Microsensors, Implantable Devices and Rodent Surgeries for Biomedical Applications
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Hi, welcome to this lecture. We are almost at the end of our course, and today we will discuss how we can develop a neuroimplant for addressing the important disease called Parkinson's. Parkinson's, if you see, is characterized by tremors. People who suffer from Parkinson's often have shaky hands, cannot hold a pen properly, and have difficulty feeding themselves with a spoon. Another thing you might observe is the gait or the way they walk. If they want to turn, there is a difficulty in turning. This disease is generally treated with medicine; one of the medicines I know of is Parkinson's medication. However, the treatment method involves using deep brain stimulation electrodes, or DBS electrodes, that go inside the brain, in some areas which we will be discussing in this lecture. We are considering whether applying electrical stimulation on the surface of the brain, rather than going deeper into the brain, might be effective. This leads us to two questions: one, what happens if we apply electrical stimulation on the surface of the brain rather than going deeper, and two, will apply electrical stimulation both at the surface and deeper structures of the brain help in improving Parkinson's?

I have a tiny video you can see here, showing a person walking. When the person is turning right, you can see that suddenly there is a freezing of gait, making it very difficult to turn. Once he turns right again, he walks normally. This is one of the things you can observe in someone suffering from Parkinson's.

As I mentioned, DBS is a deep brain electrode that goes deeper into the brain. Dr. Shabari Girishan, who is a co-instructor of this course, performs this surgery. You will directly see some of the very important procedures he carries out, not only in rodent models but also in humans. As engineers, we work with rodent models and non-human primates, but generally, we do not operate or implant devices in humans; that is done by neurosurgeons.

Globally, 10 million people are affected by Parkinson's disease, which is characterized by tremors, postural instability, and rigidity. Particularly advanced PD patients are treated with a clinical therapy called deep brain stimulation. The areas we are discussing are the subthalamic nucleus (STN) and the pedunculopontine nucleus (PPN). These are two different regions where symptoms have been improved in PD patients. However, several physiological complications are observed, and the outcomes of PPN DBS are heterogeneous. Notably, some side effects include nausea and vomiting. The questions

we are asking are: one, can we fabricate electrodes to test in animal models before testing in humans, and two, what is the combined effect of surface and deep brain stimulation? Current DBS electrodes are made of materials like platinum and gold, which have a low safe charge injection limit. Therefore, alternative materials like PEDOT: PSS, a conductive polymer, are used to improve the charge injection limit.

Mechanical flexibility is very important for deep neural implants. The red tissue has an elastic modulus range of 0.1 to 1.2 megapascals, while silicon-based implants have a very high elastic modulus, about 60 to 300 gigapascals. Polymer substrates, compared to hard implants, cause less damage when implanted in deeper structures, such as in DBS. The shape of the implant is also crucial. Sharp edges, as seen with needle-like implants, cause more trauma during and after insertion. In contrast, cylindrical-shaped implants induce less trauma due to their shape, causing less damage than sharp-edged implants.

Cylindrical-shaped implants induce less trauma. These are the advantages of deep neural implants. For surface neural implants, we have already discussed the current complications. The advantage is that, while the surgical procedure is complex due to the large grid area, the risks of infection also increase with a larger surgical area. Regarding the brain region, we are looking at an area in the motor cortex, but it is not precisely called the motor cortex. It is somewhere between this region, close to 3 millimetres, and the length from here is close to 8 millimetres.

So, we should have an electrode that can be placed in this particular section of the brain on the surface. If we talk about deeper structures, then it should go at least 7.8 millimetres deeper into the brain. Now, this is for the rat's brain we are discussing. Somewhere between SMA 1 and SMA 2 is where we refer to this structure on the surface, and it extends 7.8 millimetres into the brain of the rat.

If you want to design such an implant, you can see in this slide that we have one such design that will cover this 3-millimetre area shown here. We should have several electrodes in this area capable of acquiring signals from the brain. What are those electrodes? You can see in this design that there are five electrodes, and each electrode is 400 microns in diameter. The total area is close to 3.09 millimetres. So, it is very small. Additionally, we have the contact pads here, and the connection from the electrode to the contact pad is done in a wavy fashion like this. Why not straight? To reduce the strain when you flex the device.

