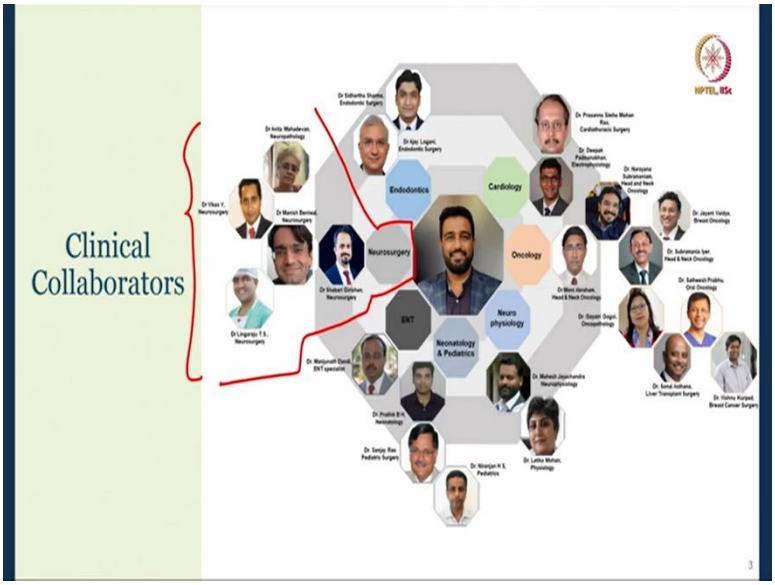
Advanced Neural Science for Engineers
Professor Hardik J. Pandya
Department of Electronic Systems Engineering, Division of EECS
Indian Institute of Science Bangalore
Lecture 2
Fabricated Biosensors and Systems

(Refer Slide Time: 02:09)



Hi, welcome to this particular session. In this session we look at the what kind of clinicians that we collaborate with and why it is very important to collaborate with clinicians for the area that we are discussing. Also, for the topic that you are working and the course that you are taking. Many things.

Advanced neural science for engineers means that you need to understand the area which is brain and for the brain, you require neurosurgeons, neuropathologist, you also require people who understand the brain interface in new Brain Computer interfacing, you require engineers who can understand the signal processing, you require engineers who can develop a band for you who can develop a probe for you require engineers who can fabricate sensors for you.

And of course, the actual gap that is generally identified is when you operate the patient. So, the neurosurgeons are the right set of people with whom we collaborate and just as much as neurosurgeons are important. So, what are the neuropathologist? So, the pathologist who will help us understanding the who works on the tissue brain tissues in particular and because as I said in my previous lecture, like that, the histopathology is the gold standard. Study of tissue is the gold standard

So, pathologist role becomes extremely important. So, that is one part of this lecture. The second part is where we will show the different fabrication facilities and I will be taking you through those facilities in the experimental laboratories with help of my TAs. And then we will see the sensors that are talking about in the first lecture right and corresponding system for that. So, that is the gist.

So, if you see the slide, we work with around 32 surgeons right now and we will be talking more about this set of people which is the neurologist, neurosurgery, whether you need a pathologist like Dr. Anita Mahadevan from NIMHANS or Dr. Vikas from NIMHANS, Dr. Manish from NIMHANS or Dr. Lingaraju from NIMHANS or Dr. Shabari Girishan from Ramaiah hospital, all people are in very, very important part for the research domain in the area of neural science and engineering.

We will be talking a lot about what are the gaps, how do we identify the gaps and what we are trying to solve in the lectures for this course. However, let us see the other collaborators as well. We also work in the area of ENT, endodontics, cardiology, oncology, neurophysiology, neurology and paediatrics. So, for endodontics we have Dr. Ajay Logani. He is chairing the endodontic surgery department at AIIMS Delhi.

We have Dr. Siddharth who is also in the same department in AIIMS. From cardiology, we have Dr. Prasanna Sinha Mohan Rao. He is a cardiothoracic surgeon also chairing the same department at Jayadeva hospital. Deepak is electrophysiologist. We have Dr. Moni Abraham Kuriakose. He is head of oncology. And with him, we have Dr. Subramania Iyer.

