Advanced Neural Science for Engineers
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Lecture 01
Introduction to Biomedical Research

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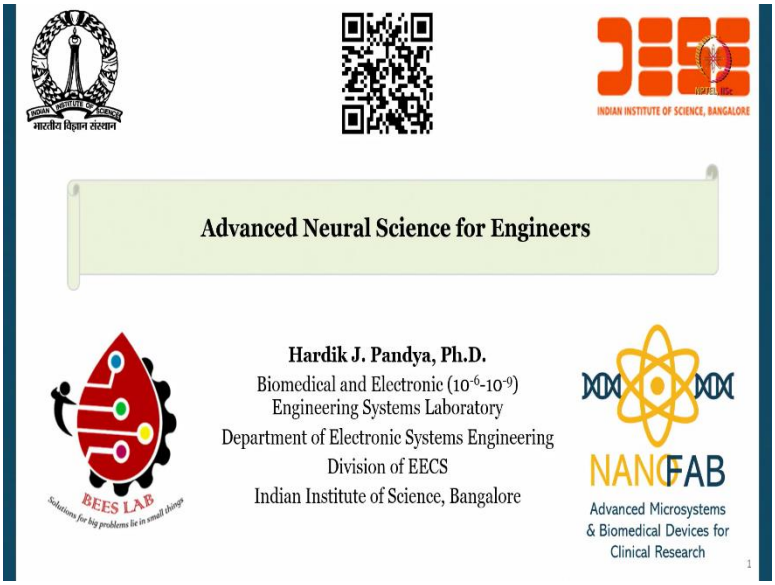

This is your first class. So, let us understand what we are going to learn in this particular course. Welcome to the course on advanced neural science for engineers, myself Hardik J. Pandya, I have my Ph.D. from IIT Delhi and a short stint in Harvard Medical School for about a year and also, about three years at University of Maryland College Park.

This was as a postdoc after joining IISC in 2017, right, the lab focus was on healthcare and advanced healthcare in particular out of which one of the areas research area is on brain. And when we understand the complexity that is involved in the brain, you will appreciate how things works, how a human works, right. It is if you say that heart is the most vital organ, so is the brain right.

And when we understand the science behind the brain, then you understand that what are the gaps, right, that one can solve as an engineer to address some of these important critical issues, for example, epilepsy, seizures in another term or fits in another term, Parkinson where you see the tremors right brain tumour itself, there are EEG based platforms for Brain Computer interfacing, a lot of interesting stuff is going around this domain because this is the frontier which is still unknown.

We kind of understand almost each and every organ of humans except brain and the idea of this course is to make you understand what are the interesting problems, to make you understand how as an engineer you can solve some of the important gaps, to make you understand how the brain a part of the brain works, right.

We will try to understand how it works and what is the science behind it, why we are assuming that designing or developing a certain system for acquiring a neural signals and understanding the signal processing right studying the signals will help to issue the problem that we are studying on.

So, with that, let us start a little bit about what exactly a microfabrication can bring a solution to the important problems. Now, before we go into microfabrication in detail, if you see the slide, you can look at the website through this barcode and this is my lab website.

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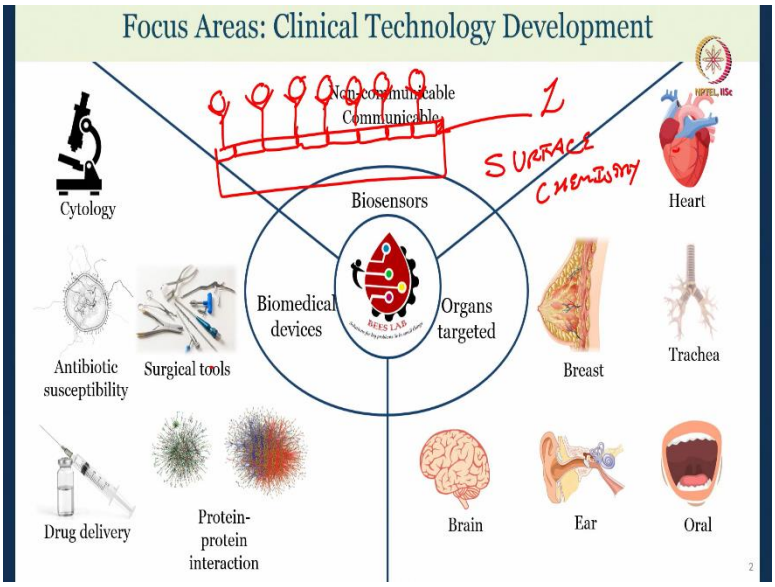

Here we have three laboratories and predominantly the work that we are focusing on is on communicable as well as non-communicable diseases, right. So, what is communicable disease and what is non-communicable disease and whether the study of the brain falls in communicable or non-communicable.

We will look into that, so, if you understand sensor and fabricate sensor, we will be talking on dimensions which are a few millimetres but the feature size will range from 10^{-6} to 10^{-9} and that is from micro to nano. So, there is a scale that we will be talking about.

Now, when we talk about micro to nano, you all know that human hair is the thickness of human hair is about 50 to 80 microns, that is the thickness of human hair. So, what we are talking about is somewhere around 10 micrometres and we go down to nanometres, it is way smaller than even the thickness of one single human hair. So, we will be looking at the technologies and how to fabricate those kinds of devices.

Now, apart from the research area which is on brain, we also focus on heart right. This first class I want to you know introduce the several research areas that we are working on in the laboratory. So at the end of the course, you will understand that learning certain techniques to fabricate a device or fabricate sensors per se how it will help you to also focus on other applications as well, right.

