Fabrication Techniques for Mems-based Sensors: Clinical Perspective

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Lecture – 23

Hi. Welcome to this is this particular module. And in this module, what we will look at? We will look at the, another modality except mechanical to find out whether the tissue is cancerous or not. And as we have discussed earlie r, we are right now focusing on breast cancer. So, when you talk about breast cancer, we have seen that as the disease progresses, the morphology also changes right. And, we have seen in the last lecture how we can understand the stiffness of the tissue or how we can measure the distance of the tissue using piezoresistive micro cantilever, right.

So, in this class, let us see that except stiffness what are other characteristics can we measure the electrical property of tissue or can we do both things together; that is electrical plus mechanical property. When I say mechanical property, it is nothing but the elasticity or the stiffness of the tissue right. So, if you quickly see, what we are discussed in last class, you will see on the slide and that will be our piezoresistive micro cantilever.

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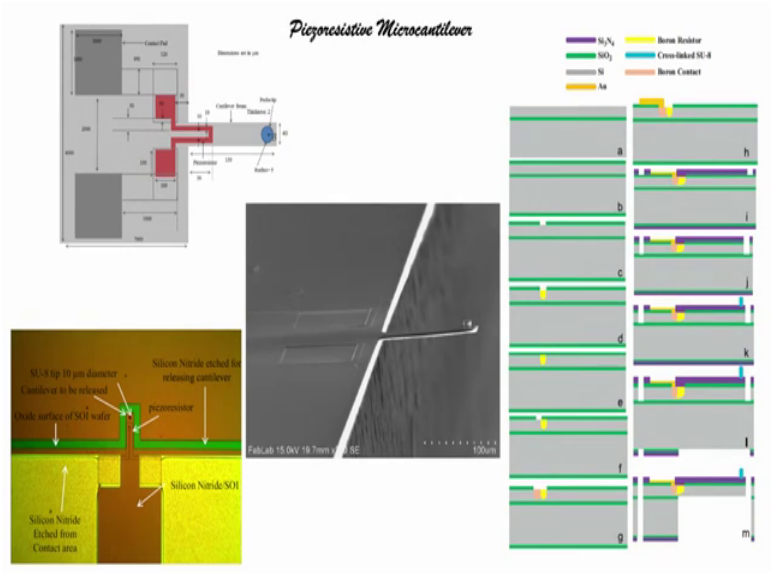

We have seen the process flow of how we can design this particular micro cantilever.

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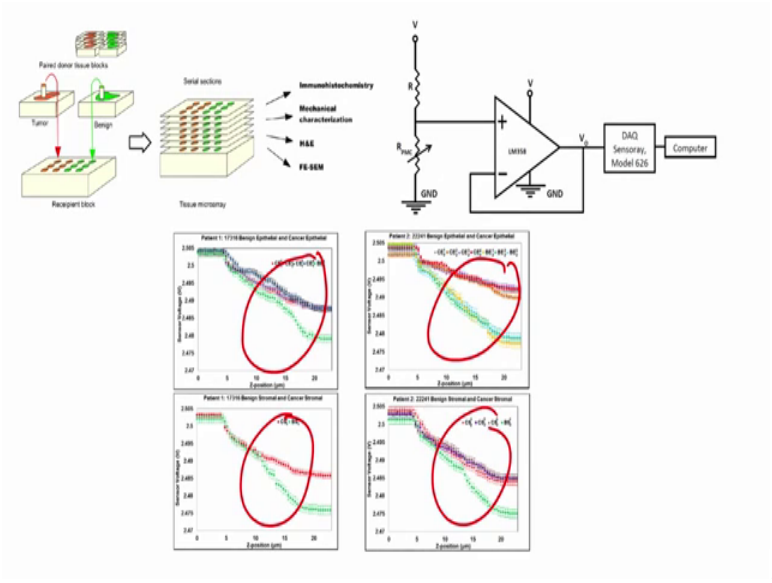

And then, we have seen how can use this micro cantilever and we have also seen the results right when we measure the epithelial region tissues from epithelial region, tissues from stromal region; also the tissues from benign region and cancerous region right. And, we can clearly see that we with the help of piezoresistive micro cantilever, we are able to delineate whether the tissue is normal or benign or it is cancer right.

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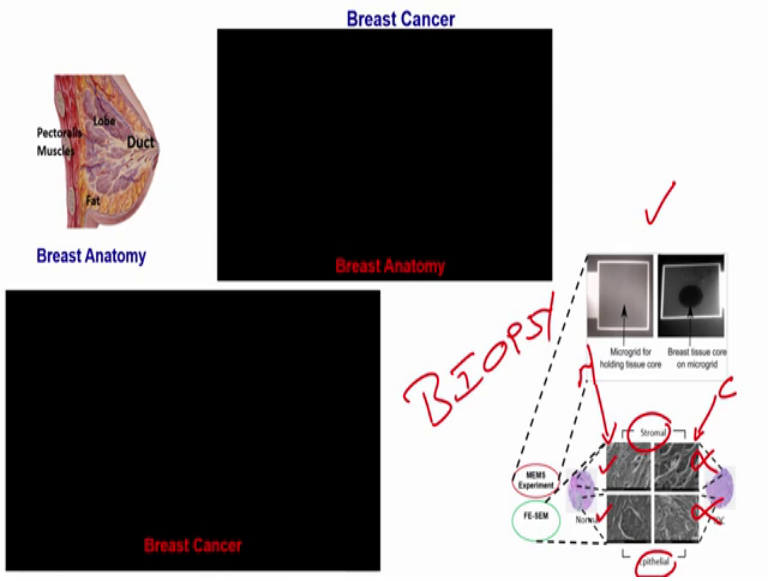

Now, in this particular module, let us see quickly what is the structure of breast or breast anatomy. Now, if you see on this particular figure, what we see is the breast consists of

lobes, ducts, fat and pectoral muscles. We also discussed this earlier right. It is just to revise and if the cancer occurs in duct, is a ductal cancer; it occurs in lobes, lobular cancer right. If it is mixed, is mixed tumor cancer; if it is inflammatory, inflammatory sensor; if it is musinest, musinest cancer right. And then, we have seen that the cancer can be 2 types; one is invasive, one is non-invasive.

So, on the right side, let us see and the right side we see that if the tissues when the tissues are taken from the stromal region and from the epithelial region and if the tissue is normal, this 2 on the left is normal on the right. This is cancer alright. So, I am just saying this particular tissues are cancer, this are normal. So, these are sem image of the tissues, sem image of breast tissues and this breast tissues are nothing but tissues that are taken out with the help of biopsy; with the help of biopsy B I O P S Y, alright.

So, when you see the sem image of the tissue normal versus cancer, we can clearly see that there is some kind of roughness in the cancerous tissues. While decay the normal tissues or the benign tissues right, they are comparatively smoother right, compared to the cancerous tissues. So, what does that mean? That means, that if the morphology of the tissue is different, if the morphology of this tissue that is normal tissues is different than the cancerous tissue, then we can probably understand it is electrical property. And it should be different while if the electrical property is different, it thermal property can also be different.

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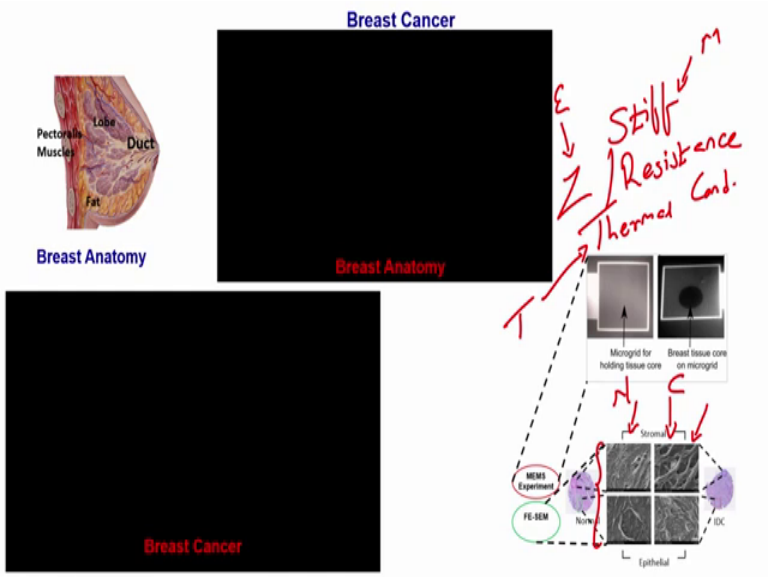

That means that, apart from stiffness, apart from stiffness of the tissue, we can measure the resistance of the tissue or we can measure the thermal conductivity of tissue, correct. We can measure the resistivity resistance or we can say impedance right. I will just write down impedance symbol Z stiffness. This is mechanical property impedance or resistance is electrical property and the thermal conductivity is thermal properties. So, E and T electrical mechanical and thermal property of tissue, alright guys.

