Physics of Biological Systems
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Lecture – 54
Cooperative transport of cargo

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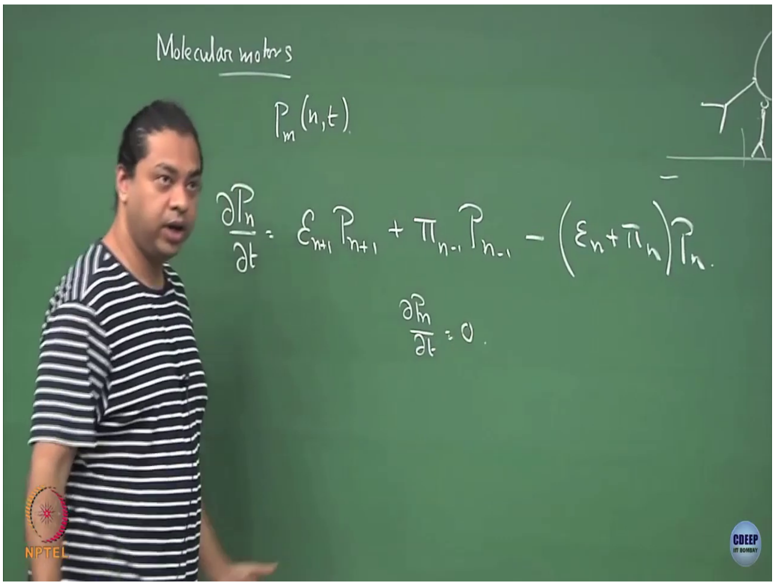

One, I equal to 0 to n minus 1 right. So, for P 2, it is P 0 into I equal to 0 to 1. Yes, so pi 0 by epsilon 1, pi 1 by epsilon 2 right. So, this is my Pn; all my Pn's in terms of this, in terms of this one unknown, single unknown P 0 and then, how can I find this P 0? By using the normalization for probability. So, I know that the motor has to be in one of these states. It must either have 0 motors bound sorry, the cargo has to be in one of these states; it can either have 0 motors bound or 1 motor bound or 2 motor bound or whatever, but ultimately it has to be in one of these states.

So, Pn n equal to 0 to n must be equal to 1 right. So, that is my normalization. So, if I do that then that gives me the solution for P 0 basically. So, yeah here so, sum over n equal to 0 to n, Pn. So, let me actually write from n equal to 1.

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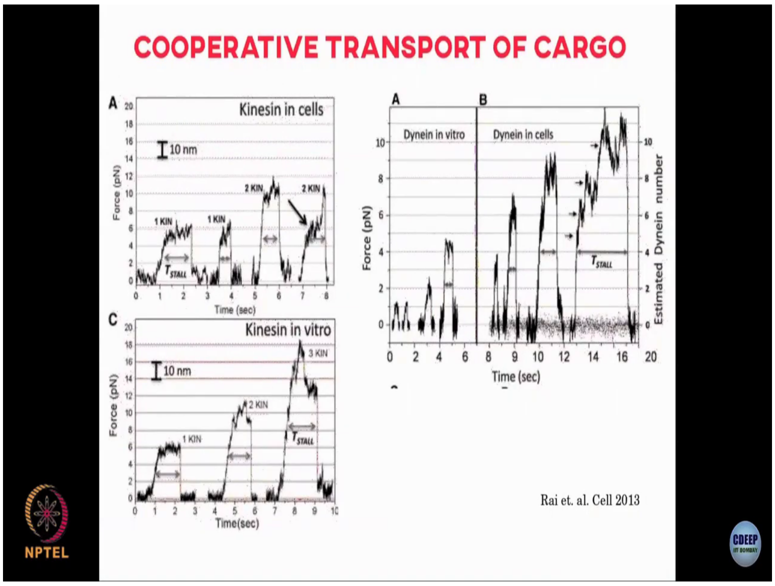

So, the first term is P 0 plus n equal to 1; P 0 product of I equal to 0 to n minus 1 pi I by epsilon I plus 1. This whole thing is equal to 1 which means that P 0 is equal to 1 divided by 1 plus sum over n equal to 1 to n product over I equal to 0 to n minus 1 pi I by epsilon (Refer Time: 02:14) ok.

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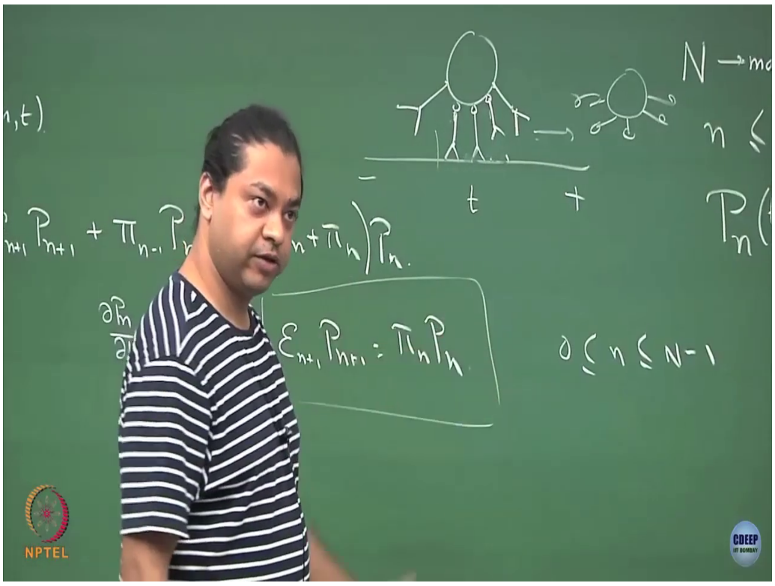

So, if in terms of these attachment and detachment rates, pi is an epsilons, I can solve for this P 0 as well as for all of these. Once I know P 0, I know all of these Pn's. So, I can solve for all of these in the steady state ok. Let me just say let me just change variables over (Refer Time: 02:50) to the most standard from. So, now, that I know this, I can calculate what is for example, the average number of bound mode. So, let me first calculate let us say. Yes?

