Physics of Biological Systems
Prof. Mithun Mitra
Department of Physics
Indian Institute of Technology, Bombay

Lecture – 53
Two state models

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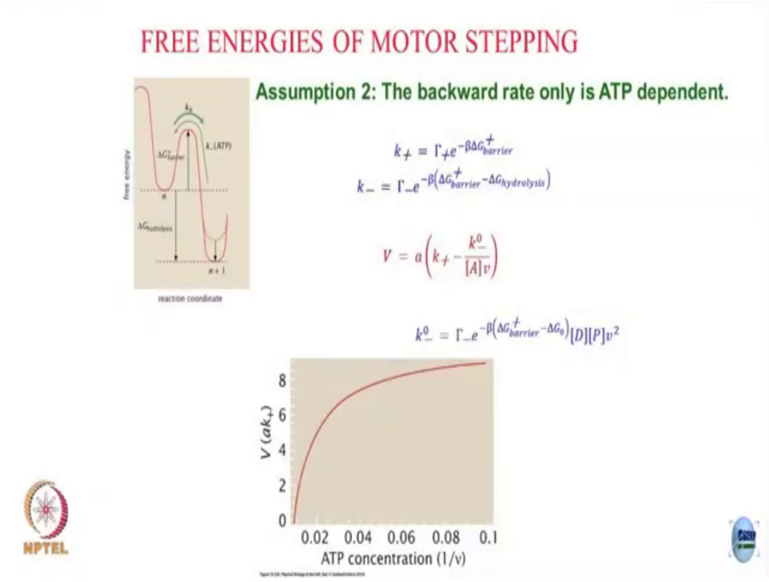

So, these sort of models are fine if you wanted a sort of qualitative understanding of this force velocity or this ATP concentration velocity dependences. But in order to do a little more realistic models what you need to necessarily consider is that these motors do in fact, have internal states and then try to take write down a model that takes into account those internal states ok.

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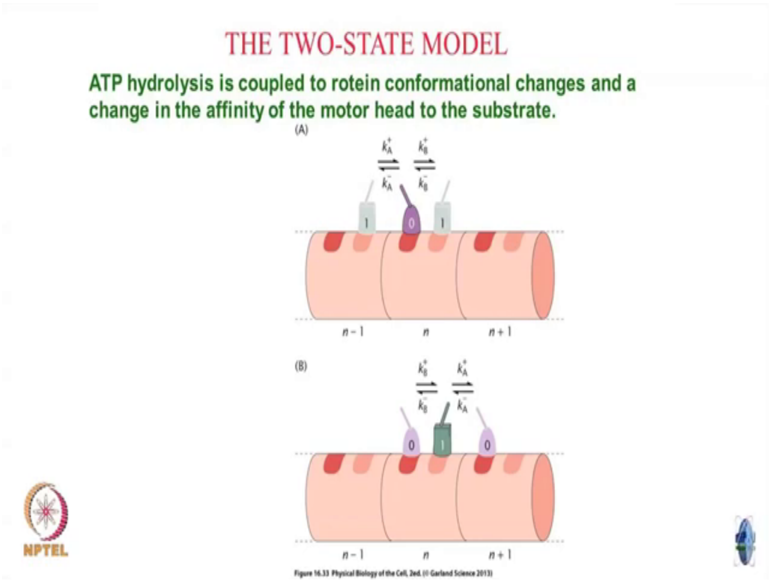

So, here is one such simple model. So, what this says is that this ATP hydrolysis and this is in fact, true for most motors its coupled to a protein conformational change in the state of the motor and it changes therefore, this change in the conformational state changes the affinity of the motor to the substrate ok. So, it has two sort of states it could have multiple states, but at least in the simplest case let us say this motor has two possible; conformational states that it can exist in 0 and 1 ok. From the same side, it can exist in a 0 state or it can exist in 1 state the colors here that whatever (Refer Time: 01:19), but at least you can see over there.

So, when it is in the 0th state, it is let us say inactive; let us call the 0 state inactive it can become activated and stay on the same lattice site. So, it can go switch this state 1 and stay on the lattice site n and that happens with some rates k B plus and k B minus this switching. Or it could switch to this one state and take a step backward; backward meaning not on in its preferred direction ok. Let us say that this motor wants to move in towards this direction. So, it could take a backward step with some rate k which I call k A plus and k A minus ok.

