Biomechanics of Joints and Orthopaedic Implants
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Lecture 41
Mathematical Modelling of Tissue Differentiation

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Good morning everybody, welcome to the lecture on mathematical modelling of tissue differentiation. This is lecture number 3 of module 8 in the NPTL online certification course on the biomechanics of joints and orthopaedic implants.

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In this lecture, we will be discussing the phenomenological model and the cell-phenotype specific model.

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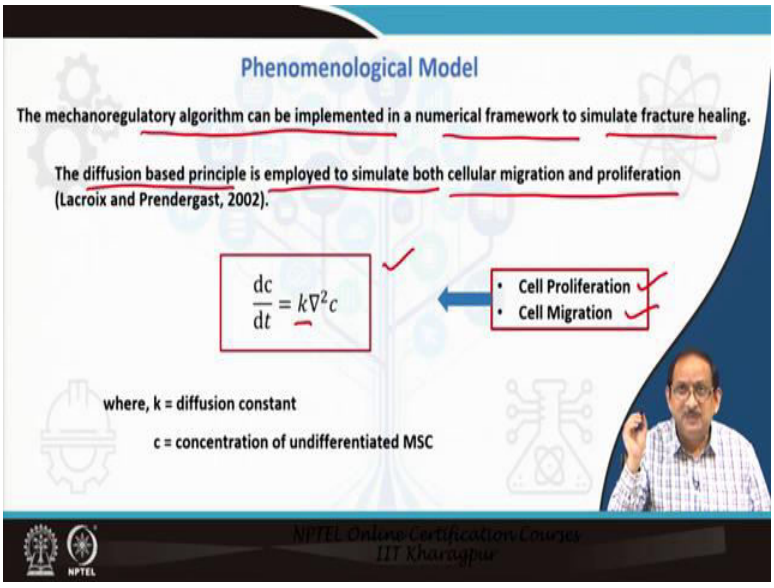

Let us first discuss the phenomenological model. The mechanoregulatory algorithm that we had discussed earlier in lecture 8.2 can be implemented in a numerical framework to simulate bone fracture healing. So, this diffusion algorithm is based on the diffusion principle and is employed to simulate both cell migration and proliferation.

So, this diffusion-based model already includes cell proliferation and migration integrated with it. So, it is given by the differential equation as stated in the slide, where k is the diffusion constant and C is the concentration of undifferentiated MSC, that is, mesenchymal stem cells.

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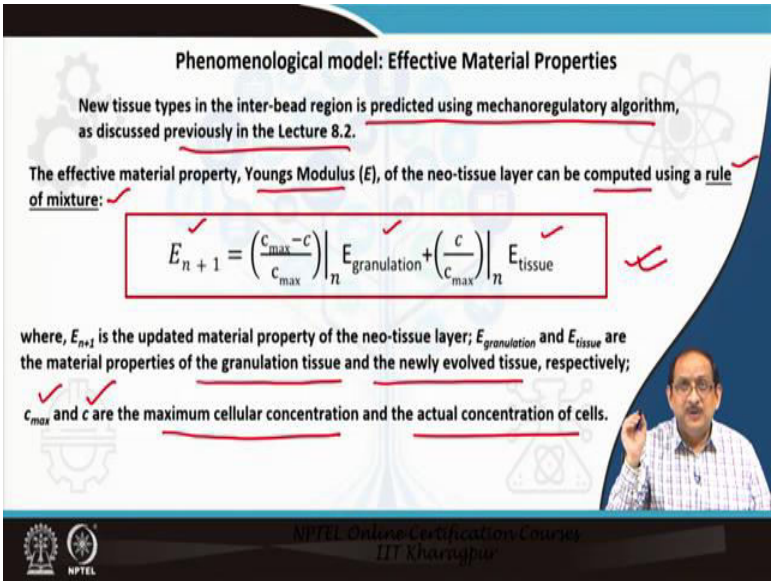

Now, the type of new tissue formed in the inter-bead region. The type of new tissue form is predicted using the mechanoregulatory algorithm, as we had discussed previously in lecture 8.2. The effective material property, that is the Youngs modulus E, of the neo tissue layer can be computed using the rule of mixture, as stated by the equation here in the slide, where you can see the updated Youngs modulus E_{n+1} can be calculated from $E_{granulation\ tissue}$ and the E_{tissue}.

The $E_{granulation}$ and E_{tissue} are the material properties of the granulation tissue and the newly formed tissue. C_{max} and C in the equation are the maximum cellular concentration and cells' actual concentration, respectively. Using the data from our previous calculation, we can update the Youngs modulus of the neo tissue layer.

