Fabrication Techniques for Mems-based Sensors: Clinical Perspective

Prof. Hardik J Pandya
Department of Electronic Systems Engineering
Indian Institute of Science, Bangalore

Lecture -27
Microchip for Rapid Drug Screening

Hi, welcome to this particular class and here today we will be talking about very interesting application of micro technology in Drug Screening. So, what I mean by drug screening? You see when we let us take example of cancer, so that it is easier for us to understand. When a cancer is diagnosed, the patient has to go through chemotherapy right, we know in general patient are given chemotherapy.

Now, if there are 5 or 3 FDA approved drugs; three approved drugs that can be administered to a patient which drug to pick from? Do we have any technology or can we propose a technology? So, my question is that for a patient x out of three drugs let us say a b c, drug a would be effective or b would be effective or c would be effective. Same thing if there is a next patient, patient y out of three drugs a b c which one would be effective?

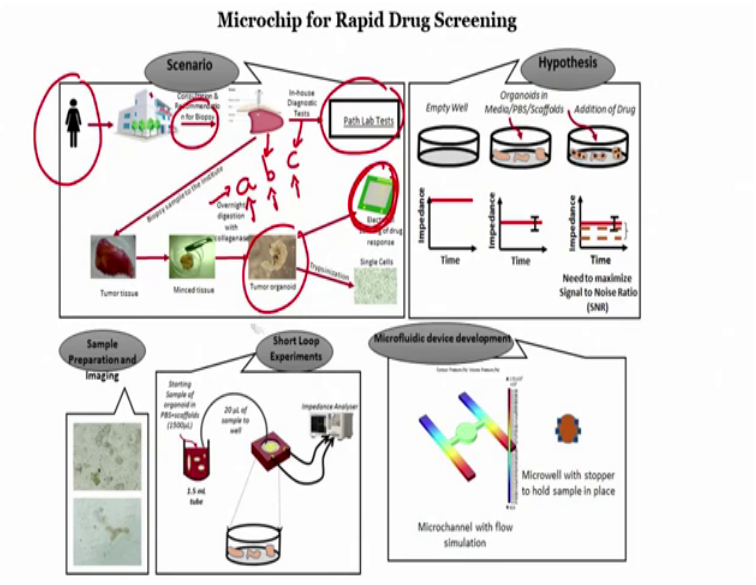
So, the question here arises is there we need or do we have a patient centric platform, that you take the sample of the cells or from the tumor of the patient, load that sample into the device test these three drugs and tell which drug would be effective for that particular patient. Then the recovery of the patient would be better rather than just giving from a b c any drug to the patient right.

So, we will be discussing today a technology, which I have named as Microchip for Rapid Drug Screening. How we can design a microchip for this particular application and can this microchip be used as a patient centric platform in case of chemotherapy? Now, it is not just limited to chemotherapy it can be used for other therapies as well where the drugs are involved right.

So, I will show you the device, and we will see how we can design it, we will see what kind of results we can get and we need to make sure that the results that we are getting it matches the gold standard the results obtained from gold standard. So, we will performing the; so, we will be use we will be looking at the experiments that we can

perform to understand the efficacy of drug or to evaluate the efficacy of drug alright. So, let us see if you see the screen what we are talking about? We will be talking about a microchip for rapid drug screening.

(Refer Slide Time: 04:55)



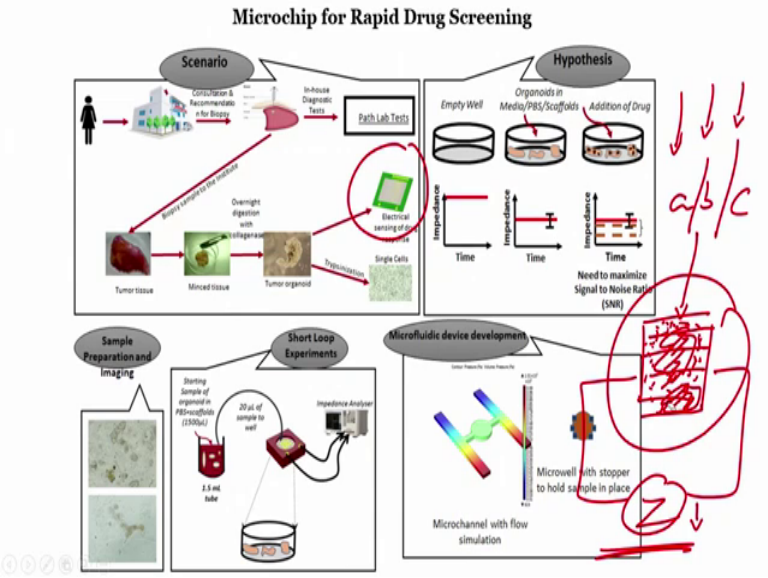
Now let us take this scenario. What happens? A patient when goes to hospital for consulting a clinician depending on the results obtained from the gold standard like MRI mammography.

So, let us take an example of breast cancer ok. So, in breast cancer the patient has to go for MRI or mammography. And if the region is suspicious then the patient would be asked to go for biopsy. Biopsy is nothing but taking the tissue out from that particular region so, that we can see or we can perform further test to make sure that a patient is suffering from a cancer or it is not cancer alright.

So, when the biopsy is performed the tissue is out and tissue is sent to the path lab test, tissue is sent to path lab test alright. Now, if a patient is diagnosed with cancer if a patient is diagnosed with cancer, then like we have taken example out of three drugs a b or c or n c, any one drug is given to the patient one of this drug a b or c is given to the patient and then patient has to wait for about 3 to 4 months to understand, whether the drug is effective or not, whether the tumor is dying or not, whether cancer is getting killed or not and to wait for that amount of time is a wastage.

So, what can be alternative technique? Alternative technique can be that you take the tumor or the tissue a slice of the tissue, that is obtained using biopsy and you get the organoid and you use this organoid on a chip and flow different drugs and can you flow different drugs means flow either drug a or b or c and get the results, and tell the patient based on our experiment drug a b and c that we have used a particular drug is more effective for your case and that will be a better approach. So, how can we design this chip right? Of course, you can go for trypsinization single cells and perform lot of other experiments related to biology, our idea is not to understand in detail biology, but to understand how we can create or how we can fabricate a device that can tell a patient, which drug will be better for his or her particular case; that means, a device which is patient centric.