We are talking about neural science, the area which is brain but if you understand how to fabricate the device, if you understand the technologies that are involved in fabricating a device, then you can fabricate different kinds of devices for other applications for other vital organs as well and that is the role of the sensors right in different application.

So, let us understand a different area that one can, you know, apply the knowledge on to solve important problems. And the first organ that we will be talking about is heart. Now, we all know that the human heart beats about 70 to 75 beats per minute, right. But if it starts pumping faster, what will happen if it starts beating faster, it is arrhythmia.

Now, if you do a physical activity, if you run right, then there is a heartbeat will increase. But if I am when I am just delivering a lecture, if my heart starts pumping extremely faster, it beats faster, what you can say, I may have arrhythmia, alright, when heart starts pumping faster but in certain cases, heart starts pumping unevenly. And of course, there is a cure for arrhythmia, and part of arrhythmia is also called A-fib. What is A-fib?

A-fib is called atrial fibrillation, all right, where the heart starts pumping unevenly. Faster is one thing, uneven means fast, slow, fast, slow, slow, slow, fast, fast, it is the rhythm is not there and how and why? So, the reason behind heart pumping unevenly is because of the misfiring of signals, electrical signals in the heart. If the electrical signal misfires, then heart starts pumping unevenly and that is what we call atrial fibrillation or A-fib.

Now, to understand which region in the heart is having this misfiring of electrical signals. For that, what we do, what we means are clinicians, right surgeons, they will insert a tube okay

this tube is called catheter and the catheter will reach the heart. Then there are electrical sensors at the tip of the catheter. So, it is a tube with electrical sensors that tip when it reaches the heart, different regions of the heart, they can perform electrical mapping, they understand what kinds of electrical signals at which regions are arising.

If there is a electrical mapping, then one can understand where exactly is a problem, where exactly is the misfiring of the signals. Once you understand where is the electrical mapping of the heart that is the certain region which is misfiring or the electrical activities are non-uniform, you take out this catheter put another catheter and ablate the tissue, which was misfiring ablation is heating.

When you heat it tissue will die tissue dies, the connectivity will not be there. Right. So, ablation, how to ablate this heart tissue by using RF frequency. So, radio frequency ablation right. Now apply a force. So, where you have to apply the force because for applying radiofrequency you have to trust the heart.

If this is the region what I'm doing on my palm right, which is causing the misfiring of signals, the catheter has to touch this region and there should be certain force that is that needs to be applied so as to perform the surgery right or the ablation. This force ranges from 0.3 to 0.4 newton that means around 30 to 40 grams. The force is required in that range because there is an optimum force for ablating the tissue.

If the force is more what will happen what you assume, if I apply a radiofrequency signal and the force is more the other region in the heart will start ablating. What we want, do we want that? No, if the force is less than the reoccurrence will occur means the patient will have the same episode even after the operation is done in two months, three months because of the issue regrowing. Now there is something called transmurality.

What is transmurality? Now when we look at like this right is 2d, but heart is not 2d, right. So, if I heat the tissue like if I ablate the tissue here tissue completely burned. Right. If tissue is completely burned that is called transmural effect, do we know that right. So, that is interesting challenging area to understand whether the heart is ablated, the region of the heart is ablated correctly or not. What is the transmurality?

And now comes the actual problem that means, does the existing commercial catheters which is a tube with RF, right radiofrequency ablation, radio frequency signals that you can apply

on the tissue right this kind of catheters are available. So, the tip which can apply to the frequency the catheter that can reach to the heart and you can apply radiofrequency and you can measure the force is available.

So, the question would be if this kind of catheters are available, then what is the gap? Isn't it? So, if a surgeon is operating a patient and he or she can see the force on the screen then what is the problem? If you know the force, you can ablate the tissue at point between 0.3 to 0.4 newton and that is it. The problem is that he can see the force but they cannot feel the force.

That means, if I am applying this force right because the catheter they operated outside, right and the catheter goes inside. So, you are operating it you can see the force but there is no haptics, there is no force feeling of the force on the operator's hand. So, when you do not have the haptics that is a gap that you identified. Can you add the haptics or haptic feedback to the existing commercial catheters?

If you add haptic feedback, then when the surgeon is performing the surgery, the surgeon will be able to feel the force. Feeling of the force while you are ablating a tissue will probably improve the way the surgery can be done. So, for that we have a collaborator from Jayadeva Hospital in Bangalore who are interested in addressing this particular issue and we are trying to fabricate a catheter.

We are successful in fabricating a force sensor with a catheter tip. We have also developed a prototype of a catheter but when I am talking about we are developing a catheter, that means a character that can be taken to the next level. It can translate from laboratory to market. That is a procedure that is a journey. Let us not worry about that a right now. My point was that this is the gap that there is no haptics and can you have or can you integrate the haptic feedback to the existing commercial catheter?

This is one of the important problems when we talk about organ which is your heart. What is another problem? So, you see there is LVD and RVD. Okay, so right ventricle disorders, this is and then there is a left ventricular. So, if there is a change in the LV, that would be corresponding change in the RV region. If there is a change, then a doctor can predict that there will be some issue in the near future. This is while the operation is done.

So, can you develop a probe like a pen that I am holding here, that it touch the tissue and can you tell there is a difference between your LV and RV and the RV is correspondingly

changing with respect to LV. From that, can you predict that your heart would get into deterioration in your future? And I am just talking in extremely layman terms so that we all understand that we are all for all other we are from science background or from engineering background, right.

