Mathematical Aspects of Biomedical Electronic System Design
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Lecture No. 11
Electrical properties revisited Thermal and Mechanical Properties of Tissues: An Introduction

Welcome everyone, today we will have another session of the course mathematical aspects of biomedical electronic system design. In a previous lecture, we have seen about electrical properties of biological tissues.

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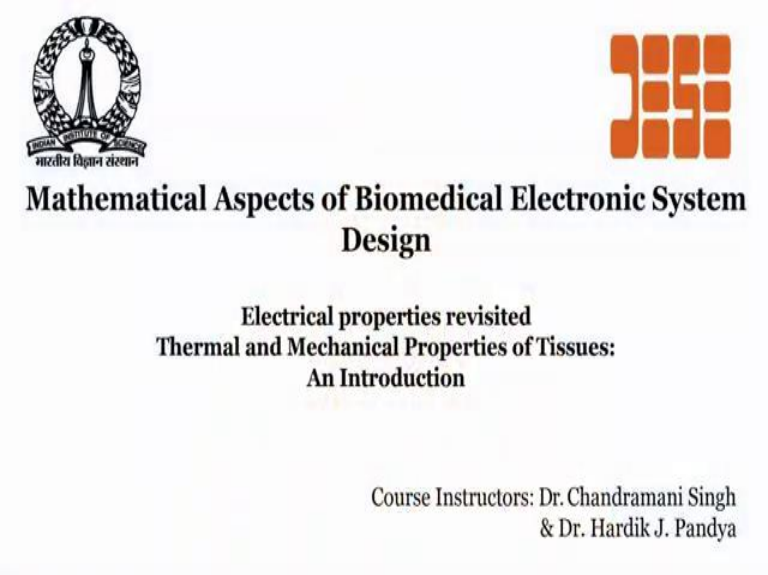

How tissue organization happens and what are the basic functional electrical equivalent model of a cell. So, today we will revisit that a bit briefly and then explore further down that road of electrical properties for a brief duration, then we will take an interlude and we will go into thermal and mechanical properties of tissues.

So, this is idea is to give you a flavor of the modeling on and the mathematical equations involved in electrical, thermal and mechanical properties of tissues. The main concepts of it has already been covered by the course instructors, Professor Chandramani Singh and Professor Hardik J. Pandya.

Here, what we are trying to do is to take you through a deep dive into the equations that are involved, give you an intuitive understanding of how these equations come about. Even though

you got a top-level understanding of the equations from the main lectures. Here, we take a deep dive and we, we run you through step by step to understand how each individual part of an equation, what is the insight behind it, what is the physical significance of that part.

And so that later on, you do not even actually have to remember the equation, if you just think about what contributes to different contributors to the property, you can actually write up the equations that should be the final aim of you trying to understand mathematical modeling, because things have to come intuitively, fundamentally, most of the things understanding to understand the equations and understand the phenomena, rate, rate of reaction, everything fundamentally comes down to mathematics.

So, can, how can we intuitively bring out the mathematics is how we are going to cover. So, that is the main agenda of this lecture. So, what we will do is we will revisit the electrical properties and then we will go into thermal and mechanical properties of tissues. Let us get started.

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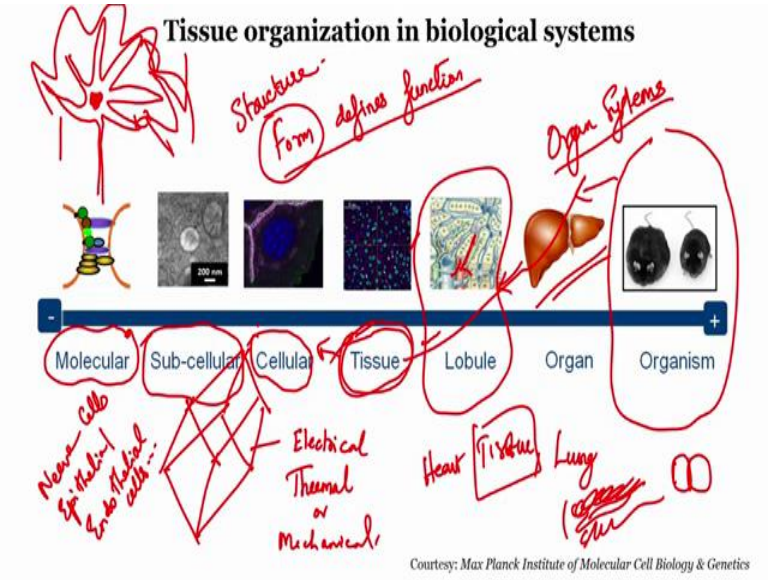

So, as a brief recap, we have seen the different levels of tissue organization. So, we know that we have seen that organism is there and then organism is composed of organ systems, organ systems are then composed of organs, we have covered all this last time, and then organs are supplied nutrients by the blood, blood vessels and the lobules.

So, this is the what he called the power delivery network of the organs, because the vascular network only gives the nutrients and oxygen all other supplies. And then the vascular network

basically gives the nutrients and oxygen to the tissues basically. So, tissues actually make up the organs the organs and the organ system.