Student: (Refer Time: 03:15).

Hm?

Student: (Refer Time: 03:17).

Generally, that is not true. So, I have made like a somewhat stronger assumption in that sense of detailed balance. Generically that is not true, but I just make that assumption and go ahead.

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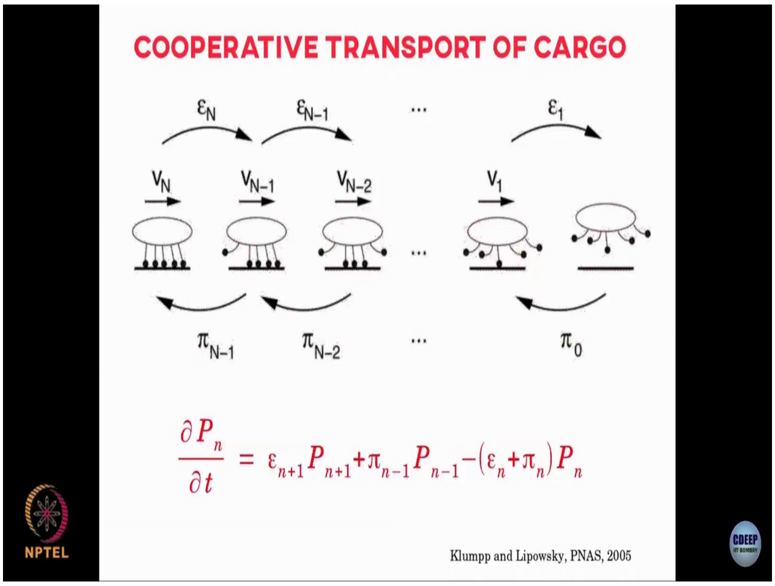

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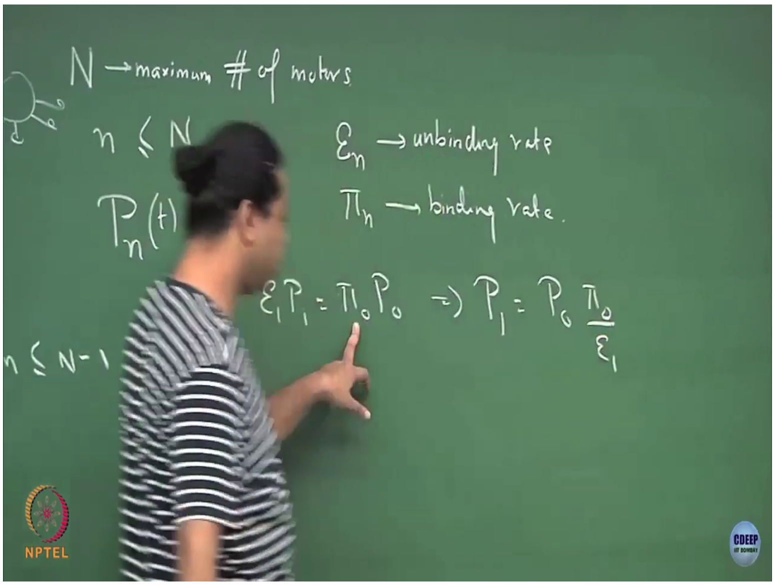

So, now for example, I could ask that what is the probability that the cargo is bound to the filament; cargo is bound to the filament which is the sum of all these probabilities that P 1 plus P 2 plus dot dot dot plus Pn right or equivalently, this is like 1 minus P naught ok. So, all of these states correspond to a cargo which is bound. The P naught state corresponds to something like this where the cargo is completely unbound ok.

So, I can define. Let me define a sort of new probability Pn prime which is what is the probability to have N motors bound, given that you know the cargo is bound to the filament. So, this is like a conditional probability and that is just this. So, I will just normalize by this 1 minus P 0. This is the probability or the cargo is bound to the filament and in terms of this, I can now calculate what is the average number of bound motors. Let us say, average number of bound motors, let us call it n P and that is just nothing but n times this probability.

So, n Pn into 1 minus P 0 sum over n equal to 1 (Refer Time: 05:24). And I of course, I know what this P ns are because I just calculated that. Similarly, you could ask what is the average velocity; you could ask what is the average velocity and that again is the velocity of a motor of a cargo which is been carried by N motors times this probability Pn by 1 minus P 0. This, I do not know yet, I will have to make some sort of an answers for this; I will come again, I will come to that later.

So, these epsilons these pi's or these velocities, these are separate ingredients that will go into the model and they will come into the model from experiments. From experiments we know how these unbinding rates, binding rates, velocity is these all change and we will put that in at some point.

But in principle you can calculate stuff like this the average number, the average velocity or you could calculate for example, something like what is an effective unbinding rate ok, of this cargo; you could calculate what is something like an effective unbinding rate right and this I define by something like this that an effective unbinding rate from the bound state is equal to the effective binding rate from the unbound state ok.

So, I define these new quantities; epsilon effective and pi effective, but now instead of defining them in terms of the single P 0, P 1, P 2, I call this from this whole probability of the bound state and here the whole probability of the unbound state. The probability of the unbound state is of course, P 0 and the bound state is 1 minus P 0 right. So, epsilon effective and you can go from this unbound to the bound state by the addition of a single motor right. The moment you have 1 motor bound, you go to this bound state which means that this pi effective is nothing but pi 0. So, now I can substitute for this P 0 that we calculated which I have dropped out.

