Electronic Systems for Cancer Diagnosis
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Lecture – 16
Portable Cancer Diagnostic Tool Using a Disposable MEMS-Based Biochip

Hi, welcome to this module. This module is the end of our understanding about how to fabricate biochip using MEMS based technology. When I say MEMS, it is micro electromechanical systems right in previous modules what we have seen how can we fabricate this chip. In this module, let us see how can we use this chip and how can we place this chip in a mechanical casing, and that mechanical casing iswe have fabricated that mechanical casing using 3D printing.

Since, 3D printing is also part of these particular lectures or course I am not going to tell more about 3D printing in this particular module, but we will discuss more about how exactly 3D printing works, what are the kind of 3D printers, and then we will actually see how can we operate 3D printer in the laboratory.

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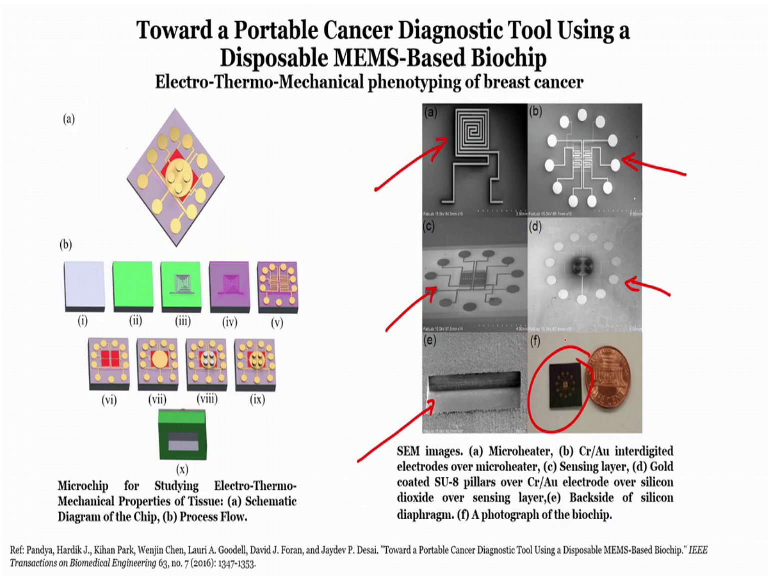

So, if you see the slide, what we have seen there is a heater; and over the heater, there is an insulator or that there is an electrode; over electrode, there is an piezoresistance sensor. On that there is a insulator; on that there is a gold pad; over gold pad, SU-8 pillars. And we are making a SU-8 pillar conductive on the back side there is a diaphragm. This diaphragm is using bulk micromachining. Finally, you have this chip.

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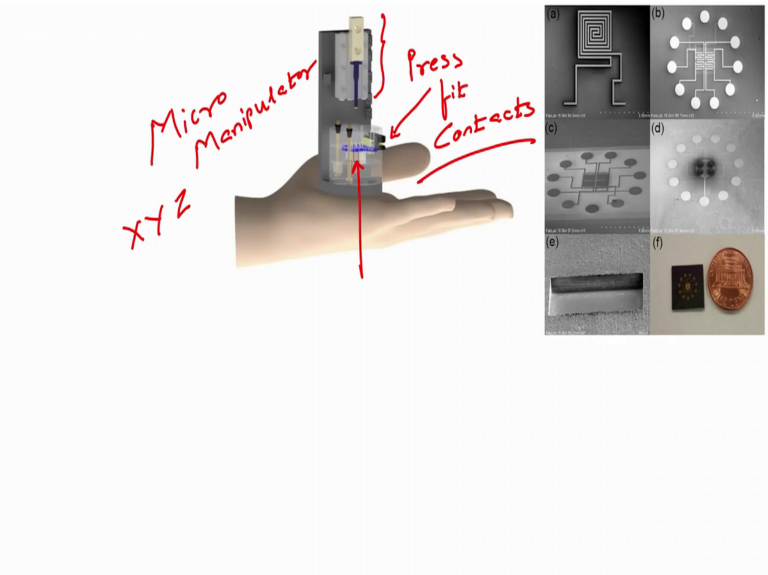

Once you have this chip, then you have to place this chip in this particular 3D printed module. I will show you the block diagram of this module in many of this particular mechanical casing in my next lecture. Now, right now let us understand how can we use this chip to understand the change in the tissue properties.

