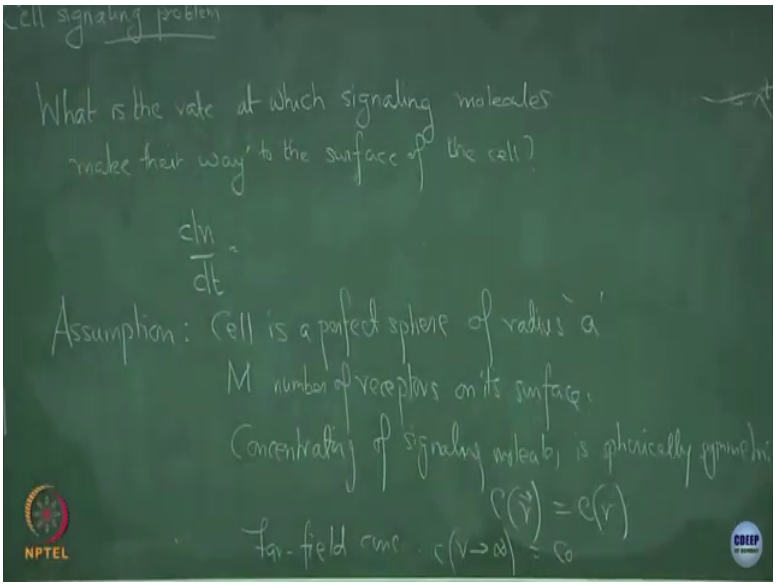
Physics of Biological Systems
Prof. Mithun Mitra
Department of Physics
Indian Institute of Technology, Bombay

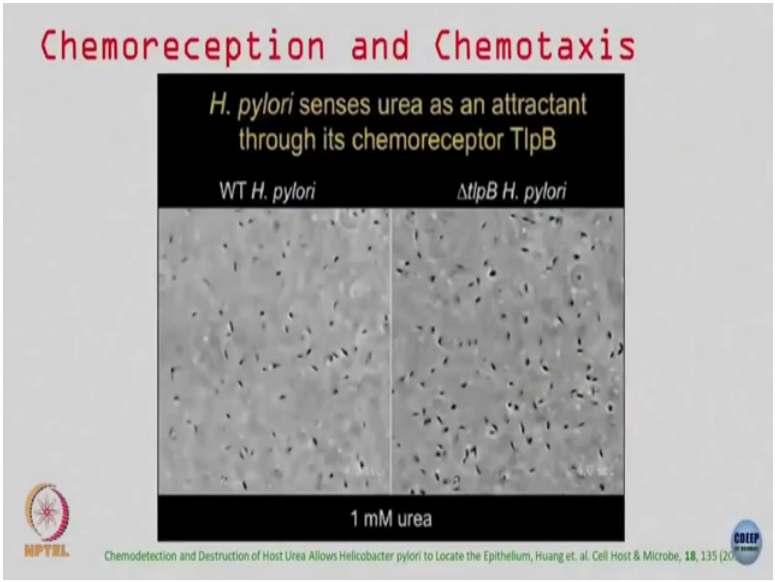
Lecture – 12
The Cell Signaling Problem

(Refer Slide Time: 00:23)



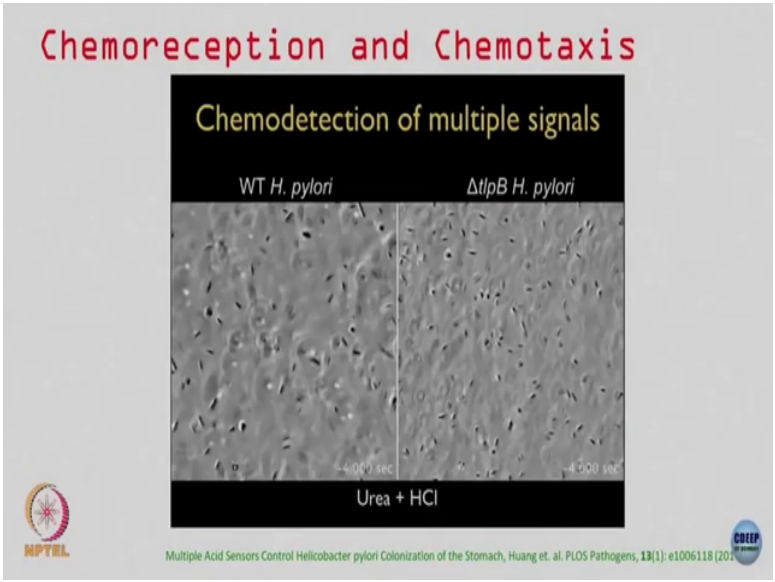
Alright, now let us come to this problem that I want to discuss today which is the Cell Signaling Problem. So, if I just to remind you so, we discussed this sort of from last class this week. So, here was this problem that I have some sort of a chemical which the cell is going to sense and it is trying if it is an attractant it is going to try and move towards that chemical.

(Refer Slide Time: 00:56)



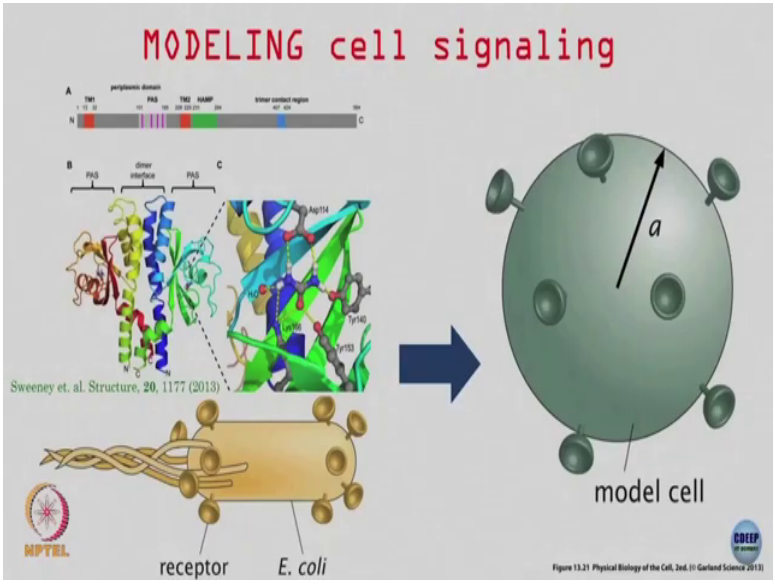
If it is a repellent, it is going to try to move away from that chemical and so on.