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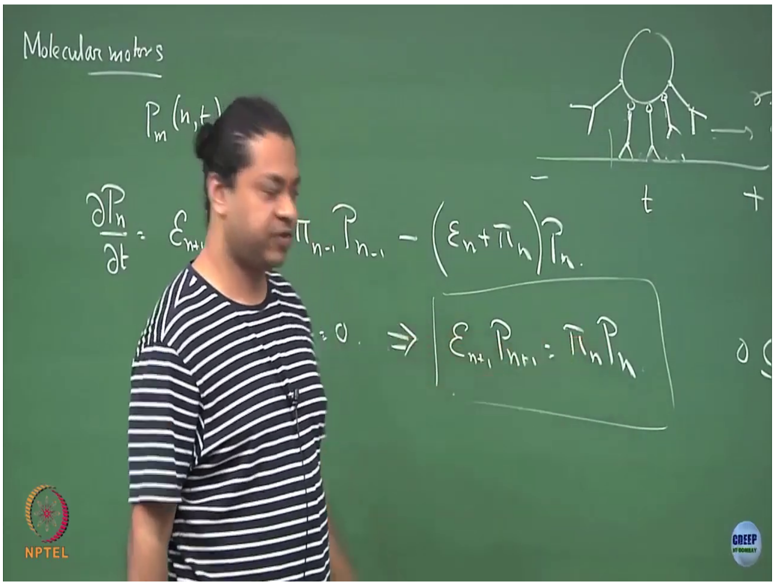

But you can substitute for that P 0 and you can find out what is this effective unbinding rate. So, I will just write that down, the effective unbinding rate comes out to be something like epsilon 1 1 plus sum over n equal to 1, N minus 1 product of I equal to 1 to n pi I by epsilon right plus 1; this whole thing power of minus 1. You can also for example, calculate you could get to this quantity, the effective unbinding rate by using the formalism of mean first passage times. So, let us try to do that and that will should give you the same result.

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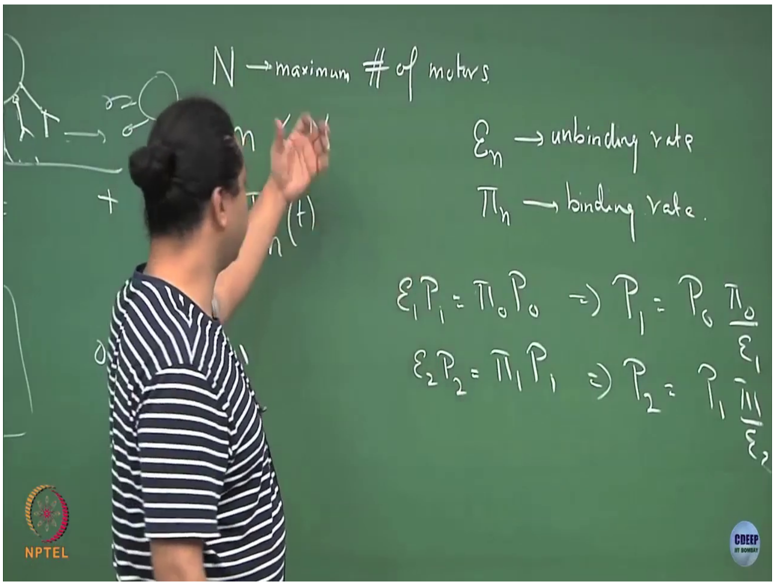

So, I could ask that well what is the meantime, it takes for a cargo which started off with n bound motors given that the maximum number of possible bound motors is capital N, what is the mean time it takes for this state which started off with N bound motors to become unbound ok?

So, I start off with this state n bound motors and I want to go to this absorbing state which is the unbound or the free cargo, where I have no bound motors and this I call the mean time taken to do that given that I start off at this mth state ok. So, you can write down an equation for this T m, N ok. So, I can write down an equation for this T m, N for example.

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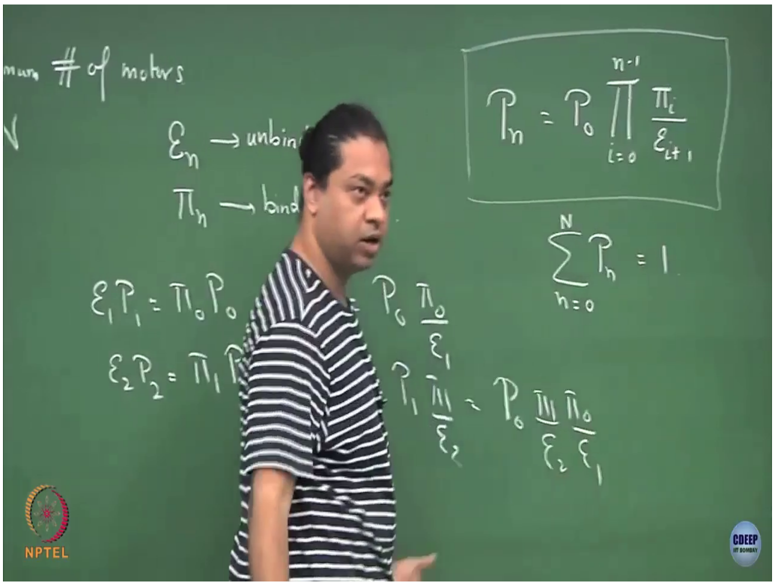

So, if I am; so, if I am in the state where my cargo is carried by n m bound motors. So, there are m bound motors. I can do two things, I can either bind 1 more motor or I can unbind 1 motor right. See if I bind 1 motor, I will go to the state which is n plus 1 right and from that state, it will take some time which I do not know, but it will take this time Pn plus 1 comma n right and with what probability will I go to this state?

Student: (Refer Time: 10:02).

Yes, Shobitha?

Student: (Refer Time: 10:06).

What is that pi?.

Student: (Refer Time: 10:12).