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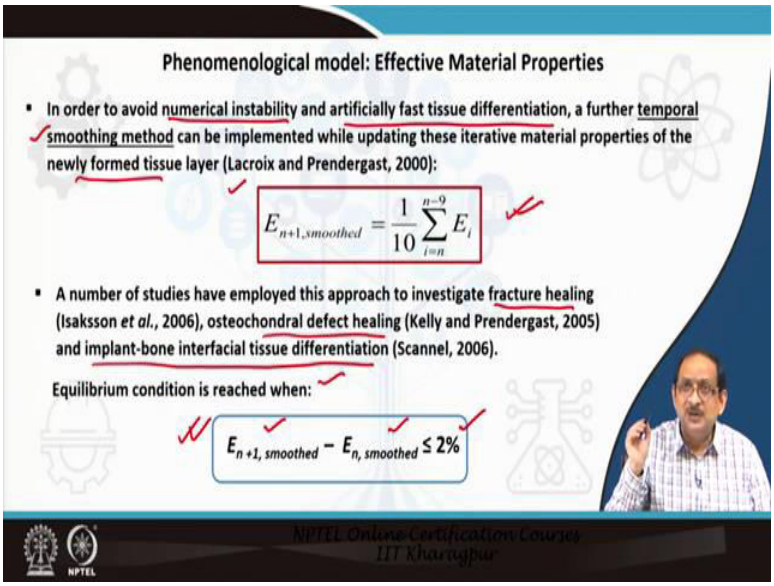

Now, to avoid numerical instability and artificially fast tissue differentiation, a Further temporal smoothening method can be implemented while updating these iterative material properties of the newly formed tissue layer. And the temporal smoothening method is indicated here, in the slide as stated and this is based on the study by Lacroix and Prendergast.

Several studies have employed this approach to investigate fracture healing, osteochondral defect healing, and implant-bone interfacial tissue differentiation. The references are cited here, which you can look into for more details.

Now, equilibrium condition in the tissue differentiation is reached, when the condition stated here is achieved, that is, the updated smoothened E modulus, the difference between the updated E modulus and the old E modulus, or the earlier calculated E modulus, the difference should be less than 2%. So, this is the criteria based on which we can say that the simulation has reached the equilibrium condition.

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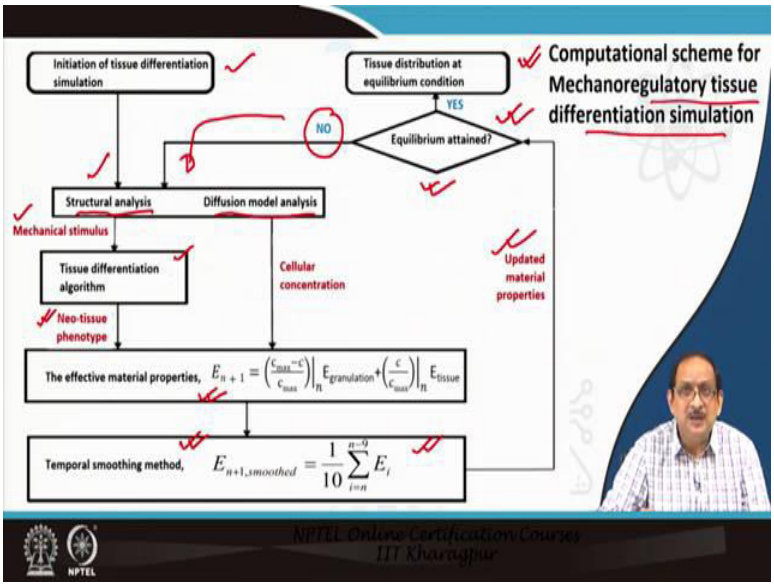

Now, let us discuss the computational scheme in the form of a flow chart. This computational scheme is for mechanoregulatory tissue differentiation simulation. Now, we initiate the simulation here. So, the tissue differentiation simulation initiation is indicated at the top left as you can see with the model loading and boundary conditions included. We can perform two parallel simulations or two parallel analyses; one is the structural analysis, the other is the diffusion model analysis.

Now, this structural analysis would give me the mechanical stimulus and then we can apply the tissue differentiation algorithm based on which we will; we can determine the neo tissue type or type of the neo tissue that is formed due to tissue differentiation. After that, we can calculate the effective material property of the neo tissue layer. We have just discussed how we calculate the effect of effective material property using the rule of mixture.

Then we can apply the temporal smoothing method to update the E modulus. So, we feed the updated E or material property to the decision making zone. If the equilibrium condition is achieved, we obtain a distribution of the neo tissue layer or the newly formed tissue layer, which is only after the equilibrium condition is attained. If not, we iteratively rerun the whole procedure until it reaches the equilibrium state.

So, in summary, the whole computational scheme has been presented here in this slide, and it is an iterative procedure, and the E modulus gets updated in successive iterations. More recently, several cell phenotype-specific algorithms have been proposed, wherein the different cellular activities of each of the cells and their influences on tissue differentiation have been explicitly modeled, which we will discuss in the latter part of this lecture.

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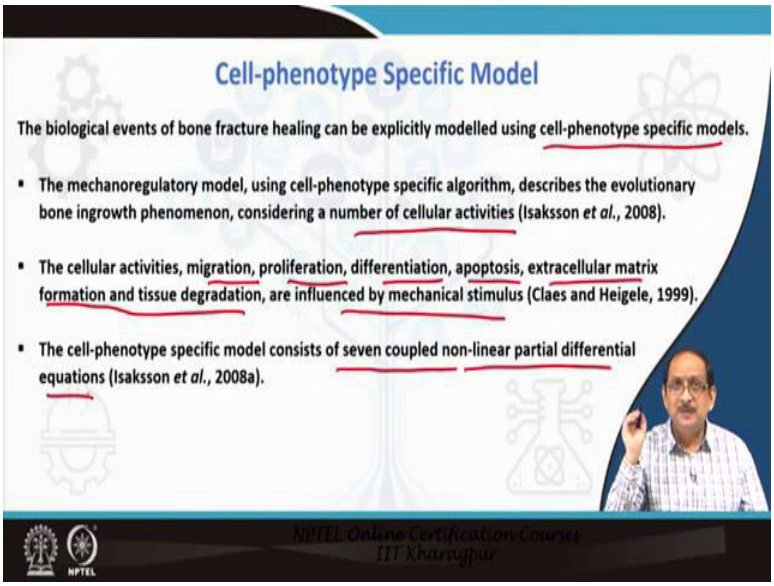

Now, let us come to the second topic, which is the cell-phenotype specific model. The biological events of bone fracture healing can be explicitly modelled using cell-phenotype specific models; please note that this is a far more detailed and complex modelling procedure than the earlier phenomenological model or modelling procedure.

