Physics of Biological Systems
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Lecture - 39
Depletion Interactions

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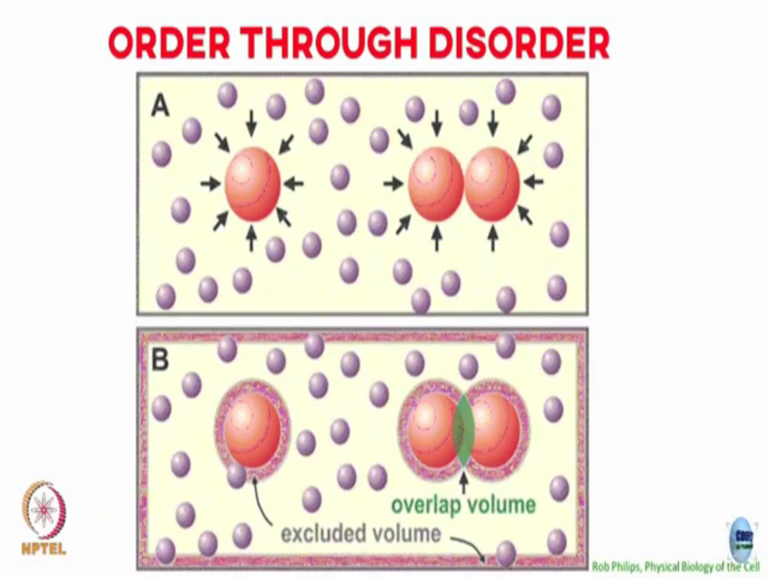

So, this Depletion Interaction over this imagines is that let us say I have; let us say I have a system where I have many many of these routers which is some sort of small molecules, and also mixed in with that I have some bigger molecules something like this, ok.

Now, what I know is that my equilibrium state is going to be one that maximizes my entropy, right. And if you think about this small molecules. So, let us say my big molecules have some radius R and my small molecules have some radius small r. Then the closest the small molecules can approach is somewhere like this which means this big molecules have a zone of exclusion around them extending 2 r plus small, capital R plus small r, right.

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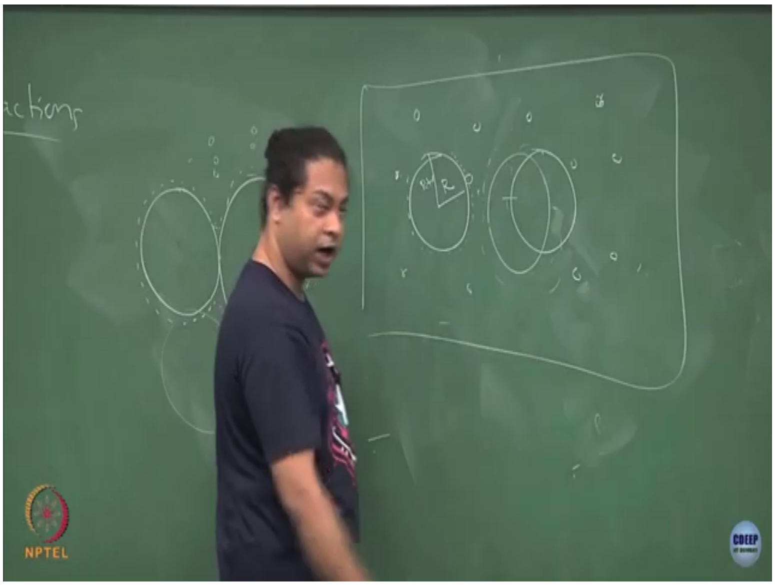

These small molecules, the centers of these small molecules cannot come closer than a distance capital R plus small r of these bigger molecules, ok. So, what this, so from an entropic point of view what these small molecules would like to do is they would like to increase their entropy which means that they would like to increase the space that is available to them in order to roam around, right. And you can max, so it can increase the volume that is available for them to perform their random work or whatever is by minimizing this x volume that is excluded to them by this bigger spheres, right. And when will you minimize the volume?

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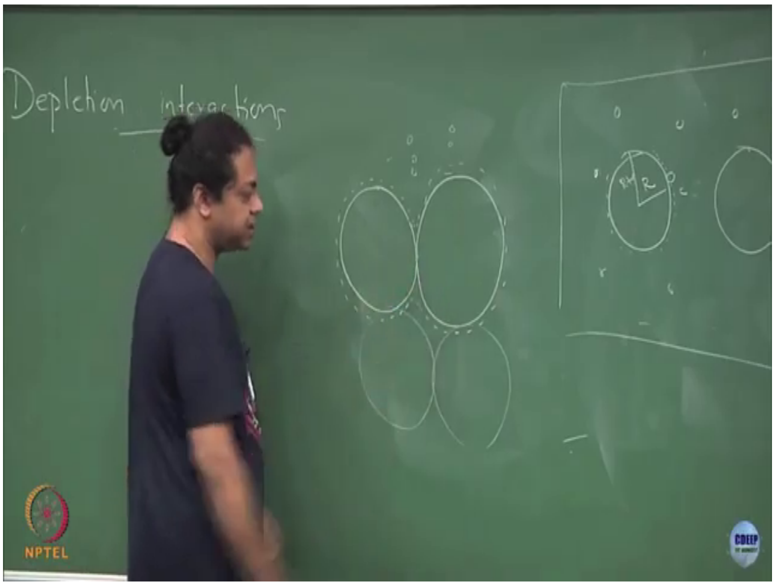

So, you can minimize the volume by making these bigger spheres for example, come very close to each other. If you make them come very close to each other they will exclude a volume which is like this, right. In this region there is some common volume which is now extra common volume which is now going to be available to these smaller particles in order to diffuse, ok.

