Electronic Systems for Cancer Diagnosis
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Lecture – 20
Assembly of the electro-mechanical sensor

Hi, welcome to this particular module. In this module, we will be looking at how to use the sensor that is flexible sensor to understand the tissue properties right. So, if you remember in the last module, what we have seen group of modules, what we have seen how can we design a sensor with a piezoresistors, and as in a gold pad with an SU-8 pillar. Now, what is the role of that sensor and how can you measure tissue property?

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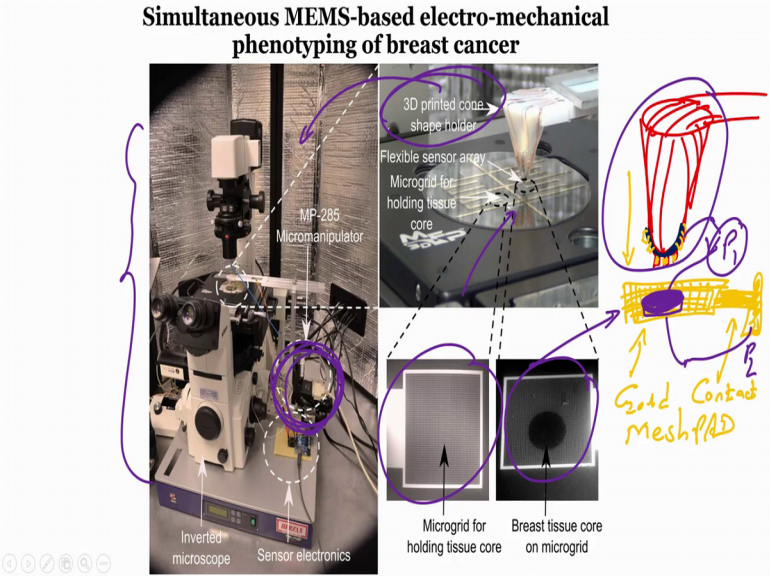

So, if you see the slide you, you have to concentrate on this particular figure ok, and here what you see is a 3D printed cone. So, if I draw it is a 3D printed cone with a shape like this, the shape like this, over this we are attaching our sensor. So, it is here sensor, there are SU-8 pillars and there are lot of wires, lot of wires that is connected to that is connected to a holder right. You see these are wires right, sensor is right over here.

So, if I draw with a different color it will be little bit easier probably. I am attaching my sensor right over here the tip, because the flexible sensor I can attach it like. This right on the sensor I have my contacts right. I have my contact pads like this and on the contact

pads, and finally, I have a SU-8 pillar right which is also conductive, and I have my sensor with a piezoresistive material as well.

Now, if I have bottom plate, bottom plate which is conductive like this, which is a mesh, gold mesh, gold mesh right. On that if I place the tissue, if I place a tissue right, and so I can have a contact to that right, this is the contact pad, contact pad. So, what will happen If I indent this, if I indent right so, if I press this tissue, if I press this tissue, and there is a piezoresistor on the sensor right.

So, depending on the stiffness of the tissue, depending on the stiffness of the tissue, depending on the stiffness of the tissue right, my sensor will bend. And that will show so the change in resistance, because piezoresistor can be used to understand what is the elasticity of the tissue, what is the elasticity of the tissue.

Now, you know that there are gold pads, and there is a gold pad on the sensor. So, if I apply a voltage, if I apply a voltage across the tissue by applying. Let us say V 1 here and between two pairs there is a P 1 here and P 2. If I apply a voltage between O 1 and P 2, and if tissue is in between then what will happen, there will be flow of current there will be flow of current depending on the resistance of the tissue right. If I apply voltage between pad 1, which is my gold pad on the sensor, and pad 2 which is the gold pad on the glass on which the tissue is placed. And since these gold pad on the glass is conductive right, I can apply voltage between P 1 and P 2.

And if there is a sense, if there is a tissue in between the depending on the resistance of the tissue, I can see change in current right that means, I can measure the resistance of the tissue yes the cancer progresses. Or in another way depending on the type of cancer, the resistance of the tissue may be different and we can measure using this technique right. So, that is what is shown here this is a micro grid right with a glass wafer on which there are pairs like this, which is here right. There is a mesh, you can see here SU image, right SU image.

And now when we place the tissue, we can see the micro grid with tissue right. And then we have a 3D printer cone as a part of this particular lectures, I will explain you what is 3D printing, how can we use it. And right now you assume that we have printed a cone using 3D printer, and flexible sensor, I already discussed, and this is connected to a holder right.

Now, you come back to this particular image. In this image what we look at, we look at again please look at the slides. In this image, what we see we have a inverted microscope, we have an inverted scope right. Inverted microscope is there tissue a holder is there, holder is there, on which this 3D printer cone is attach right, right over here. And this is connected to a MP 285 micromanipulator, MP 285 micro manipulator.

As a part of again the lab component, we will show it to you how the MP 285 micromanipulator can be used for such applications ok. And how can you move in x, y and z with the precision of few microns. And you can use this MP 285 micro manipulator to indent issue with micron precision. And then we have a in a sensory electronics, which is a electronic module and there is a arduino board as you can see here, you can use a raspberry pipe depending on whatever controller you like the idea is to change the resistance to a voltage value and, and, and, and this one you can you can.

So, the main question in this particular study is why we have made a grid of micro array instead of making is as a complete gold pad like what I mean is that you see here right, this one is gold pad, now like this. Suddenly why we have created a mesh, why we cannot create a complete gold pad like this, because our idea is to use this pad right as a to apply a voltage to the tissue right.

