Physics of Biological Systems
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Lecture - 42
Introduction to Rate Equations

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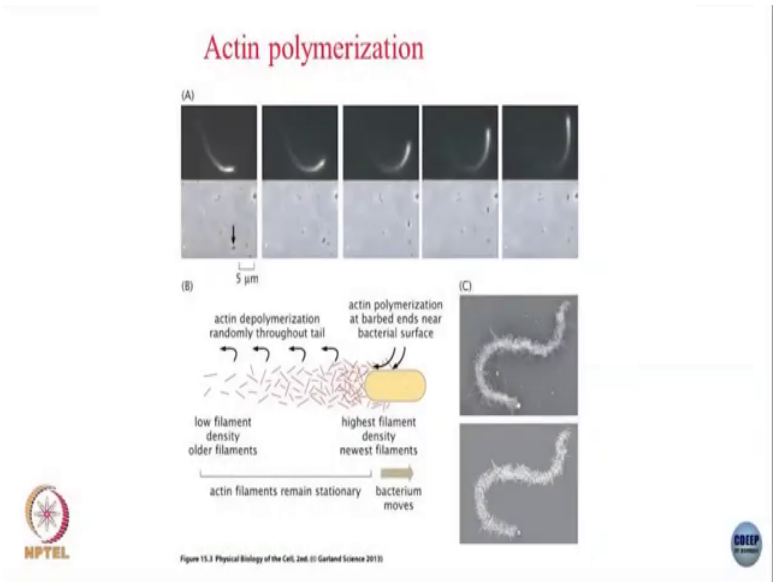

So, that is what we will try to do, we will try to look at these sort of time varying processes; whether it is cytoskeleton, motives or even simple chemical reactions. So, what we will start off today is just by setting up the machinery, corresponding to chemical reactions and then we will apply to these sort of systems next class.

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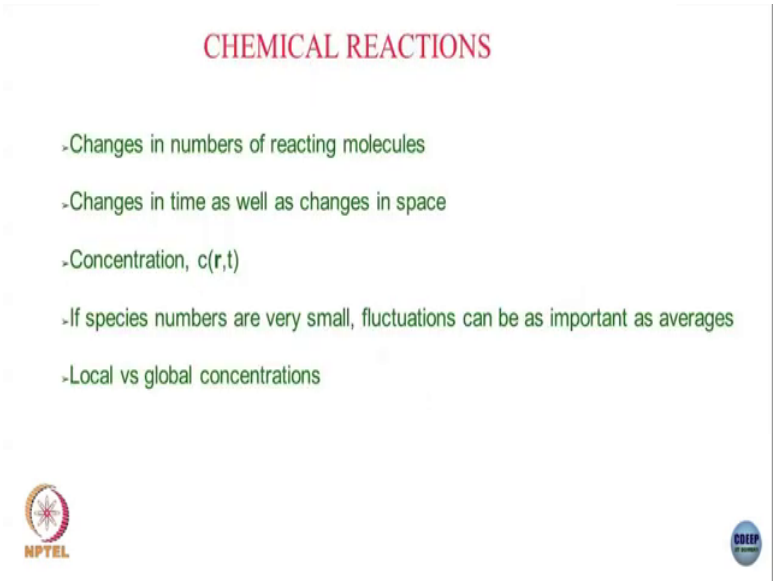

So if I think of chemical reactions; what this involves is the changes in the numbers of reacting molecules. So, you have some species, let us say some protein and as time goes on you have changes in the numbers of this proteins inside the cell; for example, there could be changes in time as well as in space, right. The protein concentrations if I am thinking of proteins, they need not be uniform in inside the cell, they need not be uniform in time.

The time path we saw in the first slide whereas, the cell cycle progresses the number of copies change; but it is also could be localized in certain areas where that protein is particularly needed. So, it is in principle the function of both space and time. So, we denote this the relevant variable that will try to work with is this concentration, which is a function of space as well as that time. And the thing to realize is that, we will talk about these concentrations.

So, the moment we say that we will talk about concentrations; what we are saying is that, there are enough number of copies of that molecule, such that fluctuations are relatively small. If there are only one or two copies, then you cannot really write down sort of things that I will write down. You then have to look at trajectories of these individual molecules in time and in space, so stochastic trajectories and then analyze the trajectories themselves.

