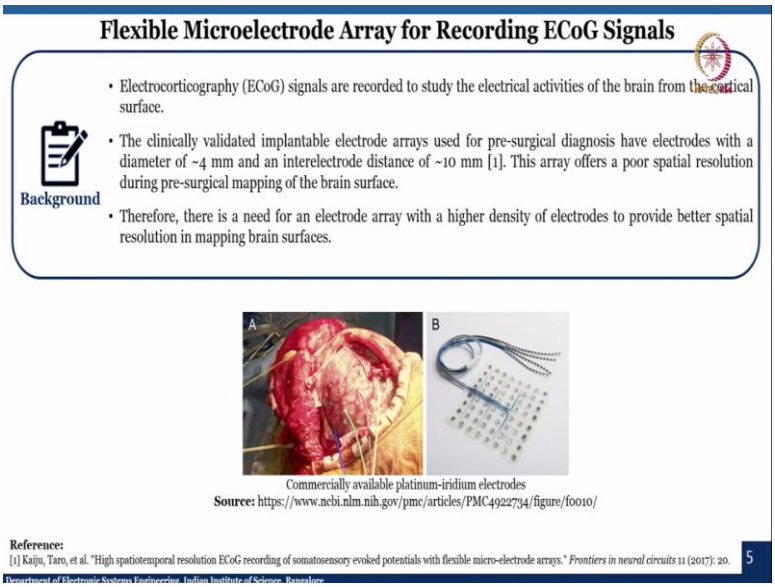

So, let us now go or dive deep into how to fabricate this kind of devices. One of the devices which is platinum iridium electrodes are shown here. It is a flexible device that you can place on the brain of a patient and you can see the corresponding image right over here. So, it can take the signals directly from the brain surface called electrocorticography and these are recorded to study the electrical activities of the brain and it is from the cortex.

So, cortical surface the clinical validated implantable electrode array is used for pre surgical diagnosis have electrodes with diameter of 4 millimeter. You see the size of the electrode and an interelectrode distance of 10 millimeter you can see this one, 4 millimeter and 10 millimeter. The array offers a poor spatial resolution during the pre surgical mapping of the brain surface.

So, that means that you have to have a higher density microelectrode grid array with 4 mm with 10 mm is not too good to get all the signals when particularly the resolution can be improved if you have a smaller number of electrodes and larger number of electrodes at a lower distance between 2. So, therefore there is a need for an electrode array with a higher density of electrodes to provide a better spatial resolution in mapping brain surfaces.

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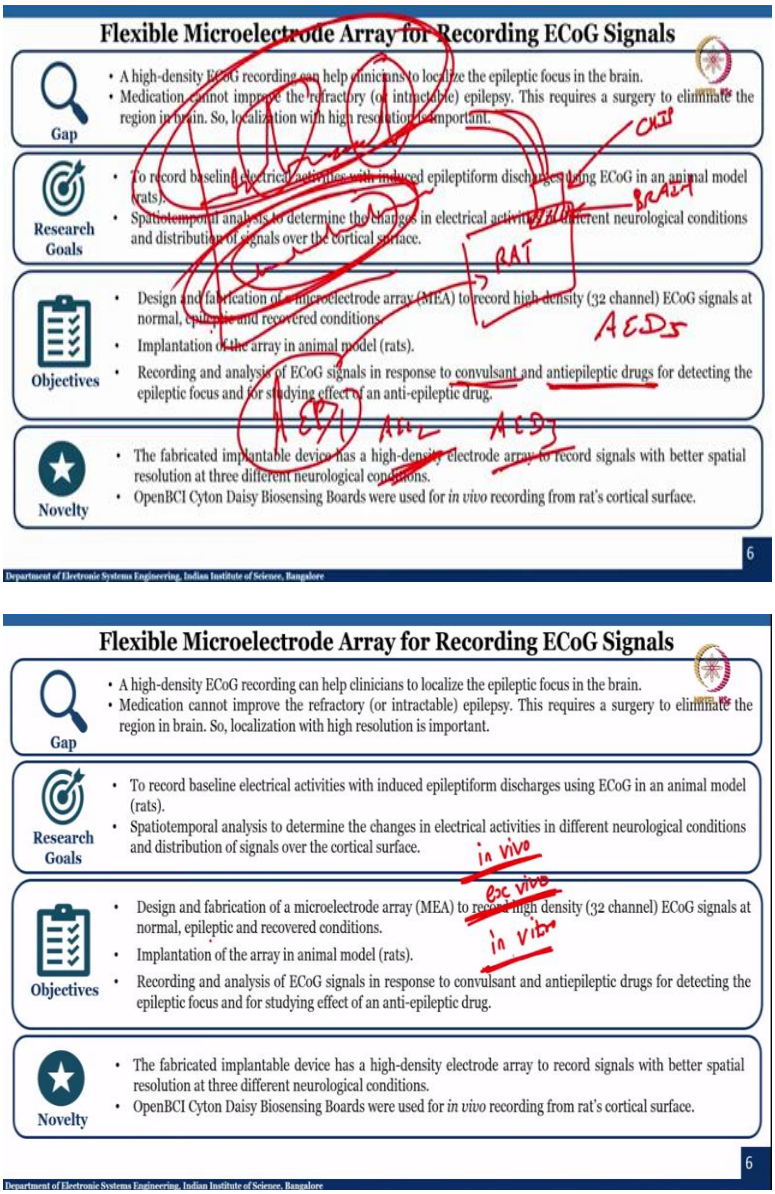

So, what are the gap? The gap is a high density ECoG recording can help clinician to localize the epileptic focus in the brain, right now we do not have that. Secondly, is medication cannot improve the refractory or intractable epilepsy and this requires a strategy or this requires a surgery to eliminate the region in the brain. So, localization with high resolution is extremely important.