So, if I use this is a gold pad instead of making a mesh, can I use it or not, what is the purpose of making a mesh, why you cannot use a gold pad like I am showing it to you right over here right. What are the limiting factors, why we have not selected a thick pad and why we are going for a micro grid array right that is our query, that is our question right. Why, it is very important to understand, why something is why, we are using a particular design, then what is the purpose of that design, then how we are going to fabricate that design right, how they fabric in that pattern.

So, my question is can I use this pad a thick pad instead of, instead of the mesh that I have shown it to you in the design right. If I place the tissue on this right, if I place the tissue on it, right still I can intend the tissue; I can still intend the tissue. And I can apply voltage between this pad and the one on the sensor right apply voltage. So, when I apply voltage here and here right.

So, what is the purpose of having this mesh design? If you think hard, it makes sense to have a mesh design over a complete pad, because we are using a, we are using an

inverted microscope. So, the light will not pass through the gold pad. But if I have a mesh structure on glass the light will pass through that mesh structure, and thus I am able to see where I am indenting the tissue, because my sensor tip is extremely small extremely tiny right, thus it make sense of using a mesh over the complete gold pad.

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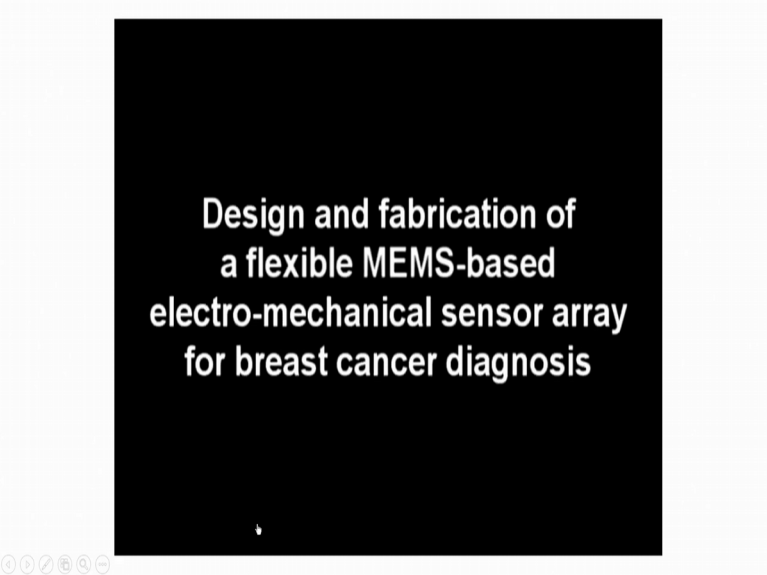

Now, let me run the video right this work was done earlier as a part of a research project in Maryland. And let me run the video and you will see the details about how we have used the MEMS based flexible sensor for breast cancer diagnosis.

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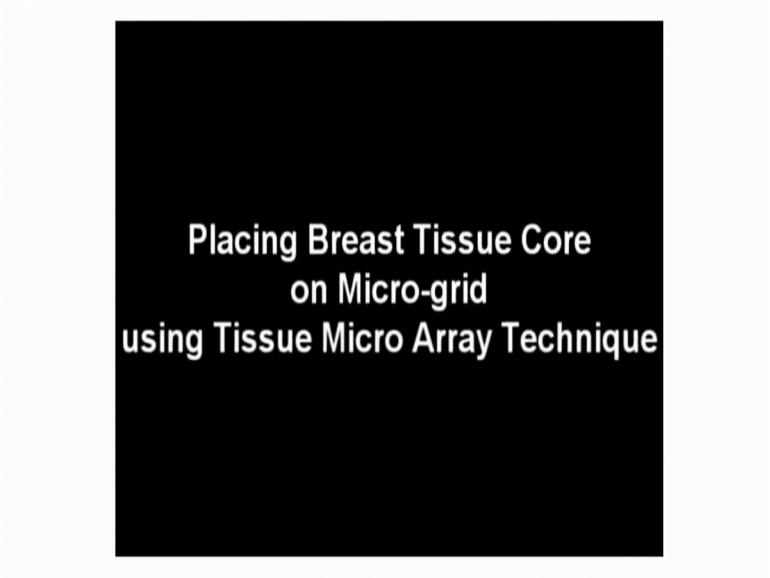

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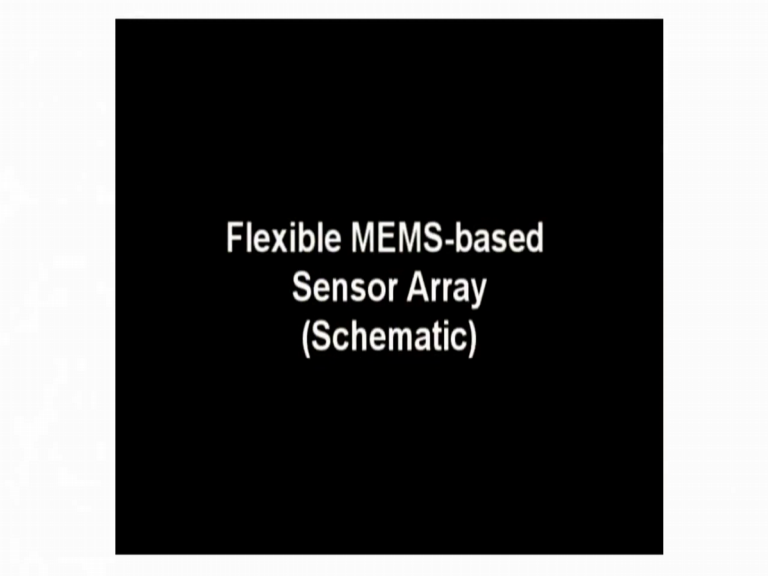

