Microfluidics

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Lecture - 39
Micro Needles and Microparticle Separation

Okay, so today we will talk about you know Microneedles, and then we will talk about Microparticle Separation okay. So first to talk about microneedles, when we take an injection we typically use a capillary hypodermic needle which has a size typically of the order of 1 millimeter or a few millimeters in diameter okay, so that causes pain while drug delivery, and if you are using a hypodermic needle for aspiration of body fluid then it may cause you know injury and in some cases infection okay.

The one approach that have been developed to get around this problem is to develop what is called microneedles, so these microneedles have diameter of the order of you know tens to hundreds of micron in size, and they stay out of you know the dermis layer okay the hypodermis layer, and they do not interfere with the blood vessels and the nerves cells okay. So that is how we are able to get painless drug delivery.

And also if you are using you know the needle for aspirating body fluid, we are avoiding any injury okay. So let us look at how microneedle works.

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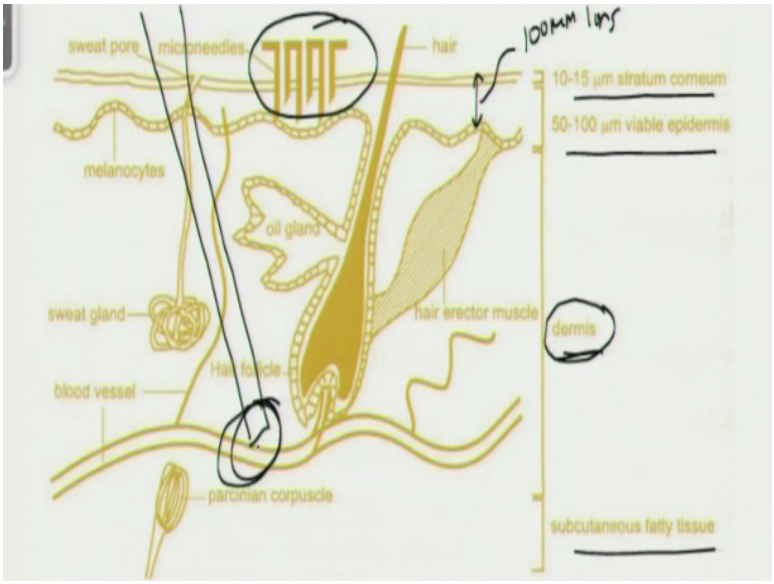

So if you look at this section of our skin this is how it looks like, we would have 10 to 15 micron of the top layer of the skin which is known as stratum corneum, and the next 50 to 100 micron is about is called the viable epidermis, and then we have a thicker layer which is called dermis okay. So and then under the dermis we have the subcutaneous fatty tissue, so the blood vessels are found in the dermis layer okay.

Now when we put a large hypodermic needle for injection it interferes with the blood vessels okay and it interacts with the nervous system okay that is why we are able to feel the pain, and since it interacts with the blood vessels then sometimes we have bleeding and chances of infection okay. Now this microneedles they stay out of the dermis layer okay, and you know the drug we injected with in the first 10 to 30 micron or 100 micron layer at the top okay.

So typical microneedle thickness be 100 micron long, so it is a stays out of the layer major part of the dermis where we have the nervous system and blood vessels okay, so that is how we are able to get painless drug delivery and without causing bleeding okay.

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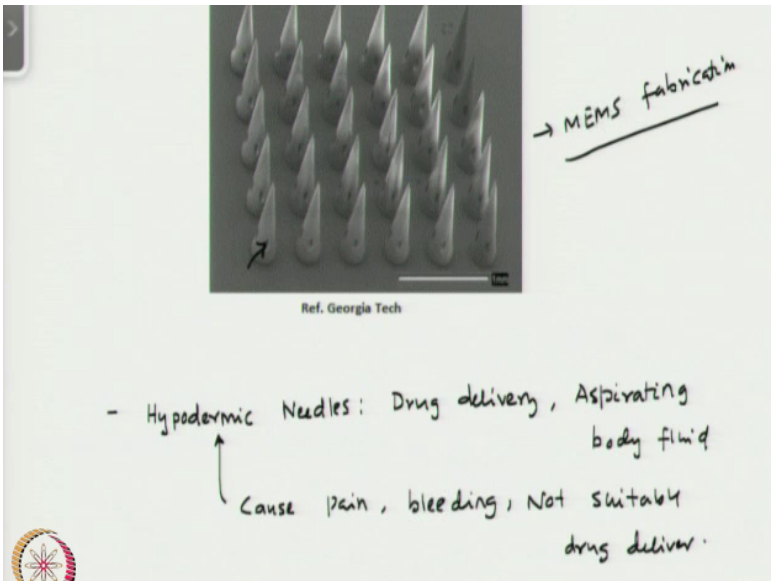

Now if we so here we look at one example of microneedles which has been developed at Georgia Tech, so these microneedles have been fabricated using MEMS fabrication okay, and as you can see these are pointed structures which can pierce into the skin and the there are some openings as you can see here which through which the drug can come out okay. So first let us look at why we use microneedles?

So typically we use hypodermic needles for drug delivery and for aspirating body fluid, and this hypodermic needles large needles cause pain and also bleeding, and they are not suitable for targeted drug delivery okay. So for example we want to inject a particular amount of drug at a precise location in the body we will not be able to do that using the conventional hypodermic needle, because the sizes are of the order of millimeter okay.

The diameter of the needles are of the order of millimeter, but we may be able to achieve that using microneedles which have the diameter of the tens of the microns to hundreds of microns okay.

