Cellular Biophysics
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Understanding Chromosomes as Statistical Polymers
Part 02

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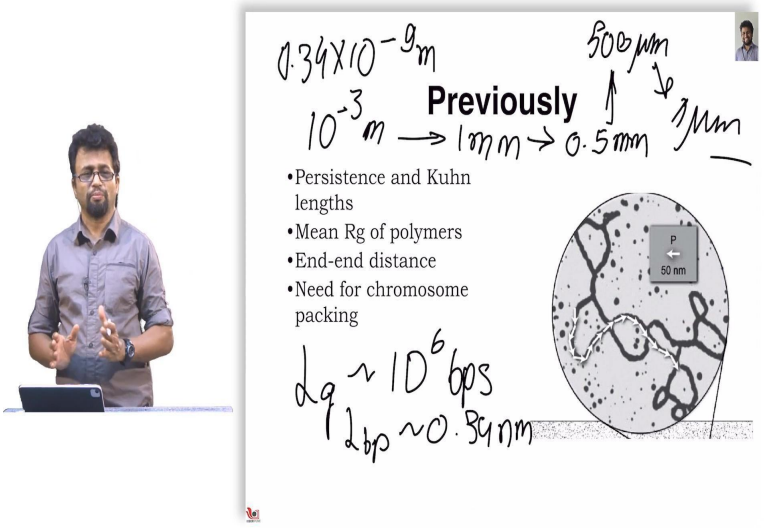

Hi, welcome back. So, today we are going to talk about chromosome packing. And these two pictures are meant to sort of remind us that when we have a very long string of wool, we do not want it to lie around. This is a practical purpose, obviously, that you want it kept in one place, you want it neat, you want to be able to access it and you will be able to make a sweater out of it. And perhaps from a functional perspective, one can imagine that our chromosomes which are themselves made up of very fine strings of DNA may also be packed to be organized. Biology is a bit strange, we always think about function, we need to think about the function because that is what evolution selects.

But for the cellular biophysics course discussion, we are going to deal with it in the context of what we had spoken about earlier, which was some of these very foundational principles of polymers, we had spoken if you remember about persistence and Kuhn lengths, which relates to the fact that certain segments of a polymer can be statistically considered to be effectively rods, the flexibility can be quantified in terms of persistence length, that if you put a random walk polymer in our system at equilibrium in bath constant temperature, evidently, pressure also then it will achieve a certain distribution, which can be calculated from the underlying microscopic mechanics of the filament of the polymer to give you a mean radius of gyration.

And radius of gyration, as some of you if you have studied biology, biochemistry, you know that this can also be measured in an experiment. So, theory and experiment can be matched with one another. We also talked about end to end distance and the fact that the same theory that allows us to calculate radius of gyration also allows us to estimate numbers that can be put onto the DNA fiber for example and what is the expected position of the two ends of a linear filament, linear polymer. We briefly discussed the need for chromosome packing in terms of sizes and if you remember, we asked us a very simple question.

And I can write this for you, which is that the L_{genome} the length of the *E. coli* L_{genome} in biophysics is 10^6 base pairs, the length per base pair is 0.34 nanometers which is 0.34 x

10^{-9} meters. And if we now multiply this, we end up with 10^{-3} meters which should be approximately 1 millimeter. This is the absolute contour length of a polymer of bacterial DNA. Now we also know bacterial DNA circular. So, even if we want to be simplifying, we can say this can be even up to 0.5 mm, half, you circled it so it is a diameter of a circle and you stretch it out, you somehow imagine a rubber band that is stretched out. In such a case, we are still talking about 500 microns.

But a bacterium like e coli has a length of only 1 micron. So, how does it fit in? That is the real motivation for the need for chromosome packing and for understanding it is what we are going to talk about today.

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TODAY

1. Chromosome packing models
2. Linear packing density
3. Tethering of chromosomes & measurement of distances
4. Random-Walk Giant Loop Model
5. Experimental techniques to measure e.g. HiC
6. Computational models
7. DNA Looping, Entropy and Enthalpy: J-curve and plasmid ligations

So, we will discuss some standard models of chromosome packing from what we understand from biochemistry and cell biology and molecular biology. Then we will discuss some measures or quantitative approaches to understanding linear packing density. We will then go on to discuss how tethering might happen. And these tethering are very difficult to measure. So, they involve some experimental approaches that are quite interesting. And they have been fundamental to improve our understanding of chromosomes. We will then discuss something called the random walk giant loop model. And if you remember, we have talked about random walk models before this giant loop is an additional factor.

And, then we will go on to some methods that have become very, very powerful, called HiC or chromosome confirmation capture. These allow a bioinformatics approach to be applied to a polymer mechanics problem. This is really fantastic. This is a technology that is driving our understanding and allowing us to test the physical principles of chromosomes and chromosome packing. And we will end with some summary of a few computational models and entropy, enthalpy interplay and how they explain what is called the J curve. This is been done primarily using very primitive methods called plasmid ligation.

So, those of you who are doing biochemistry and molecular biology that you know what a plasmid is extra chromosomal DNA. So, it is interesting that this can apply so nicely to what is a fundamental chromosome problem. So, let us see how this works out.

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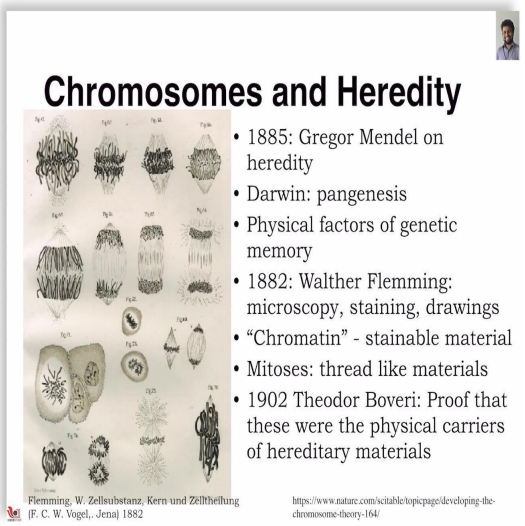

Now, if you look back at the history of genetics and basic biology, the basis of heredity itself, the fact that there is such a principle, as the parent decides, determines the nature of the

offspring was described initially, by Gregor Mendel, many people knew this. I mean, if you look around you, the person who is tall has a tall child and the rabbits that are white in coat have white in coat, baby rabbits and brown coated rabbits or brown coated babies. So, this is obvious. But Mendel made a specific discovery, which showed that the mixing of characteristics of the same species gives rise to very precise ratios of the offspring. We know these as Mendel's laws now, I mean, it is very rare in biology that we have a law and I think these were really fundamental to our understanding of biology in some senses.

And at a very similar time, this is 1885, by the way. In fact, Gregor Mendel experiments were done in 1857. This is an important year in India, but for different reasons. So, we were fighting, they were doing genetics, I mean, it is a bit sad. But Darwin came up with an idea of pangenesis, which also suggested that these hereditary materials have a physical basis. And this has set off from 18, late 1800s, almost 1900, a series of discoveries and experiments that went to get more and more detail about the physical basis meaning to say biochemical, mechanical, cellular material that governs the principles of heredity that Mendel came up with.

This search for the physical factors of genetic memory has led in 1882, Walther Flemming to start doing some of these beautiful microscopy images. By the way, these are hand drawn. They are drawn based on microscopic observations and camera lucid drawings by Flemming where he managed correctly. So, in fact, today, if you do the same experiment, you will get the same answer with very sophisticated microscopes showing us that the process of chromosome metaphase plate formation, separation splitting into two, moving apart the sort of funny spindle shaped structure anaphase and cytokinesis are still confirmed today.

And what was interesting for him was the thread like structures, which he could stain with dyes that as we today know our DNA specific but at that time, they were acidophilic dyes, which he called chromatin because of the Greek word Chroma, Chromo color or material that was stainable that he could observe dense material. And, Mitoses because they were threadlike, again a Greek word. This is common in early 1900's biology, Germans, French English scientists, they always named things after the Greek words for it because it was sort of considered to be classic.

So, Theodor Boveri, who then came in 1902 showed that these were also responsible for heredity and used a worm called ascaris. This is related to some of the pathogenic worms, but suffice to say these were transparent, so he could see inside them. And with clever use of

stains and careful genetics, he could demonstrate that they were the physical carry. So, chromosomes as far as scientific understanding or what is sometimes called the Chromosome Theory of heredity has been around with us since 1900's. And, then work by Sulston and whole series of investigators continue to improve our understanding building on these fundamental insights.

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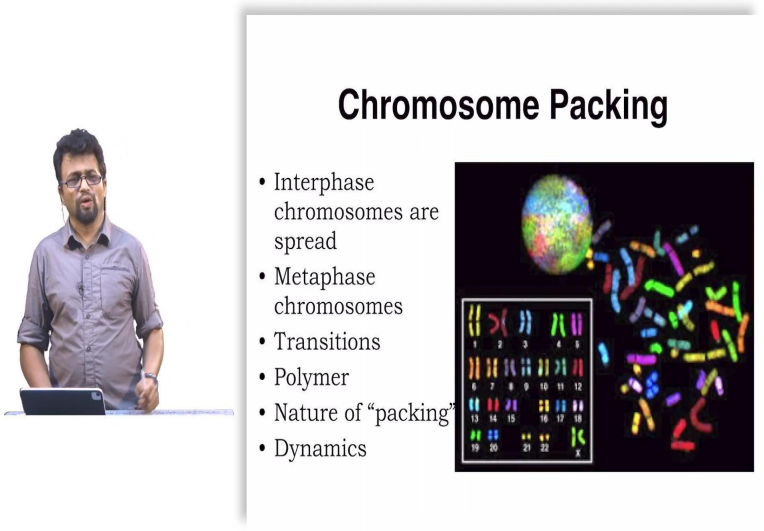

We are going to take a turn towards the biophysics and ask how this business of interphasic chromosomes, which look like a ball of wool that is all mixed up, like a cat came and just threw the wool around goes into the state where they form these beautiful X shaped structures, which are 23 chromosome pairs, which in fact, you can line up like this like a rogues gallery. This is some really amazing experimental technique, which some of you may have an opportunity to learn, called FISH or fluorescent in situ hybridization using a combinatorial DNA label, which is combining the mixture of dyes and DNA specific probes.