So, purely from an entropic point of view if you have many many many of these small molecules, what they are going to try to do is they are going to try to push these bigger particles closer to one another, right. And therefore, if you were just looking at these bigger particles what you would see is some sort of an order emerging for these bigger particles that is driven purely by entropy arguments.

So, generally we think of entropy as sort of promoting disorder, but in a system like this if I just focus on one component of the system which is these big molecules, this sort of a interaction this crowding or this excluded volume interactions what they can do is that they can promote order for this one specific subsystem of this whole system that I have which is this bigger particles you can promote order formation in this bigger size particles.

And in fact, if you which is what we will try to do is that you can calculate the entropy as a function of the separation between these larger particles and you can calculate the entropy and therefore, you can calculate the free energy.

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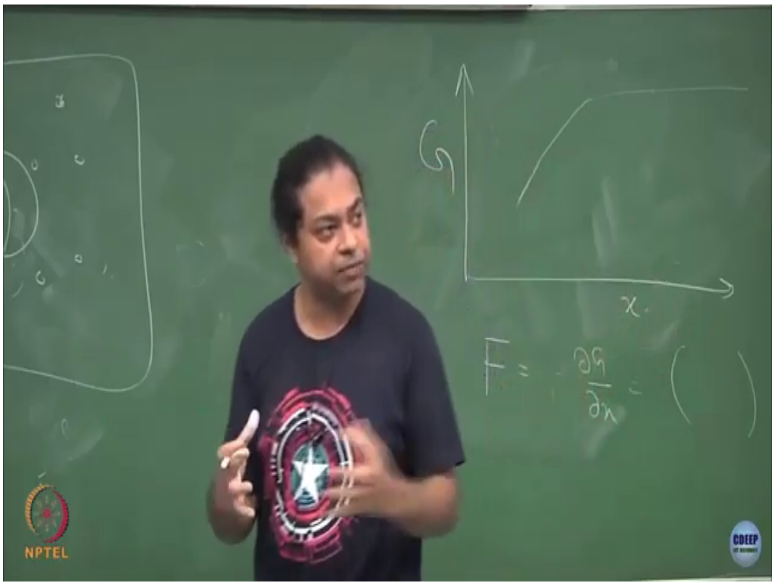

So, let us say I can calculate which I will do, you just want to say what I am going to do. So, I can calculate the entropy or the free energy let us say G as a function of the separation between these bigger particles, let us call it x.

If these bigger particles are very far apart, let us say here and here and I bring them a little closer. So, I bring this particle, so I did not mean to make this spear larger, this spear is the same size, they bring it a little closer. It does not really make a difference because it still has the same amount of excluded volume. Only when it comes closer than this whatever 2 times R plus small r will I see a change in this excluded volume, which means if I plot this and if I plot this free energy I will see something which is constant for very large separations.

But when I approach this 2r plus r region I will see increase in the entropy and a consequent decrease in the free energy as I push them closer and closer, right, which means that I can calculate an effective force. Remember again this concept of conjugate variables, so I can calculate an effective force by taking the derivative of this free energy with respect to the separation of the particles.

And what therefore, what I; and let us say I will get some value of the force and therefore, this entropy simply by introducing a large volume of crowders or these small molecules what is going to result what I am going to observe experimentally or affect effectively is as if there is some force which is trying to push these bigger particles close to one another. And this force is going to lead to some sort of ordered structure for these larger particles which is, so it is a very sort of counterintuitive effect where you have this emergence of order through an entropic or disordered based argument.

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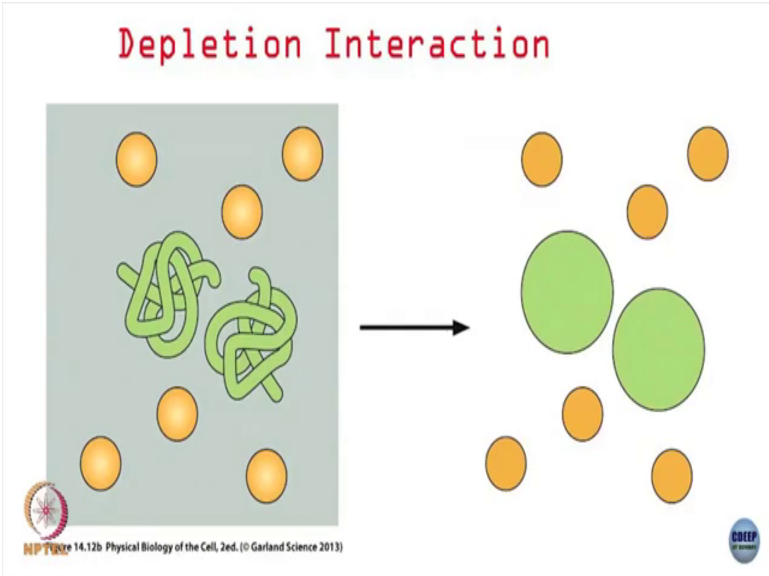

