Electronic Systems for Cancer Diagnosis

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Lecture – 52
Demonstration of Cleanroom Equipments:
Micromanipulator

Hello everyone welcome to the course on Electronic System for Cancer Diagnosis. Today, let us study more details about Micromanipulator. Even before we get into understanding what is a micro manipulator, let us understand something a basics about soft tissues and their biomechanics. It the research says that when diseases is being diagnosed there are structural changes in the cells or tissues. So, these changes in the structural features can be leveraged using the change in stiffness parameters.

I am sure you have heard of the word called palpation which doctors use. They use this patient is nothing, but touching your skin or a texture where there is lesion and they press or stiffen try to understand the property stiff how stiff your lesion is. So, it is just pressing across any organ of your body. This is done by a surgeon or a doctor in order to understand if there is a lesion or a stiff, you know fibroid which could cause some kind of disease like in case of breast cancer you see lumps which is a diagnosed just by palpating the organ.

So, these are general this is how diseases are being diagnosed externally which is termed as palpation. But what about lesions which are formed inside the organ say if it is liver or kidney? So, how are these lesions and how are the stiffness parameters? So, when we when what literature says is a part of tissue organ; if it is diagnosed if there is some kind of a disease which is affecting, this could be seen by understanding the stiffness of the of the infected area.

So, how do they say that this stiffness the underlying structural features of the infected area shows a different mechanical property. When we talk about mechanical property there is a term called Young's modulus which would quantify the physical parameter called Young's modulus would quantify this mechanical property what we call I mean the mechanical property which is used to test understand the stiffness or any other parameter of the salient issue infected with disease it. The it is also understood that the changes in the structural features or the stiffness or any other elastic property, it is not just because of any disease; it could even be related to age related parameters.

So, how do we classify them? How do we understand these the variations in all these phenomenon? The conventional technique to understand the stiffness of tissues or organs the mechanical testing regime is uniaxial test. What they do in uniaxial test is a part of the biopsy sample. It could be a skin for example, the skin is treated even before the test is conducted once. Once it is treated like they remove, the blood cleanse the tissue structure and then it is subjected to forces uniaxial force.

When we say it is on the tissue is stretched on either sides on say, you could use my fingers and then just try to analyze how uniaxial test its pull just like you take a rubber band and do them pull them. You pull the tissue across and then you stretch them until they are broken on. So, this gives you stiffness elasticity property of the skin for example, what we had considered. So, what is this how do we quantify the physic parameter? As I mentioned earlier Young's modulus is the ratio by definition, it is the ratio of stress to strain. When we say stress it is the amount of force that is applied per unit area and when we say strain, it is the change in length from the original length how much it has changed.

Say it is of X length and then when you pull there is and then release there is there it is no more X and it would be X plus delta x. So, there is an increase. So, this change in length is what is quantified as strain. Now how do you quantify the amount of force that you apply and how do you quantify strain how do you measure these? Like I mentioned in the conventional techniques the uniaxial test, you pull the sample material which is under the test process and then understand and then release them and then understand how much is the change in length? And you know the amount of force that you are applying externally.

So, in this way the stress and strain ratios in conventional mechanical technique techniques are studied. Apart from the uniaxial test, it there are many other techniques like biaxial test where it is not just a stretched in one direction, but it is stretched on 4 sides like; one, 2 this way and also on the other 2 sides. So, this is biaxial test where all 4 sides the material is stretched to; it is all done just to understand the mechanical property of tissues.

So, every part the organ the soft tissues and the hard tissues. The hard ones the soft tissues like the skin and the organs, they are elastic in nature. So, what happens is when they lose their elasticity they there is a disruption in their functionality. For example, when we consider the trachea say there is this cartilage which you could see externally. Cartilage is used stiff. What happens if it loses its stiffness property? It becomes more flaccid becomes more loose and then it is no more stiff and every time you breathe in breathe out exhale, the amount of forces that you are inducing on to this trachea it.