On the other hand if the motor is in state 1 so, it is in the active state. It could hop forward which is what it would like to do. So, it would go to the n plus 1 state and become inactive because it spent ATP in process with some rates again k A plus and k A minus and it could switch back to an inactive state on the same side with these rates the this k B plus and k B minus ok. So, now, I will say instead of saying that I simply have a probability distribution to be at site n, I have a probability distribution to be up site n at time t, but also coupled to whether it is in state 0 or state 1 ok.

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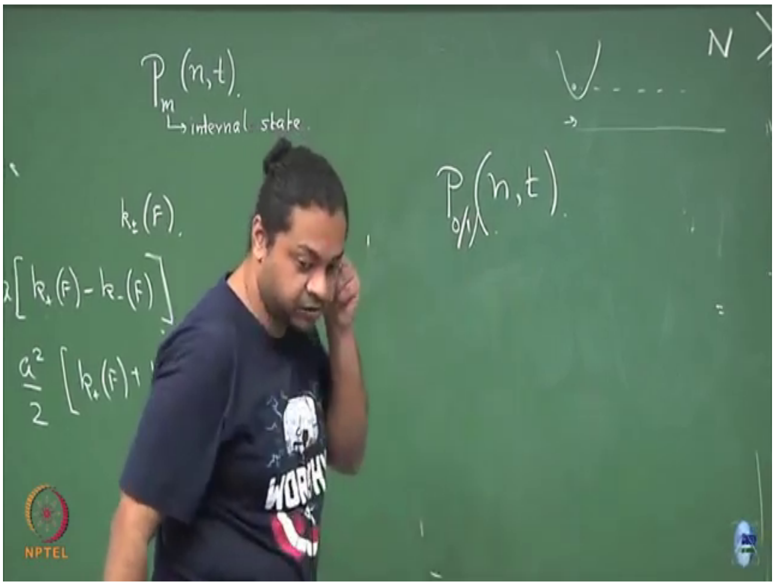

And in principle of course, this could be multiple more complicated motors you might need you might have multiple conformation states that it goes through coupled to wait. For example, if it needs multiple ATPs to work, each of these ATP binding and hydrolysis could be coupled to a different a conformational changes. But in the simplest case something like this definitely, it needs to have at least two conformational states and you can then write down the associated master equation.

So, for example, let me now write. So, let us say I write for del t 0 del t at n comma t. This could come from P 1 at n minus 1 comma t right. So, if the motor takes a forward step like this; if the motor takes a forward step like this that is k A minus and it could come from motor going from active to inactive on the same side so, which is plus k B minus P 1 on of n comma t. Hopefully this way and then the last term.

So, these are the gain terms and then the corresponding loss terms sorry did I write the k minus correctly no, it is k plus to go in this direction. So, then there is a k A minus P 0 of n comma t and then k B plus of P 0 of n comma P right.

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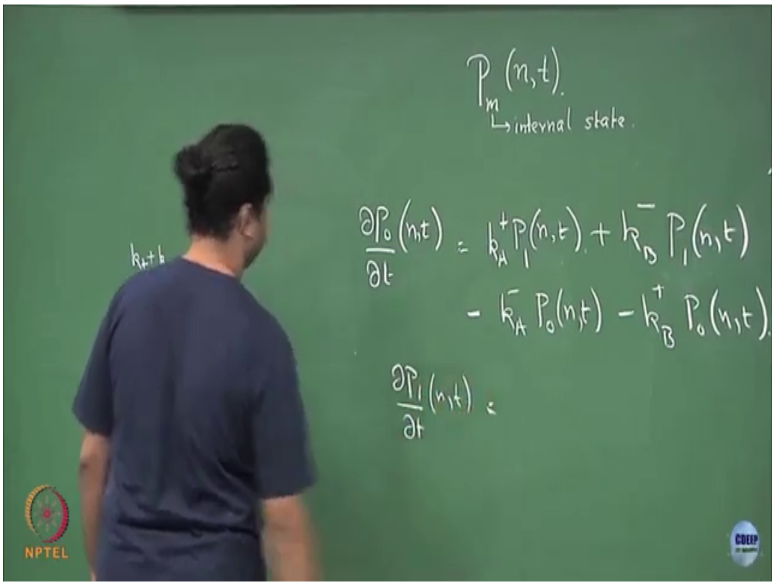

And similarly of course, for del P 1 del t similarly for del P 1 del t.

