Mathematical Aspects of Biomedical Electronic System Design
Professor –
Indian Institute of Science, Bangalore
Lecture - 24
Thermal properties of a Tissue and Cells

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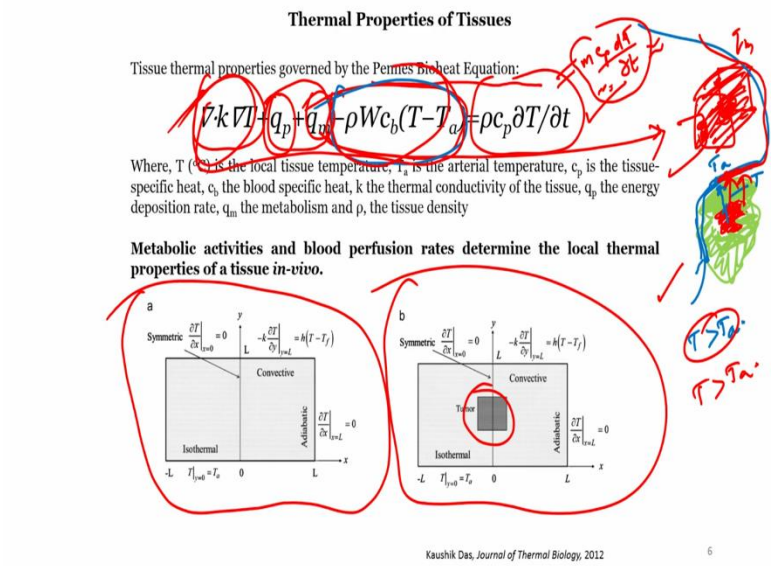

Welcome, everyone. As we all know in the previous TA session, we stopped at understanding the different components of the Pennes Bioheat Equation. What we will do now today is to quickly revisit the Pennes Bioheat Equation to recapitulate what all components were there; and how did the equation come to be. And then I will quickly run you through two specific used cases. As you understand this is a TA session where we look at specific use cases. The main core of the topics have been covered by the professors for the course.

So, this, in this TA sessions we are trying to introduce you to specific examples where you can apply these equations and help you with a deep dive into the mathematics, and the rigor involved in mathematically modeling a biological system, biomedical system. Because this course is all about mathematical modeling for biomedical systems; but it is not all fancy like biomedical system, you fundamentally it comes down to many rigorous equations. And we need to be able to intuitively write down those equations given a scenario.

So, first today our agenda is that first we will revisit the Pennes Bioheat equation, understand what are the, quickly understand again what are the individual components of the equation. Then what

I will do is, I will run you through how can you thermally model a tissue; tissue, tissue interface in-vivo tissue. And then what will happen if there is a tumor tissue, tumor inside the tissue. So, how do we model that? What are the different interfaces that we will cover today?

And then we will look at an example from a literature from a team in South Korea, where they have tried to measure, it is a very interesting study; they have tried to measure the thermal conductivity of single cells, which is very very challenging. So, we will understand what are the challenges in that and how they have tried to measure that. This is our agenda for the day, now let us start.

So, you have all seen Pennes Bioheat equation. It is different from the normal Fourier law of thermal heat transfer; because there are some additional corrective terms that will help us better estimate the thermal conduction. So, in this what are the different terms? There are this q_p q_m term is there, which we have seen. This is heat deposition rate and metabolic heat generation rate. Basically, q_m is a metabolic heat generation, q_p is a heat deposition.

What does it mean? I am quickly telling q_m is the heat generated because of the metabolic activity happening inside the tissue. Heat generated because of the metabolic activity happening inside the tissue that is q_m; and q_p is any heat that is given to the tissue through some external media like a coil connected to the tissue. Then $\nabla . k\nabla T$ or $k\nabla^2 T$ or $\nabla . k\nabla T$ is the thermal conduction inside the tissue, given a, given a local spots of heat generation are identified like q_m and q_p.

How does the heat evenly distribute through the tissue; that is this term. It defines the conduction of the heat throughout the tissue and this term is coming from blood perfusion. How does the heat get taken away by blood perfusion; that means if there is a metabolic heat generation area site inside the tissue. Let us say this is the heat generation site and we have the full tissue here.