(Refer Slide Time: 01:00)



So, we saw this H pylori movies which had we had this H pylori movies when we saw it moving either towards urea or away from HCl and so on.

(Refer Slide Time: 01:12)



So, this was the picture that I have this cell. The cell has certain chemo receptors on it is surface which are proteins which can detect and recognize the chemical. What I want to know is that if I have some chemical source far away at what rate is the cell going to detect these chemicals with the help of these chemo receptors, ok. So, that is that is the basic problem that I will try to answer.

So, let me write down the proper question. So, what I want to ask is that what is the rate what is the rate of rate at which signaling molecules which are like your urea or the HCl in the case of pylori make their way to the surface, make their way to the surface of the cell ok. Or in other words, let me say I want to calculate something which is like this rate so, dn dt.

So, the number of signaling molecules coming to the surface of the cell per unit time, that is what I want to ask at this as far as the cell signaling growth of course, ok. So, we will make a

number of assumptions and I will see. So, your cell could be whatever arbitrary complicated shape, right; for example, E coli is like this sphero cylinder we saw, if you take an animal cell that is soft; so, it can take variety of shapes. But, what we have solved this for is this model cell which is a spherical cell spherical cell ok, spherical cell yes ok.

So, let me write down my assumptions. So, I assume if the cell is a perfect sphere. The first step to doing a physics modeling of anything is that assume it to be a perfect sphere, but it is not a very hard constraint to relax. Of course, if you take arbitrary shapes writing down analytic solutions becomes difficult, but you can always solve it numerically following the same technique.

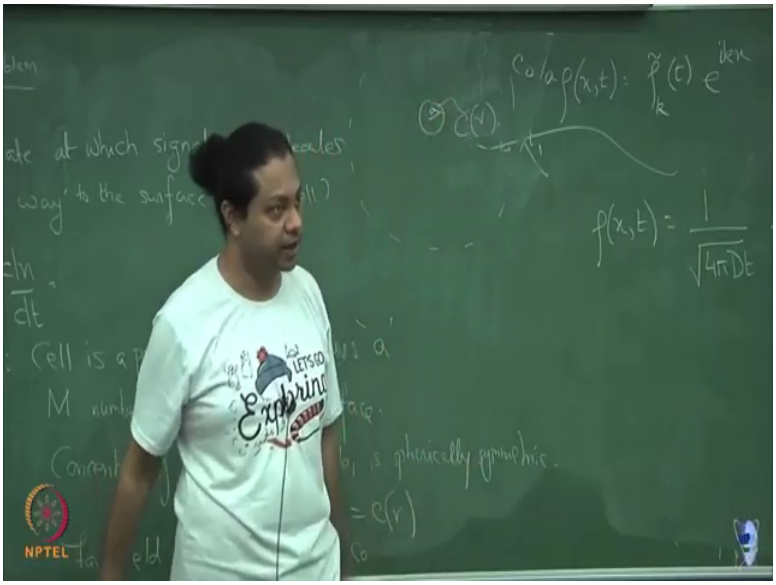
If you have some other shape for example, well defined shape with some symmetry for example, a cylindrical cell or something like that then you can again do it analytically, the mass will just become a little more complicated. So, I will do it for the simplest case which is a perfect sphere and let me say it is a perfect sphere of some radius of some radius. So, that is my model of the cell; let us say it has some M number of receptors, M number of receptors on it is surface which are distributed homogeneously uniformly on the surface of the cell.

So, often we will see you will see that for example, even in this cartoon of the E coli, the chemo receptors are clustered at the ends of the cell, ok. As far as this calculation goes I will not take anything like that into account, I will say that the receptors are sort of spread uniformly over the surface and there are M of them. So, because it is a perfect sphere and the receptors are spread uniformly on the surface.

Let me make another assumption that the problem is spherical. So, the concentration is spherically symmetrical spherically symmetric. So, the concentration of signaling molecules is spherically symmetric, which means that if I write this concentration. In general, it is a function of the vector r right, it might depend on which direction you are looking at and so on But, I will just say that if I make the spherical symmetric approximation is just a mag distance away from the cell that is the only thing that matters, ok.

And I will assume that you have a source of signaling molecules somewhere which was your pipit in these pylori experiments far away from the cell. So, I will assume a far field concentration, I will assume a far field concentration which is c. So, as r tends to infinity, I will say that my concentration goes to c naught, ok.

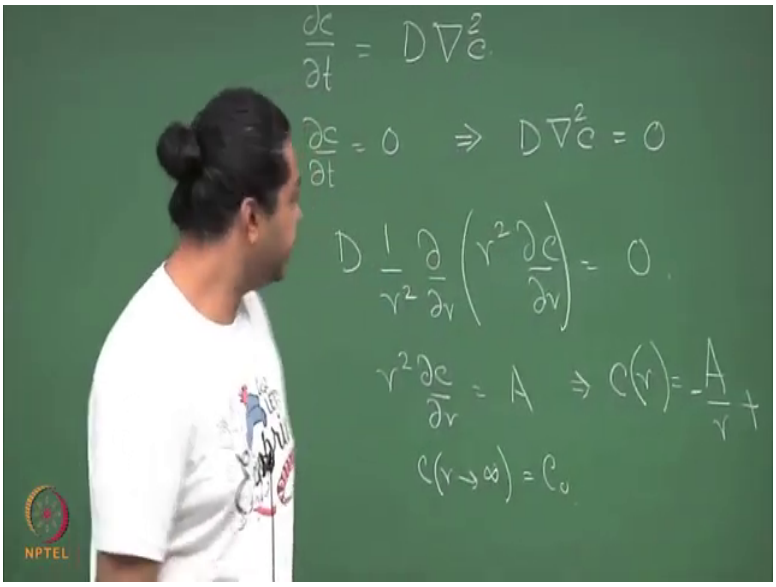
(Refer Slide Time: 05:50)



So, this is then my thing that I have a cell over here of radius a, far away from that at infinity. I maintain a concentration of c naught using some apparatus that I have and if everything is spherically symmetric look what I want to solve for is the concentration profile in all of this space in between, ok. So, I want to solve for the concentration profile and because I have made the assumption that spherically symmetric, it only depends on the scalar r not the vector r, ok.

And this; so, these signaling molecules are being maintained at a constant concentration here, they are going to diffuse, right; they are going to perform a random walk through this space until they hit the surface of the cell. At the surface of the cell, you have these receptors which are going to absorb the signaling molecule and then respond to that by moving in some particular direction, ok.