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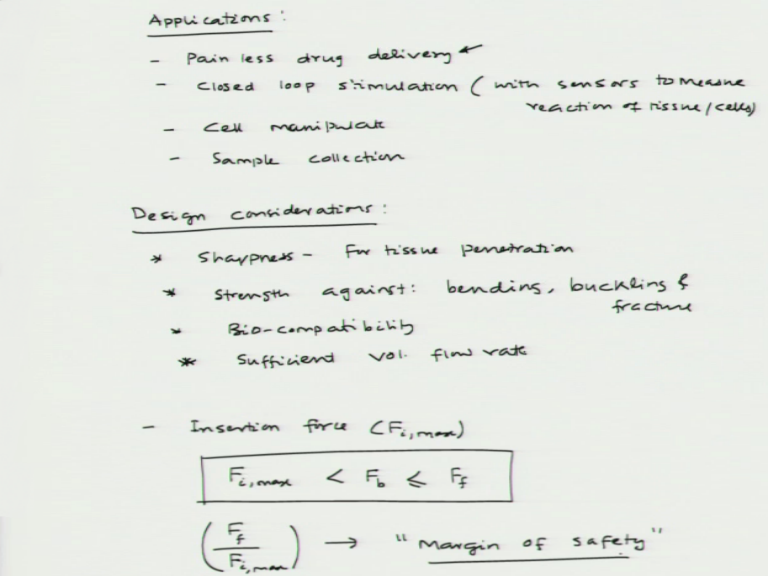

So the applications of microneedles or painless drug delivery, and closed loop simulation okay, because so painless drug delivery is because of this size closed loop simulation meaning they say we want to measure the reaction of certain tissue we subject the tissue to certain chemical or certain force and you want to see what its reaction is, then we can you know putting the microneedle and integrate with the sensor to see a reaction of the tissue,

So we can with sensors to measure reaction of tissue or cells okay, then it can be used for cell manipulation to manipulate cells to move cell from one location to another, it can also be used for sample collection okay, for collection of bio samples. Now what are the design consideration, we look at design considerations the most important thing is that the microneedle needs to be sharp okay in order for easy penetration into the skin okay, so sharpness for tissue penetration.

And the second thing is that the microneedle should have enough strength to withstand bending, buckling and fracture okay, so strength against bending, buckling and fracture. The third important thing is biocompatibility, the microneedle need to be compatible with our body. The fourth thing is it would be able to deliver enough volume flow rate okay, so sufficient volume flow rate.

Now if you are inserting a microneedle into the skin, the insertion force need to be <the buckling force and it should also be <the fracture force, otherwise the microneedle will break before it is

inserted okay. So the condition that the insertion force let us call it Fi max, because the insertion force varies as it penetrates into the skin, so we are talking about the maximum insertion force so <the buckling force and it should be <the fracture force.

And the ratio of the fracture force to the insertion force is known as the margin of safety okay. Now as I said the insertion force when you are trying to insert the microneedle into the skin varies with depth okay, so let us look at, how does the insertion force vary as the microneedle penetrates into the skin?

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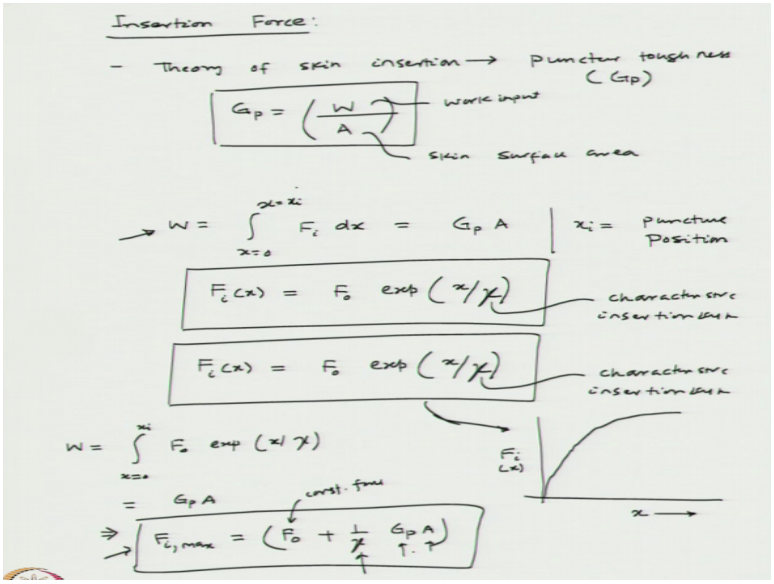

So we look at insertion force the theory of skin insertion is based on the puncture toughness, the puncture toughness of the skin which is expressed as symbol GP, so the puncture toughness can be expressed as the work input the amount of work that we do/the surface area of the skin okay, so this is the work input and this is the skin surface area okay. The total amount of work that we do will vary between x=0.

Let us say x=0 is the top surface of the skin and it goes to some xi into the skin and Fi is the force*dx okay, so that will be equal to that work will be =GP puncture toughness* area, as you can see from this situation, and this is where xi is the puncture position okay. So from this we can find an expression for insertion force Fi x is going to be F0*exponential x/some characteristic length scale okay, where x here the oblique x is the characteristic insertion length.

So what do we see here? We see here that the insertion force varies exponentially, so as if this is x into the depth of the skin, then the insertion force is a function and it is going to increase as the needle penetrates more and more to the skin and it is going to reach a steady value okay. So this is the nature of how the insertion force would vary. The work input we can find from here, so x=0 to xi F0 exponential x/characteristic length scale, so that will be=GP*A.