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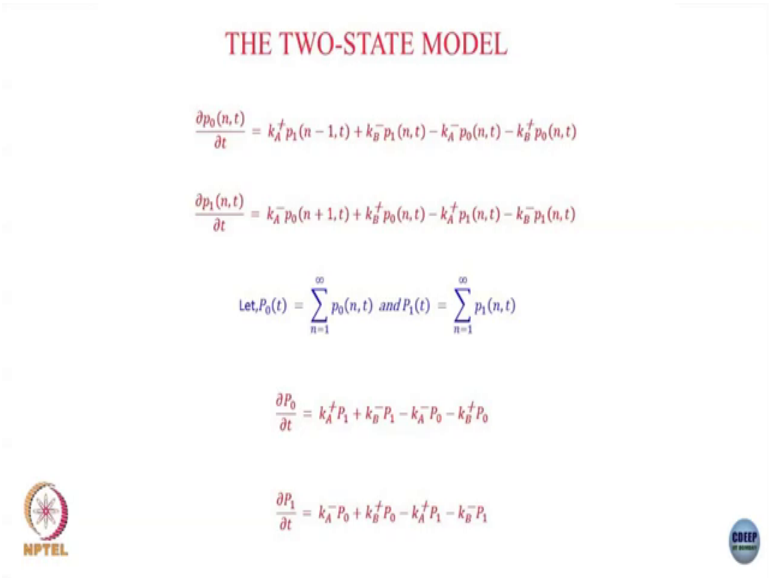

So, you can just write down. These equations hopefully k A plus k B minus minus k plus minus minus (Refer Time: 05:05). So, these are the two sort of equations that you now get. You have the motor existing in two states and therefore, you have these two probabilities P 0 1 P 1. You can of course, now try to solve this for arbitrary k A plus k B plus and so on that is somewhat more time consuming. So, what I will do is that I will just do a simple thing. So, let me say that I define the probability P 0 as probability of the motor is in state 0 irrespective of what site it is in.

So, I just sum over all ends of P 0 n comma t and similarly I define corresponding P 1 which is the probability that the motor is in state 1 irrespective of what site it is in. Then I can just sum over these equations and just write down how this P 0 and P 1 change with time right and then. So, the del if you sum over this you get a del capital P 0 this will give a capital P 1 and so on.

So, you get this equation and you get this you sum over all of these terms, you will replace them by the appropriate P 0 is capital P 0, then P 1s and you get this sort of an equation ok. Now, let me say that well I will again look at the steady state of this model.

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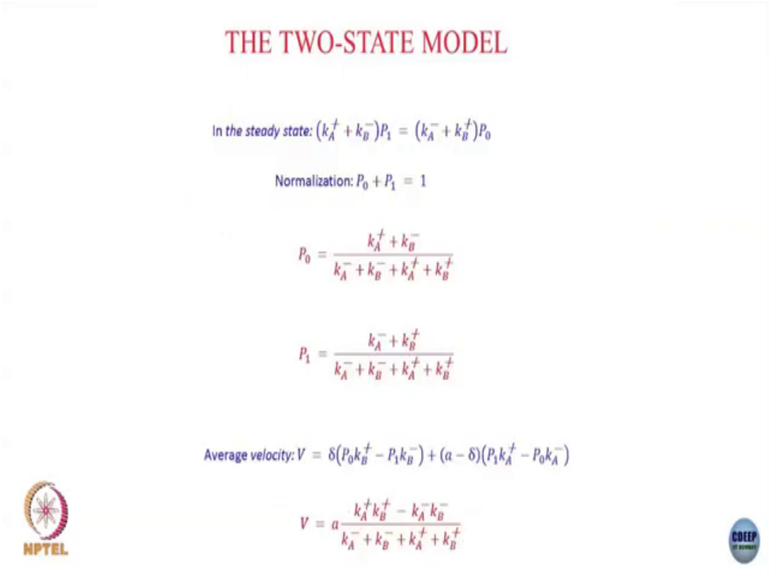

So, I will look at this thing is equal to 0, these probabilities do not change with time and that would give me then this sort of a relation that k A plus. For example, k A plus plus k B minus into P 1 is equal to k A minus plus k B plus into P 0 which is what I have over here. So, first let us go back sorry here. So, k B is the rates of switching from the active to the inactive states or backwards.