So, what we will try to do is, so the idea is this that when you have these large macromolecules DNA, proteins whatever they have some structure of course, so there are some sort of a polymer. But effectively this polymer has some rg some typical size and I can approximated by some big sphere of size rg in the presence of many many small crowds and these could be small ions, this would be other small proteins or whatever.

But there are many of these small small crowders and then I have some of these bigger particles and we can calculate how this smaller particles will drive aggregation in these larger ones. So, you can have two proteins coming together simply because of these crowding interactions of these depletion interactions.

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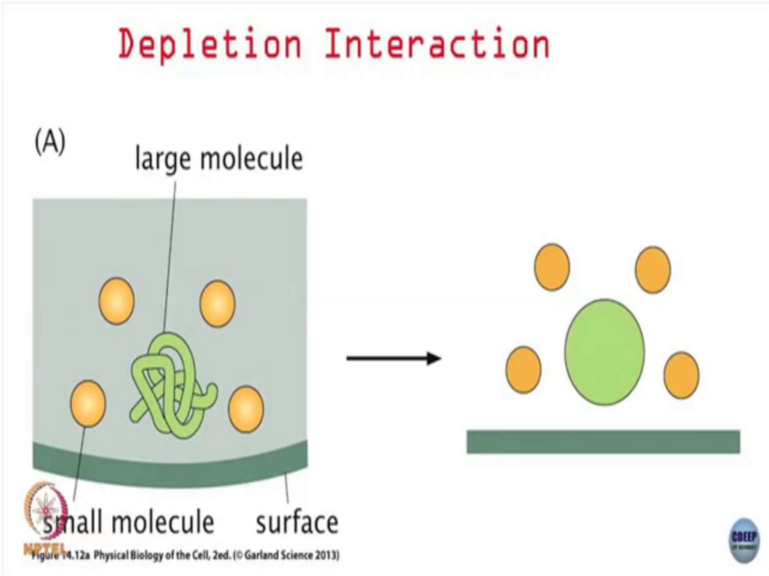

You can have for example, large molecules being attracted to a surface again because of the same sort of a principle. So, have this large molecule I have the surface, both of which have their excluded volume excluded zones and by pushing this molecule closer to the surface I can minimize the excluded volume and therefore, maximize the entropy and that will again lead to some sort of an attractive interaction between these large molecules in the surface.

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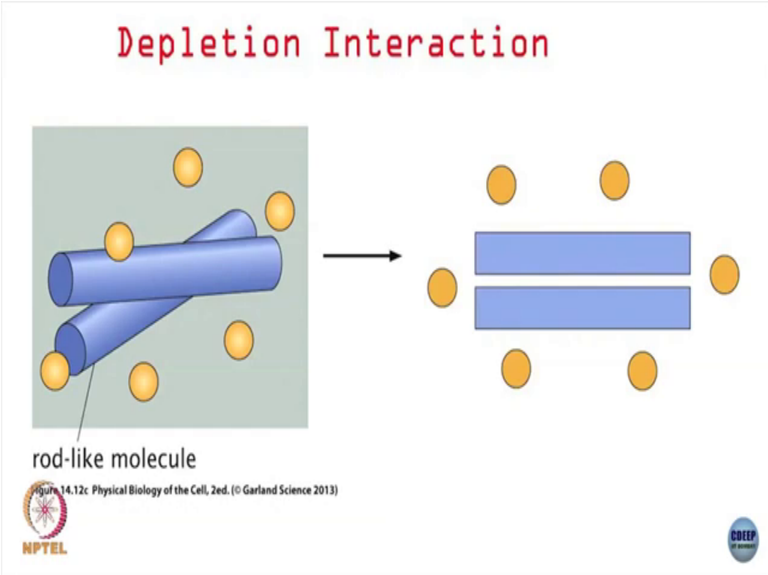

Or you could even alliance if you had rod like molecules for example, in the presence of again many many crowders you could show that this sort of a depletion interaction will lead to alignment of rods you could maximize the entropy if you what you have the rods kept in sum in the same in the same orientation, ok. So, it is a very general principle. It is not true just in biology or anything this is the biology because the cell is so crowded offers an extreme system where this sort of interaction or attraction the depletion attraction is going to be very common, ok.