So we can find Fi max is=F0+1/x*GP A okay, so that is how we can express the maximum insertion force, so this is constant force okay, and this is the characteristic length puncture toughness*skin surface area okay. Now a typical microneedle will have diameter of the order of let us say 50 micron and length will be about 150 micron, so the mode of failure would be a bending, buckling or fracture okay. So let us look at different modes of failure we talked about bending, buckling of micro needle and fracture of microneedle okay.

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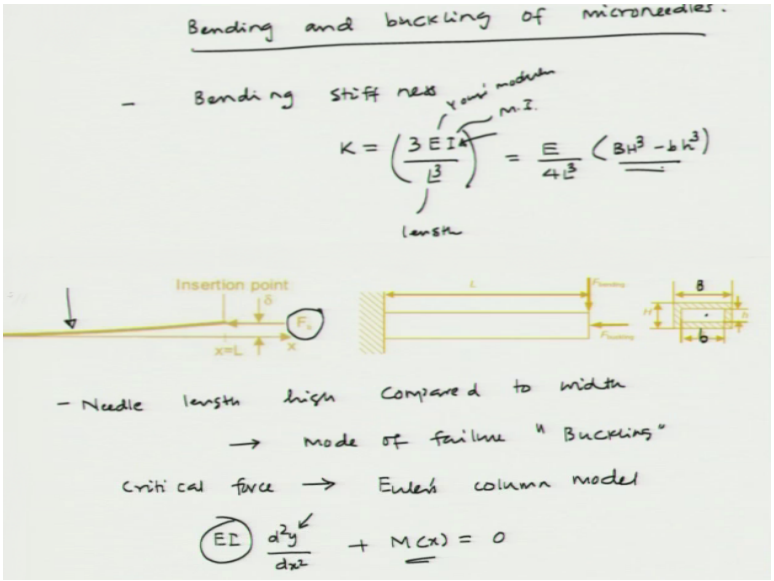

So first let us talk about bending and buckling of microneedles, so the bending stiffness of a needle so let us call it K which is given by okay 3 E I/L cube okay, so basically this is a cantilever type of structure the microneedle becomes like a cantilever type of structure, and this is the buckling force which is applied here. And this leads to deflection of the cantilever okay, so if the length is L, and I is the moment of inertia.

Then you can write the bending stiffness 3 E I/L cube, so this is moment of inertia, and this is the Young's modulus okay, and this is length, so we can write K=E/4 L cube*B H cube-b h cube okay, if you substitute for the moment of inertia of a rectangular cross section, then you can write the expression for the stiffness. And the rectangular cross section is it is a hollow needle, because we will have a drug present inside the fluid present inside.

And the dimensions is here B is the internal width, h is the internal width sorry, small b is the internal width, large B is external width okay, this is actually B and this is b, and capital H is the external height and small h is the internal height, so we can write an expression for the moment of inertia so that is how we get E/4 L cube*B H cube-small b h cube okay. Now the needle length is high compare to width that is typically for a microneedle.

So the mode of failure, the first mode of failure is buckling okay. So now to find the critical force, the critical force can be found using Euler's Column model okay, which tells that E I*d square y/dx square+ M x is the moment=0 okay, here y is the deflection so as you can see here this cantilever case y is the deflection, x is in this direction along the direction of the beam length of the beam, this is the Young's modulus*the moment of inertia, and this is the moment about some x okay, so that is the Euler's Column model.

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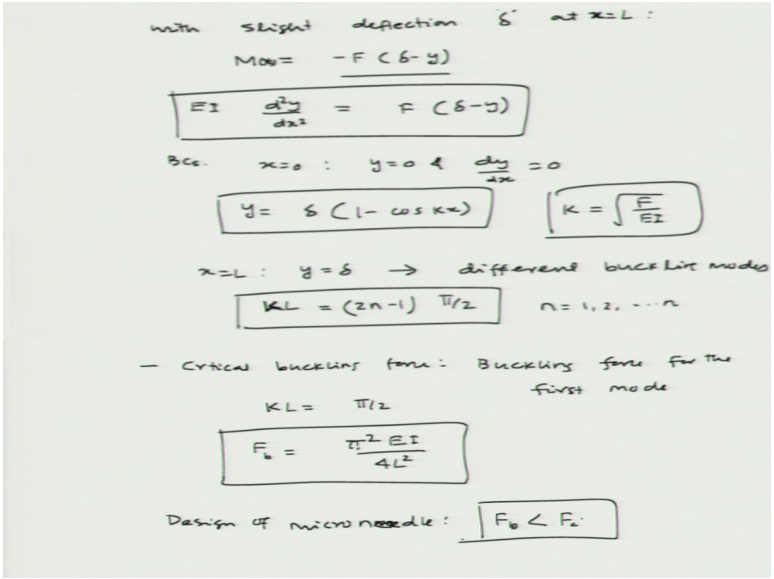

And with a slight reflection delta at x=L which is the end of cantilever, the bending moment M can be written as –F*delta-y okay at a particular x this can be written as –F*delta-y, so we can solve this equation d square y/dx square=F*delta-y. Now to solve this equation what are the boundary conditions we have available, the boundary conditions are x=0 at x=0 that is the clamp and the deflection=0, and also the slope dy/dx is going to be 0.

So in that case the deflection y will be delta*1-cos K x, and where K=F/E I square root okay. Now if we apply x=L y=delta then you can find the different buckling modes okay, so K*L can be written as 2 n-1*pi/2 okay, where n=1, 2, up to n okay. Now to find the critical buckling force and we find the buckling force for the first mode, so in that case K L n=1 so K L will be pi/2, and if K L=pi/2 from this equation we can find an expression for F okay.

