Microsensors, Implantable Devices and Rodent Surgeries for Biomedical Applications
Course Instructor: Dr. Hardik J. Pandya
Department of Electronic Systems Engineering
Indian Institute of Science, Bangalore
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Now, let us understand what we have learned, and then we will start understanding how to fabricate neural implants, okay? So, we have learned what the substrate looks like, which is silicon. We have learned what the substrates are like they can be silicon, glass, or polymer. We have seen physical vapour deposition techniques, and we have also understood a bit about chemical vapour deposition techniques. We have seen the photolithography process, and we have taken a few examples of how to use photolithography to pattern certain materials. We have also looked into etching techniques, whether it is wet etching or dry etching. Within etching techniques, we also discussed reactive ion etching, plasma-based etchants, and deep reactive ion etching. Now, bulk micromachining and surface micromachining will be taken in the next class because there we will be kind of understanding how those processes can be used when it is a silicon-based process technique to fabricate a cantilever or to fabricate a diaphragm for certain applications such as gas sensors. But in this class now, what I want to teach you is the fabrication of microelectrode arrays. So, let us understand why we want to learn this microelectrode array and what exactly this array is.

So, let us take an example of epilepsy, okay? Epilepsy is also known as fits or seizures. Generally, these fits or seizures are treated by using medication called anti-epileptic drugs, but there is epilepsy which is called intractable epilepsy in which the drugs are not effective. So, to cure that kind of epilepsy, a surgeon has to open the skull, which is a craniotomy, reach the area that is causing these seizures or epileptic episodes, and reset that area using surgery.
So, the electrodes are implanted, because we need to understand which area within the brain is causing what kind of electrical activity and where exactly the seizures are occurring. So, the electrodes, which are potassium iridium electrodes, these arrays are there and are implanted onto the brain, okay. So, this is our skull, this is our head, and when you open the head, you will find a skull. When you open the skull, there is a dura, and when you open the thin layer of the dura, there is a brain in CSF cerebrospinal fluid. In that part, we have Dr. Shabari Girishan, who will be teaching you in detail about the brain and brain-related activities because he is the one who implants the device, and he is a functional neurosurgeon. So, also implants a DBS electrode, which is a deep brain stimulation electrode for Parkinson's.

So, let us understand those details about how it is done through a neurosurgeon. I will be talking more about whether this is a process, how to implant or how to fabricate this implant, and why we need to fabricate this implant. So, the current implant, as I told you, is made up of platinum-iridium electrodes, and the electrode size is quite big, and also the resolution is poor because they are not too close; it is not high density. So, we had two ideas: one, can we fabricate high-density electrodes using the microfabrication technique for acquiring the ECOG signal? So, what is ECOG? Now you understand the signals that we acquire from the scalp, right, from the head; they are called EEG signals or electroencephalograms.

ECOG stands for electrocorticography. So, when you acquire the signal from the brain using these electrodes, we call this ECOG electrode. We want to have high-density electrodes. Why? Because otherwise, we need to import these ECOG electrode arrays, and a customized version is extremely costly. So, how to bring down the cost is one of the facets, but the main thing that we are focusing on right now, and I will be teaching you, is how to fabricate this high-density electrode microelectrode array. So, once we have a clear idea about why it is used we can finally use it in humans.

So, if the resolution is better, the area which is causing these episodes we can acquire it or we can know it precisely. Second, if we have this microelectrode array and we want to test the efficacy of a drug, which is your anti-epileptic drug, whether the drug is effective or not, right? Then we can use, or probably use, this array to understand the efficacy of the anti-epileptic drug. So, with these two purposes, we started fabricating this device, and this device we call a microelectrode array. Why a microelectrode array? Because there are electrodes that are in micron dimensions and it is high density, but to start or to reach humans, we have to start with animal studies.