So, this chip is placed here all right. And there are press fit contacts, what is it, press fit contacts. The advantage of press fit contacts over shouldering and wire bonding is that you can easily load and unload the chip into the mechanical casing. Then what you see here is a micro manipulator. Now, this section the representation is such that we are using piezoactuator, but you can use micro manipulator micro manipulator; this will press the chip with micron prison. Now, when I say pressing the chip that is it will move in x, y and z, x, y and z in micron micrometer range with micrometer range precision.

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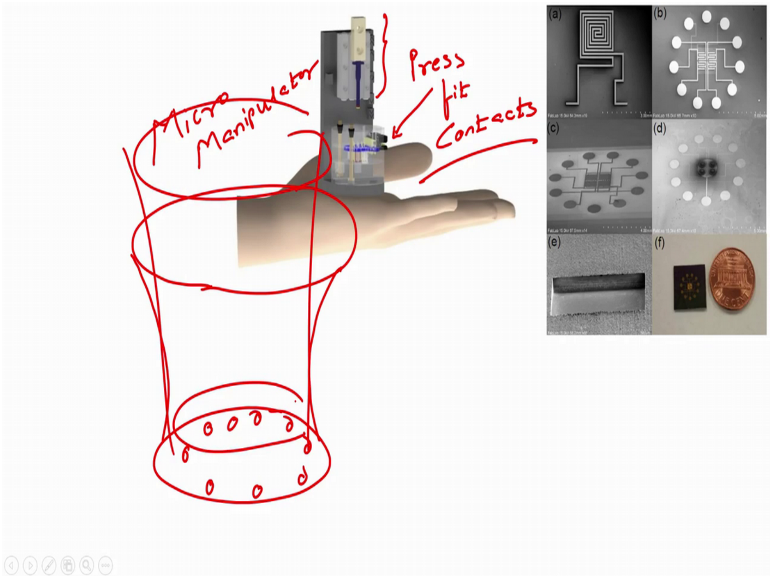

So, what we, how we will take advantage of this thing? Now, if you see this particular section is like a funnel is like a funnel. So, I will place the chip there is there is a chip in the bottom right. And through this funnel, through this funnel like this and all right, and this is our chip. Through this funnel, we load the tissue, we load the tissue. Now, let me just draw different colors so that you can understand what exactly I mean.

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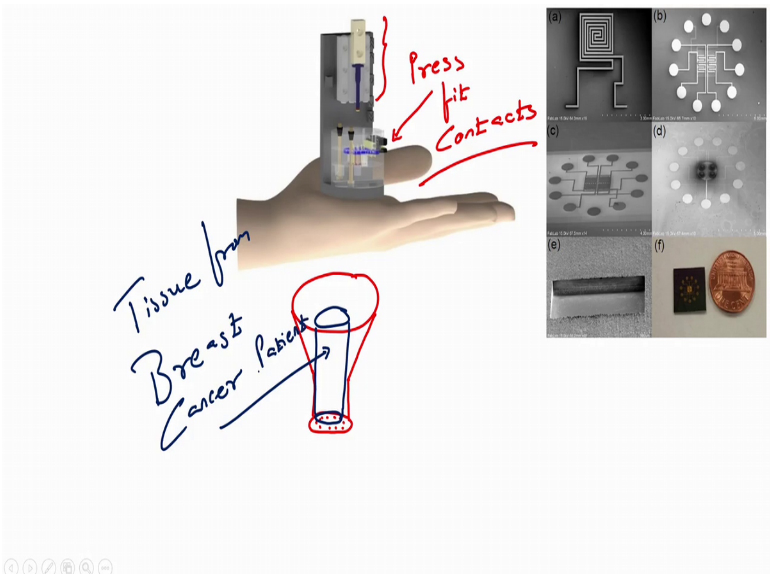

You see you have a funnel; there is a chip at the end of the funnel. This chip is the one that we have fabricated all right. And you are loading a tissue. You are loading a tissue such that tissue the bottom of the tissue will contact the chip, the bottom of the tissue will contact the chip. This is your let us say if it is breast cancer is a breast tissue from breast cancer patient, tissue from breast cancer patient.