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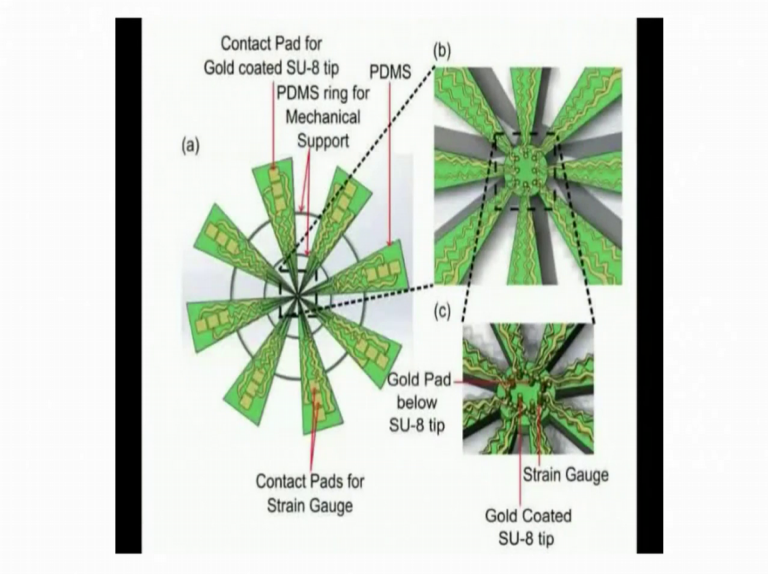

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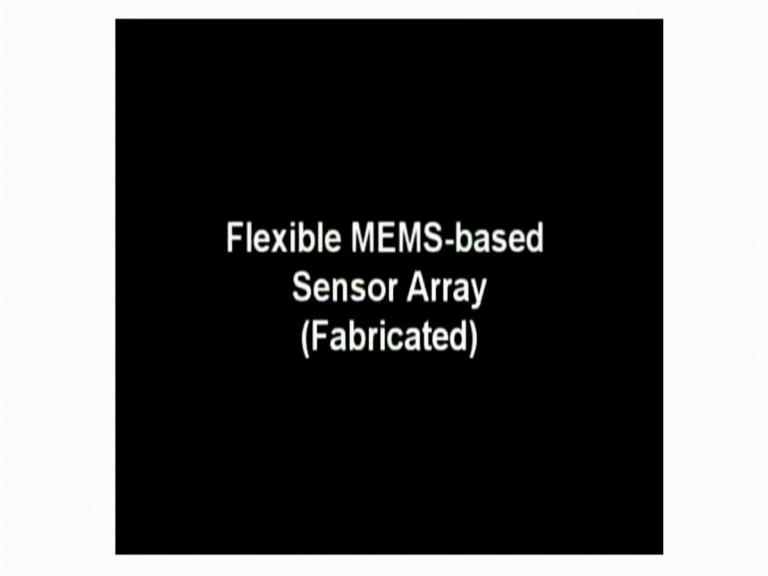

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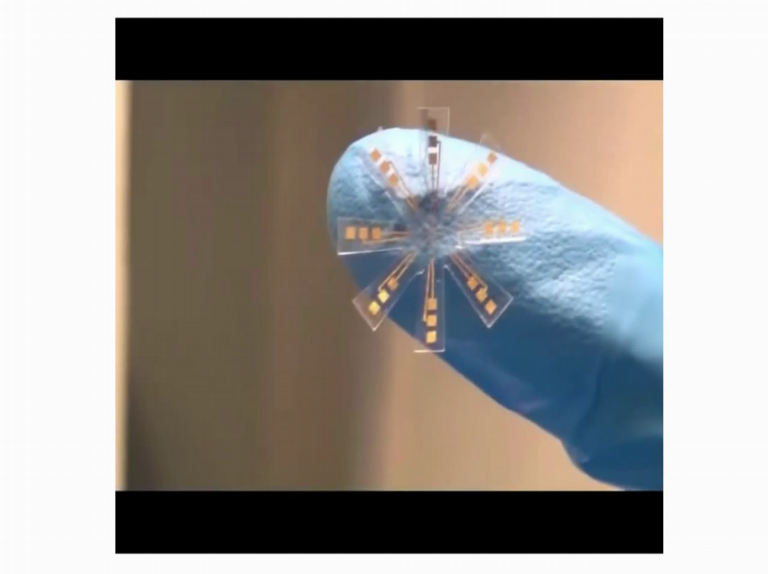

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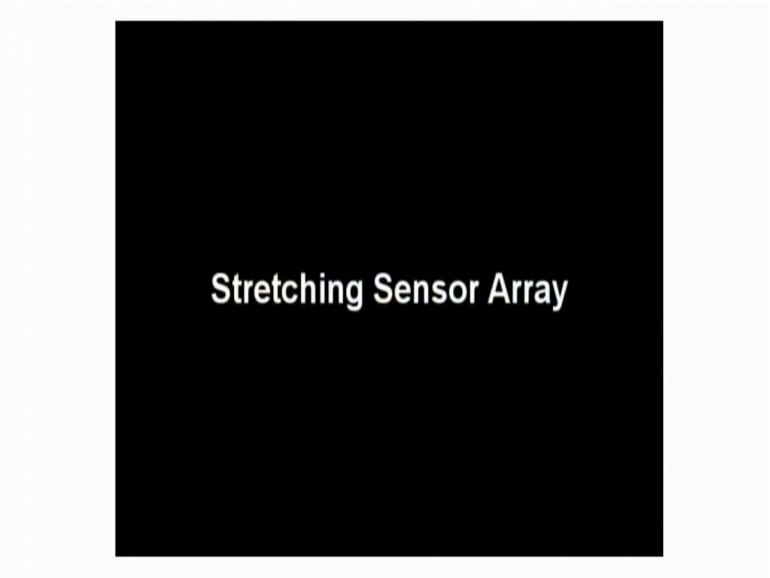