Let us say this is a tissue and this is the heat generation site, and let say we have a blood vessel going nearby. I had covered this earlier, but for sense of completeness I am covering it again. So, there is a blood vessel going here; this heat gets transmitted through conduction to this interface. And from here how does the heat gets transmitted through the blood; that is that how do you model that?

That is modelled through this, this part of the equation which is $\rho\omega c_b(T - T_a)\omega$ or w. Here T_a is arterial blood temperature, arterial temperature, and T is the temperature of the tissue. So, for any thermal conduction you need to have a temperature gradient; so, this will be the temperature of the tissue T, and this will be the arterial temperature, T_a. And most often T will be greater than T_a; so, the thermal gradient will be this side.

So, most often T will be greater than T_a, not most of all in all cases T will be greater than T_a, provided there is a heat generation site. So, there will be a heat flow from here to here. And this heat flow will then, heat up the blood, blood that is flowing; and that blood will take the heat to the rest of the body. This way terminal transport through the tissue also happens; this is that term.

And this right-side term is how effectively how all these competing factors contribute to the increase in the tissue temperature. This is the, another form of the mc_pdT equation, divided by time ∂t; so, this is like a power per time change in temperature, per unit time change in temperature. Or how does it happen? But, this how what are the things, what all factors contribute to this is what we have seen in the Pennes Bioheat equation.

So, it is a very important equation to model the bioheat parameters. So, let me just clear the screen once. So, we have seen the Pennes Bioheat equation, different components of it. But, till now we have only seen the mathematics of it; we have not seen practically how it will be applied. So, here we will try to do that.

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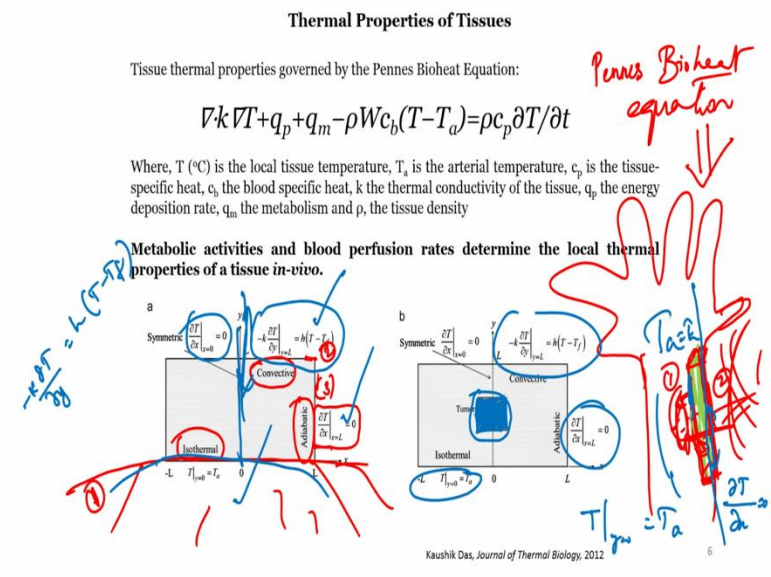

Now, that we have understood the Pennes Bioheat equation; let us see how we model or understand a tissue section. Let us take, let us take an example of a tissue piece on top of the skin. Or, you can say we are looking at thermal conduction in one layer of the skin like this. Let us say this is our arm, let say this is our arm, and we are trying to see the thermal conduction in this cubical volume of our hand; that is what we are trying to see.

Why we need to see in a systemic level is we need to understand interfaces with which that heat generation, heat generated would interact. So, that is very important for us to understand. So, let us look at this, so we have we can see that this if we take this tissue as our volume of interest. You take this tissue as our volume of interest; let us see what are the interfaces, with which the heat generated can have to interact.

So, let us look at this image here. See, this is the bottom portion of the skin that is this part. One let me mark it 1, this is 1; this is the remaining part of the skin. So, automatically this portion becomes the outside surface-2. And this portion becomes the cross sectional like this 3, so those are different interfaces this which has been modeled in a 2-D way here.