What are the research goals if you want to pursue a research in this domain. If these are the objectives that you need to create a microelectrode array with high density electrodes then the goal should be that first let us record the baseline of electrical activity with the induced epileptiform discharges using ECoG in animal models then this spatiotemporal analysis to determine the changes in the electrical activities in different neurological conditions.

And distribution of the signals over the cortical surface. For that we can design electrode or microelectrode array to record high density ECoG signals and now we say that why 32 channel is high because now we are talking about an animal model that too also rodent model. Rodent means rat and mice rat we are talking about rodent, so we are talking about the rat's brain and it is very small.

And that is why 32 channels would be a high density recording electrode array. Implantation of array in animal models, recording and analysis of ECoG in response to convulsant and anti epileptic drug. So, what are we doing? So, let us say you have a rat here and you have placed chip inside the rat's brain. Let us say just assume that this is the rat's brain. Now, what we do is this chip has multiple electrodes.

And corresponding you will get electrical signals like this and you can say channel 1, channel 2, channel 3 and so on with respect to the time. Now, what I want to do is initially I want to create an epilepsy if I create an epilepsy which I will just mention the baseline. Baseline would be a normal EEG signals and then once I measure the baseline I will create an epilepsy by using the convulsant.

So, convulsant are drugs that will create or cause the epilepsy in brain and once you have the epileptic episode you have seen that right either this or some discharges compared to the normal signals without the convulsant would be like this. So, this episodes that occurs is because of the epileptic activities that can be created in the brain of the rat. Now, once it is there we will inject antiepileptic drugs here AEDs.

So antiepileptic drug can be induced or can be injected into the rat's body which will pass through and will reach the brain and it will cause the baseline from this signals random signals to a better EEG signals. Now, what you are observing here in this case is that this epileptic episode has been disappeared. If you can observe that means that AED that you have given is effective.

That means that if you have AED 1, AED 2 and AED 3 then you can understand which AED is better to recover the baseline from the epileptic signals. So, you can now test the efficacy the drugs antiepileptic drugs depending on the EEG signals that you can obtain with the help of the chip that is implanted in the rat's brain. When we say EEG I mean that ECoG which is electrocorticography signals.

Finally, from the novelty perspective the fabricated implantable device could have or should have high density electrodes because we have performed this already. So, that is why in this has high density since you already done it, but in reality if you want to just go through the gaps and if you want to find the solution then it should be the fabricate device should have a high density electrode to record signals with better resolution at three different neurological conditions.

OpenBCI Cyton tool were used for in vivo recording. We have discussed and all of you now know in vivo, ex vivo, in vitro, in vivo inside the animal body, ex vivo take out the tissue of animals, blood anything when you take it out and do the study in the lab by this ex vivo study on those samples. In vitro is something that you grow inside the laboratory and perform the studies on it.

So, the work we are now focusing on is the in vivo studies which is within the body, in vivo recording from the rat's cortical surface. So, let us see how it looks like.

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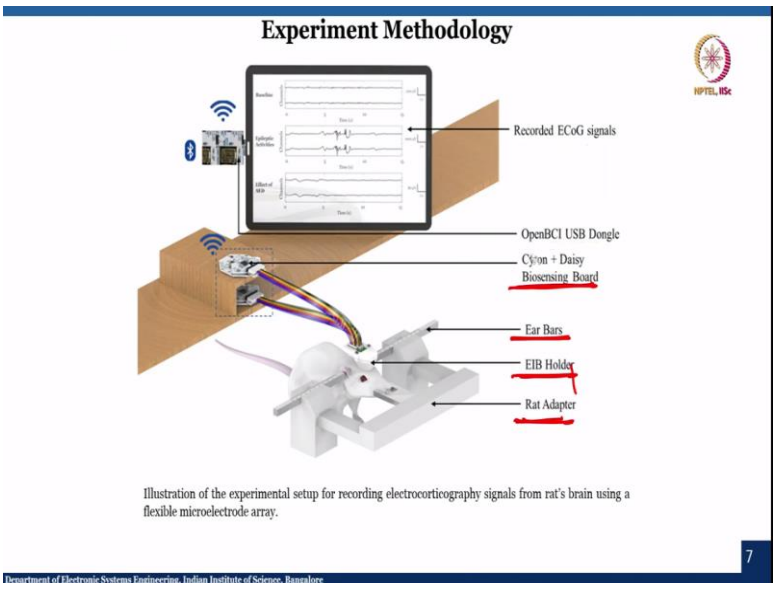

So, here you can see that there is a rat adapter, there is a EIB holders, there are ear bars, Cyton plus Daisy biosensing board, OpenBCI with USB dongle and these are the recorded ECoG data. So, the y axis is your number of channels which is this number like this and the x axis is time which is this one x axis here you can see is time in seconds and like I have drawn earlier the baseline that is initial baseline when you apply the convulsions you have the epileptic episode.