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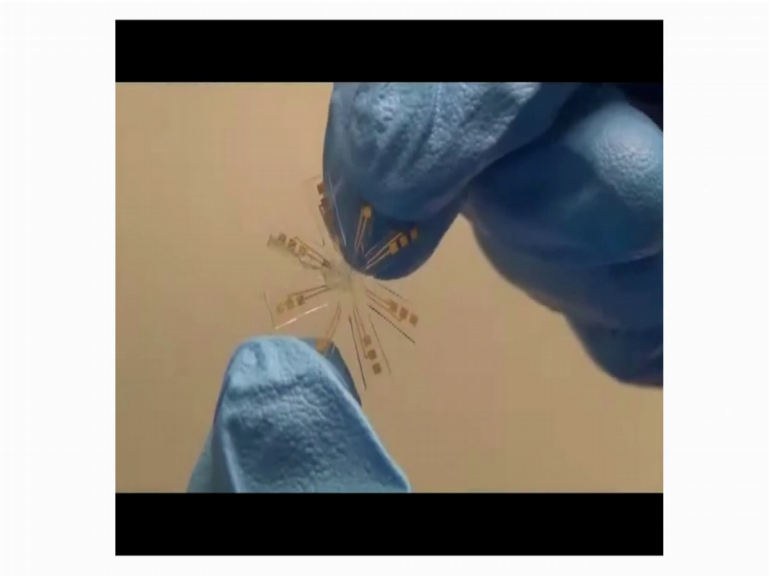

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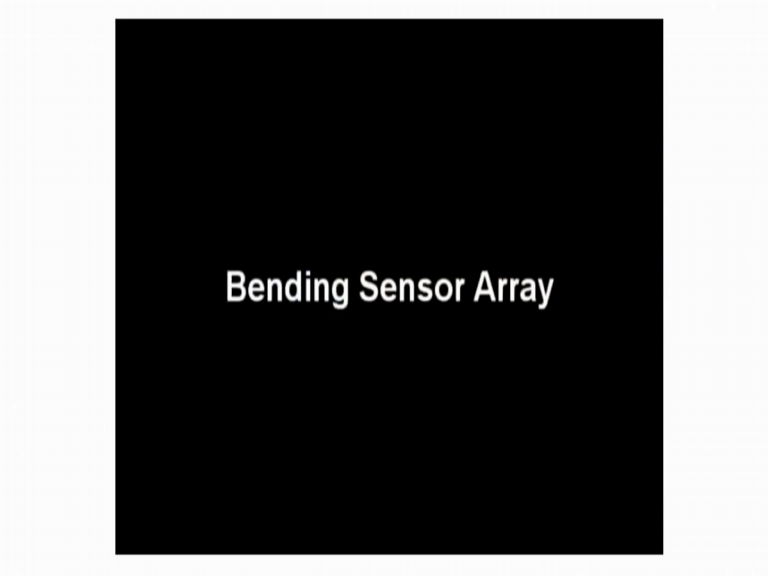

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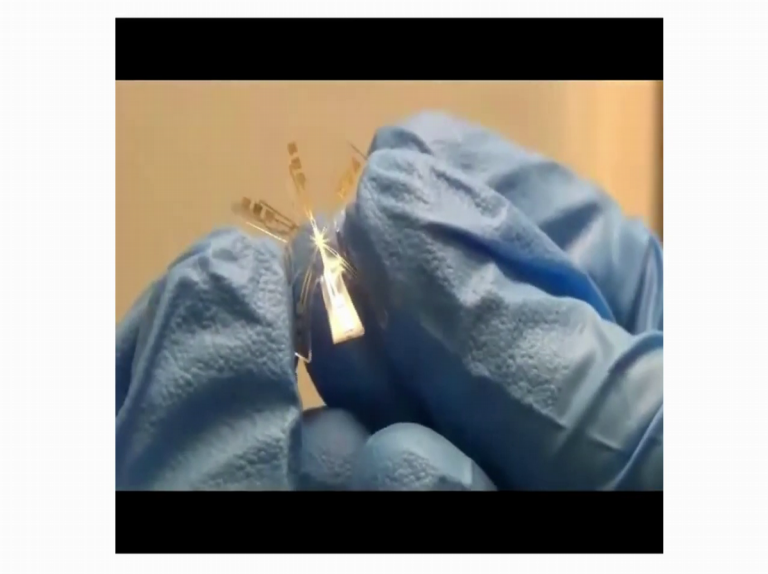