The mechanoregulatory model, using a cell-phenotype specific algorithm, describes the evolutionary bone ingrowth phenomenon, considering a number of cellular activities. The cellular activities, like migration, proliferation, differentiation, and apoptosis, apoptosis is cell death; please remember, apoptosis means cell death, extracellular matrix formation, and tissue degradation. So, all these cellular activities are influenced by mechanical stimuli.

The cell phenotype-specific model consists of seven non-linear and seven coupled non-linear partial differential equations, already reported earlier by Isaksson in 2008.

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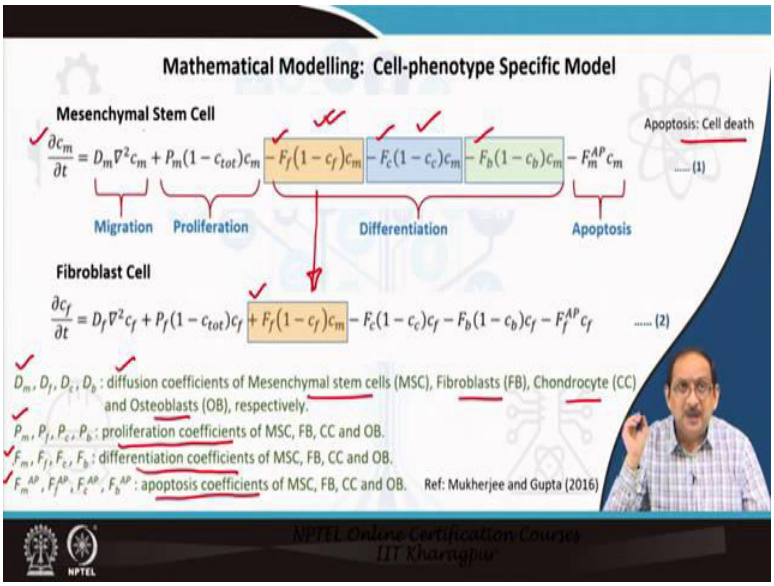

As stated earlier, the cell-phenotype specific model consists of seven coupled non-linear partial differential equations corresponding to each cell phenotype. The partial differential equation presented in this slide is equation number one, corresponding to mesenchymal stem cells. Now, on the left-hand side of this equation, you can see, the rate of change of cell concentration with time has been presented.

Each of these four equations that we present subsequently has four parts representing cell migration, cell proliferation, cell differentiation, and cell apoptosis; apoptosis means cell death, as indicated in the slide. Now, we will present the second equation corresponding to the fibroblast cell. Now, please pay attention here because some terms of one equation is connected to the same term in the other equations.

Now, this can be explained in the following way, when one cell differentiates into another, the concentration change is subtracted from the parent cell, for instance, this one, this one, and this one. So, when one cell differentiates into another, the concentrations change, the concentration change is subtracted from the parent cell-phenotype and added to the new cell-phenotype, I will show you by using coloured boxes.

So, please pay attention, the orange box here indicates the fibroblast cell concentration, differentiated from the first equation and with a negative sign. This term is added to the

corresponding new cell-phenotype, the fibroblast in the second equation, with a positive sign. This is a crucial step in the whole mathematical modelling of the cell-phenotype specific modelling approach.

Similarly, the cell concentration of chondrocyte cells, differentiated from the mesenchymal stem cells will be added in the chondrocyte cell, phenotype equation presented in the next slide. The green box here corresponds to the osteoblast cell concentration, which is differentiated from the mesenchymal stem cell, this will also be added to the corresponding osteoblast cell activity presented in the next slide.

So, the blue box and the green box are the cell concentration change, differentiated from the mesenchymal stem cell activity, which will be added to the corresponding new cell-phenotype activity presented in the next slide. Now, apart from this, we have the diffusion coefficients corresponding to each cell-phenotype; it is mesenchymal stem cells, fibroblast, chondrocyte, and osteoblast.

So, this is the diffusion coefficient is represented by D, the proliferation coefficient corresponding to each cell-phenotype is indicated here, or by P. And the differentiation coefficients corresponding to each cell-phenotype is indicated here by F, whereas F_{AP} gives the apoptosis coefficients corresponding to each cell-phenotype.