Now, these each of these interfaces are special in its own way, how? This interface if you see isothermal interface which is the interface of this surface with the rest of the skin. Ideally, there will not be any temperature gradient and most these both these surfaces would be this inside bulk

and the surface will be at the same temperature; because already thermal equilibrium has happened. So, it will be in same temperature; that is why it is an isothermal, isothermal layer.

Now, what is then let us look at this outer layer, it is very very easy. You can say that even if there is some heating happening, there is wind and air blowing outside through which this heat gets taken away through conductive cooling. So, that is why this interface is convective. So, we understood why the bottom interface is isothermal, why the top interface is convective.

Now, if you take the cross section, it is an adiabatic interface. What it means is that the energy is within that constraint only; it does not get exchanged with an outside system, which is true. Because this is our control volume to understand; so, the energy is inside this. So, that is why at the interface, it is an adiabatic system; at this interface it is a convective system. It is a, it is a first level approximation of the whole tissue cooling process. So, now what we have got, what we have done is we have taken, we have written the equations for all of this.

So, what does this mean is let us say if it is adiabatic; it means that $\frac{\partial T}{\partial x}\Big|_{x=L} = 0$. That means x is in this direction that means in this direction. Let me draw it with another color; that means that in this direction, if you go this way or this way, there is no change in temperature with distance.; that is $\frac{\partial T}{\partial x} = 0$, which is kind of like, which is kind of like isothermal sorry adiabatic layer. So, that is why even in this interface $\frac{\partial T}{\partial x}\Big|_{x=0} = 0$. So, that is the equation for the adiabatic surface.

Now, let us say look let us look at the isothermal surface which is at the bottom. So, for the isothermal surface what it means is that the tissue temperature at y = 0 is equal to that overall tissue temperature of a; tissue temperature of the artery or the bulk of the tissue. This is a T_a, what it means is that this interface temperature is equal to T_a; so that is what it means. Now, that is either case is a healthy tissue.

Now, let us say, we have a tumor inside, tumor can act like a source of heat generation; because it is a, it is a site of intense heat activity. It can act as a source of heat energy; sorry we forgot to see the equation for the convective layer. Convective layer is again $-k\frac{\partial T}{\partial y} = h(T - T_f)$; h is the, k is the thermal conductivity, and h is the what you call parameter for, to decide how much of this temperature gradient translates to the actual convective cooling.

So, this is like how well the temperature gradient gets setup; depends on how well the convective cooling is. That is why the temperature gradient would be $\frac{\partial T}{\partial y}$. That is how quickly is the temperature dropping as you move in the y direction; that is $\frac{\partial T}{\partial y}$. So, $-k\frac{\partial T}{\partial y} = h(T - T_f)$; where $(T - T_f)$ is the temperature difference between the outside and the tissue surface. So, that is convective cooling equation.

But, in the case of tumor, we have not shown the equations here, which is because it is a, it is a quite involved (disc) involved, quite an involved discussion. So, the surfaces remain same, but there will be another internal heat generation. So, there will be another internal heat generation; so that needs to be modeled properly. So, that is how a tumor tissue would be modeled in a skin interface. I think, now you are understood, you have understood how to model the interfaces.

In any given tissue interface, you look at what all interfaces are coming; like what all equations might be applicable, what all surfaces are there. Main thing is to identify what all kind of thermal systems are there at each interface; like is it a convective interface, is it an adiabatic interface, is it an isothermal interface; those things you need to see. You need to first see which all interfaces are there? Then find, use the equations for that and then try to solve for it; that is how thermal modeling of a tissue will be done.