(Refer Slide Time: 07:53)



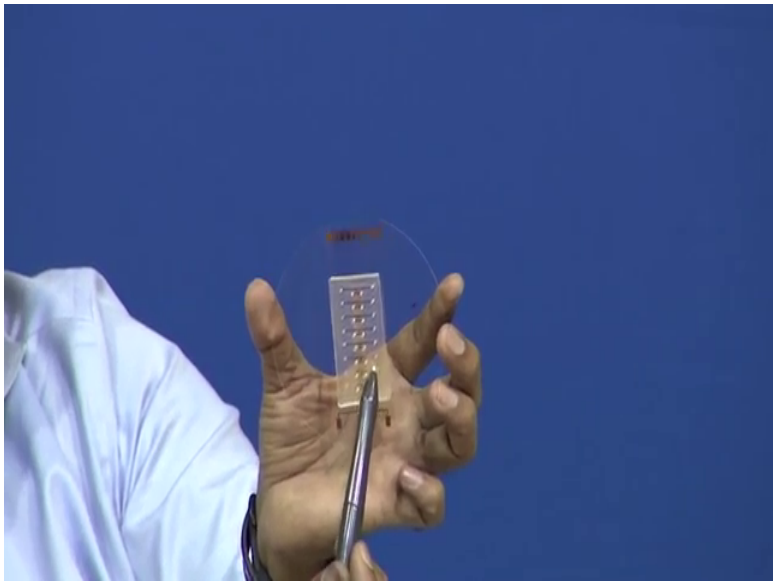
Now, if we create an interdigitated electrodes, if we create interdigitated electrodes right like this and we place the tissue or spheroid on this interdigitated electrodes then what we will get? We will get a impedance value right we will get a impedance value. Now if I load a drug let us say drug a or drug b or drug c then if the drug is effective, there will be the tissue or the organoid right the tumor will start dying; and when it starts dying the conductivity would increase conductivity would increase and impedance would decrease, this is one way of doing it this is one way of testing drugs a b or c.

Now, the difficulty with this is, that the drug is in continuous contact with the tumor this is a static platform let us say if I say a drug with dotted points like this right the drug is shown by this kind of dotted points in this particular device what we see is the drug is in continuous contact with the spheroids, but our body is not static this is sorry this is a static platform our body is not static our body is dynamic.

Thus a static platform to understand the efficacy of drug, to understand the performance of drug is not a solution. So, what is an solution? The solution is to fabricate or to design and fabricate a micro fluidic platform; because in micro fluidic platform we can we can mimic the in vivo situation and that will be a dynamic platform similar to our body right, but the concept we got is that if we load the drug on the interdigitated electrodes with tumor, then we can see the change in impedance; that means, if we can use impedance as a modality or electrical property to understand whether drug is effective or not.

So, electrical property of tissue which is our impedance can be used to understand which drug is effective. Like I said if a drug is effective, the tissue will die, the tumor will die, the cells will die and thus there is a increase in conductivity and decrease in impedance. Thus impedance can be used as a marker to understand which drug is effective or not, but the problem here was that we are using a static platform. So, now, let us see how can we create a dynamic platform and how are dynamic platform will look like right.

(Refer Slide Time: 11:23)



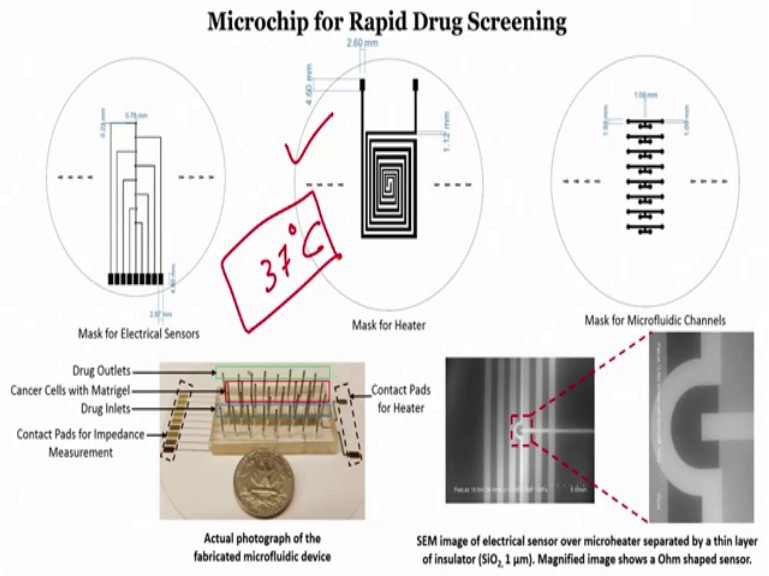
So, I have a chip right in my hand, and I will show it to you and this chip we are looking at we will be looking at how to how to design this chip today, I am holding this chip in my hand this is the micro fluidic chip. It is just a micro fluidic chip, and it has a micro heater, it has an interdigitated electrodes and it has a channel made out of PDMS.

So, we will be looking at how we can create this chip that can be used to understand or can be used to rapidly screen different drugs. And as you can see there are lot of lot of context here this context are for the electrodes; and if you see the another two context the bottom right you can see another two context at the bottom then this context here right here this one, these are for heater this context are for this context are for the electrodes right. This one and two this contact are for heaters; now you can see further that there are lot of holes right there is a long channel here you can see very long channel here 1, 2, 3, 4, 5, 6, 7, 8 and there are shorter channels next to long channels right you can see here there is a shorter channel here to here one next one, here to here then here to here.

So, there are long channels and there are short channels on the back. So, in the front side only there is a heater as you cannot see through the PDMS, I am showing it to you from the back side here is a heater you can very clearly see there is a heater and there are interdigitated electrodes.

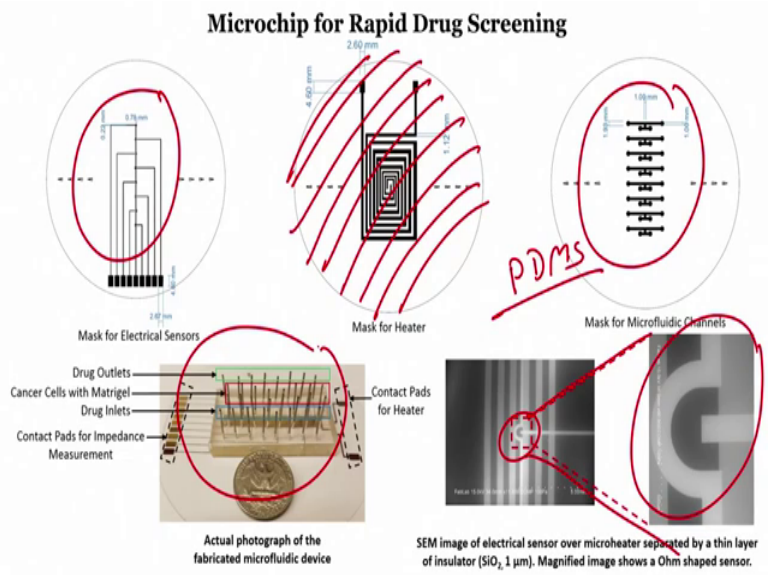
So, how can we fabricate such a sensor? How can we fabricate such a micro fluidic chip right for rapid drug screening right. So, let us see the screen if you see the screen what we have?