So now, before we understand how we can design a sensor that can measure this electrical and mechanical property of the tissue, let us quickly see what is the breast anatomy. And also, let us understand what is breast cancer and what are the stages of breast cancer alright.

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So, the video here right, that is about the breast anatomy. Well, the second video will show you what exactly breast cancer means and what are these stages of breast cancer.

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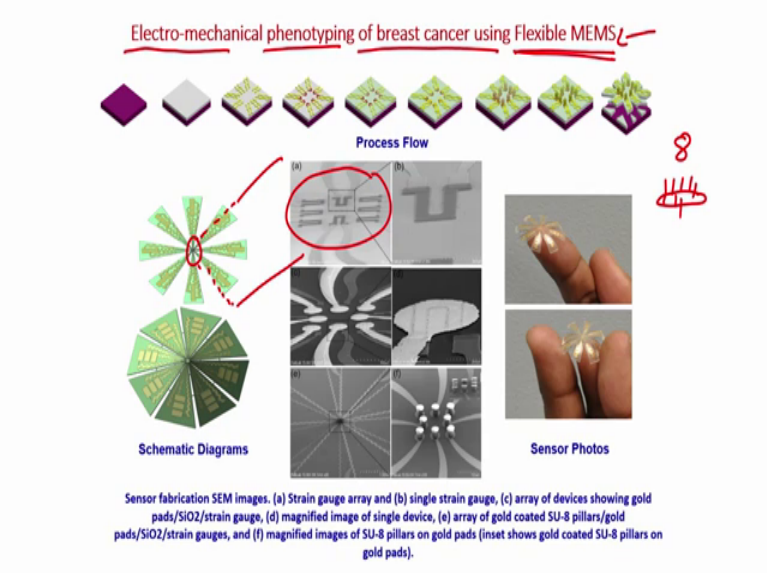

So, as you can see from the video right, breast cancer have different stages and it at certain point, we can understand whether it is invasive or non-invasive type of cancer right. Now, for a given tissue, for a given tissue from the biopsy, can we measure the electrical and mechanical property of tissue? That is why, we say electromechanical phenotyping of breast cancer using flexible micro electromechanical sensors, using flexible micro electromechanical sensors.

So, what should be the role of this sensor? This sensor should be able to delineate cancer and normal with the help of electrical sensing and the help of mechanical sensing. How can we do that? How can we design such a sensor? So, if you see this particular image, this is a schematic, we have drawn this schematic with the help of solid works, with the help of solid works.

In the center of this chip here, the center of this chip, there are 2 sensors; one strain gauge and second electrodes; one strain gauge and second electrodes, alright. Now, when you talk about strain gauge, so, if you see this particular image right, what do we see? There are 1 2 3 4 5 6 7 8; 8 strain gauges, 8 strain gauges. The reason of using so many strain gauges is to cover the entire area of tissue and to see multiple points in the tissue and to understand multiple points within a tissue. That is why we have 8 sensors; 8 strain gauges, alright.

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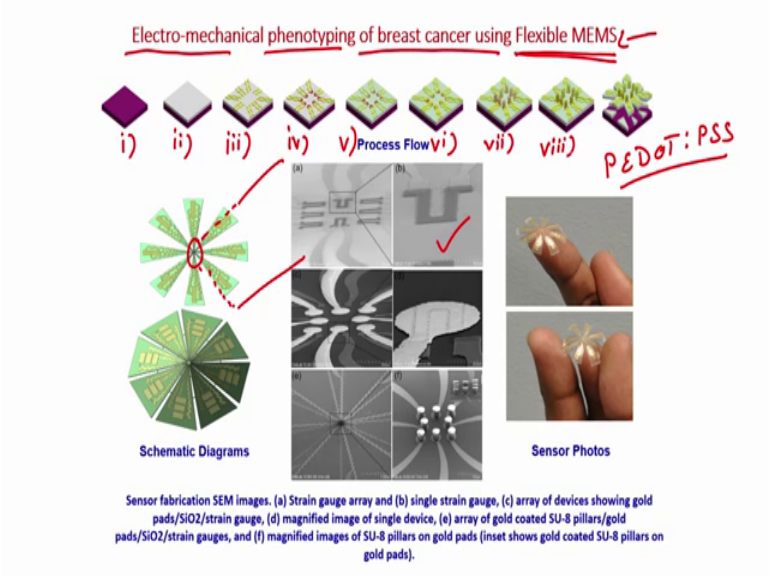

If I magnify it further, then I can see a single strain gauge which is shown here in the b section of our image alright and the material that we have used to fabricate the strain gauge is P DOT PSS P DOT PSS. This is a conducting polymer; this is a conducting polymer ok. Now, what we have done? Let us see what we are done, you see this ok. This is the silicon wafer.

Now, we have grown oxide on silicon wafer. So, I will just hide 1 2 3 4. So, it is easier alright; one we have silicon wafer, second we have oxidized silicon wafer that means, we have grown oxide. Third, we have created contact pets contact pads for strain gauge; Fourth, we have fabricated strain gauge; fifth, we have deposited insulating film on strain gauge; Sixth, we have now deposited and pattern gold electrodes; Seven, we have SU 8 pillars on coal electrodes; Eight, we have made SU 8 pillars conducting and Ninth we have released the sensor; we have released the sensor right.

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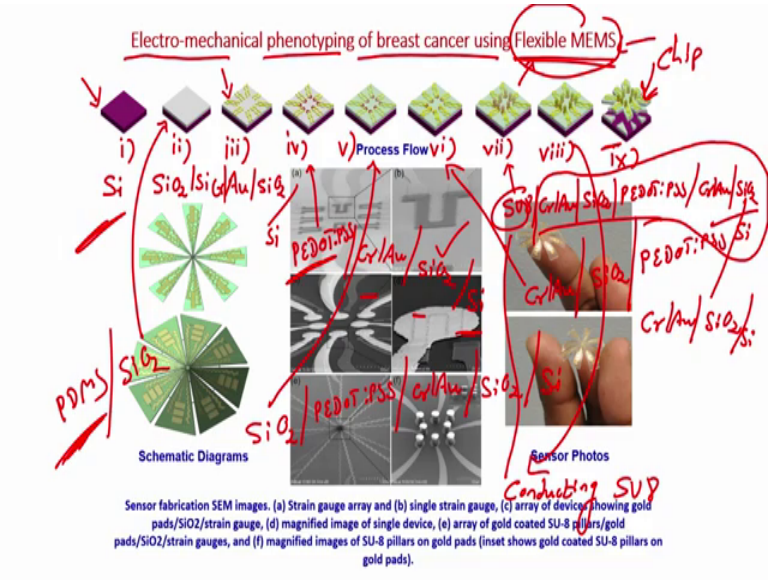

Once again, let us see slowly first step. First step is take a silicon wafer; second step grow silicon dioxide on silicon right. What is third step? Third step is we have now deposited electrodes right using chrome gold on silicon dioxide which is on insulator which is an insulator and this silicon dioxide is grown on silicon wafer. Fourth step 4 the Fourth step, now we have deposited SiO 2 on chrome gold on SiO2 on silicon and how we do that? You know it right.

So, you see for patterning, this we are using a photolithography technique; that means that we will deposit chrome gold, will deposit chrome gold right. And then, we will pattern for chrome and gold with the help of photolithography alright. Now, in this case, on this pattern electrodes we have deposited; am I correct no. So, you see in this particular case, we have P DOT P S S P DOT P S S for strain gauge.