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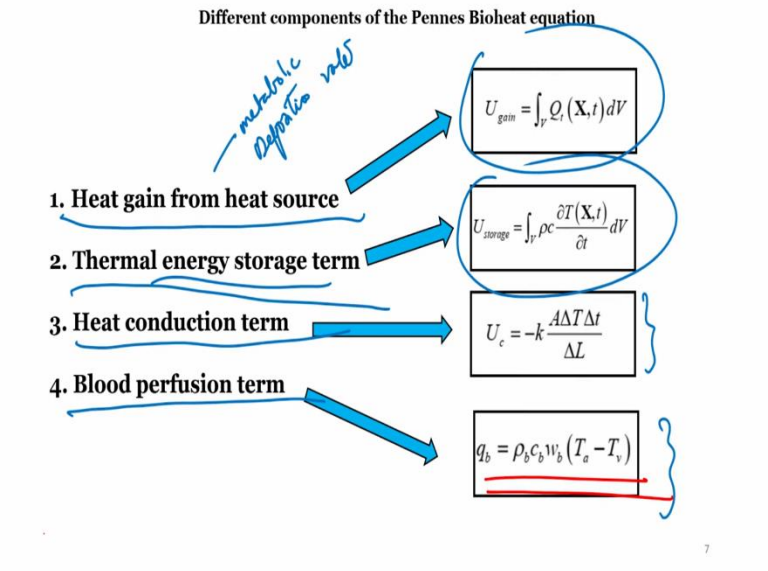

Now, let us, let us look at; so, this we have already seen. Basically, what are different components of the Pennes Bioheat equation; you know that there are heat gain sources, which are the metabolic heat generation, and the deposition rate. Then thermal energy storage term, this because if the input heat is much higher than the output heat; or that heat that is convected away there will be a accumulation of thermal energy inside, which leads to an increase in temperature that is the thermal energy storage term.

Then heat conduction term as you understood, it is like solid conduction through the tissue. What is the equation that governs it and we have also seen the blood perfusion term; this we have covered properly in the previous session. If you have any doubts, please feel free to ask us in the forum.

So, this is how, this is how perfusion term, heat conduction term et-cetera would be modeled; and then they constitute to form the Pennes Bioheat equation. So, you have understood the Pennes Bioheat equation, you have understood how you can model different interfaces of a tissue using the equation, and finding out different surfaces in it.

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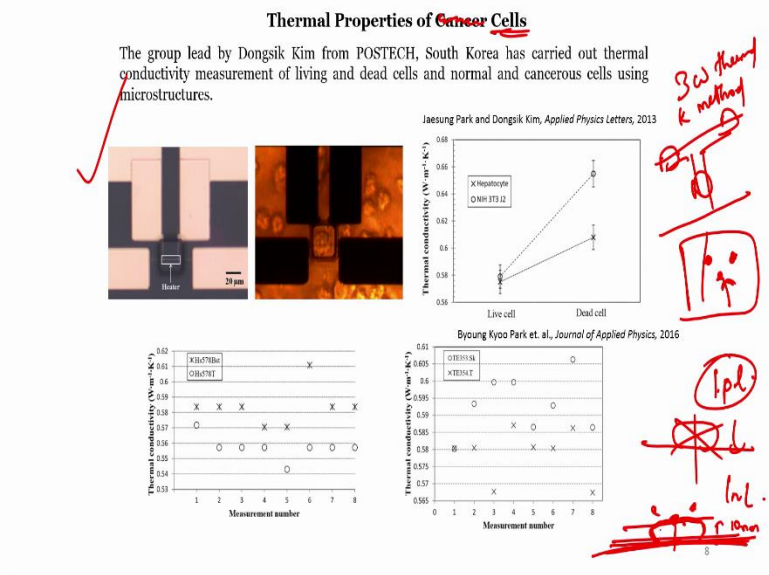

