Biomathematics

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Lecture No. #37

Statistical Thermodynamics of Biological Systems part– IV

Hello welcome to this lecture on biomathematics. We will continue to discuss how we can use mathematical techniques and the ideas from statistical thermodynamics to understand some of the biological system.

We have been taking DNA as a an example and then learning how to calculate free energy and partition function etcetera etcetera. So that these things can be used to compute calculate something that is experimentally measurable in a lab.

We briefly mentioned that if we can get free energy the derivatives of the free energy will give you things that are measurable in a lab. For example if we could get free energy as a function of force or pressure we can get the end to end distance of this the size of a DNA.

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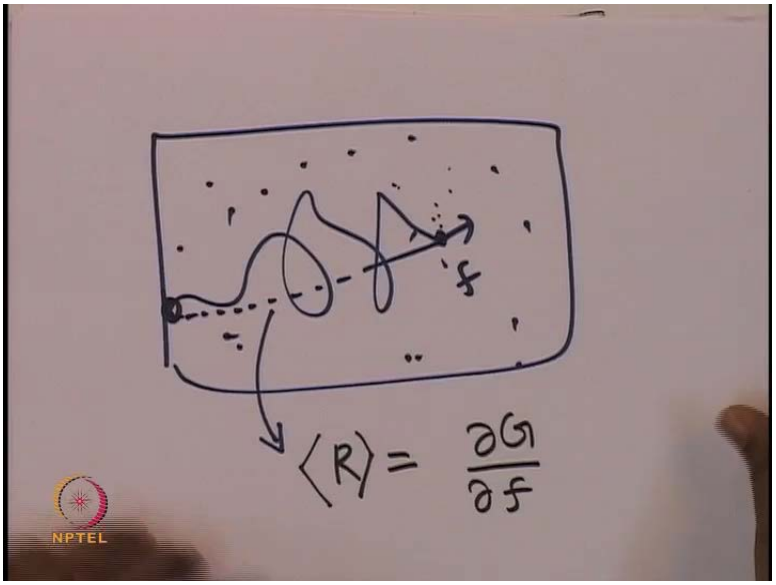

So what we basically were saying is that if you have a DNA let's say in a solution and then you apply a force so there is medium here and you apply a force f then you ask the question what is the distance from this end to this end?

If you apply a force and this will give you. So if you how do you get the answer the answer the distance from this end to this end so let me call this R this R can be computed by taking the derivative of the free energy with respect to force. So, if you can calculate the free energy and if we can calculate the force.

We can get the average end to end distance so if you imagine you hold this end of the DNA there will be always thermal forces on this and the end will fluctuate a bit. So, what you will be calculating the average of this fluctuation.

So average end to end distance so R here is the end to end distance what I am going to mark now this dotted this distance will be R this is your R and this can be calculated by taking the derivative with respect to force. So, if you do an answer do an experiment by holding ad N a and applying a force Pull the DNA for each force there will be an end to end distance and this can be calculated by taking the derivative of the free energy with respect to the force.

So, today we will today we will discuss this here on how to calculate this free energy for a single stranded DNA. So, this relation if you have this relation if you have a given force in the given extension such relation can be called force extension relation.

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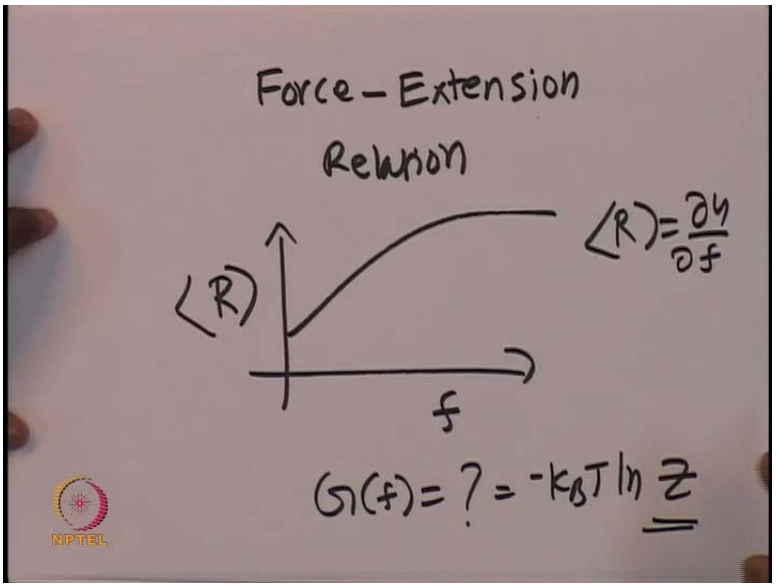

So you can think of this apply a force so what this people call force extension relation you apply a force and calculate how much is the extension because this is like you may plot force and the end to end extension of the DNA.

And we said that it can look something like this and we will see how exactly it looks like it today but, this relation can be calculated by 5 taking the derivative if you do so this is average R can be calculated as del G by del f and we can calculate G as a how do we calculate this? If you know G as a function of f then we know how to take the derivative then we calculate R. How do we calculate this of course? This has to be minus k B T log z and how do we calculate z with force that is what we are going to discuss today so basically first we will discuss free energy of a single stranded DNA under force f.

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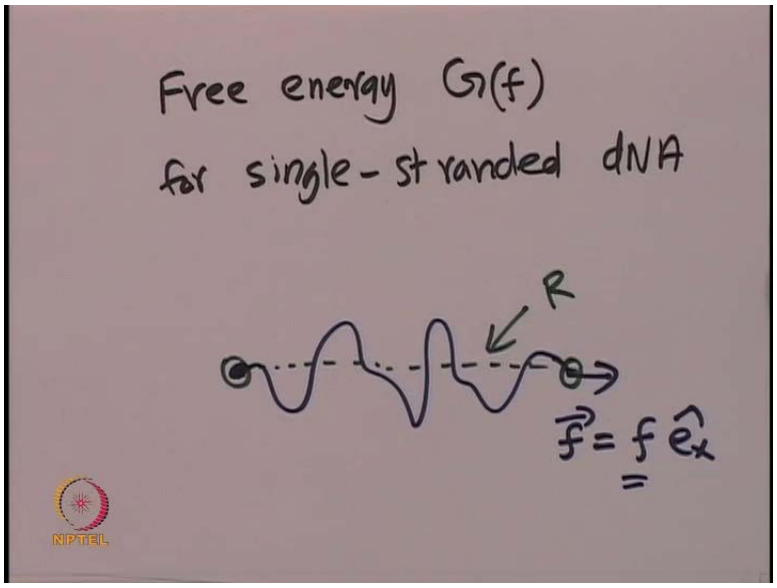

So, that so that is what we are going to discuss now free energy G of f for single stranded DNA. So what are we doing we are going to up we have we have a single stranded DNA and we imagine that 1 end of the DNA is fixed at a at a point and then the DNA is free to have anywhere. Then you apply a force let us say we are applying this force so this is one end of DNA and other end is somewhere here and we are pulling it in this direction this force f is applied and the X is direction so this is f e X so it has some value f the magnitude is this f and this is applied in the X direction.

So, this is the force we are going to apply on a DNA and for a given value little T this f what is this distance from this point to this point. So, we want to measure actually this distance from here to here so this distance this is what we are interested in this end to end distance for a given force so this is R. So, now first we have to calculate the partition function and the partition function for a single stranded DNA, when I say single stranded DNA what does that mean so we discussed that there is a bending energy for DNA but, that is only for double stranded DNA. Single stranded DNA is can be thought of as a flexible a chain It does not Cost any energy the bend is floppy flexible so bending energy is nearly 0.