So, if the numbers are very small. So, that the fluctuations sort of overwhelm the averages, then you have to deal with different then there are different methods. And again if these are not uniform, you have to sort of think about what is a global concentration or for example, if a protein is a membrane protein, it will not be found inside the cells.

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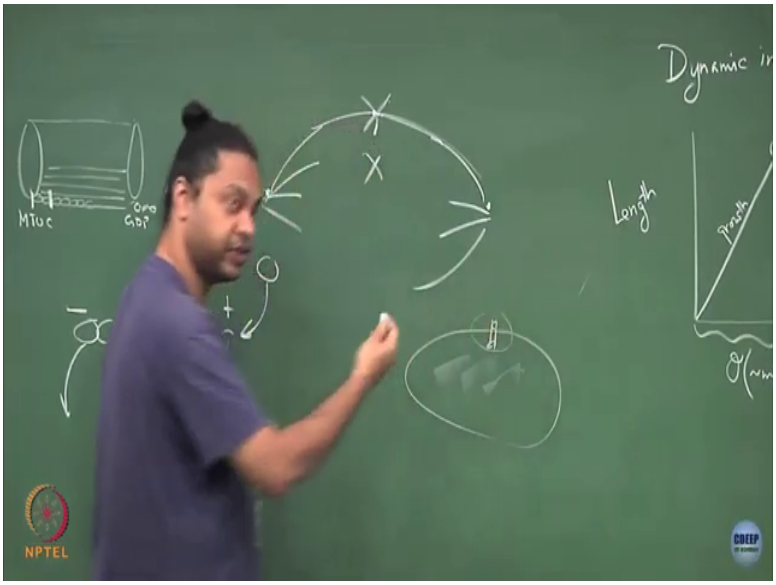

If I have a protein which is a trans membrane protein like this talking about the concentration throughout the cell volume does not make any sense. One has to talk about local concentrations, relevant to the area where that protein is found to be localized.

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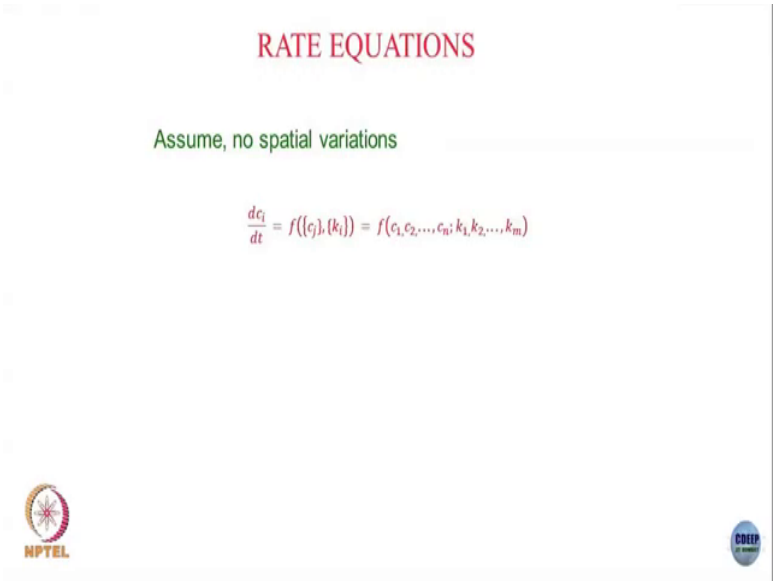

So, in general we have this c of r comma t which is my concentration variable. So, for the time being what I will do is that, assume that there are no spatial variations; these proteins or whatever I am talking about these are well mix. So, if I think that they are well mixed and everywhere it is sort of homogeneous; then I drop the space and I just write the concentration in terms of time.

I will relax this constraint in subsequent classes to look at how to deal with systems that vary both in space and in time; but for the time being let us start off by assuming that there are no spatial variations and I can write down these rate equations simply by looking at fluctuations

at time, ok. So, if I have multiple species all interacting with each other I can write down rate equations like this; dc dt the change rate of change of concentration, that will in principle depend on the concentrations of all other species that interacts with and various rate constants.