So, I am trying to make myself as easy as possible so that we all can understand what is a problem? So, there is a problem of understanding the chain in the tissue property in the heart, LV versus RV. For that, we are developing a probe that is integrated with NIR and integrated with EIT. We will talk about what is NIR, near infrared rays.

What is EIT? Electrical impedance tomography and we will see that how these two different modalities can be integrated together even for delineating the tissue in brain. So, when you understand how to use certain modalities for one particular disease, or one particular application, the similar kind of modalities can be used for other applications as well.

So, we will be talking about NIR electrical impedance tomography, ultrasound sensors, interdigitated electrodes, force sensors for understanding the visco elasticity. So, this will we will be looking at all these kinds of sensors and corresponding modalities as a part of this course and we will focus on brain when we go into depth, okay. The so now, if you see the screen what we had talked about, we talked about heart correct because heart okay.

Now, I just need a little bit deviated from the first point that is communicable and non-communicable disease. So, communicable disease are diseases like COVID right we are we have been through this tough time in last few years right and we know that it is communicable, it can be transmitted.

So, the infections can be transmitted communicable. The disease which cannot be transmitted, right, are non-communicable disease, again to keep it in an extremely easy way, right. So, we work both on cancers, we work on certain important communicable diseases like bacterial infection called sepsis, neonatal sepsis, or we talk about COVID, right.

So, we had an upsurge on chips for measuring the presence of the virus right in from saliva, so, that is a communicable disease. Okay, and actually, when we say virus is not like really live virus, we can take the protein from the virus, it is called S protein and N protein, and those proteins we can measure quickly on the chip. So, there is a basic technique, let us not worry about it.

The point is that the lab focuses on communicable and non-communicable disease out of which right now, what we talked about is heart disease which is a non-communicable disease, okay. Now, we talk about something different we talk about the trachea. What is trachea? It is a trachea is a windpipe, we all breathe right. Try to breathe where how it goes in through the wind pipeline as a food pipe.

Wind pipe is called trachea. Now, when infants particularly we are focusing on infants who if for certain reason are kept on ventilator okay, then the trachea gets inflammated, that means the windpipe gets inflammated. Now, if the wind pipe gets inflammated that means in an easier term even I am sure that everybody knows what is inflammation right. But to even make it easier, you assume that you have a hollow pipe okay and hollow pipe is now filled at certain region with some kind of material.

So, what will happen? If you flow the water through the hollow pipe and now the hollow pipe is filled with certain material at certain region, the flow rate would be different. It will get affected. Same thing happens when the inflammation is that there is a narrowing of the windpipe in a certain region right. So, that is called tracheal inflammation, easy right.

So, what is the difficulty? The difficulty is that when there is inflammation, then there is a difficulty of breathing and when there is a difficulty of breathing, you know what happens. So, what is a gap on what are the gaps? The current technique, of course is bronchoscopy. Bronchoscopy is used to understand where a narrowing is of the windpipe requires an expert, skilled surgeon, paediatric surgeon.

There is something called Kirschner wire. It looks like an allen key it put it on different sides of allen key crude method of measuring whether windpipe is inflammed or not. So, can we develop a tube again what we call as a catheter with some flow sensors and if I place the tube in the windpipe, when you breathe in and breathe out the flow sensors the rate of the flow of the wind or the air right and we breathe in breath out.

So, the rate of the flow of the air would change depending on the inflammation. So, to precisely plays the flow sensor on the catheter, second is if the tissue whichever the in the trachea is inflammated, when to know, what is the visco-elasticity of the tissue? For that, we need to add the force sensor on the catheter. So, what is this? Flow sensors. Second is force sensor on the tip of the catheter, right. Two things.

So, if I have the catheter that goes in the trachea in the windpipe, right I have to touch the windpipe. If you see there is a hollow. So, you go in and you have to touch it touch when the area is inflammated, when you touch it means you are applying certain force right then you know what is the change in the stiffness because of the force sensor.

Force sensor can be piezo resistive, force sensor can be piezoelectric, we will look at both the force sensors in detail. Do not worry about it, it can be piezo resistive that means when you apply a force a change in resistance, apply a force a change in electricity that means voltage piezoelectric, change in the resistance, piezo resistive very simple.

If you apply and now we have to touch the tissue but how can you touch the tissue? Catheter how can you manoeuvre the catheter? How can you move the catheter? You can manoeuvre the catheter with the help of nitinol. What is that nitinol? Nitinol is called Smart actuators. So, we will be looking at the way the smart actuators are indicated onto this tube, how the force sensors integrated to the tube, how the flow sensors are integrated on the tube.

And when you insert this tube in the trachea, how the flow change of the flow can help us to understand where exactly the trachea is inflammated. And we can also understand the viscosity and we can also manoeuvre the catheter. We can move the catheter so there are two springs on two sides. Yeah, right.

And there is a reason of using SMA smart actuators so that we when we heat the spring will contract, right and when you when you cool it down, it comes back to its original state. We will look into that in detail. So, what we have seen now? We have seen if you see the screen, we have seen the trachea windpipe, Isn't it? The next problem that we are addressing on is on breast cancer.

Now, please do remember this is for you to understand how different gaps can be filled with the solutions by using microfabrication technology. But our interest would be on brain finally. Okay, so I am not talking about brain right now because I will just cover the other research areas. And then finally we will go into the area of brain.