So, let us see once again silicon, silicon dioxide and on silicon. Then, third step is chrome gold electrodes on silicon dioxide which is on silicon 4th step is P DOT P S S. That is patterned again using help of photolithography on chrome gold on silicon dioxide on silicon. So, the bottom layer is silicon next layer would be silicon dioxide; next layer will be chrome gold electrodes. On that layer, we have P DOT P S S strain gauges which you can see on a and b of the sem image.

Next step fifth step process number 5. Now, we have silicon dioxide on P DOT P S S on chrome gold on silicon dioxide on silicon ok. Next step, which is 6th step, 6th step would be now we have gold electrodes. So, we say chrome gold on silicon dioxide on P DOT P S S on chrome gold on silicon dioxide on silicon right, 6th step will be SU 8 pillars, SU 8 pillars on chrome gold on silicon dioxide over P DOT P S S. That is your strain gauge over chrome gold over silicon dioxide over silicon.

Last step right no 7th, 8th step itself would be we make this SU 8 we make the SU 8 conducting we make SU 8 conducting. So, SU 8 conducting and then entire this process is that. So, SU 8 on silicon gold on silicon dioxide on P DOT P S S on chrome gold on silicon dioxide on silicon right. And, a final the ninth step would be you take out the, you detach the sensor or this bio chip from the substrate. How can this bio chip from the substrate can you do that? You cannot do that, right.

So, when you grow silicon dioxide on silicon, on that you can on you can use PDMS. So, we see the screen, see the screen the silicon dioxide, we said here right, silicon, then silicon dioxide right. Second step would be this step would be silicon dioxide right. On this silicon dioxide, if I have PDMS, then I can detach it at 9th step.

If I do not have PDMS, then I cannot detach my sensor or cannot detach my chip from the substrate, from the substrate. Why we have to detach the chip from the substrate? Because, these are flexible MEMS and when you talk about flexibility, we have to use PDMS or any other flexible substrate, right.

So, the silicon or the oxidized silicon will help will help to form the base of the chip alright. So, in this case in this case if I want to detach the chip from the substrate, then I had to use PDMS or a flexible material and on that I had to do or I had to perform this entire process flow, alright. But, if I do not want to detach it, if I want to use a solid sensor, if I do not want flexible MEMS, then I can directly use oxidized silicon wafer ok.

So, let us see once again. So, that we are sure right that both of us you guys and me we are on the same page. So, what we do?

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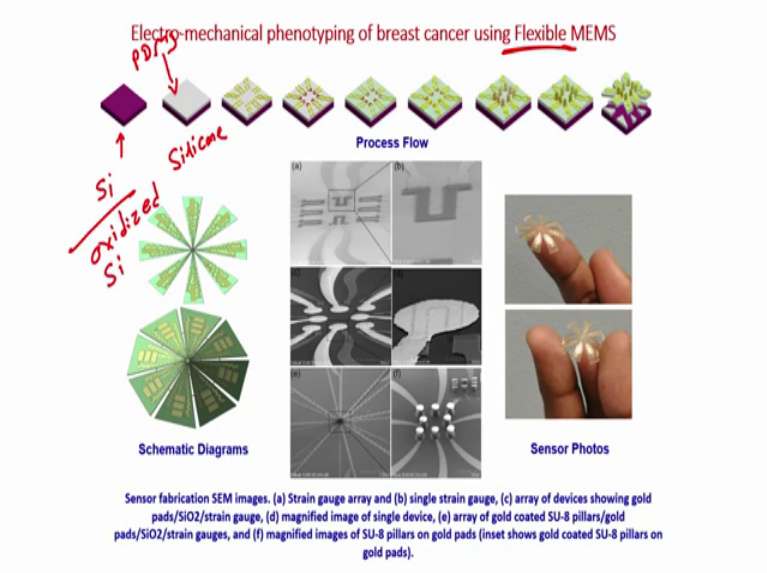

We start with in silicon or we can say oxidized silicon, oxidized silicon. If I want to have flexible MEMS, then this layer can be PDMS alright, can be PDMS or silicon is a s i l i c o n e flexible. It is a polymer PDMS or silicon on the oxidized silicon. This can be PDMS on oxidized silicon.

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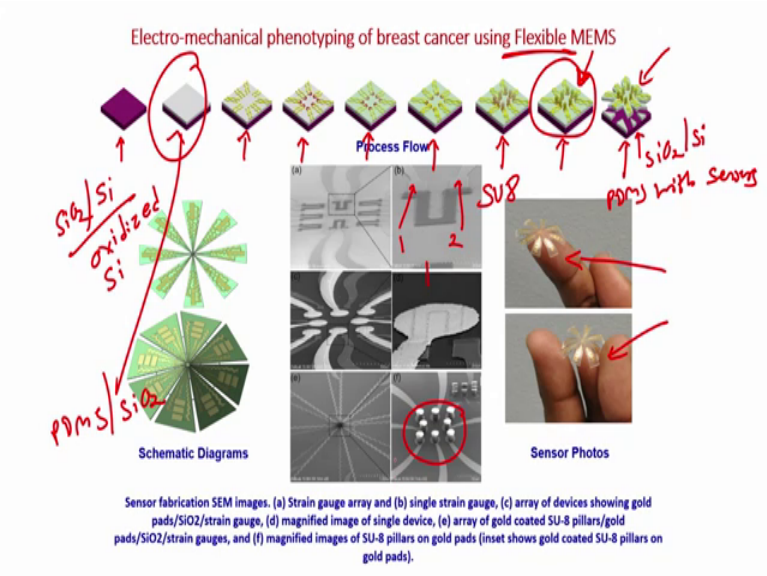

Then next step is you are designing a contact pad for strain gauge. Next step would be to fabricate strain gauge, next step would be to deposit an insulating material on strain gauge; next step would be to create a gold pad. You see here, goal pads. This is single,

these are multiple gold pads right, 18 number because we have 8 sensors, 8 strain gauges.

Now, we have 8 gold pads, ok. How you can fabricate this gold pad? Using photolithography on this gold pad; we have now SU 8 pillars. You can see here, SU 8 pillars. There is a next step now SU 8, SU 8 is non-conductive polymer. So, we can make it conductive by depositing or by coating SU 8 pillars with a metal which metal we can use again chrome gold, right.

So, here we have coated SU 8 pillar with a metal and finally, we are able to detach the chip or the sensor or the MEMS device from the base from the base which is our SiO2 right. All silicon we can detach PDMS with sensors completely and this would be our flexible sensor, this will be our flexible sensor. If we do not use PDMS in this particular stage and we continue to fabricate the device, then at the end of this, we will end up somewhere here. We will not be able to detach the device. That is fine for some application this kind of devices also, will also work, ok.

Now, if you see on the right side, what do you see? This is the detached device and it is flexible. These are detached device and it is flexible. So, how many contact pads would be there? You see for a strain gauge; we require 2 pairs. You can see 1 and 2 right, 2 pairs for strain gauge and how many pad for electrodes? 1, just 1 for the electrode, right. So, we now we consider electrode is the gold pad over which there is an SU 8 pillars gold pad. So, gold pads on which there are SU 8 pillars or if we talk about one single than gold pad with a SU 8 pillar and that SU 8 pillar is conductive because, we have coated with a metal, ok.

Now, we have a sensor. So, let us see how we can use this sensor further how we can use the sensor for our application. That is, our application is to delineate or to understand the electromechanical phenotyping of breast cancer. We have to understand whether the tissue is cancerous or not.

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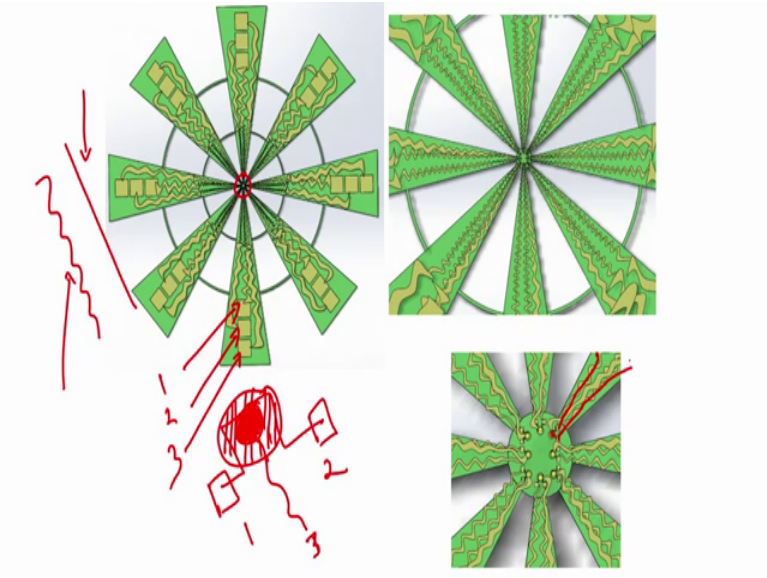

So, if you see here, like I said for each strain gauge how many pads we require? We require 2 contact pads; 1 and 2 and then, on that there is insulator on which the reason electrode on and that electrode consists of a SU 8 pillar.