So that F which is the buckling force will be pi square E I/4 L square, so when we are designing a microneedle we need to find out what the buckling force is for the particular microneedle, and we have to make sure that the insertion force does not exceed this buckling force okay. So in design of microneedle Fb< the insertion force okay. In many applications it will be easier to use a tapered microneedle for ease of insertion okay.

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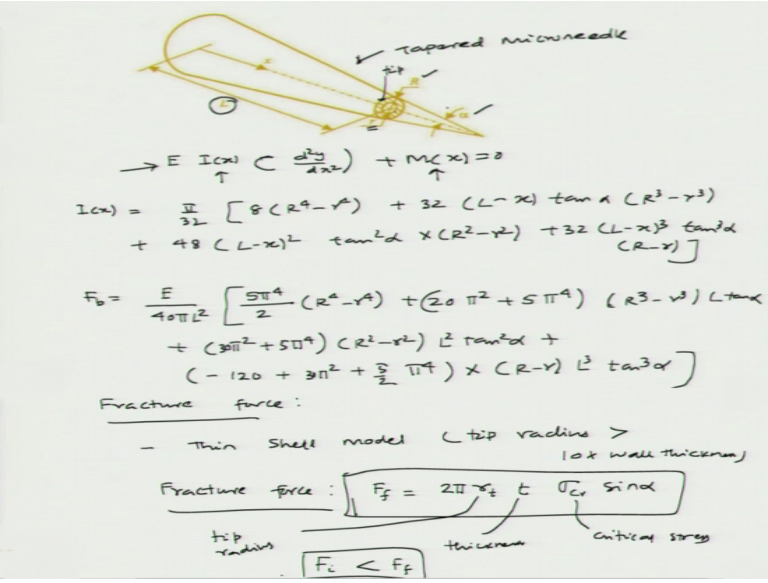

So one such microneedle is shown here, so this is the tapered microneedle, and for the tapered microneedle we can write down E*I x*d square/dx square +M x=0, the M x is varying, I x is

varying, so the I x for this tapered microneedle is given by the expression pi/32*8 R4-r4+32*L-x*tan alpha*R cube-r cube+ 48*L-x square tan square alpha*R square-r square+32 L-x cube*tan cube alpha*R-r, so this is a long expression for the moment of inertia for this tapered microneedle.

The buckling force can we found out using by solving this equation which is given by E/40 pi L square*5 pi 4/2*R4-r4+20 pi square+5 pi 4*R cube-r cube*L tan alpha+30 pi square+5 pi 4*R square-r square L square tan square alpha+-120+30 pi square+5/2 pi 4*R-r L cube tan cube alpha okay, so this is the expression for the buckling force for this microneedle length, so L is the typical length of the microneedle, capital R is the outer radius of the microneedle at the tip.

So this is the tip so capital R is the outer radius and small r is the inner radius, and alpha is the tapered angle okay. So with that you can get an expression for moment of inertia and the buckling force okay. Now the fracture force we can write down the expression for fracture force for a hollow tapered needle, the fracture force is derived from thin cell model meaning the tip radius is >10 times the wall thickness okay.

So in that case the fracture force Ff is given by 2 pi rt *t sigma critical*sin alpha okay, so here this is this would be the tip radius, and t should be thickness of the wall because we are talking about a hollow microneedle, and this is the critical okay in fracture right. So you know we also have to ensure in the design that the fracture force is you know it is not exceeded by the insertion force, so the insertion force has to be <the buckling force, and it also as has to be <the fracture force, so the insertion force has to be <the fracture force.

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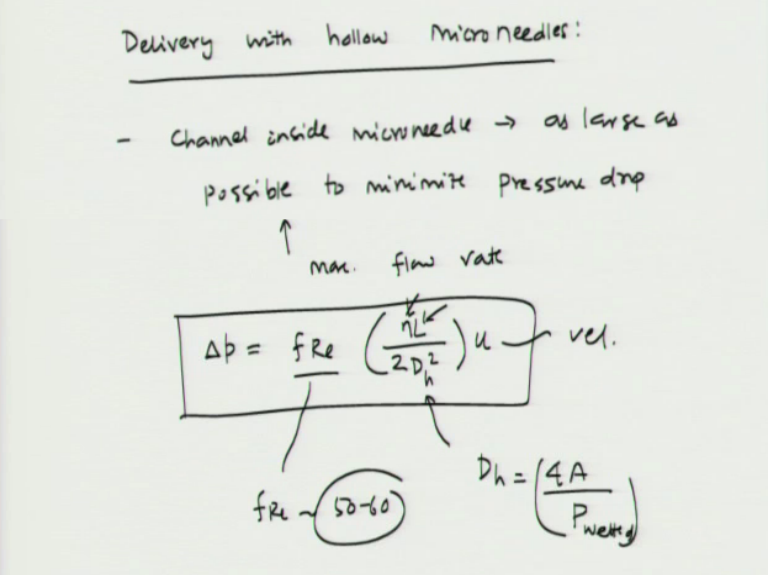

So now let us look at the flow characteristics of a micro needle, so look at the delivery with hollow microneedles, so you know one of our goals while designing microneedles from the perspective of flow is that the pressure drop has to be small as possible okay, and for that we need the inner bore of the microneedle has to be as large as possible to reduce back pressure okay. So we need the channel inside microneedle as large as possible to minimize pressure drop okay.