Pi m that is the rates divided by pi m plus epsilon m right. The other thing I can do from this state is to is to unbind 1 motor which means I land up in the n minus 1 state and from that state, it will take some time Pn minus 1 in that state I will go with the probability which is this un proportional to this unbinding rate epsilon n again by the same by pi n n plus epsilon n ok.

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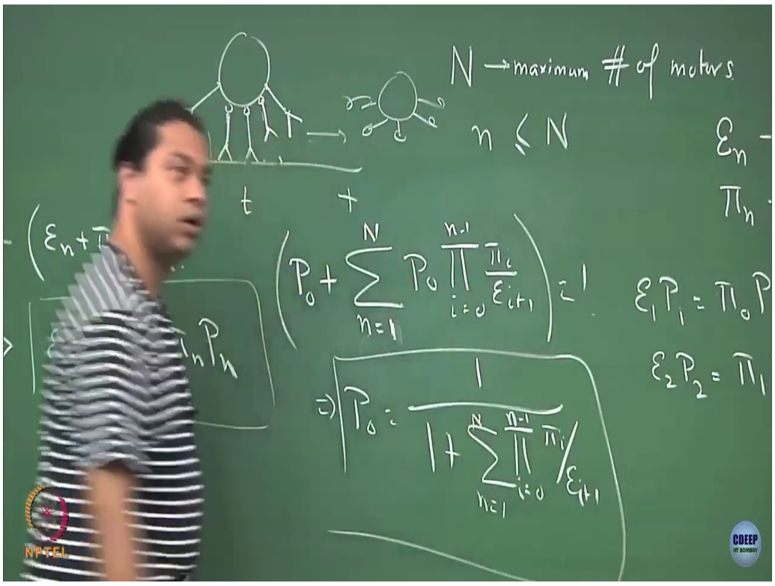

So, these are the two things that I could do I could bind the motor or I could unbind the motor or I could just do nothing if you just sit in that state for some time at least and what is the typical time I will sit in that state for? Given that my two rates of escape from that state are pi m and epsilon m. So, for example, if I am if I attach a motor with a rate of 1 per second and if

I detached a motor with another rate of 1 per second, then typically in that state how long will I stay?

Student: (Refer Time: 11:20).

That 1 over the sum of these rates right because the rate of escape from that state is 2 per second which means on an average, I will stay in that state for half a second which is 1 by pi m plus epsilon m; this is clear. So, in this state, I will stay for a typical time. Remember these are mean times ok. So, on an average, I will stay in that state for this time. With this probability, I will go to that state and from that state, I will take this time and with this probability I will go to the n minus 1 state and from that state I will take this diagram.

So, what I have done is that I want to find out this quantities P m comma N. What I have done is I have written down a set of recursion relations between these various states right and I can write down the boundary the boundary time. So, for example, if I started off with the state where all these motors were bound right, all capital N were bound, then I have nothing more to bind ok. Because my maximum number of motor is capital N which means this sort of a term will not be there. The only thing I can do is that I can unbind the motor.

So, I will typically I will stay in that state for the inverse of the unbinding rate and the only thing I can do is that I can go to the n minus 1 comma n state with probability 1 right. So, that is one boundary condition on the higher side. On the lower side, what is the mean time to become unbound if you start with 0 motors that is simply 0, that is just an absorbing boundary right. If you start with no motors bound, you take no time to reach the unbound state. Is it clear?

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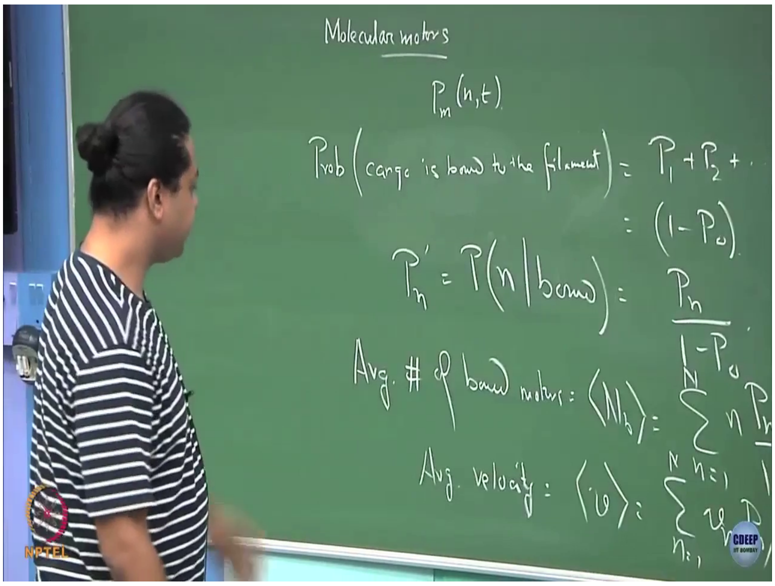

So, I now have a set of recursion relations which is a self-consistent set of equations. I have these n unknowns; this T m comma N; n of capital N of these and I have n equations. So, I can solve for this. So, you can start off you know by doing it, you can write down what is T 1 comma n for example? T 1 comma n is 1 by pi 1 plus epsilon 1 plus pi 1 by pi 1 plus epsilon 1 into T 2 comma n plus something into T 0 comma n which is 0. So, I do not care.

So, I have written down T 2 comma n in terms of T 1 comma n. I put in the next time, I can write T 3 comma n in terms of 1 comma n and so on. So, I can solve this whole set of equations. Ultimately, so you should try to do that. So, if you do that, I will just write down the answer what you get for T 1 comma n in terms of these, in terms of these pi's and epsilons.