So, this is a top view. It looks like this, right. Somewhere your electrodes is like this, alright. I am not just making it solid; so, that we can understand. So now, how many contact pads for here? 1 right, how many? So, we can name it as 3. So, how many contacts pads for here 1 and 2. So, total is per chip per sensor. So, if I go back, if you see here right, this one, there are 3 electrodes; 3 electrons because, one for the there are 3 contacts; 1 for the electrode and 2 for the 2 for the piezo resistive sensor hm.

So, that is why, you see here, 1 2 and 3, 2 for this strain gauge and 1 for the electrode. One more thing if you have observed is, here we have a zig zag pattern or a ribbon pattern for the contact. Why we have not made a straight contact? Why we are not use this kind of pattern for contact? Why we have used a ribbon pattern? The reason is that; we have on to reduce the stress. We want to reduce this stress because, this sensor would be flexible, would be flexible in nature.

So, we have to bend this sensor, we have to bend the sensor. Now, if you see this one. So, these sensors are right in the center right, there is extremely small and if I go on

magnifying it, I can see here clearly one. This one for gold pad for the gold electrodes and this one and this one is for piezo resistive sensor, correct.

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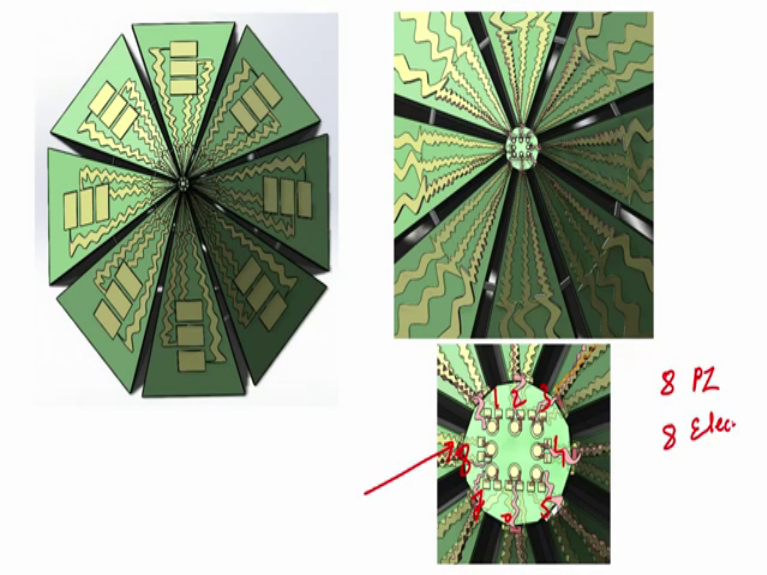

Now, this is another diagram. You can see here very clearly what I mean. So, we have strain gauge and when we have electrodes, 8 strain gauges and 8 electrodes right, you see 1 2 3 4 5 6 7 and 8; you have 8 strain gauges and 8 electrodes; so, 8 piezo resistive sensors, 8 electrodes.

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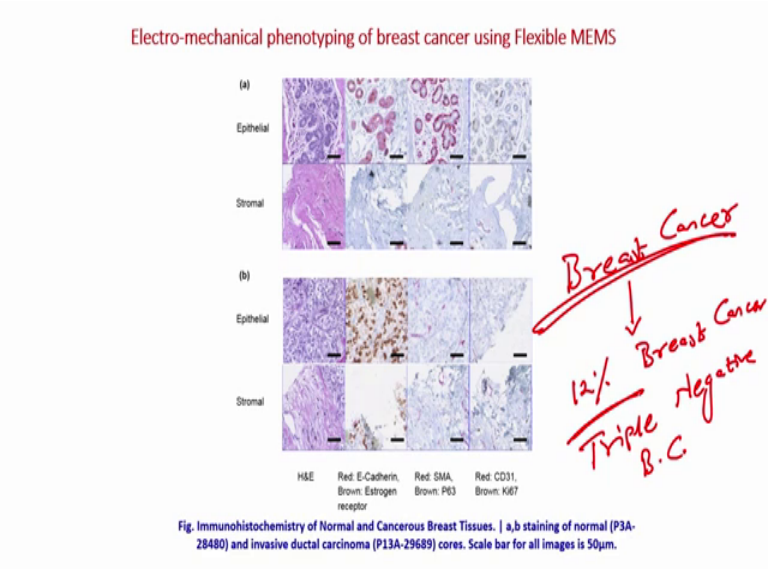

And, there are certain biomarkers that are there through which we can confirm whether there is cancer or not. Some of those are prostrating biomarkers, estrogen biomarkers, KI 67, then we have H & E images. So, these are all images of the tissue using different biomarkers and from this, the fat lab will tell us whether there is a cancer or not, ok.

Now, now there are certain biomarkers; there are certain cancers within the breast cancer. Within breast cancer, there are approximately 12 percent of breast cancer within breast cancer. They are called triple negative, triple negative breast cancer. Within the bigger umbrella of a breast cancer, there are around 12 percent of breast cancer which are known as triple negative breast cancers.

Why because, none of the biomarkers are present in the breast cancer tissue. None of the biomarker which are biomarkers estrogen biomarkers, prostogene biomarkers, H E R biomarker right, none of the biomarkers are present.

So, it is very difficult to identify such tissues and that is why, the device that we are fabricating or we are understanding is comes into play which is very important or plays our extremely important part in identifying those tissues which cannot be identified with the existing biomarkers and that is not a claim. This we have just done study using some patients or few patients and we had to make sure that we have enough number of patients to claim that this particular device can play an extremely important role to identify triple negative breast cancer.

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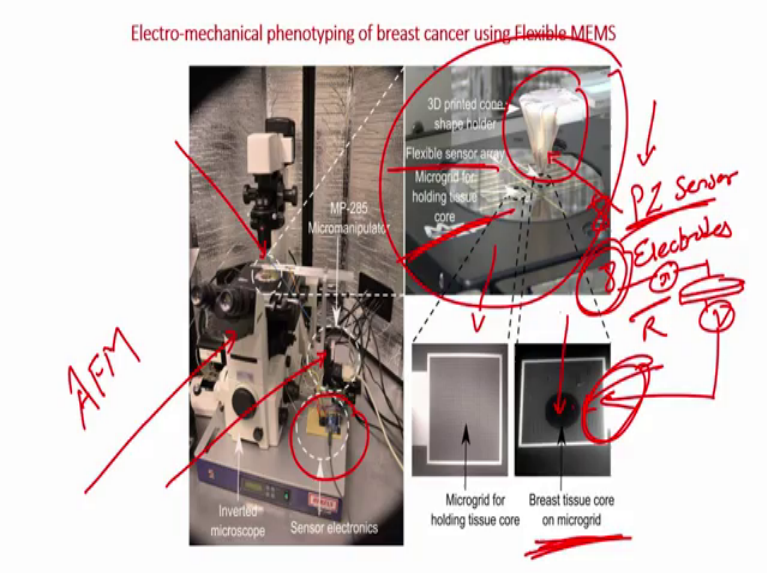

So, how? Now, we are identifying or delineating the normal tissues from the cancerous tissue, ok. So, for that, we have to load it, cancers load the sensor on the 3 D printed cone, why? So that, we can we can we can indent the tissue, we can indent the tissue. So, let us see on the screen. What we have? We have a 3 D printed cone right over here and we have attached the, we have attached the flexible sensor right onto the 3 D printed cone.