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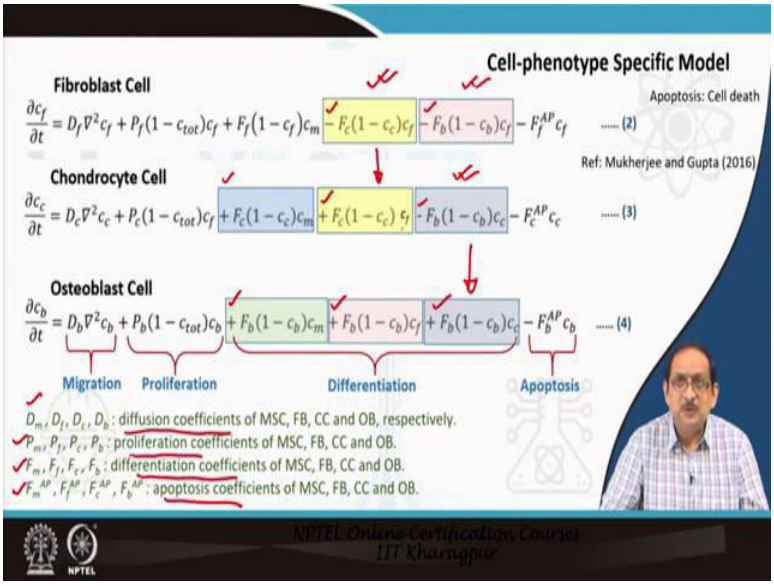

We now move to the next slide, where we repeat equation number 2, as you can see, which corresponds to fibroblast cell. We present the other cellular activity, equation number 3 for chondrocyte cell, and equation number 4 for osteoblast cell. Again, we present each term on the right hand side of the partial differential equations, representing cell migration, cell proliferation, cell differentiation, and cell apoptosis.

Now, again we will be discussing the concentration change from the parent cell phenotype. So, we take up the yellow box, or the yellow box is represented here. So, this is the concentration change of chondrocyte cells differentiated from the fibroblast cells with a negative sign, this term is added to equation number 3, which corresponds to the new cell-phenotype of chondrocyte cell.

Now, similarly, the concentration change of osteoblast cells, differentiated from the fibroblast cell activity, is marked here as the pink box. So, you can see that it has a negative sign because it is differentiated from the fibroblast cell. This term is added as a positive sign, in the osteoblast cell activity, in the partial differential equation number 4. So, this is indicated by pink boxes.

Next is the grey boxes, which again represents the activity, similar activity here. The concentration change of osteoblast cells differentiated from chondrocyte cells in equation number 3 with a negative sign is added to the osteoblast cell activity equation number (4) with a positive sign. Now, you may recollect that I had indicated one blue box and one green box earlier in the differentiation terms with the negative sign of the mesenchymal stem cells presented earlier. So, those terms had a negative sign.

So, now they are added in the corresponding cellular activity of chondrocyte cells and osteoblast cells, in the equations presented as 3 and 4. So, these are the two blue and green boxes corresponding to the cellular activity and corresponding to the new cellular activity in the chondrocyte and osteoblast cells, respectively.

So, similar to the earlier slide here, we also present the diffusion coefficients. The diffusion coefficients corresponding to each cellular activity are represented by D, the proliferation coefficients are represented by P, differentiation coefficients are represented by F, and F_{AP} represents apoptosis coefficients.

We had remarked earlier that there are seven coupled non-linear partial differential equations, out of which four have been presented here. In the following slides little later, we will present the other three partial differential equations, which now partial differential equations 6, 7, and 5 repeat the partial differential equations 5, 6, 7, which represents the mass of tissue formation, corresponding to each type of cellular activity.

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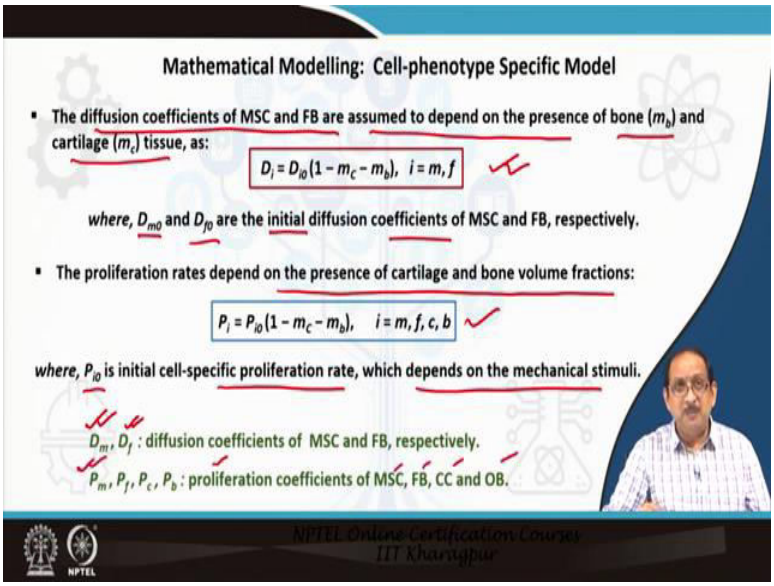

Now, let us discuss the diffusion coefficients of MSC and fibroblasts in the modelling procedure. The diffusion coefficients of MSC and FB, fibroblasts are assumed to be dependent on the presence of bone mass indicated by M_b, and the cartilage tissue as stated in the equation in the slide, where D_{m0} and D_{f0}, are the initial diffusion coefficients of MSC and fibroblast respectively.

The proliferation rates depend on the presence of cartilage and bone volume fractions, as given in the equation, where P_{i0} is the initial cell-specific proliferation rate, which depends on the mechanical stimuli. The chondrocyte and the osteoblast cells are assumed to migrate and that is why the diffusion coefficients for these cells, chondrocyte and osteoblast are not defined in this slide. The chondrocyte cells and osteoblast cells are assumed not to migrate.