So, plus is the switching from inactive to active minus is the switching from active to inactive that is k B, k A is at the stepping rates ok. So, from n minus 1 to n or from n to n plus 1, the forward rate the forward stepping rates are plus, the backward stepping rates are minus. So, you could think of this as being my hydrolysis rates, let the conformational change rates the k Bs and the k As as being my stepping rates ok.

And these are coupled in that whenever you step you change sort of this conformation as well 1 will always go to 0 step. And of course, you have normalization that if you summed over this P 0 plus P 1 that should give you 1, all motors must either be in the inactive or in the active state. So, then you can solve given these two equations when the steady state you can solve for what this P 0 and P 1 is going to look like and that is what is your P 0 and P 1.

And you can calculate some sort of an average velocity by making may be some sort of an approximation that this is again a very qualitative assumption what this says is that ok. Let me show in the figure when it makes a transition like this on the same site from the inactive to the active or the active to inactive, it changes position by some small amount delta and when it hops from one side to the other, it changes by A minus delta.

So, that together you get a change of A which is your lattice spacing. You just break it up into a small change delta corresponding to this hydrolysis step and A minus delta corresponding to this actual stepping and then you can calculate an average velocity this delta is some parameter. So, you can calculate an average velocity, but then you substitute for this P 0 and P 1 that you obtain and you can get a velocity in terms of these rates alone this k A plus k B plus and this lattice constant d. This delta will drop out ultimately. So, it does not really matter ok. So, this is how the and then of course, you must properly account for how these rates.

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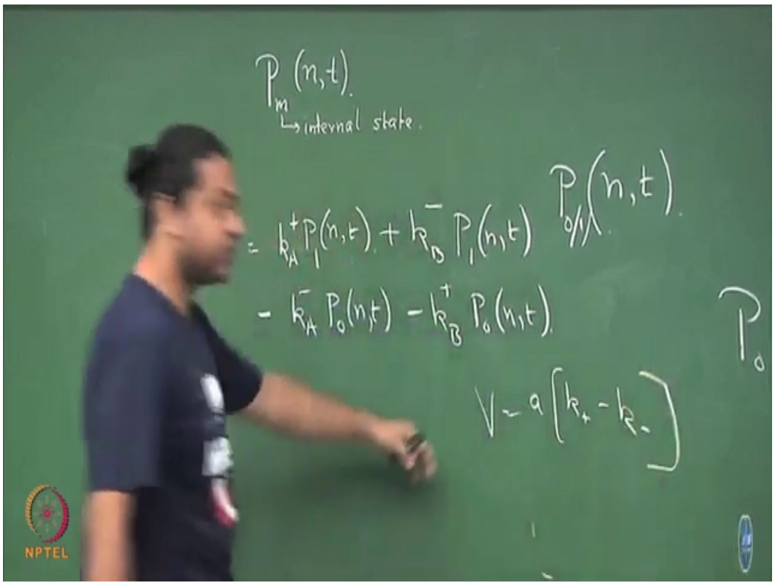

So, this is the analog of this V is equal to a times k A plus minus k plus minus k minus for the simple one state model. This is the analog of that for the two state model ok. It is much more complicated because you have these four rates now. But this is the expression now of course, you need to go back again and do this analysis of how these k is will depend on the hydrolysis rates, how they will depend on the forces and so on ok. So, that is more complicated. It will differ a little from motor to motor, but at least in the spirit of these models; these give a fairly good match to the experimental data.

