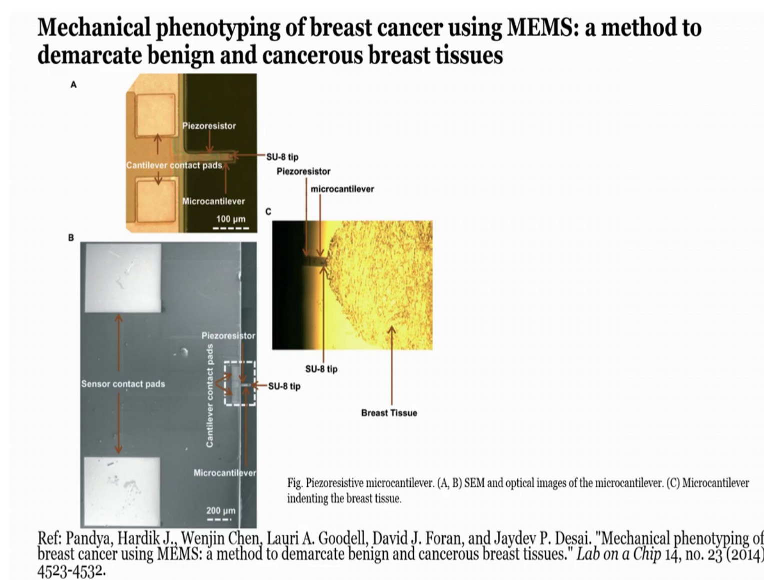
Electronic Systems for Cancer Diagnosis
Dr. Hardik J. Pandya
Department of Electronic Systems Engineering
Indian Institutes of Science, Bangalore

Lecture – 17
Mechanical Phenotyping of Breast Cancer using MEMS

Hi. Welcome to this module. And in this module what we are looking at we are looking at the mechanical phenotyping of breast cancer and a method to demarcate between benign and cancerous breast tissues. So, here I have understanding is that if we can design a piezoresistive based microcantilever then we can probe the tissue and you can find that tissue properties, that is mechanical properties.

(Refer Slide Time: 00:55)



So, if you see the slide what our idea is to design a piezoresistive microcantilever with a SU-8 tip this is a piezoresistor piezoresistive microcantilever, the piezoresistor is here and the contact pads are here, alright. And this is the actual chip.

So, if I show you the chip I have brought with me, I will just show it in a while you can see the contact pads that we are talking about this is cantilever contact pads that we are talking about is this one, this is the chip. So, this is what we are showing you in this way; let me just. So, this is a magnified version of this cantilever. This we cannot even, is not shown here. So, as you can see is extremely tiny structure, right, extremely tiny structure.

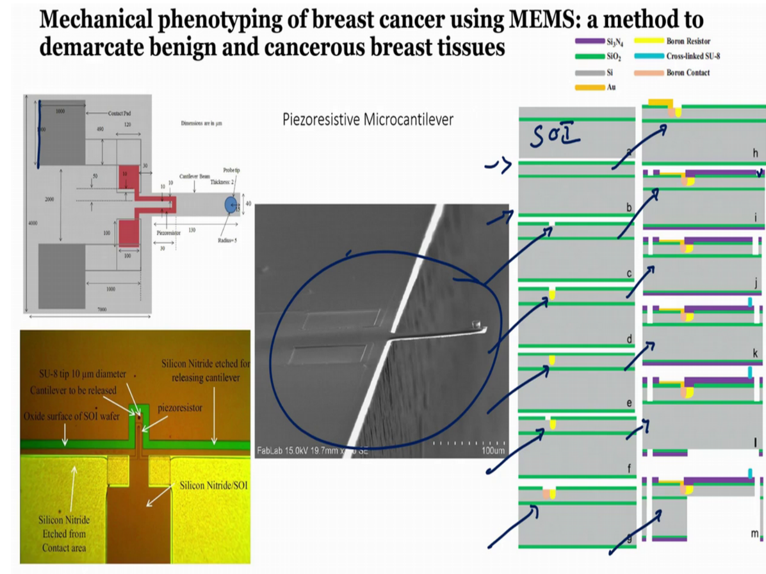
Now, if I have the cantilever and I have the breast tissue then I want to press this breast tissue. So, now we understand; if you can see what I am showing it to you here in my hand. So, this is a cantilever, let us say this my hand is a cantilever, right let me show it to you like this hand is a cantilever and I am growing a SU-8 tip base cantilever like this, alright. So, this is the SU-8 tip, this is the cantilever, I want to press a tissue which is let us say this one.