The substrate thickness is polyimide, about 20 microns, which makes it flexible. The electrode material we use is titanium and gold, and sometimes we also use conductive polymer to improve the charge injection capability. I already mentioned the electrode diameter is about 400 microns. The interconnect line width is 25 micrometres. The

thickness of the titanium-gold is 30 nanometers for titanium and 3 nanometers for gold. The reason for using titanium is to improve the adhesion of gold onto the substrate. Gold generally suffers from poor adhesion, so people either use chrome or titanium.

Chrome-gold or titanium-gold are the two different materials. Titanium has excellent biocompatibility and adaptability to MEMS-based fabrication processes. Every electrode can support up to 1.25 milliamperes of current when gold electrodes are electropolymerized with PEDOT. The improvement in the charge injection capability is achieved by using PEDOT on the gold electrodes. Coating it on the gold electrodes or electropolymerization improves this capability.

The surface implant is placed on the left and right motor cortex of the rat's brain for these studies. Before doing that, we need to understand how the fabrication works. The first step is to take the substrate, such as a holding substrate (for example, a silicon wafer). On that, you spin coat polyimide and cure it. On this polyimide, you deposit a thin film of titanium and gold, and then you pattern this thin film in this fashion. This is your titanium-gold layer.

After this, you coat another layer of polyimide, which you can see here. Then, you open the windows for the contact pads and recording electrodes. After opening the windows, the actual figure shows the gold pads and gold electrodes shining compared to the other areas. This is because there is no polyimide on this particular gold or the contact pads. When you remove the polyimide, it acts as a substrate or as an insulating material.

After this, you can peel off the device, as shown in this photograph. Again, you start with silicon, coat polyimide, cure it, and deposit titanium gold. Then, you proceed with lithography.

So, again, if you want to see, you start with a silicon wafer, and coat polyimide on it. On the polyimide, you deposit titanium and gold. This is your polyimide; this is your silicon wafer. On the titanium-gold, you spin coat photoresist. Using a pattern, you can differentiate between the areas. Then you perform a soft bake and load a mask, assuming we are using a positive photoresist, and expose this photoresist with UV light. Once you do that, you unload the mask and then pattern the photoresist.

When you unload the mask, your polyimide remains intact, and your titanium-gold remains as well. The photoresist will now have the pattern because we are using a positive photoresist, so the same pattern on the mask gets transferred to the photoresist, and the area not exposed becomes stronger.

After this, you spin coat another layer of polyimide. Polyimide can work as a substrate or as an insulating material. After this, you spin coat the photoresist. I apologize, this is not

a positive photoresist; it is polyimide. Positive photoresist can be used, but negative photoresist can also be used. The mask has to be designed accordingly.

After that, you perform a soft bake, load the mask, and use a dark field mask because the area not exposed will become stronger. You need to be patient when learning microfabrication, as small mistakes will result in restarting the process from the first step.

This is your dark field mask. After exposing the photoresist using UV photolithography, you develop the wafer. What you will have after developing the wafer is shown here. We missed something in the previous steps: etching the titanium and gold. After hard baking and etching the gold followed by titanium, you will have this device, where PI and titanium gold are not etched from the areas protected by the photoresist.

So, when you unload the mask your PI remains as it is ok and your titanium gold also remains as it is and your photoresist now we will have like this correct. Because we are using a positive photoresist so, the same pattern that is on the bright-filled mask will get transferred onto the photoresist or the area that is not exposed becomes the stronger same thing. Now what we will do after this we will again so, this is step this is the step which is your C here ok you have a pattern this one this one. Now after this, we will again spin coat your polyamide layer because polyamide can work as a substrate but polyamide can also work as an insulating material. After this we will spin coat we will spin coat photoresist.

I am sorry, this is not a positive photoresist; this is your PI. Positive photoresist can be spin-coated, but you can also use negative photoresist, and the mask has to be designed accordingly. After that, you soft bake and load the mask. Now, we know that we need to open the contact region correctly. We will use a dark-field mask. It is called a dark-field mask because the area that is not exposed will get stronger. You need to be a little bit patient when learning microfabrication because a small mistake can result in restarting the device from stage 1.