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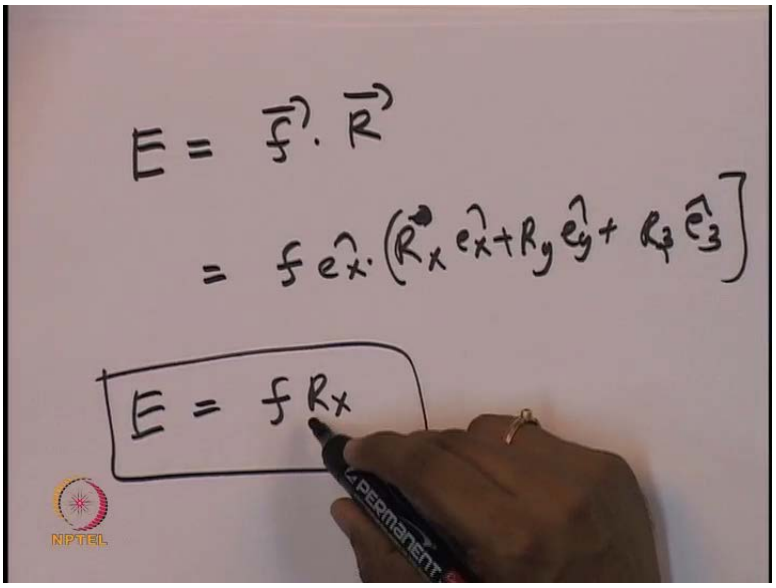

So, we said that bending energy is essentially we said that bending energy e is a into sum over i 1 minus t i dot t i plus 1 for single stranded DNA this a is very small so that this energy can be neglected. So we for single stranded DNA bending energy for single stranded DNA we can take it as a 0. So, there is no bending energy for single stranded DNA now what else it has what else what else it has energy? So, what it has is basically if you are going to pull something here you have to do some here you have to do some work or to pull it so that energy is the energy work done by pulling it so always work done by applying a force is force into distance so there is an energy force into this change in R this R increase in R that much work has to be done.

So, this so if you take this so think look at this diagram I said that the force is in the X direction and R is the vector in this direction. So, if the work has done by pulling work done for pulling the energy for pulling is basically force into distance R. So, this is basically f e X dot R is R can be thought as R X e X R y e y it has plus R z d z in 3 d you can think of it as a vector having 3 components. So, f X e X so as we said in vectors' X dot e X is 1 e X dot e y is 0 e X dot e z is 0 so the answer is f R X. So, this is the work done for pulling so bending energy is 0 but, then work done for pulling is f R x So this R X can be basically found turn out to be this R X will turn out to be Cos theta, if you take the angles properly.

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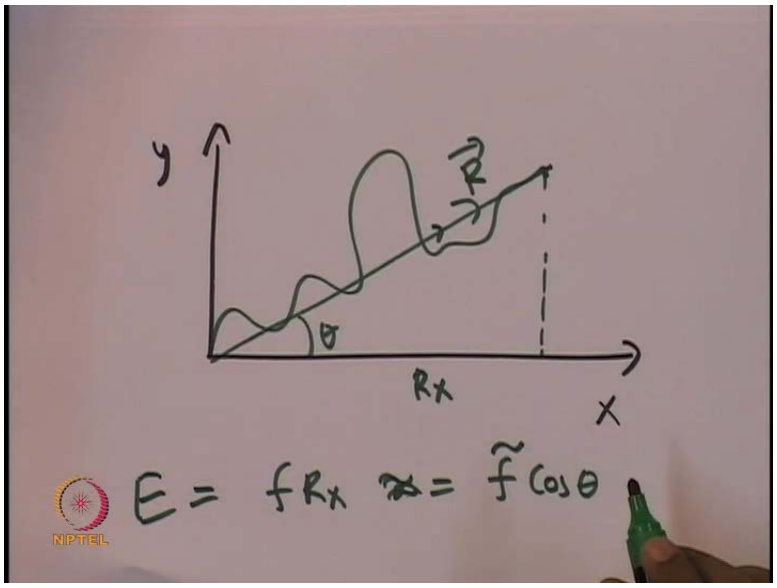

So, imagine for example, lets imagine that for simplicity lets imagine that this is our X axis and this is here y axis and imagine that the end to end distance as some particular the DNA is in this particular direction and this end to end distance will have some vector R and if the angle is theta, this is R X so this is R vector and this is R X and R X is basically nothing but, R Cos theta so this this angle of this is Cos theta. So, f R X can be written as f into Cos theta into some constant so with these entire constant the absorbed I calf tilde so let me let us call this f tilde Cos theta. So, this will be the energy the energy will be f tilde Cos theta because this is Cos theta.

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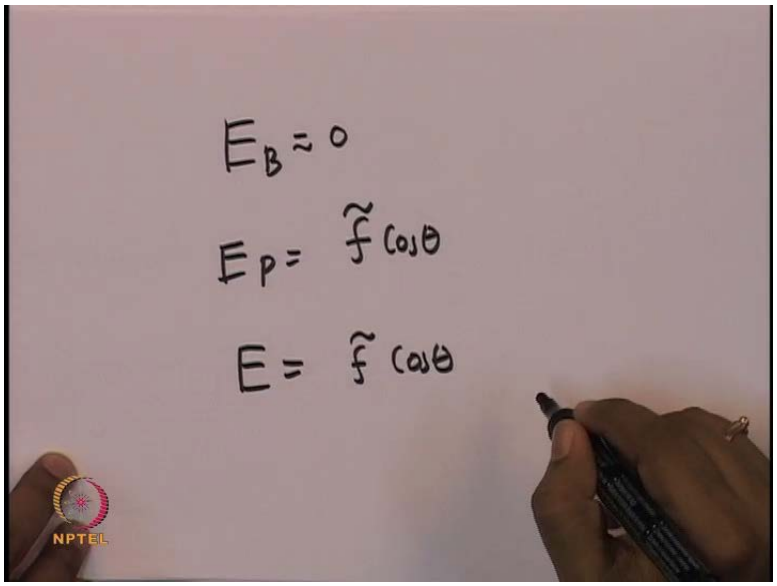

So what we have we have 2 energies we have energy which is basically bending energy is 0, pulling energy is f tilde Cos theta. So, basically what do we have is a total energy E is 0 plus f Cos f tilde Cos theta f tilde Cos theta so f tilde is f into distance some distance d or and so f tilde Cos theta is basically your energy.

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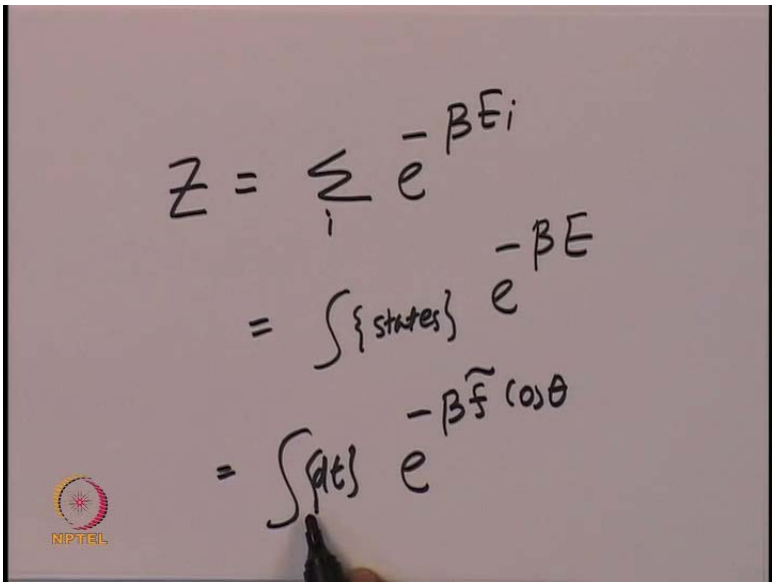

Now let us write down the partition function. The partition function is basically we said that partition function z is sum over i e power minus beta E i or this is integral all possible states all possible states e power minus beta E. So now E is f tilde Cos theta so this is integral all possible states so that means all possible tangents like we discussed before e power minus beta f tilde Cos theta.

