Electronic Systems for Cancer Diagnosis

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Lecture – 18
Electrical characterization of Breast Tissue Cores

Hi, welcome to this module and in this module we will be looking at another way of understanding the tissue property that is using the electrical modality. Until now until now what we are looking at the tissue properties, where one a bio chip that can help us to understand the electrical, mechanical and thermal property. Then we have seen a piezoresistive microcantilever that can help us to understand the elasticity of the tissue.

Now, let us see another sensor that we can develop to understand the resistance or impedance of the tissue right. And then we will also see flexible sensor which can understand the electrical and mechanical property of tissue. So, this is this will be the complete lecture the, for us to understand.

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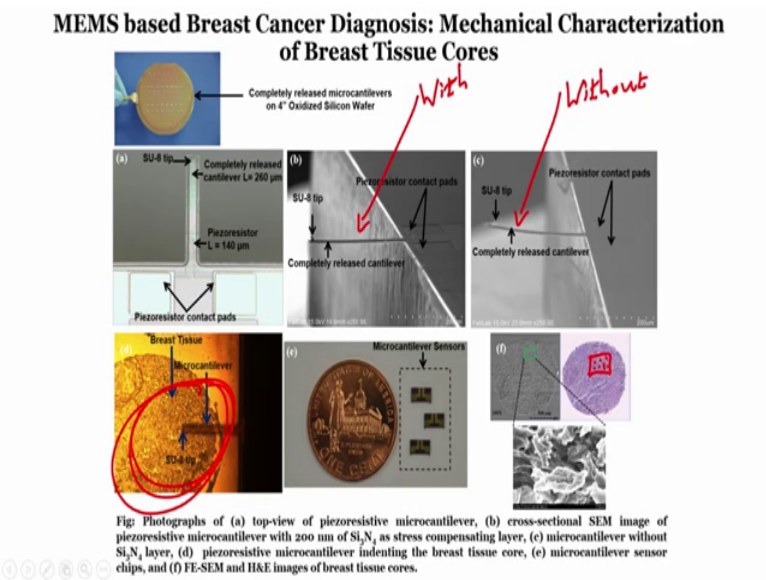

So, let us see the slide, in the slide what we have seen is the what we can see is the piezoresistive microcantilever one with silicon nitride and one without silicon nitride this is without and this is with silicon nitride.

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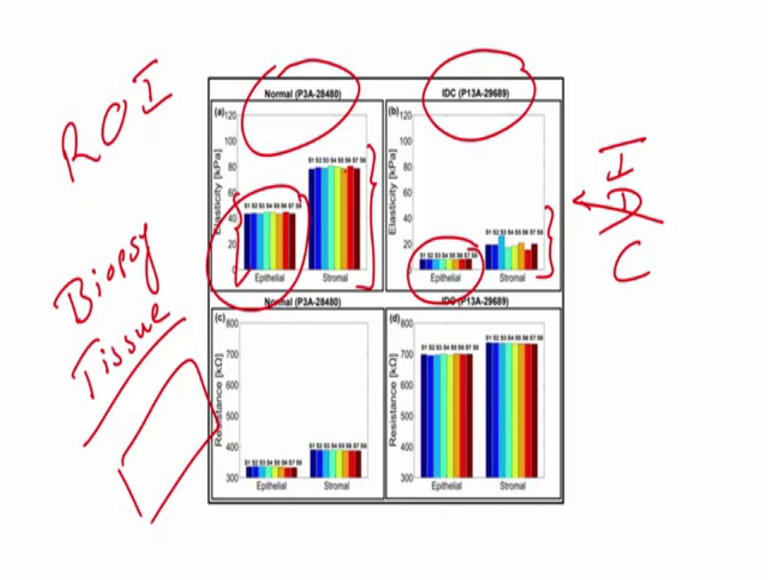

So, if I use this piezoresistive cantilever to indent the tissue, what will I find? I will find the elasticity of the tissue and you see the elasticity parameter right over here, I do not worry about the resistance now, we will see how can we measure resistance at some later stage of this module. But you can see here that if I consider 8 different patients and epithelial region in a normal so, single patient we have done for 8 different patient, I am showing it only for a single patient. A single patient tissue the all about tissue from a single patient using biopsy.