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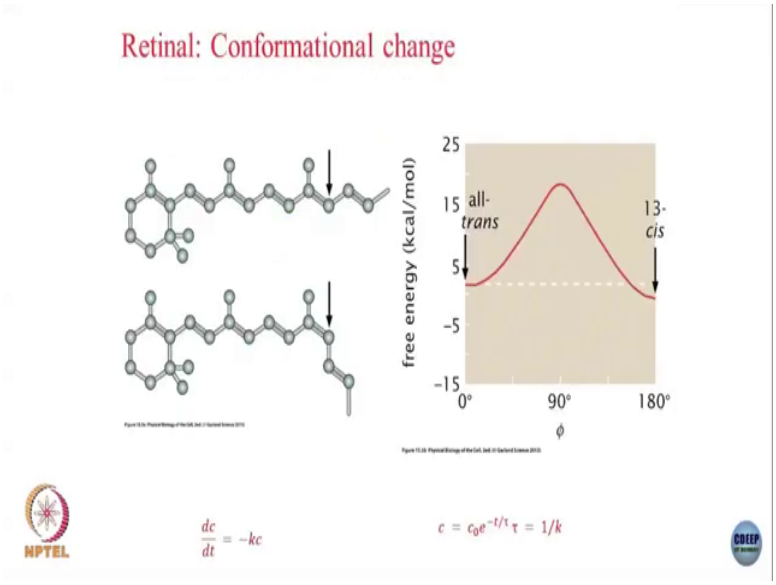

So, it start off with a simple example. So, this is for example, protein called retinol, this is found in the rod cells of your eyes, the rods and cones cells it is important for color perception. And it is sort of found in two states; one is called this all trans state and the other is called is 13 cis state and there is some sort of an energy barrier to go from one of these states to another, ok.

So, if I am I was thinking about just let us say any one of these states; let us say this all trans state and I asked that what is the rate of and there is some rate at which this all trance goes to this third this other conformation the 13 cis. Then I could write down a rate equation for this

all trans conformation which is something like this; it is sort of decays from this state to that state, it decays from this state to that state with some rate constant k.

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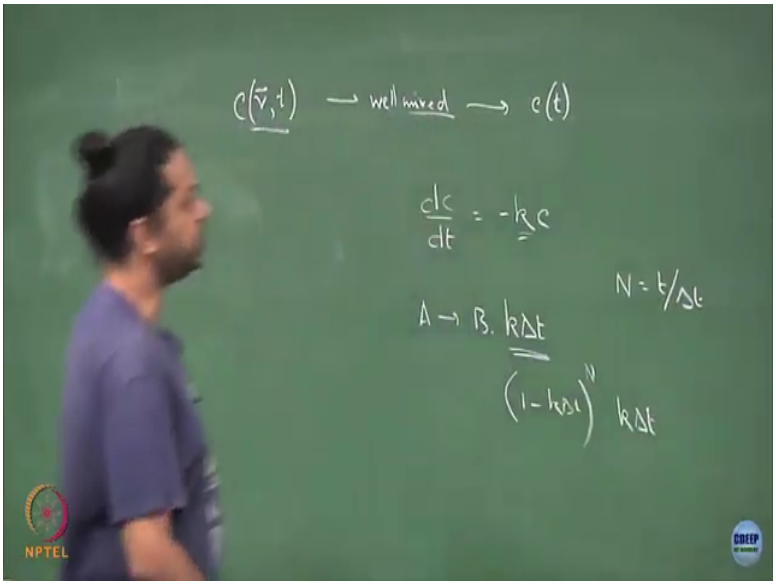

And I would therefore, write down the concentration of this protein; it is minus k times c. So, the rate of decay is proportional to the concentration itself, the number of protein copies that you have and this constant the rate constant I call as k, ok. This is something very basic and then of course, this will have a solution c is c naught e to the power of minus t by tau; where tau the characteristic times, this the inverse of the rate constant.

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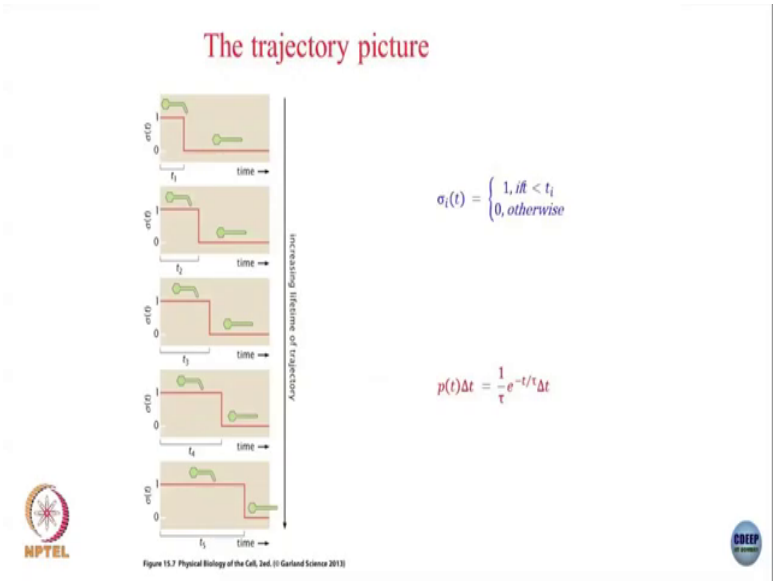