So, if you solve this certifications, what you get is T 1 comma n, you can solve for all of course. I will just write down this T 1 comma n this T 1 comma n is 1 by epsilon 1 1 plus sum over n equal to 1 to n minus 1, product of I equal to 1 to n pi I by epsilon I plus 1, which you will notice is nothing but the inverse of this effective unbinding rate ok. Because the time it takes to go from this state with 1 motor bound to no motors bound is the effective time, it takes for this motor to unbind complete sorry this cargo to unbind completely from the micro tube.

So, this T 1 comma n is nothing but the inverse of this effective unbinding rate and that comes out from this calculation. So, now, you need to put in the forms of if you wanted to actually see what all of this means, you need to put in forms of these epsilons and pi's and so on and there, we use sort of phenomenological estimates of what these rates look like. So, let me write here. So, let say I want to write the unbind let me first do the case when there is no force; 0 force.

So, remember you could also like pull on this cargo, let say the these are Kinesin motors which want to go this way. You could pull on it with an opposing load and that will change these rates. First, let us first say what it will be for the 0 force case.

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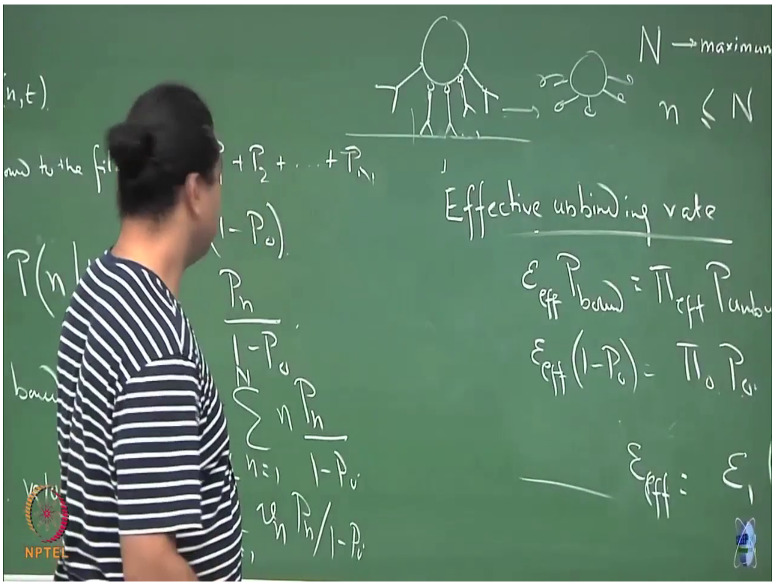

So, for example, if I want to know if the unbinding rate for a single motor is sum epsilon ok. I want to know what will be the unbinding rate, when I have small n number of motors bound and there what we say is that this is nothing but n times epsilon because if any one of these N motors unbind, you will go from the n state to the n minus 1 state ok.

So, the effective unbinding rate is the sum of all of the unbinding rates of these individual motor; so, n times epsilon. Similarly, you could write down what is going to be the attachment rate and that is something like write n minus n times sum pi; let us call it pi. So, when there are no motors bound, when n is 0, you have some rate which is n times pi.

As more and more motors buying then, that rate falls because it becomes more difficult to bind the filament. So, that rate becomes smaller the more number of motors that are bound and you could say that the velocity does not depend on the number of motors at least in the 0 force limit, to the velocity with N motors bound is the same as the velocity with single motor bound.

The interesting thing is of course, what happens to these relations when you apply an opposing load, you apply an opposing load and there again experimentally, people have found that you can write things like this. n epsilon exponential of sum f by n times the pi n remains the same and the velocity goes as v a into 1 minus n (Refer Time: 18:01).

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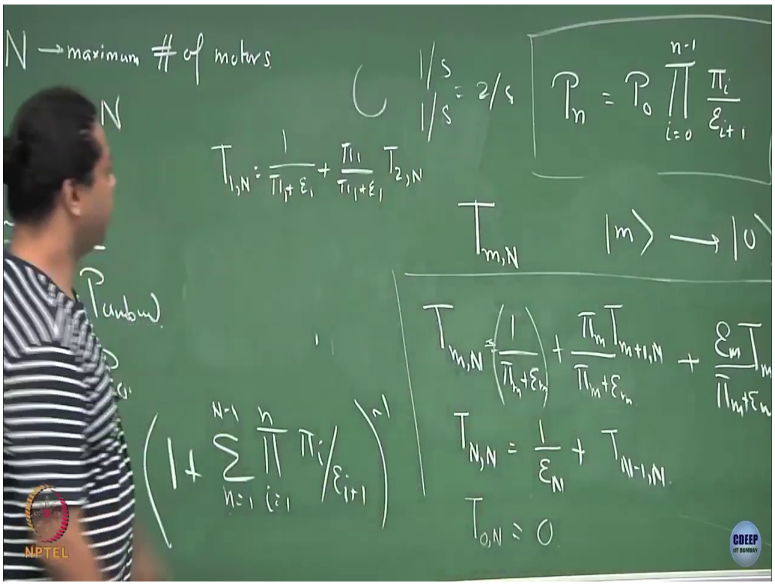

So, what this says is that if you have a single motor bound, then the moment you apply an opposing load which is equal to the stall force Fs, your velocity will go to 0. If you have two motors bound, then you need to apply twice the stall force which is what we saw in those experimental curves earlier on that anyway this is what we saw in the experimental curves earlier on if you remember there were some peaks at 6 right. If you had 1 motor bound, then to completely stall this cargo you need a 6 pico Newtons. If you had 2 motors bound, you need a 12 and so on.

So, the force that you need to apply to stop a cargo which is being carried by N motors is n times F s and it varies linearly which is sort of an experimental approximation. Its true in some cases it is not true in some other cases and here for example, it says that the unwinding rate also grows exponentially with force with some force scale which is F d. So, the harder you pull it back the harder you make it for these motors to unbind which as we discussed is true for kinesins, but not for dynein's, but let say it is true for this case. So, let say we have modeling kinesins.

