Physics of Biological Systems
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Lecture – 51
Molecular motors

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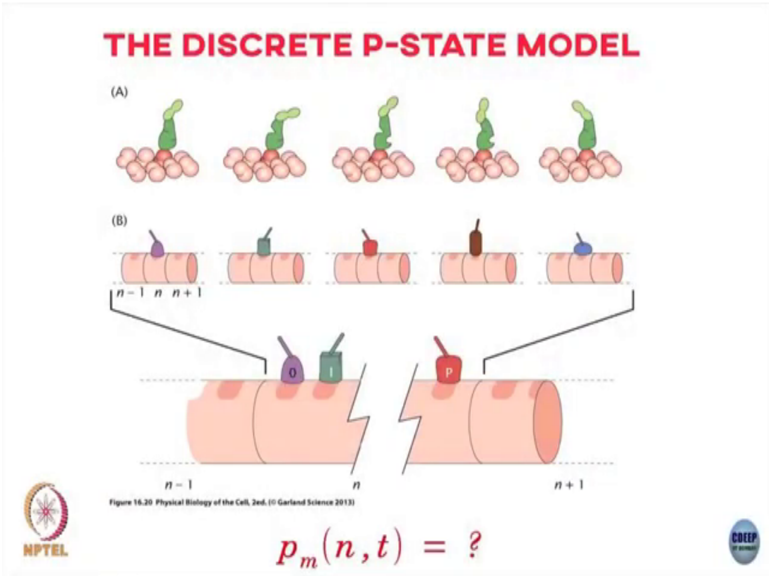

So, what we are doing is Molecular motors and that is what we will continue yes. So, what we were talking about is how to write down equations for these motor kinetics and what we said is that we can sort of think of motors as having multiple states in principle and then hopping along this underlying lattice the microtubule other actin.

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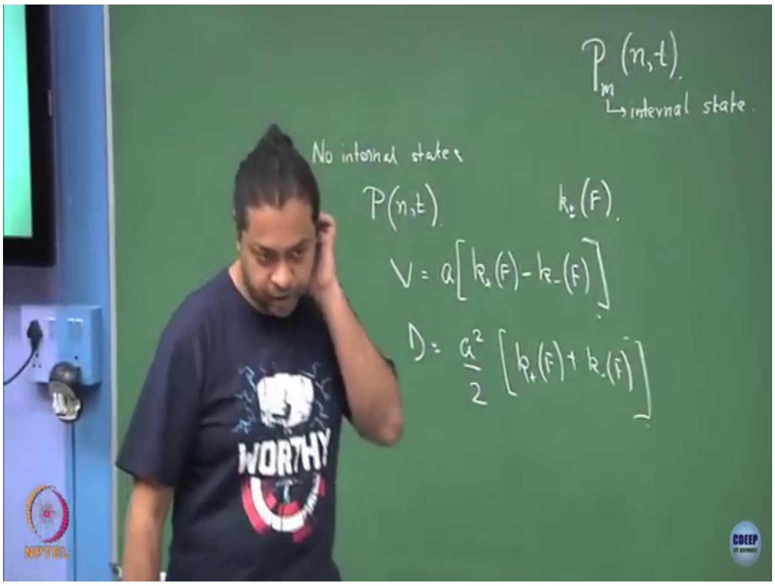

And we will write some sort of probability to find the motor in the m th state at position n at time t and then write down the evolution equations with that. And in the simplest case what we said is that let us forget that these. So, this m is the internal state marker is the internal state marker.

So, in the simplest case what we started off is that there are no internal states, there were no internal states. So, you simply had something that what are the probability to find the motor at position n th time t right. And given a position of the motor on the lattice.

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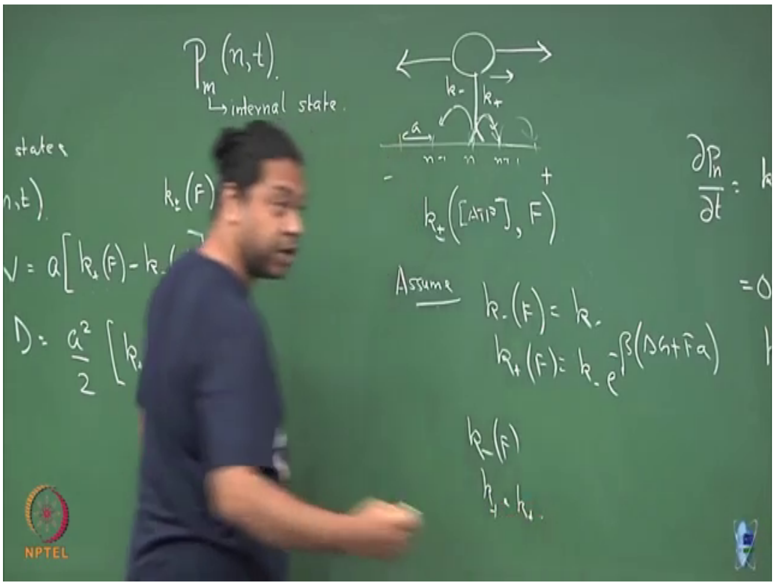