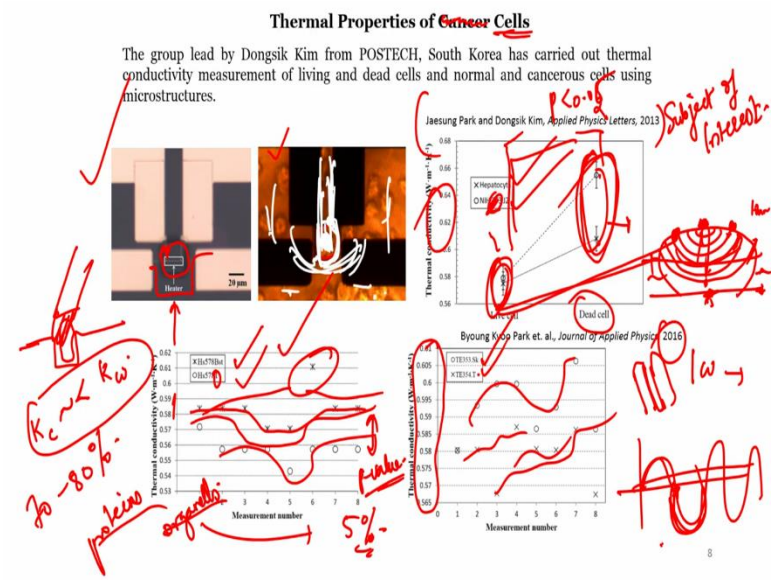

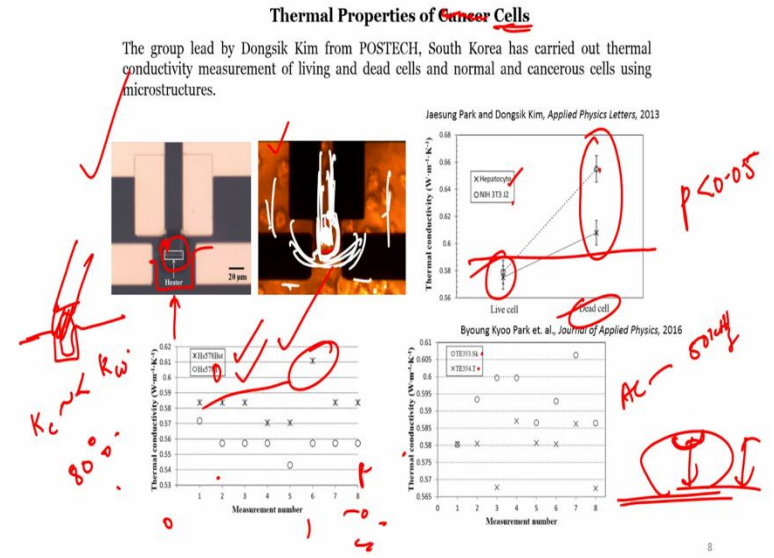

Next, we will see another interesting example of how people have tried to measure the not necessarily cancer cells here. But, generally of cells, thermal properties of cells. Now, here the challenge is you need to understand that there this group has tried to; I am putting in this example so, as to understand make you understand that the importance of both building biomedical systems, and also knowing the mathematical and physical fundamentals behind what you are trying to measure.

So, there might be limitations in the way your targeted specimen is which can be obviated or resolved by using micro systems; which is what we kind of do in the lab here with professor Chandramani and professor doctor Hardik. And so, the point is that in order to measure the thermal

conductivity of single cells; what will be the challenges? And how should we engineer a system, so that we will still be able to measure the thermal conductivity of cell.

So, if when I tell you that you will be able to appreciate what they have done. So, a single cell sitting on a surface will be having a volume of only one picolitre; this is as per literature. And they have very less, very less volume; maybe you can big cells may might have one nano liter volume that is it.

Now, if you are measuring thermal conductivity, there are different ways of measuring thermal conductivity. I will go over that process also in a in a later lecture I think that will be useful. So, there is one way of measuring thermal conductivity using something called as 3 electrode system. There is a particular structure for it and that is called 3 omega thermal conductivity measurement method.

This literature has tried to use the 3-omega method only; so, what it means is basically that, what we do in 3 omega method, roughly I am telling, it is not the exact explanation; but for you to understand. You are because the audience will be a general audience to understand, very simply I will tell, that you will have a heat source. Let us say this is the surface of the tissue, and we are seeing it from top like this.

So, we have a, we will have a heat source, we have temperature sensors which are again coils only, but can double up as temperature sensors if they are not actively heated. One temperature sensor is actively heated and it is actively heated and other two detects the thermal conductivity through the surface of the cell.