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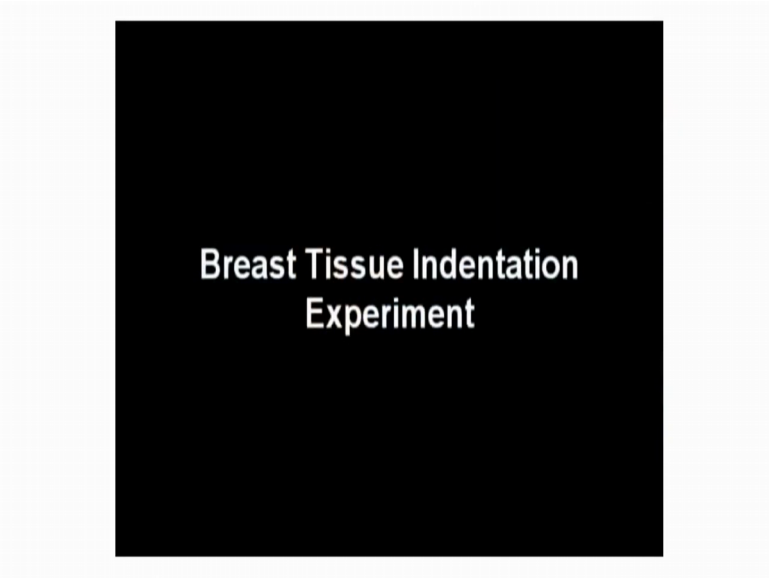

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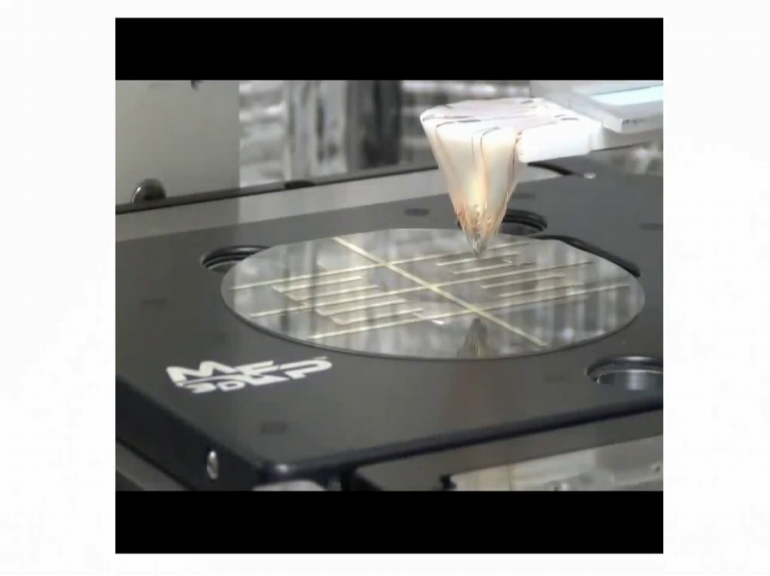

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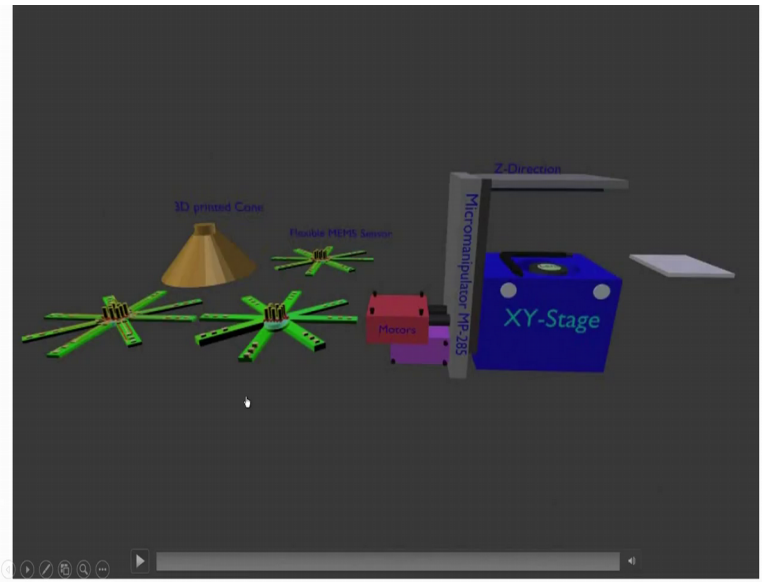

Now, another important point is to use software to make understand how exactly our sensor will work. And you can use software called Maya to do thisto present your work right, it is animation software right. And I use it to explain what is the purpose of the, the sensor design and how we are going to use the sensor for understanding the tissue property. So, I will run this thing, and you will understand what is the purpose.

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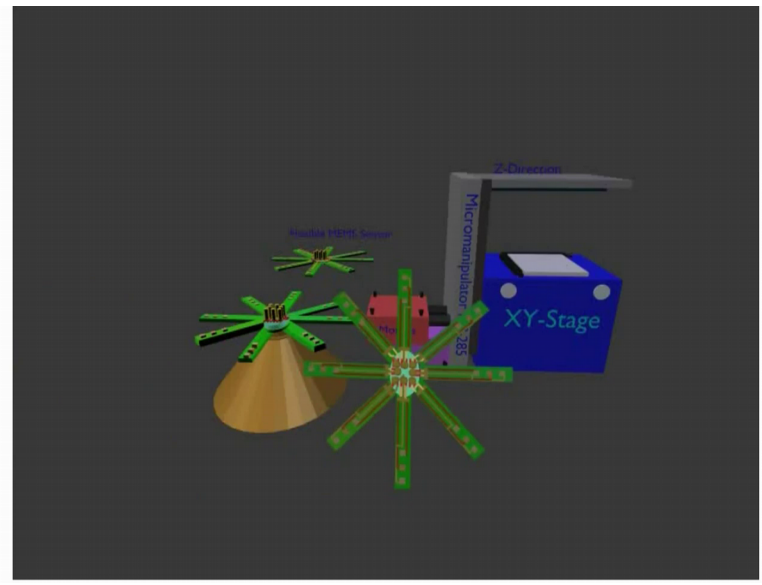