(Refer Slide Time: 06:49)



So, the setup is clear. So, because they are diffusing, I will solve the diffusion equation for the concentration of signaling molecules del c del t is equal to D Laplacian of c, ok. So, here is my diffusion equation that I will solve. So, let me say that I want to solve it in the steady state, ok. So, when everything has come to nothing is changing with time anymore which means that I will take del c del t is equal to 0 which means the equation that I am looking to solve therefore, is D Laplacian of c is equal to 0, all right.

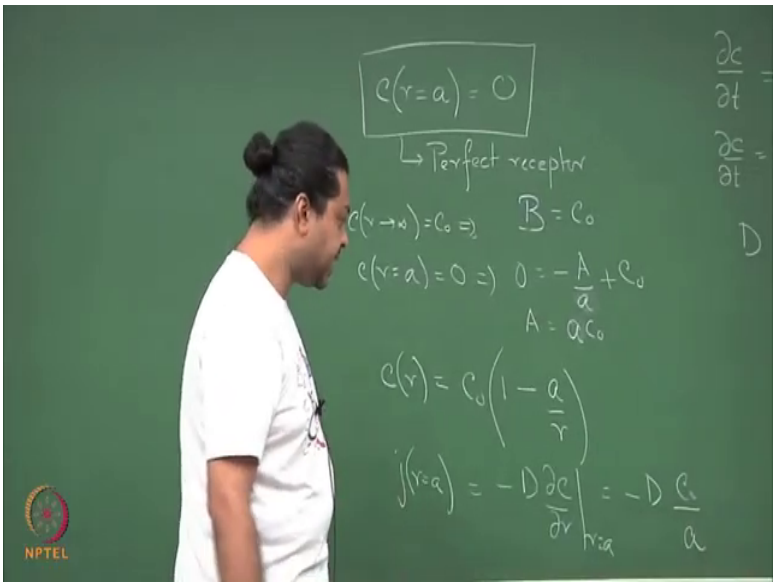
So, in what coordinate system should I be solving this you can of course, solve it in any coordinate system, but the most appropriate choice given that this problem that I have defined. I have a spherical cell and then there is a spherical symmetry is that I will solve it in the spherical coordinate system, ok. So, I write down the Laplacian the spherical coordinate system. So, what I have is D into 1 by r square del del r of r square del c del r is equal to 0 is really the Laplacian in the spherical coordinates. So, this is what I am looking to solve.

So, if I solve this what this means is that r square del c del r is some constant independent of r. Because, del del r of that quantity is 0 which means that I can write down my I can write down my concentration profile as a function of the scalar distance r as sum A by r plus B, right. So, if you solve this differential equation properly, the solution comes out to be c of r is equal to A by r plus B, there is a looking for the minus sign over here, ok. In order to determine the constants A and B, what I need to do is that I need to specify the boundary conditions of the problem.

Now, one boundary condition I have already talked about which is at the power field concentration is c naught that c as r goes to infinity is equal to c naught. So, that will fix one of the constants for me, but I need one more one more boundary condition. So, and that boundary condition will most naturally occur at the surface of the cell itself, the surface of the sphere.

So, what I will do over here is I will make an assumption. I will make an assumption that these cells are these receptors are sort of perfect receptors which means that whatever sort of signaling molecule comes to these receptors gets absorbed instantaneously and completely.

(Refer Slide Time: 09:31)



Which means that what the other boundary condition that I will choose is that c at r at r is equal to a the surface of the cell is equal to 0, ok. So, this is an assumption it is called the perfect receptor assumption perfect receptor assumption and basically it means what I said that once you anything that comes to the surface of the cell gets absorbed, ok. So, which means which is why that the concentration drops to 0. We will relax this in a few minutes and we will see what happens when we relax this constraint, but for the time being let me make this simple assumption that these cells are these receptors are perfect receptors, ok.

So, now let me I have these two boundary conditions, let me now put them in this solution and see what I get for A and B. So, if I put that c at r is going to infinity is c naught then what; that means, is that when r goes to infinity this term will drop out. And therefore, what I will get is that B is equal to c naught, if I put this condition that c at r equal to a is 0. What that

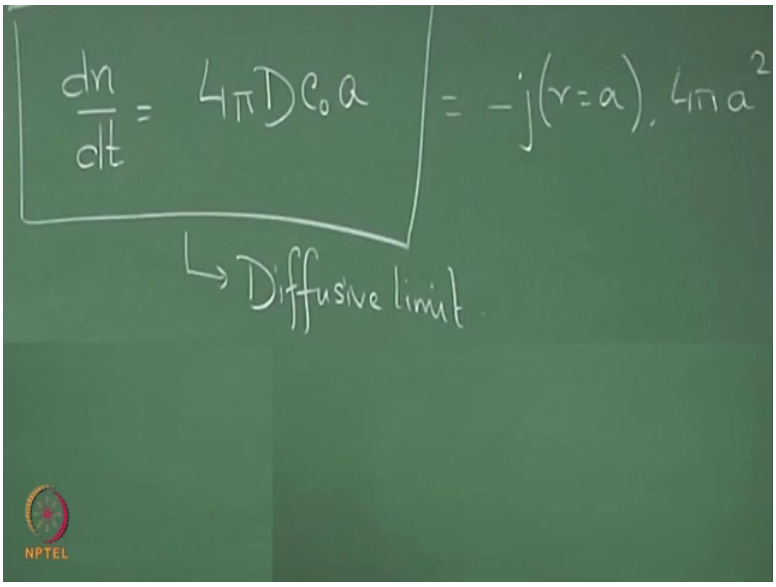
means is 0 is equal to minus A by r plus c naught which means that A is equal to rc naught, right.

So, sorry I made a mistake this is at r equal to A; so, this is A. So, this is capital A is equal to this small a times c naught, ok. So, what I have if I substitute back this A and B into that equation is a concentration is a solution for the concentration at any r and that turns out to be c naught which is common 1 minus a by r, right.

So, it satisfies the two boundary conditions that r goes to infinity this comes back to c naught when r goes to a, this c goes to 0, ok. So, it satisfied my boundary conditions. So, this is how my concentration profile will look like given that I make this assumption of perfect a absorbance, ok. So, now, from here I could ask that well now that I know the concentration profile, I can ask that how many particles makes it to the surface of the cell per unit time and to do that you can calculate first the flux.