And by combinatorically, labelling them, you can actually uniquely label 23 chromosome pairs. And 22, somatic and one sex chromosome. So, the question is, when we go from this ball of wool to these very organized structures and back again, that is what happens in mitosis and back again to interphase and back again to mitoses and back again, how does the cell keep doing this repeatedly? And what is the nature of packing?

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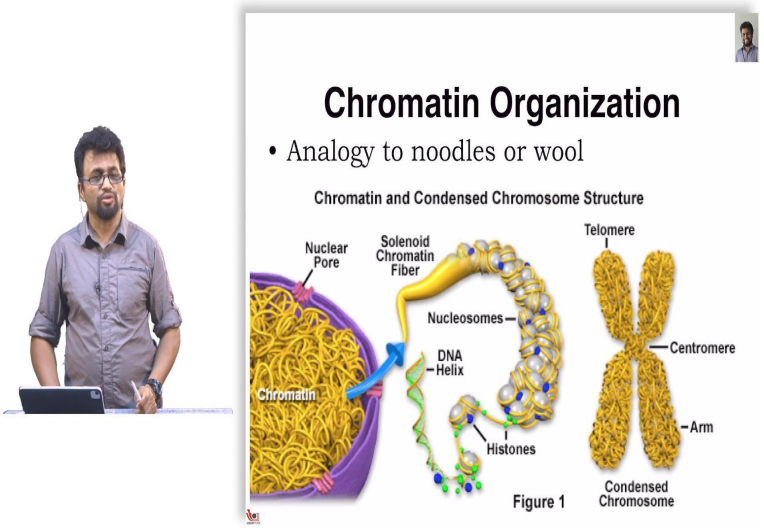

So this is the question that we are going to try and address and what we know about it as far as the standard theories are concerned. This analogy to noodles or wool is useful only to the extent that it is not like this chromatin is not in this form of a bowl or noodles, but in fact is organized in a hierarchical manner. And we say that there are initial naked DNA which are coated with histones, which allow this winding structure a ball on bead on chain, as it is sometimes referred to which themselves form a higher order structure called the solenoid chromatin fiber, which themselves go into forming higher and higher structures.

And what you are familiar with the metaphasic chromosome looks something like this, which is that it has a centromere, it has arms, it has telomeres and they are the condensed form. This is what get segregated during mitosis.

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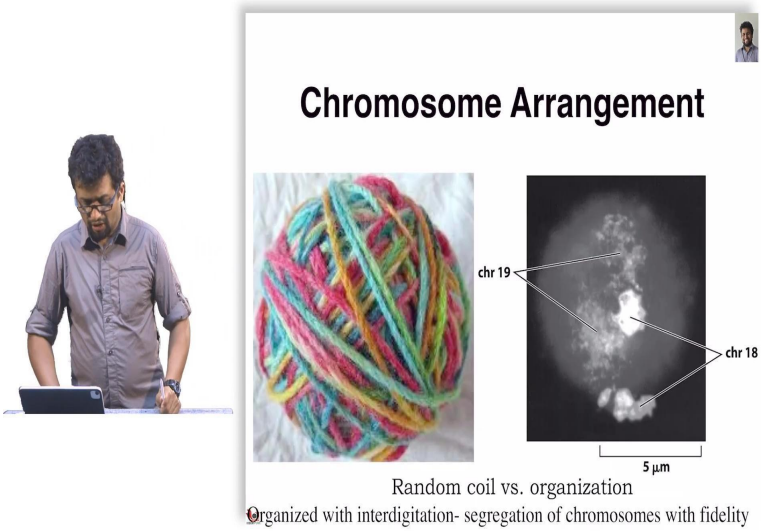

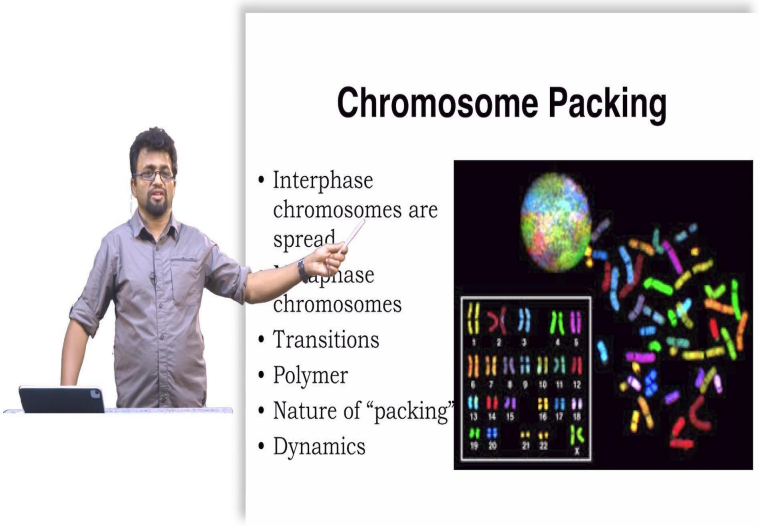

The chromosomal arrangement, in fact and there is a lot of debate about this in the literature is, in two extremes thought to be random coil versus organized. The proof that it is not a random coil comes from again, fluorescence in situ hybridization staining, which show that certain domains of the nucleus are occupied by certain chromosomes. And here you are looking at chromosome 18 and 19. It is evident that unlike a ball of wool, chromosomes can interdigitate meaning to say that bits of chromosomes folded into loops can go into each other. This is why this earlier picture of interphasic chromosomes looks like this because things are kind of mesh, the boundaries are not sharp.

Because there is no membrane there is just chromosomes, one chromosome, another chromosome and some fuzzy business intersecting between each other. So, borders are not

very clear, although people have spent a lot of time looking at chromosome territories. And are trying to understand whether chromosome territories are themselves rigid structures, which allow channel like movement, more and more evidence from experimental biology microscopy. And the fundamental basis of polymers suggests that this is unreasonable, it is more likely to be a smooth transition going from one chromosome to the next.

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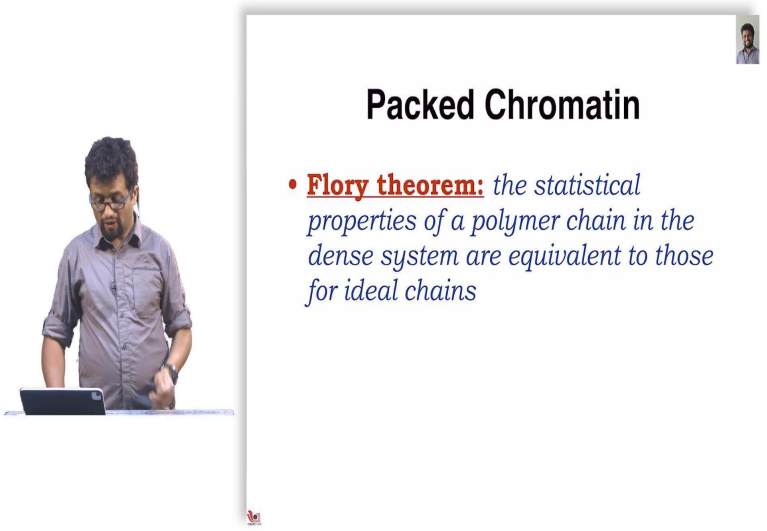

So, going ahead, packed chromosomes follow polymer theory based on what is called the Flory theorem or rather the Flory theorem can help us justify the use of polymer theory equilibrium polymer theory, even for something as densely packed as chromatic. Because the Flory theorem states that the statistical properties of polymer chain of a dense system are equivalent to those of an ideal chain. And if you remember, our ideal chain was this random of polymer which can cross I mean, fibers can cross through each other. We do not care about that it is not. So, that model is a little more complex.

And every time we add more complexity to the theoretical models, the solutions become more complex and harder to test. And so if a simple model can explain everything, that is great and if it does not, then we build up complexity.