So, if you put in all of these now if you put in these forms of these epsilon, the v and the pi's into all of these equations, you can calculate what this model would predict for example, for these average number of bound motors, average velocity, distributions of walking distances, unbinding rates and so on. So, here is what it says. So, for example, if I want to find if I want to find this is the prediction for the effective velocity as a function of this opposing load for cargo that is carried by different different maximum number of possible motors. So, this is capital N. So, this curve is capital N equal to 1. So, there is only one motor that is possible its either 1, 0; this one is N equal to 2, this one is N equal to 3, 5 and 10.

So, what it says is that for example, if you have consider this single motor cargo which is being carried by at most one motor and capital N equal to 1, any force greater than 6 would mean that the velocity is 0. The motor the cargo has stopped because you have cross the stall force of the motor. As you carry as you are attached to more and more number of motors, you can walk with an appreciable sort of velocity even when you have a large force. So, for example, at even a 10 pico Newton, this case with 10 motors walks with almost 0.8 times, the maximum possible velocity.

Similarly, if you look at the average number of bound motors in this case of course, its 1 because your capital N is 1. Therefore, it can be nothing but 1, but in these other cases as we apply more force, let us look at for example, this case this capital N equal to 10 case; as we apply more force, the number of motors that are bound on an average at a given time, it will sort of decrease with force. Ultimately, at some point when you reach the stall force of these 10 motors, no motor will be bound.

Similarly, if you look at the average distance it is walked which I have not calculated, but you can calculate. Again, that and plot that as a function of force. The more the number of motors that is carrying your cargo, the more the distance that you can walk on an average and these are not linear functions. So, these do not grow these do not change linearly with force this changed on sort of non trivially depending on the number of motors that are bound ok.

So, the behavior for a single motor can be very different from the behavior for multiple motors bound. Similarly, you can not only look at the average sort of distance that it walks. But you can also look at distributions of these walking distances, you can calculate from this formalism, the full probability distribution. Again, which I have not done, but which you if you go to this paper you can take a look and for example, if I look at this high force case when I am pulling back with a force which is around 10 pico Newton, these cases with the cargo is being carried by very few motors 1 or 2 or 3, it is a very sharp probability distribution peaked around 0 which means most often it will walk very little distance before falling off.

On the other hand, if you have more number of motors that are carrying the cargo, it can walk an appreciable distance. So, even at 3, 4 microns you have a reasonable probability that the cargo will get that far. So, the cell can; so, the cell can use this multiple motors, the this cooperative effects between multiple motors in order to carry cargo large distances. You are asking something?

Student: (Refer Time: 22:58).

Yes?

Student: (Refer Time: 23:00).

Yes.

Student: (Refer Time: 23:05).

Which is going to one?

Student: It is going (Refer Time: 23:08).

That is because I have normalized my probabilities with this conditional probability. So, I am only considering the subset of cases, but at least the cargo is bound to the filament. So, this 1 minus P 0 is there. This is because once the motor unbound unbinds sorry, once all motors have unbound the cargo set of drifts off. So, experimentally it is a little difficult to compare with that. On the other hand, it is easier to compare with this conditional probability that given that it is bound how many are there; how many motors are bound.

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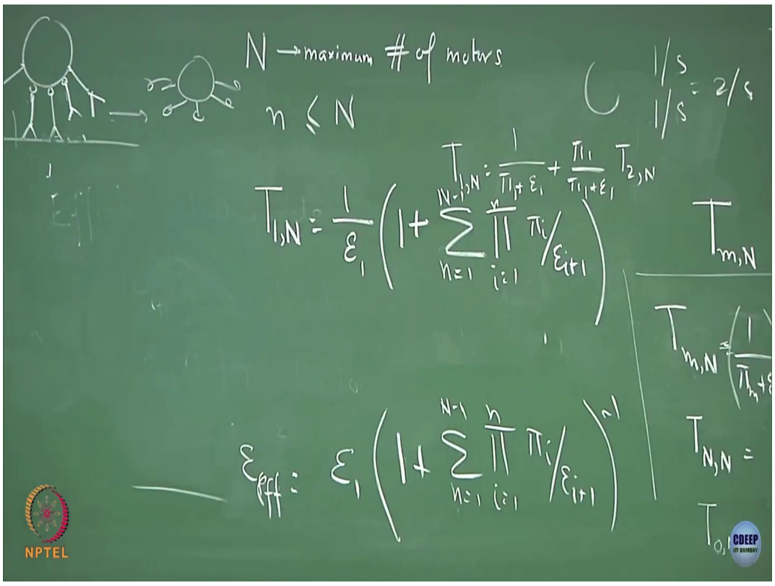

So, you can do a. So, this is of course, in some sense a mean field estimate I neglect sort of fluctuations. I only calculate average quantities, you can do better and better. You can take into account what is the effect of fluctuations; you can take into account what is the effect of opposing motors and so on, but you can do it in a sort of similar spirit, you can write down these sort of master equations, you can solve them numerically if not analytically and then, try to see what it predicts for this sort of cooperative behavior.

So, multiple motors is not just 1 motor scaled up n times. The f x can be fairly non trivial and that non trivial f x comes because of these non trivial force velocity or force unbinding rate sort of dependencies from the micro tube ok. So, this T 1 comma N is nothing but the inverse of this effective unbinding rate and that comes out from this garage. So, now, you need to put in the forms of if you wanted to actually see what all of this means you need to put in forms of these epsilons and pi's and so on.

And there we use sort of phenomenological estimates of what these rates look like. So, let me write here.