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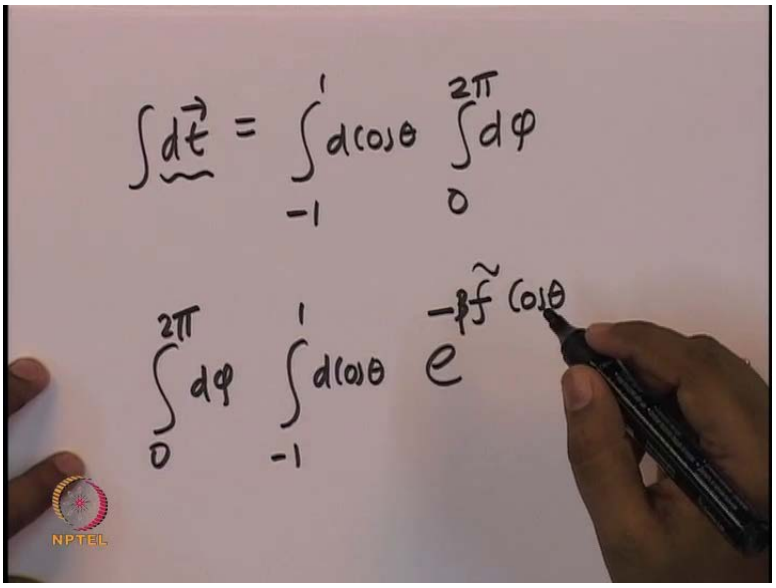

So and it turns out that like we did before this d T integral can be written as d T integral can be written as integral d T can be written as integral d Cos theta integral d phi minus 1 to plus 1 0 to 2 pi So this is basically converting the vector in 3 d this is basically a volume element in 3 d into spherical polar coordinates. So, this is spherical theta and phi are spherical coordinates. So, if we do this if we can convert d T into this particular form the integral will turn out to be like the integral we did before and the integral will be essentially e power the so basically d phi. This will give 2 pi and minus 1 to 1 d Cos theta e power minus minus so there is a f tilde Cos theta so this is basically f tilde Cos theta and there is a by k B T so let me put a beta there so beta f tilde Cos theta.

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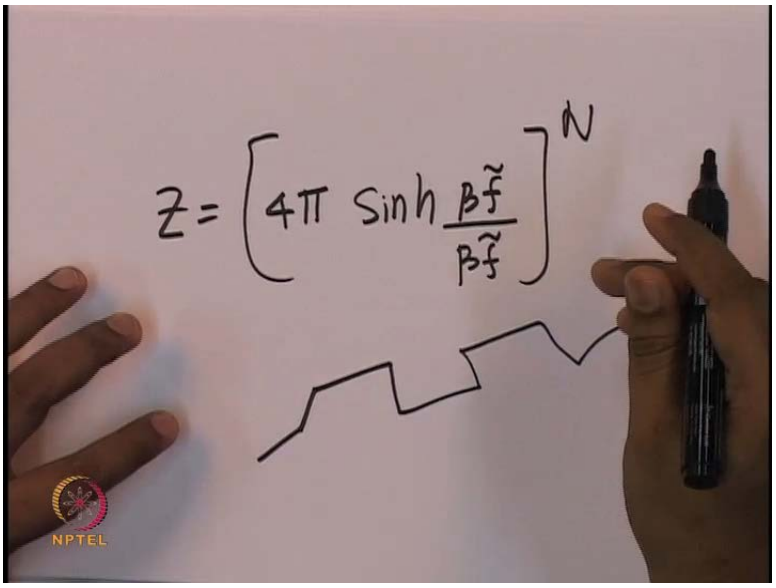

So like we did before the answer will turn out to be 4 pi. So, the answer will turn out to be 4 pi sin hyperbolic beta f tilde by beta f tilde like we did just did yesterday the other day in the previous class for the calculating the partition function for a point double stranded DNA. Single stranded DNA with force will turn out to be a similar answer and the answer is basically f beta f by beta f whole power n. So, it depends on the force you apply and it depends on the number of monomers we have if the DNA how many monomers we have in the DNA and the length is the chain. So, what would this give this is the partition function and what do we need what we need is the free energy and if you calculate the free energy.

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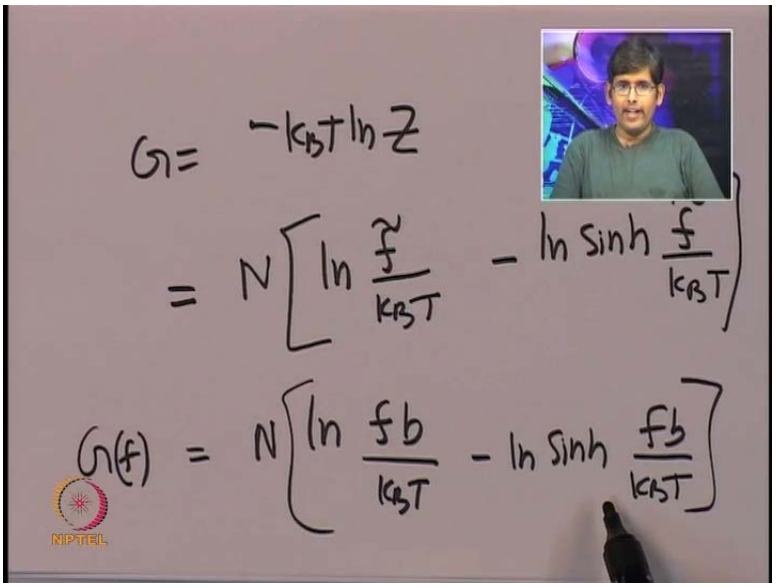

Which is minus k B T log z and it turns out that the free energy will be if you do this properly N log f tilde by k B T minus log sine hyperbolic f tilde by k B T so it will depend on the temperature so this is just taking the log of that partition function that we had wrote which basically is e power minus sin hyperbolic f tilde by k B T by sin hyperbolic So, if you take beta as 1 over k B T and then you take the log of the z and take a minus sine you will get this particular answer. Now what do we need is now we look at here this is a function of force so we can write N into log of f into so this tilde if you if you properly look at it this will turn out to be B here f b by k B T minus log sin hyperbolic f b by k B T so for each…

Uh now from this if you calculate the derivative of this so this is basically over G of f So now we have free energy as a function of f here now what we need is to get the end to end distance R average G as a function of f here now what we need is to get the end to end distance R average R X average basically in the X direction we said this.

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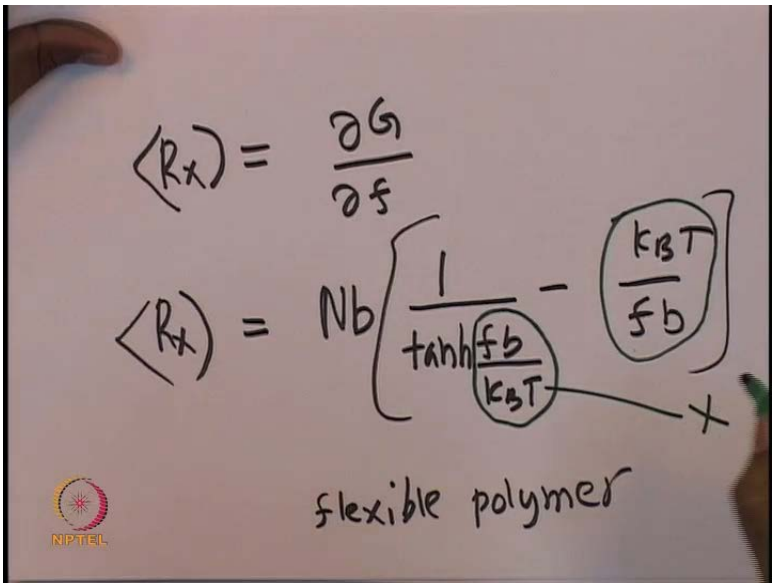

So to get this R X average what we need is del G by del f. If you do this calculation then find the derivative of this G with respect to f. There is an f here there is an f here if you do this derivative with respect to f then the answer you would be getting is basically this is equal to N b 1 over tan hyperbolic f b by k B T, tan hyperbolic f b by k B T minus k B T by f b this is what you get. So, here is a relation between force and the end to end distance average. So, just by calculating free energy you got a relation between the force f the temperature and the end to end distance.

So for a flexible DNA so this is for a flexible polymer any polymer this is for 2 polymers like DNA or even a protein which has no bending energy. And only energy is to pull this so this is the answer you would get so this is the measure of the quality you can do experimentally measure this and you can see few things so I take if I take this f b by k B T as let let me call this f b by k B T as X so I call this f b by k B T as x. So this is k B T by f so this will be 1 over X so this quantity I call it X.