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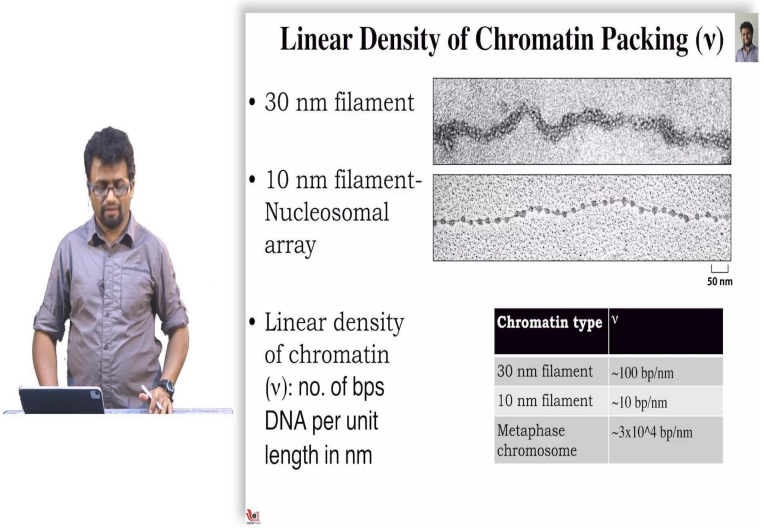

So, in terms of packing, we can of course describe chromosomes as minimally being made of DNA, like we did earlier for the bacterial DNA. Or we can ask that they are nucleosomes structure and bacteria do not have nucleosomes, they do not have histones, it is only a eukaryotes. It is only seen in eukaryotic systems. They have histone like proteins but not bonafide histones and DNA does not form these kinds of beads on chain structures. The 10 nanometer filament consists of a nucleosomal array these little beads you see the beads on chain that I keep referring to, they are the nucleosomes packed and in this beautiful electron micrograph you can actually see that there is a regular spacing between those nucleosomes.

In fact, recent data from publications, if you are interested, you should read shows that in time, these nucleosomes are dynamic they it is like, it is like if I take a necklace and do not put beads on very packed to each other and I just move it around, just shake it a bit, those beads will keep colliding with each other and going back and forth. So, in the living cell, the picture is more dynamic, but the electron micrograph tells us that if we take a snapshot, we will see regular spacing. So, this is the interplay between dynamics and static is very important.

But for now, we are going to assume that this average picture of equal spacing is valid, because we can see it, then above that is the 30 nanometer filament. And you can say that this parameter called linear chromatin packing density is in units it is linear. So, its base pairs per unit length. So, 30 nanometer filament has 100 base pairs per unit length meaning to say 100 base pairs are packed into 1 nanometer linear distance, 10 nanometer filaments evidently

because it is less packed is 10 base pairs per nanometer. And metaphase chromosomes, which are the highest pact density that we know of, they are at 30,000 base pairs per nanometer or 3 into 10^4 base pairs per nanometer.

So, the linear density now gives us a way to quantify where some chromatin may be tightly packed, medium packed or loosely packed. And so, in order to ask whether chromosomes are packed in one way or the other a vital experiment needed to be done.

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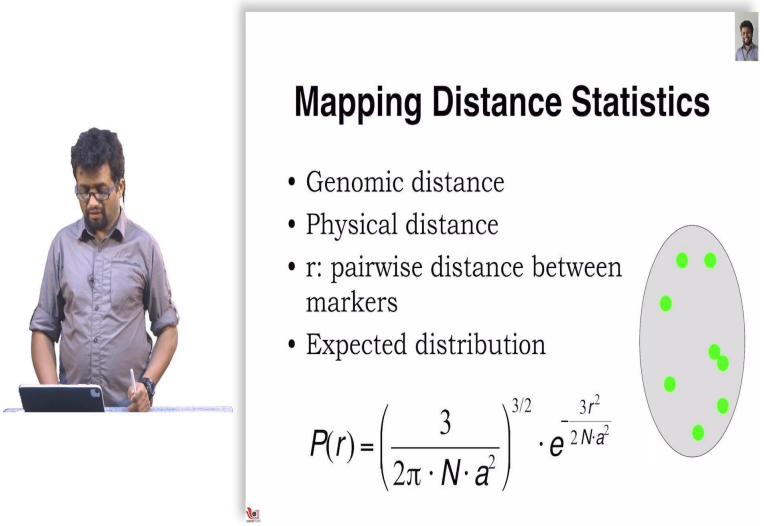

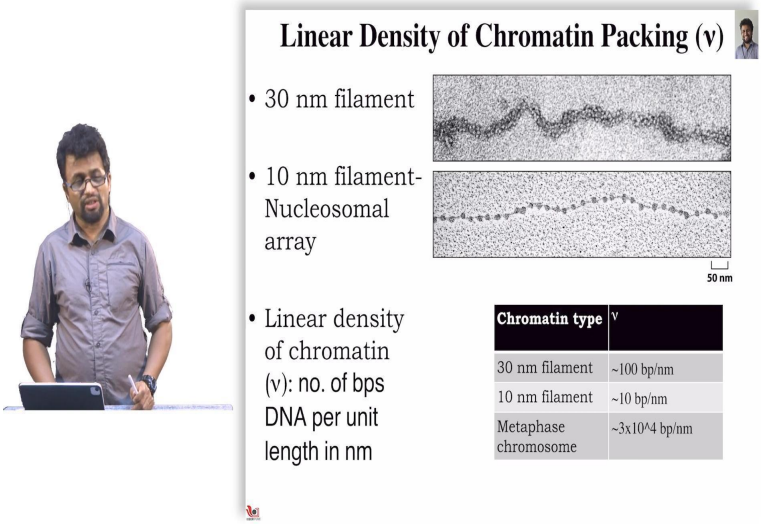

And that was called the mapping the distance mapping experiment. This distance mapping experiment is stated as follows. There is a certain genomic distance meaning to say you know that gene for let us say, a gene A is located at a certain position and another gene B is located

at a certain position along the DNA, what is the distance in base pairs between the two? This is the genomic distance. But there is also physical distance meaning to say if I now look inside a cell and have a probe, like we talked about the FISH, meaning to say sequence specific complementary regions, that can bind to a specific region and we have two search probes, then we can find the physical distance meaning in micrometers or nanometers or length units, what is the distance between these?

The pairwise distance between the markers then can be mapped in terms of a probability distribution, which fits to this exact expression. Based on Polymer theory. This is why we call it the expected distribution meaning to say the model predicts that Gaussian, a 3D Gaussian describes the pairwise distance between markers r being the pairwise distance, P being the probability and this being constant, N being the number of base pairs, a is Kuhn length and then the rest of the terms you are familiar with already N and a.

So, this is coming to my last week's last times lecture. And you should go back and look at it if you have any problems in terms of what the terms mean? Now, if we do this, we also need some experiments to compare to this theory. So, we do it in the following way that we label one cell with a pair of such markers, measure the distance, then we do it again, we do it again and we do it again till we get a whole series of such measurements that hopefully give us statistics.

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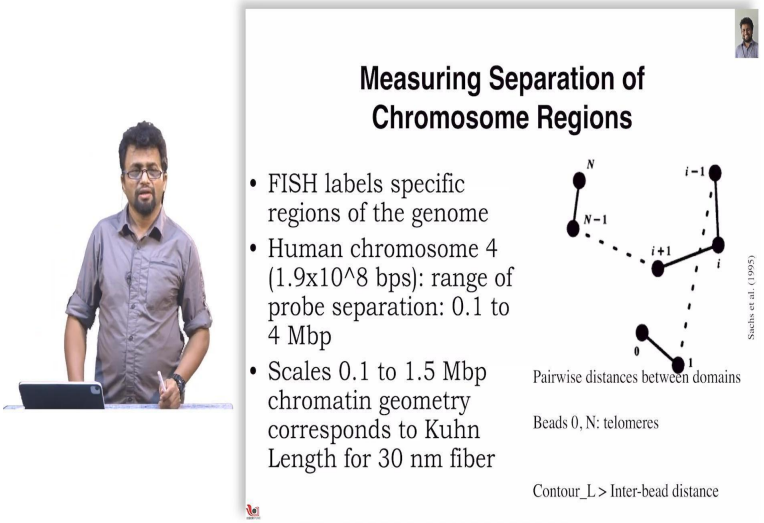

So, this experiment was done in 1995 by Zach's at all, where they did FISH labels or specific regions of the genome, like we just discussed and they took one chromosome, because 23

chromosome pairs in humans and it took human chromosome 4 and they looked at it in cell culture cells, where the range of probes separation was 0.1 to 4 mega bases. This scale of 0.1 to 1.5 Mbp of chromatic geometry corresponds to the Kuhn length of a 30 nanometer fiber. And, the idea was that potentially one will get an idea of what is the nature of packing based on this pairwise distance map and the contour length should be greater than the intermediate distance.

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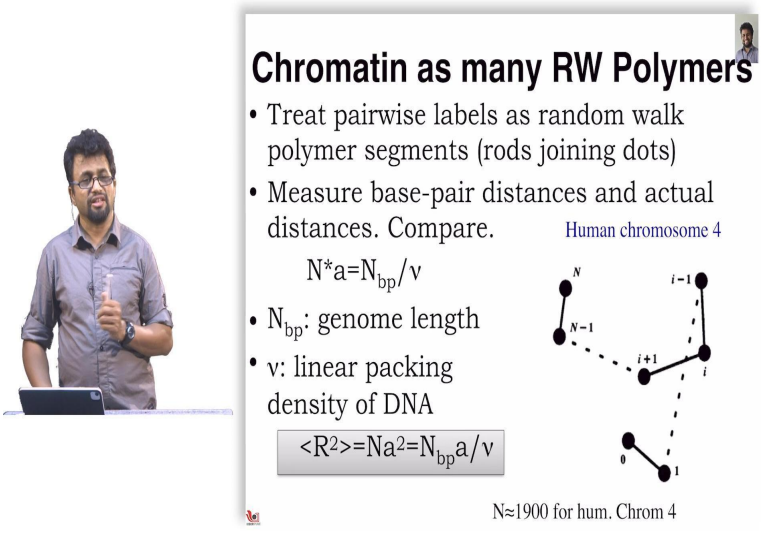

So, according to our ideas of random walk polymers, the pairwise distance squared or the mean square display distance between the two pairs should be equal to the product of the number of base pairs times the Kuhn length squared on an average, which if we reformulate it can be expressed in terms of number of base pairs times the Kuhn length times divided by the linear packing density nu. N for the human chromosome is 1900, that is the number of bases so. So, that is the range that they were able to estimate. So, the distance statistics of the random walk polymer then looked like this in the case of this same chromosome number 4.