So, the CC and OB cells are not assumed not to migrate and that is why the diffusion coefficients for the chondrocyte cells and the osteoblast cells are not defined in this slide. So, here we have

the D_m and D_f, the diffusion coefficients of MSC and fibroblasts and the proliferation coefficients of each cell: MSC, fibroblast, chondrocyte, and osteoblast are indicated here as P_m, P_f, P_c, and C_b.

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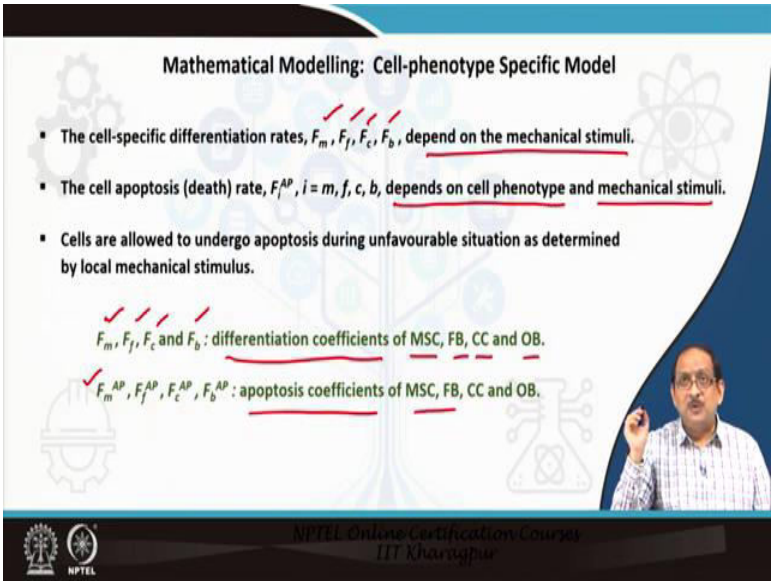

The cell-specific differentiation rates F_m, F_f, F_c, and F_b depend on the mechanical stimulant. The cell apoptosis, or death rate corresponding to each cell, depends on the cell phenotype and the mechanical stimuli. So, cells are allowed to undergo apoptosis during the unfavourable situation as determined by the local mechanical stimuli or stimulus.

So, in this slide, the differentiation coefficients of MSC, a fibroblast, chondrocyte, and osteoblast are indicated by F_m, F_f, F_c, and F_b and the apoptosis coefficients corresponding to each cell-phenotype is indicated here, generally as F_{AP} and then the subscript corresponding to each cell-phenotype.

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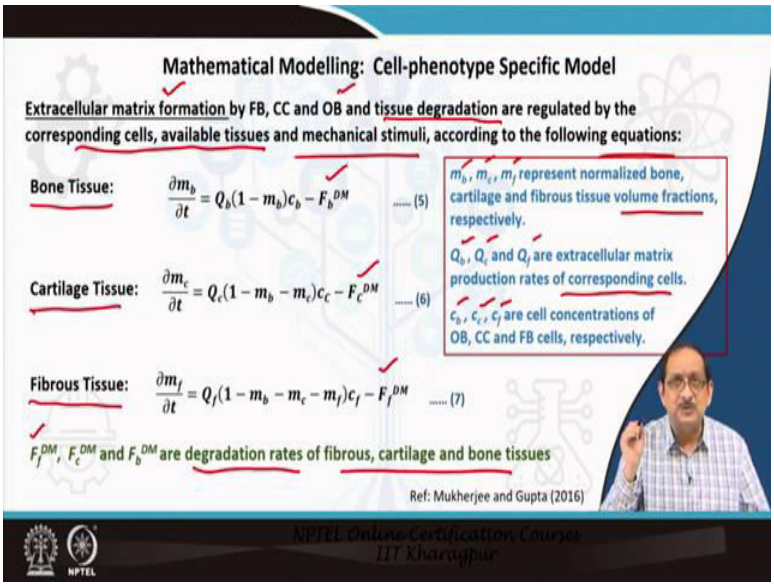

The extracellular matrix production rates of corresponding cells depend on the local mechanical stimulus. The extracellular matrix formation by fibroblast, chondrocyte and osteoblasts, as well as tissue degradation are regulated by the corresponding cells available tissue and mechanical stimuli, according to the following equations presented here in the slide.

So, these are equations 5, 6, and 7, and part of the 7 coupled non-linear partial differential equations that I mentioned earlier. In earlier slides, we had presented partial differential equations 1, 2, 3, and 4 for each cell-phenotype, mesenchymal stem cells, fibroblasts, chondrocyte, and osteoblast.

Here we present equations numbers 5, 6, and 7, corresponding to extracellular matrix formation. And here you can see the equations correspond to the first equation number 5 corresponds to bone tissue, equation 6, cartilage tissue, and equation 7, fibrous tissue.

Here M_b , M_c , and M_f , represents normalized bone, cartilage and fibrous tissue volume fractions, respectively. Q_b, Q_c, and Q_f are extracellular matrix production rates of corresponding cells. And C_b, C_c, and C_f, and are the cell concentrations of osteoblasts, chondrocyte, and fibroblast cells, respectively.

Now, in the equation, the tissue degradation is indicated for each cell phenotype. So, the degradation rates of fibrous tissue, cartilage tissue, and bone tissue are given here as F_{DM}, corresponding to each cell-phenotype, fibrous tissue, cartilage and bone tissue. $F_{f\,DM}$, $F_{c\,DM}$, and $F_{b\,DM}$ are the degradation rates of fibrous tissue, cartilage and bone tissue, in the equations 5, 6, and 7.