Now, when you simply heat when you simply heat a point, the heat this is a very small volume; one picolitre and usually one cells dimension is around 10 nanometer. If you heat it very quickly, this heat can transmit and reach the bottom surface or the liquid; that is that the cell is on; which can actually impede with your measurement of the thermal conductivity.

So, then the work around it is that we should be able to heat the cell in such a way that only the cells area is covered, and the heat generated for measurement does not get into, does not get into the area outside the cell. So, that means what? What it means is that let us say I am enlarging it, this is a cell on the surface I am heating here; we should ensure that the heat that is transmitted

through the cell only reaches a part of the cell, and it does not reach the bottom. Because then the surface and the liquid that the cell is in will also start contributing to the thermal continuity.

Now and then the sensors here can measure what is the temperature, and how well is the temperature (accum) transmitted through the heating source to the sensor. And with that we can calculate the using 3 omega method we can calculate the thermal conductivity. Now, how do we control the heat being only staying within the cell? This is controlled by using a, by heating the heater with a alternating current at a high frequency.

That is the first frequency, 1 omega you can say; and we (freq) we heat the heater using an alternating current. This is an alternating current, so that in one cycle it heats, transmits the heat thermal waves through the cell; such a way that it does not. And before we, before it can touch the surface, the positive wave ends; because of which the sensor cools down and the heat energy does not enter the surface of the cell.

So, this way if we control the frequency, you can limit it to within the cell, because after this point it just cools down because of the negative cycle of the alternating current. So, this way we can confine our thermal energy to the to our subject of interest, subject of interest so, as to remove any artifacts. So, we can control how we heat the heater by heating it through an alternating current; so that the thermal profile stays confined within our subject of interest. And other items near subject does not come into the measurement.

So, how did they achieve this? And another, another interesting fact is that this we, I have shown it with a small dot here. But, actually already this is only very small, this is under 10 nanometer. That means that your heater should be very, very, very small like 1 nanometer feature size. So, that is what they have done here, they have made a heater here; the cell will come and sit here.

I will draw with a white one. So, the cell will come and sit here, the heater is there; and these are all other temperature sensors. So, the heater will be on top of the cell here that is from here. It will heat and the thermal energy will get transmitted, and these these electrodes gain will pick up the transmitted heat; means we can calculate the thermal conductivity.

So, this is a very nice engineering challenge that has been addressed. So, they using a micro fluidic well, they were able to confine, using a micro fluidic well, they were able to confine the cell within

this small volume, where the heater will come in contact heat it and these sensors will detect the thermal energy transmitted through the cell; and thereby calculate this thermal conductivity. So, this is the experimental setup and the sensor design.

So, using this the authors have tried to measure the thermal conductivity of different types of cells. So, hepatocytes NIH 3T3, wait one second let me change the color. Hepatocytes NIH 3T3 Hs578Bst, Hs578T, TE354T, TE353Sk these are all different cell types some are carcinoma cell lines, some are normal cell lines, some are murine cell lines; so, there are lot of cell lines. This is tumor cell line with the name only we can figure out.

So, so these are different cell lines and we have discussed what cell lines are. So, they help us perform experiments on biological samples in an, in a much more easier way than performing such short loop experiments on human samples. So, using these cell lines the authors have been able to measure the thermal conductivity of each of the cells; and they found something, somethings very interesting.

The first observation that they make is that they, before they measured with cells, they first calibrated with a known solutions of methanol ethanol water et-cetera, because it is actually a well. If you see, if you take the, if you look from here as a cross section; what we will see is a well will be there, on the surface here. And you can keep the cell here and then your heater will come on top here to heat the T cell.

Now, before they use the cell, they measure the standard volume, small volume peculator volumes of methanol, ethanol water et-cetera and measure the thermal continuity to ensure that it is matching with the literature. Now, what they observe is that the thermal conductivity of the cells are only very slightly lesser than the thermal conductivity of water; so, this makes real sense. I will explain to you why.

What they have observed is that let say we say that thermal conductivity of cells is K_c is almost equal to or slightly less than the thermal conductivity of water. Why is that and why is it slightly lesser? The authors have also asked the same question. Why is because the cells are also composed of 70 to 80 percent water; we should never forget that fact. We have the cytoplasm which is full of water, we have the nuclear plasma which is full of water; where ions are also there.