Let us say this is n this is n plus 1, n minus 1 and so on. We had hopping rates, so it could go forward with some rate, it could go backward with some rate because, these motors are direction that is they take in energy and they move preferentially along one direction let us say towards the plus end. These rates were different from each other and we also said that these rates in principle who are going to be functions of both ATP concentration as well as the force that you apply on ok.

The force could come from in vitro experiments like optical traps you could pull on the motor explicitly or it could arise cooperatively due to the effect of opposite kind of motors if they were both for example, (Refer Time: 02:32) and kinesence bound then one of them each would exert force on the other type of motor.

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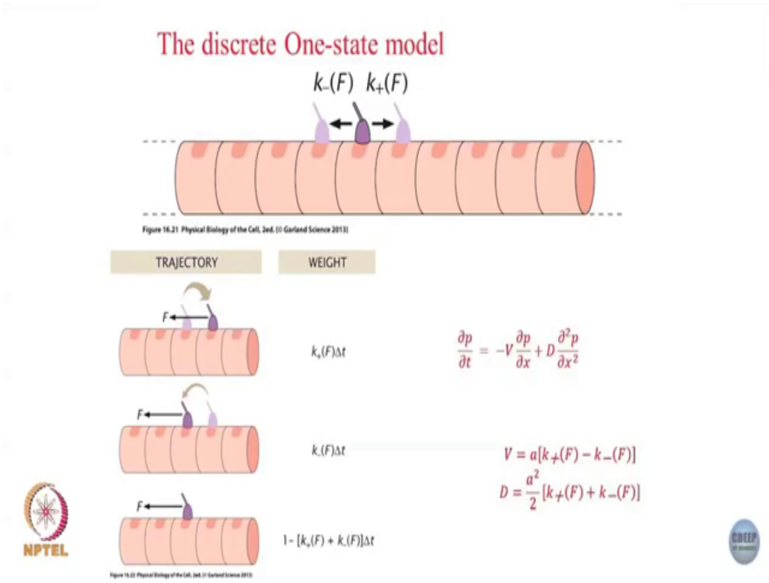

So, in this sort of a framework, the simplest thing that we said last day was something like this that if I have let us say I forget about this thing there is no internal states and I say that my rates are simply functions of the force I forget about the ATP concentration also for the time being I can write down the master equation what is del p del t. I if I take the continuum limit it gives me a velocity of the motor and diffusion constant of the motor.

So, the velocity is V is a k plus as a function F minus k minus is a function of F and the density is a square by 2 k plus plus k minus right. This was easy enough and in the continuum sense of course, if you solve this advection diffusion equation; you will get some sort of a Gaussian profile that moves and not only does it move it also spreads right.

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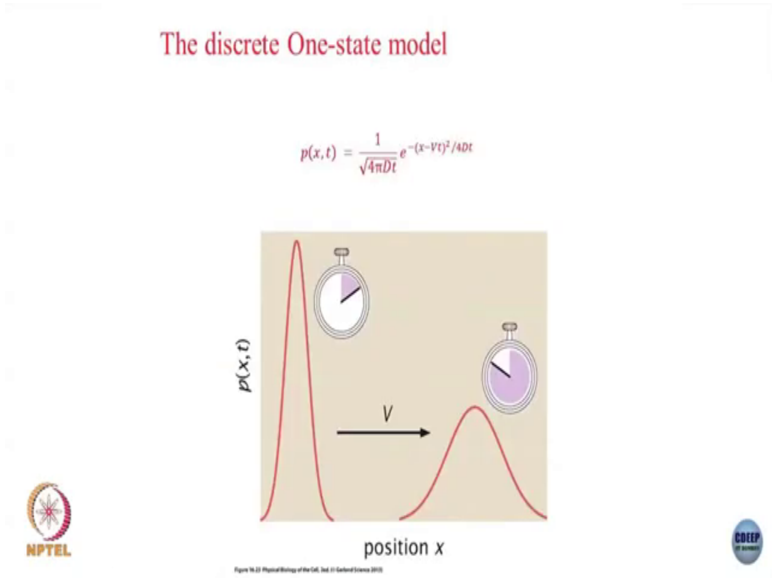