The tissues can be of different, different types we have seen, heart tissue is different from brain tissue, which is again different from lung tissue, skin tissue, all are different, they are different in how the cells are organized, they are different in how much cells are there per unit area, the different in the shape of their cells. And they are different in the amount of collagen matrix, or the extracellular matrix that is there in the tissue organization.

So, as we have seen previously, tissue architecture, tissue micro architecture, three dimensionally, how are the cells and other components of the tissue arranged, this tissue architecture, micro architecture is very important for us to finally be able to model the a different physical properties of the tissue, like its electrical, thermal, or mechanical properties of the tissue, for us to understand how the tissues will respond to an electric stimulus, or how they will respond to an applied heat, or they how they will respond to an applied mechanical stress, we need to understand actually how the tissue organization is, that is why we covered that in detail last time.

So, tissues are again, in turn made up of cells. Cells can also be different, different types of cells are there, nerve cells, epithelial cells, lot of different types of cells are there, epithelial cells, endothelial cells, So, different types of cells are there and the shape of the cell define its function. So, form defines function is a, is an important concept in biology form, or the structure, structure dictates the function actually, form defines function, a keep it in mind.

So, that is why nerve cells are actually shaped like this, I think if you have seen nerve cells are shaped like this, nucleus will be there at the center. So, this is because, they can actually interact with other nerve cells, like this and synaptic joints can transmit the electric signals for neural conduction. So, that they will have maximum surface area for neuro conduction with other nerve cells, that is why their structure is like this.

So, form this form defines the function, because the form is like this, it is able to function as a nerve cell. So, this is a brief, brief interlude. So, basically what is it tissues are composed of cells and cells inside are composed of the different sub cellular components, which we have seen the nucleus, cytoplasm, cell membrane etc, and other organelles inside the cell. Then we have the

molecular aspects of the sub cellular components, which are the proteins and the proteins, other small molecules like carbohydrates etcetera.

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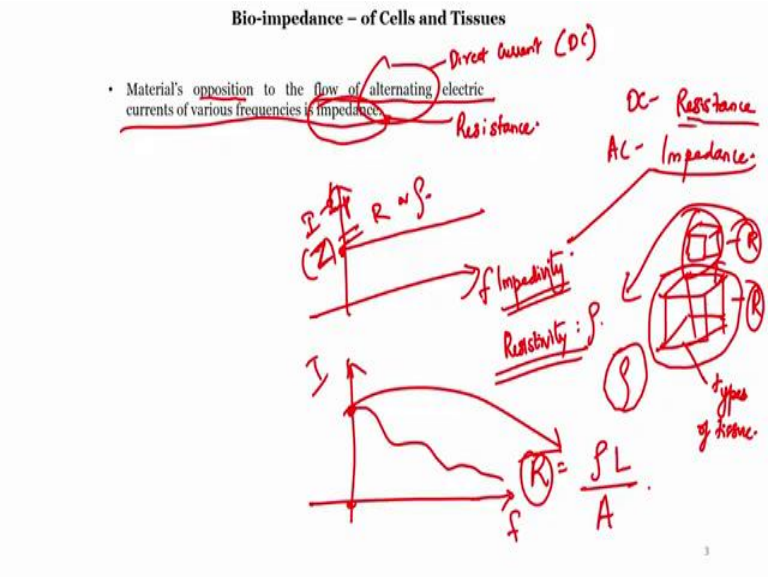

So, next what we will see is, we will just quickly revisit the bio-impedance, that we talked about off cells and tissues. What is basically impedance, again we will see basically impedance is a materials opposition to the flow of alternating current of various frequencies is impedance. So, if this alternating current is direct current, which is DC, we can call this impedance as resistance, all of you are aware, I think. So, DC it is called resistance and AC it is called impedance.

Now, there are specific values for this, resistance is a bulk value, it is like if I take 1 centimeter by 1 centimeter by 1 centimeter tissue, it will have one resistance and if I take a 5 centimeter by 5 centimeters by 5 centimeter tissue, it will have higher and it will have different resistance, mostly it will have a lower resistance, because resistance is depend on dependent on the area of cross section and length. By then how do we compare these two?

We compare these two by this specific property, which is resistivity, which is ρ, and impedance the specific property is called impedivity. Why is it called a specific property? Is called specific because, it is specific to the type of tissue and does not depend on the dimensions of the tissue, it does not depend on a dimension of tissue, that means a one centimeter by one centimeter one centimeter tissue, as well as a five centimeter by five centimeter by centimeter tissue will have this

reasonably same resistivity. Because it does not depend on the dimensions, that is why it is called a specific property, because it is specific to that tissue type.

Now, how do we get resistivity? This is basic class tenth physics ρ, or resistance, we can get resistance R is given by

$$R = \rho \frac{L}{A}$$

like that impedivity also you can calculate, I we can note it in like in some whatever way you want,

$$I = Z \frac{L}{A}$$

it is a rough equation, we need to actually take separate out the imaginary and real parts of the impedance and then do the impedivity calculation. Otherwise, by default impedivity will be a complex quantity.

Because as you know, there is phase information involved and capacitance inductance effects will be there. So, there will be both real and imaginary part in the impedance, like, like

$$R + \frac{1}{j\omega C}$$

Gωj, lot of factors like that the Lω inductive, inductive reactance it is called inductive reactance X_L, this is called capacitive reactance X_C. This is just the resistance R.