So, it is a biopsy tissue on which we are indenting the piezoresistive micro cantilever in this way and we are indenting at 8 different places within a given ROI within the given region of interest we are indenting tissues at 8 different places. And we saw that if you if this is the tissue for example, this is a tissue and this is a region of interest this is a region of interest and will indent in this region at 8 different places to get the tissue property out. So, when we do that, we can see that for epithelial region in a normal patient right the tissue taken from a normal patient, the elasticity is less when we take a tissue from stromal region it is more. Compared to stromal and epithelial for a normal elasticity is less compared to stromal, but if I compare invasive ductal carcinoma; this is invasive ductal carcinoma.

So, this is a cancer tissue from the cancer region and what we see here is that the elasticity in epithelial religion compared to the epithelial region of a normal patient is extremely less is actually around 15 kilo Pascal or 10 kilo Pascal where you can see that elasticity will lose for epithelial religion in case of normal is around 40 kilo Pascal. Even we talk about the stromal region, you can see that the stromal region here is about 20 kilo Pascal where here is around 80 kilo Pascal. Thus what we see that there is a change in the elasticity of the tissue or the stiffness of the tissue in case of cancer patient compare to normal patient. And thus using a piezoresistive cantilever, we can understand whether a tissue is from a normal patient or is from the cancerous patient based on the elasticity value right.

Those our exercise of understanding or fabricating or understanding the process flow for designing the pizeoresi resistive microcantilever helps us to measure the tissue property in particular elasticity or you can say stiffness right. So, that was the idea of making you understand the importance of piezoresistive microcantilever.

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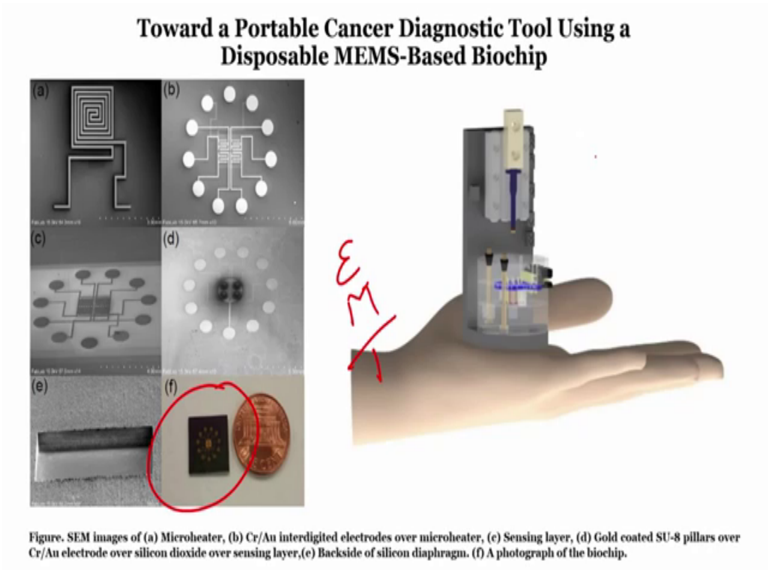

Now, let us quickly see what we have seen. We have seen a biochip that can help us to understand electrical properties, mechanical properties and thermal properties of a tissue right; electrical properties, mechanical properties and thermal properties of issue.