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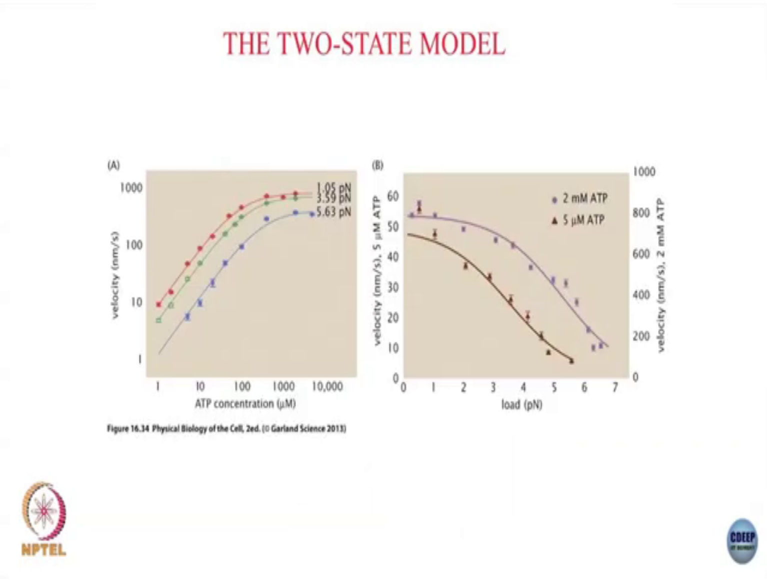

So, for example, again I think these are experiments on myosin. If I remember correctly, no these are experiments on kinesin I am sorry. So, these are experiments on kinesin. The velocity of the function of ATP concentration at three different backward load forces 1 piconewton 3.5 5.6 piconewton. So, as you expect the expect the experimental curve shows that as you increase ATP initially your velocity increases right. Then as you read saturating ATP concentrations, it sort of flattens off because you cannot go more than that.

The value at which it flat and saw depends on the load force that you are applying. It is highest for lowest values of the load force because you are pulling much less backwards. The more you pull, the lower this saturating value of the velocity ok. These curves are predictions from this sort of a two state model with more complicated assumptions for what this k plus k A plus k B plus looks like ok.

But the idea is that this sort of two state models can actually capture this dependence not only a. So, this is the velocity as a function of ATP concentration there is the reverse case that the velocity is a function of load for two different ATP concentrations. And again this is qualitatively what I would expect that is I increase the load by velocity sort of drops off and it drops off faster when you have smaller amount of ATP versus if you have more amounts of ATP right.

And this sort of a two state model, the ideas of this sort of when you take into account these internal states, you get a pretty good match with the experimental values provided you have modeled your rates reasonably and physical this one this is 0 at n. So, k A plus n minus 1 then k B minus this is n that is fine k A minus that is also n; these are fine right. k A so, tell me the what term you wants to write k A minus P 1 into n plus 1 comma t.

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No.

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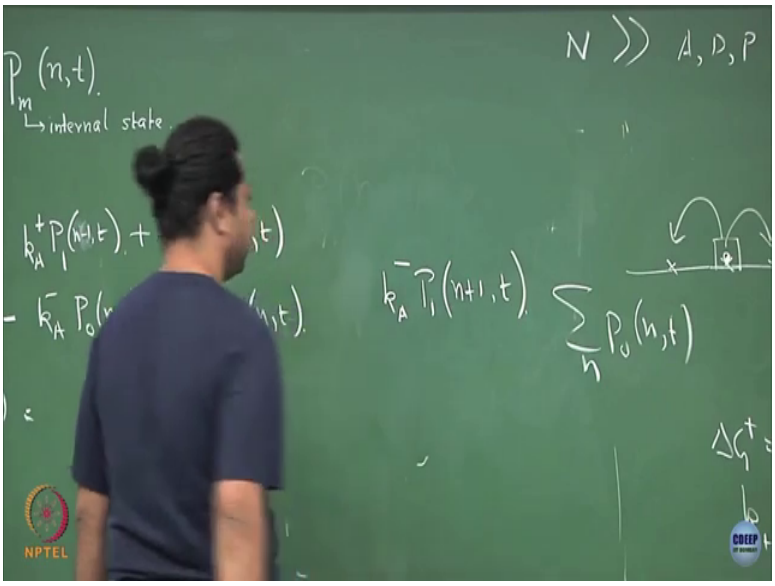

k A A minus ok. See because when you take so that is that is part of the model that when you are taking a backward step, you have to go from a 0 state to a 1 state and then transition back to the 0 state on the same side. It is not a single step process.