So, Dr. Subramania Iyer is the head and neck oncologist from Amrita hospital. We have Narayana Subramaniam, Narayana Subramaniam is head oncologist, chair of the department from Shankara hospital. We have Dr. Jayant Vaidya breast cancer oncology from University College London. With Jayant we have multiple papers we have filed. And then also we have multiple papers with Dr. Gayatri Gogoi.

We also filed a patent with Dr. Gayatri Gogoi. She is an oncolopathologist. With Jayant we have interesting concept on developing the probe that can be used during the interoperative surgery for breast cancer. We also have Dr. Satish Prabhu as oral oncologist from London. We have Dr. Sonal Asthana liver transplant surgeon. With him we are developing e-nose for people suffering from liver cirrhosis, liver cancer.

Then we have Dr. Vishnu Kurpad. Dr. Vishnu Kurpad is a breast cancer surgeon from Shankara hospital. Then we talk about neurophysiology very important area. We work with Dr. Mahesh. Dr. Mahesh is a scientist and of course, the scientist. He is collaborating with our lab. Dr. Latika Mohan she heads the AIMS Rishikesh physiology department. We have we have Pratik. Pratik and Niranjan, they are both in the neonatology area and we work with them in Indira Gandhi hospital for Child Health.

And we have Sanjay Rao. Sanjay Rao is a paediatric surgeon with Majumdar. So, Medical Foundation and these are some of the doctors that we work on. Of course, we have ENT surgeon, Dr. Manjunath Dandi with whom we work on this neonatal hearing screening. Now, what is the reason of me talking about all these doctors to you as part of this course?

The reason is that when you talk about the clinical technology development or when you talk about a medical device development or when we talk about biomedical engineering research domain, you cannot and you should not just sit in the laboratory and think about the problem and start working on the problem.

The right way of working in this research area or domain is by communicating with the set of clinicians that have actually, identify the problems while they are on their duty. So, either in terms of surgery or in terms of diagnosis or in terms of screening, even in terms of delivering the drugs.

So, this is very important thing that as a student, you learn that when you want to work in the area which is related to the biomedical or medical or clinical studies, you have to and you should have a right set of clinicians. So, all these people, a great, great enthusiastic people with a lot of passion towards their research and you understand that they are already overwhelmed with the number of subjects that they have to, you know, treat or diagnose or screen but still finding time for research is something that is really commendable.

And we as a lab are fortunate to have this set of clinicians. There are many more that I have not listed here, but we are just started working with them.

(Refer Slide Time: 07:34)

So, moving to all these fancy sensors that you are talking about, from where exactly you will fabricate those devices. So, you need to have a right set of ecosystem and infrastructure to address the important problems and to fabricate devices for the same. So, we have a lab which is called as the NANOFAB Advanced Microsystems & Biomedical Devices for Clinical Research. It is in the ground floor of this department, this department is Electronic Systems Engineering under the division of EECS at IISc.

So, if you stop by in a group right sometime, I can show you some of the facilities that we have. Now, we hold several equipment in this particular lab from a sputtering system to E-beam thermally efficient system. We have wet benches, microscope, photolithography system, operating microscope, not just metallurgical microscope and the stereo microscope but also, we have inverted microscope and operating microscope for performing the surgery.

(Refer Slide Time: 08:53)

So, if you see the screen, this is the yellow room that is there in the screen which is a photolithography unit. And then there is a spin coding unit if you can see the screen so you have this yellow room. The reason of using yellow room is that you cannot expose the photoresist, so we use for this everything I will teach you, do not worry, there is something called photoresist.

Its short form is PR let me write down the full form, photo, P-H-O-T-O resist, R-E-S-I-S-T, this photoresist we cannot expose the photoresist in the UV light and that is why we had to use a yellow room. I will tell you what kind of photoresist are there and how we can use it in the patterning of different materials. And we use silicon we use polyamide for fabricating several sensors.