So, that is how impedivity is different from resistivity, but the idea is that impedivity is a more general term, we can always derive resistivity from the impedivity value. Because what is impedivity? Impedivity is the specific property of the opposition to the flow of current, normalized to the basically specific property means it is normalized to the dimensions as a function of frequency, frequency impedance.

Now, at zero frequency whatever impedivity value we get ideally that should be equal to the resistivity correct, because at zero frequency the capacitive reactance, inductive reactance are not taken into consideration basically, basically the capacitor if there is, there is indeed a capacitance in the path, it will become it will act like an open circuit.

So, the impedance values, zero frequency value is the resistivity basically, provided the circuit does not have any capacity components. Let us say I am taking a pure resistor and I am taking an impedance spectroscopy of it, my impedivity value will not have a relationship to frequency. So, the impedivity for a purely resistive component will be a straight line, it does not depend on frequency, it has a constant impedance value, which is equal to the resistivity, resistance, or resistivity, if depending on whether you are plotting impedance, or impedivity here.

So, that is about resistivity and resistance. So, basically the resistance to flow, just wait a second let me clear the screen. So, basically, the resistance to the flow of alternating current is basically called impedance and to direct current is called resistance.

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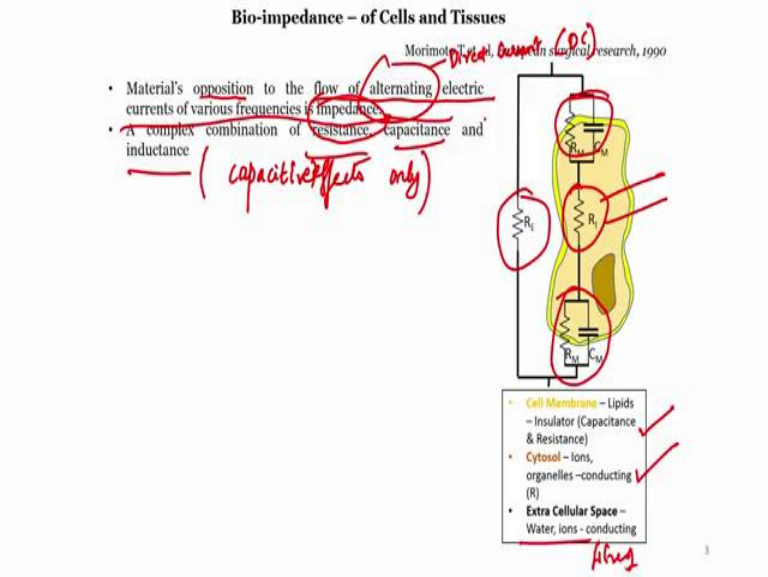

Now, basically a impedance is a complex combination of resistance, capacitance and inductance. But for sense of understanding, usually biological material do not have inductance, they mostly have capacitive effects only, they mostly have capacitive effects only.

Now, this is the electric equivalent circuit model that we have seen last time. Basically, you have the cell membrane that is modeled as a combination of capacitor and resistor, the intracellular space model as a resistor and again kept a membrane model as the resistor capacitor combination and the extracellular space model as a resistor, we have seen a justification, or explanation for why this model comes to be you can refer the last lecture and you know that the cell membrane consists of lipids and insulating components.

So, it acts like a capacitance and cytosol, or the cytoplasm has mostly ions organelles, so they act as conducting area and extracellular space is model mostly consists of water ions and the fibers, collagen fibers, as a result of is this is also mostly conductive.

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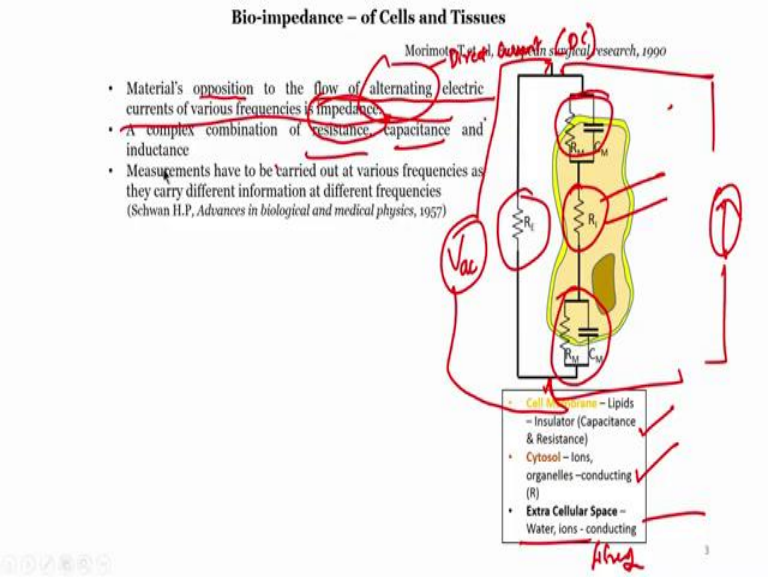

Now, measurement, measurement can be carried out the impedance measurement can be carried out across frequency, like we can, how do we take do this measurement, we connect a supply to it, to do the measurement, if the supply is a AC supply, we can actually do and maybe if we measured the impedance separately, or measure the current injected into this circuit, or current consumed by the cell to drive this voltage, we can actually get the frequency dependent impedance value.