So, we will focus in these few lectures on rodent models, we are using rats. So, we will see how we have fabricated the device and how the device can be implanted, or rather implantation, again I will leave it to Doctor Shabari's lecture, but once the device is implanted, how we acquire the signal, and how can we create a seizure or fit or epilepsy in rodent models and how a device can be used to understand the efficacy of an anti-epileptic drug, okay. So, these are a few of the things that we will be discussing. So, if you see the slide, this slide shows electrocorticography signals that are recorded to study the brain from the cortical surface. If size already, what is ECOG, but more than that, let us first see this particular figure or schematic, or no, it is not a figure, it is a figure of commercially available platinum-iridium electrodes, which you can see here and the electrodes when they are implanted onto the brain of a patient. So, the clinically validated implanted electrode arrays, which are, let us say, this, are used for pre-surgical diagnosis have electrodes with a diameter of 4 millimetres.

So, each electrode is 4 millimetres in diameter and the distance between two electrodes is 10 millimetres. So, as I told you earlier, this array offers poor spatial resolution during the pre-surgical mapping of the brain surface and thus there is a very clear gap that we can find a solution to fill that gap and that is that there is a need for an electrode array with a higher density of electrodes to provide better spatial resolution in mapping brain surfaces. The application or one of the applications can be epilepsy. So, with that, these are the gaps, what are the research goals, how the objectives can be designed and what can be the novelty of the device that we will be fabricating? These are some of the things that can be also of importance for students who are pursuing their master's research or PhD studies to see that once you understand the gap, how can you fill the gap and how to put your slides together to understand the novelty factor, to understand what can be objectives to reach to achieve the aim, and what can be the research goals. So, the gap as clearly can be seen from the first statement, a high-density ECOG electrode recording can help clinicians to localise the epileptic focus in the brain, but this is not there, high-density electrodes are not available.

Secondly, medication cannot improve the refractory or intractable, epilepsy; this requires surgery to eliminate the region in the brain. So, localization with high resolution is important, which is not available or which is not possible with the current electrodes. So, the research goal can be to record the baseline electrical activities with induced epileptic form discharges using the ECOG animal model and to understand how spectral temporal analysis determines the changes in electrical activities in different neurological conditions and the distribution of signals over the cortical surface.

So, once you have the device implanted in the rat's brain, let us say these are the electrodes touching the rat's brain then one is that you can obtain the ECOG data, but the second is to understand that if there is an episode somewhere, let us say this is the episode and these electrodes, let us say this one is 1, 2, 3, we can have many, but I am just giving some examples then this is not how the electrodes are so uniformly placed because the brain is extremely plastic, but let us say 4 and 5 are showing high electrical activity right. So, you will see that other channels will show less and this will show very high activity like scissors alright like this something like this and we will see in the next slide.

So, the one is to understand the high electrical activity and the second is to understand the effect of the existing drug. So, for this, the objectives are to design and fabricate a microelectrode array which is a high-density microelectrode array, in this case, we say 32 channels is high density, but you say 32 channels how can be high density because we are talking about rat's brain and for a rat's brain which is extremely tiny. So, for a rat's brain, 32 channels is a high-density ECOG microelectrode array and we have to implant this in the rat's brain and record and analyze the ECOG signals in response to the convolution

and anti-epileptic drug. What are convulsants? Convulsants are the drugs that will cause epilepsy.

So, bicuculline is one of the convulsants and we can also give electrical stimulation to the rat's paws to create epilepsy episodes or seizures which is as per the literature. We do not do any novel drug formulations, but we rather focus on the fabrication of the device. So, once we implant the array in the animal model the next thing is recording and analysing of ECOG signal response to the convulsants and anti-epileptic drugs for detecting the epileptic focus and for studying the effect of anti-epileptic drug or efficacy of the AEDs anti-epileptic drugs. So, there are multiple novelties, but let us understand first what are we talking about what we are talking about is we will have rats we will do the craniotomy implant a device once the device is implanted we acquire a signal. You can see the baseline signal which you can see here because these signals are acquired and processed through the cyton-daisy biosensing board.

Generally, a cyton-daisy biosensing board is used to acquire the EEG data from humans, but we have used this cyton-daisy board to acquire the ECOG signal from the rat brain. Once it is acquired, it can be transmitted via Bluetooth using the USB dongle to the display, and we can see the ECOG data channel-wise on this display. Now, when we load the convulsants or apply electrical stimulation to the rat's paws, the seizures would occur. Also, we can see with the same device implanted in the rat's brain. When we administer an anti-epileptic drug, the baseline is recovered. So, the first and third should be very close, and the second channel is for the first experiment to acquire the signal, which we call baseline, the second experiment is to create epilepsy, and the third one is to recover the baseline, not recover, but to see whether the baseline is recovered or not by using the anti-epileptic drug. So, if the drug is effective, you will see that 1 and 3 would be kind of similar, but if the drug is not effective, then the seizures will continue, and the epilepsy is not treated.