(Refer Slide Time: 13:19)



We have at the bottom at the first step is your micro heater or a heater why we require heater? So that we can achieve 37 degree centigrade for the cells to be alive right. So, we can keep cells alive, if we can have 37 degree centigrade temperature. Now, which is similar temperature to the incubator similar temperature the incubator?

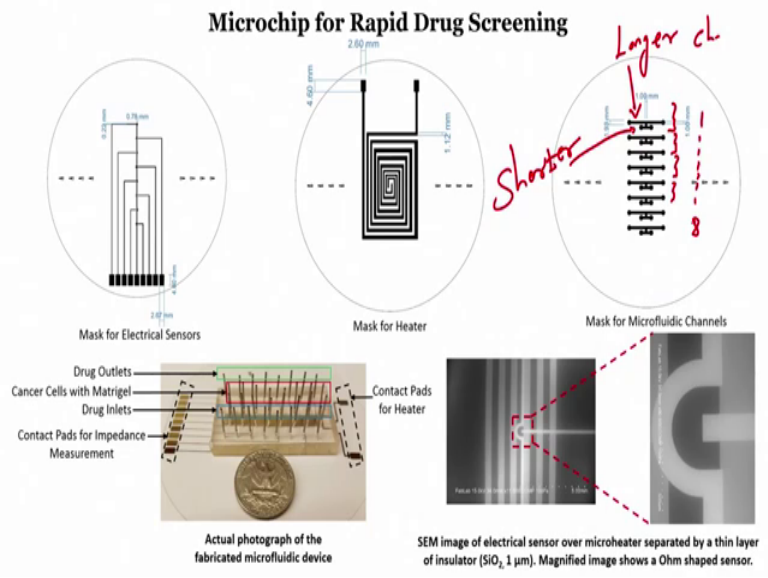
(Refer Slide Time: 13:57)



Over this micro heater, there is a insulator. On this insulator there are interdigitated electrodes. If I zoom in then I can see here each electrodes has a shape which is shown here right.

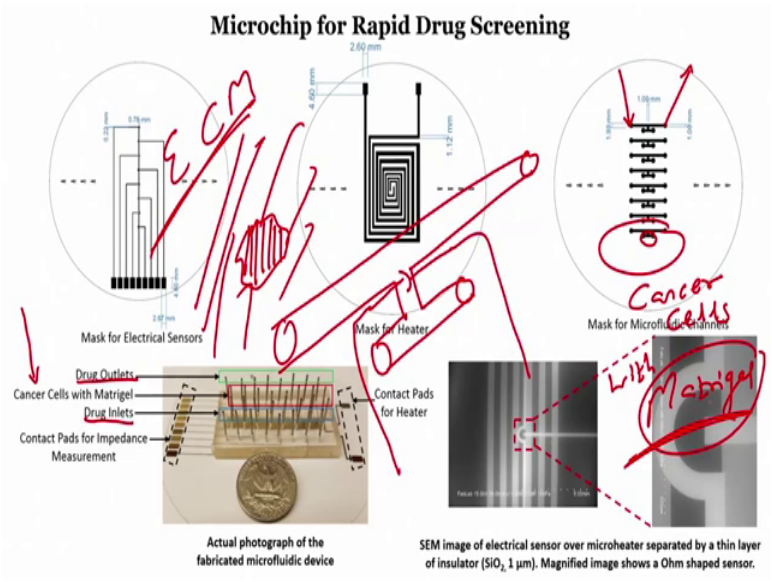
So, what is the first step? First step is my heater, second step is the insulator, third step is the fabrication of interdigitated electrodes, next step would be to fabricate or to fabricate a chip with different channels right and this channels we can create in PDMS ok. So, we will be learning how to fabricate this particular micro fluidic chip and if you see the chip, if you see the chip what you see here is see there is a drug inlet see I will I will just draw it here this one is your longer channel longer channel right.

(Refer Slide Time: 15:11)



This one is your shorter channel; small channel shorter channel right. So, let us consider one then there are similarly there are 8; 1 to 8 alright. So, what we are discussing here? We are discussing only one channel, which is a longer channel and a shorter channel it is a longer channel.

(Refer Slide Time: 15:43)

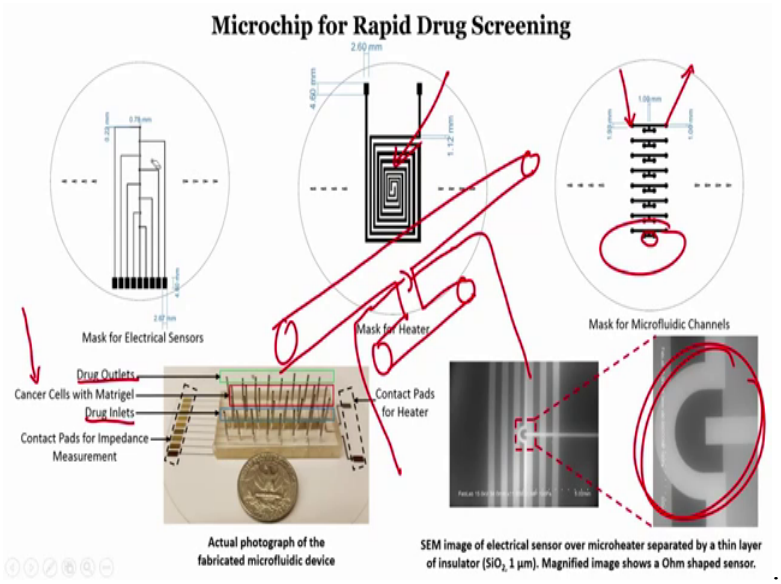


We had to load the drug from here we have to take out the drug from here we load the drug from one end we will take out drug from another end this is what is written here drug inlets, and drug outlets.

Now, if you consider the shorter channel, we load the cancer cell we load here in the short channel will load cancer cells, you can also load spheroids, you can also load organoids right like a tumor. Ccells with metrigel metrigel what is metrigel? Any cancer when we see a cancer is always surrounded always surrounded by ECM Extra Cellular Matrix extra cellular matrix any cancer is surrounded by extra cellular matrix. This extra cellular matrix we can replicate by using metrigel by using metrigel thus cancer cells are mixed with metrigel, you can see here right and can be loaded into the shorter channel.