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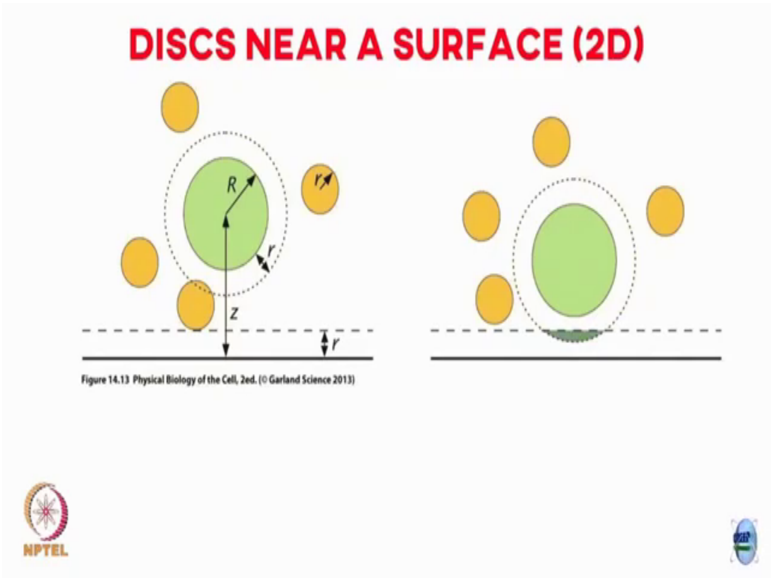

So, now I will try to do this sort of a calculation that I sketched and try to find out what sort of an effective force are we talking about, ok.

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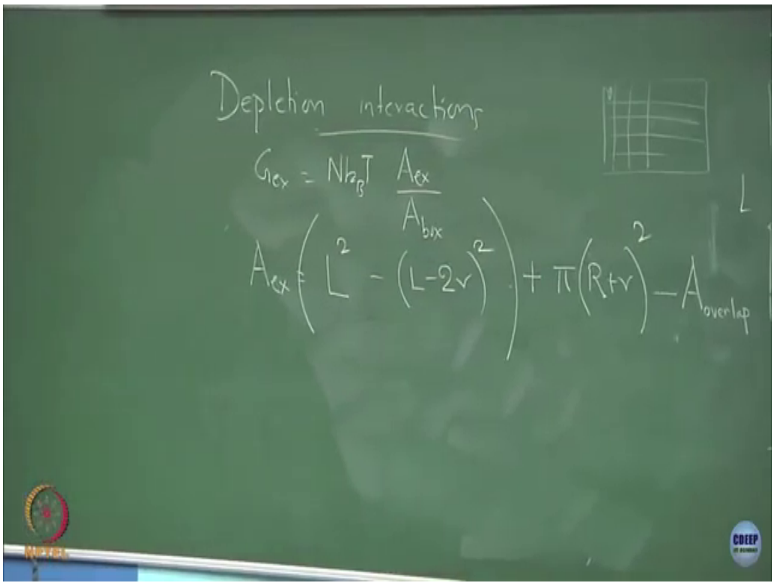

So, we will do this case first where I have discs near the near the surface. So, let us say I take a box, and I have a large, so I will do this calculation in 2D a later I will do one more calculation in 3D. So, let us say this is a 2D calculation. So, my large sphere becomes a disc of radius R, right, and I have many many smaller crowding agents again of radius small r.

And like I said, so this sphere will have some zone of exclusion around it which is capital R plus small r, this is capital R plus small r, so will this wall have some zone of exclusion around it. Again in the width of that zone is going to be small r, the smaller molecules cannot approach closer than that this is nice squared box is something (Refer Time: 08:43).

And what I want to do is that I want to compute this entropy or the free energy as a function of the distance between the center of the sphere and the wall, so let me call that Z, ok. And the idea is that once I have calculated the free energy I will calculate a force exactly like I said I will do del G del Z and that will give me some forced if there is a force towards the wall that I can compute that as well, ok. So, how do I do that? So, let us say I start off by saying that there are no small there are no large particles I only have the small small particles, and let us say that the volume of this box is some V box.

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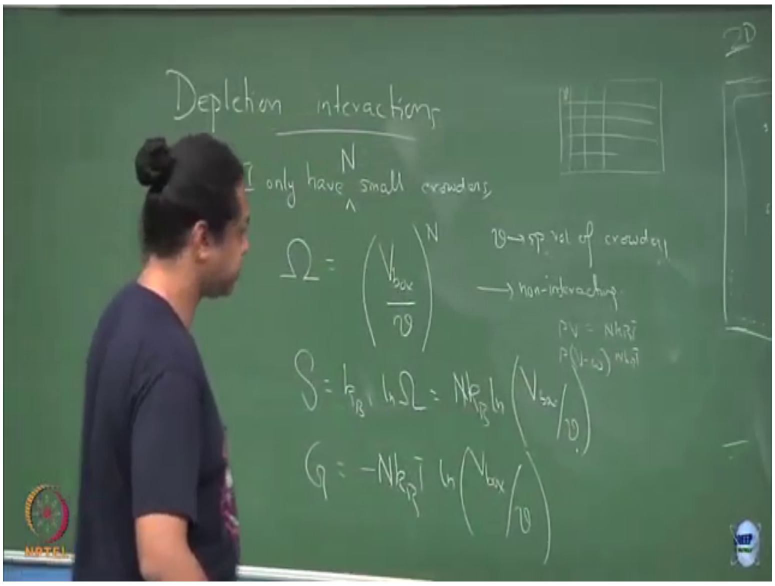

So, if I only have crowders, if I only have small these small crowders I can calculate the number of microstates let us say this crowders are non-interacting, I can calculate the number of microstates that is available to me when I have these crowders in a volume V box and that is simply going to be. So, let us say if I have N of these; N of these small crowders this is simply going to be V box by the specific volume of these crowders whole to the power of N, right. That is like saying that I break up this V box into small small cells each of which has a volume small v, N of these cells are occupied and therefore, that gives me the confirmation of the entropy, right.