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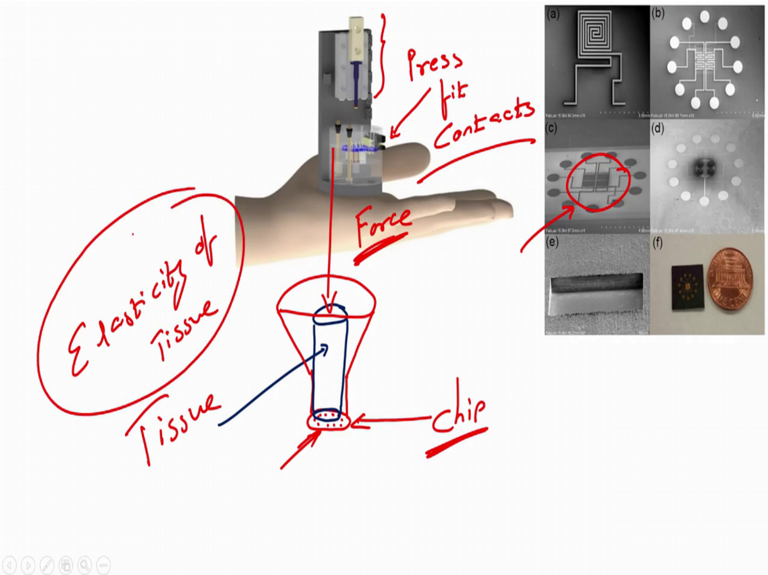

Now, what you will do, what you will do, if I place the tissue in the this particular funnel, what is my idea my idea is that if I press the tissue if I press the tissue what is on the chip, this is a chip. What is that on the chip the chip is having a having a piezoresistive sensors right.

So, if I apply force to this tissue, this force will be transmitted on the chip which has piezoresistive sensors. And based on the elasticity of the tissue, based on the elasticity of tissue, based on the elasticity of tissue, based on the elasticity of tissue, the amount of force applied and the amount of force measured will be different right. If I have few million internal force how much force is actually transmitted to the chip or to the piezoresistive sensor will depend on the elasticity of the tissue correct.

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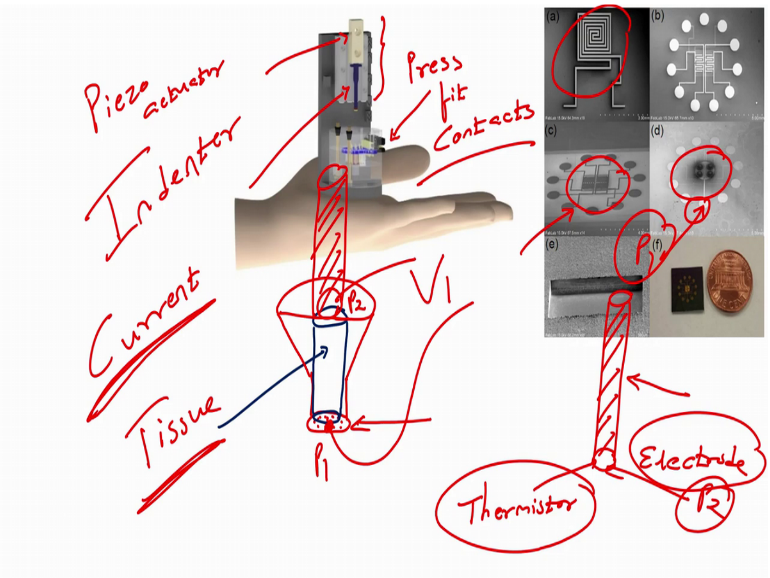

Second so how we will apply force, I will apply force to the tissue using indenter. This guy is called indenter, is like this and is connected to the piezo piezo actuator, is a piezo actuator piezo actuator indenter piezo actuator. This is I indenter. And at the tip of the indenter and the tip of the indenter if I have so right now we are pressing the tissue with the help of indenter that is one thing right. Now, in at the tip of the indenter if I have thermal sensors or thermistor, thermistor, thermistor is used to measure the temperature ok. Now, my chip is indicated with what is indicated with micro heater.