You will get some sort of Gaussian moving a Gaussian wave which moves with a velocity V and also spreads by some measure given by the diffusion coefficient to do something more with this model. So, this is a very simplified model of course, we are not taking any internal states which we know must be there for the moment we are not considering the dependence on ATP concentrations, but still let us go ahead with this simple model and then let us see what we can say from this model itself ok.

And we will introduce all of these other factors slowly one by one. So, you can think of this system like this that you have some sort of an energy landscape, you have some sort of an energy landscape like this let us say ok. This is your motor in the nth state let us say this is your motor in the n plus 1th state, you have some barrier and because the barrier you have some barrier crossing wave on this way and a different wave this way right keep there all functions of forces. So, the barrier height to go in the positive direction is just this much right.

The barrier height to go in the negative direction is from here, so it is this much, so it is a higher barrier. So, therefore, a smaller rate right so came up. So, you have a higher rate k plus of going forward because the barrier is smaller here you have a smaller rate of k minus of coming backward because the barrier is higher there.

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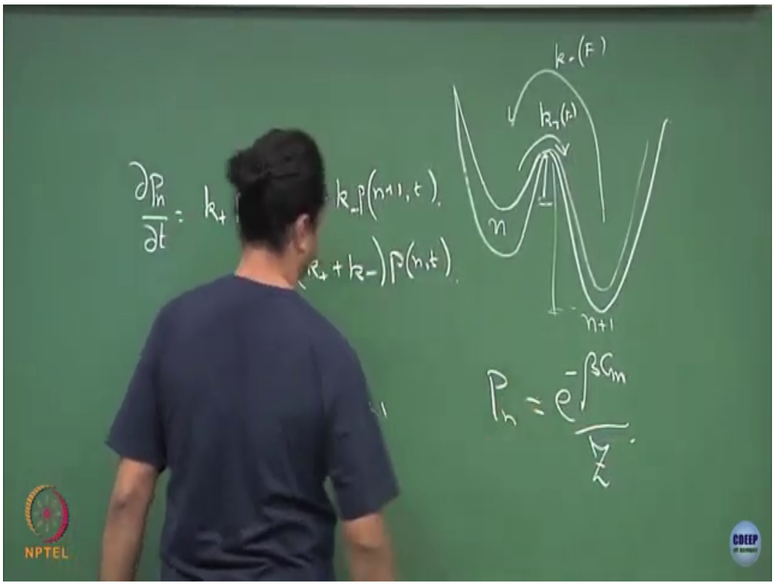

If you apply forces you will tilt the balance of these free energy minima’s corresponding to the n and the n plus 1 state.

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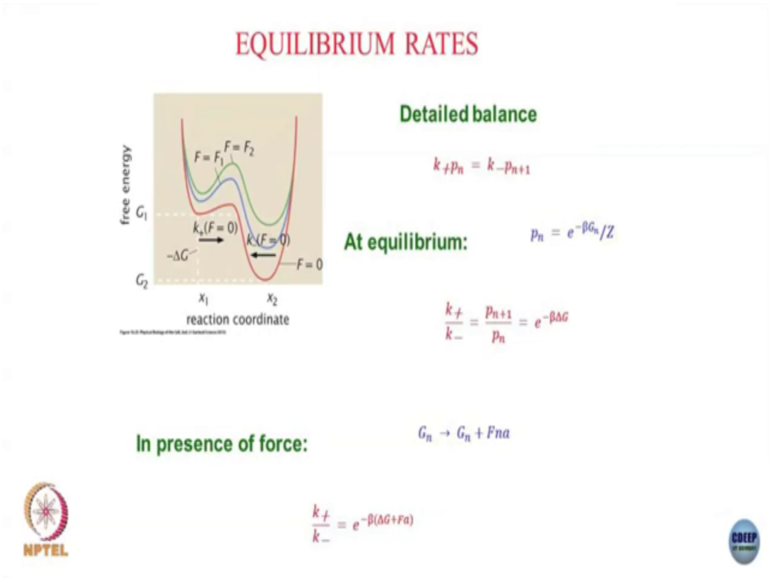

So, for example, so here is the sort of picture that I have let us say that this red line is my force equal to 0 curve, then as I apply some force the landscape changes and it becomes something like this blue and then I apply more force the landscape changes even more and so on.