As I told you earlier, this is a sputtering unit in the previous slide we were able to see the thermal evaporation and E-beam operation. We will go through all this equipment in detail in the experimental laboratory, these are wet benches, acid bench for solvent and here you can see thermally operation system. This is BSL 2 system, there is an industrial refrigerator. This is the operating microscope.

Now, we are moving to the biology side of this. Lot of students get drained as a part of the course that I teach in this particular department. But overall also when you will learn even through this online platform, you will kind of understand a lot of interesting techniques and the technologies that can be used for fabrication. So, let me go to the next slide.

(Refer Slide Time: 10:30)

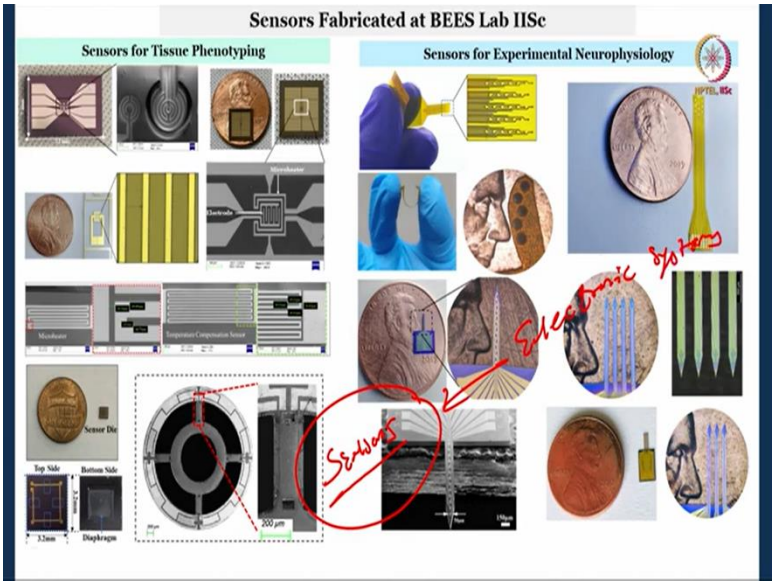
The next slide is on the another lab that we have which is under characterize and facility we call this as a biomedical and electronic in the bracket we have 10 to the power minus 6 to minus 9 because micro to nano engineering system laboratory. We also call it as bees lab B-E-E-S L-A-B. So, if you Google bees lab IISC right you will know a lot of things that we are working on in the laboratory.

So, we have several equipment and also the tools that can be used for characterizing the devices. We also use a central facility called CeNSE. There is another facility in the Institute for the other processes like etching, particularly dry etching, or cataracts and like SEM, XRD, TEM right, we will talk about that later. We have here NI DAQ you can see here that we have micromanipulator.

I will be talking about micromanipulator in fact, we will be taking a class on that. So, micromanipulator we have NI DAQ, we have impedance analyzers, oscilloscopes, power supplies and related items in the laboratory. You have designators to hold the devices and equipment and you have autoclave and we also have a BSL 2 on the second floor. This is a non-conventional class 10,000 clean room, there are classes of cleanroom.

We have 10,000, we have 1000, we have 100 and we have 10 and since there are classes of cleanroom, depending on the class and the cleanroom the purity is understood. We will tell that how these classes are identified in the next lecture.

(Refer Slide Time: 12:17)



So, now we talk about the sensors that we fabricate at the laboratory. So, each sensor quickly I will tell you how it is fabricated in right now, but I will tell you the application of the sensors but I will teach you how to fabricate these sensors as a part of this course., the first sensor that you see here right it is having an electrical and thermal sensors into it.

So, these are actually a chip, we can say chip is a chip that is integrated with is a chip that is integrated with interdigitated electrodes and microheater and thermistors (or temperature sensors). So, where exactly this all things are there? Where is interdigitated electrodes, where is microheater and where are thermistors. So, this all sensor, we call the sensors are within this area here.

And when you zoom in right you see that the same image of that. So, there is a interdigitated electrode right over here, the microheater in the centre and one of the temperature resistors site you can see here, the thermistors we can say and then there is a trench here. Trench is a pit that you create so that when you hit the microheater this heat should not cause the change in temperature of this particular temperature sensor.