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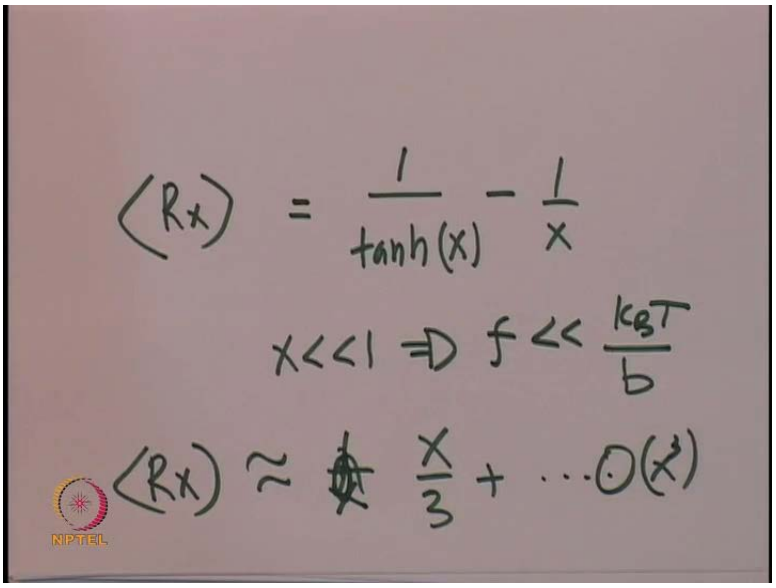

If I do this I can rewrite this R X average as R X average is basically 1 over tan hyperbolic X minus 1 by X and if I expand this when X is very small less than 1 this would imply that f is much less than k B T by b. If you apply a very small force f is much less than k B T by b there is much less than 1. this will this this this will turn out to be R X average will be approximately equal to 1 over X sorry X by 3 plus some something of X cube. For small X plus dot dot dot. So, this is so there will some quantity of the order of X cube so this will be X by 3 plus something. So, what does it say for a small force that in the end the extension and X is basically f b by q B T.?

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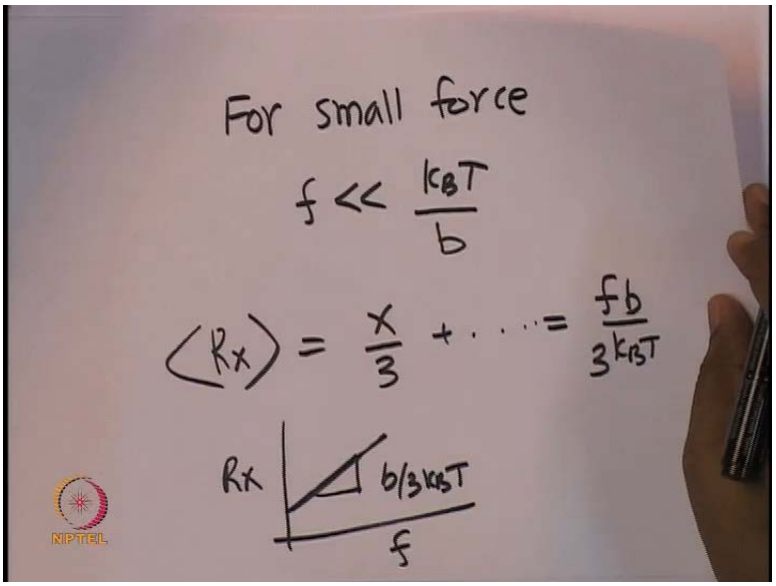

So, let us write this for very small force for very small force for small force that is when f is much smaller than k B T where b is the monomer length size of a single sub unit it will turn that the end to end distance goes as x. So, R X average the end to end distance is equal to X by 3 plus some constant plus some factors which is small factors. Which can be neglected so the leading factor will be X by 3 would mean that small force this will go linearly. So the first part is linear. So, this is we wanted to plot R X versus X which is f so this is basically f b by k B T. So this as a force this will go linearly here with a slope given by b by 3 k B T.

This is the slope of this so you will get if you plot R versus f for small f you will get a straight line which is slope which is B by 3 k B T. So, this is interesting now what do we have for a large force. For a large force what do we get is so let us say what will about the look so we have this expression which is tan hyperbolic X minus 1 by X and for large f when f is very large.

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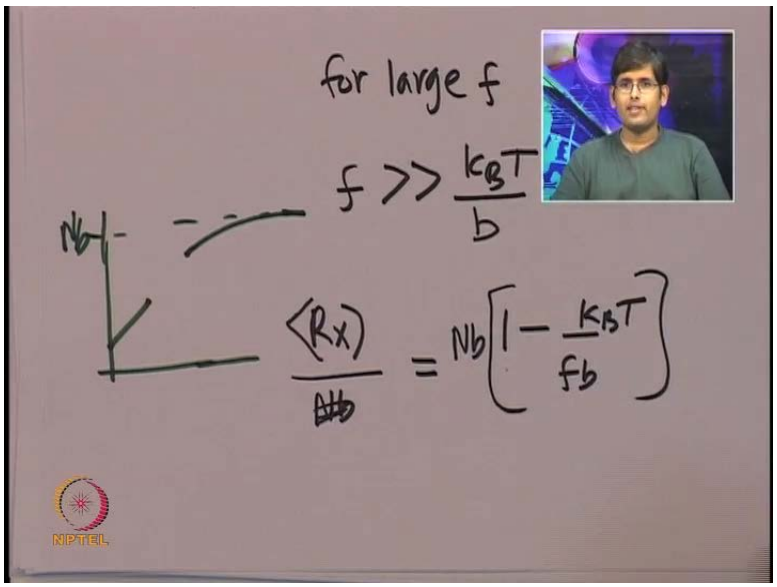

So, for large f so that is f much larger than k B T by f k B T by b it turns out that this end to end distance will go as look so this is basically scale with some factors. So, let me call this N b will be equal to 1 minus 1 by f b by k B T. So, this is what you will get 1 minus so, this would mean that R X will go as N b times this is what you will get. Which says that this goes as 1 minus 1 by f so R X for large force will go like this? If you plot this you can see that this is saturate it will for large force for small force it is linear and for

large force it is going to saturate to a value for f with infinity this is 0 and this is N and R X is the N b. So, this is going to saturate to a value N b so you can see that for large force this will have this particular relation.

So from this we can figure out given a system how do we calculate. What we discussed is basically that given a system how we calculate the partition function. And how do we calculate free energy and from free energy how do we calculate something that is measurable in a lab. Whatever something that is measurable experimentally so we had this thing called force extension relation for single stranded DNA. For double stranded DNA it is little more complicated because the energy is also taken account binding energy.

So, we wouldn't discuss that but, it is possible to calculate some limit of it analytically and using you can write down formulas in some limit but, the full expression has to be calculated numerically using computer. It cannot we cannot write down and expression for double stranded DNA if you pull double stranded DNA how much will be the if you apply a force f how much will it get pulled cannot be written down as a formula analytically but, an exact formula cannot be written down. You can write down some approximate formulas but, you can still calculate the partition function in a computer. So, anything that cannot be done by pen and paper you cannot do it using computer and people have done it and then they could plot the force versus.

If you apply force how much will get pulled relation for what is the use of all this by people also do experiment by pulling DNA. And from this pulling experiments we can understand a lot of things about lot of things things about structure of DNA plus various DNA protein direction now we can imagine that then when protein is bound on DNA you can pull the DNA and then you can know that how much is force is needed to pull out this protein and there by understanding something about the protein DNA interactions.

So, you can learn about protein DNA interactions by applying force and then calculating force extension relation. So, this can be extended to a protein DNA case and we can learn something about protein DNA interactions which is little more complex people are doing research on it. So, I wouldn't discuss it the class here but, it is good to understand that by leaning such things by learning how to calculate partition function how to calculate free

energy of DNA under force and we can extend this calculations to DNA plus protein under force.

So, if you pull the DNA which is bound with the protein for example, you can imagine that a DNA is histone protein d N a is wrapped around histone proteins.

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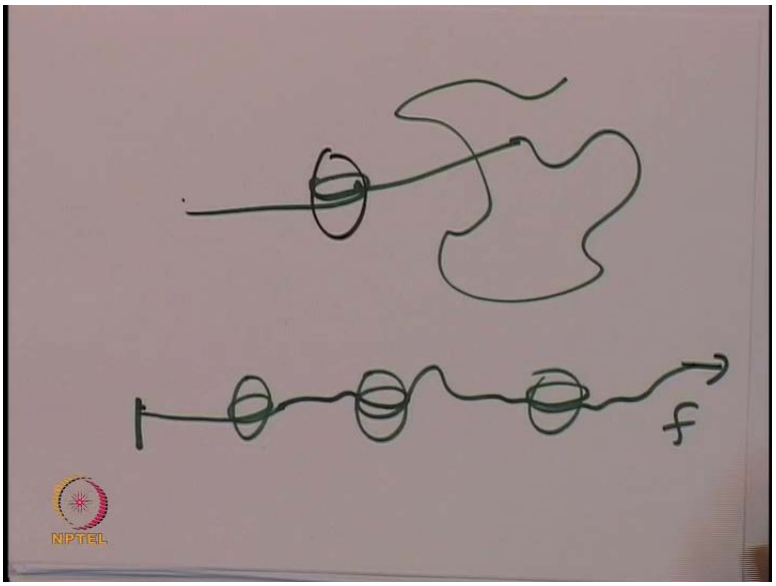

So you can imagine that you have a histone protein so this is a histone octomer DNA is wrapped around this histone protein. Then and this DNA has various shapes there could be many histone proteins so you could imagine that there are like many histone proteins. So this DNA is wrapped around this and wrapped around this and wrapped around this.