And then when you induce the antiepileptic drugs these episodes are disappeared that this drug is effective in image. So, this is how we perform the experiments. This is the schematic of how we perform the experiments.

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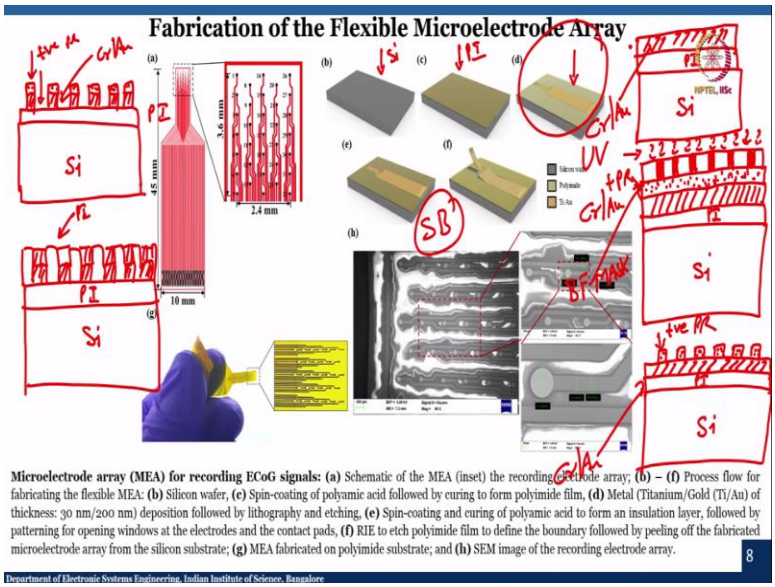

Let us go to the fabrication of the device. Now, in the fabrication of the device we have to learn that how the device should look like, how to implant the devices, where to implant the device all these things would be a question. The first thing let us understand this particular block what you see is a schematic of flexible microelectrode array. Now, where is the array? The array is right here.

If we zoom in you will find that there are 32 electrodes in this array. The dotted square box where is it, here is about 3.6 millimeter by 2.4 millimeter. So, it can be placed easily inside the rat's brain on to the area of our interest. The size of the device is 45 millimeter by 10 millimeter, but the microelectrode arrays that are 32 electrodes are covering only 3.6 millimeter by 2.4 millimeter.

The question is how you can fabricate such a fine structure or our miniaturized device. So, for that let us understand the process flow here. So, you take with silicon wafer and on the silicon wafer you spin coat polyimide which is this one this is a silicon wafer, this is your polyimide then you deposit chrome gold and pattern it. Now, how can we do that we all know I will just draw for you so that becomes easier for you.

So, we have a silicon wafer, on silicon wafer we have a PI polyimide on that we have your chrome gold. Now what we do is you load the mask, this is a representative image so do not worry about it. Now, what do we do our PI you have chrome gold so you have chrome gold here. On chrome gold you spin coat photoresist which kind of photoresist, positive photoresist. After coating positive photoresist what is the next step it will go for soft bake.

After some soft baking you can load the mask, this is a mask, what kind of mask is this? It is a bright field mask. So, this will be my bright field mask. All of you know the next step, next step is your UV lithography. So, you expose the photoresist, where photoresist, here and what is this light, this is UV light. So, when you expose the photoresist with UV light and you have the bright field mask it is a positive photoresist the same pattern will come on the wafer.

So, what we will have? We will have a silicon wafer with PI and chrome gold followed by the pattern that we are supposed to wet. So, what you have here? You have actually let us not draw this you have your PI and then you have your chrome gold, this is silicon your photoresist will stay like this and what is this, this is your chrome gold and below that is our PI. This is what you get why because you have a bright field mask and you have positive photoresist.

So, whatever the patterns are there on the mask will come on the photoresist. Once you have this you have to perform the hard bake, hard bake is done at 120 degree centigrade and for 45 minutes on hot plate. After you do the hard baking then you dip this wafer in gold etchant followed by chrome etchant. Whenever you dip any wafer with the photoresist or perform any chemical reaction you have to wash it with DI water.

So, whenever you dip the wafer in gold etchant you take it out and then you can dig the wafer in the gold etchant and once you dip the wafer in the gold etchant you take it out and you rinse it with DI water. Same thing is what is below gold there is a chrome. So, when you take out from the chrome etchant after gold you dip in the chrome etchant you take it out rinse it with DI water and then dry it and then go next step.

Always remember when there is a chemical involved you have to dry it with nitrogen and before that you have to rinse it with DI water. So, once you have this particular pattern what is the next step if you see the slide once you have the positive photoresist on the chrome gold and you are dipping the wafer into the gold etchant followed by DI rinse, followed by chrome etchant, followed by DI rinse then what you will have you will have a PI.