So, depending on whether you are applying. So, here is my motor which is carrying a cargo depending on which direction I apply the force I can change the balance of these k pluses and k minuses. So, let us say if I let us say the motor wants to move in this direction and I apply an opposing load, what that would mean is that it would get more difficult to go forward because, I am pulling it backward which means that there let us say that the depth of this barrier would increase relative to this. So, maybe it becomes something like this right.

On the other hand if you were pulling it forward if you were pulling it in the direction that the motor wants to go, then you will tilt the free energy landscape the other way. So, that this the forward barrier becomes even smaller right. So, that is the idea that these rates will have some dependence on the forces and let us try to see if we can do something with that ok. So, if I have this sort of a master equation for this P n and I want to have let us say I will work in so, right.

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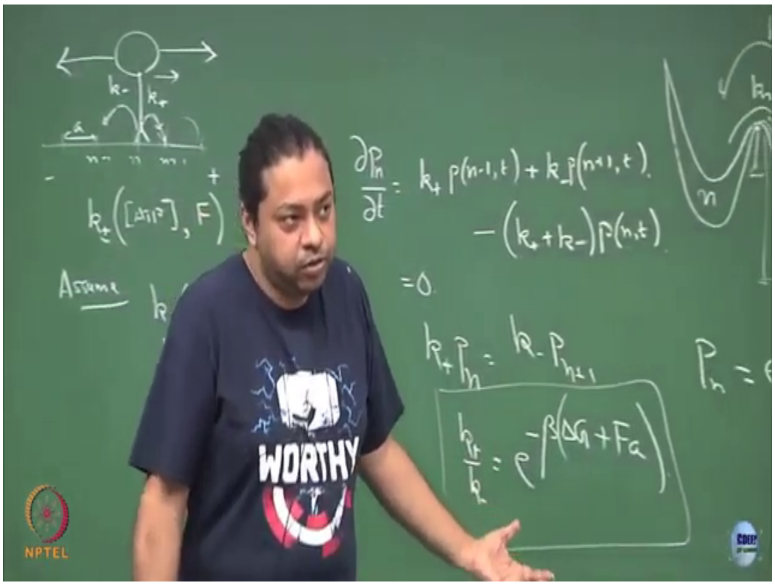

d P n d t right, it has some rate of coming from n minus 1 some from coming from n plus 1 and then they skipped its k plus plus k minus P of n comma t right. There is a right step from n minus 1, this is a left step from n plus 1 and these are the right and left steps from n.

So, if I wanted to set this to 0, if I want to look at this problem in the steady state then I can satisfy this detail balance of the steady state condition by saying that this sort of a thing that k plus P n; k plus P n is equal to k minus P n plus 1 let us say. So, then these terms will cancel out pairwise and you will get a 0. So, that is my detail balance condition also I know that at equilibrium, I again I make an assumption. So, if I assume the equilibrium probabilities, then the probability for the motor to occupy this state is equal to e to the power of minus beta G n right by the partition function of course, these P n, I can write in an equilibrium approximation, these are like e to the power of minus beta times the free energy of that state divided by the partition function.

So, which means if I so, if I substitute for P n and P n plus 1, what I get is the ratio of these two rates, the forward rate and the backward rate. So, what I get is that k plus by k minus is equal to e to the power of minus beta times, the difference in free energies between these two states ok. In one case you have G n plus 1 and in the other case here G n. So, we take the ratios what you get is that k plus by k minus is e to the power of minus beta delta logic. Now, what happens if I am now pulling on this let us say this is the 0 force result ok.

So, whatever is the free energy landscape in the absence of force that I encode in this that k plus this ratios of these b rates is e to the power of minus beta delta G. If I now pull on this with some force, how will the free energies change; remembered in the free energies we have whatever E minus T S plus terms like J dot X like a force times the displacement.