So, this is how we will use it I will tell you later, this is one of the chip that we have fabricated in the lab. The second chip that you see in this particular case, is our gas sensor but it is not a complete gas sensor because the material that is used to identify the gas is not present but it is a sensor which is integrated with microheater and interdigitated electrodes. You can see here the electrodes are in the centre.

The microheaters surrounds those electrode. So, everything is fabricated right in this region which is marked with a white rectangular box. So, this is the and then all the gold pads that you see are the contact pads., the contact pads and I will teach you that the good thing is you do not do even see on the slide but you learn how to fabricate this thing.. You do not worry about it.

This is the gold but this is on glass. And again, there are a lot of interdigitated electrodes. Each electrode is about 10 microns in width and 10 microns in spacing. What do you mean by that? Suppose I just take one electrode and then there is so, let us say, we draw a line like this and then there is a second electrode. Then there is third electrode. You see that you will see that the electrodes are not touching the second side.

So, the electrodes which is here is not touching this line is not touching this line So, what I mean by this line. It is the same gold I am just drawing different patterns so that you understand. So, if you see if I say this is A and this is B, then the electrodes this is number one and number three are not touching B but number 2 the electron number 2 which is this one is touching B and not A.

These are called interdigitated electrodes or finger electrodes. The width of this electrode width is this space. Space is this the width and space. This space is 10 microns that is what I mean. So, when you have this region when you zoom in then this is the image. Each line is of 10 microns and width is 10 microns. So, we can fabricate these kinds of devices with the micro fabrication facility that we have in the laboratory.

Some of the techniques like RI I will tell you what is RI and other things that we had to use the other labs. These are microheaters, temperature composition sensor, you can very easily see microheater here microheater right, it is like a coil. Then we have a force sensor, this is a force sensor, these are four Piezo resistive sensors integrated on to silicon.

So, for creating piezo resistive sensor you have to dope boron into polysilicon material and this boron is p type silicon is n type. So, you create a piezo resistive sensor and there are four sensors 1, 2, 3 and 4. 1, 2, 3 and 4. So, four sensors are there integrated onto a chip where that makes up four sensor but this is silicone. So, if you press silicone, it will not bend So, you need to create something called diaphragm.

This diaphragm is created using bulk micromachining. Bulk micromachining. So, when you create a diaphragm then when you apply a pressure in the front here, the diaphragm will bend because of the bending right there is changing the resistance of the piezo resistor that is a concept. Now, we have this another chip here this is also a force sensor. It is a ring type four sensor and here you have the bridge.

There are four bridge you can see it 1, 2, 3 and 4. Each bridge has two piezo resistive sensor. So, each bridge has one here and one at the end, 2, 3 and 4 And you can see the zoom-in image of this one single bridge This is very small actually, it is just like about two millimetre closer to 2 – 2.2 millimetre, the diameter, which is just 2 - 2.2 millimetre.

So, that small sensor is integrated the tip of the catheter that we talked about, remember atrial fibrillation, so there is a catheter tube. So, the tip of the catheter this sensor is integrated. Now so this is a force sensor when you apply a force in the ring at the centre all the sensors will change uniformly. If you apply a force at a certain end like this end, then those corresponding force sensors would change accordingly.

So, it is a very sensitive ring type force sensor with four bridges. Now let us go into this particular side of the slide. We have and we will learn about this, a flexible sensor with 32 electrodes at the tip at this small region here. He is having all this design right, there are recording electrodes, there are contact electrodes and you can use this by implanting this chip into the rat's brain.

When you implant the chip into the rat's brain, you can measure what we call as a brain signal. But what is brain signal. Something we already learnt in either our engineering or science class or in general, is ECG, EEG, EMG. ECG is electrocardiography or cardiogram. EEG is electroencephalogram, EMG is electromyogram. muscles, muscles, these are brain signals, this is heart signals, heart. This is brain. These are muscles So, ECG, EEG and EMG.