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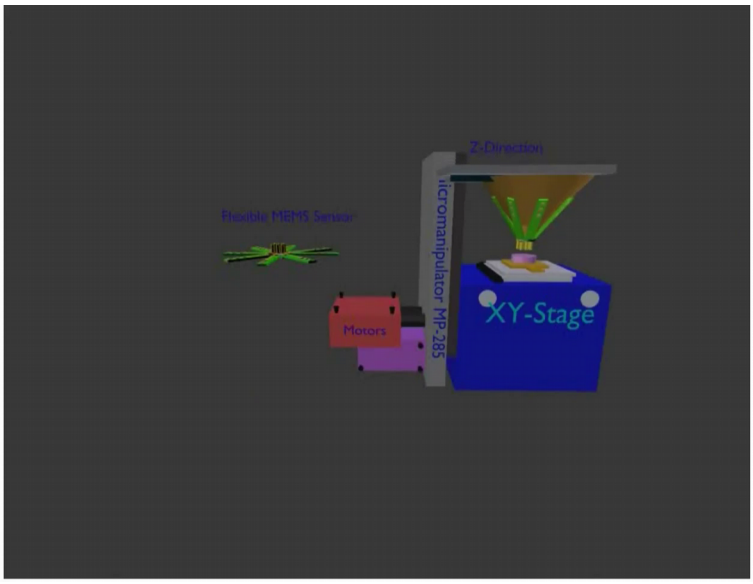

Ok, so you have seen the video right.

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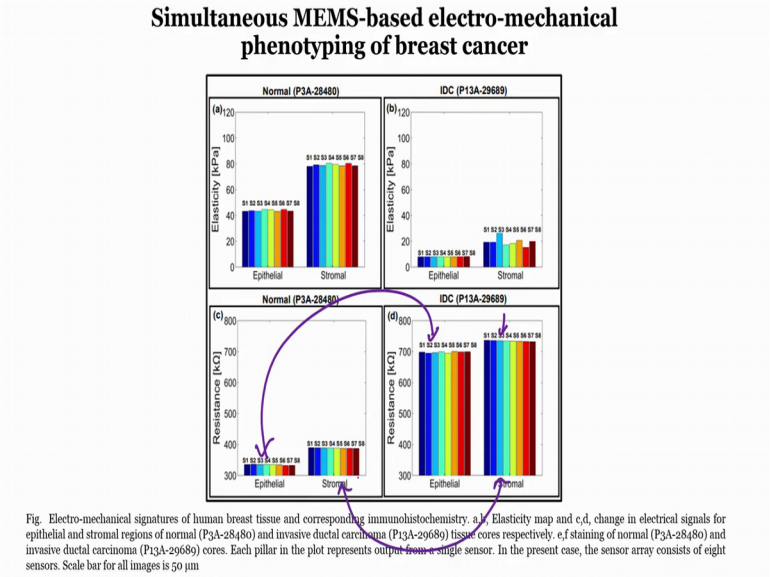

Fig. Electro-mechanical signatures of human breast tissue and corresponding immunohistochemistry. a,b, Elasticity map and c,d, change in electrical signals for epithelial and stromal regions of normal (P3A-28480) and invasive ductal carcinoma (P13A-29689) tissue cores respectively. e,f staining of normal (P3A-28480) and invasive ductal carcinoma (P13A-29689) cores. Each pillar in the plot represents output from a single sensor. In the present case, the sensor array consists of eight sensors. Scale bar for all images is 50 μm

Now, what you see are the results obtained using the MEMS based electromechanical phenotyping of breast cancer. So, using electromechanical sensor, we have phenotyping breast cancer tissues. And what we will be looking at are the results obtained through the experiments particularly you will see the elasticity and you will see the resistance values. Elasticity in a normal patient, and resistance in a normal patient tissue from the normal patient versus elasticity in the in the tissue obtained from a patient who is suffering from

a cancer. In this case, we are comparing normal and IDC, IDC stands for Invasive Ductal Carcinoma. So, we will see and we will also compare epithelial versus stromal region 70 percent of the cancer occurs in epithelial region. So, we will understand how the epithelial tissue is different than a stromal tissue. You will also see how the epithelial normal will look different than epithelial cancer, and stromal normal will look different than stromal cancer right.

So, if you see the slide that is what is shown here that there is elasticity values, there is a and here you can see the epithelial values and stromal values. And here also in case of IDC you can see a epithelial values and stromal values. These values are significantly different, while these values are also significantly different as well as these values are also significantly different. We have done this statistical analysis to understand the it is statistically significant or not in all the cases, we found that the results are statistically significant.

Thus we can,thus we can use this sensor to delineate the, the tissue obtained from the cancerous region versus the tissue from the normal or benign region. If you take the another patient or tissue from another patient, you can easily again see that there is a change in the elasticity, when we talk about epithelial versus stromal region. In case of normal tissue while when, you take the tissue from the patient suffering from invasive ductal carcinoma, there is again a change in the epithelial and stromal region in terms of resistance. But if you compare two different cases, then you can clearly see a huge difference between the epithelial region in case of the tissue obtained from a normal patient versus tissue obtained from the IDC as well as this stromal region, also you can see a huge difference right.