Now you can apply a force here and keep this end fixed and then pull this and then applying a force and pulling it and knowing it the end to end distance by taking into account this interaction between protein and DNA also. And plotting the… how much force is needed for this to be completely stressed will tell you something about the interactions between proteins and DNA. If the interaction is very weak small force would suffice to stretch it completely if the interaction is very strong you need a large force to stretch it completely.

So by studying the force extension relation of a protein DNA complex one can understand something about the protein DNA interaction how strongly proteins interact to DNA and this has been we used to study a various kinds of proteins and very

interesting research have come out. So, I wouldn't go into that detail here is sufficient to say that such studies can be extended to other cases also and learn many useful things but, at the moment aim of this course is to give you a glimpse of how do we do how do we use mathematics to predict calculate some quantities that you would be needing to use.

Now you can ask the question that in general when there is this bending stiffness is also taken in to account. There are few other interesting things people write down mathematically to describe.

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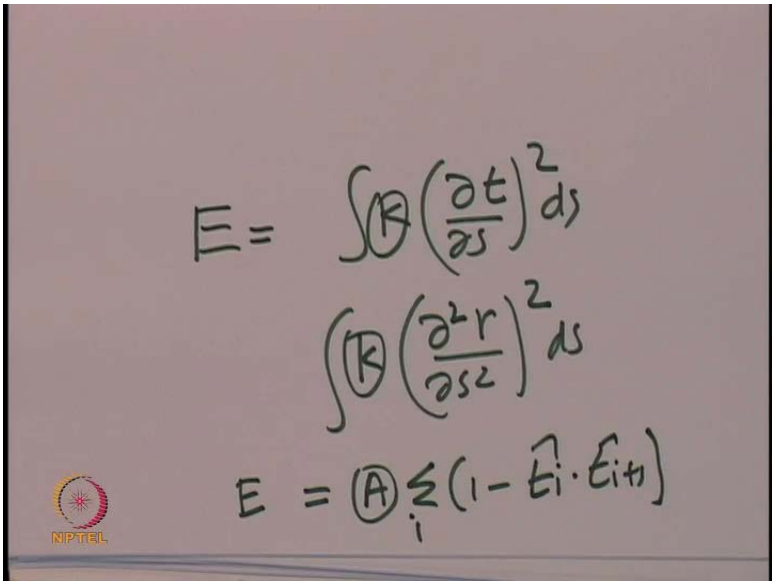

So we said that the energy of a worm like chain model and we call we wrote this yesterday the other day as energy. We wrote in 2 ways we wrote integral kappa del t by del s whole square or del square r by del square whole square kappa and there is an integral d s. Now we also wrote this as in the discrete form a into sum over i 1 minus t i dot t i plus 1. What is this kappa this kappa or k is related. So, this is related to bending stiffness. And there is a quantity related to this known as something known as persistence length and this is an important quantity for all bio polymers.

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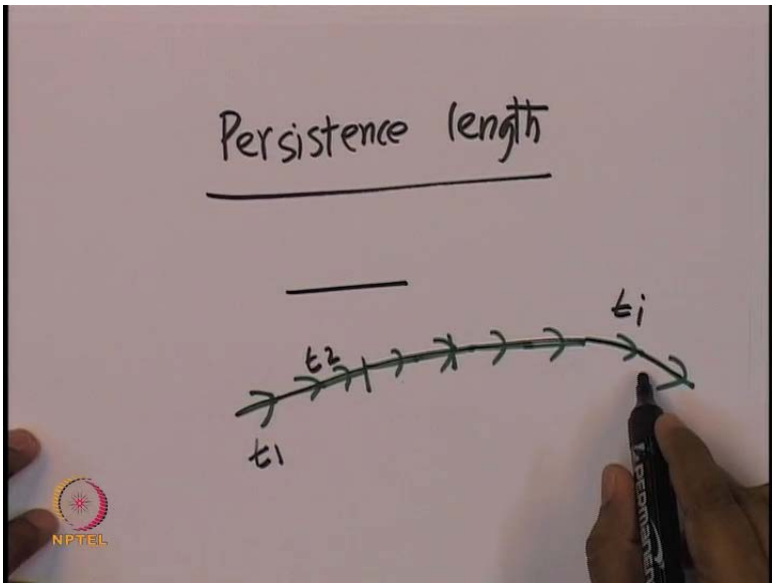

So there is something of persistence length and I want to discuss this and what does that mean and how do we write down how do we what is this persistence length typically means. So, what persistence and physically means is that this is the length beyond this any filament will start bending. So if you take imagine that you take very small iron rod it will be pretty much straight. If you take a very large iron rod So like very very long so you might have seen like long iron rods which is like 10 20 meters long. For example, used for making buildings. So if it is very long then start slowly bending similarly DNA or any polymer for that matter. DNA, actin etcetera when they are very short they are very straight when they are short they will be very almost straight but, when they are long Ah they will be like there will be banding's. If you take the short segment from here this will be straight but, if you take this long segment they will be slightly bent.

So if you think of tangents here so if you draw many tangent vectors here So if you take all this as tangents vectors so this is tangent 1 this is tangent 2 and like this is let us we call this tangent i. So this and this are not in the same direction they have shattered this tangents this direction this tangent is this direction.

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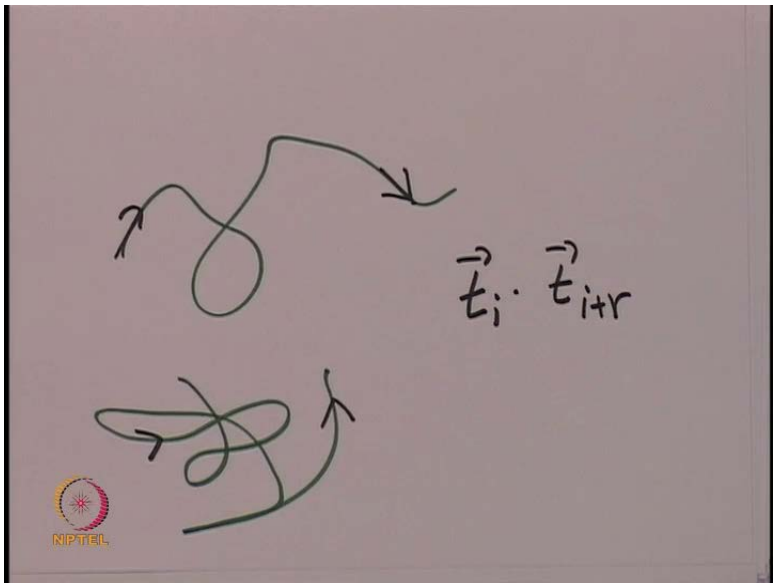

Now if you think of a completely bent DNA think of this confirmation so here the tangent is in this direction here the tangent is in this direction. If you think about some other confirmation of DNA here the tangents in this in this direction here the tangent is in this direction. So, if you think many many many X confirmations and you take some tangent i tangent this is i some tangent I and then you tangent take some other tangents far away. And find the dot product of this tangents so i plus r.

So, if you take tangent far away and take find the product of this if this is completely if this is completely straight line if the filament was not nope if the filament never bent.