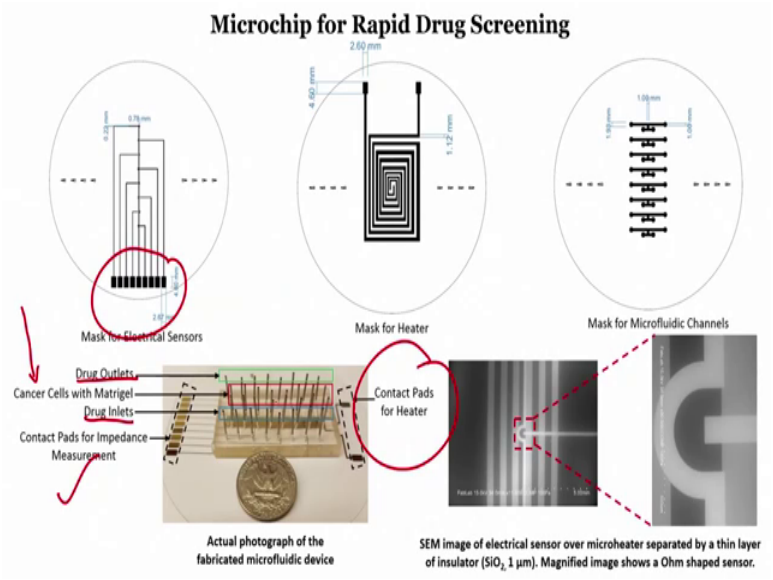
So, cancer cells with metrigel right are loaded into the shorter channel here. Now if I enlarge this particular gel then it is like this and below this channel there is this interdigitated electrodes which one the one is here right.

(Refer Slide Time: 17:51)



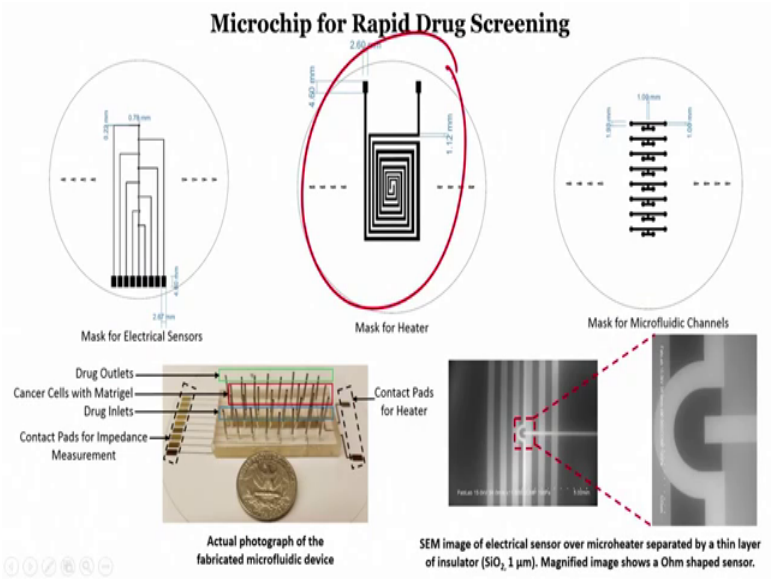
Below this channel there is interdigitated electrodes. Below interdigitated electrode there is a insulator and below insulator there is a heater you got it. So, first layer is your heater, second layer is your insulator, third layer is your interdigitated electrodes and fourth layer would be your channels made out of PDMS made out of PDMSlet us now see how we can fabricate the device and we will discuss in detail, how this device can be used for rapid drug screening right.

(Refer Slide Time: 18:25)



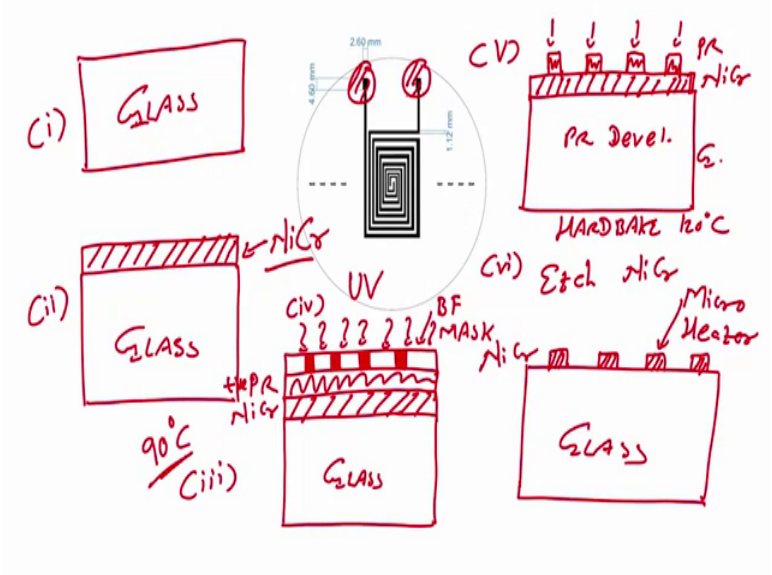
The electrodes for sure this these are used for impedance measurement which is given here the heater contact pads that we have just seen I have shown you the device and the contact pads are used to apply power so, that the heater can achieve 37 degree centigrade temperature right.

(Refer Slide Time: 18:45)



So, let us see one by one first step is we have to fabricate a micro heater right.

(Refer Slide Time: 18:49)



So, how can we fabricate a micro heater? N ow everything is on glass right. So, we take a glass, we take a glass and we deposit a metal for micro heater; let us say my metal is

nichrome right. So, I have deposited a metal which is nichrome for my heater. What is the next step? My next step would be next step would be I will I will spin coat photo resist right you see I have spin coated photoresist which one? Positive photoresist right this is first step. You can always say that I take a glass is a glass substrate I can consider this as first step to take a glass substrate right and make it ready by cleaning it for fabrication, second step can be depositing nichrome for heater third step can be positive photoresist spin coating positive photoresist on the a metal coated glass.

Next step next step after positive photoresist, this is photoresist, this is my nichrome and this is my glass right next step which is my forth step forth step would be to load the mask right. I have to load the mask so, that I can perform photolithography correct. So, I am loading a bright field mask what kind of mask I am loading? Bright field mask now what kind of photoresist I have? Positive, photoresist. So, if I expose this mask is exposed this whole glass wafer right along with mask and positive photoresist with UV what will happen? The area which is not exposed, so, which one? This one which is bold like this. So, the area which are not exposed will be stronger and the area which are exposed would be weaker.