The flux j of r at r equal to a; the flux at the surface of the sphere the incoming flux. Remember, the flux is nothing, but the number of particles per unit area per unit time so, that from Fick's law is given by minus D del c del r at r equal to a, all right. So, if I take del c del r then I will get; so, let me see minus D into del c del r will give me 1 over r squared. So, c naught by a by a square because I am calculating at r equal to a; so, this is my incoming flux, the negative sign simply says that your particles that are coming into the surface and getting absorbed.

(Refer Slide Time: 13:19)



So, this is my incoming flux and from there if I want to calculate the number per unit time, the number of particles per unit time remember the flux is the number of particles per unit area per unit times. So, if I want the number of particles that comes into the surface per unit time dn by dt that is nothing, but the flux at the surface times the area of the surface itself.

So, if I do D c naught a into 4 pi a square so, what I get is nothing, but 4 into pi into D into c naught into a, all right yes, all right. So, this is the number of paths in the case where I have the same diffusion going on and I have these perfect receptors, there is a number of particles per unit time that comes into the comes to the surface per unit time.

So, the dn dt is nothing, but what I did is minus j at r equal to a into the area of the surface, itself; so, which is this 4 pi D c naught a. So, this is very important limit it is called the diffusive limit, it is called the diffusive limit. And, what it says is that you if you have sort of

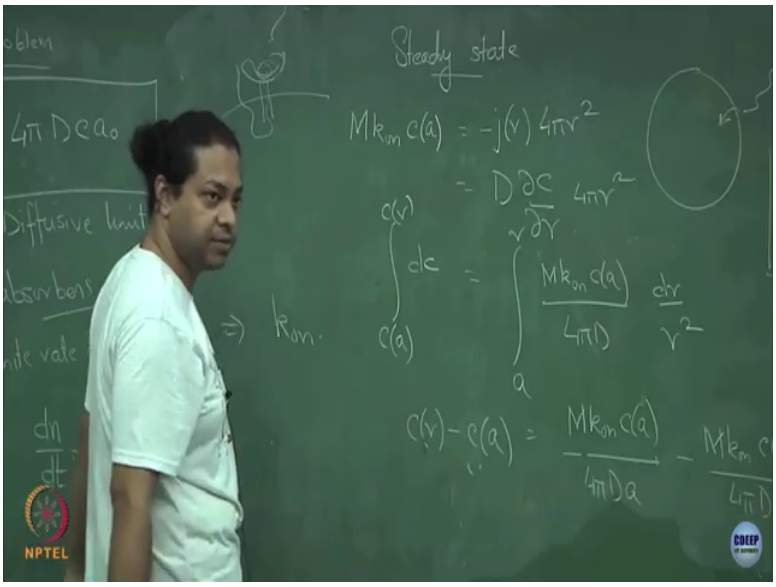
a chemicals which are diffusing and then getting absorbed at some surface like this r equal to the spherical surface at r equal to a. And if this process is happening simply by diffusion, then this is the maximum number of particles that you can absorb per unit time at this surface, ok.

So, it provides a limiting case and it is called the diffusive limit. So, as we go along in the course you will see that this we will use this diffusive limit sort of again and again. You might say that you know we are we have done this sort of more simplistic case which is that I have this perfect sphere and so on and most organisms will not be perfect spheres which is true.

But what; that means, is that what will happen is that this pre factor that I have this 4 pi that will sort of change, but roughly it will be of this order. You will have some correction terms maybe which are of order one depending on what geometry of the cell that you choose, but roughly this is going to be your limit the fastest that you can absorb particles providing these particles are simply diffusing, ok.

If you have other active processes which are being driven and so on then of course, you can go faster than this, but if you are relying purely on diffusion for the signaling molecules to reach your surface of the cell, this is the maximum speed that you can achieve. So, let me now just relax this constraint of this perfect absorbance. So, let me say imperfect absorbance.

(Refer Slide Time: 15:54)



So, it is good to have, it is good to have a clear idea of what assumptions you are making whenever you are trying to model. So, if you can if you want you can systematically relax them 1 by 1 in order to go closer and closer to an experiment real experimental situation, ok. So, it will not relax the others for now it is the spherical and so on, but at least I will relax this perfectly absorber approximation; so, imperfect absorbers I say, ok.

So, I will say that these receptors have some finite rate of absorption, there are some finite rate of absorption of signaling molecules which is let us say k on, ok. So, it will absorb these signaling molecules with some rate which is characteristic of the receptors which I will call as k on, ok.

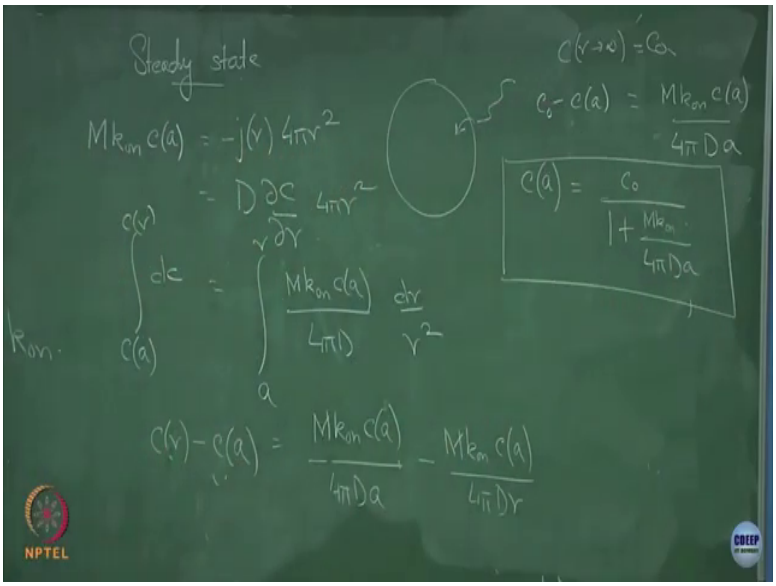
And remember, there are M absorbers which means that the number of molecules per unit time that gets absorbed at the surface of the cell is going to be M. If you have M absorbers,

each absorber is going to absorb with a rate which is k on and the concentration at the surface of the cell, ok.

So, if you have some concentration at the surface of the cell these molecules will get absorbed at some rate in x given absorber and you have M of those absorbers, ok; so, that is my rate of absorption I need to calculate this. Of course, k on and M are some parameters which I say whatever the cell has some number of receptors it has some rate of intake and I need to solve for what is the c of a, ok.

So, now unlike in the perfect receptor case, this boundary condition no longer hold this a right at r equal to a, this is no longer equal to c right because not if these are not perfect absorbers. So, some molecules will stay there at the surface of the cell, ok.