So, this is your dark-field mask. After the dark-field mask, you expose this photoresist using UV photolithography and then develop the wafer. When you develop the wafer, what will you have? Did you miss something? Alright, you see we missed something here, here, and here. Did you miss something? We missed it, right? What did we miss? So, I'll draw it. In this case, whatever we have drawn, I'll draw it again. What happened is we missed etching the titanium and gold, do you realize this? See, we have PI on silicon, and then you have titanium gold. On that, you have this one. These boxes were your photoresist, right? So, you have your photoresist. Don't worry about this for now, okay? Don't worry about this one. So, you have this photoresist, and after that, we perform hard bake and then etch the gold followed by the titanium. Once you do that, you

will have this device where the PI and titanium gold are not etched in the areas protected by the photoresist.

If I dip this wafer in acetone, then I will have the PI with my titanium and gold. In that earlier case, we forgot to etch the titanium gold, as you can see here. So, let's not worry about this, okay? Now, let's say we have this wafer. After this wafer, we hard-bake the PI. Once we do that, we have etched the gold, followed by the wafer (gold is on top), and then we rinse it. Then, titanium is etched again, and we rinse it with DI (deionized water), dry it with nitrogen, and dip the wafer in acetone. Once you do that, you end up with this structure, let's call it A. After dipping the wafer in acetone, you get this structure. Now, after you have this, what's the next step? After having this structure, I will draw it here. You have your PI, and on this PI, you have your titanium gold. On this titanium gold, I will spin coat my PI again, because PI can act as an insulator and as a substrate. And here are my titanium gold patterned electrodes. After this, I will spin the coated photoresist and load the mask. If it is a positive photoresist, then we can have a mask that looks like this, which is your dark-field mask. After we load the dark-field mask, we expose the photoresist with UV. When exposed to UV (since your photoresist is positive photoresist), the unexposed region will become stronger, and the exposed region will become weaker. This is your UV light. After that, you develop it, and what will you have? You will have silicon, PI, titanium gold, PI, and photoresist.

Now, if I do a hard bake, and after that, I can remove the PI using oxygen plasma. What happens is that the areas not protected by photoresist will have the PI etched away. Once that happens, the final result will be that the substrate has the PI (this is the holding substrate), on which we have titanium gold, and the PI on the titanium gold will get etched, as you can see here. So now, this is your PI, and these are your titanium gold patterns. This is the insulating material, and now you have a substrate that is also PI. You peel it off, and once you peel it off, you will have the mask. Sometimes, we wonder why we only use positive photoresists and what happens if we use negative photoresists. If we use negative photoresist, the mask will look like this instead of what we use for positive photoresist. So, let's say you have your electrodes—1, 2, 3, and 4—with PI underneath, and now I want to use negative photoresist.

Now, you see that the pattern is exactly on the electrodes. This dark region is on the electrodes. So, if I have this mask with a negative photoresist, and I expose the photoresist through UV light, what will happen? The unexposed region will become weaker, and the exposed region (this region) will become stronger. The photoresist here will form a pattern similar to this one. You see this mask versus the other one—it is exactly the opposite. Wherever the transparent region is, it is dark, and where the dark region is, it is transparent. Simple.

So, don’t worry about using positive or negative photoresist. You can work around it by developing the mask accordingly. This is how microstimulation works. We have an open site on the DC board. Initially, we used current mirroring blocks with the PSOC 5 prototyping board. Later on, we had our electronic module. The electronic and circuit design has been discussed in the TA classes. The stimulation parameters required for stimulating the rat's brain include a biphasic current of 40 to 120 microamps, pulse frequency of about 300 Hz, on-time of about 200 microseconds, pulse train duration of 39 milliseconds, frequency of 1 Hz, and a 10-second simulation run. What we observed in the video is that we are in the motor area, which is why the rat's paw was moving. This is an operation theatre for a rat experiment (rat surgery), and you can see the patient (the rat) in the stereotaxic equipment here. The electrical stimulation circuit is right over here. There is a jacket that we place on the rat after the surgery. The electrical stimulation can be given via this jacket.