At the bottom, at the bottom which you can see here right, there is an electrode or a micro grid for holding tissue for holding tissue and this is the image where we can see a breast tissue core on micro grid, right. Now, what will happen if I indent this tissue? If I press this tissue, then the piezo resistive sensors on my MEMS device would bend and that bending will be corresponding to the elasticity of the tissue, correct. You know right, this sensor this chip has piezo resistive sensors and it has an electrodes 8, right.

So, when this sensor touches the tissue which is placed on the micro grid, what will happen? Because of the stiffness of tissue, the piezo resistive sensor will bend and this bending will cause change in resistance and that resistance corresponds to the elasticity of the tissue. Second part, there are about 8 electrodes on the sensor or there are 8 electrodes on the MEMS device.

When I apply a voltage between the micro grid, that is here right, apply voltage between micro grid and the electrodes and these electrodes and the tissue is in between right tissue is in between apply voltage between this 8 electrodes and a micro grid. What will happen?

There will be change in the resistance of that there will be change in resistance or we can see that this we can see the different resistance depending on the resistance of the tissue how you can see the resistance is very difficult to measure the resistance or see the resistance right, change in resistance. But, what we can do is when we apply voltage, we can we can measure the, we can measure current right.

This change in current will correspond to the change in the resistance of the tissue. Thus, we are not only able to measure the elasticity of the tissue with the help of piezo resistive sensors, but we are also able to measure the resistance of the tissue with the help of applying voltage across the tissue with the help of electrodes and the micro grid.

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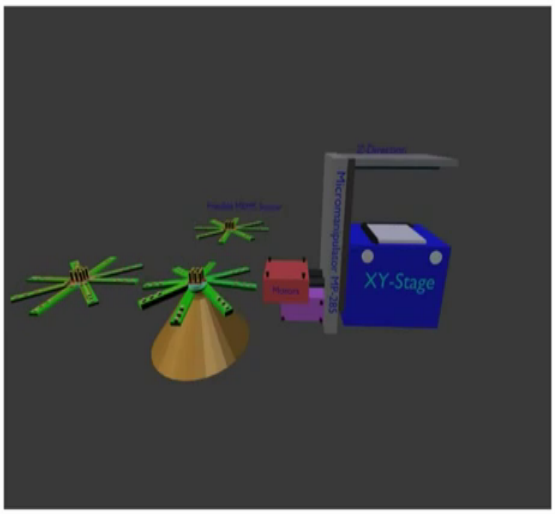

So, how this thing works? How the thing works, right? So, you can quickly see this video that 3 D animation that I have created with the help of Maya and this is a stage. Now, we have placed the bottom micro grid array this 3 D printed cone and on this cone, we will be loading our MEMS device.

The MEMS device consists of piezo resistive sensors and electrodes. When we attach the MEMS device onto 3 D printed cone, we have to load the 3 D printed cone onto the micro manipulator, onto the micro manipulator we loaded the cone. Now, we will place the micro grid on this stage, on that we will place the tissue and then we will press the tissue. As you can see clearly right, we are pressing the tissue and we are measuring the electrical and mechanical property of tissue right.

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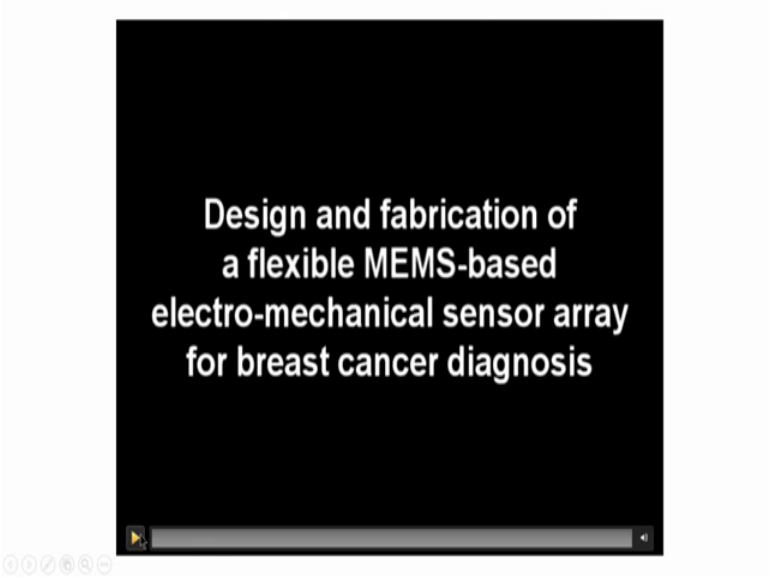

So, same thing goes here, same thing goes here.

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This is where we are placing the tissue, you can clearly see right.

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We can we are placing the tissue onto micro grid.

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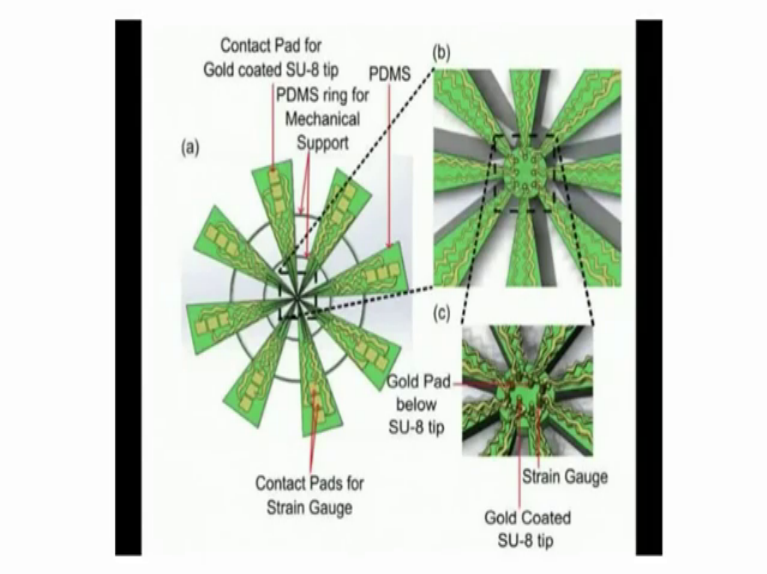

We have just seen the schematic of the sensor.

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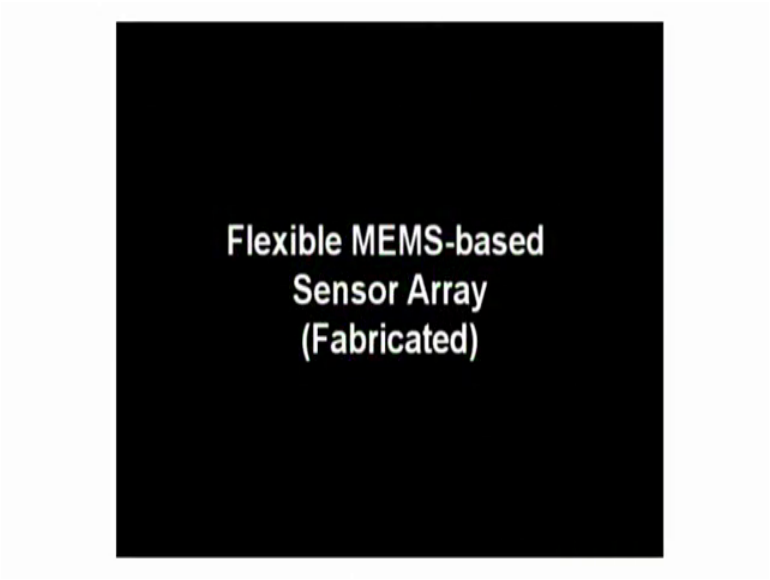

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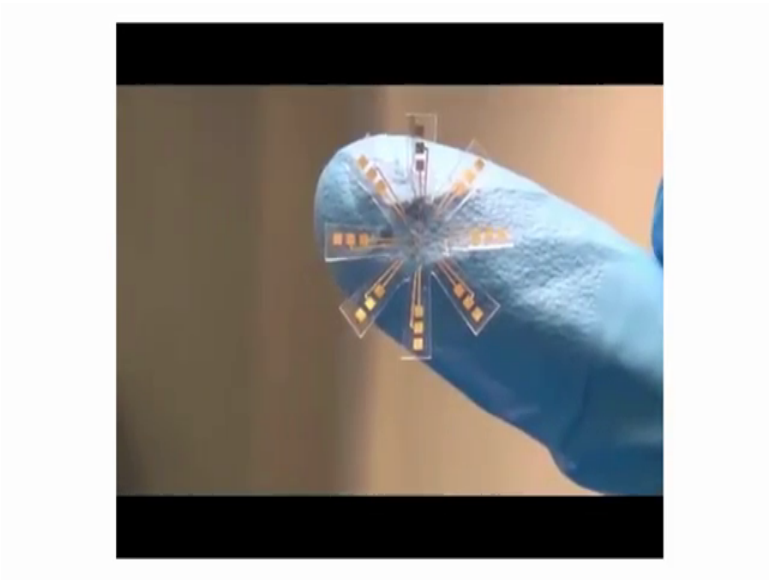

And now, the sensor or the MEMS based device.