I am showing representative do not worry about how 6 becomes 4 or let me just draw it for you because sometimes you copy exactly same thing whatever I draw. So, let me just draw exactly what you want to see and that is the silicon and you have your polyimide and then you have 1, 2, 3, 4, 5, 6 and that is the chrome gold and above the chrome gold there is 6 photoresist. So, this is our positive photoresist and below is your chrome and gold.

So, why you cannot see anything here because the area is not protected by your photoresist that is why you cannot see. After this you can dip the wafer in acetone if you dip the wafer in acetone then what you will have you have silicon, PI and you have chrome gold that is it. So, once you have this that means we are here. These are process to pattern the chrome gold on to your PI. Now, instead of chrome we are using titanium it also works equally well.

It is used for improving the adhesion of the gold on to the substrate because directly if we deposit gold it may not have a better adhesion. Now, what you do once you have it you again coat PI again coat polyimide everywhere and then you only open contact at the required region. You only open contact in the required space is like this. So, everywhere there is PI this is your polyimide and here is your contact.

So, it will be like almost in the same level. So, I will just make it close to the gold level like this. So, polyimide is only kept at the places where you want to take the contact. Now, what does that mean let us see in the schematic it becomes little bit easier. So, what I said is once you have the chrome gold which is pattern you spin coat your PI once again cure it and then you go for lithography only open this contact window.

You can see here black dots these are all the recording electrodes these black dots are your recording electrodes. So, you only open those and you open the contact electrodes here there are 32 contact electrodes. So, 32 contact electrodes are open, 32 recording electrodes are open and remaining area is all protected by your polyimide or PI. Once that is done you can release the device because it is a polyimide.

And you can easily pull that off after cutting it from the substrate. So, how the device looks like it is like this, it is flexible in nature and if it just zoom in the recording electrodes you will see that there are 32 beautiful electrodes, there are pattern which are electrode material is platinum and gold. So, we have now device what to do with device? First, let us see the SEM image.

So, when you see the SEM image you will see that we can very easily and clearly see the contact electrodes always understand that wherever the contact electrode is there the metal is there. When a metal is there you will not have any discharges. Here you can see that lot of discharge is happening this is on the PI and not on the metal. So, this is how one single recording electrode will look like and I have shown that this is the complete device and this is the recording electrodes area.

The recording electrodes area is nothing, but what is the dimension 3.6 by 2.4 millimeter. Why we say this is area because this is for the rat experiment. This is what it is if you read the caption it says that schematic of MEA inset is showing the record in electrodes b to f is process flow for fabricating flexible MEA from silicon wafer is spin coating of the PI followed by curing, metal deposition followed by lithography and etching.

Spin coating and curing of PI to form an insulation layer followed by opening windows at the electrodes and contact pad side at the electrodes this dotted points we have to open the windows. A window is that so that we can remove the PI from that because PI is an insulator it will not make a contact with the brain the Ti Au is conducting material that has to be in the contact with the brain.

Finally, you have RIE to etch polyimide to define the boundary following by peeling off. So, you can use RIE which is right technique, but if you do not have it do not worry about it you can still go for a little bit bigger, but with a blade you can cut it little bit bigger dimensions. Now, g where is g, here, this g is nothing, but MEA fabricated on polyimide substrate and finally the h is there the SEM recording of the electrode array.

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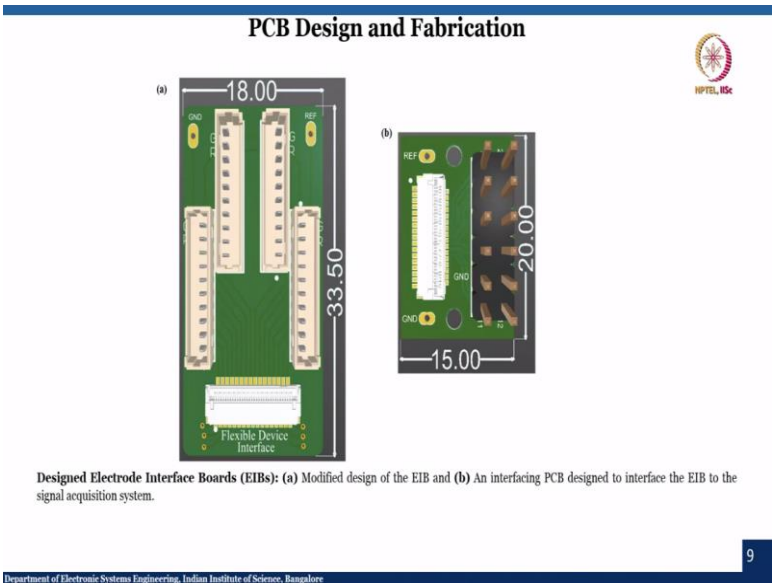

Now not only we need to worry about the sensor that we are designing, we need to also think about how to take the contact from the sensor. So, to take out the contact from the sensor we need to worry about how the printed circuit board design would be there because that will be the interfacing module from the sensors to the acquisition electronics. So, here you can see that a shows modified design of the electronic interface board or EIB and b shows an interfacing PCB design to interface the EIB to the signal acquisition system.