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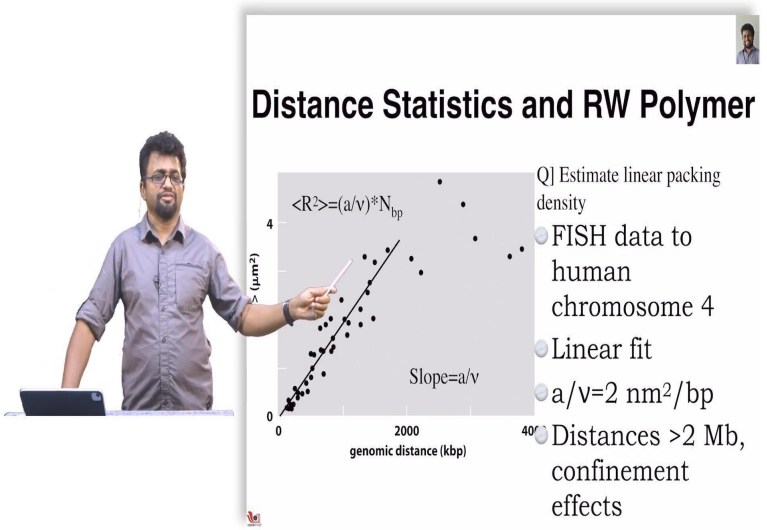

Where Zach's and company found that as the genomic distance went from 0 to 2000 base pairs, I am sorry 2000 kilo base pairs, the slope of the line was a straight line that is really nice, because linear scaling of distance suggests that as you get longer your distance of separation gets more. But please note that this separation distance is not measured as r which would be your normal separation distance measure, but as r square, I think you will remember probably from our previous lectures that the random walk polymer statistics, the pairwise distance between two points on a polymer or the two ends of a polymer scale not scale linearly, but not as r but as r^2 with distance between the contour positions or genomic distance.

So, in that sense, this part of the curve is very nicely consistent with the random walk polymer statistics simple model. And in fact, you can fit this expression which we showed earlier, which is, the Kuhn length divided by the linear packing density into number of base pairs to exactly estimate the unknown. Now, what is the unknown? Remember our aim was to know what is the packing nature of packing? And it turns out that ν for from all of this is 2 nanometers square, $\frac{a}{\nu}$ is 2 nanometer square per base pair. And for the distances of greater than 2 Mbp, confinement effects take charge.

What you can do, in fact and I have not done this for you, is and I am going to ask this in a question, what is the number ν? You need to go back and look at my old slides, you need to also go back and look at what was the value of a and that will allow you to get new and what inference we can make from it. So, you know, here we said that at greater than 2000 kilo

bases confinement effects take charge meaning to say that there is a limiting nuclear boundary. So, you cannot go beyond it. So, packing must be doing something else. So, something may be going on. And to address that the same folks and a few other groups went ahead to look at this higher order organization.

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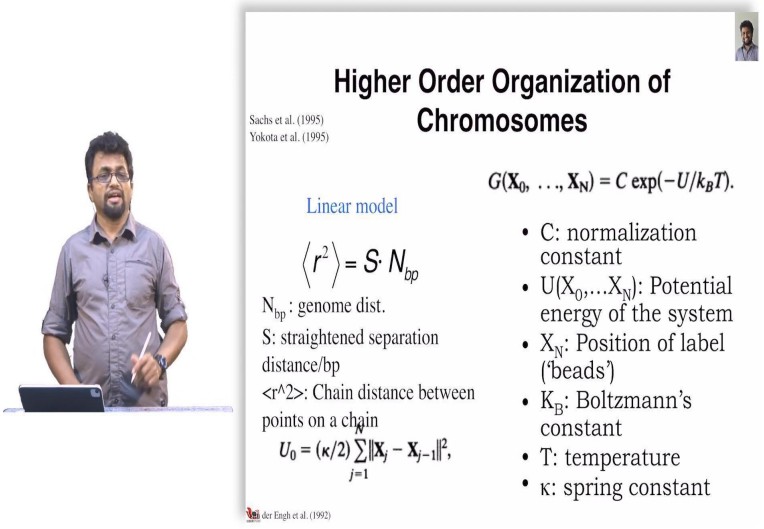

Which may exceed the kind of random walk polymer that we can expect. In such a case, the linear model tells us that it is just S into Nbp(Number of base pair). The mean square displacement is

$$\langle r^2 \rangle = S \cdot N_{bp}$$

where S is a straightened separation between base pairs and r^2 is the chain distance squared. But according to this model, you could argue that you have more complex behavior and this complex behavior was expressed in terms of this, where C is the normalization constant C into $\exp(-U/k_BT)$, U for X_o to X_n is the potential energy of the system, X_n is the position label of the bead and k_B is the Boltzmann constant, T is the temperature, κ is the spring constant.

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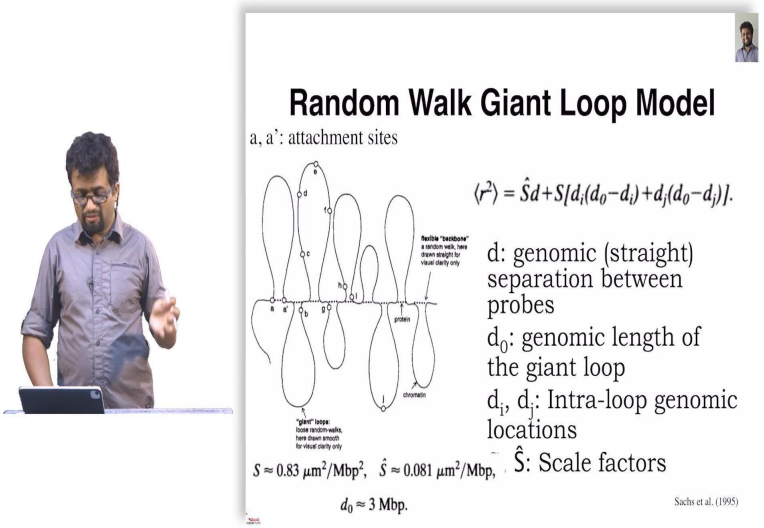

So, what does this mean? This means that, if you have attachment sites a and a'. So, somewhere along this linear scaffold, if you have a kind of skeleton that holds the chromosomes together, then you will find that at some spacing if they are packed so, there are random walks and they are packed so that they form one loop and they form another loop and they form another loop and this will give a new kind of expression for the genomic distance.

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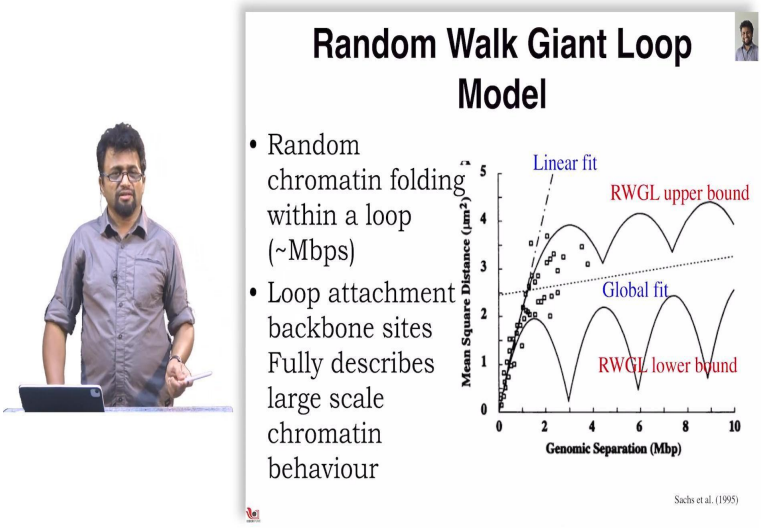

Which in turn looks something like this. And this is slightly strange, but bear with me, because again, this is data from a publication by Sachs, showing that the genomic separation as it increases on the x axis will give according to the random walk giant loop model, these kind of bumps, these bumps that come from the looping part, they go up, come down, go up,

come down and so on. And depending on the fit parameters, you will get a lower bound or an upper bound on the model predictions. Definitely, they have a better way to explain this long range data as compared to the linear fit.

The global fit on the other hand, does not agree with the short range. So, as you can see, none of these models satisfactorily explain everything, either you fit the long range or actually very badly fitted or you fit the short range.