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That is detached from the substrate is now stretched to evaluate the performance.

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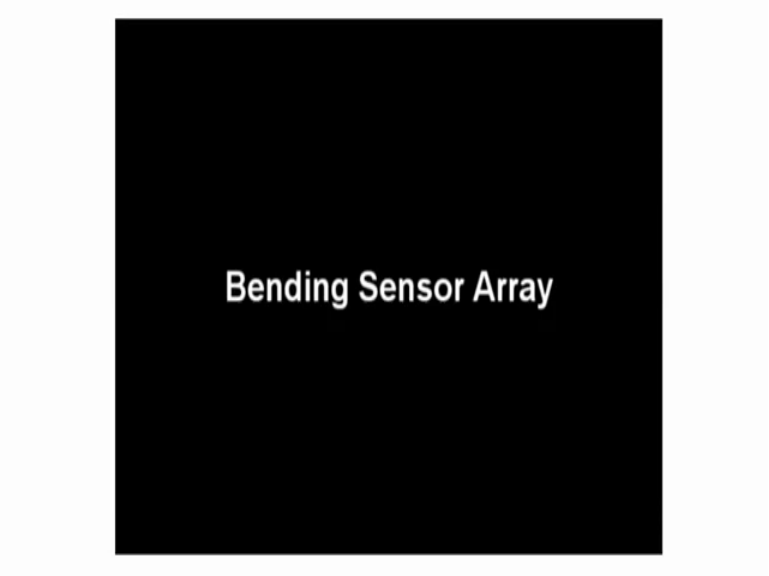

That we get the same base value of the piezo resistor and to see, whether it will break or not. We have also tested bending by bending the MEMS device, we have tested it is property.

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Now, when you load the device and you can see with the help of micro manipulator, we are indenting the tissue right goes down.

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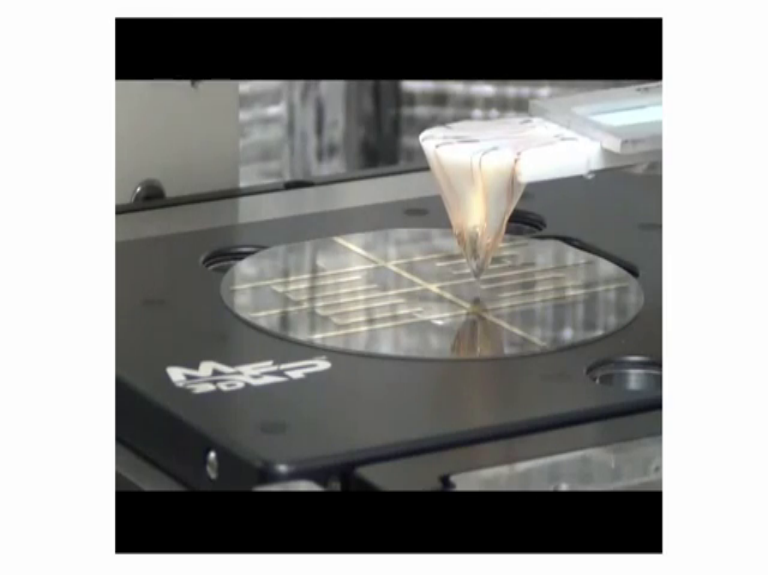

It touches the tissue indents; it gets the data comes back correct. So, with the help of this, what we can understand that we can measure the electrical and mechanical property of tissue.

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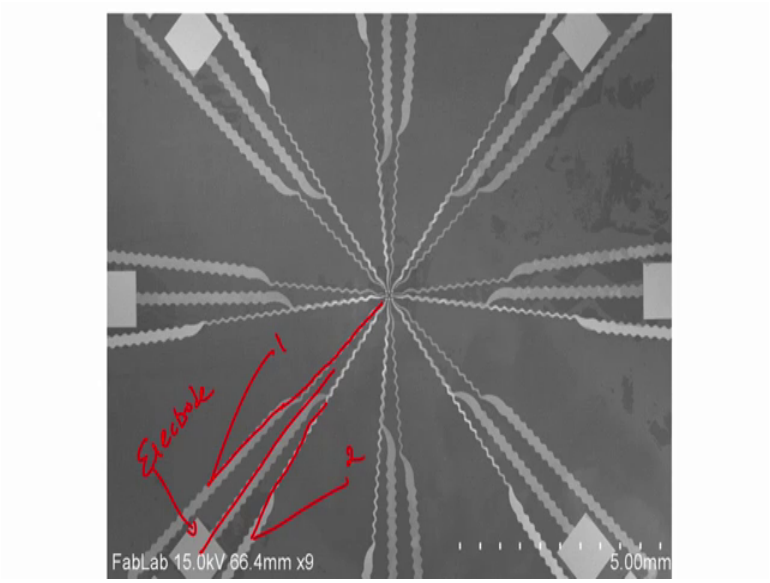

Now, you can see here. This is a sem image and is about 5 millimeter. So, total chip dimension is close to 10 millimeter right, almost double of this, little bit more than that. So, I think it is close to 15 millimeter. The overall chip is 15 millimeter. But, you see where are the sensors? Sensors are right over here, right over here, within a within an area of 1 millimeter we can have 2 sensors; one is piezo resistive sensor, another one is the electrode right.

So, this is the sem image you can see here. There are 2 lines right. That goes out of the piezo resistive sensor from here you can see one and then another one from here right and the center, one is for the contact pads. This one is for the electrodes contact pad, this one and this one will be for piezo resistive sensors piezo resistive sensor because, there are 8 sensors. We have about 24 pads; we have about 24 pairs you can see.

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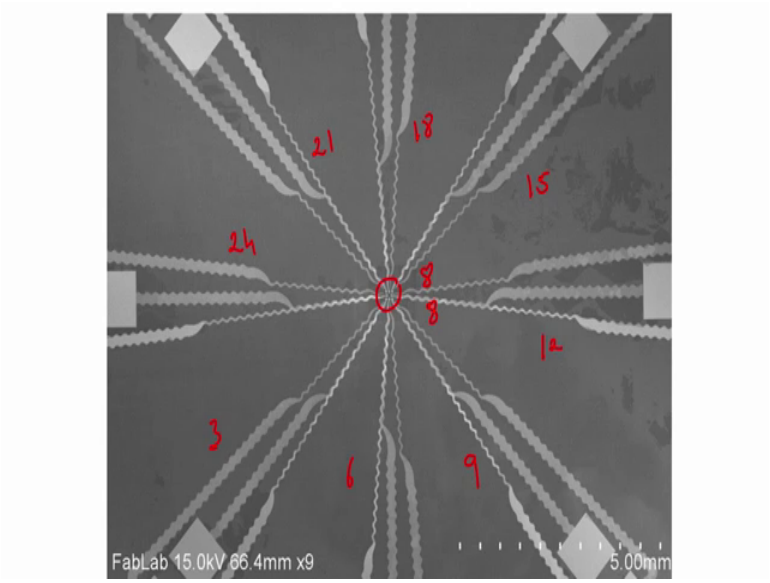

3 6 9 12 15 18 21 24 right, about 24 contact pads we have to fabricate or we can pattern using chrome gold to pick out the context from piezo resistor and electrons and how many piezo resistor and electrons are here 8 8 piezo resistors and 8 electrons ok.