And since the mechanical structure is no more as strong as it was before and said it is loose and the stiffness it has lost stiffness property. The tendency of it took collapse is very high and when it collapses, it is very difficult for you to breathe. So, in this coding this example, I am sure you understood how every part every organ the tissues and the organs have something called as a mechanical property which we also call as the bio mechanics. Like the conventional techniques what i mentioned the uniaxial test, biaxial test, there could be shear tests and they could be compressive test. So, all of these tests are to are performed to understand the biomechanics or the mechanical property of these tissues.

So, what does it require the drawback of this conventional mechanical technique is this sample has to be excised from the native place. So, it is extracted and it could cause harm or pain to the patient or you know or the animal or any more any organ from where we are trying to take the sample. And this the further test what has to be performed is X by o and it is more destructive in nature.

So, what happened over the years is, in order to overcome the drawbacks of these conventional techniques there were new techniques which came up which could be used in vivo without actually excising the sample from the native place. A few to mention there are cantilever based sensors. So, these MEMS based cantilever like the cantilevers the these are used in AFM the Atomic Force Microscopy techniques. So, what is the working principle is so, these in the cantilevers are indented on to the your tissue sample and as they indent they are pushed back because of their because of the elastic inherent elasticity elastic properties.

So, as they flow through the tissue sample, this deformation the more the movement of the cantilever is captured using a light source. So, the light source is always falling on your cantilever and then as the distance between the cantilever and the sample moves the amount of light that is reflected is captured using your photodiode. And hence you would know what is the amount of deflection what is happening in the cantilever? So, how come this our cantilever the phenomenon of this working principle has been leveraged is.

So, when we are talking about understanding the biomechanics of tissues so, we want to know what is the amount of deformation, what is the amount of force you are applying and how much is the deformation and how do you quantify this. So, there were work where AFM based cantilevers were used to indent their tissue samples. So, you know the amount of force that is being applied, but there is no feedback. So, you do not know what is the amount of the there is a change in length. So, you have just the amount of deformation what happens.

But how do you quantify the amount of force? There is light source which is coming. In order to overcome the cumbersome of cumbersome optics which is used in AFM so, you have these strain sensors embedded on your cantilever. Like Professor Hardik would have explained in one of his research work where he is used cantilever and strain sensors embedded on these cantilevers and they have tested the mechanical and the properties of breast tissues.

So, this the characterization of tissues like the cancerous, the benign the normal tissues well you know well you were they were able to characterize these tissues based on your stiffness properties by using these cantilever with a strain sensor. So, every time there is a deflection, the strain sensor there is a change this the mechanical phenomenon is being Trans ducted into electrical property. So, in this way so, we understood the we could classify the cancerous at the benign tissues benign or the malignant breast tissues just by understanding the stiffness properties of tissues using cantilever.

There are many other techniques apart from cantilever base sensors. It could even be optics based where there is optical coherence tomography laser spectral rheology. All of these are different optic optical methods where light is shined onto your sample and then the reflected light is what is captured and studied. So, all how is this I mean how does this leverage the stiffness properties? How do we understand the mechanical properties of tissues? Say for example, let me coat you the usage of optical coherence tomography in. When you are talking about studying the elasticity or stiffness properties of tissues so, it is called it comes under elastography studies.

So, when you say elastography it is nothing, but the study of elastic properties of tissues and like I was mentioning, we use OCT say OCT is technology where light is dropped on to your sample source. And then there is a mechanism where you indent the sample say at point t 1, there is light which is shining on your sample which is free of all forces external forces. So, this is point a this is at time t 1 and now I have an indenter which would press my tissue which would compress, which would apply a force on the tissue and as it applies that time t 2 there is again the light source which is shining.

And then you release the indenter which is at the bottom and then the tissue tries to regain its original shape. Through all of this time t 1 t 2 and t 3, the light source is being trapped this. When you use this light source at each instant like when the tissue is free of external forces, when the tissue is being compressed and then the time taken by the tissue to come back to its original state. When all of these are utilized and combined together and when you plot them, you would actually understand the mechanical properties of tissues.

So, you know the amount of force that you are applying over a given area and then the amount of deformation can be quantified with the plot what the reflected light gives you. So, in this way, using optical methods you could study the stiffness or the elastic properties of tissues.