Now, for this since my cantilever is at the top, right and there is a piezoresistor embedded onto this cantilever onto this cantilever if I want to press the tissue I had to reverse it down like this correct, this cantilever is like this, the let SU-8 is here, piezoresistors are here, if I want to press the tissue I had to reverse it down and then I take a tissue and I poke that issue like this, right. When I poke the tissue if the tissues stiffness is higher, right, if tissues stiffness is higher my cantilever will bend more, if the tissue difference is less my cantilever will bend less. Now, this bending of the cantilever not like this bending I am talking about from the arm, this bending, and press it how much I am bending like this.

So, that change in that structure, so if it is pressing and it is changing the structure then this stress and strain created in the piezoresistive area which in the resistance because when I applying a pressure there is a stress created in that piezoresistive region, because there is a piezoresistor embedded onto the microcantilever and that is why we can see the change in resistance. That resistance change depends on a how much cantilever is bending and that bending of cantilever depends on the stiffness of the tissue, right.

So, I can understand by pressing by poking the tissue, not exactly poking it is a more like a pressing the tissue or in another one we can also say indenting that issue indenting the tissue what is the tissue stiffness, alright. This again a work is published it is from my lab on a chip paper which was published in 14, but the interesting part here is to understand how can we design the piezoresistive microcantilever.

(Refer Slide Time: 04:30)



So, you need to focus, so that you understand, ok, so be with me. Let us see this particular image this is the same chip which is shown right over here, this is the fabricated one is the schematic structure. So, what is there? There is a contact pad the red one this one. Like we can say dark red blood red is the piezoresistor embedded or integrated on to a silicon chip.

So, how can we design this? By diffusion, my process called diffusion. So, if the wafer that I am using is a n-type wafer, n-type polysilicon and if I do diffusion or ion implantation then I can diffuse the dopant in the given region and this will act as a resistor, alright. At the tip there is a the tip is made up of SU-8. This much is easy, now let us see the dimensions the dimension of the chip this is 4 millimeter. This one is 7 millimeter now you can now because, of the schematic you cannot see very clearly, but this width this one if I say this is a width and this is length then width is about 700, 7000 microns which is close to 7 millimeter and length is 4000 microns which is about 4 millimeter.

The contact pads are 1 mm by 1 mm or 1000 by 1000 the spacing between two contact pads this is the sensor pad. So, sensor pad this we are talking spacing between two contact pads is 2000 microns or 2 millimeter of this spacing. Now, piezoresistor, ok, so piezoresistor where the cantilever is released is about 30 microns, alright. The width of the piezoresistive layer, so if I say this is my piezoresistor, right like this the width is 10

microns and the spacing the spacing here is also 10 microns. The width is 10 microns and spacing is also 10 microns, alright.

Next one, the thickness of the cantilever this thickness is about 2 microns, just 2 microns. Now, we are talking about really my new structure because a human hair is about 80 to 100 micrometers in thickness, 80 to 100 micron thickness is a human hair, alright. We are talking about 2 micrometer thickness of the cantilever. This SU-8 tip the radius is 5, so diameter would be 10, and the height of this is close to 30 micrometer, alright the length of the piezoresistor is 130 microns.

You can see this is 100 micron, so if I use this then this is 130 micrometers, alright. Now, this area and this area that we see are these contact pads and this one the piezoresistor contact pads, alright. Now, the length and width; so this one and this one now it is a cross section image. So, you cannot see exact dimensions, but it is 100 microns by 100 microns you see 100 by 100, ok, ok. So, this is what is the schematic or piezoresistive microcantilever.