So, the next topic that we will talk about is on the breast cancer. So, what is breast cancer? Now you know, there are several kinds of cancer, right. Colorectal cancer, there is head and neck cancer and then there is a neck for example, there is an oral cancer, head and neck is oral cancer and then you have this brain tumor, right. You have breast cancer and so on and

so forth. You have lung cancer, many kinds of cancer but breast cancer is the second largest cause of cancer related death in women.

And you will be surprised to know that the out of every two women identified or diagnosed with breast cancer in our country, one dies, okay, our country is India of course because sometimes the course you know, the students from different countries also register for the NPTEL course a beautiful platform that goes to many, many students, right. It is a wonderful initiative. I just love it. Okay. Because who gives you education for free, right?

You only had to pay when you had to register for the exam. This is something that is awesome. So, I am sorry sometimes I get excited because that is how the research is all about right. And when it is when it reaches to so many students not paying anything, that is how the education should be, right. So, you had to deal with my little bit of emotions here.

But the point is that now, we will talk about the breast cancer and when I said that the every second out of two women one woman dies, when it is diagnosed with breast cancer is because we are not having a good awareness program. We talk about engineering solutions, we talk about high end technologies, we talk about a lot of things that we can make in India, we can talk about other things that we can import right but where is the awareness?

Awareness is the fundamental thing that is very important, right a lot of women now all my students right or girl students here who will registering for the program or people who are watching around right would if I ask a question that what is the screening technique to know the health of the breast? Can you answer? It is difficult right.

Some of you can some of you know, right. Now, we are fortunate to have a little bit better opportunity to study more than a lot of other people. So, we assume that we should know about the screening techniques as simple as MRI or mammography. Right. But still, we do not know. Now assume that what will happen to the mothers and daughters across this vast land they have no idea what is awareness program.

Now we are trying. When I say we is of course the different government bodies are trying to aware people who will go for the screening technique go for the mammography go for the MRI, right. But the difficulty there also is how to address such a large population and get into the tertiary clinics, right or even to go through the mammography programs, right. So, there are screening camps.

If you have seen screening camps, right, though how it is generally identified, first we understand how it is identified, then we when we see what are the gaps and then we see how the engineers can help or aid by developing a technology that can be used by a clinician. So, aid to a surgeon, aid to a doctor how we can develop a technology but first is there should be a self-examination, right.

So, to check once in a month that there is no fluid discharge, there is no inflammation, right and that can be easily done right once in a month. It is called self-testing, right. So, self-test is the first point. Second is clinical breast examination means that a subject a woman has to go to a doctor and doctor will check the health of the breast.

And from there, the next step is if the region is suspicious, if the clinician feel that the certain region is suspicious, the person has to go for mammography or MRI. If still there is an image in which there is a region which is suspicious, the person is advised to go for biopsy, needle biopsy, where you punch the needle in the region which is suspicious and you take out the part of the tissue and you send it to the pathologist.

So, for the pathologist, they will slice this tissue, right and will tell weill give the diagnosis that whether it is cancer or not. There are certain markers to look into, right. Go into that HER2 +/-, estrogen, progesterone, right. So, there are certain markers which are present for the pathologist to know whether there is cancer or not.

If cancer is there then what is the stage of the cancer. So, this is the cycle. All right, there is a cycle. Now there is a gap here. Everything is well covered by some self-examination, the clinical breast examination to MRI mammography, to the pathologist and the diagnosis. There is the gap. The gap is the clinical breast examination. How many women if they feel there is some problem will be able to go to doctor and let the doctor get the test done.

When you when you understand the statistics, it is disheartening that lots of woman would not go due to several constraints. But can we make a tool that is easier for a doctor to test just with the breath of the patient? Clinical breast examination, you do not need to ask the woman to come to the clinic but a tool can go to the village where there is this screening camp and just ask patient to breathe out from the air from the breath, can you understand can you screen breast cancer is there or not?

This is one thing. That will change that will have more number of subjects, right reaching out to doctors because now you do not have certain constraints of a clinician testing a patient. By subject we do not say patient until the diagnosis is done but there is a person so anyways, we do not get into all these details, my point is that if we make a tool so that a person can be screened this is called screening.

Healthy looks like suspicious from the breath, it will be interesting concept of non-invasive breath analyzer, non-invasive we are not invading anything right. If you put a catheter it is invasive minimally invasive because everything here and goes here right. If you use a stent, right, angiography you understand it is invasive, minimally invasive, it is also part of invasive only because it goes all the way to the trachea, but let us say a glucometer right, just punch but that is minimally invasive, non-invasive is a breath, right.

So, can we have a breath analyzer, what we call as an electronic nose, that can be used to screen the patients who are likely or who are at initial stage of the breast cancer. Now, what I said initially is that out of every two, one dies, because when they come to the clinics, when the diagnosis is done, already they are at stage four or stage three, right. Why? Because screening is not done at the right time. Why? Because they are not aware.

So, awareness is the basic then comes the technology. Now, you understand this is a whole cycle in which one is that you can make a breath analyzer or an electronic nose to identify a certain VOCs. VOCs is volatile organic compounds that will be in a higher level for the patients suffering from a certain disease in this case the breast cancer compared to the subjects normal subjects assuming that we are all normal right. The breath content would be different, the VOC content in the breath would be different.

So, can you develop such tool that is one. Second is when the tissue is given to the pathologist right I said that first is self-exam, then clinical breast examination, then MRI mammography, then if the region is suspicious then the breast biopsy, right needle biopsy, you take the tissue out and that small tissue that is sent to the pathologist can you quickly get the half of the tissue because the complete tissue is never used okay it is advised to save in tissue bank. It is kept in the tissue bank.