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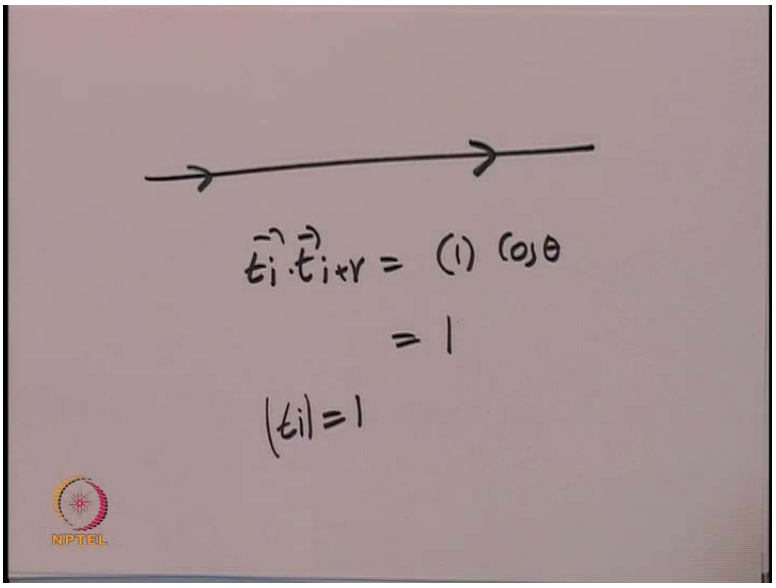

If the filament was always straight this any 2 tangents will be the same direction. So then t i dot t i plus r will be Cos theta. Cos of some mode so it will be some constant times Cos theta and this angle between this they are in the same direction so theta is 0. So this will be 1 Cos theta will be 1. So, this will be some if you take this is unit vector this will be 1 so if t i is unit vectors so this answer will be 1. So this is also will be 1. On the other hand if they are bent this will turn out to be not 1 It will be smaller than 1 so you can write this T a dot T a plus R in the continuum fashion.

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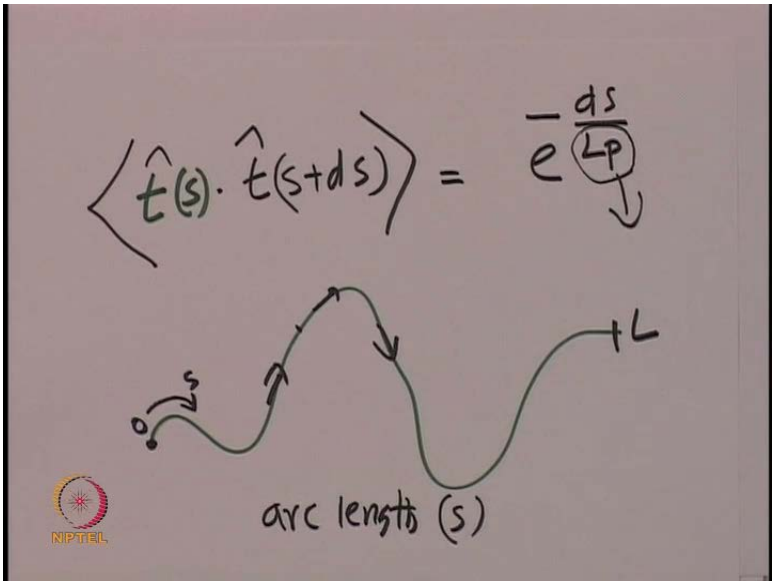

And we can write take any tangent at a distance so think about this is a continuous line and take this variable starting from here. You can call this s as the length along this contour from 0 to l. So, this length along this contour is called arc length. So, if you take the length along this contour basically s is the distance from 1 end of DNA to any point. And if you take some other point d s and find the dot product of this and find average it so this is called correlation. So this is called tangent correlation this is same as t i dot t i plus r. And then you find the average of it turns out that this wills d k exponentially and this can be shown mathematically.

And this coefficient that sitting here and this is called the persistence length. So L p and this coefficient here are called the persistence. So, this is like a correlation length so the tangent correlation length will turn out to be L p. So, the persistence length is basically the tangent correlation length for a double stranded DNA or for any any any polymer. So, it turns out that this L p what is what happens. If L p is L p is decided by basically the physical property of the material DNA the though physical property of the material property of the DNA decides what is the persistence length of the DNA.

The property of the actin decides what is the persistent for the actin so it turns out that the persistence length for DNA.

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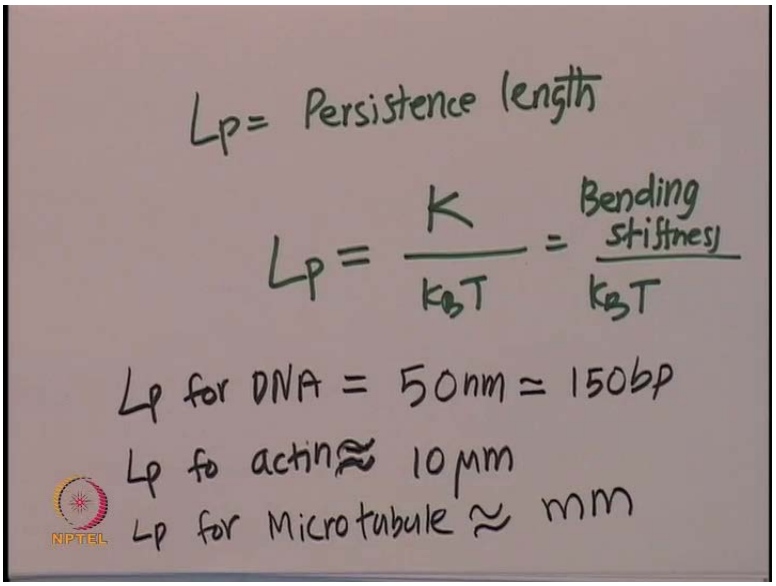

So, L p is persistence is length this tells you how stiff so it also turns out that this turns out to be this bending stiffness divided by k B T. So this is bending stiffness how stiff it

is to bend by k B T. So it turns out that this L p for DNA is 50 nanometer or about or 150 base pair. What does that mean? DNA beyond 150 base pair though so persistence length is the length beyond which DNA will start bending start wobbling start appearing vaguely. So, beyond 150 base pair DNA will start slowly bending but, up below 150 base pair DNA typically will be pretty straight. For actin the persistence length turns out to be of the order of micrometer.

So this is about for actin this is approximately equal to ten micrometer. So up to about ten micrometer actin will be pretty stiff and for microtubule this is of the order of millimeter it is like thousand micron. So this will be of the up to a millimeter length this will be very stiff so in the in the cellular length scale this microtubule will be very stiff I have actin will be less stiff DNA will be much less stiff. So DNA is highly packed has to bend is highly bend and packed inside the nucleus.

Ah the actin is pretty straight but, not as straight as microtubule is much straighter and it's very stiff. So, this is the property called persistence length. Now what we learn we learnt about partition function we learnt about free energy and if you know we know all though that if you know the partition function and the free energy you can calculate many quantities and 4 sections relation is one of the quantity that we calculated.

So we learn that from partition function. We can calculate probability for the DNA to have a particular shape or any filament to have a particular shape. So, now we want to understand what is the probability that the DNA will be forming a loop.

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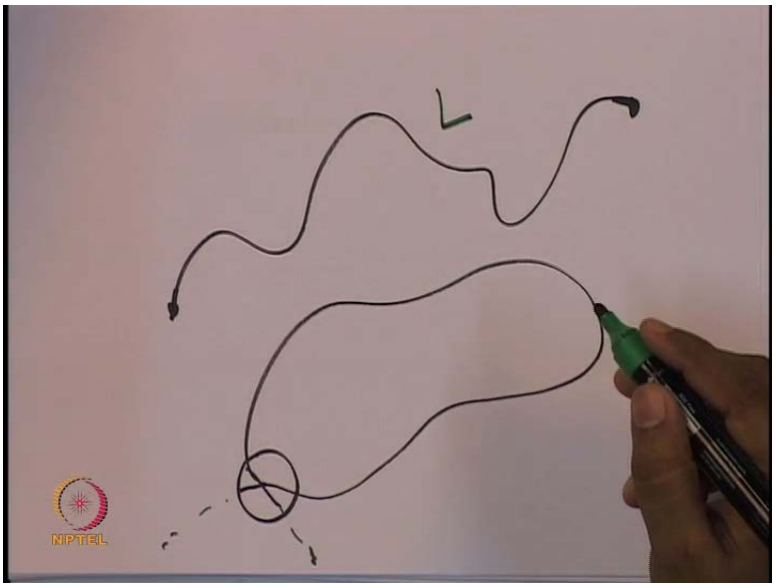

So this is some question that people can ask because DNA loop formation is an important point in by any it is important thing in biology. for example we have a DNA like this and ask the question what is the probability that the this end and this end will so there is some gene here some gene here what is the probability that the gene the gene will come together and form something like this. So, if they come together some protein can bind here and then repress certain genes there so there will be so what is the probability that there will be the two end two parts of the DNA which is L length a part will come together to form a loop like this. So, the answer to that this can be calculated from partition functions.