Here if you see then there is a silicon nitride on silicon on insulator. This SOI stands for silicon on insulator, that is what SOI stands for. So, silicon nitride is deposited on SOI wafer. And here you can see SU-8 tip, here you can see cantilever is released, oxide surface of SOI wafer you can see, piezoresistor you can see and silicon nitride etched by a for releasing cantilever you can see these particular things in this schematic, ok. Now, let us understand how can we fabricate this particular piezoresistive microcantilever, right.

So, since now you know what are the process flow and how the fabrication is done. I am not going to teach you in detail each and every step, but you just follow it here. If this is good enough for understanding the entire process for fabricating a piezoresistive microcantilever, ok. So, let us see the process flow now. We will start with a silicon on insulator wafer, SOI substrate.

As you can see here let us see this color bars silicon nitride green is SiO 2, then gray is silicon orange or you can say a gold color actually golden color is for gold, yellow color is for boron resistor, orange color is for boron contact and we have a blue color light blue color for cross linked Su-8, and of course, the purple color for silicon nitride. So, it is now easy if you understand the process flow the first step is we take a SOI substrate

which is, right over here the top is silicon, the center one green color is your insulator which is SiO 2 and the bottom one is your silicon which is in gray color. That is why silicon on insulator is your SOI.

Now, what is the thickness of the silicon? The thickness of this silicon layer is 2 microns, right. Why we are selected this thickness? Because we want our cantilever to be of 2 micrometer thickness; so, this is the thickness of our silicon. The next step is, the next step is you grow silicon dioxide you grow silicon dioxide using thermal oxidation thermal oxidation, right.

The next step, let us see next step. Next step is that you are to create a window to create a window, right to dope to dope the boron resistor is a cross section, ok. So, when I say window for boron resistor what does that mean? You see this schematic we will open this region where I am drawing only this is there, ok. Not this one, not this, not this, only the one that I have drawn, ok. Let me use some other color, so you can you can see what I am drawing. See only this region, this much. So, that is what is a cross section shown here, alright.

So, what we are doing? First we are opening the contact window or as opening the window for diffusing the boron resistor, right. So, how can we open this window? So, we can use, what we can use? We can use photolithography, right. If I have I will just show you quickly, if I have oxidized silicon wafer, right this is my oxide, this is my oxide, this is silicon, this is my SiO 2 again, but this is already available on the wafer because it is a SOI wafer, this is my SiO 2, this is my SiO 2 and this is my silicon, right, these are structure. What I want to, what I want to do? I want to open the region such that I can diffuse my boron resistor this one, for that I will spin coat photo resist positive photo resist then I will do soft bake at 90 degree then I lower the mask, right.

So, it is a cross section. So, I can just show you let us say like this, and this region will be sorry it will be a dark filled mask, it will be a dark filled mask. Why? Because the region which I want to use for diffusing my register, I want to edge silicon dioxide from that particular region into edge silicon dioxide from that region I have to save other area except this area. So, now, if I use if I do lithography or if I expose the wafer with UV, UV light what will happen? The unexposed region the unexposed region would be stronger and the exposed region would be weaker. So, after UV lithography if I dip the

wafer in photoresist I will have, I will have my photoresist which is it is here, right, yes I have to use this one. So, I will have a photoresist only here and here.

And you can see that now I can see SiO 2 be through the photo resist because photo resist has been developed with the help of photo resist developer. Since, this area has photo resist and this area doesnt have photo resist if I dip this wafer after hard making, then what will happen? The silicon dioxide that is exposed will get etched from this region; that means, like this, right. How can I silicon dioxide? By BHF.

Now, I will dip this wafer in acetone, I dip the wafer in acetone. What will happen? The photoresist will get etched, right and this will give me this will give me this structure this is a schematic. You got it, easy.