So, this is this remember this is a non-interacting approximation; this is a non-interacting approximation. You can do this better by if you use the hot sphere gas result (Refer Time: 10:48) of the time. So, I have this number of microstates which means I can calculate the entropy which is k B T log omega, is this k B T log of this number of microstates. So, that is Nk B. So, not T just k B log omega. So, N k B log of this V box by this. So, the small v is the specific volume of the crowders specific volume of crowders, ok. So, that is my entropy.

And consequently because these are I assume that this let us say I assume this crowders have may interactions with each other there is an energy term, so let me say I can just write down the free energy is just minus ps. So, that is just minus Nk B T minus Nk B T log of that whatever V box by v, ok. Yes.

Student: (Refer Time: 11:49).

One box in a many particles. So, that is why I say this is non-interacting approximation. If you remember, since it is, so this is like an ideal gas of small particles, if you make a correction which you should we will get some P V minus excluded volume is equal to Nk B T, right, the Van der Waals correction, ideally you should include the Van der Waals correction for the moment I am not doing that.

Student: (Refer Time: 12:26)

Yes, ok.

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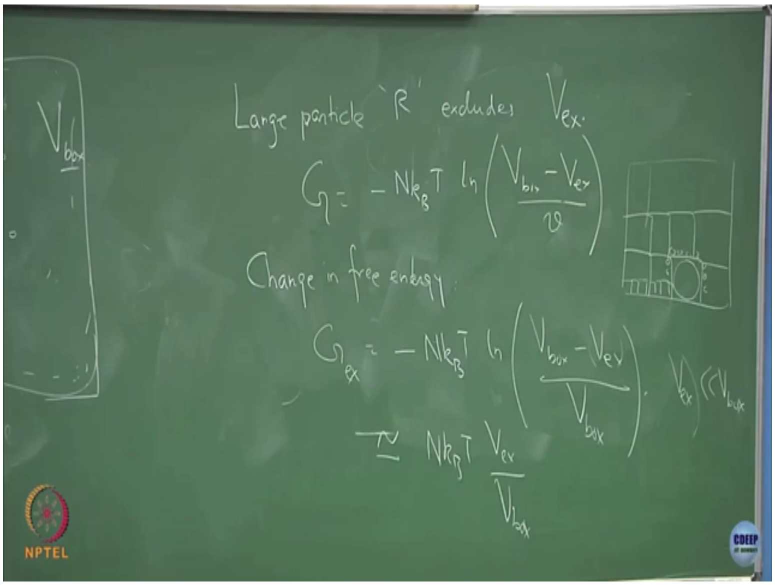

So, this is in the absence of these large particles. So, now, if I have this large, so let us say I have this large particle and that large particle excludes some volume, this large particle of radius capital R excludes a volume V excluded, ok. So, then again I can calculate what is going to be the corresponding free energy; exactly the same way I can calculate what is going to be the corresponding free energy, that is going to be minus Nk B T log of V box minus V excluded by the specific one, right. So, the large particle excludes this much. So, the smaller particles will now have to distribute themselves in the remaining one.

So, from there I can calculate what is let us say I can calculate what is the change in free energy; so, what is the change in free energy; change in free energy when I have a particle versus when I do not. Yes.

Student: (Refer Time: 14:03).

Yes. So, the reason you could of course. So, I could add some sort of a G naught over there, right, but the idea is that ultimately what I want to do is that I want to take it. So, this assuming there is no other larger particles. Ultimately what I want to do is to write take a derivative of this free energy with respect to Z, but this G naught is not a problem, not going to be a function of Z.

It is going to be whatever it is. So, whether I write it and I do not, that is not going to affect my calculation of the force that it is on this large particle due to this smaller crowders. But ideally I should, yes it also has whatever.

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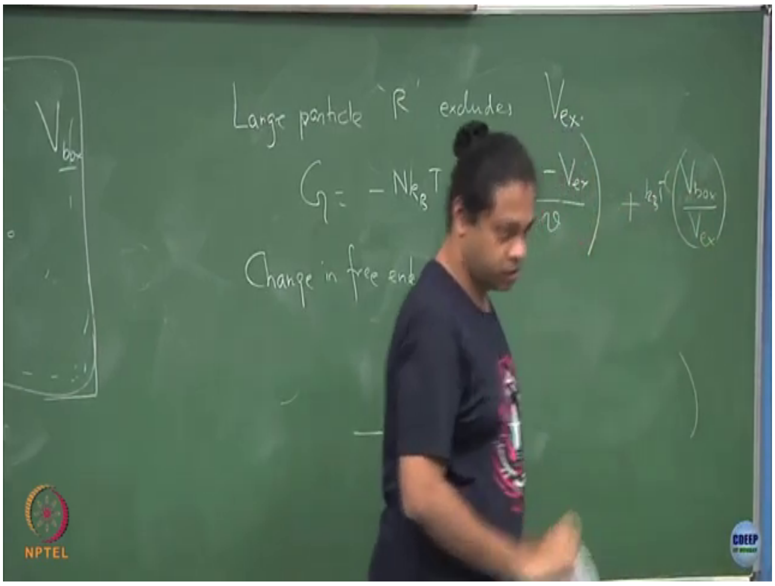