So, that is what we have told here, measurements have to be carried out at various frequencies as they carry different information at different frequencies.

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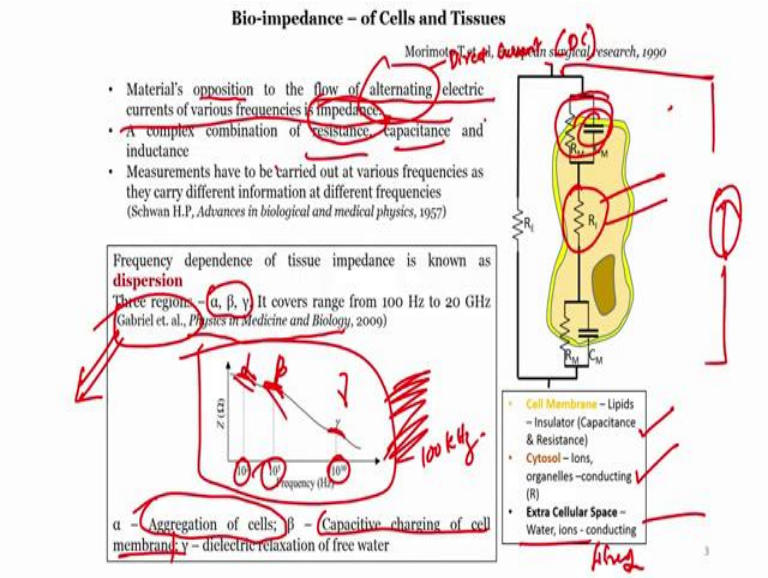

So, this different information and different frequencies is usually called dispersion of the tissue. What that means is? At per specific frequencies, the impedance spectrum has very characteristic turns like this. And several factors contribute to these major turns in the spectrum. These are called α, β, γ dispersion; α, β, γ dispersions. So, it covers range from 100 hertz to 20 gigahertz, several giga, giga hertz.

Now, what causes now what causes this dispersion? So, the alpha dispersion is majorly contributed by the cells coming together and the cells, the cells in the tissue contribute to the α dispersion. Now, at β dispersion, the β dispersion is happening at higher frequency. So, it is happening at higher frequency, because the frequency is like 10^5, it is like 100 kilohertz. That means at high frequency, if we imagine the capacitors in the circuit are constantly charging and discharging.

So, the dispersion is because of the alternating flip current and frequency of the alternating current. So, they are constantly charging and discharging. Now, this that is why the β dispersion is contributed by the capacity charging of the cell membrane, because as we have seen the cell membrane has a basically a capacitor in type C_m, that is why the capacitor in right C_m, that is why the capacity charging of cell membrane.

Now, at very high frequency that is like in gigahertz range, the contributor is not really the capacitors, because it is so higher frequency that there is no time for the capacitor to charge and discharge, because by the time it charges, the first cycle the next cycle comes. So, it does not play

much role, what plays a role is a dielectric relaxation of free water molecules in the cell and in the extracellular space. So, dielectric relaxation is what happens and that is what contributes that, that is what contributes to that γ dispersion of tissues. So, this α, β, γ dispersion is specifically for tissues.

And this was reported in a very nice paper in the journal physics in medicine and biology by Gabrielle et. al, Gabriel et.al, in fact you can go and read Gabriel et. al has in fact three, four very seminal papers, where they have discussed about the electrical properties of the cells and tissues. They are the they have done a very elaborate study, where they have tried to measure the electrical properties of different types of cell types, different tissue types, or different qualities of blood everything they have tried to measure.

So, they have published a series of articles, this is one such article and which talks about the existence of dispersion in the impedance spectra of biological tissues. This what you see is the impedance spectra of biological tissues and the existence of dispersion α, β, γ dispersion, which we have just covered. I hope this is clear. And please ask your questions in the forum, if you have any doubts in this section.

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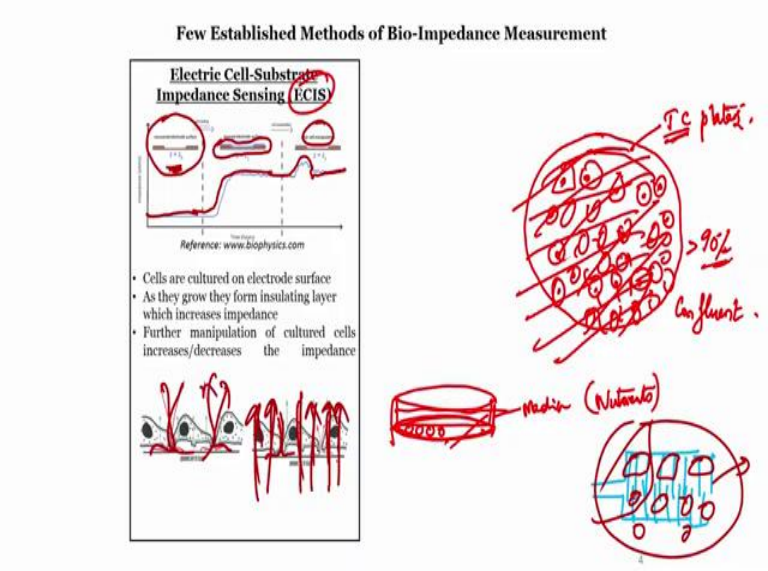

Now, we have seen basic concepts we have seen of measuring the electrical impedance of cells. But how do we like what are the, what is the practical application of such an impedance

spectroscopy? How do we use that? So, there are several technologies that are there available both as products and in research, we will quickly go through them now.