Now, what I have? Next, next layer is silicon. So, if I open the window such that if this is the top wafer, if I have opening the windows like this. Let me draw two lines, like this. So, I for opening this window I can use this particular process. Once the windows are open everywhere there is silicon dioxide except through windows I can access silicon. So, now, the if the next step if I diffuse the wafer with boron, right with boron. Then what will I have? I will have boron only in this particular region. When you when you perform the diffusion there will be a borosilicate glass and that borosilicate glass you can etch with the help of BHF the help of buffer hydrofluoric acid.

So, after this once I defuse by boron, right then what is the next step let us see. So, until now I hope it is easy for you to understand, right. It is little bit ah difficult problem, but I am going little bit slow, so that you do not miss the important steps. First one was SOI, second one is SiO 2 by thermal oxidation, third one is opening the window for piezoresistive piezoresistor to diffuse then we have boron diffusion, right. After boron diffusion I will again grow a silicon dioxide, this time I had a grow silicon dioxide, ok. So, in the e this schematic we are growing silicon dioxide on both sides of the wafer.

Next step is to open the contact area of the piezoresistor; that means, if you remember in the last step in the last process step we open this region, right, we open this region. Now, in this process step we will open this region such that it will overlap this previous region, but remaining there everything is covered with silicon dioxide, ok. Remaining is the always silicon dioxide, only the contact pads would be open this area would be open. So, for this one and this one we are showing you, right over here in f, alright.

The next step is to diffuse boron contact, to diffuse boron contact. You can see here there is a diffusion of boron contact, right. After this what is the next step? Once you have contact what you will do you have to take the contact for sensors, right. So, this one let me draw it here, so it becomes easier for you to follow I will I will need this contact and this one, right. So, I will now deposit gold on this. So, if I have this particular wafer I will deposit gold everywhere then do my lithography and I protect I finally, etch the gold from all the area except this area and this area is the cross section of this particular chip. So, you can see, we can see only a gold contact pad from the piezoresistor. Now, I can measure the resistance with the help of this gold contact pads, ok.

Next step, next step is I will deposit silicon nitride. I will deposit silicon nitride everywhere and etch silicon nitride from the gold contact pads and from two more regions, here and here, right. Next step is I have to deposit silicon nitride everywhere this is silicon nitride Si 3 and 4, and I will do lithography such that I reach to the next step which is shown as i.

So, in this step what we will do? We will open the I will remove the silicon nitride from this region and two more region here and here. The advantage of silicon nitride is that it will relieve the stress that is there in the wafer because of silicon dioxide. If you read in detail how silicon nitride helps to release the stress that is that happens due to the deposition of silicon dioxide then you understand the phenomenon, but right now we know that if I repose it silicon nitride as an layer here then it will release the stress.

Next step, once I create the window once I create the window I will etch silicon dioxide, I will etch silicon dioxide and then I will etch silicon. So, if you see I am etching silicon dioxide n silicon in j, in this process, right, silicon dioxide is etched silicon is etched. Next step is I will deposit SU-8 everywhere and pattern the SU-8 tip. We have seen yesterday how SU-8 tip can be fabricated, in when we are discussing about the electronic module or you can say the bio chip using MEMS based technology we have seen how can we fabricate our pattern SU-8 for SU-8 to (Refer Time: 24:27) as a pillars. In this case the SU-8 is used as a tip. And the thickness is about 30 micrometers, the thickness is close to 30 micrometers.

Actually, there are two different chips here what you can see is not 30 micrometer, but about 10 micrometers, ok. Another chip that I fabricated the thickness was 30

micrometer here we have thickness of 10 micrometer. So, previously if I have shown it to you that this is 2 micrometer and this is 50 micrometer or 30 micrometer you understand that this is not 30 or 50 it is 10 micrometer, alright. So, as your tip is done next step is next step is I will open the contact from the backside of the silicon wafer. You can see I have etched silicon nitride, then I have etched silicon dioxide and I can access the silicon, right.