So, I should write some V box by this V excluded and if there is a single particle, so there is no N over there to just a k B T, so something else that is true, right. I just do not write it because I know I will not worry about it.

Student: (Refer Time: 15:28).

Yes, but you see so, as far as this large; large molecule is concerned, so I divide this box into this V box into this larger boxes now and it can occupy any one of these boxes whether it is here at whether it is here, ok. So, that component that contribution to the of the entropy due to this smaller particles does not really change whether it is here or whether it is in a 0th order way. No.

Student: (Refer Time: 16:11).

So, that sort of, so this sort of, so those are sort of energetic effects. So, there are some interactions between the wall and they which could cause it to stick and sort of slide that sort of thing, right. So, that those, so these are in some sense still ideal particles. So, I am not in neglecting any sort of energy component to this, which is why when I write this free energy I just write this entropy component.

Student: (Refer Time: 16:44).

Stuck to the wall how?

Student: (Refer Time: 16:55).

Ok.

Student: (Refer Time: 17:08).

Right, of course, yes.

Student: (Refer Time: 17:21).

Yes, but that will come out through in some sense this interaction of these smaller particles with the larger particles then. I mean how many, so this has whatever. This has the smaller boxes inside as well corresponding to these smaller particles. If this my larger particle was here in these smaller particles were everywhere around like this then that would of course, restrict this larger particle to be around here, but that is what is going to come out of the calculation, right. I do not need to put that in by hand, in is what I am trying to say.

If I just had this larger particle then that has some entropy corresponding to whatever V box by V excluded to the power of the number of large particles, this sort of an restriction is going to come about because of this interaction of the smaller particles entropic interaction or physical interaction of the smaller particles with the larger particles. So, that is what is going to be the endpoint of the calculation, right, ok.

Let me go ahead. I will keep this in mind. I will try to see if I can answer it better (Refer Time: 18:42). What are they saying? Yeah. So, what I will do is that if you calculate the change in free energy for the scenario when you have a particle versus when you do not, and that is simply whatever. So, G, let me call that G excluded that is going to be minus Nk B T log of this V box minus V excluded divided by that V box the specific volumes drop (Refer Time: 19:16), ok.

And if I say that well this excluded volume even though this is a large particle compared to the box that you are in, this is fairly small. So, if I say that this excluded volume is much much small;volume is much much smaller than the volume of the box, then this is log of 1 minus a small quantity which means that I can approximate this by Nk B T V excluded volume by the volume of the box itself, in log 1 minus x is minus x. So, that is going to be this change in free energy on introducing the single large particle. So, that is what I will try to calculate. Except that now because I am working in 2D instead of writing volumes I will just write (Refer Time: 20:09).

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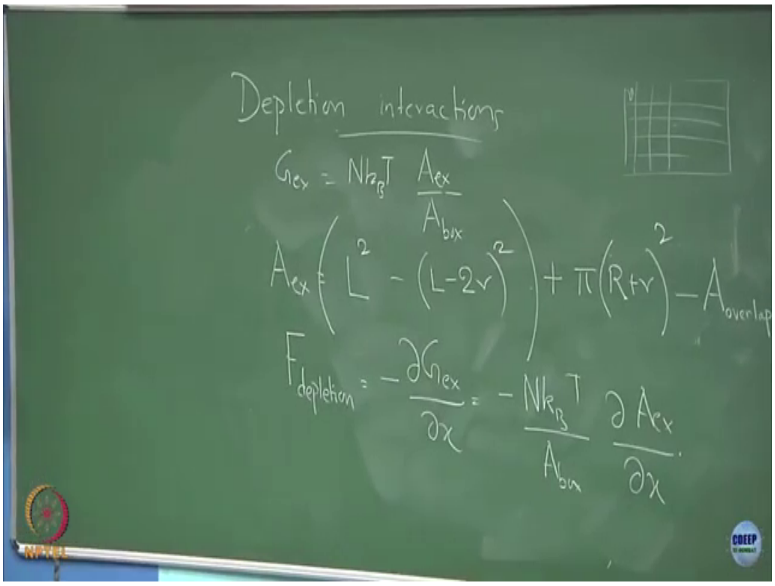

So, this G excluded is Nk B T V box sorry V excluded by V box in 2D I will just write it as the area excluded divided by the area of the box, right. Simply because I want to do a 2D calculation for simplicity, ok.