(Refer Slide Time: 18:06)



So, in a situation like this how would I define my steady state intuitively before we write it down mathematically, I can say that I will reach I will reach steady state when the rate; so, here is myself when the rate at which these diffusing molecules reach the surface of the cell is exactly the equal to the rate at which these molecules get absorbed into the cell, then I will reach steady state right make sense.

So, the rate at which this get absorbed is this we have written M k on c of a; so, we have written M k on c of a, right. The rate at which it reaches the surface of the cell is the diffusive flux times the area, right. So, minus j of r into 4 pi r square, right or so, if I write in terms of concentration j it is minus del c del r. So, D del c del r 4 pi r square, good. So, now, I can solve this, I now have an equation for c the differential equation for c D del c del r into 4 pi r square is equal to M k on into c of a.

So, I can integrate this; let us see I can integrate this between a to r some arbitrary r. So, dc from c of a to c of r and then on the other side I have integral M k on c of a by 4 pi D D r by r square from again from a to r right, I have just rewritten. So, dc is on one side, all the r terms on the other side. So, D r by r square and then hopefully these are M k on ca by 4 pi D r square, ok.

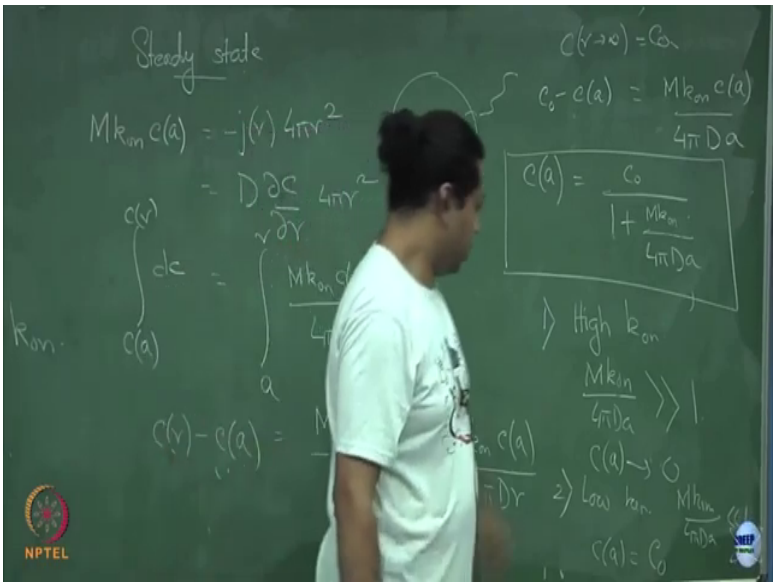
So, now, I can do this integration. So, this over here gives me c of r minus c of a this gives me minus 1 over r; so, M k on c of a by 4 pi D minus so, let me just do the lower limit first minus M k on c of a by 4 pi D r, here right. I do this D r integration between a to r, if you take the signs correctly and these are all constant M k on c a 4 pi D, all right ok.

I can now apply the other boundary condition; remember, the other boundary condition is still valid let us c at r going to infinity is c naught. So, if I put r is infinity in this equation c of infinity is c naught. So, c naught minus c of a, c naught minus c of a this term will vanish if I put r equal to infinity right 1 by infinity will be 0. So, I will I will be left with is this term M k on c of a by 4 pi D a.

So, in this everything is known except for this c of a; so, I can find out the concentration on the surface of this sphere now. So, I can solve for c of a that is going to be c naught by 1 plus M k on by 4 pi D a. So, this is the concentration at the surface of the cell many have imperfect receptors which are in up taking the signaling molecules with that way.

You can check that whether this makes sense if this receptors were very good. So, if it sort of absorbed everything that came into it which means that this k on was very high, right.

(Refer Slide Time: 22:43)



So, let me try a few limiting cases; so, high k on. So, let me formally let me write M k on by 4 pi D a this object over here is much much greater than 1, if I take this limit. So, it is almost infinitely large if k on is like infinity then what will the c of a go to what will this equation reduce to 0 right which is my perfect absorber. If my k on was so large that everything gotten

absorbed, I should get back whatever I had for the boundary condition which is c of a equal to 0; so, that is good.

On the other hand if these were very poor absorbers nothing got absorbed. So, very low k on, right or equivalently this object M k on by 4 pi D a was much much smaller than 1, then what should I expect what should this c of a equal to?

Student: c 0.

c 0 right; so, nothing gets absorbed. So, just stay as whatever the concentration at infinity was, right. So, then c of a goes to, c naught so, if this was very small then I can neglect this with respect to 1; so, it goes back to c naught. So, the limits work out very nice they work out nicely as it should, if you have very good if you have perfect absorbers your c of a goes to 0 if you have hopeless absorbers your c of a just stays at the background concentration nothing gets absorbed ok. So, now, that you know this c of a which is the concentration of, yes.

Student: Cell does not had to be absorbed (Refer Time: 24:22).

Why not?

Student: See the pylori absorbed in.

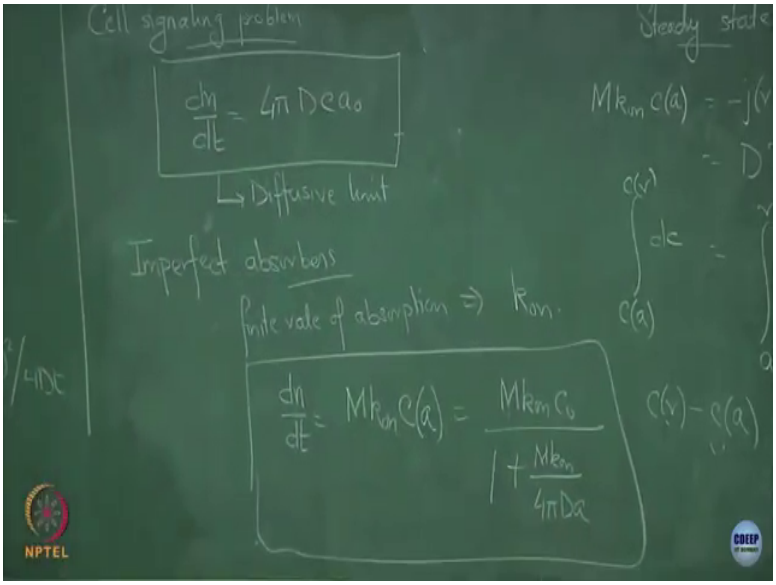
Student: Cell is at absorbing nuclear (Refer Time: 24:32).