So, 70 to 80 percent of the cell is in fact composed of water, then if we try to measure the thermal conductivity of the cell; it will come close to the water only, so, that is what happened. But, then why it is 70 to 80 percent, not 100 percent? It is because the other components itself like proteins and organelles contribute to this reduction in thermal conductivity because proteins are like amino acids, and lipids are there.

These are all very large molecules, and they generally have lower thermal conductivity; because there are not much thermally conducting elements in them. So, because of this but they would form only like if you look at the volume wise, they would form only 5 percent of the volume of the cell. But, because they are, they are there, they will actually bring down the overall thermal conductivity of the cell.

While, it will be dominated by the water content in the cell, the overall value will be slightly lesser than water; because of proteins, organelles, carbohydrates, fats et-cetera which are inside the cell, given that they try to see how repeatable is their measurement. These are the different types of measurement that you should perform; if you are a scientist and if you trying to get into do science, new science.

So, they have measured thermal conductivity of Hs578Bst and Hs578T different two, two different cell lines. And they have basically seen how repeatable the measurements are which is coming to reasonable repetition. You can see that it is only a point 01 difference in the y-axis; and so Bst cells are having a slightly higher thermal conductivity than the tumor cells. But then we cannot make any conclusion unless we do a statistical test with p value.

If time permits even though it is not within the purview of this course, we will also take a session on how to do statistics, statistics for such kind of data. So, this is one kind of experiment that they did. Now, what they did? They have also done same group or a similar same group actually, they published another paper in 2016 also, where they have tried to measure with the different two different types of cells; and seen how the thermal conductivities are obtained.

Here also they have got it in this roughly in the range of the thermal conductivity of water. Now, these two are interesting, this is just a characterizing the thermal conductivity of a particular cell line. Now, what else can we do? So, what, why, so they made this elaborate setup; what is the use of it?

There is a basic use, basic fundamental science answers that are getting solved like what is the thermal conductivity of a single cell? Can we measure it? Or do we have the technical expertise and the precision and the facilities to make such sensors to measure thermal conductivity of single cell. So, that they have, they were able to prove a point. We are also trying to do this here in IISc, you can check up the website of IISc, where different professors are trying to do very interesting things.

So, it is always good to have a global perspective about what is happening around the world; because it is scientific community does not have borders. And everybody is trying to solve unanswered questions in science. And but still it is a matter of pride, when our country is able to bring out some new discoveries and contribute to the whole knowledge of science that is happening. So, it is always good to see what is happening around the world and also see how well we are doing with respect to answering such fundamental questions.

So, then what else what are the other fundamental questions that they were trying to do? They wanted to see; they have a setup. Now, they can do different type of things. They wanted to see are live cells and dead cells any different in terms of thermal conductivity, can we actually look at that. So, they put, once they have setup, they put live cells, they put dead cells and they tried to see if there are any differences between the live cells and dead cells.

So, what they observed? See they observed that first of all, there are lot of variability in dead cells; their values are, different cell lines have different values. But, live cells, both these two cell lines have similar values. And we do not know the condition of these dead cells whether they were water content had, had been removed through a hypochlorite solution that we do not know.

But what is observed is that generally they have a slightly higher thermal conductivity as it can be seen here, as compared to live cells and they have higher variability. So, such kind of, so this can this conclusion can only be made after we repeat this sufficient times; and do a p-value analysis and find out if $p < 0.05$.

If time permits, we will cover actually a short TA session on what is p-value, how to calculate p-value; and what all different types of statistical tests are there et-cetera, which is anyway useful its all, its anyway basic math. And this is anyway instead of the mathematical foundations of

biomedical systems engineering, it is these are the mathematical techniques required for biomedical systems engineering.

So, this is also very good to know as part of the overall math involved in biomedical systems engineering. So, unless we do sufficient number of times and perform a statistical analysis, we cannot come to conclusions; so, that is why they have not told about the p-values. If you look at the paper, maybe you can find out the whether they have done statistical analysis to make conclusive, conclusive statements about the experiment.