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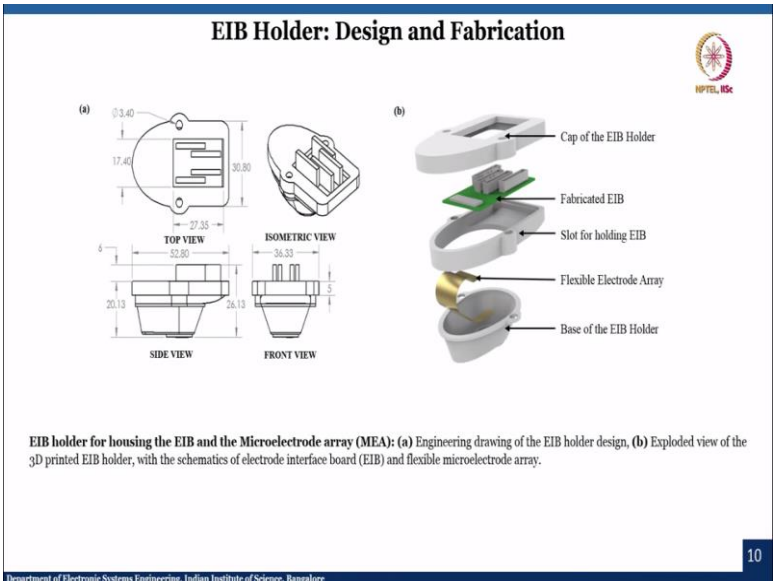

Now as I said that this area is not just only for people in neural science it is also for people in engineering, it is also for people in mechanical engineering, in electrical engineering which

has many facets like signal processing, sensor fabrication, electronic system design and UI development. So, lot of things are involved when you talk about neural science related projects.

Some projects are simpler when you already have data and you are just doing the signal processing or understanding the algorithm, but when you do the experimental procedure lot of things are on stake and that is why we have people or experts from different area working together to find a solution. Now in this case what you can see is holder to design fabrication. So, holder why we have fabricated because when you put this holder on to the rat's brain then whatever the disturbance because when the rat is moving or something else we can kind of save the animal in that particular manner.

So, a are the engineering drawings where you can see the top view, isometric view, side view and front view while the b is experimental view of the 3D printed EIB holder, what are inside the EIB holder that is what we have shown it to you.

The first one is the cap of the holder, second one is the fabricated EIB, third is slot for holding EIB and fourth is flexible electrode array followed by base of the EIB holder. So, all these things require a significant amount of time and optimization to make sure that the board you completely fit on the rat's brain.

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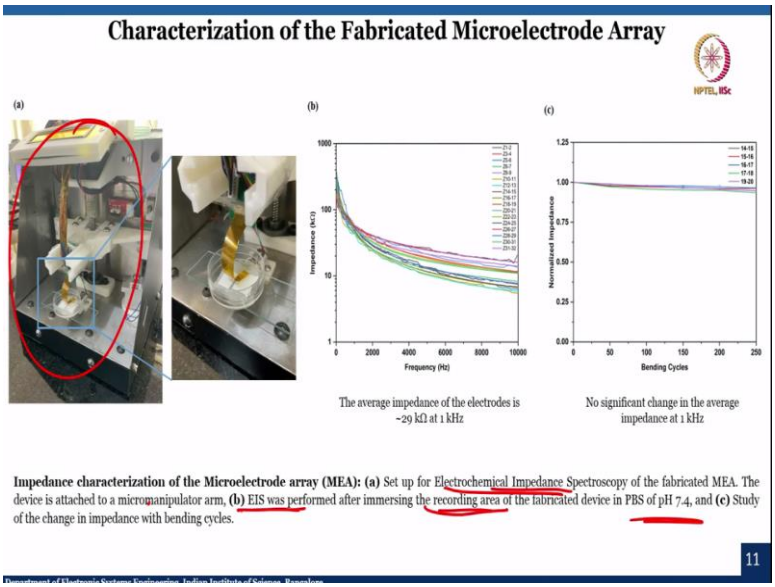

Now as long as the characterization is concerned we have to characterize every device and every channel of the device and you can see here that the impedance value of all the

electrodes when you average it out it is about 29 kilo ohm at 1 kilohertz. There are questions on how to select the frequency, but that we have taken into account. Then is bending cycles how many times it will bend so that also we need to perform the experiment.

And what we identified is that with bending cycles also there is no change as long as 1 kilohertz is the frequency. So, that is all about the characterization technique for fabricated micro electrode array and it is exactly the same thing. So, this is a electrochemical station or impedance spectroscopy for fabricated MEA the device attached to micromanipulator and EIS was performed electrode impedance spectroscopy is performed after immersing the recording area of the fabricated device in PBS at 7.4 pH. And finally the study is here is nothing, but the number of bending cycles the device can go through this is just in case.