Can you take this small amount of small chunk of tissue and can tell quickly whether this is cancer or not? How? By using a technique that we have developed called electrical, thermal and mechanical ETM right using these three modalities electrical mechanical and thermal can

you identify whether the tissue is normal or tissue is cancerous tissue. That is another thing that now we are talking about.

The next aspect would be that if this is a cancer after the pathologist says this is histopathology guys okay histopathology that means the tissue understanding the tissue and understanding what are the markers present in the tissue is the histopathology and that is the gold standard. Gold standard means across the world, this is this technique is accepted. This technique is considered a right technique or not right technique I should not say the term right say term right.

But this technique is a gold standard means this is accepted across the world as a technique by which one can say and one can guarantee that there is cancer or not. Of course, this technique has a limitation for example, there is something called triple negative breast cancer, triple negative means all the markers that are pathologic assumes that should be there or certain markers to be there, all three are absent, but there is cancer. What do you mean?

All three biomarkers are absent but still there is a cancer, triple negative breast cancer. Can we identify that triple negative breast cancer with the tool that we have developed based on electrical thermal and mechanical modalities and can tell the doctor can give the diagnosis so that we save those patients who have triple negative breast cancer right. So, 12 percent of the breast cancer cases are triple negative. Huge number.

Now, once a pathology examination is done and if the report comes as positive a person has to go for the surgery right. So, when a surgeon operates surgeon will remove the tissue and means the pre-operative MRI the region the data the images the analysis right he or she will remove the part of that particular breast right which is the suspicious part. Now, it is not any more suspicious, it is a cancerous tissue because we have gone through the gold standard and we have the images right. So, you remove it. Removing is called resection, resection, okay.

When you remove it there after you remove it, how you know there is no more cancer left? So, the tissue is sent frozen section, again the pathologists look into that and get back to the doctor. What I was trying to understand and after discussing with a few of my clinical collaborators, what we understood is that if we can have a tool a pen, a probe, that can be used or that can be given to a clinician to a surgeon onco-surgeon or breast cancer surgeon and during the surgery, the surgeon can touch the tissue during the surgery and can tell whether this is cancer or not right that will be really helpful.

So, we can develop this probe, we can develop this pen like structure by integrating the electrical modality or mechanical modality or thermal modality or NIR or ultrasound or integrating either or multiple modalities into the single probe and based on the study that can we do on ex vivo now suddenly a new term right what is ex vivo? See there are three terms that you need to understand.

The first term is called in vivo, I-N V-I-V-O in vivo is within the body. Second is ex vivo. Ex vivo is outside the body okay, that when we understand inside the body, in vivo experiments inside the body for example, ablating the tissue in vivo. Ex vivo is when you take out the breast biopsy tissue and understand the properties of tissue ex vivo.

Third term is in vitro, I-N V-I-T-R-O, in vitro alright. So, in vitro is when you perform the experiments in the laboratory. You have a device, you take the cells, you grow the cells study those cells use different drugs to understand how the cells' property would change all things are in vitro okay, three terms in vivo, ex vivo, in vitro, right.

So, now, we are talking about a probe that will be used by a surgeon during the surgery. So, what should be the modality or what should be the technique? It is called the in vivo right inside the body, in vivo. So, if you have the probe integrated with certain modalities that can be used and when you touch this area, it can tell whether it is normal or it is cancerous, it is normal or it is tumor right.

Now, there is a question that what is the tumor boundary or where is the tumor boundary. All right. It is an extremely hot topic while learning all these things if you are also doing your research, you are doing your PhD, you can think about finding a solution that can be that can be implemented to understand or to identify the tumor boundary. Very interesting problem, okay.

So, not only to identify that still there is cancer or not but also to identify tumor boundary, but let us not talk about tumour boundary right now, we will talk about just cancer or not. So, can you give a doctor a pen that can be used for identifying normal a tumor or there is just it is normal now, the surgery is done successfully. So, there is something that we are working on we have collaborators, we are working on that.

Now, when I talk about this, all these technologies, right, there is electrical or the thermal, whether it is mechanical, whether it is ultrasound with acaustic right, I will be teaching all

these modalities and corresponding sensors for these modalities. So, let us not worry about how these sensors are fabricated, we will talk in depth in the other lectures okay. So, let us come back. What you see on the slide, what you see is that the next part is the oral, okay. So, oral is oral cancer.

Oral cancer, now, oral cancer is again extremely what do you call deadly disease and it has a huge number particularly when you look into India, right or India concept or India's general then you understand that the Northeast right that region has a large cases of oral cancer that there are several reasons of course, there are the regions also in our country where there is a huge you know, data, which shows that people from certain region has a higher you know, cases are the case are very high in the certain region for oral cancer.

Many reasons, many analysis hypothesis but some things are like tobacco is one of the culprit right. How it is given in the literature or the advertisement right. Cigarettes or beetle nuts right and other things. But the problem here is that how you can identify this oral cancer quickly and the technology can reach to the last person, right, somewhere in the remote village, can you take the technology and can you tell or as a person has some kind of inflammation, some kind of irritation?

There is a patch, right. There is a burning in certain region below the tongue right on the floor of the mouth right on the inside the cheek area. So, how right with this cancer or not just some kind of other inflammation, other infections, right. So, right now, what are the techniques? The technique is, you take the swab.