And so that would allow maximum flow rate, so the delta p=f Re*eta L/2 Dh square*velocity okay, where f Re for laminar flow as you are talking about microneedle has a value so f Re is between 50 to 60 okay, and eta is the dynamic viscosity, L is the length of the microneedle, Dh is the hydraulic diameter which is 4*area of cross section/wetted perimeter, and u is the velocity okay. So these are different criteria based on which microneedles are designed.

One from the mechanics point of view you know the insertion force has to be <the buckling force and the critical force, and in order to in a supply delivery with certain low rate we have to ensure that the inner bore of the microneedle it is as large as possible so that the back pressure is less okay. So with that we complete our discussion on microneedle let us move on to microparticle separation.

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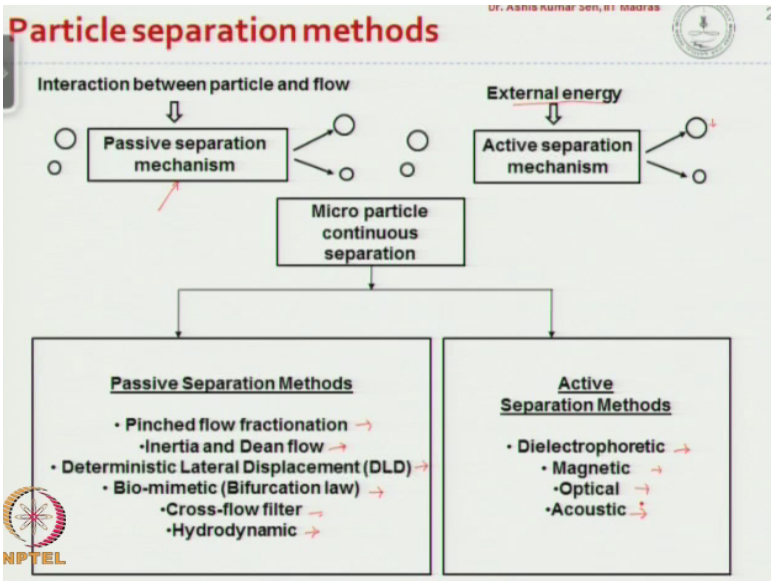

So we talked about microparticle separation, microparticle separation as different applications in biomedical and in chemical analysis, it also has applications in chemical industry, mineral industry and the many other applications that it sees okay. So let us look at the principle of different principles of microparticle separation. So as you can see here the microparticle separation is broadly classified into 2 categories, one is the passive separation.

The passive separation mechanism does not use any external energy, it uses the interaction between particles and the flow to separate particles based on physical properties. Then we have active separation mechanism which makes use of external energy, and uses the external energy like electric field and magnetic field to separate particles okay. Now here you can see there are different principles in passive and active separation methods.

In passive separation methods we have pinched flow fractionation, inertia and dean flow, and we have deterministic lateral displacement or DLD, and then we have biomimetic or bifurcation law, cross flow filter and then hydrodynamic separation okay. And in active separation method we have dielectrophoretic, magnetic, optical, and acoustic. So look at each of these techniques in detail.

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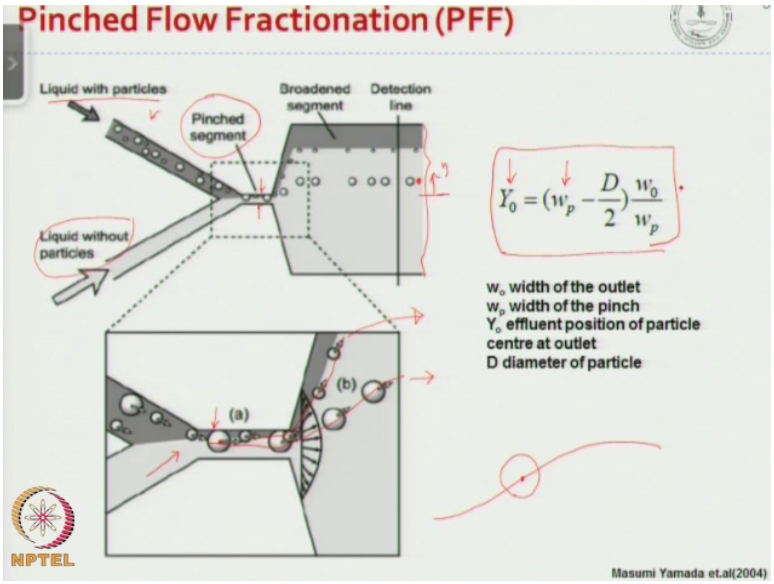

So this is the pinched flow fractionation technique as you can see here, here we have a sample that contains the particles and here we have a buffer which does not have any particle, and this sample is focused by the buffer stream so that the particles get a line to one of the side walls, and this is known as the pinched segment. So this has a lower width of the channel, and as the pure fluid focuses the particulated fluid, the particles get a line to this side wall.

And as we know the particles have a tendency to flow along the streamline passing through the center of mass okay, so the particles have a tendency to flow along the streamline that passes through its center of mass following that principal for smaller particle the streamline passing through its center of mass will be closer to the wall okay, so it will be closer to the wall, and for a larger particle streamline passing through its center of mass will be away from the wall okay.

So you know the different size particles follow their corresponding streamlines passing through their center of mass, so we would have you know after the pinched segment when the flow gets into a broadened segment, so this is basically amplifies the separation distance between the streamlines then the smaller particles will go towards the closer to the mall, whereas the larger particles will go toward the center.