So, one is what is called an electrics, electric cell substrate impedance spectroscopy. So, what that is done is to measure the confluency of cells. So, what is confluence? Let us say I take a tissue culture dish, tissue culture dish is a 2D plate, it is like a plate like this, where the bottom layer, it is not a 2D plate, it is a 3D plate, but the bottom surface we have forms a 2D layer, where that cells from the tissue are removed, the matrix everything is removed, and the cells are asked allowed to grow on the surface.

So, it will be like this. Cells are allowed to grow on the surface of that dish. Now, what is confluence? Confluence is when more than 90 percent of this area is occupied by the growing cells. So, first when we put the cells, they may not be that many in number, but then because when for culturing the cells, we also had something called media, which is basically food for the cells, or the nutrients for the cells over time, they take the nutrients from this media and the cells will grow.

So, when it is the cells occupy most of the area of the petri dish, or the tissue culture dish, or the TC plate, it is called TC, TC is tissue culture, of tissue culture plate, then it is called confluence, greater than 90 percent area is occupied, it can be called confluent cells. Now, how does ECIS help us in here, so what ECIS does is basically measure the impedance of so in ECIS what will happen is, below this culture, there will actually be electrodes a lot of electrodes, let us say in the culture dish, there are a lot of electrodes, inter digitated electrodes will be there.

And the cells are asked to allow it to grow, cells grow on top of these electrodes like this. So, that means when the cells occupy a lot of area of the electrode, the impedance will obviously change. That is how we can monitor the confluence of cells. Apart from that, we can actually manipulate the cultured cells by let us say we try to scrape out some cells from here, for sub culturing, then the impedance will drop and more than that as we have seen, here you can see here, see this is shown here.

So, this is an electrode that is uncovered with the cells, there is no cells impedance has one baseline value, which is this. Now lot of, lot of cells obtain confluence they cover most of the area of the electrode. So, the impedance increases. Now, let us say I do some manipulation by adding

something, or removing some cells, there will be a small perturbation in the impedance and then it goes back to us now another steady state, that is the cell manipulation that we are talking about that we told just now.

Now, that is how ECIS will be useful. And we have seen how high frequency, low frequency measurements actually bypass a cell and go through the matrix and how high frequency measurements will actually basically measure the properties from the cell, that is what is shown here. This is low frequency measurement, these, these parts dominate in the contribution to the impedance. And in high frequency measurement these parts contribute through the cell part contributes.

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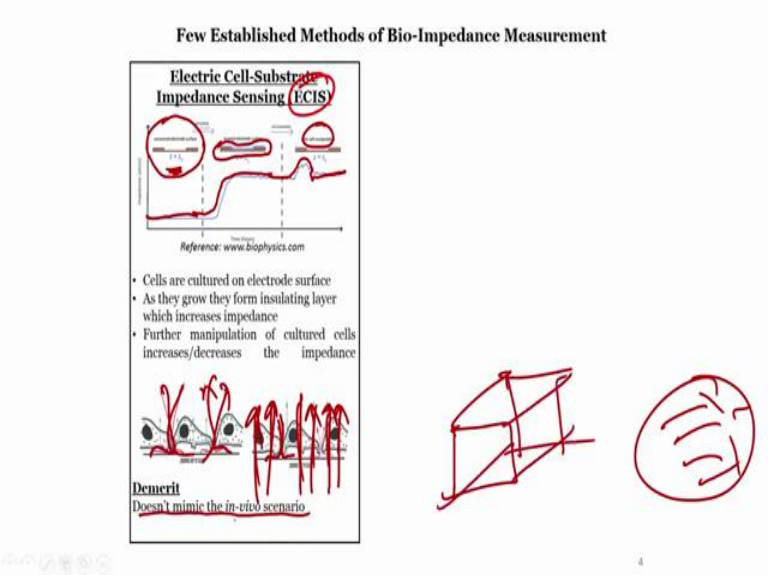