To understand all the parameters, we integrated the board on the jacket of the rat, as seen in this photograph. You can also see the top view of the PCB, using the PSOC 5 microcontroller. We have headers for programming and debugging, slide switches for the battery, an HM10 BLE header for Bluetooth signal transfer, a reset switch, and an FPC connector in this top view. We also have the cord PMOS array, indicator circuits, SPDT switches, a 5-volt voltage IC, and a JST connector for the battery. Everything is on one small platform, which is attached to the rat's backpack. The electrical stimulation is given through this platform, and the stimulation is still done through the open site on the BCI board. All the merits of this board are written here. This is a wireless electronic system connected as a backpack to the rat's body.

So this is the EIB with surface neural implants adaptation of layer 1 dental acrylic and finally the rat after recovery again there is a video where you can see the rat healthy and happy according to the rat feeding well drinking water well and based on this we were also able to collect some of the equation or the ECOG signals from rat's brain we were able to see how the when the rat is sleeping how the channels are behaving was even the rat is holding a grill versus when that is walking right so you can see that how the signals are changing for each channel. As I said we have 5 on one side for another side certain electrodes we again perform the power spectrum analysis and then you can see the frequency of the time scale for each of these activities. These are DBS arrays for humans and you can again see that this is a cylinder in structure I told you that was sharp versus a cylinder. The cylinder will have less damage to the human brain there are different types of simulation one is unipolar second is bipolar then there is an interleaving which is rapidly alternating there a multiple levels of simulation that you can given there can be directional ways of applying electrical simulation. There are several ways by which you can apply electrical stimulation but very few pieces of literature you will identify where

we have the electrodes for deep brain stimulation and that is how we came up with this particular design where we can have the sleeve module mechanism you have the deposition of gold followed by the PI again followed by gold again followed by the PI or you can use perylene so you coat the entire cylinder with gold then coat the other area with perylene again coat with gold with perylene so you will have like a sleeve mechanism. Electrode areas are on one end the contact areas are on another end this is about 3000 micrometres this is a quite big or long DBS electrode the whole design is for the Rodan model so what happens is you take a wire and you coat the wire you hold the wire between two fixed system and then you coat this thing with your sputtering or E beam you can have titanium gold or you can have titanium deposition so E beam or sputtering and then what you do is you just move this ring closer to here so this area is still protected like this it will be protected.

Now you coat and then you bring this ring also closer like this okay then what will happen everywhere you put a you coat a perylena P A R Y L E N A perylena is again an insulating material then you again coat the entire wire with gold again you bring this disc forward this disc forward so slowly gradually you will see that this sleeve kind of mechanism starts generating and this is a very interesting idea you can also use silicon dioxide but we prefer to use the perylene coating this some of the fixture design I am not going to too much detail about that because it requires another whole 3-4 classes to understand how we can design the base fixture or rotary stage or wire holder how we can add the stencils and wires on to this holder when you load this into the system how this whole rotation mechanism will work and how the coating on the cylinder will happen because you know that in thermal or E beam or even in the sputtering you cannot coat in a 3D fashion right you can only go for 2D fashion. This is a behavioural system for the right model now we will stop here okay because I want to make sure that I do not stretch to a different topic but the application of this entire neural implant is finally to test whether a rat is walking on a pad correctly or not so what we do is initially we have a normal rat and the normal rat walks on the or healthy rat that walks on this treadmill and it feeds through the container drinks the water and we can have the treadmill either in the stationary position or we can start the treadmill and rat will walk on the treadmill. Now when it walks on the treadmill or grabs food we can acquire all the signals the next stage is where we create a Parkinsonian rat. Parkinsonian rat is created by inducing a drug into the rat's brain and when Parkinson's happens the rat's gait will not be correct so the rat cannot walk properly when we apply electrical stimulation to the rat's brain using the DBS electrode that I have shown it to you in the previous slide and also using the surface electrode can we correct the gating of the rat means can the rat walk properly on this particular treadmill. So with these two mechanisms we will stop here once we have the videos of rat grabbing Parkinsonian rats improving the gating using the electronics and using the implant I will put the video for all to see in a later stage but for now, this is the

end of your class and the lecture and again as I have told you many times feel free to ask any question that you have through the NPTEL forum with this I wish you all the best take care bye.