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
Week - 01
Lecture - 02

In this class, we will look into why rodent experiments are required, what kind of experiments we have been doing, and how we can design several kinds of devices. We'll also explore existing commercial devices and examine some of the microelectrode arrays available in the literature. We will then see what kind of techniques are used for fabricating these devices. So, the first question is: why don't we directly go for humans? Why use rodent models? Why not even use nonhuman primates? Because of ethics, we need to prove that the technology or the device is performing well before we move on to larger animals. Also, generally, rats are used as models for mammalian brains, although they are not as developed as monkey brains. So, for certain applications, we can use a rat's brain or rodents for some applications where we are looking at fine motor moments. This is a motor because when we are walking, it's a motor moment. This is a gross motor moment. When we hold the pen, it's a fine motor moment because we use our fingers to hold the pen delicately. I will hold the pen, take it up, and then I can move it, right? I can manoeuvre it.

So, now, this is a fine motor moment for patients whose brain is injured in an accident or whose spinal cord is injured. Generally, the motor area is affected, and in the recovery phase, the gross motor moment is the bigger motor. This moment is possible to recover, even walking is possible to an extent. But the fine motor movements are very difficult, and that is why you see all these peripheral prosthetics that are used to help the patient do some daily routines. But why can’t we recover the fine motor moments? What is the anatomy of how the signal flows, right? These are all things that are very important for us to understand.

So, if you want to look into those kinds of research where we are looking at fine motor moments, then nonhuman primates are better because monkeys, we can see the motor moments. Rats' paws are kind of difficult. So, quickly, we can do some experiments with the rat and then move on to nonhuman primates. But if you want to understand some effects of drugs, the efficacy of drugs, anti-epileptic drugs, for example, right, then we do not have to go for humans. It is not possible to directly go to humans; we can start with rodent models. So, if you see the slide, why rodent experiments? It's because rats are used as a model for the mammalian brain. Second, some of their brain structure resembles the more primitive elements of human brains, and the research suggests that rats more accurately reflect human physiology than other species, mimicking human disease more accurately in many cases. So, the flow for implantable device research starts from the rat. Now, more or less, a cat is not allowed for research, but guinea pigs are allowed,

rabbits are allowed, we go for nonhuman primates, and finally, we go for human studies. There is a flow for implantable device research.

Anatomically, again, Dr. Shabri will discuss this in detail, but if you just understand the very top view, then let us see this B1. The frontal lobe, then we have the parietal lobe (red), then the PL which is the parietal lobe. Then the temporal lobe (green), and finally, the occipital lobe. Alright, frontal lobe, parietal lobe, temporal lobe, and occipital lobe. We are talking about the human brain. Further, if you want to understand, then there is the cerebrum, thalamus, and hypothalamus. This is your forebrain, okay? Three things: one, is the cerebrum, the Second is the thalamus, and the third is the hypothalamus. Then we have the corpus midbrain, and then the brain stem. It is the cerebrum, pons, and medulla. So, this is the internal view of the right hemisphere of the human brain with three main parts: forebrain, midbrain, and brain stem. If you see this particular schematic, which is in C, you see how the human brain and rat brain are compared, with different dedicated functions. For example, the initiation of motor actions, is the primary motor cortex, which is blue, and the same thing goes for the rat brain also; it also has a motor cortex. Then we have the somatosensory cortex or perception, which is the primary somatosensory cortex. This is a red color in the human brain; in rats also, we have the same thing.

And then we also have the visual cortex, which is the occipital region. And then we have the olfactory cortex. So, the yellow one is the auditory cortex. Then we have the primary somatosensory cortex, then we have the primary visual cortex, and finally, the olfactory cortex or olfactory bulb. So, these are the anatomical representations of human and rat brains. So, why we are talking about all these regions is because we will show you where we implant the device in which region, okay? That is the reason we are showing you the anatomical anatomy of the human brain and comparing it with the rat brain.