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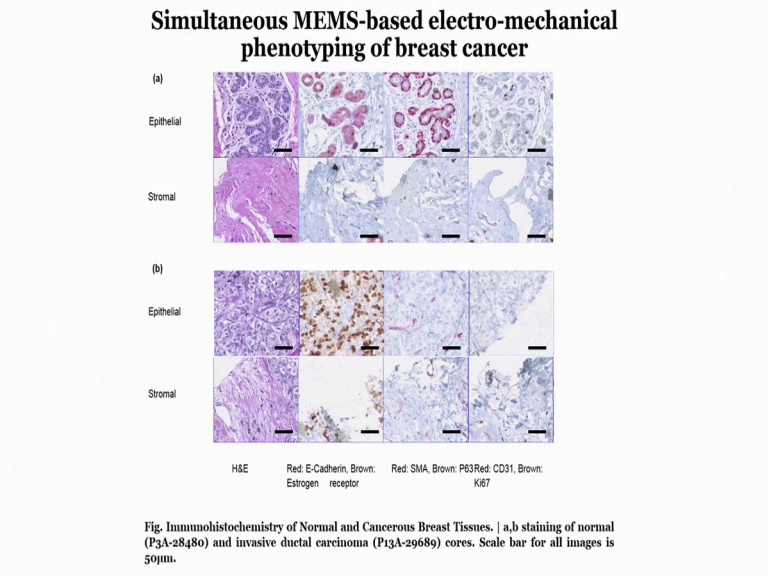

Fig. Immunohistochemistry of Normal and Cancerous Breast Tissues. | a,b staining of normal (P3A-28480) and invasive ductal carcinoma (P13A-29689) cores. Scale bar for all images is 50μm.

Now, if I go for further understanding of the immunohistochemistry, we can see that there are several kind of bio markers is that used to understand, whether there is a presence of cancer or not in a given tissue. And there is a this h and e images are epithelial versus stromal in both the cases and we can see that the, the biomarkers are (Refer Time: 16:15)cadherin, e cadherin, estrogen receptor there is a red SMA right brown P63 then we have KI67. So, these are the few of the biomarkers, there is also biomarker called HER. So, several things are used to understand, which is these are gold standards actually these are gold standards and the gold standard suffers from lot of false positive and false negative results.

And thus we have or we are trying to engineer devices such that this devices will not just rely on the gold standard, but also depending on the properties of the tissue. It will help the oncopathologist to make a decision whether as whether a tissue (Refer Time: 17:04) of a person is cancer or not thus reducing false positive and false negative result. So, these are like a helping platform for a oncopathologist, which way helping platform, the complete series that we are looking at ok.

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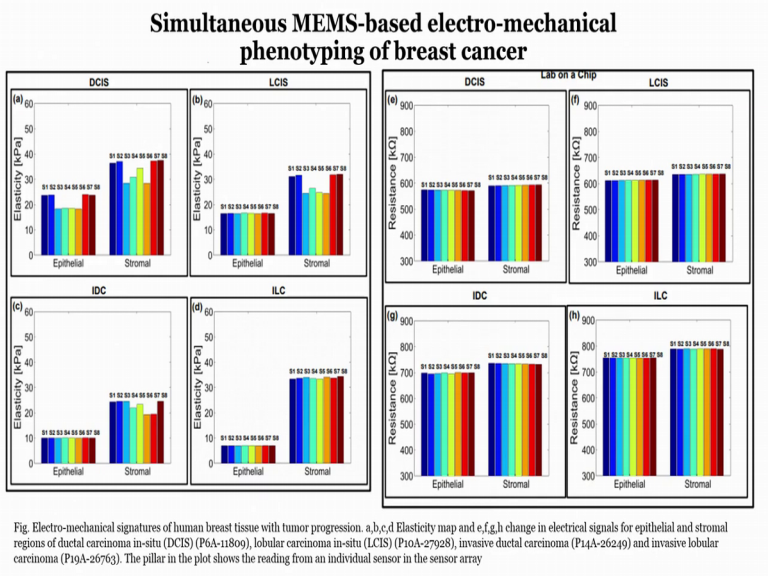

Fig. Electro-mechanical signatures of human breast tissue with tumor progression. a,b,c,d Elasticity map and e,f,g,h change in electrical signals for epithelial and stromal regions of ductal carcinoma in-situ (DCIS) (P6A-11809), lobular carcinoma in-situ (LCIS) (P10A-27928), invasive ductal carcinoma (P14A-26249) and invasive lobular carcinoma (P19A-26763). The pillar in the plot shows the reading from an individual sensor in the sensor array

If you see further and you compare the DCIS that is ductal carcinoma in situ versus LCIS which is lobular carcinoma in situ still, you can see a very clear difference in epithelial and stromal region in case of elasticity as well as in case of resistance. There is a resistance values, these are elasticity values. When you talk about IDC versus ILC, it is invasive ductal carcinoma versus invasive lobular carcinoma, also you can see a significant difference between the elasticity value in epithelial and stromal region as well as when you talk about IDC versus ILC in terms of resistance then also you can see a clear demarcation between the two values right. So, the thus sensor can not only delineate between epithelia and stromal region, it can also help us to understand, how the cancer progresses, and what are the change in the elasticity value and resistance values as the cancer progresses or from the different stage of the cancer right.