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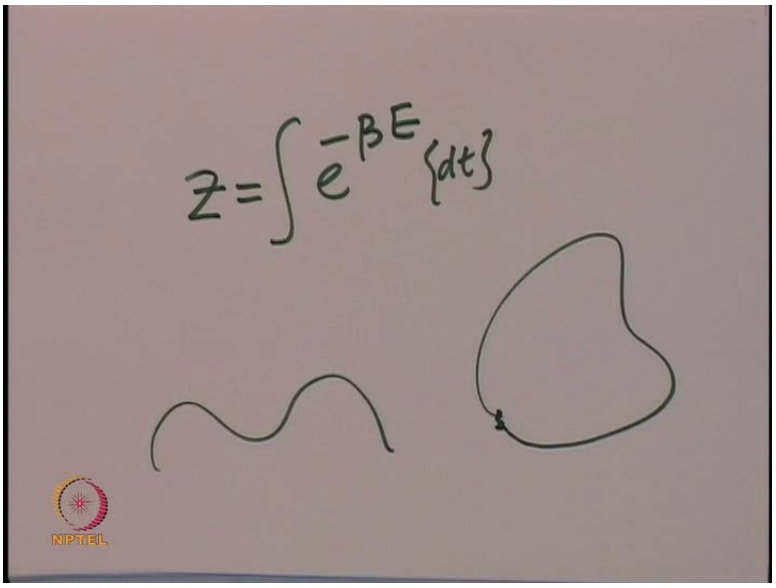

So what is partition function partition function is basically we said that z is e power minus beta E integral over all states all state for us all d t. Now what we want we want to have probability to find DNA in one particular state. So how do we calculate that the particular state is so let us say you have a DNA of length L and we want this to come together so that the end to end distance is 0? So how do we calculate that?

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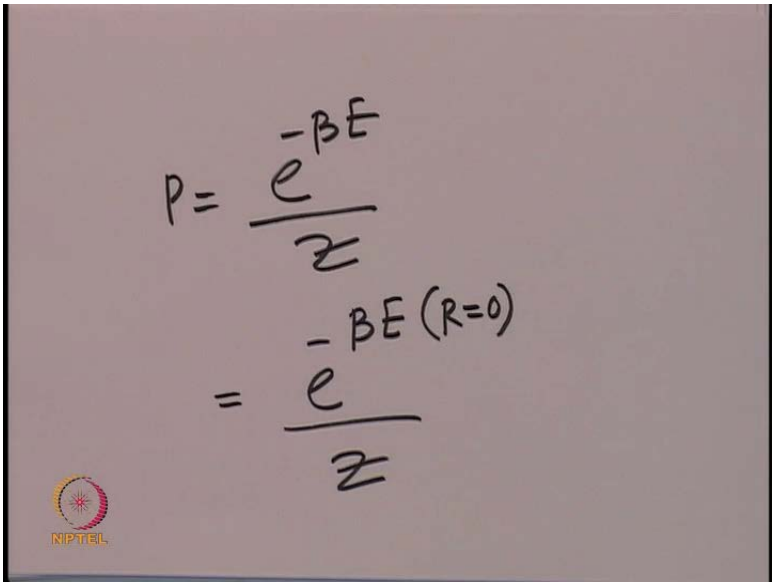

So we can calculate this by calculating the following quantity so what we say that the probability is e power minus beta E divided by z. So, we can calculate e power minus

beta energy such a way that R is equal to 0 divided by z. This will give us the answer in general we can also calculate.

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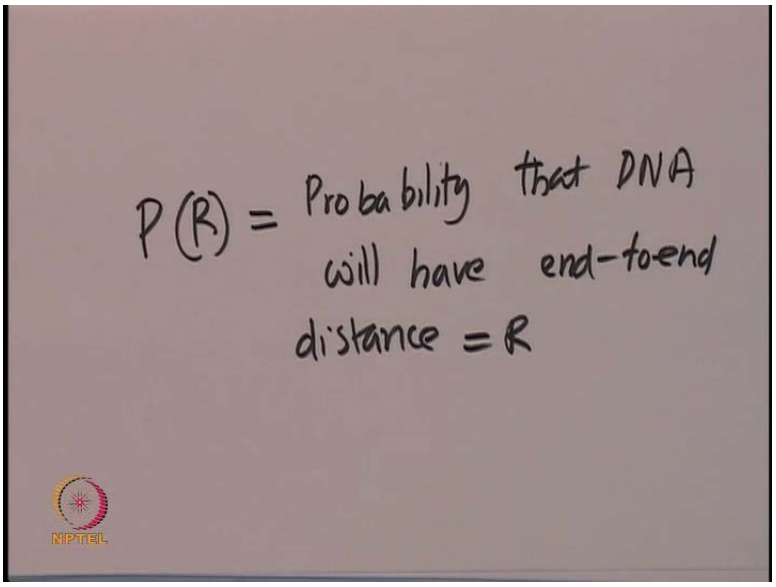

What is the probability to have? DNA to have any end to end distance R this is this is basically probability that DNA or protein or any polymer will have end to end distance equal to R. So, read test for this is applicable for DNA protein and all that so what is the probability that the two parts the DNA or protein will be R distance apart because even the case of the protein this is very important by calculating this one can learn something about the shape of the protein and the shape of the protein decides the function of the protein.

So what is the probability that two ends of the protein will be R distance apart and this can be calculated by calculating the energy and then calculating the partition function and then calculating the formula to calculate the probability? So, it turns out that if you take DNA for example, if you take DNA of various lengths. If the DNA list very short we said that the DNA will be pretty stiff because it is unable to bend.

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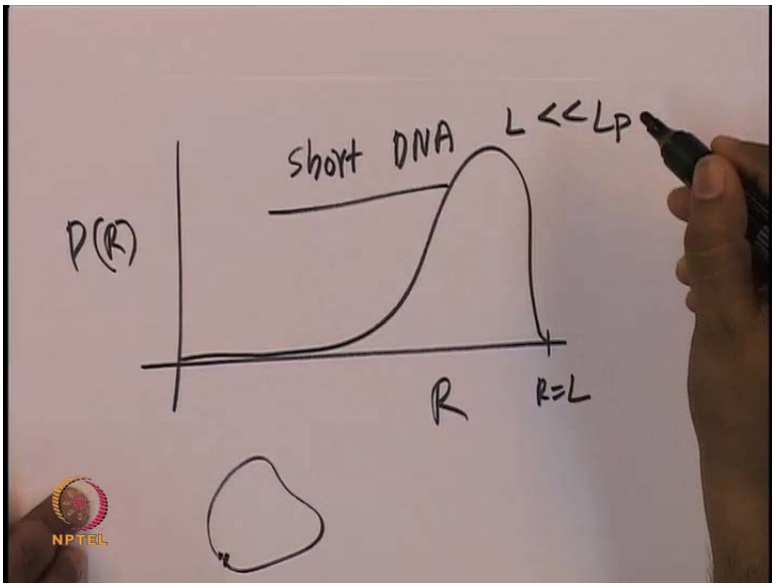

So for short DNA if you plot the end to end distance it will turn out to be something like this. So, this is p of R verses R the DNA will be most the this is R equal to l the total length where R is end to end distance so most of the time the DNA would be R will be very close to l. So, this is short DNA for small DNA which is length much less than the persistence length The DNA would look like this the end to end vector distribution would look like this.

So we see that the probability that the R is equal to 0 that means the looping probability the probability that R is 0 this 2 ends come together is very small. Is very is not 0 but, very close to 0 is very very very small. Now so this is the end to end distance for probability to have end to end distance for a short DNA.