So, now, given a setup like this I can calculate what is this excluded area, what is this area that is extruded? What is this excluded area? This is the area the smaller particles these crowders cannot penetrate into, right. So, what is this? So, my box let us say I put in some dimensions for the box, let us say with the square box of size L. So, my box has an area which is L square, right then all around I have this sort of an inner square which is excluded. So, it is r on this side, it is r on this side, right. So, this inner box is L minus 2 r, right whole square, right. So, L square is this big thing L minus 2 r is this inner thing. So, the difference is the area of this excluded zone that is one part. Then there is an excluded area because of the disk itself.

So, this is one part because of the walls plus an excluded area which is pi R plus capital R whole square, right. This is the excluded region is a circle of radius R plus r. So, pi R plus r whole square, that is in this region where the scenario is like this. If on the other hand the scenario was like that, let me just draw something like this and if the scenario was like this, but this large particle has come close to the wall then I will have some amount of overlap, right which is this precisely what I am interested in. So, I will subtract that because I am double counting I will subtract that area of the overlap from this. Make sense.

So, this is the area of overlap between these two excluded volume regions. If it is far away then this area of overlap is 0, if it is close to the wall will have some finite area of overlap, ok. So, now, I can try to calculate what this area of overlap is going to be. So, let me draw a better figure.

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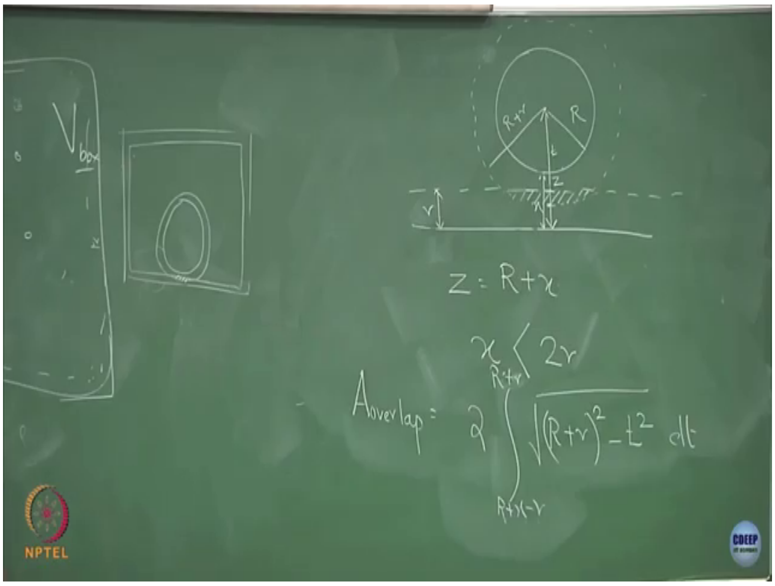

So, I am just interested in, let me calculate the simple scenario here is my wall, here is my sphere, this has the zone of exclusion around it, this wall also has a zone of exclusion around it, all right; this is R, this radius is r plus capital R. What else can I say? This height is also r, small r, this distance I am calling is Z, let us say the height from the wall let me call that as Z, anything else. That is very much of it. And I want to calculate the area of this part, this overlap between the extruded ones, ok.

So, let me first write that this Z let me write this Z as R plus x, ok. So, when for what values of x will I have this overlap volume? When x is smaller than 2 r, right because when x is exactly equal to 2 r then these two overlap volume starch. So, when x is smaller than 2r I will have a finite value for this overlap area, ok. So, what I want to calculate is this area of the overlap; what I want to calculate is this area of the overlap. So, what I do is I integrate, so this thing is R plus r. So, let me write it from then I will explain.

So, 2 times integral square root R plus r whole square minus let us say t square dt and that goes from R plus x minus r to R plus r, ok. So, what I am doing is that I am calculating the length of this line. So, from here till here is what I call this dummy variable t. So, R plus r whole square minus t square, square root is this line and then this t varies from here till here, right. So, over here t the value of t is simply R plus small r, capital R plus small r. Over here the value of t is simply R plus x minus r, ok.

Remember what is x? x is Z, so this from here to here is x, right because I have written Z is R plus capital x. So, this much is x, this much is R, so this much is x minus r, so R plus x minus r. And then 2 because one from this side one from this side. So, that is my area of the overlap. So, you can do some stuff to this. Let me, yeah this figure is up here, so let me just remove this figure, ok.

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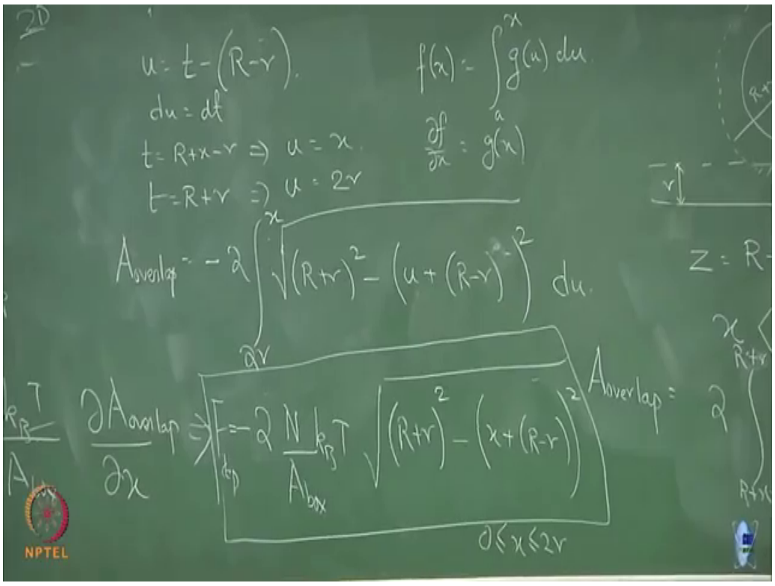