And there are many other techniques apart from optics like I mentioned one major thing what dominates the current trend in medical diagnostics is ultrasound and MRI. I am sure you have all heard of what is MRI and ultrasound these are techniques where you use the in case of ultrasound, you use the sound waves which would flow the through your organ. And then there are waves which would actually cause disruption on to which would stimulate your organ and that stimulation and then they reflected sound waves is what is captured. So, all of this is used to understand the elastic properties of your organs like liver and you know stomach and ultrasound and MRI and majorly done for on over a larger scale like the organ scale.

So, when we are talking about cells and tissues we are talking about micron scale. Now, how do we indent them? They are very minute features and indenting or palpation is not possible just using our hands or fingers. Fine finely you know precise force needs to be applied on a very small scale.

How could we precisely get the amount of force on the samples to? In order to do this so, that this is where I had this is a point why we need to understand where micro manipulator comes into place. In order to apply a force or you know very precise scale and in and if it has to be repeatable use of micro manipulator comes becomes very easy and it becomes very handy for us and using the manipulator, you can see how precisely on a micron scale you could address, you could use them to up you could use them to precisely control the entire system say you want to indent a cell or a tissue.

And in order to indent them you cannot use the indenter say, you have fabricated a tip with an indenter and you are trying to study them. So, these indenters you cannot precisely apply the force, you cannot move them in the xyz direction a very accurately and they are not repeatable. Say you have done it once the same thing cannot be repeated, then next time.

So, how do you get this precision and that is when we use the micro manipulator. Now that you have understood how and why micro manipulator plays a major role. Let us see how to use the manipulator and study how they can be leveraged to understand the mechanical properties of tissues or it could there are even they have been used to study single cell manipulation. So, their broad range of application, for our purpose let us see how we could use an indenter and a micromanipulator to understand the biomechanics of cells and tissues.

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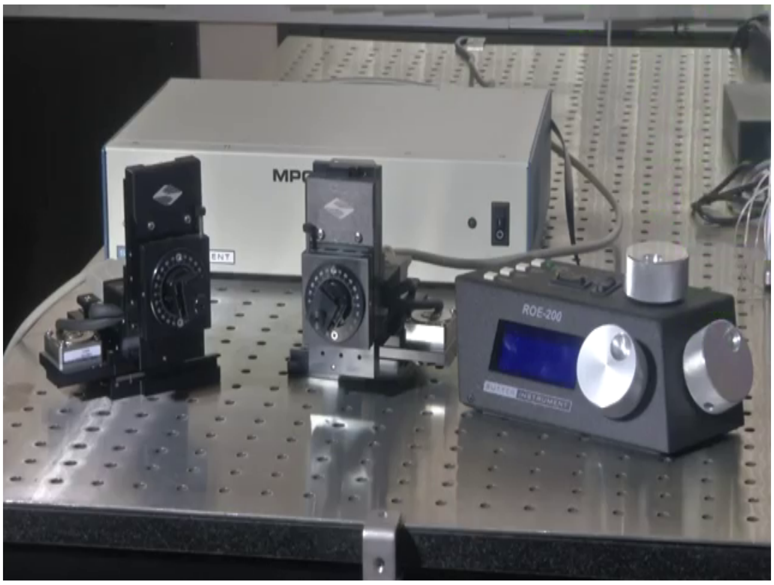

So, the entire setup of the micro manipulator is here in our workstation. So, this forms the control unit and these are the 2 arms of the manipulator and this here is the main source, the main unit which connects the control system and the manipulators each. In our case we are having 2 here. So, let us see how each of this can be used and how are they integrated all together.