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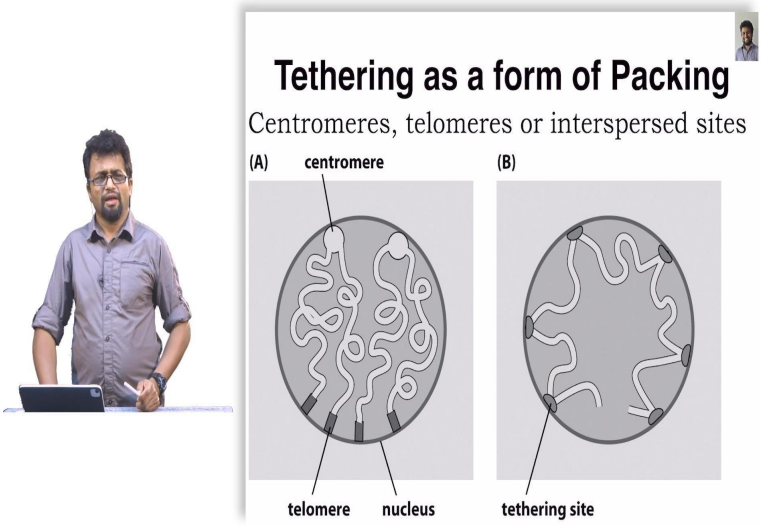

And so, tethering has been proposed as an alternative form of packing. And this is partly driven by some experimental data showing inner nuclear envelope in higher eukaryotes might have some points, where telomere may be stuck or central positions of chromosomes may be stuck to the nuclear membrane.

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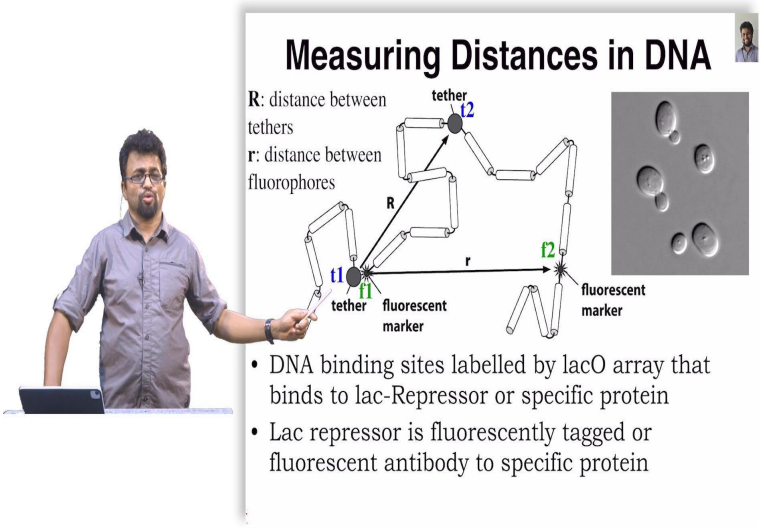

And to do this, people again did the same pairwise distance measurement, except here, this was a little more recent. So, GFP had already been discovered and the use of genetic tagging of GFP markers was possible. So, in such a case, the chromosomes were labelled at two points that are then the two stars here and here. And assuming that there are two tethers, t_1 and t_2, you can expect that the system will show you pairwise distances and your model can be adapted to this. This was done using yeast cells that is what you see here. This is one of the model organisms that we talked about at the beginning, budding yeast, brewer's yeast and the labelling was done using lacO arrays.

If you remember, the lac operon has a sequence called lacO, which is the operator site. This operator site is one where the repressor binds. Now, if you convert the repressor to be a GFP tag repressor, then the repressor protein the lac inhibitor, as it is also sometimes called will bind to the operator site and the GFP molecule will glow. And if you have many such thing and such lacO sites, then the point of glow will be very bright. And this is how you can create these kinds of fluorescent marker sites on chromosomes, this is a very common method that is used to use microscopy to get this kind of data. It is very hard to do, by the way, but it is a really powerful technique once it works. Of course, you can also use an antibody to detect the lac repressor if you do not want to use fluorescence.

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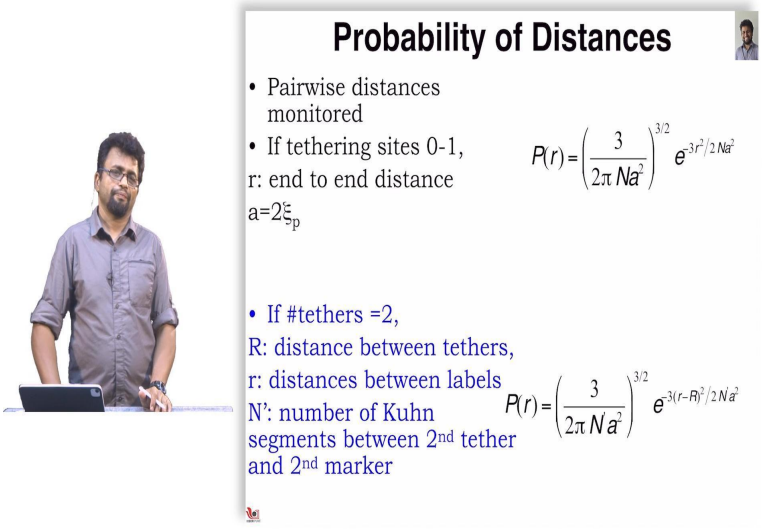

So, the probability of distance for tethering sites that are between 0 and 1 there is no tethering or 1 tethering from theory will give you a probability distribution of pairwise distance that looks like this, which looks sort of conventionally like our 3 dimensional Gaussian, but with two tether sites will be slightly modified to look like this. And this moves that we have two possible alternatives which we can compare experimental data to and which is what was done.

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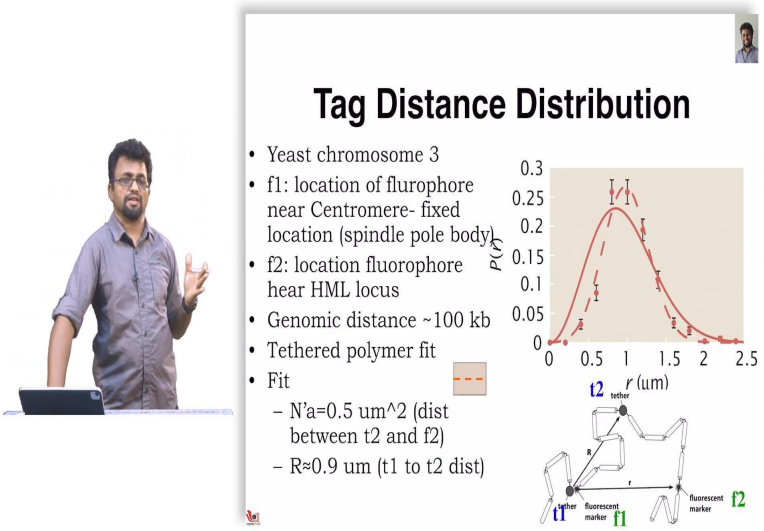

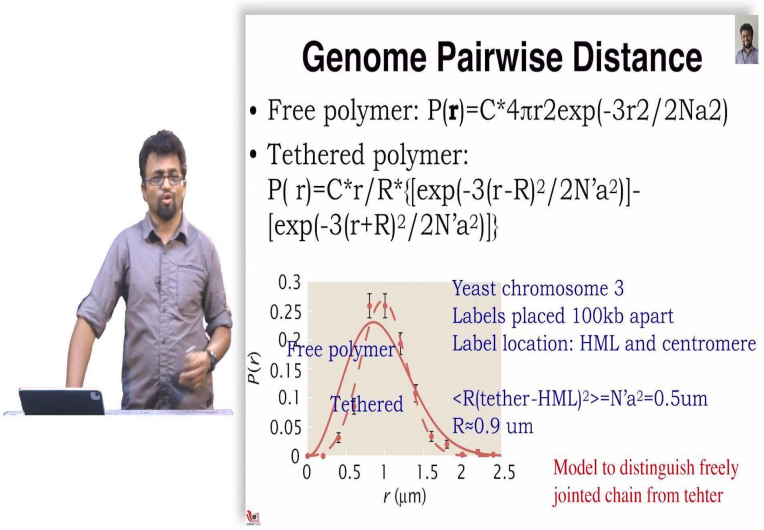

And what you observe here is that the tethered polymer fit with two tethers the dashed line, fit the experimental data much better than the untethered or one tethered model. So, this kind of expression comes from Polymer theory. But with some modifications, we are not just a pure random walk, random walk with some data points. I have no distinct I have not derived these models, because the derivation is itself fairly involved. I refer you to standard literature, which is in Polymer statistical mechanics, if you like and be happy to share some more published papers which may explain this in greater detail.

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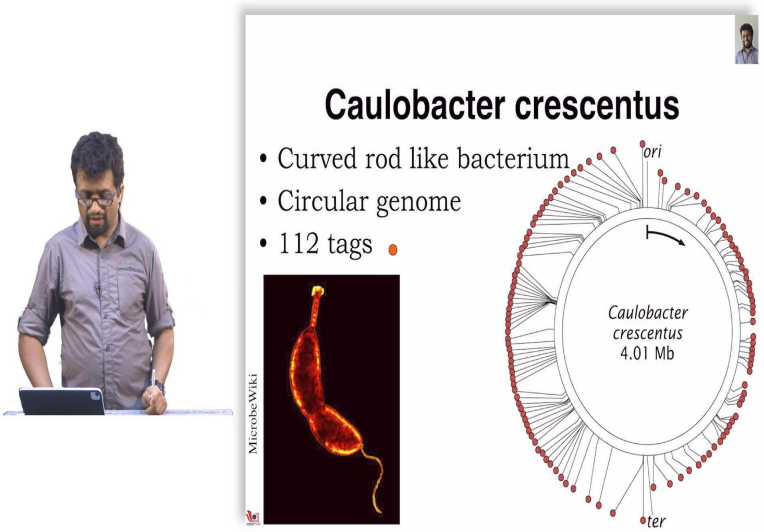

Now, we have been so far talking mostly about human and higher eukaryotic chromosomes. But it turns out even a simple bacterium like *Caulobacter crescentus*, it is a non-pathogenic bacterium. It lives in freshwater pools and is actually very cheap to grow with. If you want to

learn bacteriology. There is a very nice system. It has a chromosome a genome that has been mapped fully it is 4 mega bases and it has a origin and ter site.