So in that you know mechanism would be able to separate particles of different sizes across the channel okay, and this is important you know formula that is used for design of pinched flow

fractionation channels. So here Y0 is the position of the particle center at the outlet okay, so at the outlet let us say this is the position of particle which is Y0, so Y is in this direction so WP is the width of the pinched segment so this is WP, and W0 is the width of the outlet okay the total width here is W0, and D is the diameter of the particle.

So this is how these parameters are related okay, so Y0=WP-D/2*W0/WP, so this is the formula which is used to design pinched flow fractionation networks okay.

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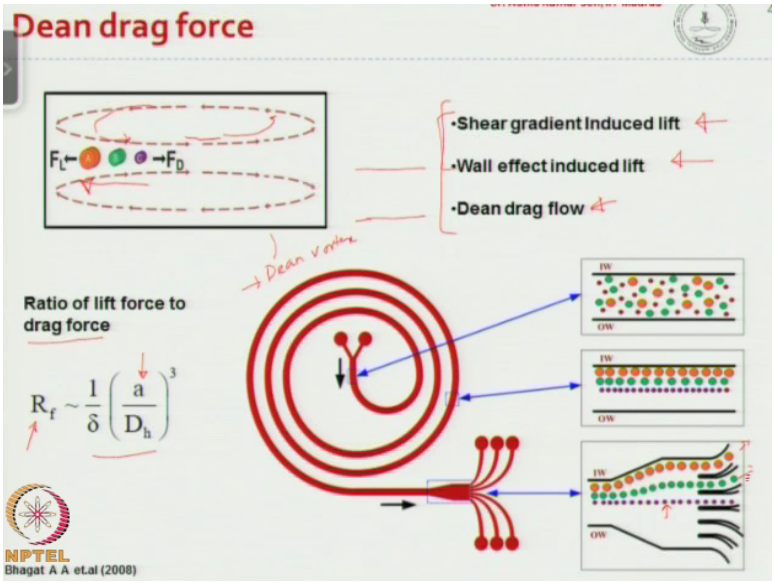

Next, we move onto a dean drag force, so the dean drag force mechanism is based on 3 different kind of forces, here as you can see we have shear gradient induced lift, we have wall induced lift and dean drag flow okay. Now when particles move inside a fluid in a channel the difference you know if a particle is moving through a channel the difference between the particle velocity and the liquid velocity is higher closer to the channel as compared to that of particle closer to the center okay.

So that generates a force closer to the wall okay and that is known as the shear gradient induced lift, so there is a lift force closer to the wall in the direction closer to the wall that is known as shear gradient induced lift okay. And there is the second force which as you know in because the speed of the velocity of the liquid is maximum at the center as compared to that at the wall there is a lift which is going to be from the wall into the center of the fluid.

And that is known as the wall effect induced lift okay, so as you can see here this is the 2 forces one is shear gradient induced lift, and the second one is wall effect induced lift okay. Now there is the third force which is called as dean drag flow, so the net effect of these 2 lift forces is outward okay, so it is going towards the channel wall. Then you know because the speed of the liquid is higher at the center the liquid tends to move outward closer to channel wall.

And to satisfy mass conservation the slow moving liquids come back to this towards the center, so as a result we would have 2 opposite vortex at the top and bottom walls okay, so these vortexes are called dean vortex okay, and the direction of the drag force that is induced because of this dean vortex towards the center okay. So the net lift force is acting towards the wall, and the dean drag is acting towards the center, and if you take the ratio of lift force drag force it will vary as this okay.

So this is the ratio of the lift to drag force which is 1/delta*a/Dh whole cube okay, so a is the size of the particle the radius of the particle, and you can see that the ratio is the function of the third power of the particle size, so based on this mechanism particles of different size will be subjected to different ratios of lift force and drag force as a result they will be separated in a direction from the center to the wall of the channel.

So as you can see here in this case there are a particle mixture is included you know infused into the channel at these inlets, and as it moves through the spiral channel because of the competition between the drag and the lift force you can see that the larger particles which have you know higher lift force as compared to the drag force gets towards closer to the channel as compared to the smaller particles. So that is how they are going to be separated based on size.

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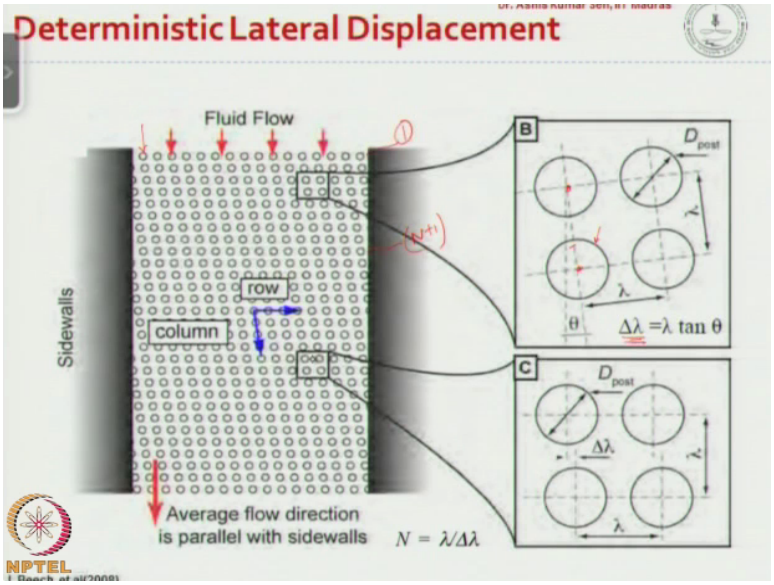

Next, we look at a technique all deterministic lateral displacement or DLD, here we have in the channel an array of post that are sticking from the channel okay, and the deterministic lateral displacement is based on the principle of steric hindrance. Steric hindrance means the wall is trying to apply force on the particle to escape from one streamline to get into another streamline okay that is known as steric hindrance okay.