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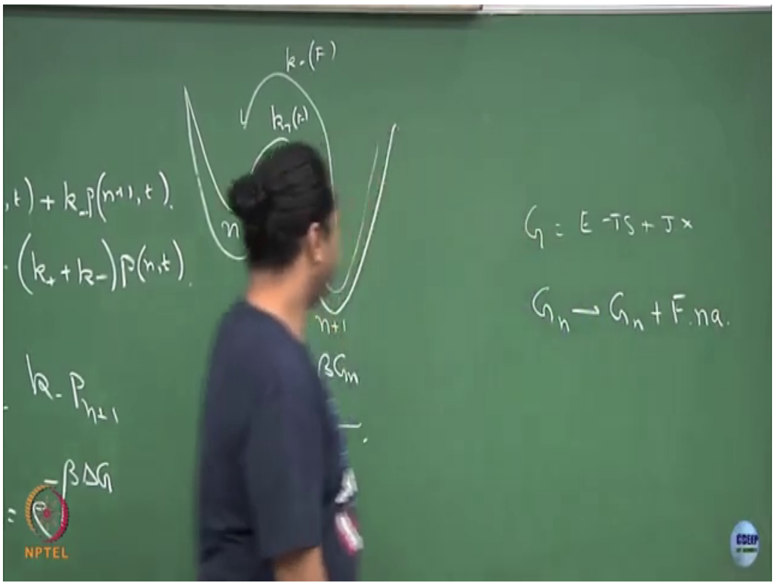

So, in this case if you apply a force, the G will go as whatever it was. So, G n will go to whatever the G n was plus the whatever let us see you are applying a constant force times n or n times since it is a distance a is my lattice constant; a is my lattice constant. So, G n goes to G n plus F na, so G n plus 1 goes to G n plus 1 plus F into n plus 1.

So, therefore, in the presence of force, this ratio becomes something like e to the power of minus beta delta G plus F a this is the difference between these two terms F into n minus F into n plus 1. So, it is a step into a the lattice. So, this is how this is generally what I can say about how these ratios of these rates will depend will behave in the presence of some force. So, e to the power of minus beta delta G plus some F a and indeed if you do experiments on these motors.

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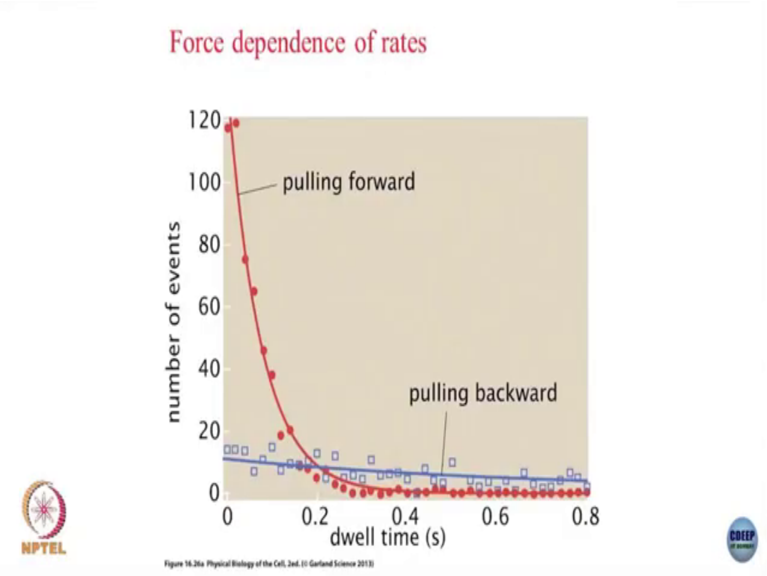

So, for example, this is an experiment on miles and motors and what is shown is a plot of its like a histogram of dwell times, for two different cases; one in which you are pulling forward another in which you are pulling backward.

So, dwell times is like the inverse of this rates. How long does it stay in a particular state? That is if that is the dwell time then this rates are going to be the inverses of that. So, if you are pulling forward. So, you are assisting the motor, you are pulling you are applying a force in the direction that the motor wants to move. You will see that the dwell time histograms sort of peaks at very small values right because it does not stay static for very long in a position it wants to hop very quickly from here to here and then from here to here and so on right.

So, you have histogram which is peaked around these very small dwell times on the other hand and very quickly sort of goes to 0. On the other hand if you would pull backward then this is a much broader distribution right you will often have to wait very long times before you take a step.

So, these rates do indeed depend on the force and that is what we will try to show or we will try to do simple models to see how these rates could depend on the force and how these models would correspond to actual experimental results ok, so that is the idea. I know the ratios go something like this very naively, but that still does not tell me about how these rates individually go with forces.