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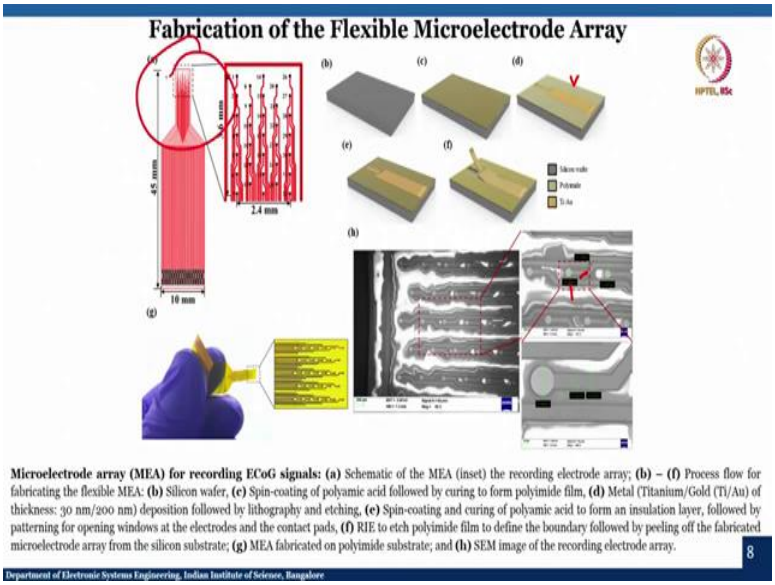

But here you can see that their device is implanted on the cortical surface of the anesthetized rat. So, this implantation procedure for a is photograph which is the 32 channel here fabricator this generally is nothing, but this one this device. So, we take this device and implants in the rats brain you can see here. Now what you so this is a photograph of actual device the b is nothing closure of the craniotomy hole using dental cement after MEA placement.

Next is immobilized rat you can see here the rat is immobilized and it is in stereotaxic so immobilized rat in stereotaxic apparatus after implantation of MEA and zoom in view with EIB holder or of the EIB holder.

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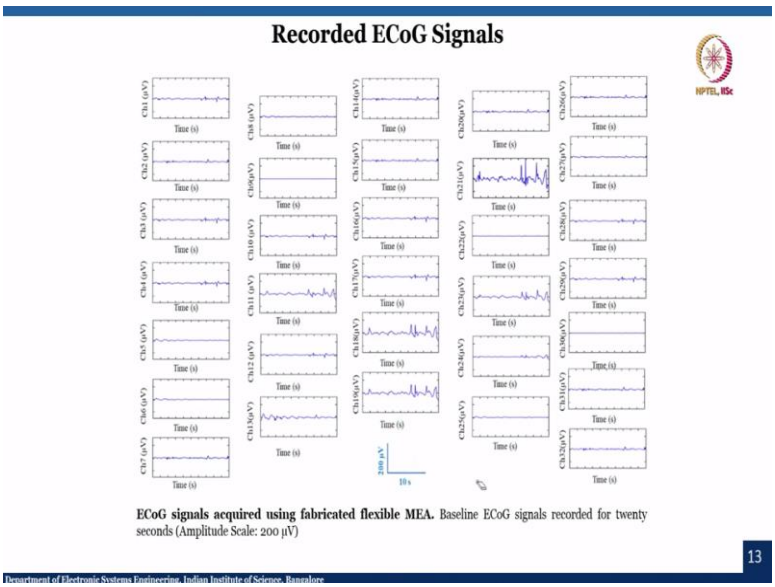