If you look here there are different rows here, and as compared to the first row the second row is offset by distance delta lambda okay, and the angle between the center you know the vertical line through the center of the first row let us say this post and the second row first column post is theta okay. So in the second row the corresponding post is displaced by delta lambda, so it creates an angle theta at the center of the first post okay.

So delta lambda is going to be lambda*tan theta, where lambda is the separation distance between the rows and columns okay. Now the first row is going to be repeated after Nth row, so N+1 row, the first row and the N+1 row which is here they are the same, they have same position but the others each subsequent are displaced by delta lambda okay, so that is the arrangement that is the geometry.

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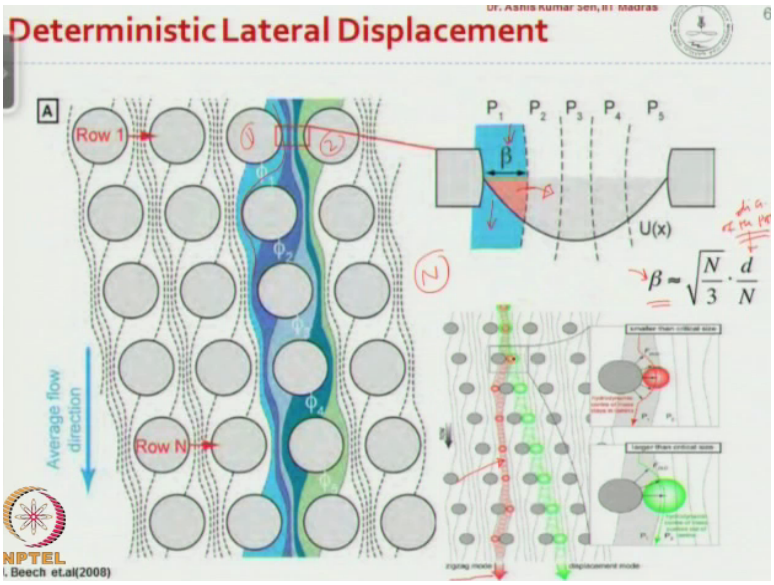

Now if you look at the mechanism between 2 adjacent post, let us say this is post 1 and this is post 2, we have different streamlines okay, so in this case we have 1 2 3 4 streamlines, now if you look at the stream between the surface and the first streamline the width is beta okay. And this beta is expressed as square root of N/3*d/N, where N is the period of the array, meaning the first and N+1th row have the same configuration okay.

So that is what we have seen in the first and the N+1th row have the same configuration, so the geometry has a period of N okay, so the geometry has a period of N and so that is how we can express beta in terms of N and d, beta=square root of N/3*d/N and d is the diameter of the particle okay so d is the diameter of the post okay so you can find beta. Now if the size of the particle is <beta<this characteristic length that we have just defined.

Then it has a tendency to stay with in this blue stream okay, so it will follow within the blue stream in what is called as the zigzag path okay, so the particle will move almost straight but in a zigzag mode okay, following this red path. So the red particle has size <beta, and so it follows the zigzag mode. If the radius of the particle is >beta then it will move from this streamline this stream into the next stream okay.

So as you can see along the green line the particle having radius >beta, it will get displaced into the next streamline and it keep on getting displaced, so that it gets into displacement mode and

the particle will exit there okay. So based on the particle size the smaller particles will follow the zigzag mode, and the larger particles will follow the displacement mode, and that is how we can separate them okay.

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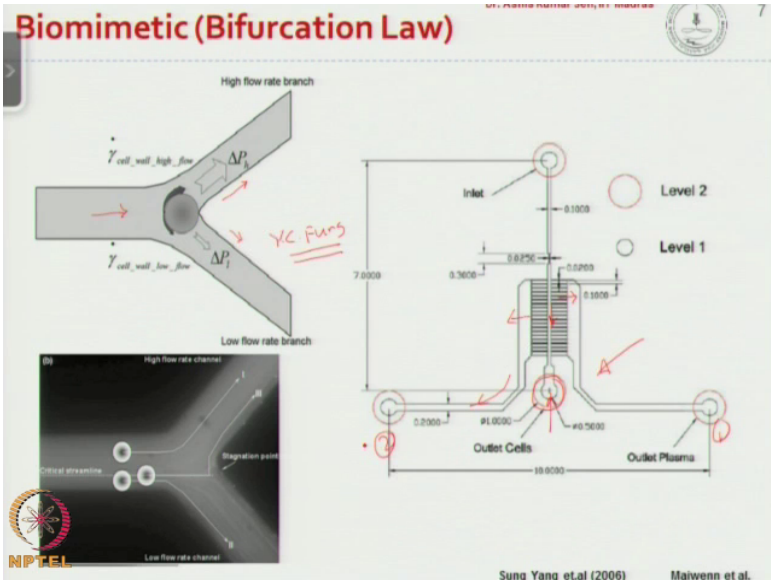

Now the next principal is based on biomimetic or it is also known as bifurcation law, and this was first reported by YC Fung, who is the father of modern biomechanics. And what he told is that a cell have a tendency, let us say a cell is flowing along a channel and it encounters a bifurcation where the flow rates are different, so the flow rate here is higher, flow rate here is lower, the cell has a tendency to get into the high flow rate channel okay.