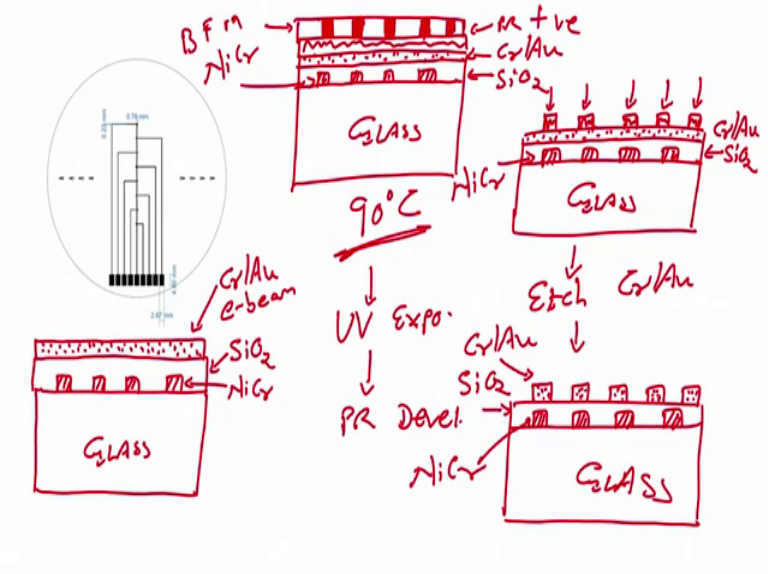
So, fourth step would be to load the mask and perform UV exposure. Fifth step would be to develop the glass develop the photoresist develop the photoresist and when you want to develop the photoresist what we get we have nichrome right and we have photoresist. So, I will get this kind of pattern correct. What is next step? Next step would be to etch load are we missing something? You see after positive photoresist what is what is a step? Soft bake right, soft bake then UV exposure after UV exposure photoresist developer. When you perform photoresist developer, then photoresist should get developed this is your photoresist this is your nichrome this is your glass right after this would be hard bake hard bake hard bake is done at one twenty degree centigrade for 1 minute right when you perform hard bake then next step would be to etch nichrome right.

So, when we etch nichrome the area which is protected by photoresist will not get etched; and the area which is not protected by photoresist will get etched. So, what we will have? We will have a glass wafer with micro heater nichrome glass correct.

So, I have now designed a process flow for fabricating a micro heater; first step done excellent what is the next step? Next step is to next step is to form interdigitated

electrodes. But before forming interdigitated electrodes I have to cover my nichrome with an insulator because we cannot have metal over metal it will be shorted right.

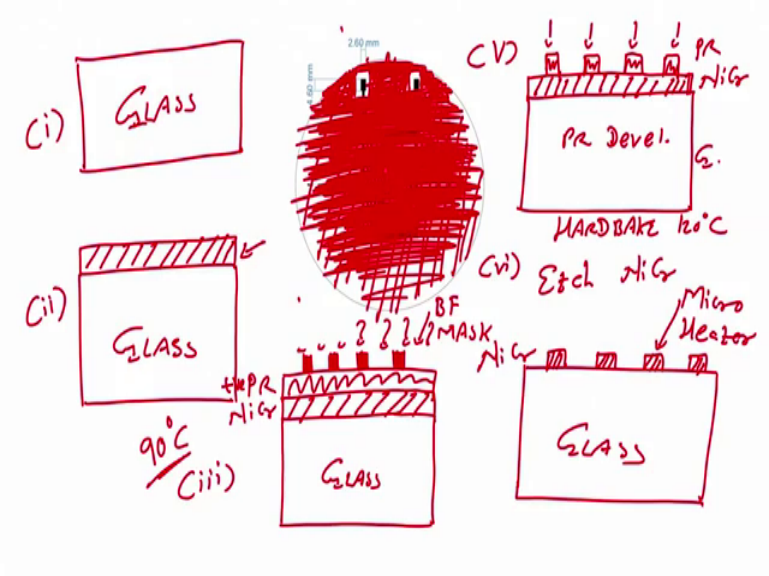
(Refer Slide Time: 24:09)



So, before I go for interdigitated electrodes what I have? I have a glass wafer with micro heater with micro heater right this is what I have. My next step would be I will I will grow I will grow silicon dioxide onto this micro heater correct. And I will perform photolithography to remove the silicon dioxide from the contact pads. You see you do not want you do not want silicon dioxide on the contact pads right you do not need, it because otherwise if there is a silicon dioxide on contact pad you cannot apply any voltage than insulator.

So, you had to perform photolithography such that the silicon dioxide from the contact pad is removed is etched ok. So, now, I am hoping that you know how to perform photolithography, so, I am just skipping that step. What I am doing is I have taken a glass with micro heater; on that micro heater we have grown silicon dioxide and then you perform photolithography such that the silicon dioxide from the contact area of the micro heater is etched here the silicon dioxide should be etched. So, if I now see a wafer right if I now see the wafer how it will look like?

(Refer Slide Time: 25:39)



You see it will look like this, assume that this is a thick everywhere there is a silicon dioxide right everywhere there is silicon dioxide except right except this area or in another way if I want to draw I will just draw like this.

So, you can understand right assume that everywhere it is silicon dioxide everywhere silicon dioxide is there alright everywhere silicon dioxide is there except contact pads except contact pads like this right everywhere there silicon dioxide like this silicon dioxide. So, heater is covered with silicon dioxide, heater is covered with silicon dioxide right; about 1 micron silicon dioxide we can grow using PECVD Plasma Enhanced chemical Vapor Deposition right what you can see? Only heater the silicon dioxide from heater contacts contact pads of the heater is out. So, once you do this, once you once you deposit or you grow silicon dioxide and you perform photolithography such that the silicon dioxide is etched from the contact pad the next step would be to next step would be to fabricate interdigitated electrodes.

So, let us see how we can fabricate interdigital electrodes. So, once I have this assuming that I have taken out the silicon dioxide I have etched silicon dioxide from the contact pads, my next step would be to deposit to deposit metal for interdigitated electrodes. So, let us say I have chrome gold as an interdigitated electrodes right how can I deposit this metal? You can deposit either by e-beam or sputtering e beam or sputtering what is the next step? My next step would be to start photolithography process right to start

photolithography process. So, what is photolithography process? I have I have chrome gold right I have a insulating layer and I have a micro heater correct.