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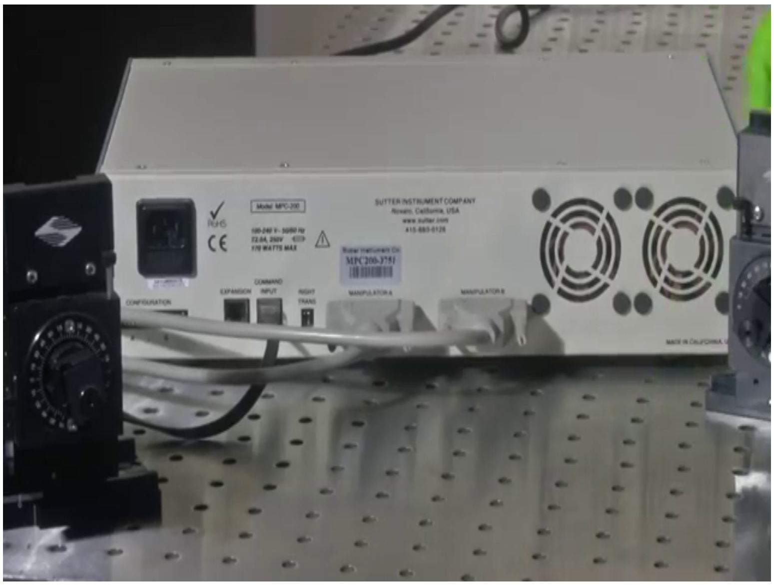

Coming to the main unit, I have flipped it around so that we could study the different components which are which goes from the main unit to the other units. So, here is your power cord and this is the configuration port A and B and here we have an expansion unit, for now the device we have 2 manipulators which are being supported. So, the expansion port is for further extension you could have further more manipulator arms connected to the unit and hence the expansion port. So, this is the command input, the RJ 45 cable which is going from the main unit to the control unit. And then the main unit has 2 ports here; manipulator A which goes to the manipulator here and manipulator B to this manipulator here.

So, these are the DB 25 connectors which are connected for communication between the main unit and each of the manipulator arm. Now that we have seen how the power unit is connected to the rest of the units. Let us see the features of the manipulator here. So, here so let us see the features of the manipulator. This is the manipulator B here, the knob which is provided here is for the tool holder. You could actually the kind of tool like I said it could be single cell manipulation or it could be the purpose of research could be indenter indentation in order to study the biomechanics.

So, all of that the indenter or the single cell that any kind of tool would sit here for example, say I will fixed this. So, this is how the tool would go in and then you could use the knob to tighten it. So, this is the tool holder and the tool holder can be rotated. There is a radial dial here and what is the precision that this manipulator could provide that is if you can see here, it is mentioned 0 to 25. It is 2.5 centimeter which is 25 mm. Each of this indicate that the entire manipulator can provide precision up to 25000 micron.

So, each micron it could you could get access to each micron change in the distance in the X Y and Z axis. So, as you can see, there is a scale here starting from 0 to 25. So, what is the precision that this instrument can give us is up to 25000 micron that is each micron can be manipulated. You can get access to each micron a control over every micron of displacement through the X Y and Z axis using this manipulator. So, this is the scale on the Y axis and here is the stage for Z axis and then behind beneath is the X axis stage.

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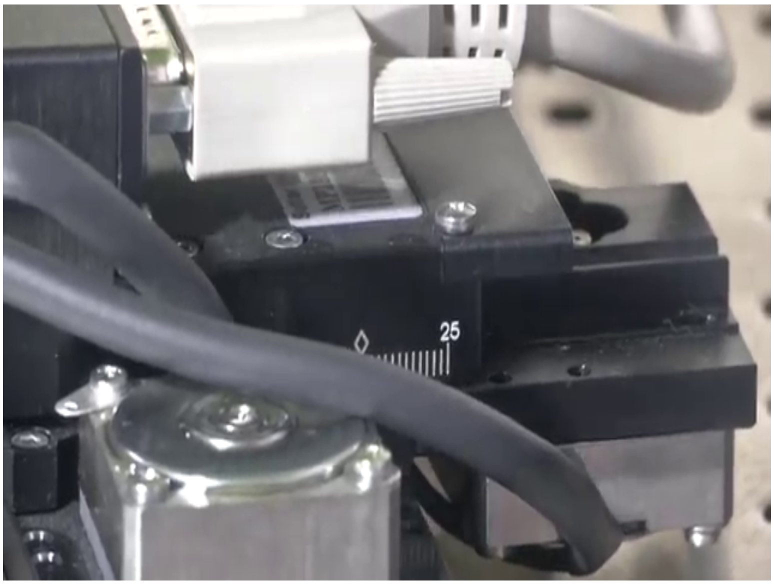

Now that we have seen the how it can be manipulated on all the 3 axis X Y and Z through various motors that are connected on each of this axis and with the similar features on other manipulator. Thus slot here also provides you with an option to connect 2 multiple indenters. So, you could customize this entire thing, the entire tool holder based on your application and purpose.