You can think of this sort of a trajectory picture that you start from one conformation and at some random time; this will switch over to this other conformation. And you could have different trajectories, so this sigma t are my trajectories. So, it starts off in at this one concentration at this one conformation and then at some time it switches over to this other conformation. So, if you repeated this experiment multiple times or if you look at multiple copies of this protein; this time at which it transforms from this one state to this other state is going to be a random stochastic event.

So, at some time t i for this ith copy of the protein, it is going to go from 1 to 0. So, that is my trajectory picture and then again you can construct. So, if I say that at each time it has a probability k delta t of making a transition from this state A to state B; then I can estimate that

what is the probability that it goes from this state to this state and within this time interval t to t plus delta t and that is again this e to the power of minus t by tau 1 by tau delta t, right.

So, again it is like the same thing. So, if k delta t is the probability of transforming, then 1 minus k delta t is the probability that it stays in that state. It stays in that state for some n steps and then in the final step it makes a transformation, right. This n is just t by delta t and then if you sum that up, you will get this the probability that it makes this transition in this time window t to t plus delta t. So, you could it is a sort of equivalent description; you could either write it in terms of these concentrations or you could write think of this in terms of these trajectories.

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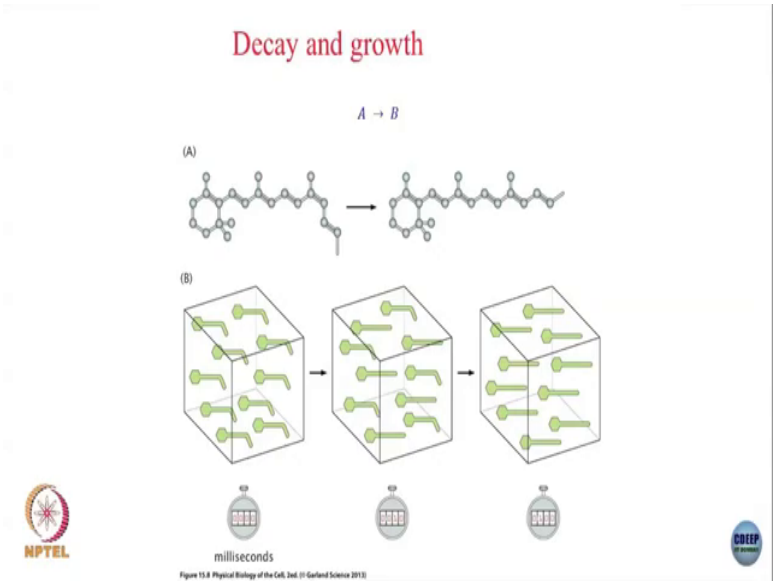

Or if you wanted, so remember I had these two states which were all trans all trance and this 13 cis.

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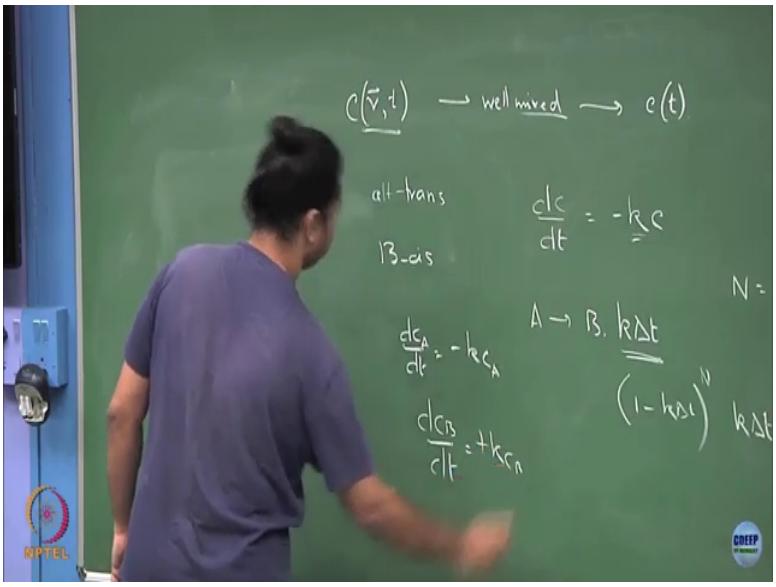