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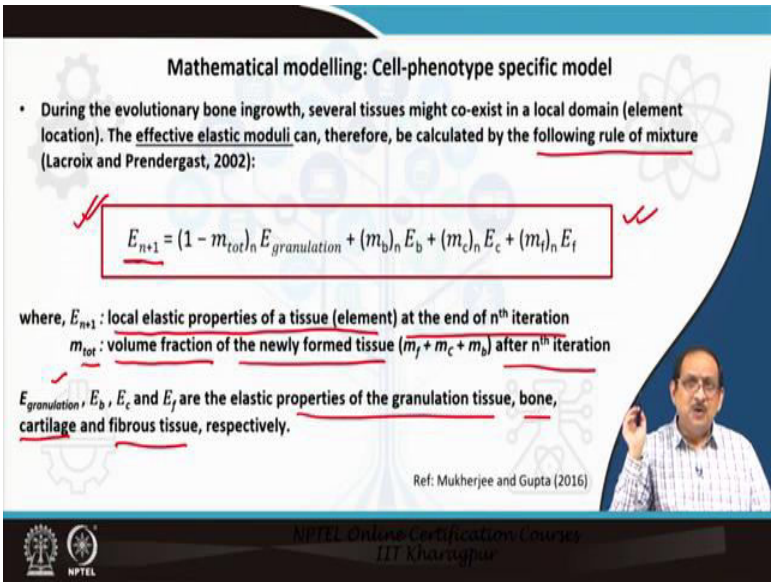

During the evolutionary bone ingrowth, several tissues might co-exist in a local domain or an element location. If you are considering a finite element model, at this level, we say that it is a local domain. So, effective elastic moduli can be calculated by the following rule of mixture, which we had introduced to an extent in the phenomenological model. So, in the cell phenotype-specific model, the effective elastic modulus can be calculated using the rule of the mixture as indicated in the slide.

The term E_{n+1} is the local elastic property of the tissue at the end of the nth iteration, and M_{total} is the volume fraction of the newly formed tissue after the nth iteration. The interbeat spacing at which the bone ingrowth takes place is initially assumed to be, or is assumed to be, initially filled with granulation tissue; that is why we start with E granulation.

So, E granulation E_b, E_c, and E_f are the elastic properties of the granulation tissue, bone, cartilage, and fibrous tissue, respectively. So, using these Young's modulus values, we can

actually obtain the effective elastic modulus of the newly formed tissue element, or a layer, as a whole.

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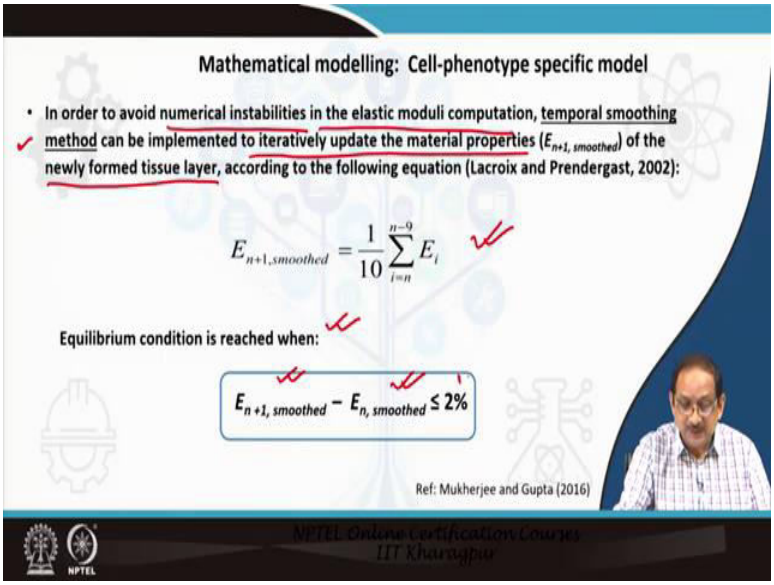

Now, similar to the phenomenological model, here also we need to avoid numerical instabilities in the calculation of the elastic modelling. Therefore, the temporal smoothing method can be implemented in the whole numerical framework to iteratively update the material properties of the newly formed tissue layer, according to the equation as presented in this slide.

Here also the equilibrium condition of tissue differentiation, or the cell-phenotype specific modelling procedure is reached, when a criterion is fulfilled, which is stated as the updated E, the difference between the updated E and the earlier E value, or old E value, the difference should be less than 2%.