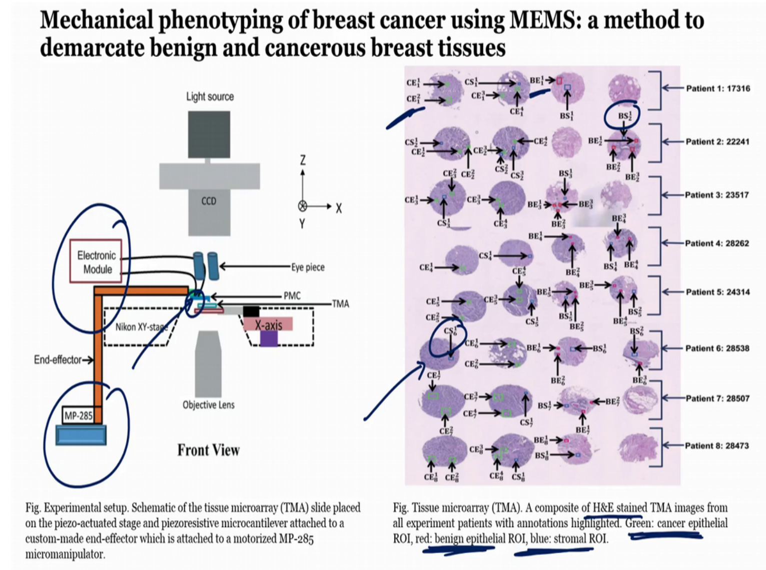
Next step is I will go for DRIE, deep reactive ion etching. DRIE will etch the silicon from the backside. It will stop wherever silicon dioxide is there because silicon dioxide sorry because silicon dioxide acts is a mask silicon dioxide, acts as a mask; that means, that silicon etchant cannot etch silicon dioxide. Now, this is a very crude statement silicon dioxide gets etched, but the rate of etching is extremely less compared to silicon compared to silicon. So, that is why we say that silicon dioxide will act as a mask when you etch silicon and here when you etch silicon using DRIE it will stop at silicon dioxide layer. Further you can etch silicon dioxide with the help of BHF and then you can just you can just realize the chip after that process, ok.

So, let us quickly see what we have done in the process flow for fabricating piezoresistive microcantilever, ok. So, the first step here is SOI, second step is thermal oxidation on both sides, third step is opening the window for boron diffusion, fourth step is diffusing boron resister, fifth step is growing thermal oxidation on both sides, sixth step is opening window for boron contact, seventh step is you deposit or the boron contact and pattern it.

Next step is gold for contact piezoresistor contact, next step is deposit silicon nitride and open the window and also open the window from the gold contact. Next step is etched silicon dioxide and silicon, so that we can see silicon dioxide. Next step is, you spin coat SU-8 and pattern the SU-8 to form SU-8 tip which is about 10 microns. The next step is you create the window from the backside of the wafer and then etched silicon etch the silicon nitride and silicon dioxide, and the final step is you etch the backside of the wafer using DRIE to realize your piezoresistive microcantilever, right raise. It may look little bit difficult, but when you concentrate and you understand the photo lithographic process you will see that it is not so difficult, it is not so difficult, ok.

So, once you have the piezoresistive microcantilever how can you use the piezoresistive microcantilever for understanding the stiff tissue stiffness.

(Refer Slide Time: 28:45)