Take the swab and you send the cells to the remote pathologist not a remote is what remote because you send it to a pathologist, who is in the tertiary clinic, tertiary clinics and then the swab the cells because you take the swab so, the cells from the swab are taken and smeared on the glass slide. Glass slide means smearing spreading, spreading of the cells on the glass slide. And these are done after doing a staining called H and E staining H and E. So, what the pathologist will look into?

The pathologist will look into different kinds of parameters, one is cell to cytoplasm ratio, double nucleation right and several other parameters but in our term right or in our understanding, we should understand that the morphology of the cells would change from onset of the disease to the progression of the disease. So, if we can identify the change in the

morphology using image processing and certain times the pathologist would miss if there is a small change but the image and the AI would not miss that part.

So can you bring the artificial neural network along with the lot of images to train the system to identify if the cell is changing its morphology and the change in morphology when the pathologist identifies if pathologist can identify a pre-malignant, the malignant is cancer, pre-malignant is a pre cancer, cancer is kind of easier way to identify because there is a certain parameters that would definitely change in pre-cancer, it looks kind of normal.

So, certain times a pathologist even the expert pathologist misses it and how I am claiming all these things because we have a collaborator from Mazumdar Shaw Medical Foundation and we have clinical collaborators, a pathologist on board who does all this work and we also submitted a paper this published you can see that. The point is that there is a gap of pathology pathologist not able to identify the pre-malignant cells okay premalignant cells which are pre-malignant in nature.

So, if and then there is a histology of course, right and if there is a histology you can train the system so that you can identify this pre-malignant cells. So, image processing plus AI is one thing but then how I said that you want to bring the technology to the last person right, say in a village, so, can you have a system just like a microscope and can you can the Asha workers, right, aggregated social healthcare workers, right.

These are the most important personal, in the healthcare system in the healthcare chain. Of course, we say that the surgeons and clinicians and all the engineers and scientists and lot of social workers but the most important according to my understanding, of course, are the other layers but the connect with the common people with the last person is done by the social workers.

So, if you strengthen them by giving some kind of technology that can be easily used by semi-skilled personnel, right, then it will be really interesting. So, what if you can make a microscope and give the microscope or keep the microscope there in the village and you the asha worker can take the swab can stain with H and E STAIN, can put the slide it is easy, okay. It is not so difficult for the semi-skilled personnel to do this much.

And press a button after putting on the scanner, press a button, the scanner will scan entire image and will identify those cells which are morphology which has changed its morphology

and those images only can be sent to a remote pathologist. And a remote pathologist will say that yes, it looks like a typical so the diagnosis is not cancer, okay.

The cell study of cell is called cytology, study of tissues called histology. So, when you study the cells, right, cytology is done still not a gold standard, it is a screening techniques, not a gold standard, histology is a gold standard but study of cells is faster is easier, right. So, you just take a swab. That is it.

So, if you have the technology, right at the village like a microscope with the auto scanner, and get the get images can be sent only the one that looks like atypical, that means the morphology has changed to the remote pathologists for quick diagnosis that will be a nice contribution from an engineering perspective to the clinical perspective. Right. That is what we call clinical technology development.

Now, another important solution that you can bring is can you again develop a probe? We are not moving away from the probe, is it not? Can you have a probe and that can be used by these semi-skilled personnels to personnel I am sorry to be used within the mouth, within the cavity, oral cavity, okay and you just touch the probe it will tell whether this cancer or not.

There are certain tools which are right now in the market but we can identify a small even a smaller change, right, by using a certain modality. And I am not going into detail of that because it is a research problem that we are addressing until we have some interesting data of which I am confident about, I will not like to just keep on talking on that particular research area.

But for other area that we were talking about until now, we have a lot of data to back up the claim that we are making. This one also, we know that we have a solution until we just get some data, right. I hope that by the end of this course, I will be able to surely tell you that okay, this is the technique by which you can identify the cancer and non-cancerous region in the oral cavity, okay.

Now, last two things in the organs that we are targeting in the laboratory. The next one is ear and since ear is associated with brain, everything is associated with brain in a way or to directly indirectly. We will be talking about the ear and the corresponding gaps that we have identified in case of the hearing screening, that is called neonatal hearing screening, okay.

So, if you understand all the babies have to go through technique or a screening technique called a BAER or ABR in right term. ABR, auditory brain response. So, to understand whether a baby can hear or not, there is a tool called BAER, which uses ABR to identify that baby can hear or not, a neonatal hearing screening technique.

Cost is around 14 lakh to 15 lakh to 20 lakh but almost none of the primary health centres has a system that means the babies who are born in villages, they do not go through the scanning technique. If they do not go to scanning technique, that means when they are only two, three years old, their parents would know whether a baby can hear or not.

And they are two three years old and that will affect the cognition, right because hearing is important for the speech development. Hearing is important for the brain development. So, the overall the cognition may get affected. So, we are working on that and I will go into depth as a part of this course. Yeah, this particular problem and the problem on the different application different diseases of the brain.

So, moving to so I am not talking more on this problem right now because we are going to learn about it, we are moving to the other part which is the protein; cytology we have already discussed, if you see the screen right, I just abort cytology with respect to the probe that we are developing for the oral cavity right, is it not?

So, we will so, this oral cancer, we had talked about probe but the same swab when you take it, it can be used with the cytology tool which is right over here, okay. Now, let us talk about the next device that we work on or we have in the lab which is focused on the protein-protein interactions, okay protein-protein interactions. So, what is protein-protein interaction?