So, let me say that u is equal to I define a new variable u which is t minus capital R minus small r which means that du is equal to dt and when t is equal to let us say R plus x minus r; that means, u is equal to x and when t is equal to R plus r t is equal to R plus r this means that u is equal to 2 times small r. So, I have changed the limits.

So, this integral the area of the overlap becomes 2 times integral square root of R plus r whole square minus t square. So, let me call that t is u plus R minus r whole square, R minus r whole square this whole thing and the square root the dp becomes du, the lower limit is x and the upper limit is; the lower limit was x, so let me write actually x on top. So, let me interchange the order of the limits, so let me put a minus sign. So, this is this, ok.

So, what I have got is this some expression for this area of the overlap. I am not bothering to evaluate it for the time being because I will not need to. And remember, so I have written my free energy in terms of this area that I have excluded and what I want to do is I want to find out the derivative of this free energy with respect to the distance from the wall which is Z or equivalently x simply because have written Z as R plus x, right.

So, what I want to calculate is this depletion force as it were, I want to calculate this depletion force which is minus of this del free energy change upon introducing this particle as a function of Z or equivalently is a function of x. And therefore, this is if I put in G this is minus Nk B T by the area of the box derivative of this excluded area with respect to x, all right.

Now, if I look at this expression for this excluded area, this term has now x dependence, this term has now x dependence, the only x dependence is in this overlap term which comes with a minus sign. So, this is nothing, but plus Nk B T by the area of the box, derivative of this overlap area with respect to x, all right. And this overlap area I have over here.

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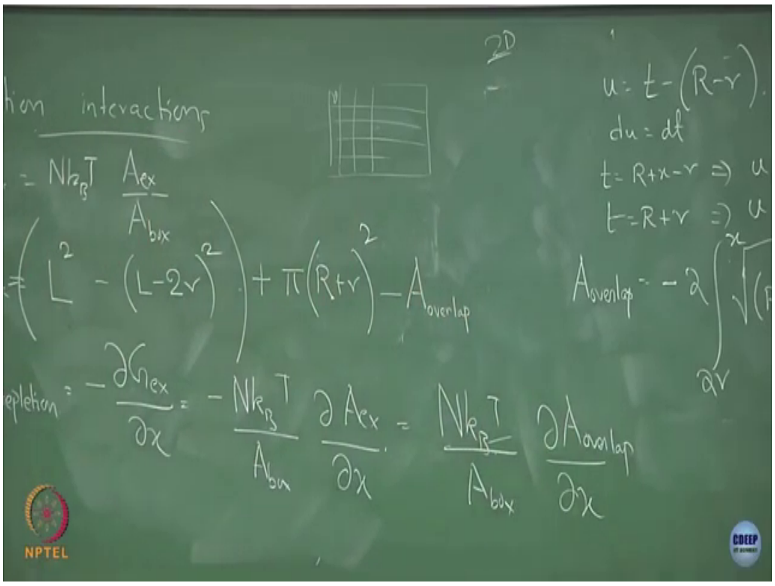

Now, this is why I leave this as an integral actually. This is an integral, I leave, I have left this as an integral, but now I need to take a derivative of this actually. So, I do not even need to do this integral. What is going to be this del a overlap del x? If effects is generally some integral g of u du from a to x, then what is del f del x?

Student: G of x.

G of x, right. Which means I can just take this integrand the value of this integrand at u is equal to x that is my derivative.

So, I have I have this minus sign over here. So, let me put it minus 2 N by A box, N by A box k B T and then square root R plus r whole square minus x plus R minus r whole square, ok. So, this is my depletion force and this is true in the range, where 0 where x lies between 0 and 2 r, ok. Beyond this there is no force, if x is greater than 2 r then there is no overlap volume at all and therefore you feel no force.

But provided x is in this range x is between 0 and 2 r what this large ball is going to feel is that as if there is an attractive force the force comes with a minus sign which means it is an attractive force, as if there is a force that is trying to push it towards the wall. And note that this depends on the number of crowders that you had put capital N, so you will see a manifestation of this force only if this crowders are present at a fairly, so this is what it is this N by A box have this written as small n, the rest is the same.

So, you will see a manifestation of this only if you have enough number of these crowders that this depletion force will actually make some effect, ok,. But provided the system is very crowded as it is inside the cell, you will see manifestations of this sort of a depletion force. So, it is a purely entropic force. There are no actual interactions that are going on, except this excluded volume interaction. But the manifestation is that this large ball is going to be pushed towards this wall.