Otherwise, just looking at the data we can always say that dead cells appear to have slightly higher like; this is how you should state. Being a scientist, you should be very careful about the wordings that you use. You should be very careful about the wordings that you use to conclude about your experiments. So, if we are not aware, or if you are, if you have not done statistical tests on the data; so, you cannot make conclusive statements.

So, what we, what we could do? How could we summarize this result? How could we summarize this result? We could say that looking at the data; the dead cells appear to have slightly higher thermal conductivity than live cells. However, a conclusive statement can be made only after repeating the experiment sufficient number of times, and performing a statistical evaluation.

Once we do a statistical evaluation and get a p-value < point 05; then we could conclusively state that dead cells have a higher thermal conductivity than live cells. Again, there are caveats, this dead cell is particularly for this cell type; it may not be the same for different cell type, it maybe the same. We need to do the experiment then only we can conclude.

There are lot of unanswered questions in science like this which we can answer; and we need to explore it in a step-by-step manner addressing each question with experimentation. So, science is fun, but science is also hard. And the hard effort also bears fruit with interesting and unknown, as interesting and unknown facts coming out to the scientific community, and as contributing to that. So, this is how this we can measure the thermal conductivity of a single cell.

You understood the challenges of not letting the thermal energy leads the surface. So, we have to limit it to a within a very small dimensional space. How do we do that? We do that by using the micro heater, using an ac wave of very high frequency; let say some 50-kilo hertz, 100 kilo hertz

et-cetera. So, that if the heater coil heats and cools and does not let the thermal energy transmit beyond the single cell. It stays within the cell and then we use a 3-omega method to detect the temperature changes, and thus measure the thermal conductivity.

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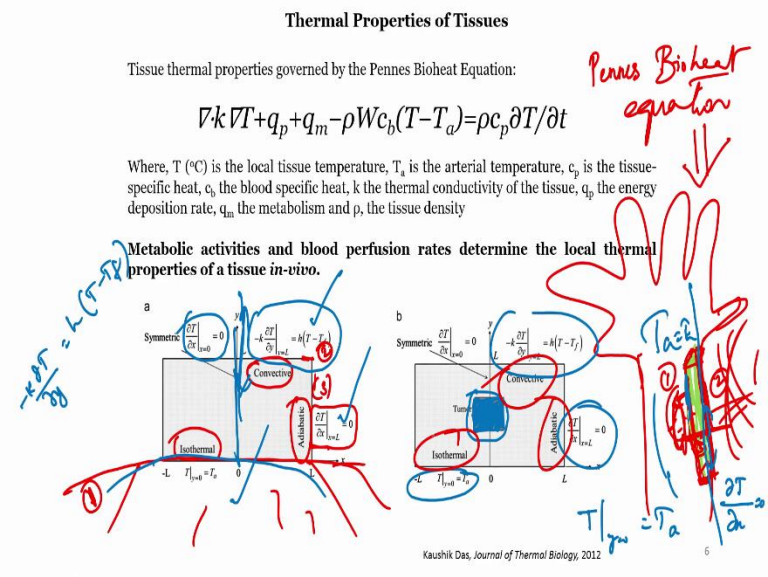

I hope this gave you a good flavor of how thermal conductivity is measured in its tissue level, and a cellular level? What are the challenges that might happen? How do we analyze it? What all equations do we use? What all, what all assumptions simplifying assumptions can we make? How do we look at the interfaces, lot of things?

And I hope this modeling aspect of understanding the thermal properties of tissue gave you good understanding about the biology itself. And how math and engineering can be used to address, address and help address unanswered questions in science. So, in another session we will look we will start looking at the mechanical properties of tissues.

And also, as I have said because for us to make conclusive evidences of all these things; we need to also understand some statistical mathematics. So, we will be taking a session on basic statistical tests that you need to do on data; so that you can make conclusive statements. And how you can, then if you do not get statistical significance, what you need to do to change your experiments to change the question that you are trying to ask or, whether there are some issues with your

experimental setup; those things the debugging can be done. So, see you in another session. Thank you.