Now, when there is let me give an example when there is a oral cancer so, oral cancer like any other cancer can be primary or secondary. Primary or secondary that means it is either metastatic or it is non-metastatic. What is primary? What is secondary? Either cancer is invasive, so you also called invasive or non-invasive okay.

What is invasive? It will invade the other region of the other organs of the body. Invade invasive, non-invasive means it will stay at a certain region, stay at certain place. Okay. So, primary secondary invasive, non-invasive, metastatic, non-metastatic okay same thing most of things are kind of similar at least from your perspective you have to understand that when there is a metastatic means when the cancer will spread through the lymph node.

So there are series of lymph node. Lymph node L-Y-M-P-H I hope that when you learn this new terms you also go and google it that what are lymph nodes right and you will understand what are the lymph nodes in human body. These lymph nodes are responsible for our immune system okay, lymph nodes are important for the immune system.

So, what happens is that when there is an oral cancer and when the cancer is metastatic that means a metastatic or non-metastatic right now, if that is the oral cancer the surgeon will take out the series of lymph nodes are present here represent here right and they are present next to legs so, you will just understand when you right now, lymph node you will see.

I will try to show you the exactly lymph nodes on the human body but the point is they will take the series of lymph nodes out to check whether the cancer has spread is metastatic or not. Right whether **MS** says this has happened or not. Now, what I said lymph node is responsible for immune system but if the lymph nodes are taken out, then the immune system will fall.

So, there are certain proteins that are present in a lymph node that will be on higher concentration when the cancer when oral cancer in general we are talking about oral cancer right now is metastatic that means it spreads to the different region of the body. All right. So, during the intra operative surgery within the operation theatre, can you identify those protein in the lymph node if present, then and then only you take out the series of lymph node.

If they are not present that means cancer is not metastasis and metastasis has not happened cancer is not spreading to other parts of the body do not take it out because it will hamper the immune system, okay. Now, limited understanding about this is again from the clinical collaborators. So, what we can do as an engineer, we can develop a sensor based on the electrical impedance or based on electro-chemical impedance, electrical impedance or electrochemical impedance.

So, I will be showing you some of the chips that we have developed in the lab and please mind it we are going to understand some of this equipment that are used for fabrication in our experimental laboratory, you will be given a video of how the system looks like, how the techniques are there, how to gown yourself before you go to the Fab Lab and how to make the device out of it okay.

So, it is not just a theory, it is a part of the TA classes where some of the important problems will be discussed. There are experimental laboratories and then there is also a lot of theory

classes. So, the point that I am making is that there is a chip that I will be showing it to you which has the electrical sensor and electrochemical sensors. Okay. So, we will be talking about that. The other idea of using the similar protein-protein interaction, protein-protein is antibody-antigen reaction, okay.

Now, if you understand antibody like 'Y' Okay like I will explain and let you see me see me and how I understand the antibody antigen reactions. If you see the screen, I will just show it to you how the antibody you can you can assume you assume like antibodies are Y. Can you see the screen please? So, there is a 'Y' right.

So, this is the FC region, this is the Fab region (Antigen-binding (AB) site). Fab region this is antibody for me this is antibody not for me, in generally how it is like of course, you go into detail it is a lot of interesting stuff and a lot of bonds are present, but for us let us understand in a very easier way. Now you understand that antibodies like this on a device present like this. All right and let us say antigen looks like a circle okay.

So, if the antigen is present or the antibody will catch the antigen like this you see again there is a reason okay there is other bonds that are present because of this antigen will interact with the antibodies and get capture on the antibodies. Now, if there is a sensor below this one then you can either measure the impedance right which is either electrochemical impedance or electrical impedance.

You can measure either electrochemical impedance or electrical impedance if there is a sensor below it okay. So, there is an interesting concept here which we call as a surface chemistry. Surface chemistry okay what is the surface chemistry and why we are talking about that because the chip that I will be showing to you right depends on the surface chemistry of this particular surface chemistry because surface chemistry will help the FC region to attach on the gold electrodes right.

So, now, let us assume, not assume let us see that this antibody okay assuming this and these are like close. Now it should hold like this correct. We are why this region FC region will attach to gold why? Because there should be certain bonds that we present on this gold surface, right. Why are you talking about gold because the chip has gold. Why chip has gold? Because there is a sensor which is made about gold right.

So, you have to perform surface chemistry so that the FC region will attach the gold and the **AB (antigen binding)** will wait for the antigen. This is a protein antibody is a protein antigen is a protein. Protein-Protein interaction that is what we are talking about protein-protein interaction. Now, let us understand if you see cricket right a lot of you students right, who are taking this course, at least know about cricket if you do not see the cricket, right and this is an example because majority of the students may have seen assuming they have seen cricket.

So, when you catch the ball generally like the boundaries it more generally generally like very-very crude example, but just in case a ball like this the efficacy of catching the ball will be higher, if you catch the ball like this or if you catch like this, if you just put it down it may fall. You may not get it right, the ball is coming from the top right, the easiest way is by this. Same thing goes for this antibody. The antibody is not sending straight to hold antigen if sending like this or if it is reverse the antigen will not get captured, okay.

So, to hold the antigen to hold the protein, the antibody should be in a certain fashion should be oriented in a certain direction and for that we use something called surface chemistry. It means that our chemicals like PEG-Saline which are used for improving the directionality of the antibody, so that the antigen can be captured both are protein. So, we call it that protein-protein interaction. I give an example of oral cancer, but we can also take another example of using the S protein and N protein which are present in COVID.