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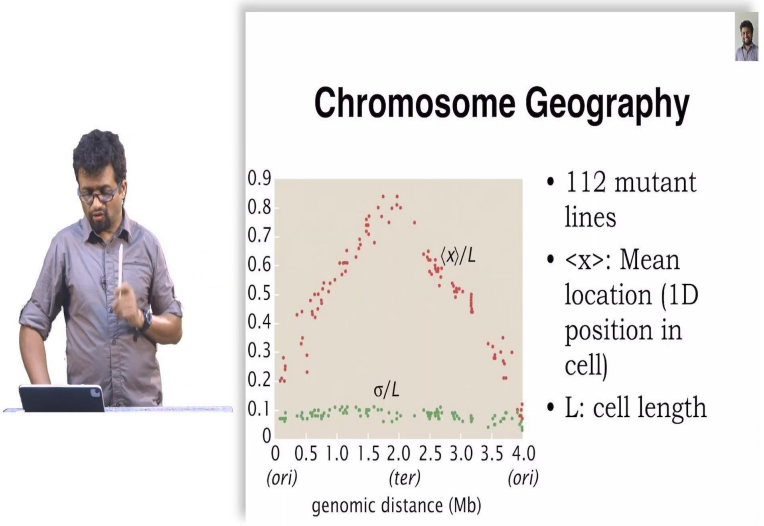

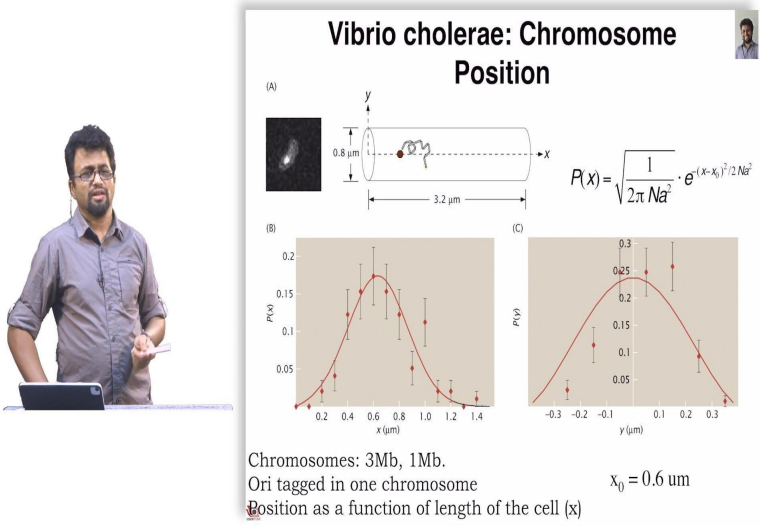

It also turns out has non-trivial chromosome packing based on genomic distance and position mapping of *Caulobacter* chromosome geography, it was found that both that and *Vibrio cholerae* match to the one and two tether models.

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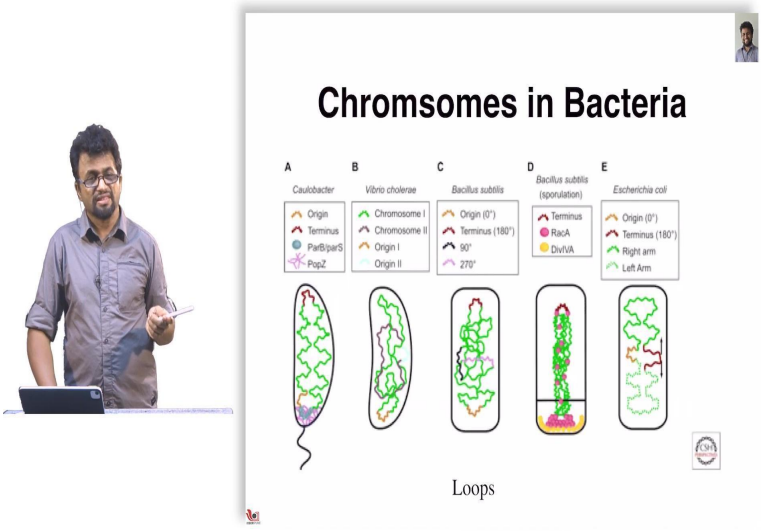

And this suggests that chromosomes and bacteria do not have random organization as many people have proposed in the past. And this is just a comparison between *Caulobacter*, *Vibrio cholera*, B*acillus subtilis* and *Escherichia coli* and *Escherichia* be an exception, because it is the simplest in some senses.

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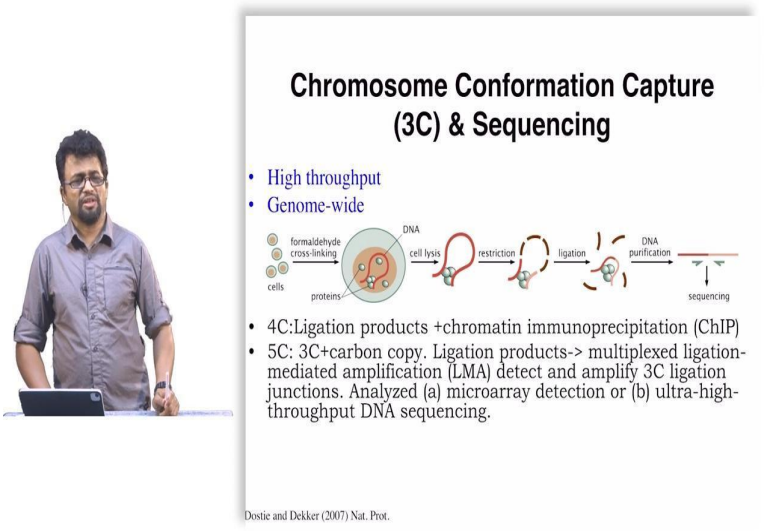

So, it brings me to a technique which I mentioned I will cover which is called chromosome confirmation capture and sequencing. So, chromosome confirmation capture becomes 3C. If it is done on a chip, it becomes 4C, if it is done on a chip with some further modifications, it becomes 5C, 6C. So, therefore, people call this high C, high number of Cs are in the acronym. It is a kind of experimentalist joke, but suffice to say formally, the technique is

called high C and it is also high throughput, so, this kind of matches. The advantage of this method is that because it is genome wide and it involves no detailed engineering of cells, you can do this very fast you can do this for many cell types, you can get huge datasets and you can characterize it, the only problem is, it is a very expensive technique.

So, not all labs can conduct such experiments. The bottom line is that the method involves taking cells, formaldehyde cross linking the chromosomes in such a way that DNA that is close to each other gets stuck that which is far away does not, then lysis the cell, then restriction digest it. So, you are familiar maybe with restriction enzymes which cut at a certain known sequence, ligate the fragments such that those things that are close to each other, they join and they form one DNA sequence, purify the DNA and then sequence it.

And if there is a chip involved in it, then that may also be the case. This kind of ligation product with chromatin immunoprecipitation, which is where the immunoprecipitation chips may come in, allows us to know not just what parts of the DNA work close to each other, but also what proteins bound to it and that is part of the chromatin immunoprecipitation. The immuno part is to detect a certain protein that is on a certain chromosomal region.

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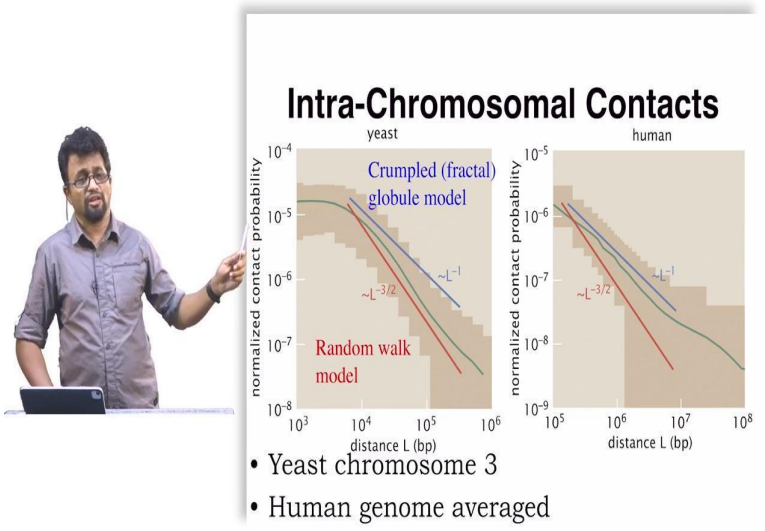

So, all these methods give us these amazing data sets, which are chromosome contact maps or intra chromosomal contacts. On the y axis, you see the normalized contact probability, which is some kind of metric, which is number of contacts divided by the total number of contacts. So, you get a probability term. And the x axis is the Length in base pairs and you see that it ranges from 1000 bases, to 1 million bases 10^6. This is a huge range by the way.

And it is very hard to achieve this using the kind of microscopy techniques and FISH techniques that we spoke about earlier. And it is a high throughput.