So, here for if you are going to take a backward step so, this is a backward step right. If you are going to take a backward step like this, you need to be in this 0th state and then you need to go back one state and that will land you in this conformation one. So, this is what the model. So, this is an assumption of the model its sort of tied with how kynaston hydrolysis ATP and changes its conformation. So, if you wanted to go to this sort of a state from there, you would have to do it through two steps.

Student: (Refer Time: 13:23).

And then it goes back right ok. So, within this scheme, these are the only four terms that will come in this model this is the thing. So, it says that if you have these two state models, this does a fair job of explaining the experimental data. However, you could also ask that well are there any other signatures, can I get the sort of more direct evidence that there are this sort of multiple steps happen.

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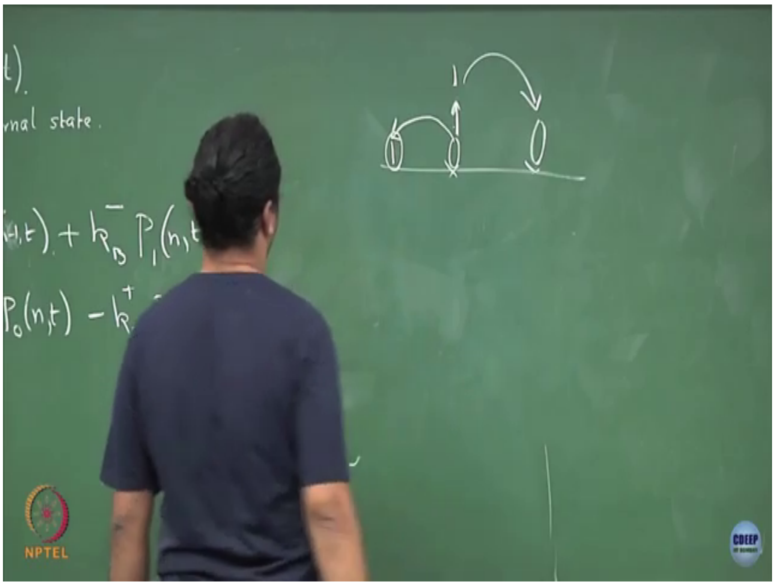

So, what this is saying is that if you wanted to step forward, you are in the 0 state you stay in this site and you go to the 1 state and then you hop forward over here and in this hopping you change from one to 0 right that is the basic assumption of this model. So, if you are if what you are observing is that the motor is going from here to here, it is actually going through two steps; 0 to 1 and then the hopping. So, can I sort of observe that a little more directly? So, that is the assumption we have made in this modeling, but you can also observe that a little bit more directly.

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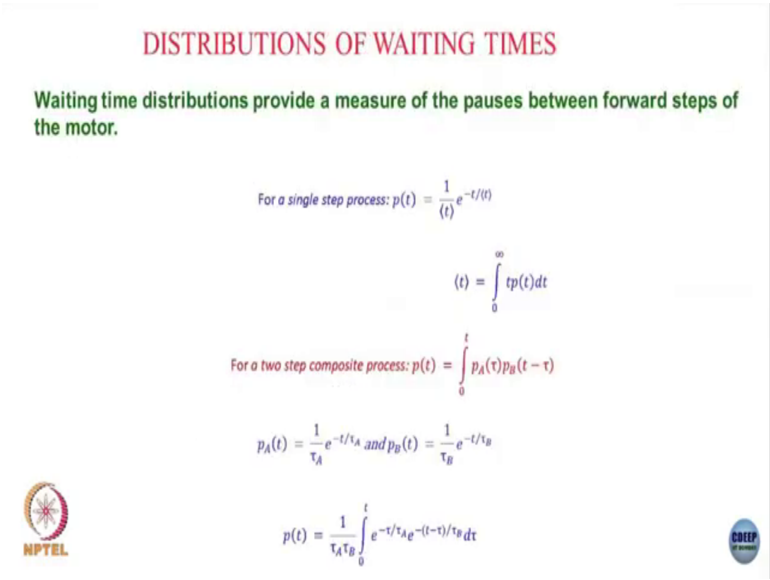

And which is to see you look at distributions of waiting times ok.