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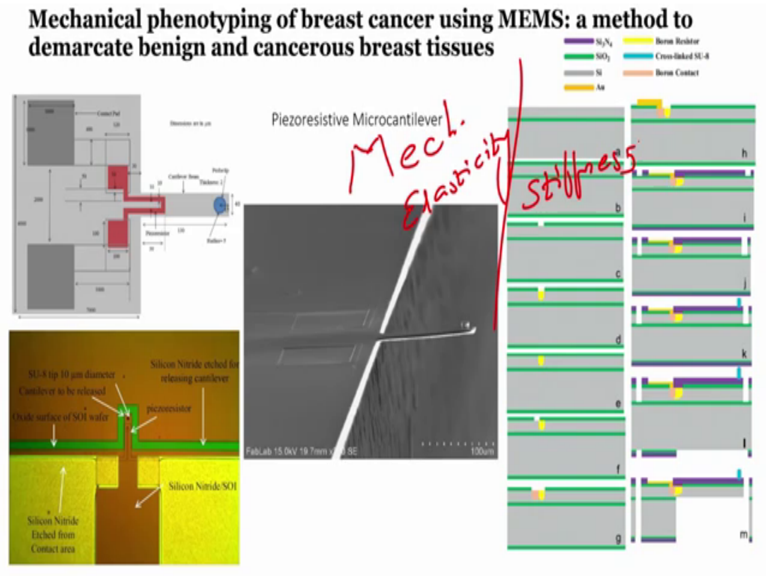

Then we have seen a piezoresistive microcantilever that can help us to understand the mechanical property of tissue mechanical property of tissue right. So, mechanical properties are elasticity or you can say stiffness right; elasticity or stiffness. Now let us see a different sensor that can help us to understand the electrical property of tissue all right.

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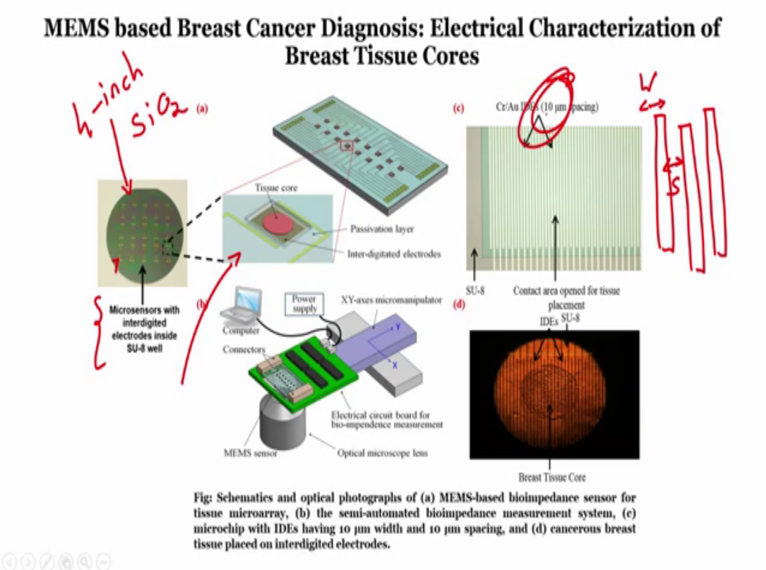

So, if you see the slide here you see is a 4 is a 4 inch 4 inch oxidized silicon wafer on which there are several sensors around 30 sensors and each sensor has an interdigitated electrode its each sensor has interdigitated electrodes. And over the inter digitated electrodes we have a we have a SU-8 boundary. So, what does that mean?

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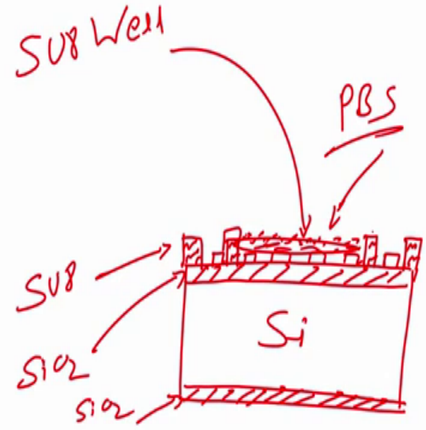

Let me show it to you what does I mean. I mean that, there is a SU 8 well and in that the SU 8 well. So, actually this is a oxidized silicon wafer, let me draw it little bit bigger diagram. So, you get you guys get it the cross section oxidized silicon wafer. So, we will have a oxide, will have oxide here right. On the oxide, what we have? We have interdigitated electrodes and over that we have SU 8.