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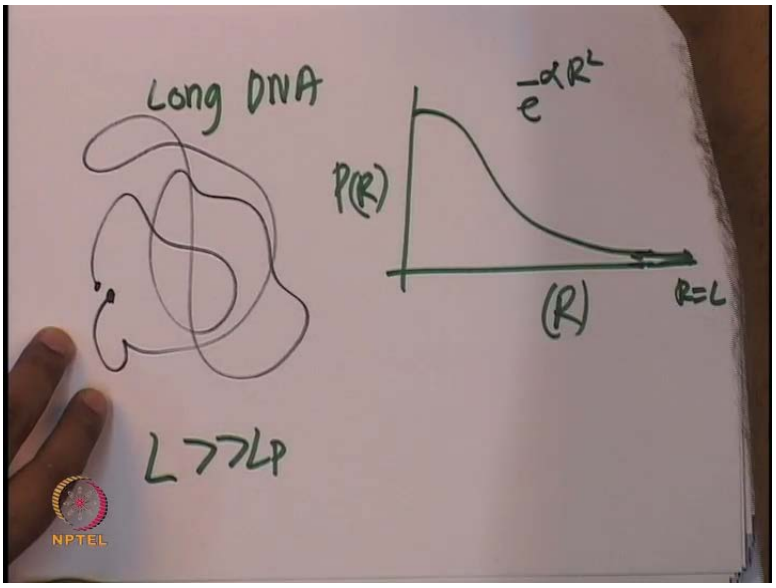

For a very long DNA what happens is that? You can imagine that for a long DNA they will take all kinds of shape so very highly probable this two ends come together. So, for long DNA the long DNA the length of DNA is much less greater than the persistence length. This will look something like this. This is p of R verses R. The probability that R is 0 is pretty high and the probability that to have very long the completely straight so this is R is equal to L will be very small. So, this will look like actually for very large this will be Gaussian function which will be e power minus some constant alpha into R square this will be this particular somewhere of the intermediate length you will get something in the middle. So, for some length so for a DNA for which for which length is comparable to the persistence length.

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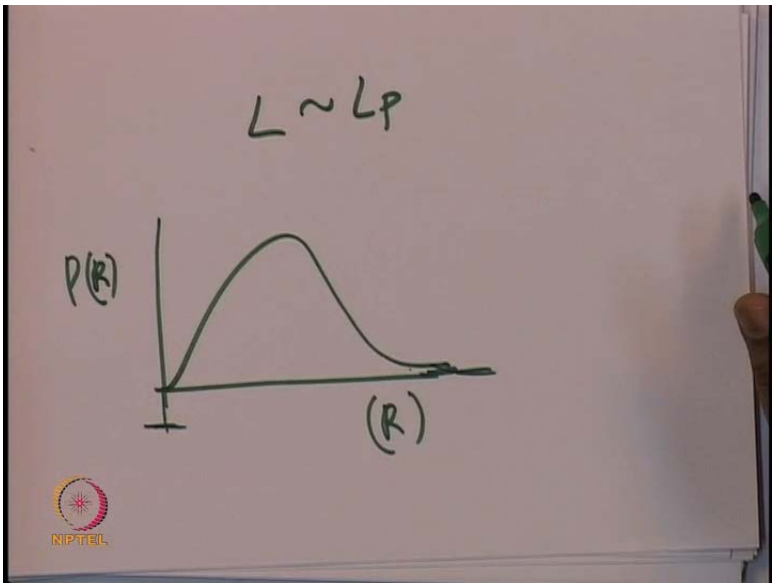

If L is comparable to the persistence length what you will get is something like this you will get something like something like this so p of R verses R. For some intermediate length you will get something like this so the the is not 0 actually ah 0 will be somewhere here. So, this some some positive value and then you will get finally, fetching this is 0 so, you can imagine this, for this intermediate length DNA now you can ask the question what is the probability that it will come together.

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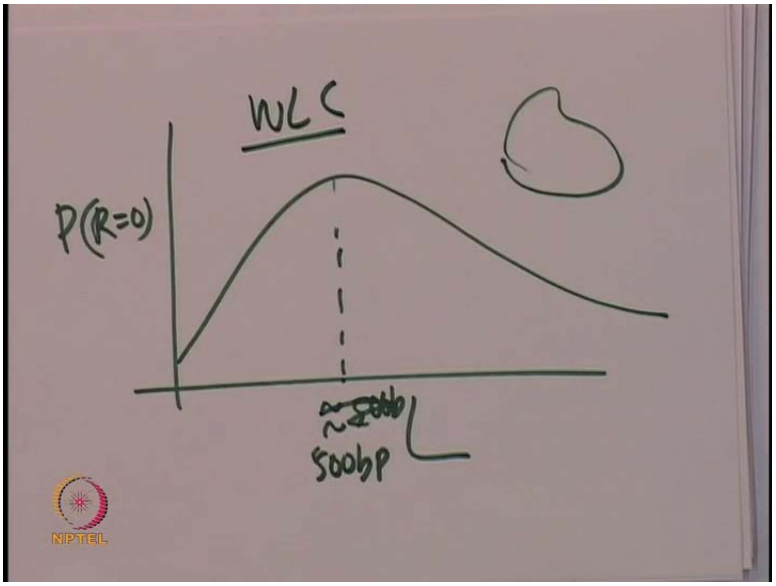

So this is now we can plot p of R equal to 0 this all can be calculated either numerically or using the same techniques that we discussed verses l. It turns out that it has some behavior which is non-monotonic that means it depends it increases and decreases so it increases and decreases in a particular manner. So I wouldn't discuss the detail here but, this has a non-monotonic shape. That means the probability there is an up there is a particular length and this length turns out to be close to 4 times the persistence length which is very close to 500 base pair this is close to 500 base pair. This is maximum probability to form loop like this.

So for very short DNA is highly less probable for large DNA this is again much less probable. So, this is sum according to the worm like chain model of the DNA this is the p of R what does this mean. This means that this is basically this is due to there are 2 terms free energy as we said there is an energy and entropy this is e minus T s or G minus h minus s is the free energy.

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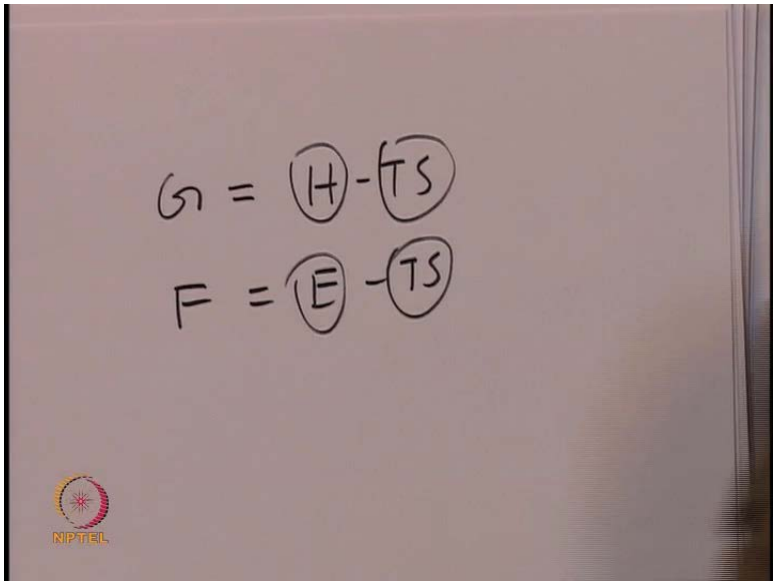

So when we write free energy so this is another way of thinking about it then we write G this is basically H minus T S or F is E minus T S so there is entropy and energy this is also energy and entropy. So energy want energy does not want the DNA to bend because if you bend the DNA it Costs lot of energy so energy want for the short filaments energy dominates so that is the first part of the curve so this is basically this part is basically

where the energy dominates. So the DNA behaves according to like the energy part of the free energy dominates.

And here the entropy dominates and somewhere in the middle it is a combination between energy and entropy which makes it non monotonic. So pretty much every system that you can think of in biology can be thought of as some combination between energy and entropy. So energy wants it one way and entropy wants it in other way. As we have discussed in statistical thermodynamics that always free energy will be combination of energy and entropy and they will compete and say we want to we want to state for which the free energy is minimum.

So there are many such qualities that we can compute and we can use mathematics and statistical thermodynamics to compute all these quantities. So these are DNA I just took one example one can think of many other examples ah and compute various other quantities which can be seen in some of the books that we had given as the part of this syllables we had prescribed set of text books like physical biology of the cell or biological physics which has in detail how do we calculate this for various quantities we is being described so we can have a look at those books and this read them there.

So this is just as an example I discussed a couple of examples. So, just to tell you that we can compute calculate all this quantities using ideas from mathematics applied to biological systems and applied the laws of physics. If you apply you will get this predict quantities and we can predict them. So with this I will stop today's lecture and see you for the next lecture bye.