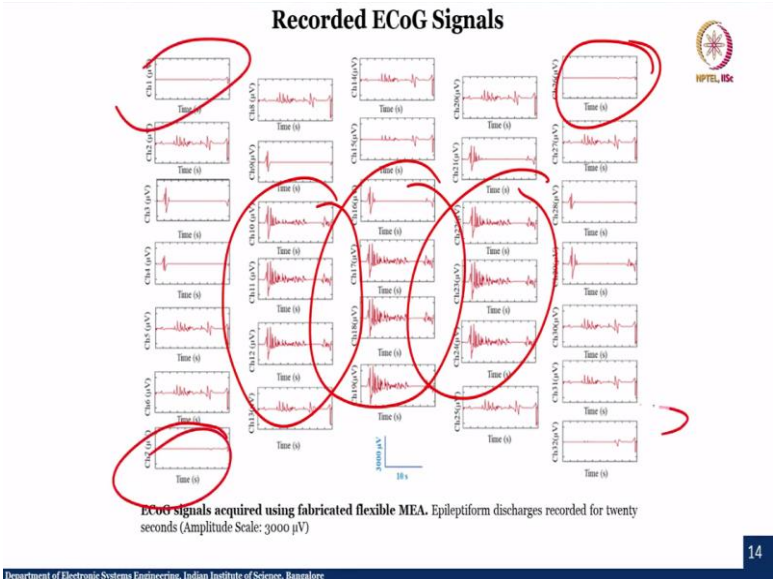

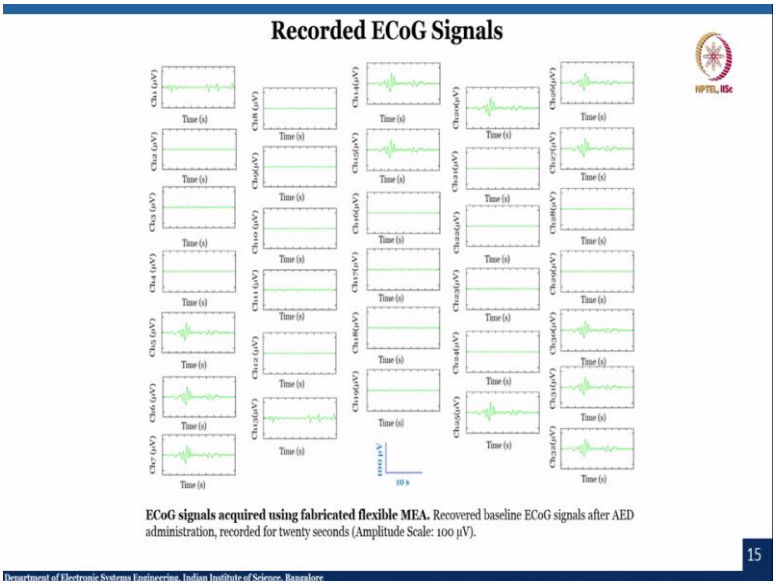

So, what happens like I said that we need to understand what happens when we measure this ECoG signals from the brain. So, when you are going to measure the ECoG signals from the brain then you will have the baseline. What is baseline? Baseline as a signal which are within few microvolts because we already know that EEG is within few microvolts. So, here you can see that all the electrodes are showing the change except 1 or 2 because it may not be touching the cortical surface region or surface of the brain.

In this case you just focus on the brain surface. So, we can see all 32 channels y axis microvolt and the x axis is 10 milliseconds. So, all this data that we are showing it is only for 10 millisecond of recording.

But when you use convulsion then what happens is certain area, certain region in the brain it starts like what happens when you apply convulsion either it is generalized. A certain part of the brain starts the epilepsy and it moves to all the region or it is everywhere. So, it is generalized or it is focal and it moves to other region so focal to generalize. So, depending on whether convulsion you are placing on the brain of the rat.

So, when you do that what you observe is that certain channel will show a higher epileptic episode as you can see on the screen while certain channel may not because wherever the epileptic episode is there, there you can see the burst of signals if you see the screen you can see the burst of signal in some of the channels compared to the other channels like this one channel 1, channel 7, channel 23 or 32 and so on and so forth.

So, certain channels will show a higher change certain channels will not show the change that means that the regions of interest is somewhere in the center here. So, let us see further. So, at the epileptic form here this is 3,000 microvolt you see here 200 microvolts versus 3,000 microvolt. So there is significant increment in the voltage levels, the amplitude levels and that is due to the burst or spike or slow waves or spike plus slow waves or sharps. It maybe for several reasons, but the point is looking at the signal it is an epilepsy data.

Now, what we do is that you administer the AED in the rat and then you will find that in sometimes you are able to recover the baseline as you can see from this particular schematic. Here the y axis is only 100 microvolts and then x axis is 10 seconds and you can see this is way lower than your 2,000 microvolt and even lower than the 100 microvolts in the like you can see one second 200 microvolt which is the normal region.

And it is lower than the 3,000 one and when you recover the baseline it is only 100 microvolt. So, what I am saying from this stuff is that if the epilepsy or anti epileptic drug is effective you can recover the baseline. Why you can recover the baseline? If you see the baseline it looks like this. Now, when you create epilepsy it looks like this, if the epileptic drug is good it looks like this you see so you have recovered the baseline that is what it means.

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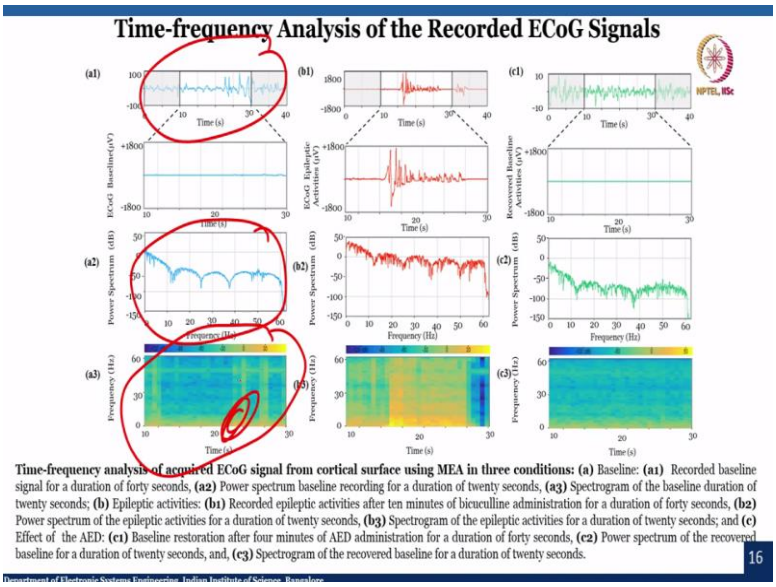

And let us see the time frequency analysis of the recorded ECoG signals. Here again the time in x axis is 40 seconds we are only considering 10 to 30 which is 20 seconds of the data and the y axis is minus 100 to 100 and then you have minus 1,800 to 1800 when it is epileptic episode. You can see that how the time frequency of the required ECoG signal from cortical surface varies right in presence of the AEDs.