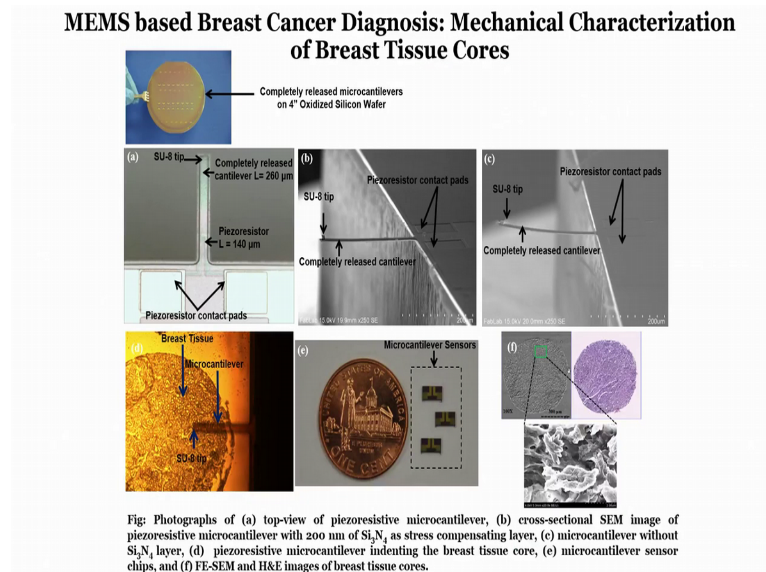
So, this is the front view of the experimental setup where you can see that we can place the tissue, right, this is a tissue microarray it is on the glass slide you can have tissues like this where you can see here. And then what we are doing? We are using a micro manipulator MP-285 at the to which there is a XY-stage and here there is a piezoresistive microcantilever attached we can see here, right, a piezoresistive microcantilever.

Now, this a inverted microscope that is why you can see a eyepiece that is a help us to understand which region we are indenting and then there is a objective lens of course, because the inverted microscope there is a CCD camera and a light source. So, TMD stands for tissue micro array the array of tissues like as I have shown in the glass light, like here, like this schematic. The glass light on which there is a TMA and these are H and E images, H and E stained images of the tissue micro array which is shown here. When you press the tissue then there will be change in the piezoresistor and that changes we can measure with the help of electronic module. So, if the you can see the slides here as a tensor epithelial region is denoted by CE, benign epithelial is BE, benign stromal is BS, right. So, we have noted different things.

So, benign epithelial, benign stromal, cancer epithelial, cancer stromal, right and these are 8 different patients on which we have the tissue is extracted from 8 different patients.

And we can see the green color boxes are cancer epithelial, the red color boxes are benign epithelial, then blue color boxes are stromal region of interest. Again, if I reiterate it is an H and E stained tissue micro array images, alright. So, this is the experimental setup of how to indent the tissue to understand the change in the piezoresistive material.

(Refer Slide Time: 31:06)



Here you can see a oxidized wafer with lot of piezoresistive microcantilever. So, there is a lot how many of those are there if you see 1 2 3, and 1 2 3 4 5 6 7 8, 8 into 3 is 24, about 24, 24 piezoresistive microcantilevers you can fabricate on a 4 n silicon wafer, wafer is SOI, ok. And you can clearly see the difference when you use the silicon nitride, silicon nitride for relieving stress and when you do not use it when you do not use it to have the cantilever which is bent because of the stress, when you use it you get a clean cantilever released from the SOI wafer or using the SOI wafer, right.

There is a SU-8 tip you can see it, completely release cantilever, completely release cantilever, but there is a stress, there are (Refer Time: 32:07) contact pads. Here what you see is cantilever with a piezoresistor, here the length is 140 microns, the total length microcantilever in this case is 260 microns, again SU-8 tip here is to contact. This is when we are actually taking the measurement from the tissue we are understanding the tissue property and you are pressing the tissue with the help of SU-8 tip. Again, when I explained you earlier that when you press the tissue depending on under tissues stiffness piezoresistor will bend, the cantilever will bend and the piezoresistor will change the

resistance, and that resistance we will capture the help of electronic module. And when you do that you will see that the we can understand the change in the stiffness of the tissue.

So, now if you go to f, this f one is that you have SEM image, you have H and E image, and when you zoom it you will see the FE-SEM image of the breast tissue course, right. As we as I have told you about 200 nanometer of silicon nitride can act as a stress compensation layer, that was we have used. And finally, using this piezoresistive cantilever we can understand the change in the tissue property particularly when cancer progresses from normal to benign to DCIS to IDC, alright.

So, in the next module I will show it to you how can we get different or how we can how we are able to obtain different results using the piezoresistive microcantilever. And how can we de-market between the tissues whether they are normal or they are in the cancer (Refer Time: 33:47), right. And then you take care. I will see you in the next module.

Bye.