Now, when you look at this data for yeast cells and compare this to human cells, the people who did this work, found that for yeast chromosome 3, the data best fit to a scaling of $L^{-3/2}$. So, it is an inverse flow hence minus 3 by 2. So, if the minus negative slope gave them agreement with random walk model, one would assume that the same thing applies to humans. But here for some reason, this model does not agree very well with the experimental data, this is the random walk model again. So, something is going on that we need to find better agreement. And so a more complex model called the crumpled globule model or the crumpled fractal globule model was devised.

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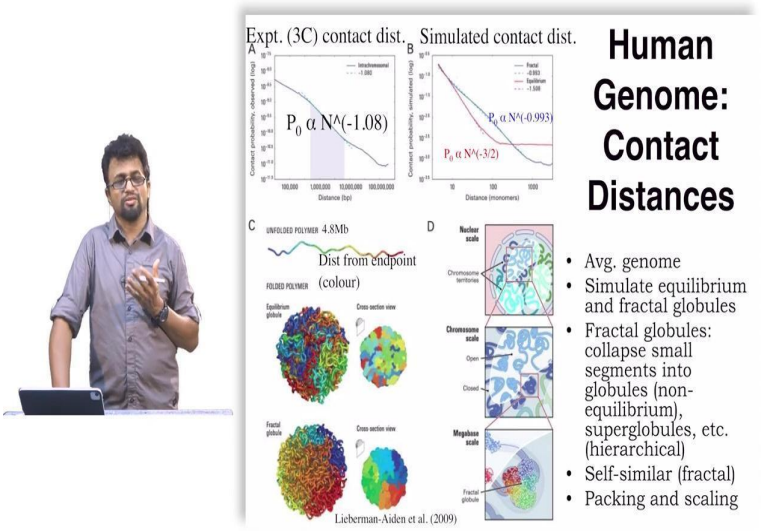

In this model, the idea is that as you build complexity meaning to say as the chromosome fiber is packed, it does it in a certain region, it is parceled off into a little globule and the whole chromosome is divided into sub such little, little globule segments and then they are folded into a slightly higher organization and they are folded into higher organization and so on so, this is called a hierarchical structure. And this is why it is also called fractal because as you dive down into the detail or zoom out into the larger chromosomal structure, it is self-similar in terms of its packing.

And this kind of a model or simulation, in fact, in this case, gave us scaling of $N^{-1.08}$, which agrees very closely with what the crumpled globule model, I am sorry with the experimental data and can explain in some senses what is going on. So, in a sense, you could argue that this

is probably and this is work from Lieberman Aidan and company shows best agreement with experiments.

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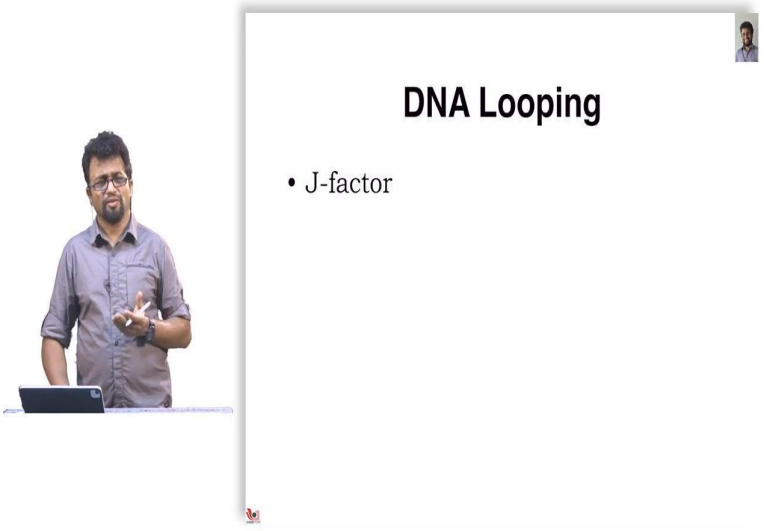

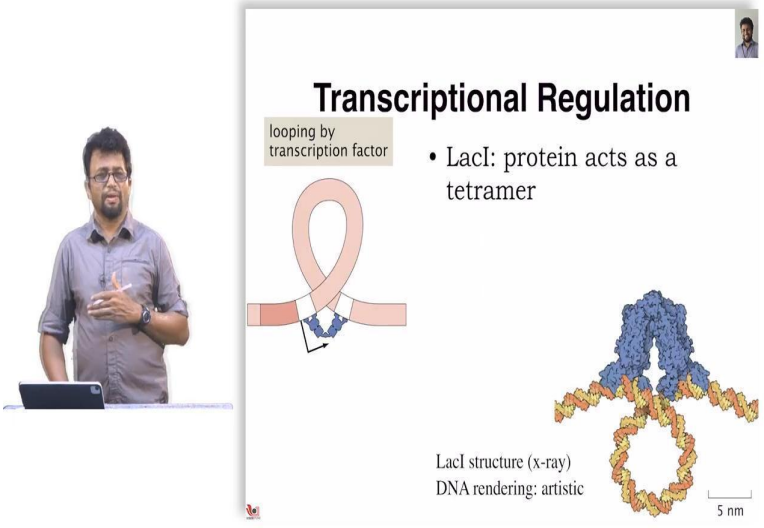

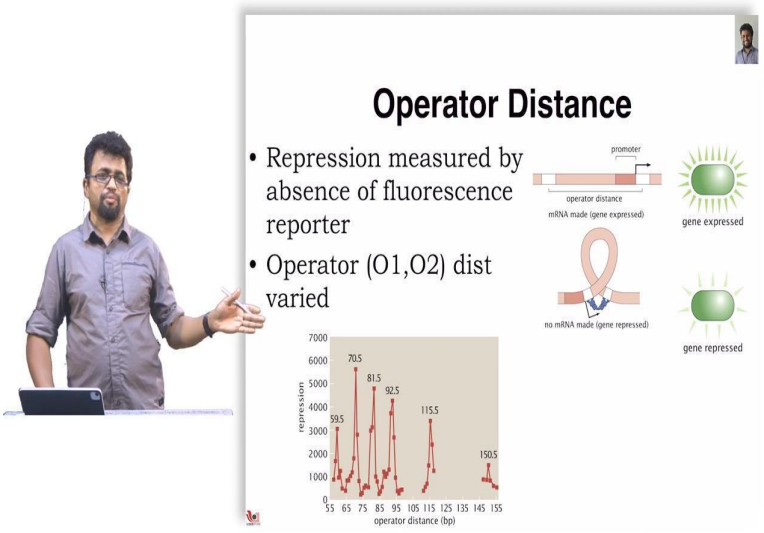

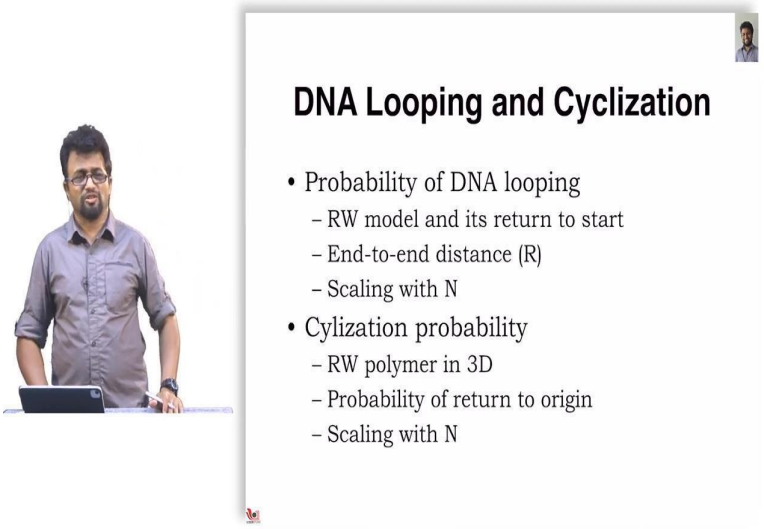

Finally, I will come to a last part, which is a conventional, very old set of studies that examined again DNA packing in chromosomes and ask the question, what is the statistical trend as a function of length? So, again, LacI protein, which acts as a tetramer was used for this and operator distances were measured using fluorescence. And to show that DNA looping appears to have a periodicity in it, in order to explain this cyclisation experiment was done, where you take DNA of different lengths and try to make a circle out of it. Now, if the DNA is very rigid, it will be less likely to make a cycle, if it is very long, it is more likely to make a cycle. And the characteristic stiffness of the DNA will tell you what the cyclization probability is.