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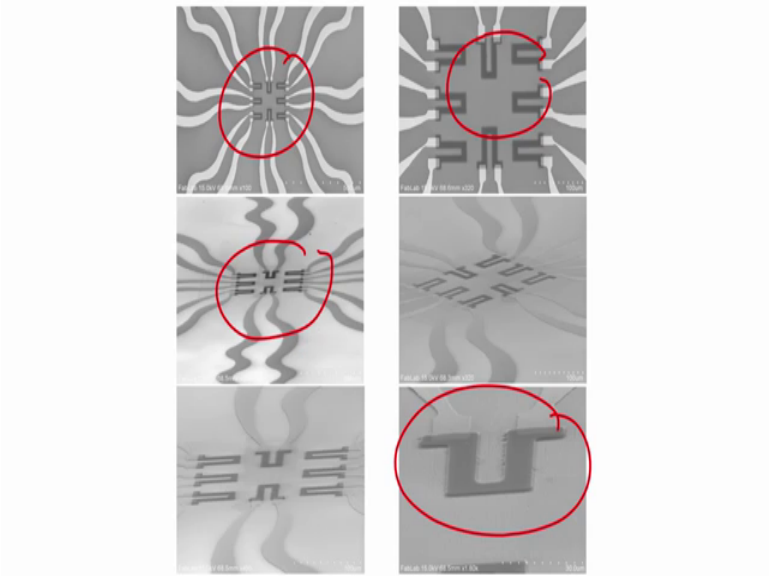

You can see here. Now, we have strain gauge. We have strain gauge, array of the strain gauge. This is top view, top view, cross sectional view, cross sectional view of strain gauges sem image and you can clearly see a single strain gauge right sem image of a single strain gauge.

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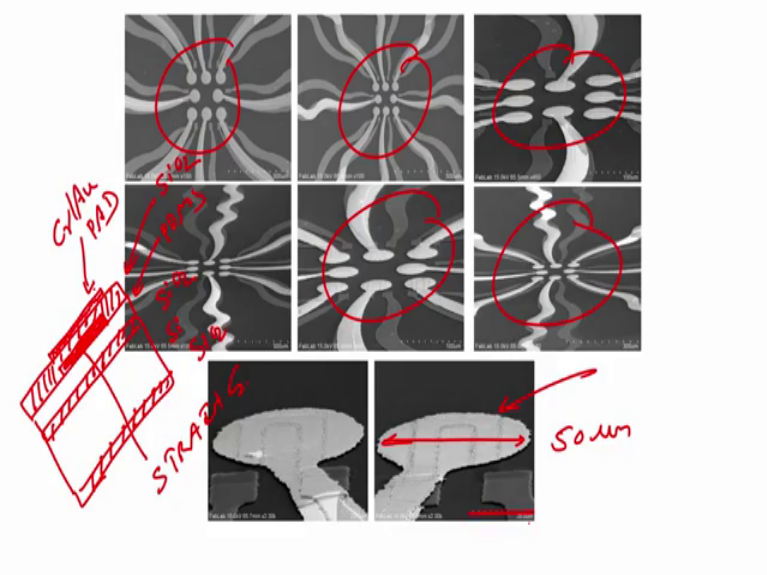

Now, these are gold pads you can see gold pads on insulator on strain gauge. So, that what does it mean we have a substrate we have oxidized silicon wafer it is oxidized SiO2 right, SiO2 we have silicon and this one is our PDMS right on PDMS we have this strain gauge right.

So, let me just draw one strain gauge. So, it is easier for us to understand and say this is a strain gauge right, on this strain gauge we have insulating material which is our SiO2. These are strain gauge right on this strain gauge. I will have the I will have the chrome gold pad which you can see here correct ; single pad you can very clearly. See in this image, there is a strain gauge and then there is an insulator over which there are there is a gold pad was a size 20 micron is this size 20 micron, the bar line shows 20 micron.

So, it is about it is about 50 microns, it is about 50 micrometer diameter ok, clearly see the sem image of a gold pad on insulator on strain gauge. So, where are SU 8 pillars? Let us see where are SU 8 SU 8 pillars. You can see this image and this is in this image. What we see in this image? What we see?

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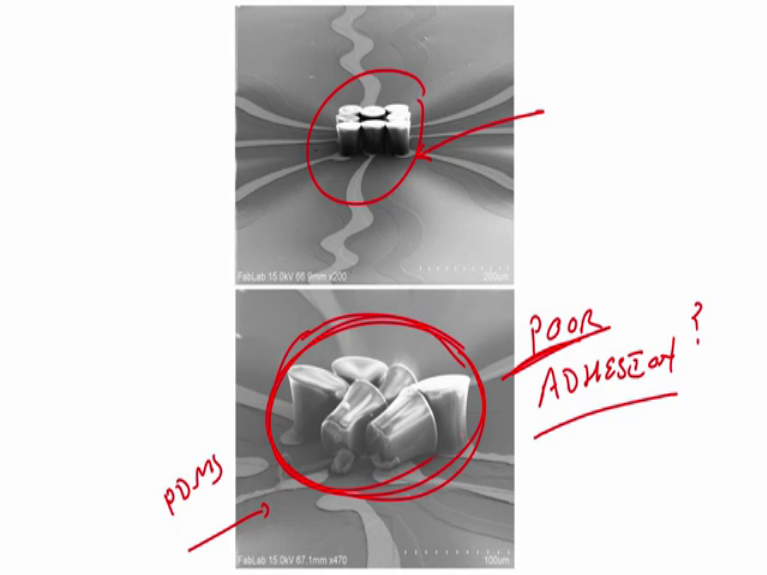

There are SU 8 pillars right, you can see this is SU 8 pillars and in the next image, you see that the SU 8 fillers are like they are not tucked well on the PDMS. But, they have fallen down right, because of the poor adhesion right poor adhesion and why there is a poor adhesion. Why? There is poor adhesion because of the moisture content one of the possibility is because of the moisture content on the layer on the PDMS layer. This SU 8 pillars have fallen down.

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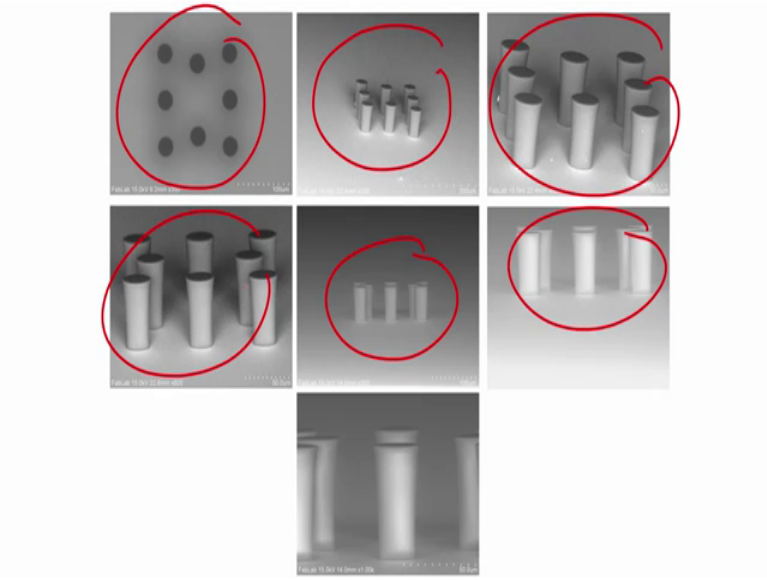

You can see SU 8 pillars. This is a top view; cross sectional view or side view here see SU 8 pillars.