Now, there is one more term called ECOG. EEG, ECOG. EEG is electro encephalogram but ECOG stands for electro cortiography. Electro cortiography, E-L-E-C-T-R-O-C-O-R-T-I-O-G-R-A-P-H-Y, electro cortiography. ECG signals when you take the signals directly from the brain right not from the forehead. When you take signals on the forehead from the head it is like 10 to 20 system is used for measuring EEG but when you take the signals I acquire the signals from the brain, then it becomes electrocortiography.

So, for electrocortiography we have the device that is that you can see in the screen. There are 32 recording electrodes, you see this is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 same way you can go to 32. In this small area, you have 32 electrodes. This is meant for a rodent experiments, rodent R-O-D-E-N-T. What a rodent means? We use the rat as a animal model.

So, we operate the rat, perform the surgery, place the device onto the rat's brain, and then acquire the signals and then study different diseases. One disease that we focus on is epilepsy.So, we will see how these devices are fabricated and how we can study epilepsy.

So, this is the another device that you can see here, this is also for recording the electrical signals from the brain or you can say ECOG and here there are 10 electrodes, how many electrodes? 10. Here there are 32 electrodes. Then you see this device right this device is this one. These are how many? 5 electrodes. 5, 32, 5, 10.

Why we have different kind of electrodes on the device because depending on the region so now this study that we are performing right now which is this electrodes five electrodes you can see 1,2,3,4 and 5. These five electrodes we use it for a disease called, Parkinnson. We are understanding how the surface electrical simulation will be different than the deep brain simulation

We will talk about that in the neurophysiology topics What is Parkinson? What is epilepsy? How what kind of difficulties there in the Parkinson? What are the gaps and for addressing those gaps what are the current techniques and what we are proposing? So all these are not only advanced research, but because the course that you have seen is focused on advanced neural science so it should be all the research that I am showing it to here.

All the teaching would be really of cutting engage technologies that we are working on and will teach you how it can be used to address gaps in the neural engineering neural science. So, the point is these devices are placed somewhere between motor area one and motor area two. I will tell you what is motor area as well. Now, this is a micro needle right, you can see this a micro needle and each needle has several electrodes.

Electrode one, electrode 2, 3 you can see the dots So, if you assume that you can see these dots you see this dot one and many-many dots are there. So, there are 13 electrodes onto this single microneedle and this single microneedle is about 150 microns in width. This width is 150 microns and this is an SEM image and let us acknowledge the central facility we call

CeNSE, at IISC, which we have used to fabricate this sophisticated device because we use something called deep reactive ion etching.

We will go through all these terms later D-R-I-E deep reactive ion etching. So, acknowledging the central facility of our institute this is an SEM image of the one single shank with multiple electrodes not just multiple but many electrodes 13 electrodes and we use this thing to implant in the rat's brain. This device will go in. Now, when it goes in, it will record several signals from something called cortical column.

So, there are areas called cortex right cortex and there are arrays which makes this cortical column. Each column is divided into six layers 1, 2, 3, 4, 5 and 6. So, when the needle goes in, so what is the role of column so, four layer four is an input layer. One, two and three is a processing layer and five and six is an output layer input processing and output. When you put the needle when you put this needle into this particular column which we call cortical column.

We can record these signals coming from different layers. We can record the signals coming from different layers. So, what is the use of that so that we can study the LFPs which is called local fill potentials and study the effect of drugs or study the effect of electrical stimulation on this particular signals right that is that it enters the column and that processes within the column and what are the output through the single micron needle.

We have single micro needle we also have so this column somewhere is about 200 microns 200 to 250 microns. So, because it is 200 to 250 microns this width is kept as 150 micron so that it will not puncture the column it will not puncture the column. So, now, this is about a single needle but what we can see in the next in this particular image in this image and in this image what we can see, we can see that there are four shanks right instead of one single needle or single shank, there are four shanks. F_O-U-R S-H-A-N-K-S right four shanks.

So, four shanks are there and each shank has multiple tetrodes, two tetrodes. Tetrodes is so, if you see and understand the neuroscience right you have multiple wires fused together to form the tetrode. So, you can say that like this is as the tip you will see 1,2,3 and 4 this is wires that are fused together to form tetrodes. This electrodes are used to capture the signal from the brain from the surface of the brain. But can you have tetrodes on the needle itself?