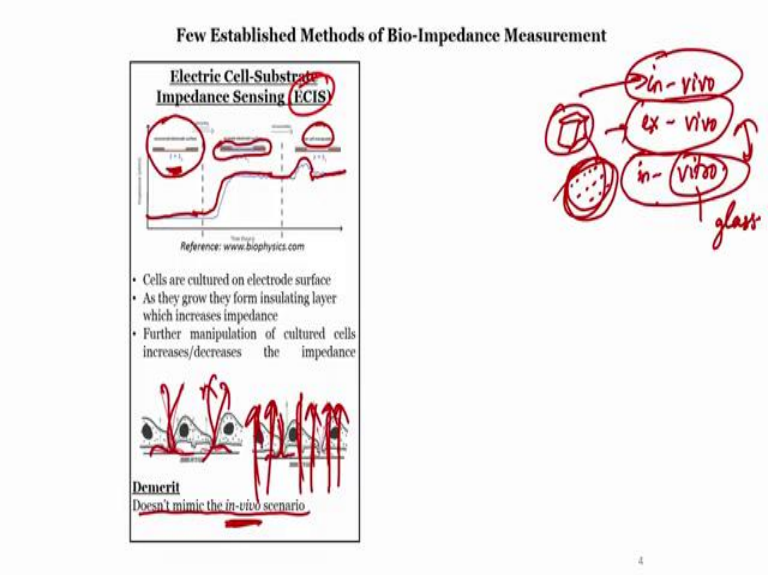

Now, that is one system that is ECIS, it is available in market and many of many labs use this for different applications. So, seeing confluences is one application that I talked about that a lot of other applications. Now, what is a demerit as we have seen, what is the demerit with such a system as we have seen, it is a two-dimensional culture of cells, only one dimension is there, what actual scenario the tissue is three dimensional.

So, we are not actually measuring that. So that is why it does not mimic the in vivo scenario. What is in-vivo? In vivo means it is inside the body, it does not mimic what the scenario inside the body, it is an ex-vivo scenario, there are three things, in vivo, please listen to this carefully, ex-vivo, in-vitro. In-vivo is simple, it is basically inside the body, ex-vivo is you extract a tissue and it is kept outside the body, in-vitro is when you crush the tissue, take the cells out and make these cells grow on a plastic, or glass dish surface.

That is why it is called vitro, vitro in Latin, or I think I am not sure the origins Latin or Greek, vitreous means glass. So in vitro means something in glass, that is why the cells have to be cultured, that is called that kind of situation is called in vitro, people get confused between ex-vivo and in-vitro, usually, this tissue culturing is not called ex-vivo, it is called in vitro cultivation. But you can assume that in vitro is a subset of ex-vivo, but this kind of measurement directly with tissue is not in-vitro, it is only ex-vivo.

So, I think it is clear for you in-vivo, ex-vivo, and in-vitro, in-vitro, these are the main three types of studies that can be performed. So the ECIS system as it is very evident. Let us not mimic the in vivo scenario, because it is measuring a two, two-dimension layer.

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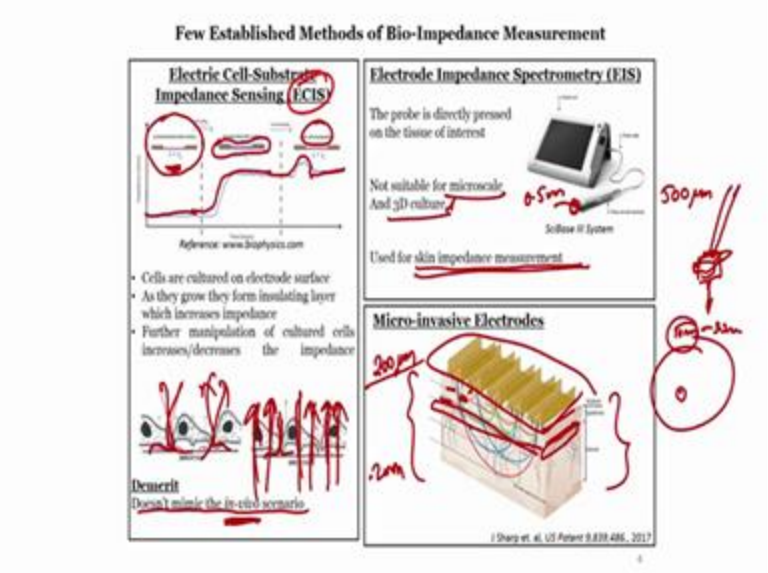

Then, then, next one is electrode, electrode impedance spectrometry, this is the basically like an impedance probe, where you directly attached to the tissue. Let us say I take a tissue piece, and I put the probe like this on top of the piece and measure the impedance. So, we are not actually measuring across the tissue, but we are just touching it and measuring the let us say, sheet impedance, or the sheet resistivity the surface impedance of the tissue.

So, that is why it is, it is more commonly used for skin impedance measurement. So, you can get the skin impedance and by form skin impedance people are able to detect early onset melanoma and all and see if any, any skin cancer possibility is there to start off and this is not actually suitable for micro scale or 3D culture, because the tip is quite big, you cannot go and take this probe and put it inside a cell culture dish and try to measure, that is not possible.

Because this tip is very large, cells are like only around 10 nanometers in dimension 10 to 30 nanometers in dimension, this tip is clearly more than at least 0. 5mm, or 50, 500 micro meter in dimension. So, it cannot be used in the micro scale, or for 3D cultures that is the shortage of electro electrode impedance spectroscopy, but it still but it is a very nice technology.

Now, the same electrical properties, people have used as micro invasive electrodes to like measure record from the nerves, nerve signals and for other applications. This again from a US patent application, but what does micro invasive electrodes do is? They, they, they are fabricated like a patch of electrodes, this is becomes a patch.