Now, let us understand the fabrication, and you use all the understanding till now to focus on this slide. So, what we have done is you start with the silicon wafer, which is the base substrate to hold the actual substrate, which is our polyimide. But, you have silicon on this, and we can spin-coat the polyimide, which is here, and then we cure the polyimide on which we deposit titanium and gold because titanium helps in improving the adhesion to gold. So, we have titanium gold, and then this titanium gold everywhere is patterned. It is patterned, and then finally, the electrodes are covered by another PI layer, and only the contact pads and the recording electrodes are opened, followed by realizing the device. So, now, what I said you see once you pattern this. Okay, so this much is easy, let us understand how to pattern it. Okay.

I will just give an example with one electrode, and then we can take it further. So, as I said, we have a silicon substrate and on the silicon substrate, we have a polyimide layer.

On polyimide, we are depositing titanium gold, and then we have a silicon substrate on this. We spin-coat photoresist, let us say it is positive photoresist, and on this photoresist, we have the mask. This is a cross-section, we have the mask. Now, of course, when we spin-coat photoresist, what is a step? The step is that we have to soft bake, and soft bake is done at 90 degrees centigrade for 1 minute on a hot plate. Now, this is our bright-filled mask. The fill is bright, and the pattern is a dark, bright-filled mask. So, after soft bake, we load the mask, and then expose it to UV light, then you unload the mask, and develop the photoresist.

Developing the photoresist, what will we have? We will have this pattern, right? Because it is a bright-filled mask and is a positive photoresist. So, we will have a photoresist like this, and then what will we do? We will do the hard bake at 120 degrees Celsius for 1 minute on a hot plate, followed by Ti Au. So, Ti is at the bottom, Au is on the top right, first, is titanium followed by gold. So, first is Au etching. Dip the saffron Au etchant, then DI rinse, DI ionized water rinse, then titanium etchant, and again DI rinse, followed by drying in N_2 nitrogen.

If we do these steps correctly, what will we have? The titanium and gold will be etched from the area which is not protected by the photoresist. Titanium and gold will get etched from the area that is not protected by the photoresist, correct? We have seen this, forget the colour, it does not matter, we will use the same colour. So, the area which is protected by photoresist, you see the gold and titanium protected by photoresist is intact. The area that was not protected by the photoresist got etched. First is gold etchant, the gold is on top, followed by DI rinse, followed by Ti etchant, followed by DI rinse.

Once you do that, then you dip this wafer in acetone. If you dip this wafer in acetone, what will happen? You know acetone is an etchant for, or it is a stripper for the photoresist. So, a stripper for the photoresist. The photoresist will be stripped off. When the photoresist gets stripped off, you have the following pattern which you can see here, this is your PI and this is your Ti Au, correct? Now, this figure on this, what we are doing, we are kind of covering silicon. The PI, again, is polyimide, because polyimide can also work as an insulator. And now, what we are doing, we are opening the only contact pads remaining area. We want to have polyimide, why? Because you see here that these lines, right? Everywhere, the line should be protected by the photoresist, by the Pi, which is an insulating material.

So, that there is no short circuit. Only the contact pads, which are this one, this one black one is a contact pad, and the recording electrodes 1, 2, 3, 4, all the way to 32, only those electrodes, the PI, which is the insulator, should be etched, do you understand? So, first, everywhere, we have the gold titanium pattern, Ti Au pattern, followed by an insulator is your polyimide. So, this is an insulator. So, first, you deposit the gold pattern, the gold,

then spin coat the insulating material, which is the same material which is your base material, which is polyimide, okay? So, you spin coat polyimide, and then from the recording area, which is this area, the circles, okay, the circles are recording area dots, and from the contact pads, because if you have an insulator on the contact pad, you cannot take the contact. If you have an insulator in the recording area, you cannot record. That is why the PI, which is an insulator on the recording area and the contact pad, we are etching, that is what it is here. Now, you have PI, and now you have to create a window.