So based on this principle the particles and liquids can be separated, so as you can see here one such device has been fabricated by Maiwenn et al, and it was demonstrated that blood having the cells and the pure fluid which is the plasma, by establishing the channel geometry such that the flow rate in this direction is higher as compared to in the lateral direction, the cells would be collected here in the high flow rate channel they can flow, and can be collected at this outlet.

And the plasma which is particle free fluid can flow in the side channels and be collected at this outlets okay. So that is how we will be able to separate cells and plasma from blood using the biomimetic or by bifurcation law method okay.

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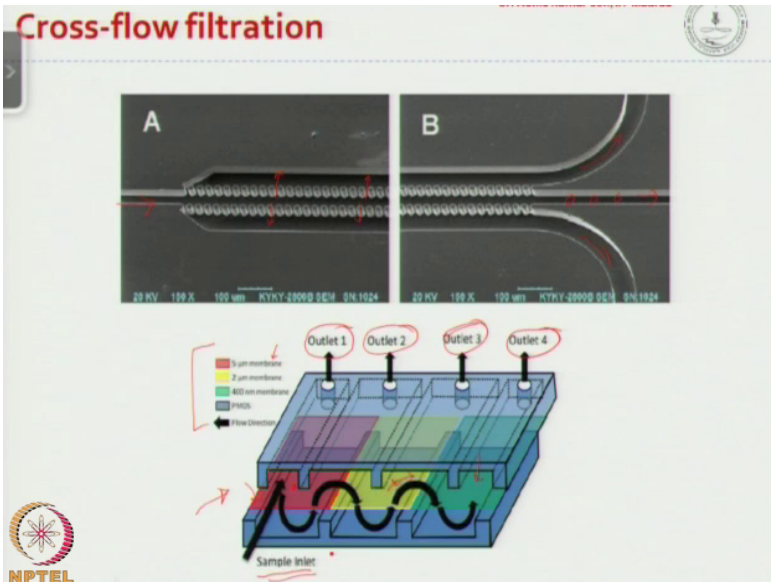

So next we move onto cross-flow filtration, in cross-flow filtration you know we have so as you can see here let us say the particles sample comes in here. And you know the difference between the cross-flow filter and the dead and filter is that, in cross-flow filter the filtration occurs in a direction perpendicular to the normal to the flow direction okay, so that is how the pores of the filter do not get clogged and continuous filtration is possible.

So in this case we can see that as the sample containing particles comes in the gap between the post on the sides of the channel the pure fluid can escape where the particles cannot escape, so the pure fluid escape through the posts on both sides, and the pure fluids are collected here and the particles are collected here okay. So that is the principle of cross-flow filtration. This is another work that has been reported as you can see here.

The sample comes in here with different size particles, and there are membranes of different size as you can see here, the red is 5 micron membrane, and yellow is 2 micron membrane, and the green is 400 nanometer membrane. Now as the sample comes in through this filter, since it has 5 micron size filter, the particles <5 micron size will get filtered and come up okay, and the particles that are >5 micron will come out through the outlet one.

Similarly, then next it will go to the 2 micron membrane, then particles of size <2 micron will come up and the particles <2 micron will come in outlet 2. Similarly, here you know in particle 3

what will happen is the particles of <400 micron will come here, and the particles >400 nanometer will come out in outlet 4. So that is how we will be able to separate different size of particles in a sample using cross-flow filtration.

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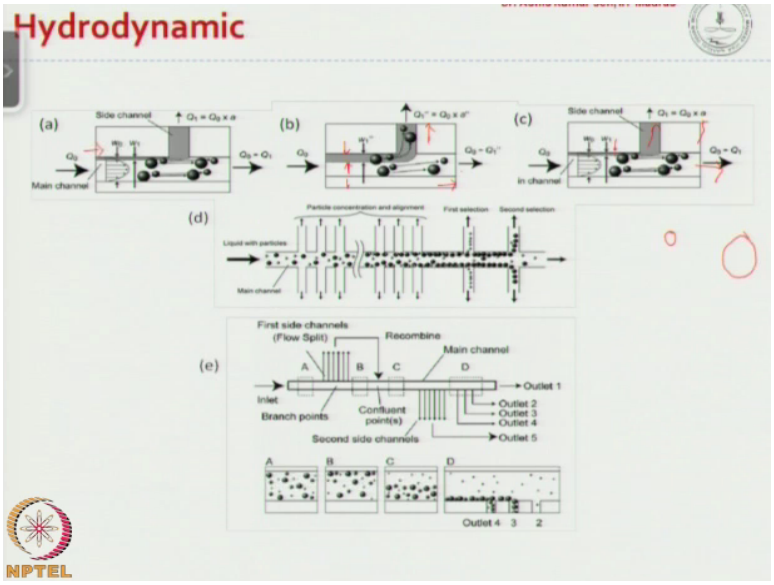

Next, we talk about hydrodynamic technique, in hydrodynamic technique you know the particles mixture comes from the channel here, and if you can adjust the flow rate ratio of this branch channel to this main channel such that the stream width here okay, the stream width that is stepping into the side channel is >the radius of the largest particles that is present in the sample. Then most of the particles will get into the side channel okay even the larger particle will get in the side channels, and some that are present here will escape straight.

Similarly, if we adjust the flow rate ratio such that the stream with here is <even the smallest particle that is present in the sample, then all the particles will go into straight okay. Now if we can adjust the stream width such that it is >the radius of 1 set of particles, whereas it is <the bigger particle, then selectively particles can be collected at different outlets. So that is the principle of hydrodynamic filtration. So with that let us stop here, we will continue our discussion on active separation in the subsequent lecture.