Let us say this is your skin, you put the patch on your skin, then you will be like oh so many electrodes are there I will get pain. It will be so painful. No, it will actually it will be it is almost painless procedure. This is because the nerves that cause pain to you, when something like this sharp needle pricks you are actually located as specific distance below the top surface, I have not sure about the exact distance, but it is located some distance below.

Let us say we assume that, this is located around 200 micrometer, below the skin surface, let us assume, or 0. 2 mm, then these micro electrodes do not reach this near the end here, somewhere in between. So, that you and when the micro electrodes do not actually touch that nerve, you do not get the pain. And you can still do what you want to do with the electrodes. So, that is why it is called micro invasive electrodes, because they are not really painful, because they do not touch the nerves, which are a little bit down. So, that is the interesting application of these technologies.

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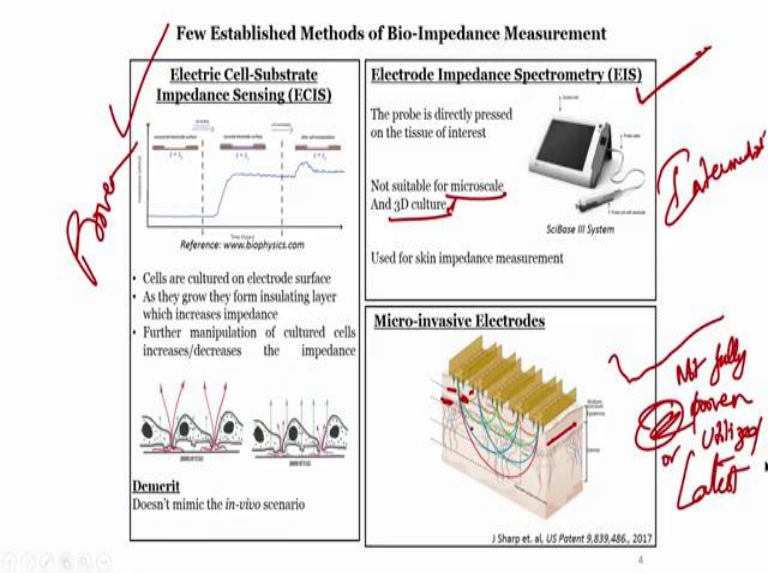

So, we have seen electric cell surface impedance spectroscopy, which is a very well established technique, and it is available in market and people use it very much for different applications. So,

this is a very proven technology. Electron impedance spectroscopy has also been there for a long time, but it is used is only being explored now, not fully utilized.

And this is purely a research, in research and people are trying to do this, this is the latest technology, this is a proven technology. And this is somewhere in between, intermediate, this is the latest, but not fully proven, not fully proven, or not fully utilized. So, we wanted to show you the different spectrums of equipment that are there, that are used for bio impedance measurement, that is why we went through this part.

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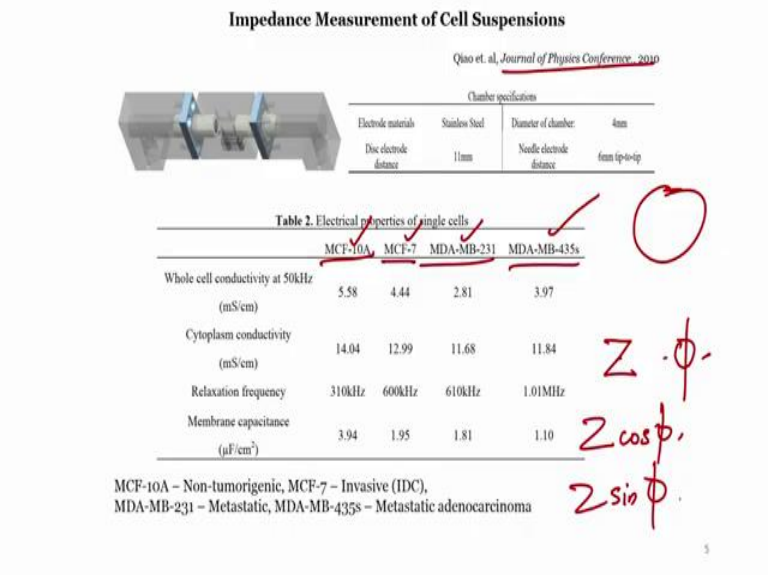

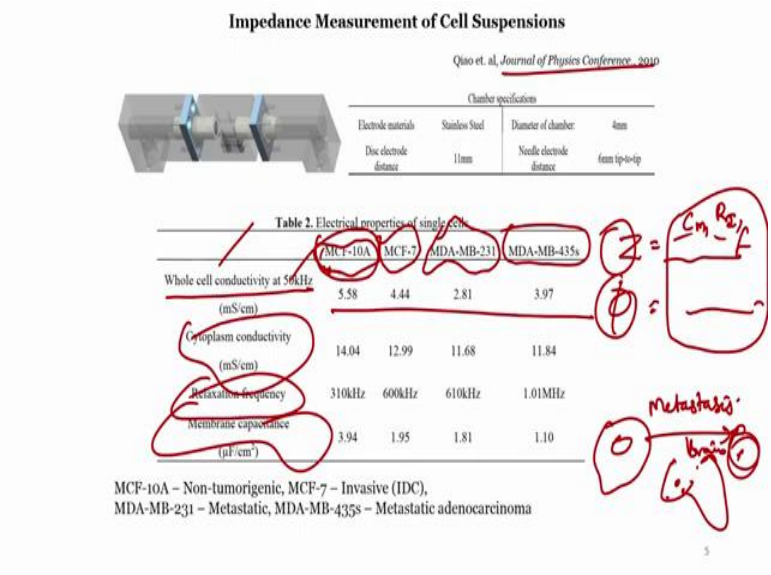

Now, the obvious question that you will ask now is what would happen if I am able to measure the individual impedance of a single cell? So, people have done there are, there are, there are different conference publications, this is from one such publication, where they have what they have done is, they have made a setup, which can actually pass single cells.