So, that you can as the PI from the substrate. So, what we had I will just put a different pattern. So, it is easier 3 4 and 5 and then on that, we had a PI and here also we have a PI ok PI on silicon then PI as an insulator and here we have a titanium gold electrode array. What we will do is we will spin coat photoresist soft back and load the mask this will be our dark field mask and then after loading the dark field mask we will expose the photoresist through the mask with the help of UV light because it is our UV lithography is not it ok.

This is your dark field mask if and then what will we do of course we are forgetting one thing, what we are forgetting is that there is a photoresist because we have to spin coat the photoresist. So, this dot that I am drawing here is my photoresist positive. So, on the PI which is my insulator, we are spin coating positive photoresist soft peak followed by the UV light. Now you know that the unexposed region will be stronger and the exposed region will be weaker because it is a positive photoresist. So, we have a PI layer we have gold titanium and then we have a second PI layer.

So, then we had an insulating we had a photoresist. So, this is a photoresist layer because the unexposed region becomes stronger right and this cross that I am drawing here is a PI right because PI is an insulator PI is a substrate this is silicon this is titanium gold. Now what we will do we will do the hard bake and then we will etch the PI with a dry etching process. So, when you etch the PI with the dry etching process you will have you have PI you have your titanium gold and you have your PI protected by the photoresist here and from this area which is the area not protected by the photoresist the PI is etched right the PI is etched. Now we will dip this wafer in acetone when we dip this wafer in acetone what we get is our silicon we have the PI then we have our microelectrode array recording electrodes and contact pads where there is no PI.

So, here are your microelectrode array and a recording like contact and recordings for this recording forget about and recording and contact pads ok recording and contact pads and you can see that on recording and contact pad there is no PI because PI is etched right. So, after this, we will etch the PI from that area that is not protected by the photoresist you can see here followed by acetone dip. So, the photoresist is stripped off and we have this particular thing where we have a microelectrode array right on PI and

the remaining area the PI is protecting the pattern ok easy. So, now if you see this particular figure again you will understand it I hope that you understand it a little bit better that you start with your silicon substrate, then spin deposit your titanium gold, then pattern your titanium gold, then you deposit insulating material and then you open the contact pads which is here and open the contact pads and recording area contact pads means electrodes means that you remove the PI from the recording electrodes and contact pads because PI is an insulator followed by realizing a device by stripping the PI from the substitute which is your silicon substrate. Once you have that you will get a flexible microelectrode array with electrodes and the contact pads no insulating material everywhere else as an insulating material.

Now the question is why do you insert materials everywhere else when you implant now in this case only this section is implanted, it goes into the brain remaining section stays out because we are using 3.6 mm by 2.4 mm which is slightly smaller than the rat's brain. So, it very well fits with the rat brain the point is everywhere there is an insulator only the recording electrode insulator is not there and the contact pad insulator is not there because if the recording electrode insulator is not there then it can record well it can acquire the signal and there will be no short circuit between the electrode lines because PI is there. What is the insulator silicon dioxide what is the insulator silicon nitride, in this case, a PI can act as a substrate and Pi can act as an insulating material.

So, these are the implantable microelectrode arrays that are shown here in this photograph these are the SEM image scanning electron microscope image and each electrode also you can see close to 50 microns in dimensions. So, we will \l stop here and then in the next lecture we will see how to integrate this. Now we know how the device is fabricated how to integrate an EIB board right into the electronics interfacing board and then how can we create a casing. So, the device can be placed through the casing that sits on the head and the device should go on the brain right then how can we connect it with the open set on the BCI system? So, the idea is to not just show you the device, but also to take it further how to integrate the device and acquire the signals and then perform the experiments and understand how the device is performing. So, we also have a recording for wherever possible for the surgery, we have recordings for all the PVD, we have recordings for photolithography right, we have recordings for 3D printing.

So, it will give an understanding of different tools that need to be used for fabricating and implanting this device or microelectrode arrays into the brain in this case of a rat so we say rodent models. So with this, I leave you here and I will see you next lecture with more discussion about neural implants till then take care. Thank you very much.