Can you capture those protein immediately onto the chip? If yes, is a screening platform right. So, there can be many more examples of this. There is another example of antibiotic susceptibility where we capture the bacteria onto this antibodies against the gold surface. Now you again think that why we are not going into advanced neural science right for engineers. These techniques are all based on these sensors and sensors are also used for your advanced neural science course.

And that is why we are talking about all the possible applications or certain application these are not all possible but still applications that we are working on so that I can tell you in detail. There is something next call antibiotic susceptibility that means that in this bacterial infection, bacterial infection called sepsis, S-E-P-S-I-S sepsis.

Now, generally there is bacterial infection, right. We are we give blood and then the report comes in 2-3 days and then we are given a certain tropical antibiotics right initially and for the neonates right, new borns, the waiting for two or three days is a life threatening episode

right. There are certain bacteria which are already presents these are called gram positive bacteria and gram negative bacteria and out of gram positive and gram negative bacteria, about 15 of them are there but eight are present in most of the cases for gram positive, for gram negative can you capture those bacteria onto a chip from the blood okay from blood.

Now blood has RBCs isn't it? So, this blood may coagulate right you generally take the blood in the anticoagulant, so, blood will not get thickened. So, what we can do, can we study the can we understand the presence of these bacteria from the serum or plasma so that RBC would not be there, right.

So, how the plasma can be taken if they get blood put in a centrifuge right revolve for higher rotate for high number of rotations per minute and the RBCs will settle down, the plasma will come up to take the plasma and the plasma has the bacteria you will know probably that what is the bacteria and what is the concentration of that bacteria using the chip that we have.

We have done this testing with PBS, we are under we are now using this chip for the blood sample as well. Okay, so, this is for the neonatal sepsis. Now, why we want to use a chip, the question is the question is why we need to use this chip because there is a gap that it takes about two days for the report to come back when there is an infection in the neonates. Can you reduce the time to let us say two hours or three hours or four hours or six hours right?

So, even one-fourth of the time that it takes from the diagnosis point of view, then you can save a lot of lives of the babies. The next device that we are addressing on or we are developing is on the intra-muscular drug delivery tool. So, you have seen in movies right or you may not have seen then Google EpiPen, E-P-I P-E-N okay.

So, and there is when there is an allergy, allergy can be of peanut allergy can be a pollen allergy can be of milk, right. People have several kinds of allergies and certain people are very sensitive to this kind of materials and if the allergy episode happens, it is life threatening, they have to rush to the hospital, they had to get treated, otherwise they will die. So, to immediately counter this allergy effect, right there is something called epinephrine and that is a drug that is used for that gives time for the people to at least reached the hospital.

The way to deliver this drug is by a device called epipen. This device, you have to open it, I will show it to you one device how we can use it, you had to open it, take out the device, put in the muscle, right, which is the thigh you press it again assuming that I will demonstrate it

later but you take the device and then put it in a thigh assuming this is a thigh. It is not a thigh okay, I am just giving an example I will show you an actual demo.

So, when you press it, then only the needle will come out and deliver the drug that is present in the EpiPen. The cost is 200 to 300 dollars. The difficulty is when this episode process to open it take it out deliver it right so there are some issues with that. So, we are we have developed in fact, some device called epi shot, E-P-I S-H-O-T and it has recently won a Dyson award.

So, what it what kind of new design that we brought it we brought a design which will help a patient to open with single hand, single hand operated. Now safety features are three safety features. Until you touch and press and then you press a button then only the drug will deliver. Otherwise just pressing a button that drug will not deliver. Then the needle will retract once a drug is delivered.

So, those are some advantages, the important advantage is that it can be reused and because we have made it here, the cost comes down to one-fourth of the cost of the device that is in the market. So, there is a drug delivery tool, we are also working on intra-dermal tools, we are also working on micro needles with a patch that you can put the patch and the drug will be delivered or you need to understand the needle will absorb or will be bio absorbed into the body.

That means, once you put the patch the needles that are in the patch, these are not steel needles, nope. These are polymer needles and the material is as it can be absorbed in the body without causing any toxicity. Okay, this is called advanced research. So, we are working on that to deliver a drug just by using a patch as small needles, people will not feel they will not there is no pain okay because it does not touch the nerve which will cause the pain. So, we will we are working on that research domain as well.

So this is all about the clinical technology development and what kind of research area that we work on. I will stop here and the next class, we will go through the clinical collaborators that we work on then going to the facilities that we have and then we start going into details about how different sensors can be fabricated, followed by how these different applications whether it is epilepsy or Parkinson and how we can develop device that can be implanted in rat’s brain, how take the signals, all these things we'll be discussing as a part of this course.

Till then you take care. I will see in the next class, you can see this lecture in 15 minutes, if you want to like, because sometimes it becomes overwhelming to understand lots of different topics in a short span of time. I will try to keep it as crisp as possible but I also want to show you that what are the tremendous opportunity that lies in front of you when you understand the technologies that we are working on and when you learn it, you will also see the importance of that.

We will keep talking we will keep discussing, there is a portal through which you can reach us right. Reach the TAs, and then we will try to address the queries as much as we can. Right. I will try my best to answer most of the things through TA and I look forward to an interesting exchange of ideas. Sometimes you may have a very cool idea. If it is really cool, you can send me an email as well. And if possible, and if I have some solution, I can help you out during that time.

Till then you take care. I will see you in the next class and we will talk about the other-other important research domain. Bye-bye.