It can so, it up it this you have the surface of the cell right where you have this receptor and the signaling molecule comes. It can bind to this receptor and cause a cascade of changes which causes the cell 2 so, but this thing is no longer free in solution, ok. So, the signaling molecule is no longer free in solution it causes the chemical reaction they are getting absorbed with the receptor. It can even get internalized in some cases where you can get (Refer Time: 25:05) ok. What was I saying?

Student: (Refer Time: 25:14).

Right; so, now, I know this c of a which is the concentration of signaling molecules at the surface of the cell.

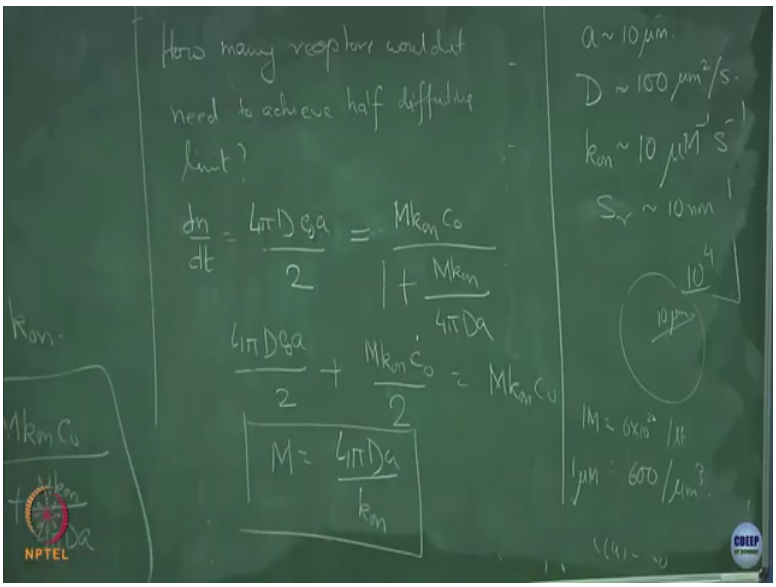
(Refer Slide Time: 25:22)



I can just substitute that here to find out what is this new dn dt, I know what was it in the case of the perfect absorbance. So, for this case it is then just M k on M k on c naught by 1 plus M k on by 4 pi D a, right. So, for the case of imperfect receptors, this is the rate at which signaling molecules get absorbed by the cell by the surface of the cell, ok. The better the better the receptor so, the higher k on the better this dn dt higher the number of receptors that you have higher M higher this dn dt and so on, ok.

Remember that this rate that we have calculated this dn dt that is going to be limited by this diffusion diffusive limit right, this is the best that you can achieve because it is the case of perfect receptors. So, this dn dt is definitely less than this.

(Refer Slide Time: 26:32)



So, what we can ask is that well, if the cell sort of keeps on increasing the number of receptors that I that it has on it is surface, how efficient is that how better does it do. So, to do that what we will ask one question which is let us say how many receptors would the cell mean; so, I will ask how many receptors would it need would it need to achieve a half the diffusive length. So, here is the maximum speed the maximum rate at which it can take.

So, they say that well as long as I am in the order of magnitude is the same, I have done reasonably well right, let me say that how many receptors. So, what would be the number of receptors that I need to achieve half this rate? Ok; so, that is the question that it was. So,

basically the dn dt that I am looking for the dn dt that I am looking for is half of this maximum rate. So, 4 pi D c a naught by 2 and I want to find the number of receptors M that will give me this rate.

So, M k on c naught by 1 plus M k on 4 pi D a. Question is here ok; so, this question is here I have the imperfect receptors with a certain rate at which it absorbs the molecules which is k on. I ask how many of these imperfect receptors would I need on the surface of the cell to achieve this specific speed which is half of the maximum speed I could achieve, ok.

So, this is this you can solve. So, 4 pi D c a naught by 2 plus 4 pi D a; so, M k on c this I have put the this c naught and that it a M k on's c naught by 2 is equal to the right hand side is this M k on c naught, right. I want to solve for M; so, the solution for M is then this is what M is. What is M, 4 pi D by k on 4 pi D a by k r, right.

So, this is the number this is the number of receptors that I would need provided the receptor has a rate k on at which it takes the cell has a size a the molecules of this diffusion coefficient D. This is the number of receptors that I would need in order to achieve half the diffusive limit, ok. This by itself of course, does not tell you much what is 4 pi da by k on. So, what we will do is that we will put in some typical numbers now and see how many receptors does it translate to, ok.

So, let me see; so, let us say a typical you carry eukaryotic cell. So, let me stake a as some 10 microns, right. So, my cell is a sphere of 10 microns which is roughly a cell size as we discussed let me take a typical diffusion constant. Which is again roughly let me say 100 micron square per second I will need a k on for which I use again. So, these are all order of magnitudes roughly in the same correct order of magnitude.

So, 10 per micro molar per second and at some point maybe I will also need the size of receptor; so, let me just call that something all right now. So, a typical; so, receptor is a protein molecule right. So, typically let me say size of receptor let me call that something S r a sum 10 nano meters. So, these are just order of magnitude estimates.

So, typically eukaryotic cell, typical diffusion constant, typical uptake rate and some typical size you can substitute this back here and find out how many receptors that does that translate to; so, but before we do that. So, for at least; so, this is the cell of 10 micron size right. How many receptors would you expect on the surface of this cell? Order of magnitude ten, hundred, thousand, million, billion from our estimates of protein numbers and so on in the first class, this is just the case I mean this is. Anyone?

Student: 10 to the power of 4.

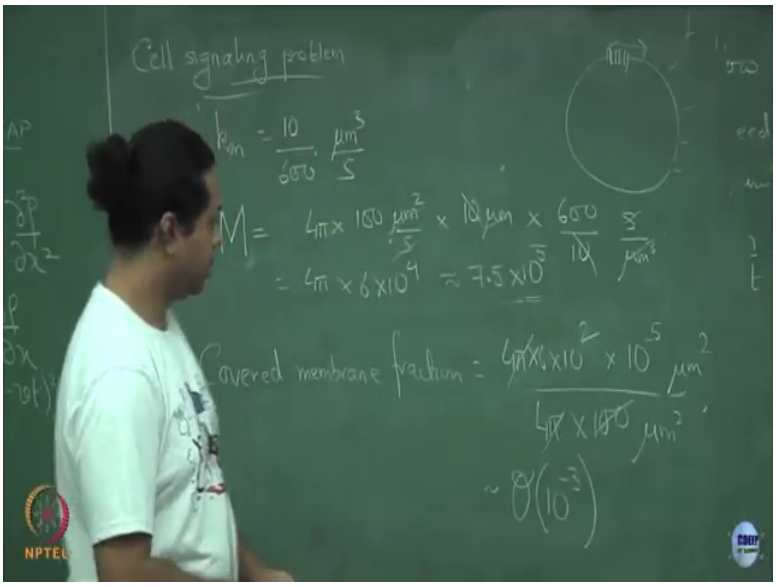
10 to the power of 4, good we will start off with that and see ok; so, now, who is going to put in these numbers and tell me. Remember, we should put take everything in the right units; so, what is 1 molar, 1 molar remember is Avogadro's number. So, the six point, let me just say 6 6 into 10 to the power of 23 molecules per liter, 1 liter is, what is 1 liter in micron cubed, this 1000 cc.