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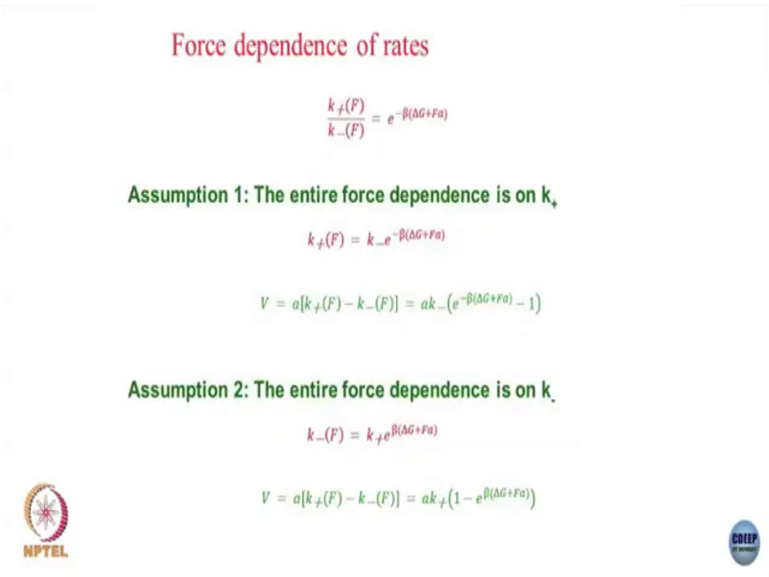

So, to do that I will make an assumption. So, this is what I know that the ratios of these rates go like e to the power of minus beta delta G plus F a. To go further than this, we will do is that we can make two sort of assumptions. So, which are the sort of two extreme limits and then see what each of these assumptions say. So, for example, I could say that well let me assume, so this is a pure assumption, there is no biology behind it. Let me assume that this k minus does not depend on the force ok whereas, the k plus depends on the force.

So, this in this ratio the entire force dependents will come from the k plus term and nothing from the k minus. Well, I just make that assumption. So, this entire force dependence is on k plus ok, which means that this k plus of F is equal to k minus which is now a simple number it does not depend on the force and then e to the power of minus beta delta G plus F a. So, I satisfy this ratio yes.

Student: (Refer Time: 13:54).

So, it is not justified, its justified in the sense of that you know that lamp story you do what you can. If there is a lamp, you search underneath it, but still so, the thing is that you make the simple assumptions you see what this gives and then you try to see whether it matches with the experimental results. If you are lucky one of the simple assumptions might match, if you are not lucky you might look you have to look at the more general scenario where both of these have some sort of complicated dependence on the force such as the ratio is still this, but the best case to do is to at least hope that maybe one of these simple things will work out. It does not seem.

Student: (Refer Time: 14:35).

It does not, there is no way I can justify it because, it is not it is a arbitrary assumption in that sense, but we will still want to do it and see what that gives for the result. So, if I have this, I can now calculate what is the velocity because I know what is the velocity in terms of k plus and k minus. So, my k plus f is k minus e to the power of minus beta delta G plus F a right. So, I can calculate the velocity by substituting these two in this velocity equation and I get some expression for the velocity that this is a k minus comes out common and then e to the power of minus beta delta G plus F a minus 1.

So, then what this says is that what does it say? So, if I were to plot let us say this velocity as a function of the force applied, what would this curve look like? This e to the power of minus beta delta G plus F a plus 1, it would look something like that, it would look something like this right. Because of this e to the power of minus the important term is this e to the power of minus F a term, it will look something like this. On the other hand you could say that well you know the other easy thing I could do is to say that the entire force dependence is on k minus, so just the reverse limit.

So, I say that k plus does not depend on force, it is just some k plus and then this entire dependence is on k minus. So, k minus f is something like this. So, again you get back that ratio comes out to be the same and again I can substitute this in the velocity formula to find out what the velocity looks like. And then of course, the velocity looks something like this k plus comes out come in 1 minus e to the power of beta delta G plus F a. What does this curve look like roughly? 1 minus exponential, so I guess something like this right ok.

So, we have made these two simple assumptions that in this case the entire dependence is on k plus, in this case the entire dependence is on k minus and this predicts for you two different forms of the force velocity curve right. Now, I can go back and look how the force velocity curves in actual experiments looks like and I think this is again experiments on myosin ah.