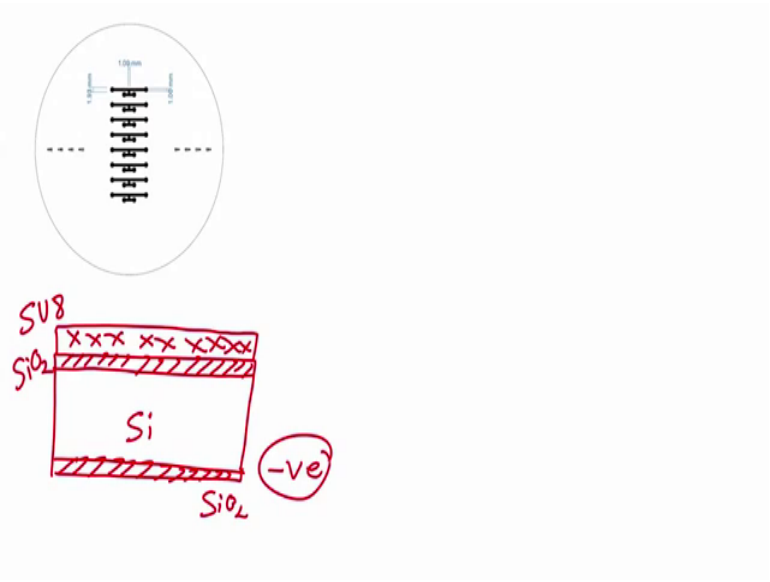
On this I will deposit or I am not a deposit I will spin coat photoresist photoresist chrome gold silicon dioxide nichrome glass right on this; what is the next step? After this we have to prebake; prebake at ninety degree centigrade next step would be to load the mask correct. So, I am loading the mask I am loading a bright field mask right I am loading a bright field mask, for creating interdigitated electrodes this is my bright field mask.

Next step would be next step would be UV exposure. Next step would be PR developer right. So, after I perform UV exposure and PR developer what will I have? I will have chrome gold silicon dioxide glass nichrome and photoresist developed right. The area which was which were exposed the areas which were exposed with UV where weaker the areas which were not exposed got stronger because we use positive photoresist we use positive photoresist right positive photoresist.

Now what is the next step? Next step would be etch chrome gold when you etch chrome and gold you know how to etch chrome and gold, first you have to etch gold and then chrome because chrome is at the bottom gold is at the top when you etch chrome gold area which is protected by the photoresist will be saved it will not get etched and the areas which are not protected by photoresist will get etched.

So, what you will have? You will have a wafer a glass substrate right a glass substrate with interdigitated electrodes at the top SiO 2 next to it at the bottom there is a heater and the substrate is your glass you got it this is what you got. Now what you have a heater at the bottom insulator in between your electrodes and the heater good what is the next step?

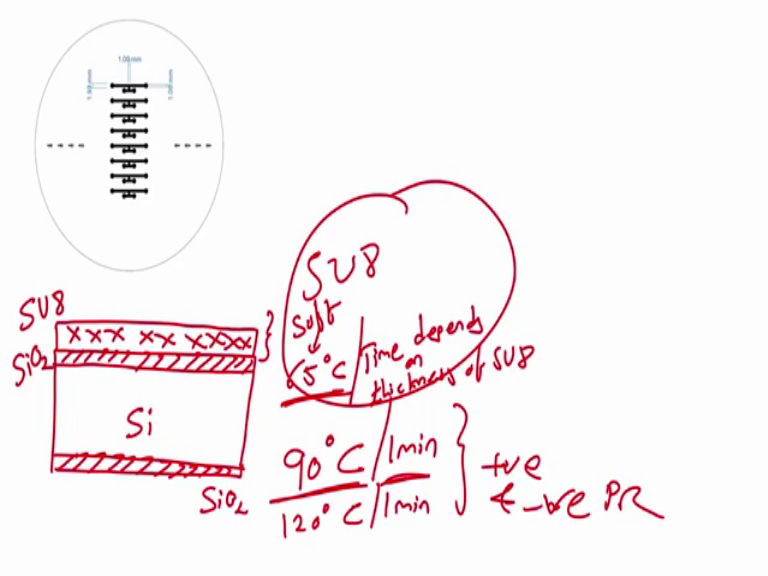
(Refer Slide Time: 33:27)



We have to create channels right we have to create channels this is super easy super easy there are two ways I will show you one way today and then sometime in the next modules I will show you the another way of creating this channels alright. Today we will be learning the creation of these channels by using a mold that is fabricated using SU 8. And then next time we will see how we can create a mold to create this channel using DRI that is by etching silicon itself.

So, let us see how you can fabricate this particular channels and how you can use the mold. So, for that you have to take silicon oxygen silicon right that is oxidized silicon SiO 2 SiO 2. On this you spin coat SU 8 what you do you spin coat SU 8 alright SU 8 is which kind of photoresist SU 8 is negative it shows property similar to negative photoresist ok. Now what we want to do? We have to create this channel right after you spin coat SU8 after you spin coat SU 8 you have to prebake it.

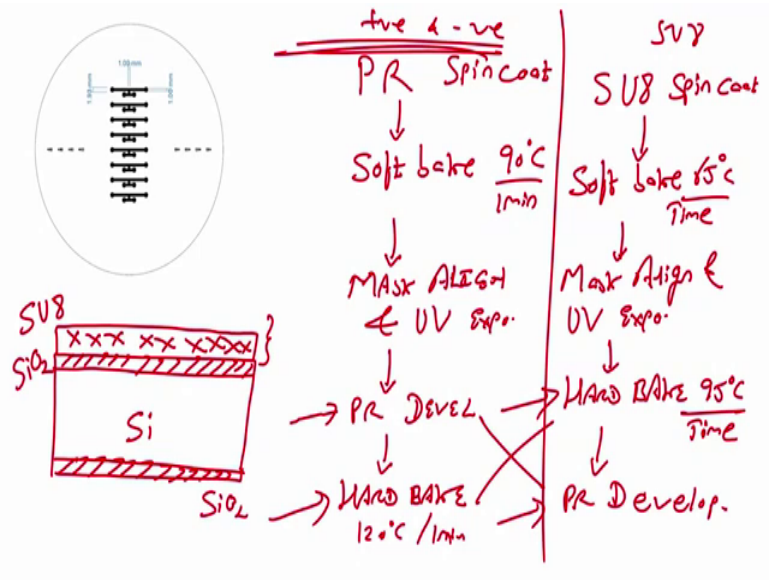
(Refer Slide Time: 35:13)



Now, for the prebake temperature is somewhere around 65 degree centigrade and depending on the thickness of SU 8 the time also varies right for positive photoresist and negative photoresist what we are discussing? We were discussing till now that the soft bake temperature or prebake temperature is 90 degree centigrade and if you use hot plate then you can heat it for or bake it for one minute.

The post bake temperature was 120 degree centigrade again if you are using hot plate you can bake it for 1 minute this. For positive and negative photoresist right,. But for SU 8 65 degree is your soft bake the time depends time depends on thickness of SU 8 alright that is the first step that you have to understand. Second step is second most important point in while using SU 8 is that in our photolithography process in our photolithography process standard photolithography the steps are like this spin coat photoresist.

(Refer Slide Time: 36:29)



Next step would be soft bake, 91 minute, next step would be mask aligning mask align and UV exposure right next step would be PR developer, next step would be hard bake 120 degree centigrade again 1 minute on hot plate; this is our standard lithography process right.