So, what is this? This will become like a well this is SU 8. this is silicon dioxide, silicon dioxide, silicon right. This is SU 8 well. This is what is shown here that micro sensors with interdigitated electrodes inside SU 8 well. To the schematic or a schematic representation of this device is shown here where there is a passivation layer because it is a silicon that is why we are using silicon dioxide is a passivation layer. There are interdigitated electrodes which you can see the actual photograph right over here and then our chip consists of those interdigitated electrodes.

Now what we will be doing? We will be measuring the impedance or the resistance of the tissue; we measuring the resistance or electrical property of the tissue when you place the tissue on the interdigitated electrodes. Now if you see here, each electrode has 10 micron spacing and the width is also 10 micron width and spacing is micron. What I mean by width and spacing is, like you see this kind of lines right like interdigitated. So, like this lines are there right this kind of lines are there here 1 2 3 right.

So, the width is 10 microns and the spacing is also 10 micron; width and spacing is 10 micron in this particular case right. That is what we mean by interdigitated electrodes with 10 microns spacing. So, now, let us see, if I place a tissue on this interdigitated electrode. This is what is shown here in this schematic that we are placing a breast tissue on interdigitated electrode, what will happen? When you place the breast tissue on the interdigitated electrode, there will be change in the impedance or resistance of the device right.

Because right now interdigitated electrodes are not touching each other and these are metal lines. So, your resistance should be infinite because they are not touching right. When you place a tissue on this because of the resistance of the tissue, what you will find? You will find that the tissue from cancerous region would have a different resistance, a tissue from cancerous region would have a different resistance compared to the tissue from normal regions. So, a normal tissue or benign tissue will have a different resistance compared to a tissue taken from ductal carcinoma in situ or invasive ductal carcinoma.

So, now it is easy way of understanding the electrical property of tissue just by placing tissue on the glass slide containing a SU 8 well and inside the SU 8 well, there is an inter digitated electrodes; such that the electrodes are on the oxidized silicon wafer and on this side there is a SU 8 well what is the point of making SU 8 well? The point of making SU 8 well is when you load the tissue; you have to keep the tissue in a saline solution. So, that it does not deteriorate. So, when you load PBS if you do not have the SU 8 well, the PBS will be spelled out from the tissue region.

So, if you see here the low if I place the tissue right over here right over here, if I load the solution the solution will be contained this is like let us say PBS force or line. The solution will be contained in the SU 8 well. If I do not have the SU 8 well, my solution will be out right. So, let us now see how can we fabricate the interdigitated electrodes on oxidized silicon wafer all right.

So, let us quickly see its very easy just two mask process, it is a to mask process.

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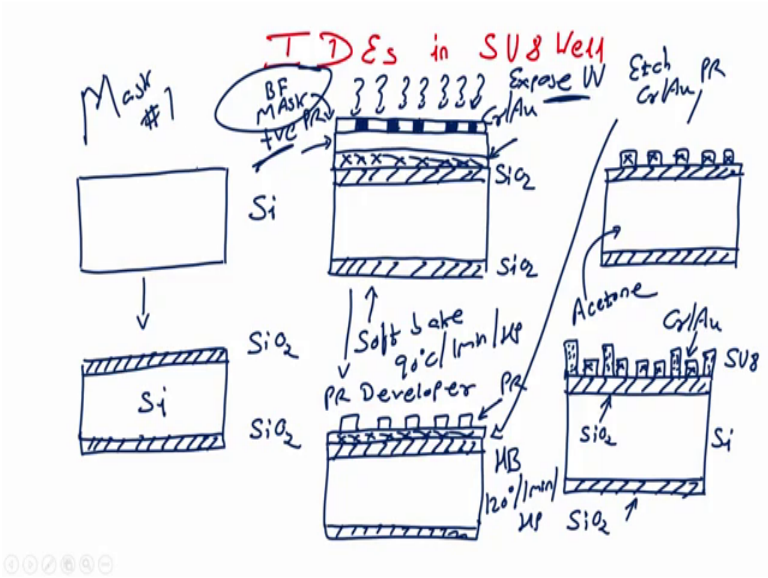