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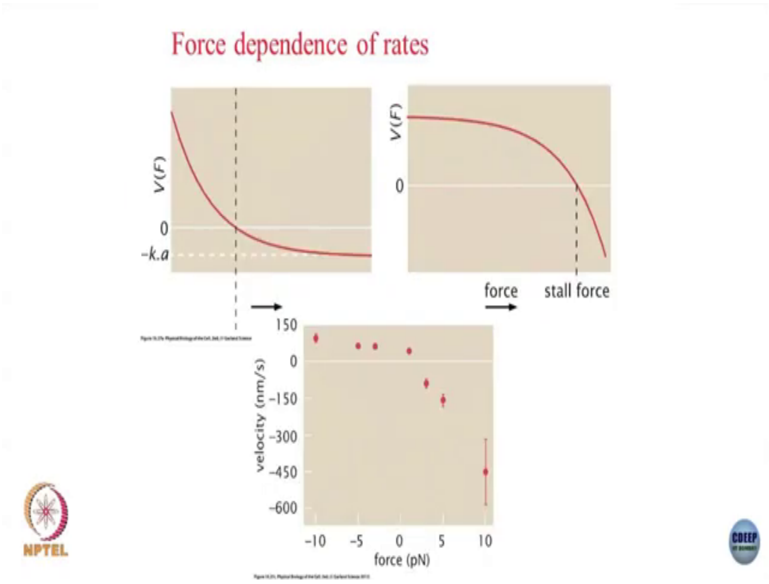

So, these are the two predictions. So, this is when k plus is a function of is the entire force is dependences on k plus, this is when the entire force dependencies on k minus. And here is an experiment on myosin 5, particular type of myosin motor which says that here is how the experimental measurement of velocity dependence on force looks like.

So, looking at this sort of a curve, I would say that well if I want to live with such a simple model; the correct thing to do within the assumptions of this model would be to say that well k minus is a function of force and k plus is simply some constant, it does not dependent on force. That is the best I can do well at least within the simple sort of approximations.

This is the set of approximation that comes closest to reality and you can then tune of course, all of these numbers. So, that you get a bit good match with these experiments what is this bear k plus and so on you can tune to spit with these experiments and that would be an effective model for this sort of a motor. As of course, not a perfect model because we have made so many assumptions going in, but at least it qualitatively seems to reproduce some of the features that you see in experiments particularly this force velocity relationship. So, that is one sort of thing that you could do.

One easy thing that you could measure experimentally and also calculate which is this force dependence of the velocity. You could calculate other quantities as well for example, there is another measure that people talk about in the context of molecular motors which is called randomness.

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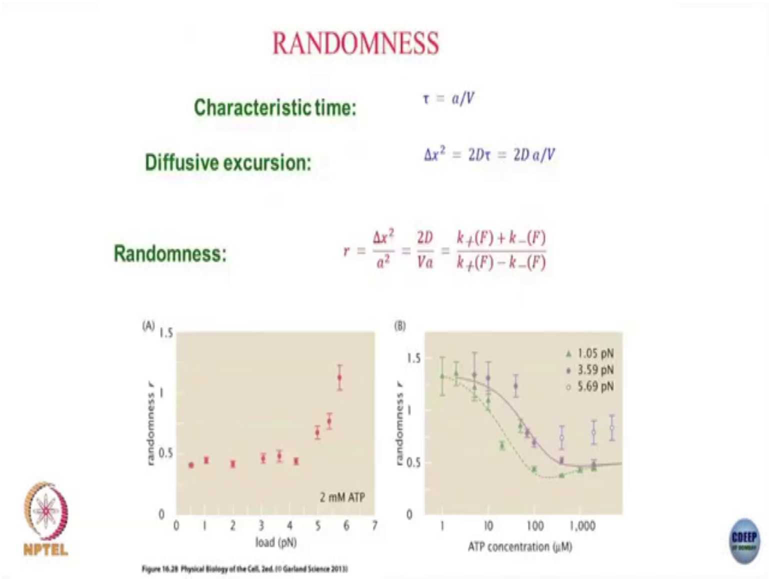

So, which is to say that well, my motor has a velocity V, which is what we have calculated and I have some characteristic length scale let us say this lattice length scale a which is. So, I define some sort of a characteristic time which is the time taken for the motor to up one lattice unit right, if given that it was moving with a velocity V. So, that is my tau, I could also because I have a diffusion coefficient as well. So, have a random nature to the motion as well in addition to this deterministic velocity, I could calculate what is the spread this random spread in this within this characteristic time tau.