So, if I apply at the bottom of the tissue let us say 37 degree centigrade I can see what is the temperature at the top of the tissue with help of thermistor right. So, I said T 2, this is T 1. If T 1 is 37 degree centigrade, what is the temperature of the T 2? So, if I apply or heat the tissue from the bottom, what is the temperature at the top of the tissue. If I want to measure or if I measure temperature T 2 and T 1, what I can find I can find thermal conductivity, thermal conductivity ok.

Third thing if I attach a electrode at the bottom of the indenter electrode ok, what is that on the chip, there is a SU-8 pillars with a gold pad. So, if I apply voltage here, this were potential difference between two points. So, point one for applying a voltage is here; point two is my electrode. Then apply if I apply a voltage, so this is this is the indenter right. If I apply voltage here V 1 across the tissue and the chip so to complicate it let me draw it easy let me just rub it down the unnecessary things so becomes a little bit easier to understand.

If I apply a voltage between the point p 1 and point p 2 that is p 1 is on the chip here p 1 and p 2 is somewhere on the indenter all right. Indenter has what point p 2 that is your electrode; chip has what p 1 which again is a contact to the gold pad. So, if there is a voltage and if there is a tissue in between tissue would have certain resistance right, it would have resistance.

So, now, if the tissue has a resistance, if I have applying voltage, then what will I find, I will find different I will find the change in current depending on what is the resistance of the tissue right. So, what we understand that we can measure with this technique, with this technique, we can measure the mechanical property, mechanical property, electrical property and thermal property of a tissue; electrical property, mechanical property, and thermal property of a tissue.

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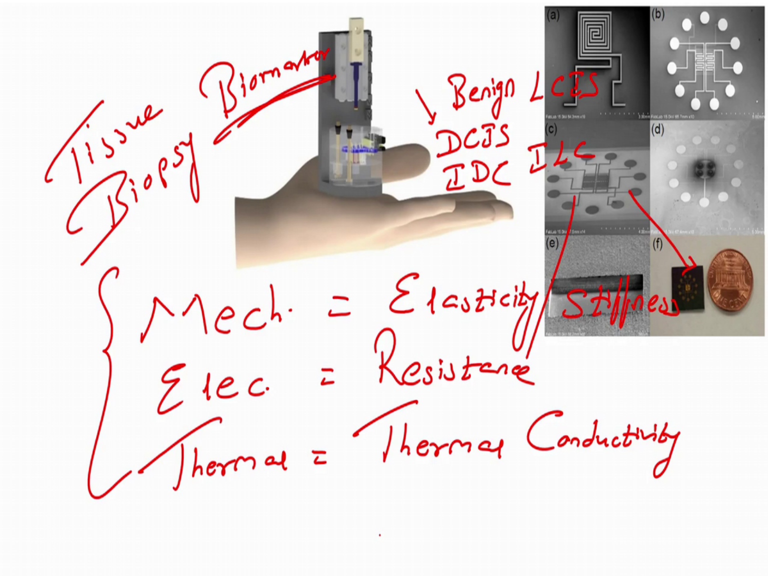

When I say mechanical, what I mean elasticity or you can say stiffness. If I say electrical, what does I mean, I mean resistance. If I say thermal, I see thermal conductivity. So, I can understand the mechanical property that is elasticity or stiffness electrical properties as a resistance, and thermal property like thermal conductivity from a single tissue from a tissue obtained from or obtained by biopsy, obtained using biopsy right.

So, this chip can help me to understand three different properties of the tissue. Now, if the tissue is from several stages let us say benign, b e n i g n, benign or it is ductal carcinoma in situ or it is invasive ductal carcinoma or let us say it is ductal lobular carcinoma in situ lobular carcinoma in situ. Lobular is cancer occurs in lobes. Ductal is ductalcancer occur occurring in ducts, and invasive lobular carcinoma.