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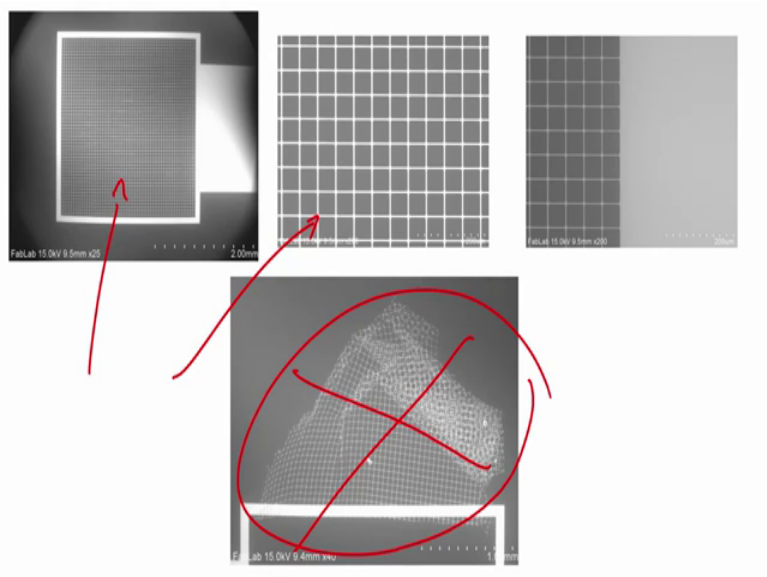

This is grid micro grid right, you can see a fine mesh here again this is because of the skipping the process or not following the recipe correctly, you can see the micro grid detaching from the pad right. This is a failure; this is a failure. But, it should be it should be like this, not like this ok. On this micro grid we place the tissue.

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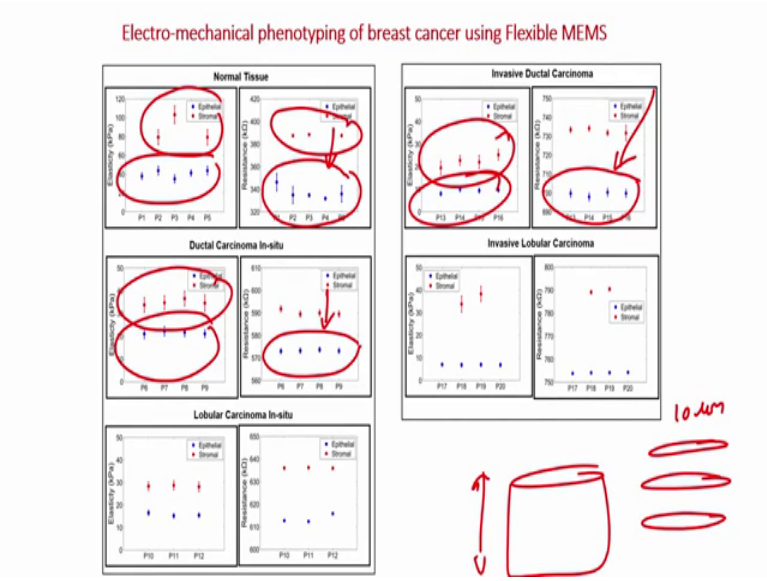

These are few of the results, few results that I have used for this particular module and here what we had to see is how the elasticity changes from normal tissue to ductal carcinoma in situ to in visit after ductal carcinoma, normal tissue ductal carcinoma in situ, invasive ductal carcinoma. These are the stages of cancer can be identified ok. While as we know, if the cancer occurs in lobes say lobular cancer.

So, from normal tissue to lobular carcinoma in situ to invasive lobular carcinoma ok how the elasticity changes and how the resistance changes. So, we can see here now within that normal tissue within DCIS or within LC is we are also measuring the epithelial and stromal region. First, let us just see epithelial region. Epithelial region is given by blue color you can see that normal tissue are somewhere around 40 kilo Pascal while the cancerous tissues are around 10 kilo Pascal.

Now, if you see in terms of elasticity, how come the elasticity of a cancerous tissue is less compared to normal tissue because, we are now cut the tissue which is from biopsy in 2 slices thin slice this slices thickness is close to 10 micrometer. So, what we think is when you decrease the size, the elasticity does not follow the same is not similar to when you have a whole tissue because, when it is a bigger tissue larger tissue, then we can see that the elasticity of the tissue which is larger the cancerous region is more stiffer compared to normal.

But, I mean when we talk about the tissues which are thinner the slice is thin around 10 microns, then the elasticity which is further from the normal tissue is close to 40 kilo Pascal. While the elasticity from the cancerous tissue is about 10 kilo Pascal, this is when we are talking about epithelial region right. And if you see DCIS, let us say DCIS. The DC is somewhere is in between the invasive ductal carcinoma and normal tissue.

What about resistance? Let us say the resistance is close to 340 330 to be like a little bit precise average value. While, if you see the resistance of the invasive ductal carcinoma is close to 700, while the resistance of ductal carcinoma in situ is somewhere in between is somewhere in between right. This one, this one and this one second if we see the red color red car is stromal region, their car is stromal region.

Stromal region, in the case of normal tissues is elasticity is around 100 kilopascal or if we take average about 90 kilo Pascal, in the case of invasive ductal carcinoma. It is

somewhere around 25 kilo Pascal while for the ductal carcinoma in situ it is somewhere around 38 kilo Pascal about 40 kilo Pascal 40 kilo Pascal, right.

So, what does that mean my point is that our sensor the sensor that we have designed the sensor that we have seen right. Now, is capable of delineating normal tissues ductal carcinoma in situ and invasive ductal carcinoma; that means, it can measure the change in the tissue property elasticity and resistance as the disease progresses or as a disease progressed. And this was case of ductal carcinoma in situ, but if you take the case of lobular carcinoma in situ.

So, if we see from normal tissue to lobular carcinoma in situ to invasive lobular carcinoma. We can again find a distinguish clear cut pattern clear pattern. We can easily delineate a tissue which is normal a tissue from lobular carcinoma in situ and a tissue from invasive lobular carcinoma. And thus, our sensor is able to measure the change in the elasticity as well as resistance as the cancer progresses from normal to invasive from normal to invasive, right guys. So, what we have learnt?

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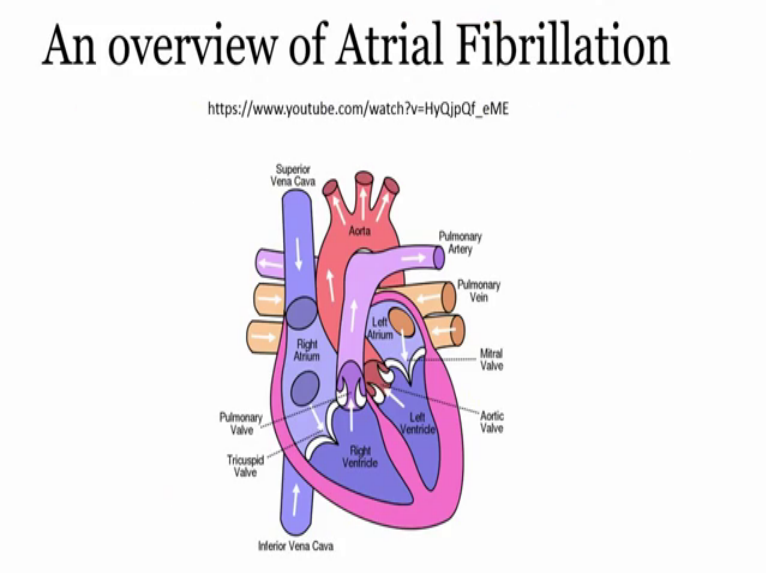

We have learn we have learned the flexible MEMS, flexible MEMS right which is capable of delineating the normal and ductal carcinoma in situ or no lobular carcinoma in situ and invasive ductal carcinoma or invasive lobular carcinoma right. Tissues for that is obtained from the biopsy obtain from the biopsy right and this is the setup the

experimental setup right. This is micro manipulator which is right over here micro manipulator mp 285 right here where we have loaded the tissue and you can see the magnified version here right. And we have some electronic module we have an inverted microscope. This is a stage inverted microscope we borrowed from the AFM unit A F M atomic force microscopy right and with the help of the experimental setup; we were able to measure the changes in the tissue, ok.

So, I hope that you guys understood what we mean by the designing flexible MEMS for applying in this particular area where we went understand or delineate between normal and cancerous tissues right. So, in the last class, what we have seen? A piezo resistive cantilever that can measure the change in the mechanical properties of tissue. In this class, what we have seen? We have seen a sensor or a MEMS based device with a multiple sensors that can that can delineate the tissue properties or tissue cancers tissue and normal tissue along with a ductal carcinoma in situ or lobular carcinoma in situ with the help of electrical and mechanical signatures.

And mechanical signature is nothing but elasticity and electrical signature is nothing but resistance alright. In the next class, let us see how we can design a complex sensor which can do electrical mechanical and thermal properties of tissue together. Till then, you go to the lecture. I will see you in the next class. Bye.