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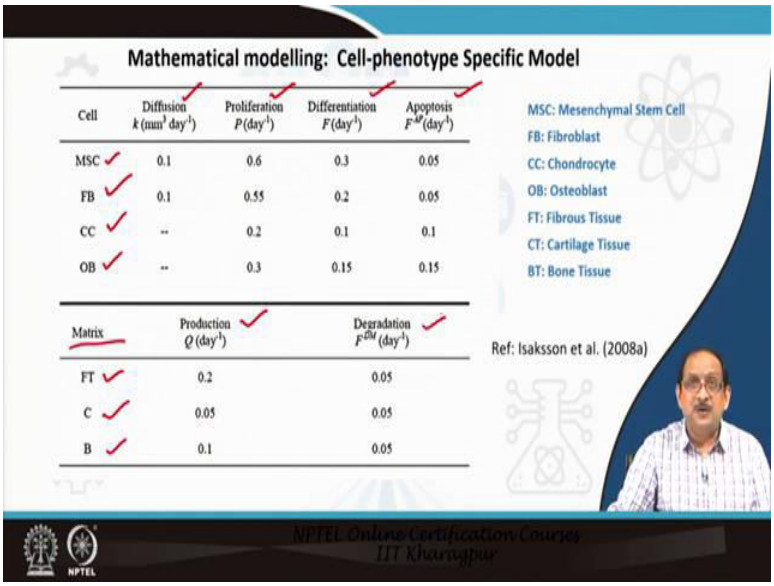

Let us now present to you the properties of the neo tissue, characterized by various studies, but summarized here in this slide, where you can see the diffusion coefficient, proliferation, differentiation and apoptosis coefficients, corresponding to the MSC, fibroblast, chondrocyte, and osteoblasts, with regard to extracellular matrix formation, the fibrous tissue, cartilage, and bone, formation rates, and production rates, and degradation rates are also mentioned in this slide.

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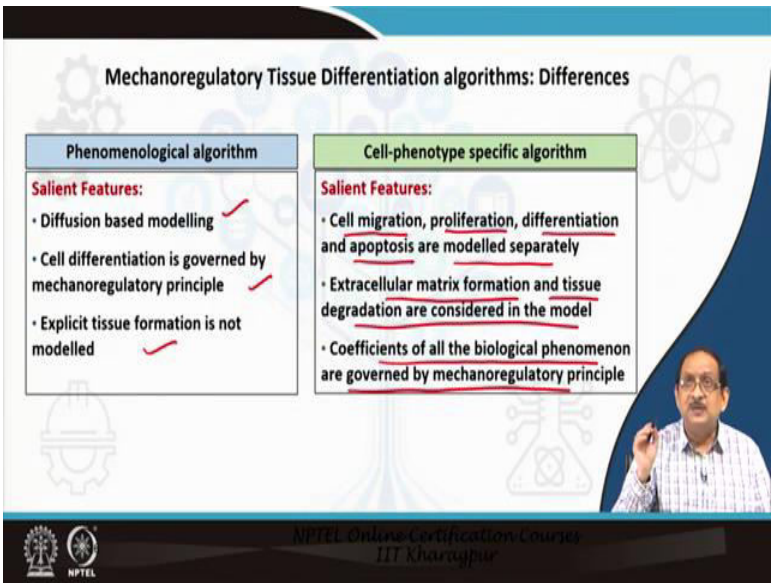

Now, we have arrived at a situation when we can figure out the differences between the phenomenological algorithm and the cell-phenotype algorithm. The salient features of the phenomenological algorithm is stated here. So, it is a diffusion made based modelling procedure; the mechanoregulatory principle governs cell differentiation.

And explicit tissue formation is not modelled in the case of the phenomenological model. In the case of a cell-phenotype specific algorithm, the salient features include here, as you can see, cell migration, cell proliferation, differentiation and apoptosis are all modelled separately. Extracellular matrix formation and tissue degradation are considered in this model.

And the coefficients of all the biological phenomena are governed by mechanoregulatory principle. I hope you can identify that a cell-phenotype-specific algorithm is a far more complex algorithm than the phenomenological model, which was stated as the first topic of this lecture.

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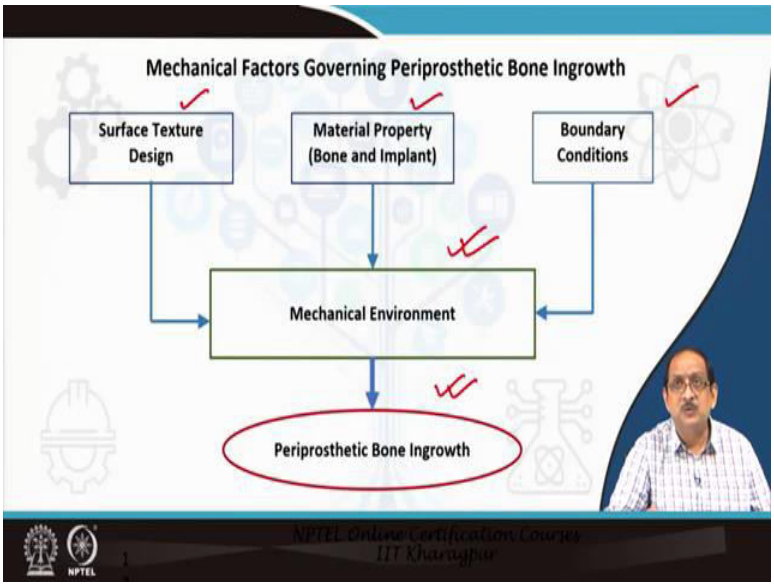

Let me now summarize the mechanical factors that govern periprosthetic bone ingrowth because we are interested in bone ingrowth around a prosthetic. So, periprosthetic means periphery of the prosthesis. And there are other fracture healing problems in which these algorithms may be useful, but we are discussing here the factors that govern the periprosthetic bone ingrowth. So, the first important factor is the surface texture design of the implant.

So, a porous-coated implant may have different kinds of surface texture designs. So, depending on the surface texture design, now the mechanical environment will be influenced. The material property of both bone material property and the material property of the implant has a predominant influence on the mechanical environment; please remember that within a reconstructed joint, or bone, that is bone with implant, the local material properties of bone can also vary from one location to the other.