So, if I have tissue from several stages of the cancer, I can understand the change the elasticity resistances, thermal conductivity and correlate that with my gold standard. And gold standard is the biomarkers that are available or that people use in the pathology lab oncopathologist will give us the understanding of what whether the biomarkers are present. And for with that study if we correlate our electrical mechanical and thermal property can we get, can we add these modalities onto the existing modalities and can tell the tissue is from this particular stage of the cancer. Thus the electrical, thermal and mechanical property of a tissue, we can measure with the help of this bio chip and if you want to if we if we are able to measure this and correlate with the gold standard, then we are helping to reduce false positive and false negative signals. You got it?

So, the whole exercise of understanding the chip design chip fabrication is to understand electrical mechanical and thermal properties of tissue. So, it is very interesting right that by learning or by fabricating a biochip using a MEMS based technology, we can understand electrical, mechanical and thermal properties of tissue.

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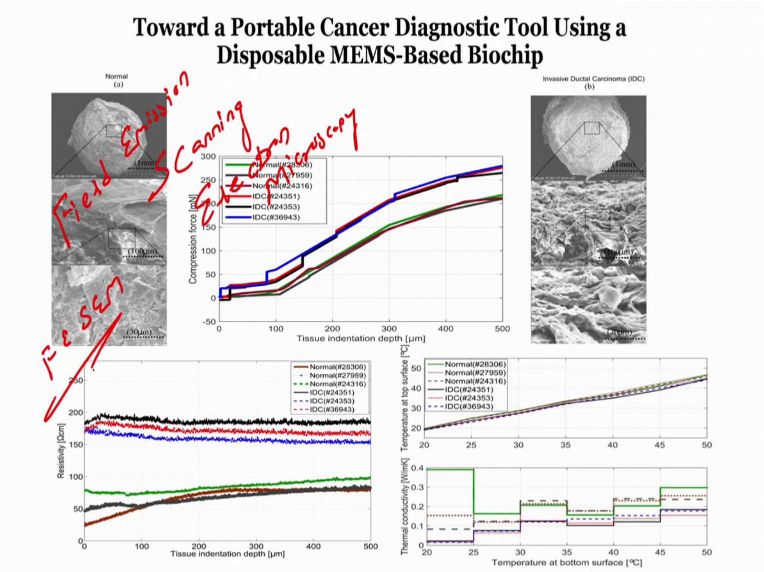

Now, whether this thing works or not, so as part of research work, which is published in I triple E transactions on biomedical engineering which I have given it to you right over here right. We found that when you understand the mechanical properties, when you understand the electrical properties, and when you understand the thermal properties of normal tissues, and invasive ductal carcinoma, then there is a change in this three these three parameters. These are the SEM images, SEM sense for scanning electron microscopy, scanning electron microscopy. SEM images of scanning electron microscopy. You can also use FESEM which is field emission scanning electron microscopy field emission scanning electron scope microscopy so is called F E S E M.

If you read you understand what is the difference between say SEM and what difference between FESEM. Now, in terms of the morphology, in terms of the topography, what you can see, you can see that the normal tissues seems to be smoother compared to the carcinoma tissues right.

So, what does it mean, that means that if the topography is so rough the resistance would be different compared to the normal tissue. The, if the resistance is different the thermal conductivity should be different compared to the normal tissue right, so that what it means. You can clearly see that there is a delineation between IDCs and normal a even we take on resistivity the same thing, thermal conductivity is the same thing right. So, you need to understand that this thing you can use it for measuring all three properties ok.