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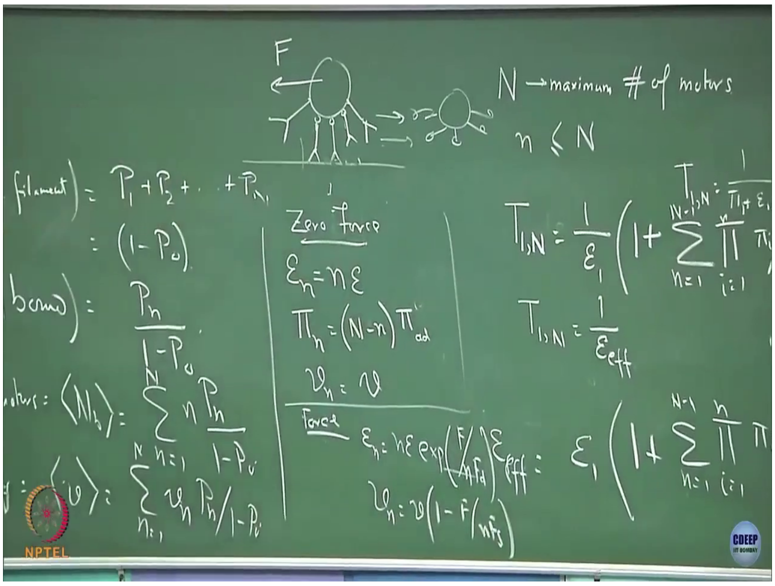

So, let say I want to write the unbind let me first do the case when there is knows no force; zero force. So, remember you could also like pull on this cargo. Let say the this is a kinesin motors which want to go this way, you could pull on it with an opposing load and that will change these rates. First let us first say what it will be for the zero force case. So, for example, if I want to know if the unbinding rate for a single motor is some epsilon ok, I want to know what will be the unbinding rate when I have small n number of motors bound and there what we say is that this is nothing but n times epsilon ok.

Because if any one of these n motors unbind, you will go from the n state to the n minus 1 state. So, the effective unbinding rate is the sum of all of the unbinding rates of these individual motors. So, n times epsilon. Similarly, you could write down what is going to be the attachment rate and that is something like write N minus n times sum pi; let us call it pi.

So, when there are no motors bound, when n is 0, you have some rate which is n times pi. As more and more motors buying that rate falls because it becomes more difficult to bind the filament. So, that rate becomes smaller the more than the number of motors that are bound. And you could say that the velocity does not depend on the number of motors at least in the zero force limit, but the velocity with N motors bound is the same as the velocity with single motor bound ok. The interesting thing is of course, what happens to these relations when you apply an opposing load, you apply an opposing load and there again experimentally people have found that you can write things like this n epsilon exponential of sum F by n times Fd.

The pi n remains the same and the velocity goes as v into 1 minus F by n into F s right. So, what this says is that if you have a single motor bound, then the moment you apply an opposing load which is equal to the stall force F s, your velocity will go to 0. If you have 2 motors bound, then you need to apply twice the stall force which is what we saw in those experimental curves earlier on that anyway this is what we saw in the experimental curves earlier on.

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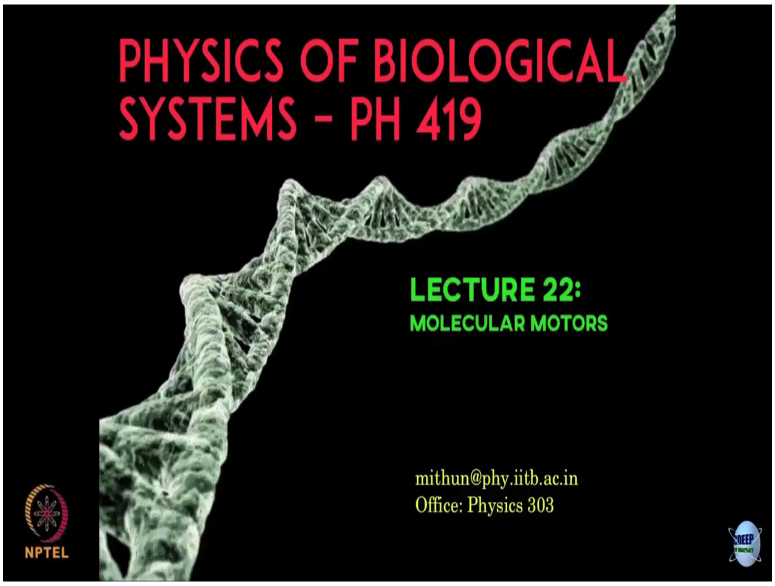

If you remember, there were some peaks at 6 (Refer Time: 28:02). If you had 1 motor bound, then to completely stall this cargo you need a 6 piconewtons; if you had 2 motors bound, you need a 12 and so on. So, the force that you need to apply to stop a cargo which is being carried by N motors is n times F s and it varies linearly which is sort of an experimental approximation. Its true in some cases, it is not true in some other cases and here for example, it says that the unbinding rate also grows exponentially with force, with some force scale which is F d. So, the harder you pull it back, the harder you make it for these motors to unbind which as we discussed is true for kinesins, but not for dynein's, but let say it is true for this case.

So, let say we have modeling kinesins. So, if you put in all of these now if you put in these forms of these epsilon, the v and the pi's into all of these equations, you can calculate what this model would predict for example, for these average number of bound motors average velocity distributions of walking distances unbinding rates and so on. So, here is what it says.