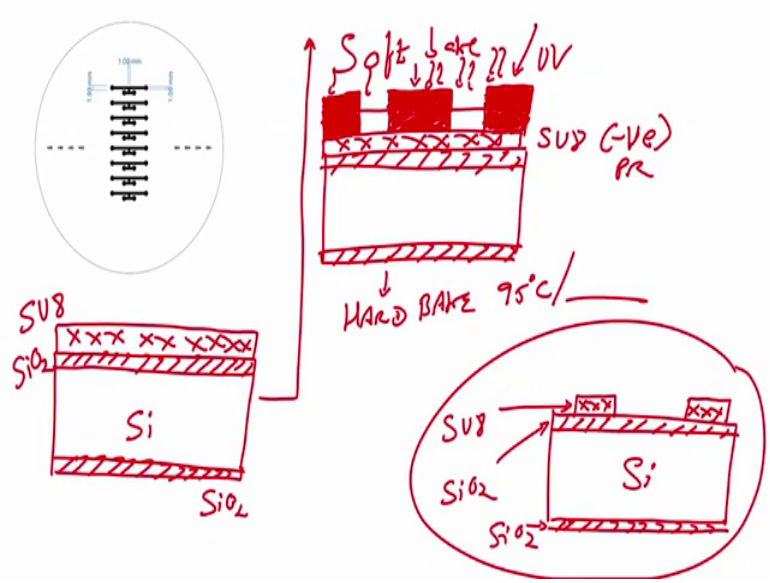
But when you want to use this for positive and negative photoresist? When you want to use SU 8? First step is PR. So, SU 8 spin coat SU 8 is similar to negative photoresist but anyway. SU 8 spin coat next step would be soft bake temperature is different, time is different I told you time depends on the thickness time depends on thickness next step would be mask aligning mask align and UV exposure.

Next step is hard bake; 95 degree centigrade for some time depends on thickness then comes PR developing what is the difference? What is the difference that in SU 8 after soft bake and mask aligning there is a hard bake before we go for photoresist developer while in normal standard photolithography once you have soft bake mask aligner there is a PR developer and then there is a hard bake you see here after mask aligner there is a hard bake and then there is a PR right this is the only difference this is the only difference.

The advantage of using SU 8 is that SU 8 is obtained or we can get SU 8 of different viscosity, and thus the thickness of the channel can be different. The SU 8 is easy first of all because just photo resists that we have to pattern second is that the thickness can be

varied depending on the type of SU 8 that. We are using there are several types of SU 8 SU 8 25 SU 8 50 and lot of other SU 8 depending on the thickness that we want alright. So, here what we have done? We are taken oxidized silicon wafer via spin coated SU 8 next step would be pre bake right.

(Refer Slide Time: 39:41)



If I go here next step is my soft bake let us say right soft bake next step would be exposure right.

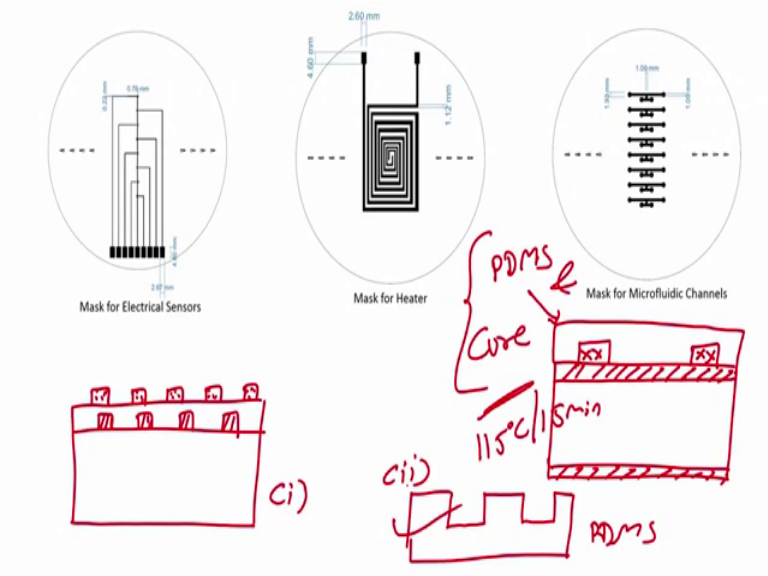
So, I will just draw wafer silicon dioxide. So, it is oxidized silicon wafer right on which there is a SU 8 on which there should be the mask right there should be mask now you have to be careful because SU 8 excess a negative photoresist excess negative photoresist. So, what you want now? You want to create a hills. So, the area which is exposed will be stronger and the area which is not exposed will get weaker, the area which is not exposed because there is a property of a negative photoresist correct. So, what we can do? We can use bright field mask we can alternative use dark field mask such that we can have a pattern a pattern that looks like the one I am drawing here and somewhere on the backside there are another pattern.

So, this is a cross sectional view. So, you should understand this is SU 8 SiO 2 silicon SiO 2 here. So, to obtain this one we have to use mask which is shown here after mask, what is the next step? Next step would be exposure UV exposure when you perform UV exposure next step would be hard bake not developer hard bake. After hard bake which is

a 95 degree centigrade for particular time depending on the thickness of SU 8 next step would be next step would be sorry this is a entire mask is like this entire mask is like this right.

So, next step would be hard bake and then we have to develop photoresist. When you develop photoresist you will obtain this particular mold now what you will do with this mold what you will do with this mold right?

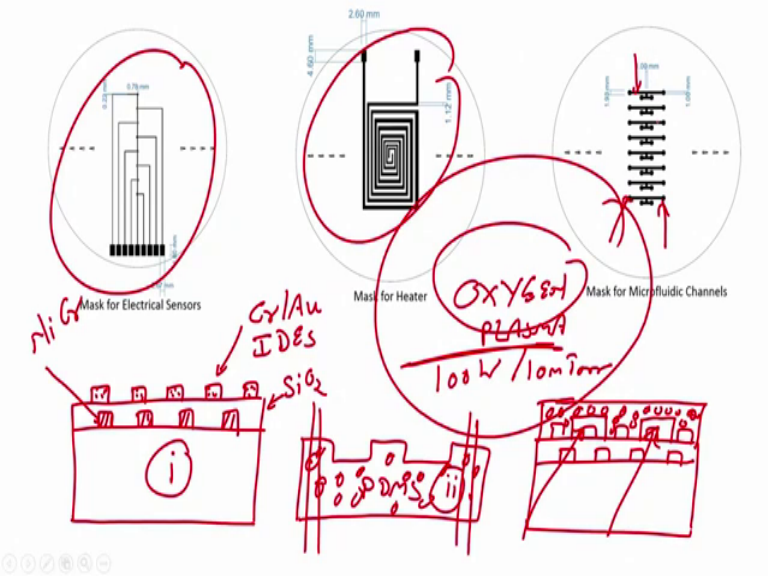
(Refer Slide Time: 43:39)



So, with this mold right SU 8 mold what we will do? We will pour we will pour PDMS and cure it pour PDMS and cure it. When you pour PDMS and cure it at 115 degree centigrade for 15 minutes then you can peel this PDMS off. If you peel the PDMS what you will get is let me just redraw it this channels right. Because there was SU 8 this is PDMS when you when you pour the PDMS and cure it and when you peel it off you will have PDMS as shown in schematic this one ok.