So, that is 2D tau right. So, I substitute for tau. So, this is this measure of this diffusive spread, the random diffusive spread is 2D a by V and then you define a randomness parameter which is which characterizes this diffusive spread. So, this randomness parameter is defined as this delta x square normalized by this lattice spacing square a square which is nothing, but 2 D a by V right and then if you substitute these are just k plus plus k minus divided by k plus minus k minus.

So, if your motor was moving very with a very high speed deterministically along its preferred direction; you would see that the randomness measure is very low. On the other hand if the motor speed was very low right compared to this diffusive excursion, you would see that the randomness parameter was very high right. So, again this is something that you can sort of measure experimentally and this is let us say what the curves look like well if you can see.

So, I think this is again this is for kinesin of some of these are for kinesin and some are for minor sense this curve is for kinesin motors, keep forgetting which one is which. So, this is a so this first set of experiments is at a very high ATP concentration. So, where basically you have saturating ATP, in that ATP concentration is no longer relevant variable. The motors have as much ATP that it wants. So, this is around 2 milli molars of ATP and then you plot this randomness parameter as a function of the load force ok.

So, when you have very low load, the randomness parameter is low because, then the motors are sort of moving zipping across in their preferred direction. So, the randomness measure is low. On the other hand as you apply more and more load, load meaning backward force sort of sort of hindering the motion. So, as you apply more and more load this motor speed sort of drops and because the motor speed drops the randomness measure sort of goes higher and higher ok.

So, that is what this sort of the curve says. You could of course, also do it. So, this is done at very high A T P, but you could also do it as a function of ATP concentrations and as a function of loads and that has a much more complicated nature. So, it sort of first decreases and then it increases as a function of ATP concentration at a given value of the load force, it sort of first decreases and then increases and so on.

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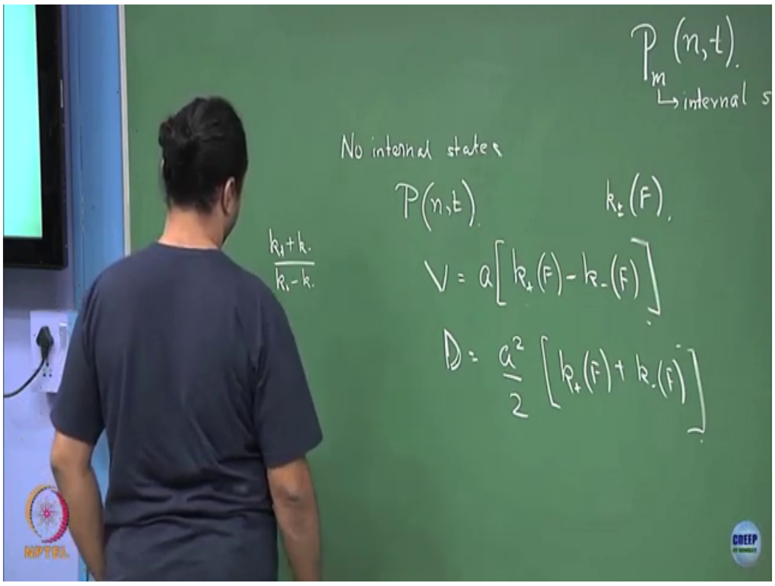

So, if you wanted to reproduce this sort of behavior within the context of this sort of a model that you know you just say that either one one of the rates is dependent on the force; you would find that this would be you could not sort of reproduce this behavior using a simple model like this. So, the (Refer Time: 22:27) out of doing such simple models is that you should know for what sort of things they work and what sort of cases they do not work see.

So, they work for something like well force velocity curve, it does not work if I were to try to characterize this sort of a randomness measure ok. To do a justice to these experiments you would need a much a little more not much a little more complicated model and we will come to that in a little bit.

Student: (Refer Time: 22:51).

Yes the lowest value that k e minus can take is 0.

Student: (Refer Time: 23:00).

Yes. So, what we have gone to is k plus plus. So, the thing to do is to just go back to this paper once and look exactly how they have defined randomness, the basic physics is of course, correct its a measure of the diffusion to the deterministic spread, but maybe in the definition there is some other factors over there, thanks. I will check it and I will let you know. The question is that why is this less than 1, if this is k plus plus something and then k plus minus something, the lower limit according to this formula should always b.

So, now as you can see that these are all. So, of course, functions of ATP which we talked about, but which we done sort of neglected. So, if I want to bring in ATP one way to do that is to sort of switch to a slightly different picture and then use an old trick to try to compute how these rates would depend on the ATP concentrations themselves.