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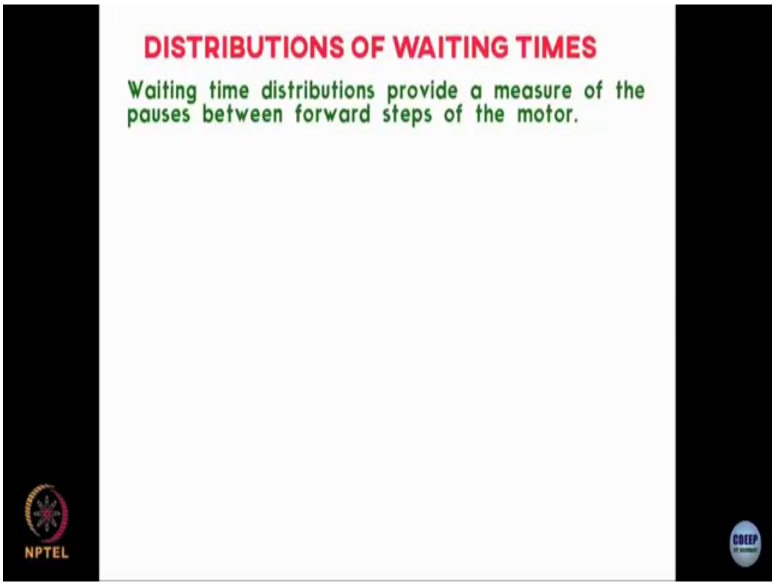

So, what this waiting time distribution is that it provides the measures of the pauses between the forward steps ok. So, you were here, how long does it take to go there? You observe it for many many steps, you plot a histogram or a probability distribution of these waiting times yes.

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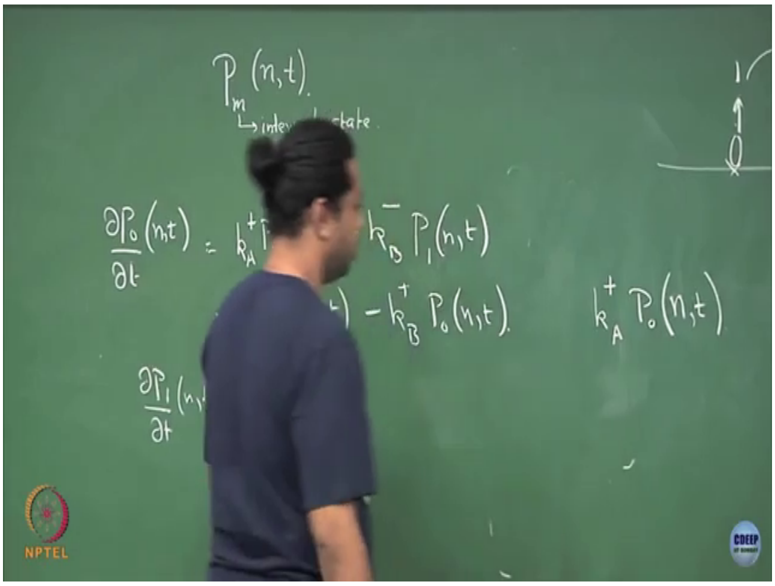

You hear only let me write one more term what k plus P 0 with a minus sign ok. Let us again go back to this. This is anywhere it kind of the k is at the stepping rates right. Here you are not stepping anywhere here at n t and you are coming from n t. So, it cannot be; if you are staying on the same site at n, then these rates are related by k Bs.

Student: (Refer Time: 15:36).

Yes. So, 0 has to go to 1 and then move forward. So, that is what I am saying see the idea is that you have this kinesin in, it binds ATP the ATP has to hydrolysis to provide the energy that is my step 1 and then once it is hydrolyzed, then the motor can step forward. So, that is my 0 to 1 and then stepping forward to the n plus 1 outside. So, that is the idea. So, you can ask about this question about waiting times that how much what is the distribution of times that I have to wait before I observe forward steps of the motor, yes.

Student: (Refer Time: 16:13).

So, what it says is that from the 0th step, you can go backward, but it lands you in this one step state right. From the 0th state, you can go backward and that lands you in this take a look at the P 1 equation a P 1. So, this is the backward step.