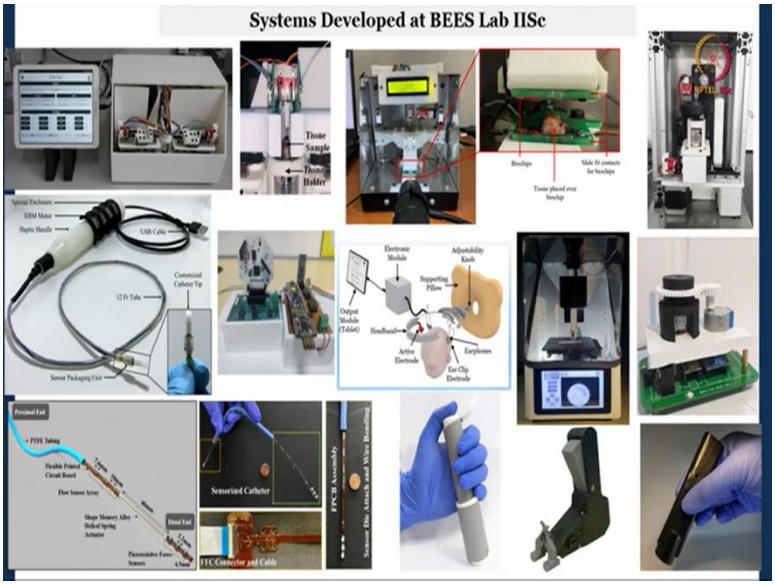
So, we fabricated multiple tetrode on one single shank that means you have four in one means four tetrode is four So, two tetrode means four plus four, so eight in one shank. So, we have how many shanks? 1,2,3 and 4, so eight into four is 32. So, 32 tetrodes 32 sorry, electrodes on to four shanks. Each shank has two tetrodes. Alright, so, four shank will have eight tetrodes. Each tetrode have four electrodes.

So, eight would be 32 right 32 electrodes into this four shank that is what we can fabricate now indigenously right in the institute and of course, here. So, these are three shank needles, these are four shank needles, this I told you that 10 electrodes, these are 32 electrodes, these are 5 electrodes, these are 13 electrodes right and these are all four shank needles, four shank S-H-A-N-K-S.

So, this is where we are, this is where we are from the chip and sensors perspective. Now, I have not shown you many of the devices in this particular slide but only sensors if you have only sensors is not enough only sensors will not solve the issue. We should have sensors that are supported with electronic systems.

Electronic systems sensors when it is integrated within the electronic system, then you have a tool to work on but the whole thing should be within a casing right at the 3D printing, I have to go find the manufacturing go for subtractive manufacturing. Finally, you have a complete tool that should be integrated with sensor and electronics. So, that is what we work on.

(Refer Slide Time: 31:38)



And that is why we will talk about the system that we have developed and BEES Lab and followed by the course that will start from silicon, how to fabricate device and so on and so forth. So, I will stop here. We will just as next lecture right we will be talking about the systems that we have developed in the laboratory right and see how each system when integrated with a sensor right or area of sensors can be used to solve an important problem in the clinical research area.

Then once we understand the systems, we go from the first topic which is on the silicon, how silicon wafers will look like what you what you can what kind of devices you can fabricate from silicon wafers, what are the important problems that you can address using those sensors that we fabricate some actuators that we fabricate.

So, the fabrication technique requires you to understand the different equipment so we will learn about thermally abrasion we learn about E-beam operation we learn about sputtering, we learn about photolithography, wet etching, dry etching, micromachining bulk and surface micromachining then once the device is ready you have to characterize the device.

Once the device characterization is ready, you have to integrate device electronic system, when that is ready, you are to put within the casing when that is ready, then you apply for use the tissues or using in vivo or uses in vitro platforms. And then once that is done, then you can try to get some data, move to next step and go to the clinic. So, there is a huge step but we will go one by one right to address the bigger problem in the neural science area. Till then I will take a leave and I will see you in the next class. Cheers.