And they are they have tried to measure the specific properties of a single cell from different cell lines, these are cell lines, MCF 7, MCF 10 a, MCF 7 MDA-MB all these are all cell lines. What are cell lines? Cell lines are perpetually going cells, that were what one point extracted from a cancer patient and they, they have they were continuously go and repeatedly. And there, they can be grown in the labs for performing studies, instead of directly relying on patient samples. That is why they are called cell lines.

So, these people have tried to measure the specific properties of a single cell by measuring its bulk impedance and then resolving it, when we measure the bulk impedance. And then we get the phase angle also then $Zcos\varphi$, $Zsin\varphi$ and are all we can do to get the individual contributing components.

Or alternatively, let us say we measure the impedance of a single cell. If you measure the impedance of a single cell, and we know the mathematical formula for the transfer function of the electrode and the cell, or cell interface, then we or transfer function will have some frequency dependent terms and phase also will have some frequency dependent terms.

And we measure the transfer function and offers Z and φ, we can actually fit for this model and get the circuit parameters like C_m, R_I, etcetera. That is what they have tried to do, they have measured the impedance and phase and then they have tried to estimate the individual circuit parameters, circuit parameters are the what we have seen till now like membrane capacitance, membrane resistance, intracellular resistance, extracellular resistance, etcetera.

So, that is what they were trying to do see, they have measured whole cell conductivity that is a conductivity, the whole cell at 50 kilo hertz, that mesh that, that measurement is there, then from that whole cell conductivity, they have tried to resolve the cytoplasm conductivity, they have tried to resolve the relaxation frequency, membrane capacitance, all these things they have tried to resolve from that data, which is a very interesting way of looking at it.

And in the cell lines also, this MCF 10A, is a normal kind of cell line, it is not and does not have cancer origins, MCF 7 on the other hand, is a invasive form of cancer, a cancer type that is used to

study invasive cancers, MDA- MB 231 is next level, where it is an invasive cancer and it is a metastatic cancer, because it has very, very strong metastatic potential by metastases, what we mean is, the ability of the cancer cells to migrate from it so its original place and go somewhere else and form a tumor there. Once its tumor is found that is called that the, the what has happened is called metastasis.

Let us say a patient with breast cancer. If the cancer spreads from the breast to the brain, it is called brain metastasis of breast cancer. It is still breast cancer, but it is with a brain metastases. Brain metastasis is means, the breast cancer, malignant cells have moved to the brain and formed a tumor there. So, MDA-MB 231 and MDA-MB 435 are metastatic cancer cell lines, so that we can study the metastatic properties of cells, MCF 10A, is a normal cell. So, that we can study the properties of normal cells. And MCF 7 is a invasive cell line, but not really metastatic. So we can study how invasive cancers behave.

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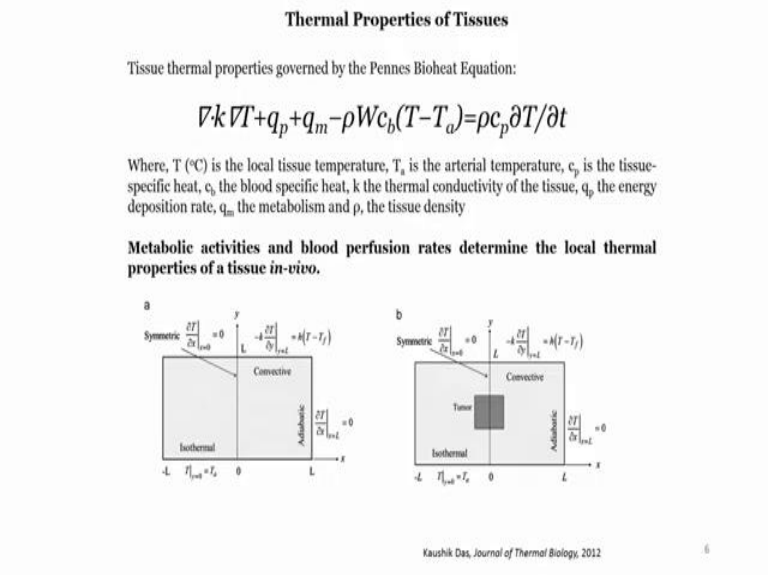

These are different interesting aspects of impedance measurement of cells, and cell suspensions. And I think we have covered quite extensively. So, that you can get an intuitive understanding about how these things are measured, and how they come to be. Next, we will go to the thermal properties of tissues.