Now, that we have seen the 2 manipulators connected to your main unit. Let us see the control unit. The control unit has three knobs here 1 2 and 3. This is again for the X axis, this is for the Y axis and this is for the Z axis. The control unit again has an option here called manipulator. Here it says 1 2 3 4. So, the control unit can control 4 manipulators; in our case, we have connected it to 2. So, we have one and 2 which can be controlled using this.

So, this knob allows us to choose the manipulator which you are operating and then there is mode which controls the amount of how quickly the knob. It is about the laps between the change in the amount of rotation you give to the knob and the amount of displacement. So, these 2 are connected. Now if you want for a larger change in the now for a larger rotation say, you want only a small displacement to happen all of that control mechanism between the amount of displacement and the amount of physical rotation what is given to the knob can be controlled using the mode.

And then there are different options home stop set work position normal or diagnostic the diagnostic is mainly say it to perform the calibration for the device. Work position the feature of this entire setup is you could save your work position say you have used the device and you have a test sample and then you have indented at X Y and Z at some position. And you could always save that xyz position using this option here work position.

This can be used save the values of X Y and Z and it could always you could go back to your home position which is nothing, but 0 0 0 on the X Y and Z scale and always return back to your previous work position. So, let us see how the entire setup can be used. Let me connect the power cord, switch it on and once its ready. I will demonstrate how each of this can be manipulated. I have connected the power cord, let us turn the main unit on. So, this is the front the display and what you can see is drive a which shows that the manipulator A, it is set to manipulator A.

The led here also indicates that the current working manipulator is the first which is nothing, but a and then mode 0. Let me explain more about mode and you could see in real how you could manipulate the relation between the physical rotation and the amount of displacement. And then the display also shows X Y and Z, Y is set to 0 X is also set to 0. So, in this case this is X, this is Y and this is Z. Now that you seen X Y and Z are all set to 0.

Now, say I would like to switch from manipulator A to the second one. Now this here the second LED glows which indicates that the second the control unit is now displaying the XYZ position of the manipulator which is the second manipulator in our case the B. So, as you can see we have only 2 active manipulators connected to our control system, the third and fourth remain an active and even you could forcefully the switch only happens between 1 and 2.

Now, let us see when it is connected to manipulator A and X Y Z positions are 0. Let us see how mode function of X can be used to control the entire movement. So, there are 10 modes; 1 2 0 1 2 3 4 5 6 7 8 9 as you can see there are 10 modes. So, what does each more do say you are in mode o and I try to change X position. So, even the I just my slightest movement is causing a lot of displacement as you can see the slight movement is causing a lot of displacement on the X direction.

Now, what happens if I change to mode 9? Let us see I use the same X position and then try to rotate. As you can see I have been rotating for almost now it is quarter distance has been covered and this is half of it, three-fourth and then one and now if you see there is a change. So, the entire circle is now this facilitates you to give this 1 micron change in their distance. So, this can give you more precise control over the distance manipulation of your stage. There are intermediate stage which can be explored for different purpose.

Now, that we have seen how each of this knobs can be used to control the X Y Z position and the functionality of mode. Now let us say we have set X Y and Z to some values and then save it as work position. Now this would be saved as work position, you could always go back to home and then this is the home button and then I come back to work position. As you can see you could see the values the previously the set values are being displayed. The previous one what I did was not saved, but this was previously saved work position and then I went I just turned moved to home and then come back to work position and you could see the saved position.