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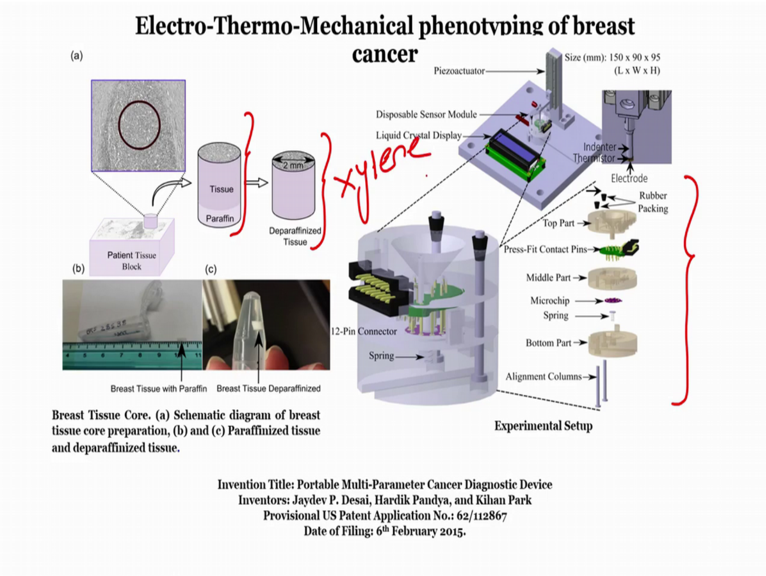

Now, this is the blown up diagram that I was talking about little while ago. And you can see here there is a this is made out of 3D printing, and we use object printing object printer. Like I said I will discuss about 3D printing in the in some other class. You can see that there is a there are alignment columns, then there is a bottom part, a spring is there, microchip is there, a middle part is there, press fit contact pins are there, top part is there and the rubber packing is there right.

When you when you this is a blown up diagram, when you indicate all the things together, you can find out this particular casing. And this casing is with a biochip that is right over here that we learn right at the process flow. Do you know other modules, and then these are the connectors that you can connect out, and you can understand different properties of tissue.

So, this is an example. As you as I was talking you can see an indenter. An indenter is attached with thermistor and electrode as a tip. So, the electrodes is used for applying the voltage between the top part of the or applying voltage across the tissue. And the thermistor is used to understand the change in temperature at the top surface when you heat the bottom surface right.

We discussed this thing. You can again connect this thing to LCD to understand the difference within properties. Once you learn of data, you can also have the understanding where this tissue falls in which particular region or it is from which particular stage.

Now, the study was done using the breast tissues, that means, the tissue is taken out is there is a freezed in a tissue bank. And as you can see the paraffin is used to store the tissue, and we have to remove the paraffin, you had to do deparaffinization that is done using chemical called xylene ok.

So, paraffin tissue deparaffinized tissue, you can see the image here photograph, but you can see breast tissue should be paraffinized. This one is a breast tissue which is paraffin embedded. And once you once you have the tissue, you can place the tissue, in this particular funnel right. This say this whole thing is placed right over here. And the indenter is pressing the tissue, this we have discussed in the previous slide all right.

So, this is how the electrical thermal mechanical phenotyping of breast cancer we have seen. And one more thing that is interesting is that this system cannot only help us to understand the change in the breast cancer tissue, but we can use this system for any tissue related cancer or any cancer related to tissue based cancer any tissue based cancer that is the right term to use. Whether it is oral cancer, whether this prostate cancer, even you want to understand the stiffness of the gray matter, then also we can use the similar you know structure. What is the change in the stiffness of the gray matter, if a person has Alzheimer; a person is normal you can see the changes are stiffness. Because stiffness is one of the properties of tissue that many people have used to understand the disease progression all right.

So, this is the last slide for this particular module and what we have seen is that a chip that is using a MEMS base technology can be a chip fabricated can be used for understanding different tissue properties. And for tissue related cancers like oral cancer, breast cancer, here we have take an example of a breast cancer, but same thing goes for the oral cancer you can place a tissue on the chip and you can understand the change in the tissue properties. Now, so what does we saw we saw that we just had only oxidized silicon wafer.