Now, you should know because we are fabricating SU 8 interdigitated electrodes in SU 8 well inside SU 8 well. So, what we will do? We will take a oxidize sili or we take a silicon wafer right silicon then we clean the silicon wafer, there we will grow oxide on both the sides oxide. Now after this next step is, we will spin coat is correct we will spin coat photoresist is correct or not what we want? We want interdigitated electrodes inside SU 8 well right inside SU 8 well. This is what we want.

So, this is our SU 8, this is SiO 2, this is silicon, this is SiO 2 all right. This is what we want. So, now, we have oxidized silicon wafer. This interdigitated electrodes these are interdigitated electrodes. This IDEs are made out of what? IDEs are made out of metal. So, we can say chrome gold. So, on the silicon dioxide what we will deposit? We will deposit a metal. We deposit a metal, how? By using PVD Physical Vapor Deposition either a beam or thermal. On this we will do lithography.

So, we will spin coat positive photoresist right will spin coat positive photoresist then we will do soft bake at 90 degree centigrade 1 minute on hot plate. After that we will load our mask, our mask will have the pattern that we want for interdigitated electrode. Now this is a bright field mask field is bright pattern is dark bright field mask and bright field mask right over this what we will do? We will expose after this, we will expose the wafer or photoresist with UV after exposure next step would be PR developer right; PR developer

When we develop in photoresist developer, what will see? We will see metal and then photoresist only in the area only in the area, which was not exposed in UV light because it is a positive photoresist right. So, unexposed area will get stronger after this after this step. Next step is hard bake 120 1 minute hot plate next step after this the next step would be etch in chrome gold. So, what you will have? You will have oxidized silicon wafer oxidized silicon wafer with interdigitated electrodes, but there is what? There is a photoresist; the photoresist.

So, next step would be to dip this wafer in acetone will strip off the photoresist right acetone will strip off the photoresist. So, here if you see the photoresist is protecting the metal which is below it, and the metal which is exposed will get etch in chrome gold etchant followed by which we have to strip off the photoresist. So, we are dipping the wafer in acetone when we dip the wafer in acetone what you will have is interdigitated electrodes; what we will have is, interdigitated electrodes. So, this is our mask 1 right, but what we want? We want interdigitated electrode to be in SU 8 well.

So, let us see how can we do that interdigitated electrodes in SU 8 well.

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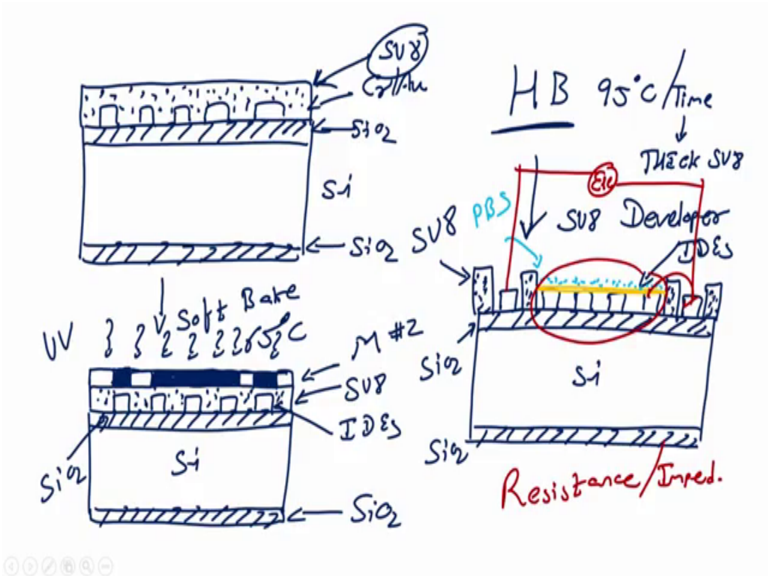