So, that variation in the local bone material property needs to be taken care of. The third important factor is the boundary conditions; these boundary conditions may include the interfacial micromotion between implant and bone and surface texture design and material property of bone and implant. The mechanical environment in the implant-bone structure is governed, which actually would influence the periprosthetic bone ingrowth. So, the mechanical environment influences the periprosthetic bone ingrowth in the implant-bone structure.

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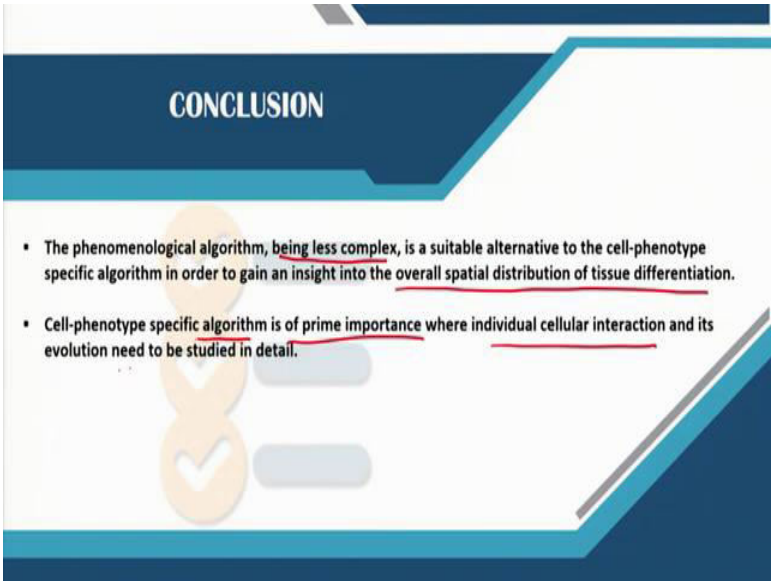

Let me now present the conclusions of this lecture. The phenomenological algorithm being less complex is a suitable alternative to the cell-phenotype specific algorithm to gain insight into the overall spatial distribution of tissue differentiation. In comparison, the cell-phenotype specific algorithm is of prime importance, where individual cellular interaction and its evolution need to be studied in detail.

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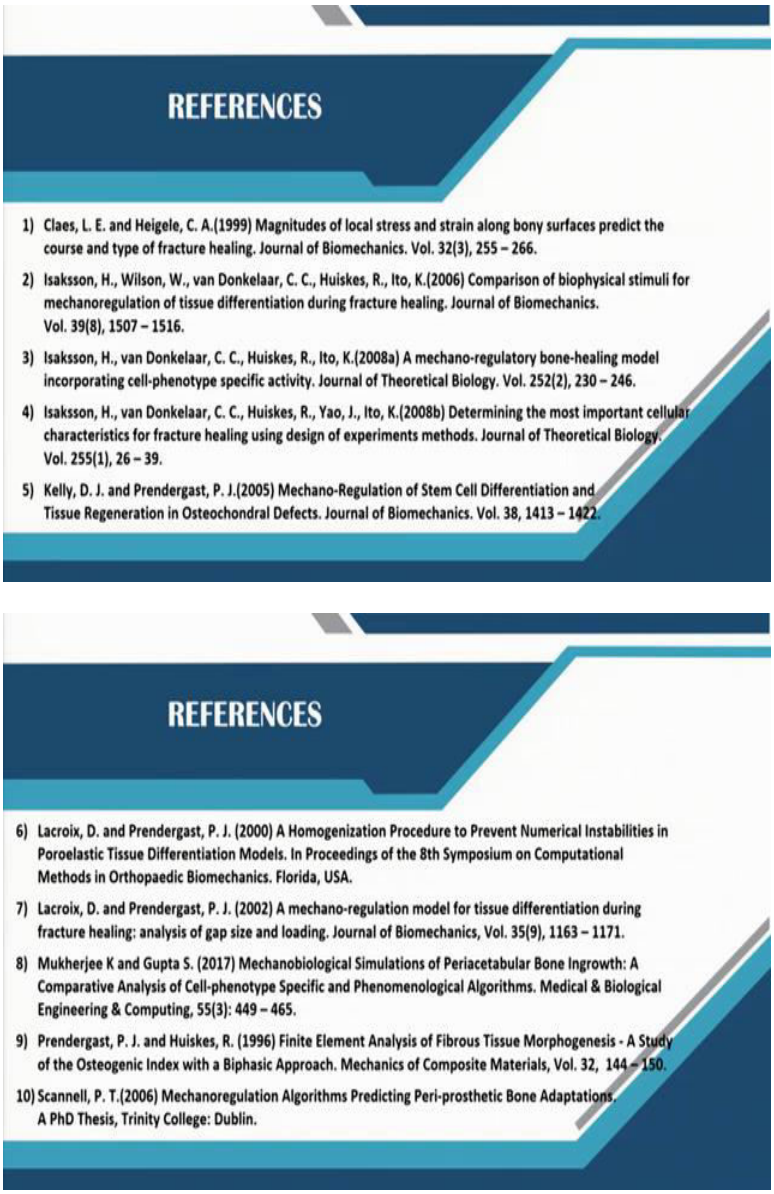

The list of references is mentioned in two slides, based on which the lecture was prepared. Thank you for listening.