So, therefore, someone 6 into 10 to the power of 23 by how many microns cubed?

Student: (Refer Time: 32:50).

10 to the power of 15, good; so, 10 to the power of 15 per micron cubed and I am talking in terms of micro molar. So, 1 micro molar is this into 10 to the power of minus 6. So, that is 17, 15; so, 600 per micron cubed right, that is 1 micro molar. So, this is 600 per micron cubed, ok

(Refer Slide Time: 33:32)



So, k on if I translate this let me do here that is getting too crowded. So, k on if I translate that k on is 10 per micrometer micro molar. So, 10 by 600 into micron cubed per second right, tell me if I am wrong tell me if I am making mistake anyways; so, that is the only conversion ok. So, then I can calculate what is the number of receptors. So, this is 4 pi into 100 micron square per second this diffusion into the size which is 10 microns divided by k on which is 10 by 600.

So, 600 by 10 second per micron cubed, right; the units work out micron cubed on top micron cubed on bottom second. So, this gives me a pure number which is as it should, there is the number of receptors I am calculating. So, this is 4 pi into 6 into 10 to the power of 4, where is 4 pi roughly 12; 12 6, 72. Let me just say 72, 75 into 10 to the power of 4 so, 7.5 into 10 to the power of 5 receptors.

So, the number of receptors that you would need to achieve half of this maximum speed maximum diffusive speed is of the order of 10 to the power of 5 receptors on the surface of this 10 micron cell. Is that a large number or is that a small number?

Student: (Refer Time: 35:27).

Student: (Refer Time: 35:28) large.

So, how would I say that, what is it large in comparison to.

Student: (Refer Time: 35:34) large.

Yes of course, it is a large number, but a.

Student: (Refer Time: 35:39).

Let me say that I have it set right on which I have placed this 10 to the power of 5 receptors, right; each of them occupy some area, ok. I could ask that given I have these many receptors 10 to the power of 5 which is a very large number; what fraction of the membrane is covered by these receptors, ok; so, what fraction of the membrane is free for other proteins.

If this is taking up all my membrane area then that is pretty bad that is pretty large right, I do not have anything left for any other proteins to do it is job. So, that is one thing I calculate, another thing I can calculate is that well maybe what is the separation between given I have 10 to the power of 5 proteins. What is the typical separation between 2 proteins and how does that compare to the size of the protein itself, right.

If it is of the order of the if it is the same as the size of the protein which means, I would need this protein sitting next to each other in order to accommodate these many things. There is a

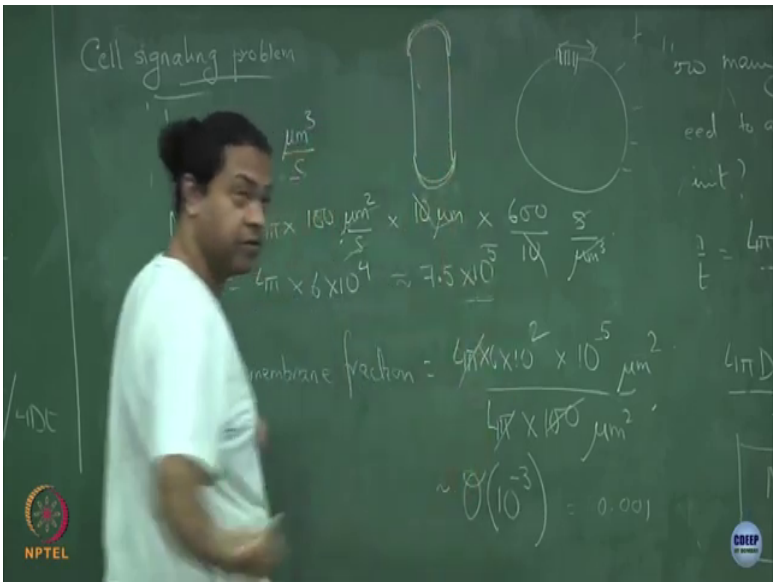
some measures that yes 10 to the power of 5 is large, but does it really fill up the cell. So, that again we can do

So, let us say let me do the area calculation, I have these many receptors. So, I want to let us say I want to find this covered membrane fraction, covered membrane fraction which is how much area is taken up by these proteins divided by the total area of this 10 micron cell. So, the covered membrane fraction is something 7.5 into 10 to the power of 5 into the area of the protein each individual protein, I will assume as 10 nano meter square.

So, 10 nano meter square and on the denominator is the surface area of the cell which is 4 pi r square; so, that is 100 micron square. So, what is that, it might help instead of writing 75, I had some 4 pi into 4 pi into 6 into 10 to the power of 4, then I can cancel off the 4 pi basically and nanometer square I need to convert to micron squared.

So, this will be 10 to the power of minus 5 micron square; so, good. So, how much is that. So, 4 pi 4 pi cancels off, 100 this becomes 100. So, roughly of the order of 10 to the power of minus 3 right, 10 to the power of 2 into 10 to the power of minus 5; so, roughly of the order of 10 to the power of minus 3. So, the fraction of the true I have 10 to the power of 5 protein molecules, but the fraction of the area that it covers out of the total area that is available to the cell, it is like something like 0.001, ok.