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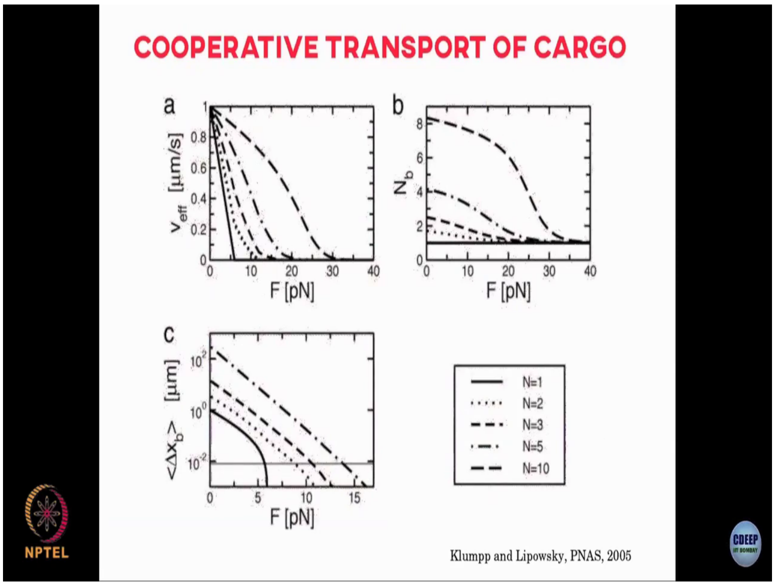

So, for example, if I want to find if I want to find this is the prediction for the effective velocity as a function of this opposing load for cargo that is carried by different different maximum number of possible motors. So, this is capital N. So, this curve is capital N equal to 1. So, there is only 1 motor that is possible its either 1, 0. This one is N equal to 2; this one is N equal to 3, 5 and 10.

So, what it says is that for example, if you have consider this single motor cargo which is being carried by at most 1 motor and capital N equal to 1 any force greater than 6 would mean that the velocity is 0 the motor the cargo has stopped because you have cross the stall force of the motor. As you carry as you are attached to more and more number of motors you can walk with an appreciable sort of velocity even when you have a large force. So, for example, at even a 10 pico Newton this case with 10 motors walks with almost 0.8 times the maximum possible velocity.

Similarly, if you look at the average number of bound motors in this case of course, its 1 because your capital N is 1 therefore, it can be nothing but 1 but in these other cases as we apply more force let us look at for example, this case this capital N equal to 10 case as we apply more force the number of motors that are bound on an average at a given time this is sort of decrease with force ultimately at some point when you reach the stall force of these 10 motors no motor will be bound.

Similarly, if you look at the average distance it is walked which I have not calculated, but you can calculate again that and plot that as a function of force the more the number of motors that is carrying your cargo the more the distance that you can walk on an average and these are not linear functions. So, these do not grow these do not change linearly with force this changed on sort of non trivially depending on the number of motors that are bound ok. So, the behavior for a single motor can be very different from the behavior for multiple motors bound similarly you can not only look at the average sort of distance that it walks.

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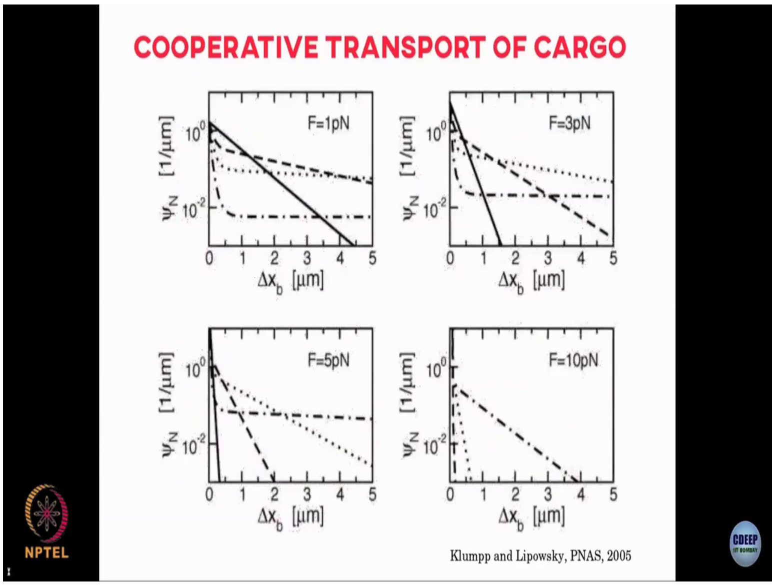

But you can also look at distributions of these walking distances you can calculate from this formalism the full probability distribution again which I have not done, but which you if you go to this paper you can take a look and for example, if I look at this high force case when I am pulling back with a force which is around ten pico Newton these cases with the cargo is being carried by very few motors 1 or 2 or 3 it is a very sharp probability distribution peaked around 0 which means most often it will walk very little distance before falling off.

On the other hand, if you have more number of motors that are carrying the cargo it can walk an appreciable distance. So, even at 3 4 microns you have a reasonable probability that the cargo will get that far. So, the cell can; so, the cell can use this multiple motors the this cooperative effects between multiple motors in order to carry cargo large distances if you asking something.

Student: (Refer Time: 32:26).

Yes.

Student: (Refer Time: 32:28).

Yes.

Student: (Refer Time: 32:32).

Which is going to 1?

Student: Its going to (Refer Time: 32:35).That is because I have normalized my probabilities with this conditional probability. So, I am only considering the subset of cases, but at least the cargo is bound to the filament. So, this 1 minus P 0 is there this because once the motor unbound unbinds sorry once all motors have unbound the cargo set of drifts off. So, experimentally its a little difficult to compare with that on the other hand its easier to compare with this conditional probability that given that it is bound how many are there how many motors are bound.

So, you can do. So, this is of course, in some sense mean field estimate I neglect sort of fluctuations I only calculate average quantities you can do better and better you can take into account what is the effect of fluctuations we can take into account what is the effect of opposing motors and so on, but you can do it in a sort of similar spirit you can write down these sort of master equations you can solve them numerically if not analytically and then try to see what it predicts for this sort of cooperative behavior.

So, multiple motors is not just 1 motor scaled up n times the f x can be fairly non trivial and that non trivial f x comes because of these non trivial force velocity your force unbinding rate sort of dependences ok.