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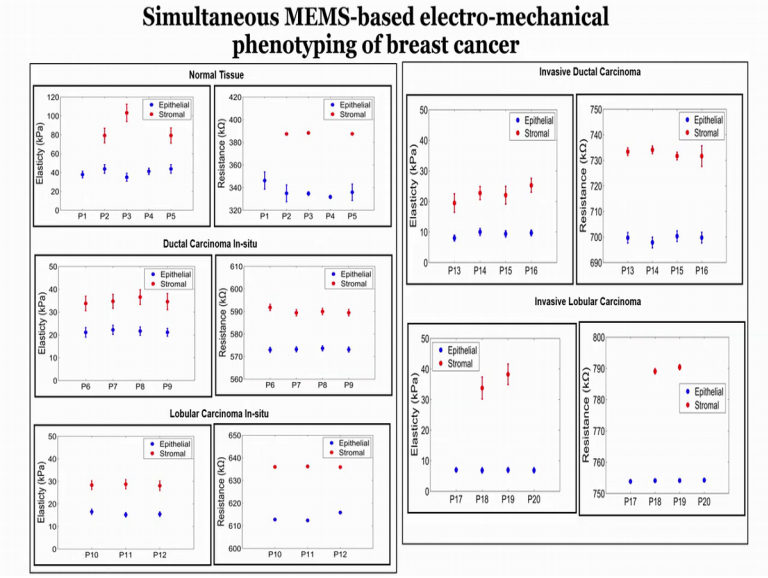

If I put it in this particular format, you can clearly see that from patient 1 to patient 5. If I take a normal tissue right then I can understand the change in the elasticity, and change in the resistance, but if I go for a ductal carcinoma in situ, my elasticity values are coming down right. And if you go for IDC, my elasticity values are even coming down right, well the resistance values are going up right. The resistance values are going up,. You can see here compared to normal, which was around 390 my resistance value for DCIS is about 590 ohm kilo ohms. In case of LCIS is about 640 kilo ohms. Well when I am talking about IDC, it is about 730 kilo ohms, when I am talking about ILC is about 770, 785 kilo ohms right.

But if you talk about elasticity, then in k from normal to cancerous region, you can see that the elasticity will you goes down. And you can see here the elasticity for the normal tissue is around from 80 kilo Pascal to about 110 kilo Pascal, where you can talk about DCIS, it is about 35 kilo Pascal to 40 kilo Pascal. In case of LCIS is about 30 kilo Pascal, IDC is about 30 kilo Pascal, and ILC is about 35 kilo Pascal.

So, what we really see is that as the cancer progresses the tissue gets stiffer, as the cancer progresses the tissue gets stiffer right. And this when elasticity value goes lower, it is less elastic smooth stiff while the resistance of the tissue increases, the resistance of the tissue increases right. Thus the sensor can help us to understand not only the elasticity, but also

the resistance property. Thus we can not only understand the mechanical property of the tissue, but also the electrical property of tissue right.

Now, let us see I will show you the sensor in my next module ah, but before that let us see what we have learned in, in group of this module, because the idea was to understand the change in the tissue property, whether it is a breast cancer or oral cancer it is the matter. The issue related cancer of course, we have to do study on oral cancer to get understand how the tissue properties are changing, when for a pre malignant region versus malignant region versus just a normal region, we do understand that. Ah

But the idea is that if you want to just understand the mechanical property of a tissue or a cell, you can use a piezoresistive micro cantilever. If you want to understand the electrical property of a tissue or a cell, you can use inter digitated electrodes. If I want to use electrical and mechanical property of a tissue or cell, then one can I use electromechanical sensor. If I want to use electrical mechanical and thermal property of a cell, what can I use electro thermo mechanical property using the chip that I have shown you in the previous modules right.

So, now we can understand the different tissue properties as the withdraw from onset till disease progression and or onset to disease progression. And thus we get a better understanding of how the, how the change into a tissue properties can be correlated with the stage of the cancer right. Having said that the electronics remains extremely simple, if you see any electronic module if I want to understand or change my resistance to a voltage, I can use a Wheatstone bridge right. And then if I want to further understand the signal conditioning circuit, then I do, I have to go for thefurther understanding of the signal conditioning module, electronic module right starting from an instrument amplifier right, and how you are going to filter it the noise, and then further how you are going to change it to a digital values.

So, to use a ADC right which are ADC you have to use and why. So, these are all details that we, we should know if you want to change the signal from a resistance values to a voltage value, there can be displayed or resistance values to the elasticity value that you want to display at the for the end user right. So, for that we need to have a lot of samples.

Now, one drawback you can say nearly see a drawback or not, but because we do not have that many tissues right now, but what happens if the person is having a different

body mass index. So, a tissue taken from a person of certain weight does it match the results are similar with the person, who is suffering from the same disease, but of a different weight we do not have the idea about that we, we have to study that.

Another point is what is a variation from the in case of age. So, that we already have said it and we found that whether you take a tissue from a, a, a young woman who is suffering from a disease or a older woman suffering from breast cancer, we see a trend that our sensor can delineate the tissue. If it is certain, if the eve from normal to cancer all right, we can understand the change into tissue property.

But with different fat content with the food habits, with the region right, we, we have to have this many data to understand the application where how when this device can be or system can be used in a actual scenario we have to go through that whole study all right. Only then we can save it accuracy that this system can be used as a helping hand to oncopathologist to determine whether the tissue whether a person that a tissue open from a person with biopsy is cancerous or is not right. Having said that you look at the modules from the first lecture till now and you will understand the importance of understanding the tissue properties with the help of micro engineer devices.

So, having said that I will end up my module in this lecture today. And in the next lecture, I will show you the device how it looks like both piezoresistive micro cantilever as well as the flexible electromechanical sensor. And then we will continue to the next set of system that relies on understanding the change in this cell morphology. Suppose, the cell is taken from a certain region, let us say oral cancer right. So, you take the cell and what can be a electronic system that can immediately screen the patient, whether patients who go for the histology or not right. So, we will talk about that in the next module.

Till then you take care, I will see you in the next class. Bye.