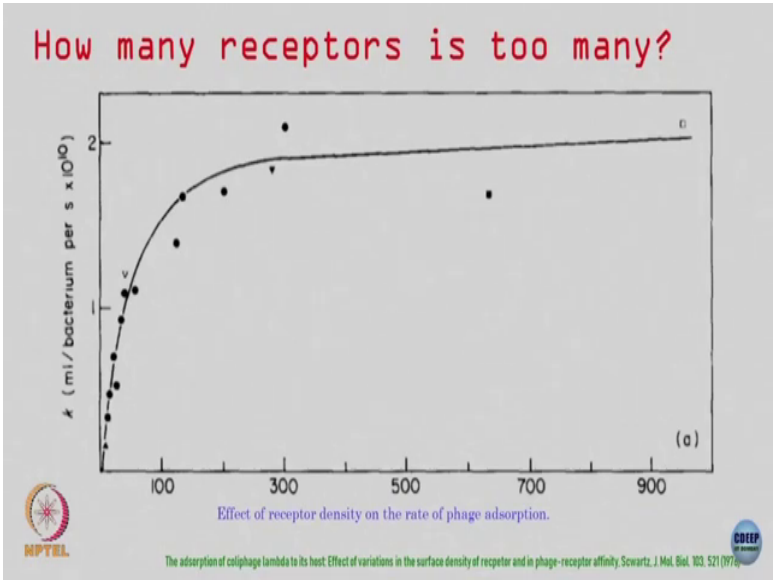
(Refer Slide Time: 38:51)



So, it is still pretty sparse and even so, it is a lot of proteins, but it is still pretty sparsely distributed on the cell, but even with this parse distribution, I have achieved half of my maximal speed. So, you can say that well instead of 10 to the power of 5, I will put in to the power of 6; it does not give you an order of magnitude estimate. Maybe you are at 50 percent it takes you to 60 percent, it is not really worth it for the cell; cell is already doing pretty well even with this sort of sparse distribution.

So, actually if you look at you can also calculate the mean separation given these many it comes to around 80 nanometers roughly between 2 proteins and a typical protein is square root of this; so, it is 3 nanometers size wise, ok. So, 3 nanometer protein separated an interest proteins separation of around 80 nanometers; so, it is by all measures on the surface of the cell it is pretty sparsely distributed.

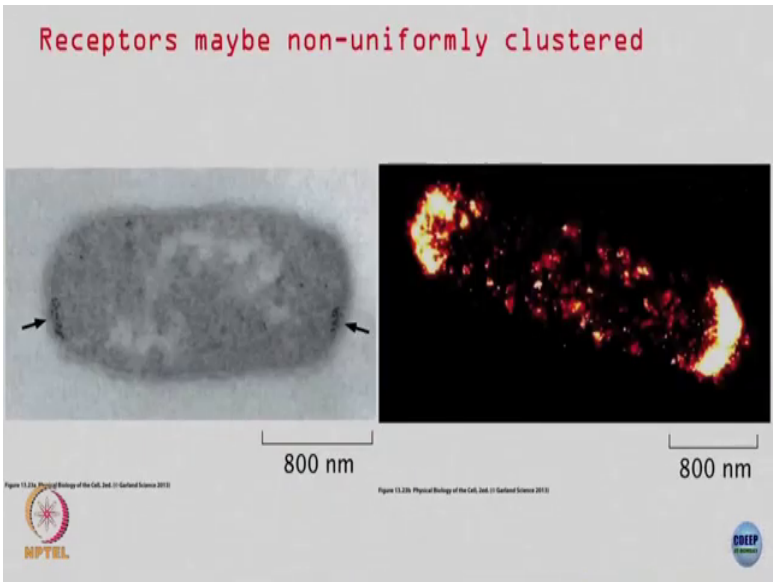
(Refer Slide Time: 39:51)



So, if you look at the effect of receptor density. So, this is some particular bacteria which I do not remember, this molecule that is getting absorbed with the virus coli phage lambda and this is the receptor density on the surface of the bacterium ok. So, when you receptor density is small as we increase the density of course, you get a lot of improvement in the absorption.

But beyond a certain point it sort of flattens out there if you put more and more receptors in the surface of the cell, it does not really make that much of a difference through the absorption performance of the cell itself. So, that is one lesson the cell does pretty well even with a relatively low coverage of receptors as far as this diffusion limit goes and then like I said of course, this majorly simplified with various approximations one can do better.

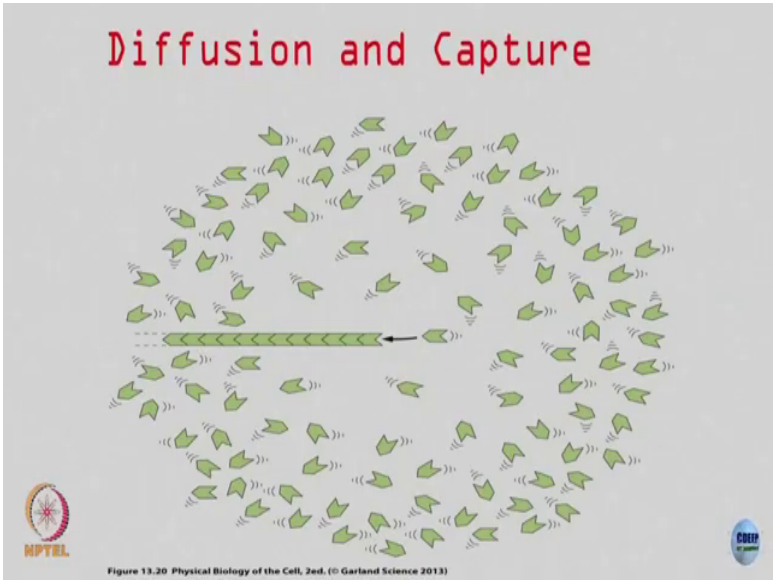
(Refer Slide Time: 40:46)



For example: if you look at the distribution of chemo receptors on the surface of the e coli you will see that there are large clusters at these two ends and very few chemo receptors over here. So, if you were to model the E coli as a sphero cylinder, then you could take that there is nothing on these cylindrical walls, but there is a large density on this hemisphere and on this hemisphere, and then ask that you know what sort of how does that change the calculation, ok.

So, realistic to model realistic organisms the spirit is the same whatever we have done for spherical cases you take the appropriate shape, you can solve it numerically or in very few cases maybe you can solve it analytically, but this is the base this is the crux of it. And, this like to discuss is also true not only for the cell signaling problem, but a similar approach would also work for this diffusion and capture sort of problems.

(Refer Slide Time: 41:42)



So, if you are talking about microtubules where the tubulins, subunits are diffusing and are getting captured at the tip of the microtubule. You could do a sort of similar calculation and ask that what is the rate at which this tubulin units subunits will arrive at the tip of this growing microtubules? So, this is these are two concrete examples they thought I will discuss one is frap the other is the cell signaling.

Next; so, we will continue with diffusion next class and we will talk a little bit about first passage properties of diffusion, ok. Alright that is all I have for today.