So, we will look into the following experiments and technologies that we are developing to understand how to fabricate neural implants that can be used to acquire signals from the rat's brain. Recorded signals include ECOG signals using open BCI tools such as the Cyton Daisy biosensing board, along with ear bars, EIB holder, and rat adapter. Schematics illustrate the implant or device that is implanted into the rat's brain, enabling the recording of ECOG signals. ECOG, or electrocorticography, allows us to study the effects of anti-epileptic drugs (AEDs). One application of these devices is to study efficacy. The microelectrode array, known as a shank, contains 13 electrodes and is implanted into the rat's brain. Data collected from this shank enables the study of AED efficacy and other phenomena.

We can also see a PCB that is connected or attached to the MEA. Okay, this rat is recovered; do

not worry about this colour. It is recovered; we used certain chemicals for surgery or during surgery, right? Because of this, the colour is like that, but the rat is recovered now, and the device is implanted, and a PCB is attached to the device. So, whenever you want, you can connect the cable and start collecting the data, right? So, that is the schematic of the device implanted into the rat's brain, okay? We will also talk about the Cyton-Desi board and how to collect the signals. I have prepared two classes, which will be taken by the TAs, talking on the programming aspect of the Cyton-Desi board and how to use it for the application, okay? Let us go to the next slide.

Now, here we will look at the commercially available microneedles. So, the question is if there is a commercially available microneedle, single shank with tetrodes. Four electrodes together are called tetrodes, okay? So, multiple tetrodes can be seen on a single shank. There are multiple shanks and three shank electrodes. You can see this is a linear array of electrodes, isn't it? So, all these things are available. What is the purpose? Why do we need to fabricate devices for our studies? The reason is that each shank, each shank, for example, this shank, costs 5000 US dollars, 5000.

Let us keep 80 rupees as 1 dollar. We are spending 4 lakhs per shank for 1 shank, and if some of the electrodes are not working, let us say some of the electrodes are not working, then the company sells this as a class B, and that costs around 700 USD. Okay, this is not the exact price. There will be some changes in the company's policy that I am not aware of. Whatever the last little bit of information we have, we are just putting it here. But you can always go to this company's Neuronexus, Thermos Recording, and look up Neuropixels right from the company open Ephy0073. So, the point that I am making here is that one, it is costing very high. Second is that we need to rely on imports. How to reduce our reliance on imports, particularly in the medical device technology area, is what we should focus on. And to reduce the reliance of our country on importing these devices, we should also attempt manufacturing these kinds of devices. And with that, that is one thing, but another thing is that if you want to have customised needles, customised shanks, customised devices, that costs very high, extremely high. We cannot even buy, when say, all of us, some of us may be able to buy, but not the majority of us. So, can we develop an affordable technology, is at par with the technology that is available in the market, and also becomes self-reliant?

When we can manufacture these things right here in our country, we should try and attempt that. In some years, we will be able to be at par with the technologies available commercially, is it not? So, with that goal, we started fabricating this device. To your surprise, this $5000 that we are spending on one shank to import, the cost of each needle that comes to us is $50, not $500 and for sure not $5000, right? Is it working? Yes. Is it as good as the commercial one at this point? No. Were we able to acquire all the signals from that region of our interest? Yes. Can we

make it better? Yes. Can we reduce the cost further? Absolutely, yes. So, until and unless you do not attempt, how can you reach or how can you achieve your goal? Without attempts, there is nothing. When you attempt, there is a failure. When there is a failure, there is a success, right? Everything is interrelated, right? If you do not attempt, there are no failures. If there are no failures, there is no success, right?

So, the beauty of attempting to micro-fabricate devices and sensors is that when you get it right, when it is successful, you can make thousands of those. For optimizing, it takes some time, alright, but we should try. So, this is one of the commercial devices that I have shown to you on this slide. You may see the slide again, and without demeaning the work or the ability of the needles around the world, this is a very good technology and is not so easy to develop as well. But the idea is that $5000 is extremely high for one single shank. So, you see the slide, another thing that you need to understand is that you see this, there are electronics and there is a cable that we connected. Further, this is the figure from IMEC. It is corporate from IMEC, and okay, you can see here, there is a recording module, the whole electronics is there, and then finally, the shank is here, right, and these are electrode arrays which you can see here, alright. This can be used for certain regions in the brain. If you calculate correctly, this is the hippocampus, so you can just design it such that the electrode goes to it. This is a longer one. So, maybe that region is the hippocampus, some other region, but the point is that we can also design similar kinds of electrodes right here.