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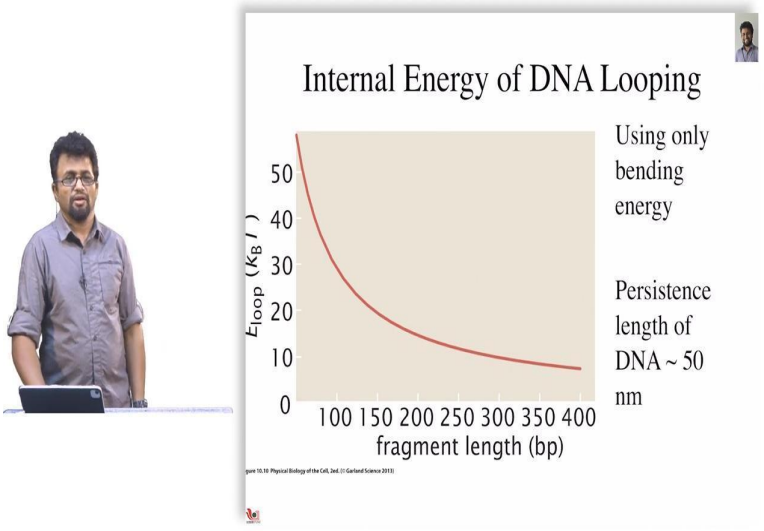

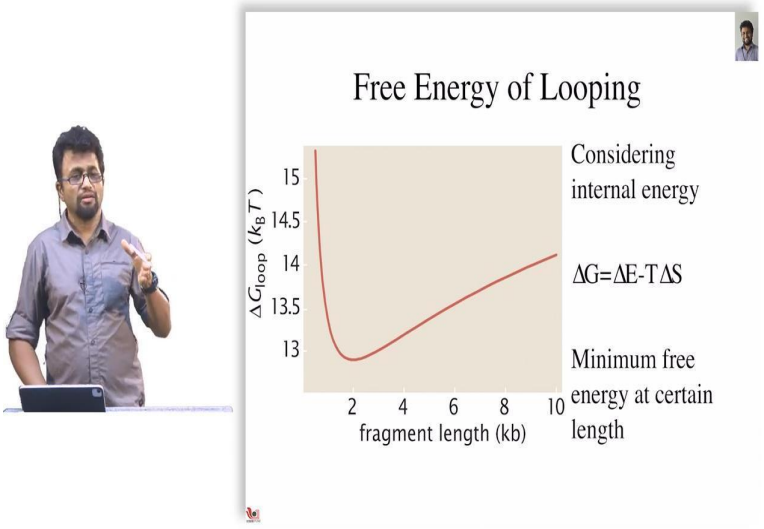

So according to a simple beam model, the internal energy of looping will give you this kind of a profile, this sort of is a decay, as the fragment length increases your probability of looping decreases. On the other hand, if you include the free energy in this calculation, so internal enthalpy and entropy, in other words, then you get something that looks like this, it decreases rapidly and at some point has a globule minimum in terms of energy of looping and then goes up again. And this is quite exciting, because it suggests that there is an optimal ΔG for looping. And this is also called the J curve, by the way so.

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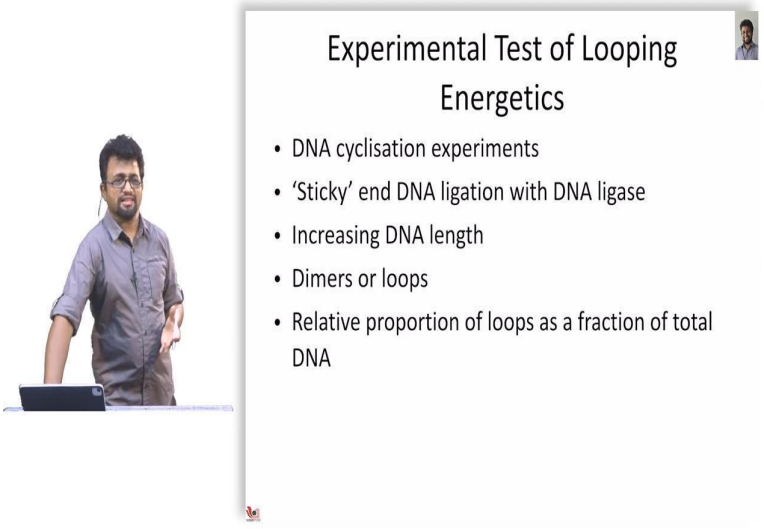

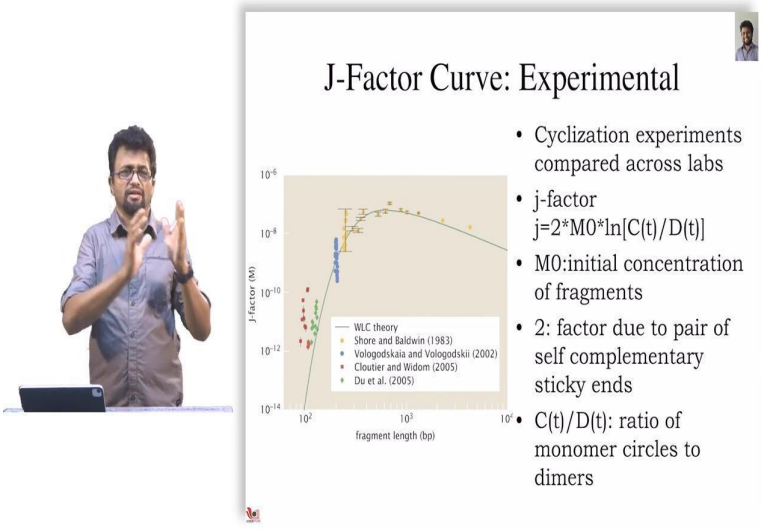

So to experimentally tested this DNA cyclization experiment of sticky ends of DNA ligation with ligase was done for increasing DNA length, to check whether this theory makes sense. And amazingly enough across many different labs, this J factor curve, so that was probability, I am sorry, that was energy. So, it was minimum energy, which means maximal probability, which means the J curve is inverted in this case. And this data confirms that the wormlike chain theory which is a little more complex than the random walk theory, in terms of polymer models, can best explain all the available data that is around and this is kind of the current state at which our understanding of polymer mechanics, chromatin packing and distance maps is at.

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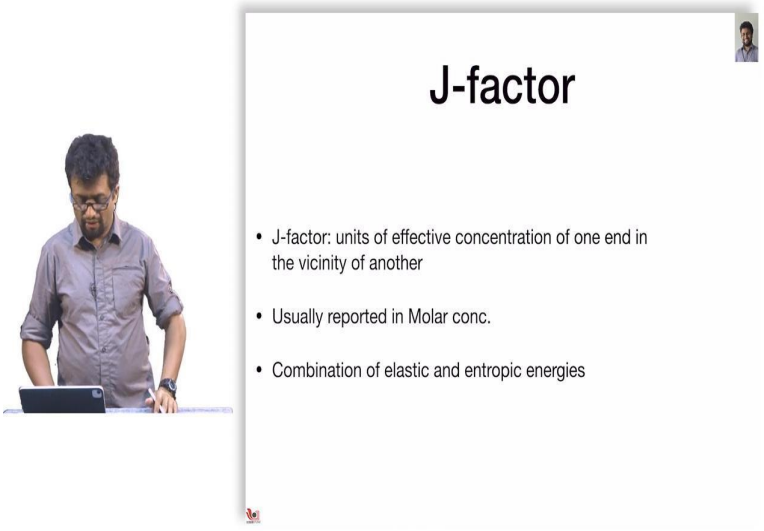

So J factor in some senses is the unit of effective concentration on one end in the presence of another and it is reported in terms of molar concentration. So, you can do these experiments in a molecular biology lab is as simple as that. So, biotechnology kind of environment. And it is important because it combines elastic and entropic energies and I will have a discussion about this in another lecture about the fact that it is like saying that the simple elasticity, the kind of beam mechanics, combined with the statistical properties are kind of acting opposite to each other. And this is what gives optima, globule optima. And this that is why J factor analysis is quite an interesting way to think about more complex biological problems in terms of biophysics.

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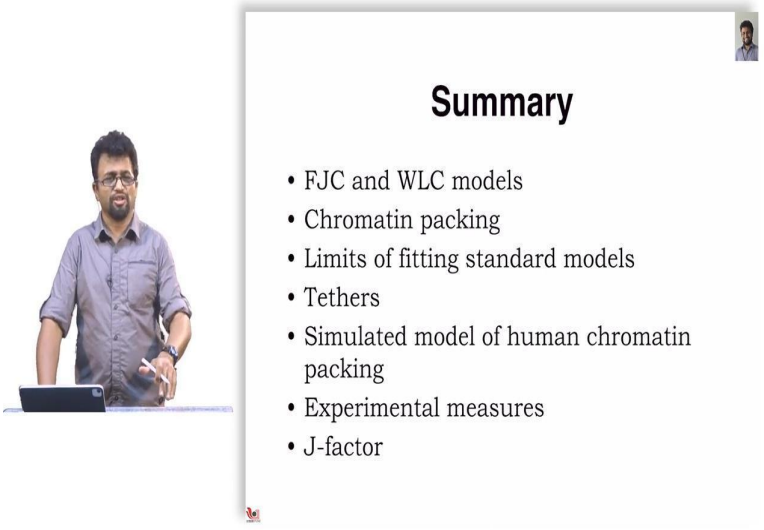

Further Reading

- Rubinstein (2003) Polymer Physics
- G. Strobl (1993) The Physics of Polymers
- Shore, Langowski and Baldwin (1981) PNAS USA
- Shore and Baldwin (1983) J. Mol. Biol
- Peters and Maher (2010) Q. Rev. Biophys.
- Alexander Vologodskii (2015) Biophysics of DNA

So in summary, we have spoken about freely jointed chain and wormlike chain models and how they may help us understand chromatin packing. We have discussed the limits of fitting standard models discussed tethers simulations of models of chromatin packing, experimental measures and J factors. And there are further readings in terms of polymer physics. In terms of J factor, this paper by Shore Langowski in Baldwin is quite useful. And vologodskii has some new insights into the biophysics of DNA. With that I would like to end this module and we will meet in future to go over the next topics. Thank you very much.