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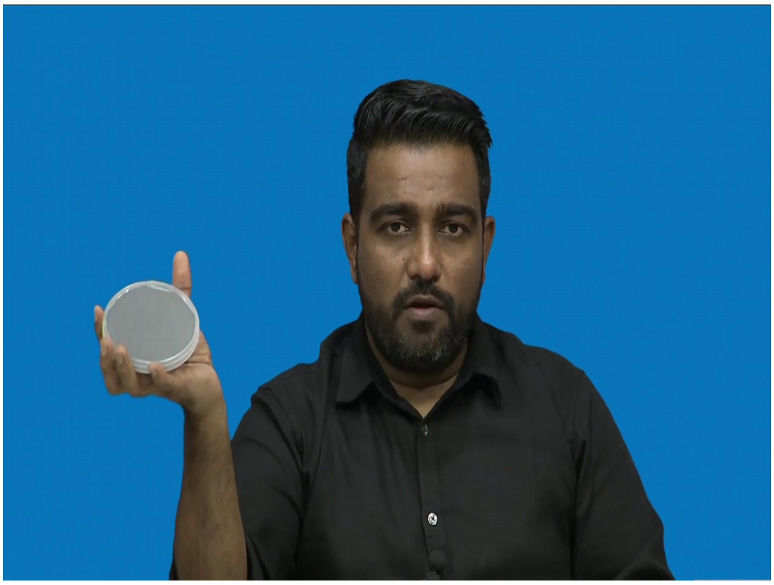

And from oxidized silicon wafer that we were using as a substrate right or in fact silicon wafer that we are using a substrate we have grown oxide; on this we have deposited a heater f competitor heater, then we had a insulator interdigited electrodes, piezo resistive sensor, insulator, gold pad, SU-8 pillar make a conductive, on the backside have a diaphragm. So, you have all three sensors indicated onto this chip.

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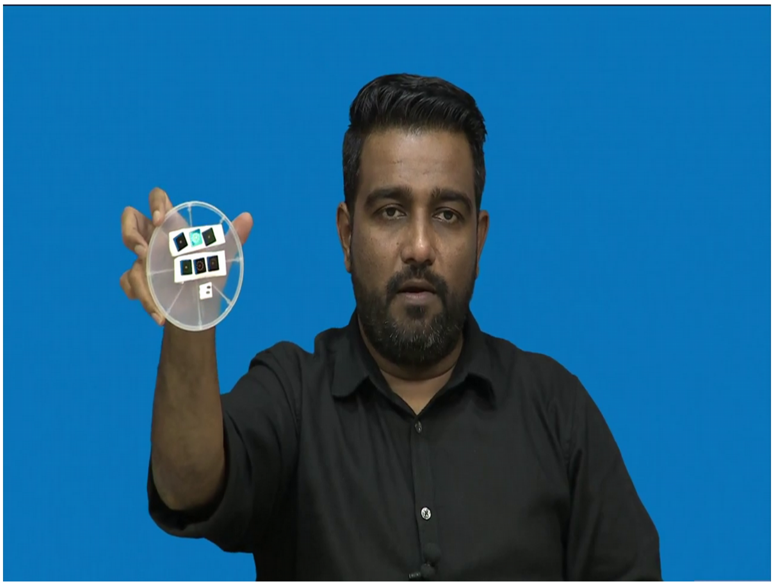

When you slice the chip, when you slice this chip, what will happen that you will have individual chips as I am showing it to you right here right. Yesterday also we have last lecture I do not know when I record it probably yesterday. So, the point is this is the chip that we obtained at the end of the process. And this chip is what we are using for understanding the change in the tissue properties, all right guys.

In next module we will discuss how can we just understand the change in the tissue properties which is mechanical properties if I do not want to have this complicated structure a complicated sensor, because it requires several mask, how can I design something which isjust for mechanical understanding it. Again yeah it depends if you are designing a piezo resistive cantilever, there are about seven mask process. So, depends and really the mask design, I am talking about the application point of view if you want to understand only these three stiffness of a cell or you want to understand only stiffness of a tissue, why to go for electrical sensor and thermal sensors right.

So, we will see in the next module how can you design a piezo resistive micro cantilever that can be used to understand the change in the stiffness of the tissue. Again same thing when I say tissue it can be oral cancer, can be breast cancer, it can be pursued cancers, can be another tissue related cancer ah, but the focus will be on how can we fabricate we will see the process flow, and we will also see what kind of mechanical properties we can you know measure with the help of piezoresistive sensor all right.

So, till then you take care, I will see you in the next module. Bye.