Now baseline is a and then a 1 is the recorded baseline for duration of 40 seconds which is here b 1 is the recorded epileptic activities after 10 minutes of bicuculline administration which is here and b 1 so a 3 is spectrogram of the baseline duration of the power spectrum you can see that only in certain region it looks like more effective. So, from this we cannot really conclude that it is present in the potential.

So, from this what we can compute that the epileptic episodes are not there in this particular signals, what we can see is only solely the EEG signals. What we can see is only showing the EEG signals. Another thing that you need to see that there is a dip after 60 hertz frequency that is because we are using here open BCI which is limited to 125 hertz and the half is about 60-65 or 60 hertz.

But if we go for your own hardware you can increase the frequency range as well, but in case of epileptic episode when you see the time frequency analysis you can very easily see this yellow band you can see here they are very faint, but when you see the yellow band in this case they are much more easily can be seen and in this case it is almost there. So, you have kind of recover the baseline very well after the epileptic episode has occurred.

And how we can recover by using the drugs that is which kind of drugs, anti epileptic drugs. It is the same thing written again and again like recorded epileptic activities and then you will have the power spectrum analysis followed by spectrogram same thing again c2 power spectrum analysis of recorded signal spectrogram of the recorded baseline for 20 seconds. So, this is all the data that is I have for you.

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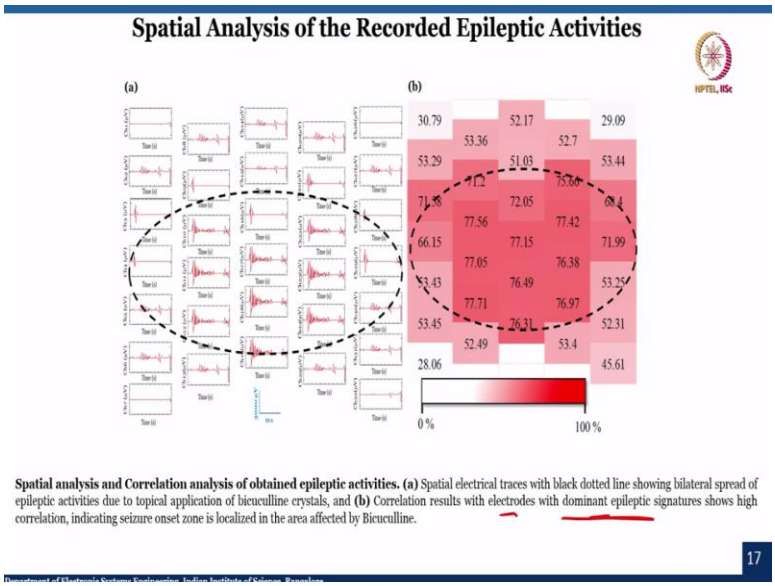

In the next class what we will see is how to take it further, but let us complete here. So, since we have observed this, so from this can you at least say that where is the maximum number of the epileptic episode we may not be able to do the source localization here, we may not be able to tell you exactly where the things are happening, but from here at least we can say that this is the region in the brain where the epileptic episode has occurred compared to the other regions of the brain.

So, this is what the image shows that this particular image where it shows the same thing. So, if you read it is a electrical traces with black dotted lines showing the bilateral spread of epileptic activities due to the topical application of the bicuculline drug. Bicuculline is a drug that will cause the epilepsy and finally b is the correlation results with electrodes with dominant epileptic signatures.

So, high correlation indicating the seizure onset and is localized in the area affected by the bicuculline. So, very interesting let us see the next set of the microelectrode array for some other application. Now here we can understand now that if you have three different drugs and if you place the electrode, you can test all this three different drugs to see which drug is more

effective and which is the efficacy of which particular drug is more compared to the second or third drug.

This can be used for the pharmaceutical industries to test the drug and see its effectiveness, but when you talk about the Parkinson and you talk about what kind of electrodes we need to fabricate, we need to design, we need to implant then the whole game is different. So, we will see that how we can design in fabricating electrodes that can be applied for a very important problem which is the Parkinson.

So, if you have any questions again as I always tell you feel free to ask me either on the forum and through the live lecture I already I am available in the live lectures, if you have further questions you can always meet online during the live lectures, you can ask me anything that you want and if there are very critical questions that we cannot address during the interactions because one hour is a interaction time then you can always send me an email.

Now, email should be informative and email should be full of curiosity that how it happens rather than saying that how can I get job in so and so place. So, I am just kind of telling you from my experience that most of the time students are confused of what to ask. NPTEL forum or a forum like this is supposed to clear your doubts since this is not one-on-one or in person teaching.

When I am in person teaching you can ask me lot of questions, you can debate with me, you can be curious as you want, but the curiosity level should not go down because I cannot interact with you in person, but I can always interact with you through the NPTEL forum in one way or other. I hope that you understood a bit on the microelectrode array, high density electrode arrays how you can use it for epilepsy.

And how to use it for understanding the efficacy of AEDs that is anti epileptic drugs. So, till then you take care I will see you next class with more about micro electrode arrays for understanding a very important disease and probability curing it and which is the Parkinson till then you take care I will see you in next class, bye.