Now, what you have you have? You have a glass wafer with heater right and interdigitated electrodes right and you have PDMS. So, this is 1 and this is 2correct these two things you have. So, let me just rub this now we know that how you can create PDMS right. So, what we have?

(Refer Slide Time: 46:01)



We have wafer one with interdigitated electrodes SiO 2 this is chrome gold interdigitated electrodes, which are this one right then we have silicon dioxide, then we have micro heater which is this one right and we have PDMS correct this is my second wafer 1 2 right. Now what I will do is I will perform oxygen plasma, oxygen plasma technique and after performing oxygen plasma technique I will stick PDMS to the glass.

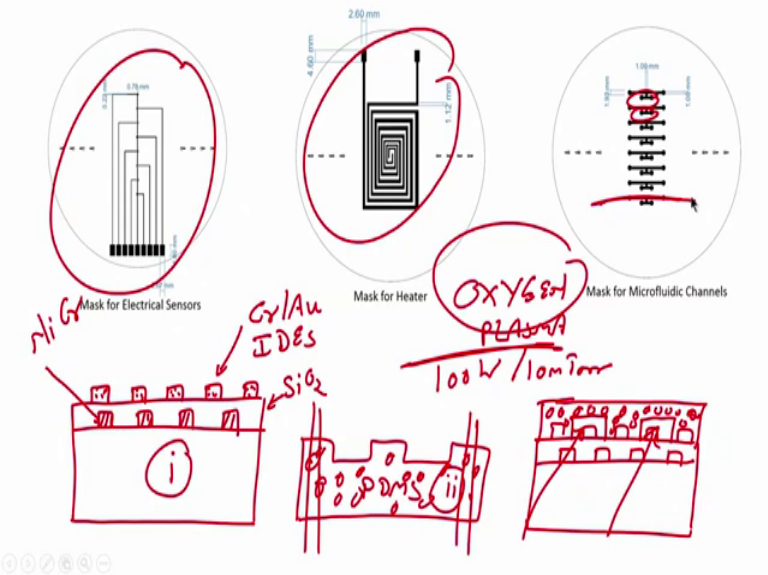
So, after performing oxygen plasma technique, this is done at 100 watts right for particular pressure of nitrogen or argon is it correct no right? Initially nitrogen can be used, but the end we require oxygen right. So, 100 watt of power and about 10 milliTorr of oxygen, ok. So, we can there is a generation of plasma that will create a surface that is functionalize the surface so, that it is ready for bonding.

Next step would be sorry next step would be I have a glass wafer, I have a micro heater, I have interdigitated electrodes on which I am loading this substrate right I am loading this substrate. So, what will I have? I will have like this something like this correct I have a feature which is like this. Because now you see if I if I draw this with let us say zero pattern, then if you see here where is my PDMS? My PDMS is here and thus I have a channel you can see a channel right you can see this channel and you can see this channel.

So, what I have done is I have sticked PDMS onto the glass substrate, which is integrated with a micro heater and a interdigitated electrodes and separated by a silicon dioxide or

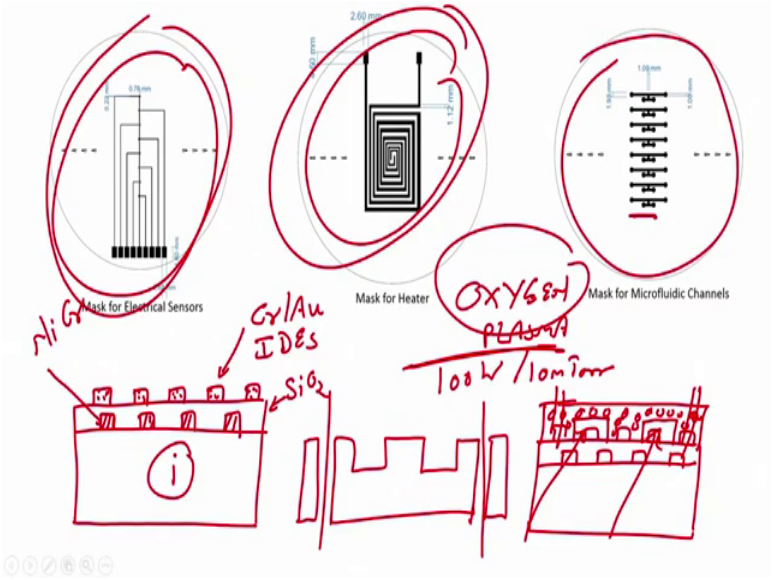
an insulator. So, once I have this device once I have this device what is a use I cannot operate anything. So, before you before you stick like this, before you go for oxygen plasma you have to create a hole in the PDMS it will create a hole in the PDMS so, that you can use for loading or flowing the drugs and loading cancer cells right in the shorter channels in the shorter channels you are loading cancer cells.

(Refer Slide Time: 49:47)



In longer channels you are flowing drugs how can you load if you do not have the inlet and outlet? So, to create inlet and outlet you have to create you have to create holes in PDMS you have to create holes in PDMS something like this right.

(Refer Slide Time: 50:05)



There is a hole there is a hole how can you create a hole? By using acu punch by using biopsy needle you can create a hole in the PDMS alright. If you have this then it is easy to connect the inlet and outlet or to lower the drug alright.

So, what we have seen? How can we have micro heater and how can what is the process flow for micro heater on that there is an insulator on that there are interdigitated electrodes over which there are PDMS channels and we are sticking all together to get a microchip. Now the question is once you develop this microchip, how can you use for rapid drug screening right. Once you once you we now know what is the process for fabricating this microchip, so, what is the next step so, that we can use this microchip for rapid drug thinning. So, we will see this in the next class in the next module of this particular lecture, and we will we will see what kind of data we can generate using what kind of drugs right.

So, there are different drugs different cells we will see the data obtained from melanoma which is skin cancer from prostate cancer cells, and from breast cancer cells. And we will see two different kind of drugs one is paclitaxel another one is carboplatin right perineum based drugs or textual based drugs. So, when we use perineum based drugs, when you use textual base drugs, what kind of results what kind of electrical properties we can we can find out depending on the efficacy of the drug. So, we will see in the next module till then you take care, I will see you next class bye.