Now, let us see the manipulator A how the setting would affects its movement in the X Y and Z direction. So, this is your manipulator A, now let us say I click on home. Like you can see home is nothing, but 00 and 0 if you observe this is back or in all the direction X Y and Z in all direction the manipulator has written back to home position. And now if I switch back to my work position like you could see it is moving in all 3 directions to the set value here the value which is saved here.

So, this is very this comes very handy when you want to save your work position go back and then when you return you still have the position saved. So, it would not it would really save a lot of time while you do your research and it gives more precise results as you want to work on the same sample at the given location. Now that we have seen how these manipulators can be moved in each direction on a micron scale in X Y and Z. It gives us a fine control over movements in all 3 direction.

Now, let me conclude with an application. So, where now that we have studied so much of micromanipulators; I have already told you how indenters can be used on these manipulators, indenters with sensors and then you could manipulate its location around the samples cells and tissues which are micron scale. So, this gives more precise control over getting studying the electromechanical features.

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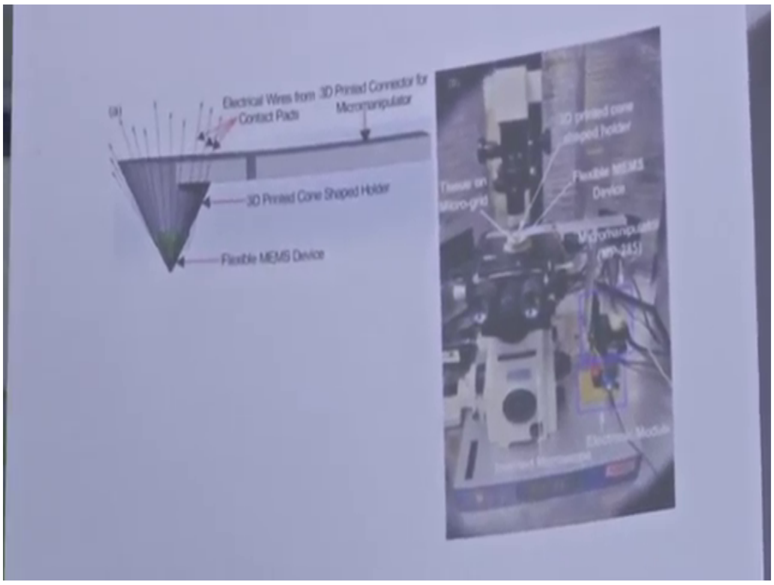

So, this one example is the sensor array which was again explained to you by Professor Hardik. Here this is your array of sensors, this is a flexible MEMS Micro Electromechanical Sensor which has 2 folds. It serves it is an electrical and the mechanical sensor; more details would have been covered during your coursework. So, this was the electromechanical sensor was designed and fabricated to study the electrical and mechanical properties of tissues.

Mostly it was tested on cancer breast cancer tissues and they were using this you could clearly understand that there is a change in the electrical and mechanical properties when you compare the normal with the malignant tissues. So, the now this is the sensor and how the sensor this is a 3D printed cone on which the sensor is mounted. The strain sensors which is not clearly visible using the image, but I am sure this was clearly demonstrated during your coursework.

So, there are strain sensors which are used to do the mechanical characterization and then that tip had these SU8 pillars with gold coatings which did the electrical characterization and this is mounted on a 3D printed cone. And there is the cone standing this entire cone setup is on a manipulator, the micro manipulator in this case. Like you see the manipulator is usually integrated with a microscope this we have understood the functionality, but otherwise in practice they are integrated on a microscope.

As I mentioned we would be working on a micron scale this is a cell sample cell or tissue samples and in order to indent them in the right position, you would use this microscope to do the analysis and then here is the cone structure which is being supported on a manipulator. So, this is one such application where the sensor array is mounted on 3D printed cone and the entire control over the movement is done using the micro manipulator.

Hope the entire demonstration about the use of micro manipulator would help you understand the purpose of using the manipulators for fine precision, control, repeatability all of these advantages is why we use micro manipulator to do the indentation or in otherwise you could also use it for single cell manipulation, multiple purpose. So, these can be used for a fine control over your movements while you do your research. So, that was the detail study about the use of micro manipulators.

Thank you.