So, in the last slide what we had is oxidized silicon wafer and on oxidized silicon wafer we had interdigitated electrodes right; we had interdigitated electrodes. Now this is chrome gold, this is silicon dioxide, this is silicon and this is silicon dioxide. Now what we want? We want SU 8. So, we will spin coat we will spin coat SU 8 which is a polymer hence a negative photoresist, it behaves as a negative photoresist.

So, we will spin coat SU 8 after spin coating SU 8 you know what you have to do? Do soft bake soft bake is done at 65 degree centigrade for how much minute depends on the thickness of the SU 8 depends on the thickness of the SU 8 after that what is a next step? Next step is I will load the mask right I will load the mask what I want? I want to protect SU 8 in certain region and etch SU 8 from the unwanted region right. So, here the unexposed region would be weaker unexposed region would be weaker right.

So, I want to have a mask such that my unexposed regions becomes weaker. So, I will have a mask like this and is this correct no right what we have do we have to open the region over the interdigitated electrodes and over the contact area right over the contact area right.

So, now, this is my mask 2 this is SU 8, these are interdigiated electrodes, this one is silicon dioxide I have silicon wafer what is the bottom layer silicon dioxide on that what we will do? We will expose the wafer will expose the wafer with UV right with UV after that next step after exposure for SU 8 would be to hard bake not to developed first to hard bake. Hard bake is done at 95 degree centigrade again the time depends on the thickness of SU 8 time depends on thickness of SU 8.

After hard bake I will go for SU 8 developer. I will go for SU 8 developer if I go for SU 8 developer what will I have? I will have oxidized silicon substrate with interdigitated electrodes and SU 8 well right. I will have oxidized silicon wafer with interdigitated electrodes inside SU 8 well. Easy that becomes your chip and on this chip on this chip what we will do? We will place the tissue place the tissue and we will also use a solution. So, keep the tissue intact that solution is our PBS all right.

Now if I want to measure the resistance I can measure between these two contact I can measure the electrical property. Now if you understand in detail what is a different between resistance and impedance you will say that we should measure impedance, because there is a parasitic capacitance also there is a double layer capacitance and other parameter that comes into effect. So, we cannot rely on resistance, we should rely on the impedance measurement and thus we will see that when you place different tissues on the interdigitated electrodes or over the interdigitated electrodes, you will see that the impedance of the tissue changes as cancer progresses. Thus you can use electrical property which is an impedance as a parameter or as a modality to understand the change in the tissue property when the tissue is cancerous or is the tissue from normal region or the tissue from intermediate region right.

So, the change in the tissue property that is electrical modality can act as a parameter to understand what is the stage or what is a type of the tissue that we are measuring right. So, now, what we have seen? We have seen a mechanical way with this elasticity, we have seen electrical way which is impedance. We also seen electrical mechanical and thermal way which is a biochip. So, in the next module what I will teach you is a flexible sensor that is integrated with a piezoresistive sensor and a gold electrode, but now everything is on flexible material which is our PDMS. So, till then you concentrate on this particular module. If you are any questions; feel free to ask us through the forum right ah

And this is just one example where I am asking you to use the sensor and place the tissue on the sensor to measure the change in impedance, but you can also use this for understanding the change in the cell property stiffness of the cell right. If you can measure stiffness of tissue, why cannot measure the stiffness of cell with a cantilever? You can. Why, if you are measuring the resistance of the tissue, why cannot measuring resistance of a cell? you can right.

Are you are welimited with only breast cancer? No, we can use any tissue related cancer oral cancer, prostate cancer, right you can use any tissue related cancer to understand the change in the electrical property right. Till then you just to look at the module and I will see in the next class bye.