What are other flexible microelectrode arrays that are available in the literature? So, one of the arrays you can see here is for ECoG measurement. Figure A shows the exploded view where you can see there is silicon and then there is SiO2 on silicon. This is highly doped silicon nanowires on nano wells, and on that, you have the bioresorbable substrate on which it is designed. You can have a degradable substrate or a bioresorbable substrate, and you can measure the ECoG and the number of channels, right? CAR 4 and 256 channels at the bottom right. So, the point is that people have already attempted such kinds of devices, and in fact, not just attempted, but also placed on the right side of the brain, as you can see here, and acquired the signals. You can see that when one is asleep, what is the activity when measured with the cortical electrode, what are the activities versus the bioresorbable electrode when there is spiking activity, what are the signals and how it looks like when we compare with the control electrode versus bioresorbable electrode. I am sorry, I said cortical instead of control electrode. Okay, control electrode versus the bioresorbable, same thing when there are seizures, like spiking activities, how it looks like, these are spikes, you know it's a seizure. So, how compared to the control electrode it looks like, and then can you understand the fast spindle oscillations, what are the theta bursts? Are there any theta bursts because as I said, we can divide these signals into several frequency bands? So, anyway, the whole idea is to show that the bioresorbable devices can be designed, can be fabricated, and can be used for acquiring neural signals, including activities like seizure activities, which are in the form of spikes. But the question is how to make these neural probes, isn't it? So, we have something called thin film deposition, in which we have two techniques.

The first one is called physical vapour deposition, and the second one is called chemical vapour deposition. Physical vapour deposition and chemical vapour deposition, are the techniques for depositing different materials. It can be metal, it can be semiconductor, it can be an insulator. If you want to deposit, you can use one of these techniques.

So, now in the physical vapour deposition technique, we have three techniques. The first one is called thermal evaporation, the second one is called electron beam evaporation, and the third one is called sputtering. Thermal evaporation, E Beam operation, and sputtering, and we will understand each of these techniques in detail in the next classes. While in CVD, there are several kinds of CVD. There is called low-pressure chemical vapour deposition, there can be plasma-enhanced chemical vapour deposition, there is atmospheric pressure chemical vapour deposition, there is thermal ALD which is atomic layer deposition, and so on. These are all micro and nanofabrication techniques. How it works, we will see in the following classes. Now only depositing metal would not be enough, so we patterned the metal. How can we pattern? We can pattern with the help of lithography. So, lithography is a word that comes from Greek origin, lithos and graphics. So, it means carving from a single stone or carving on stones.

So, with lithography, if I use UV, I will say it is photolithography, okay? Photolithography is a technique by which we can pattern certain metal materials, and it includes several different sub-techniques. For example, in lithography, we have to use a mask, photoresist, and the exposure time for etching, whether it is wet etching or dry etching, right? So, several things are associated with lithography to finally pattern certain materials of our interest. Then we look into etching, whether it is anisotropic etching or isotropic etching, and we will also look into machining, whether it is called bulk micromachining or surface micromachining, alright?

So, all these techniques will go step by step in the next class. We'll start with the silicon wafer, what the substrate looks like, and how we can identify different orientations like 1 0 0 1 1 1. Then we will proceed one step further to understand deposition, followed by exploring different types of deposition and their principles, and limitations. Subsequently, we will delve into lithography and micromachining, and then begin the fabrication of various devices. In between, we will also discuss systems like headbands for neonates or adults, understanding epilepsy from the 10-20 system, and gaining insights into EEG signals, ECoG signals, and EMG signals, and how we can acquire them, along with their signatures.