So, what I did initially was to write this concentration profile of any one of these which is minus k c; but I could also write the concentration. So, let us say this is A, I the concentration of this other one if I call that B that is simply the inverse of this k c B. So, whenever this decays I have a growth in this other one, so these are sort of coupled and in principle I could write a coupled equation between these as well.

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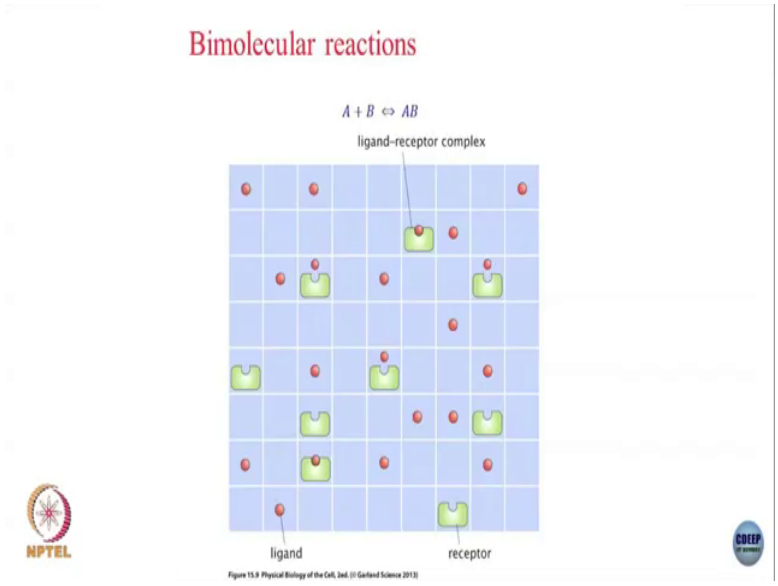

I could also think of slightly more complicated reactions like the ligand receptor complexes. Again I can think of this from this rate equation perspective that, if I have two molecules let us say as ligand and a receptor and they interact together to form this ligand receptor complex. Again I could write down equations for these concentrations of free ligands, concentrations of free receptors and then concentrations of this ligand receptor complexes, right.

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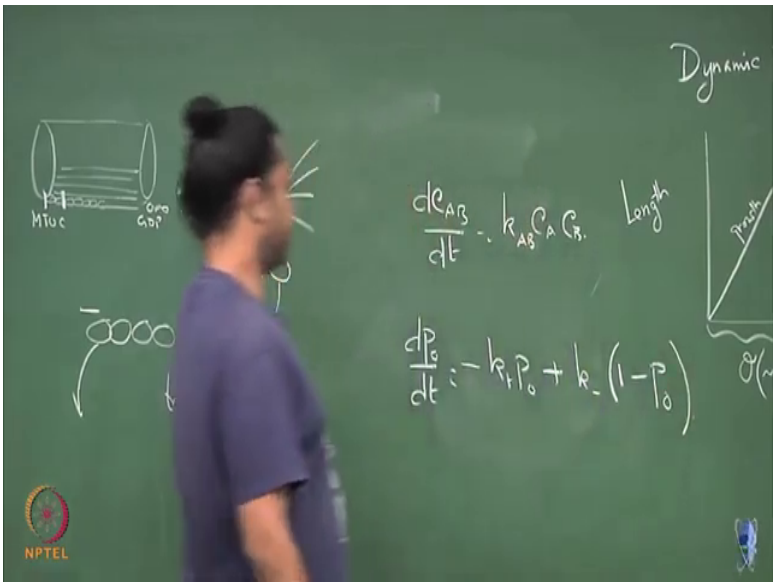

So, for example, I could write d C A B d t which is this complex depends on the concentration of A and the product of the concentrations of A and B and some sort of constant A B.

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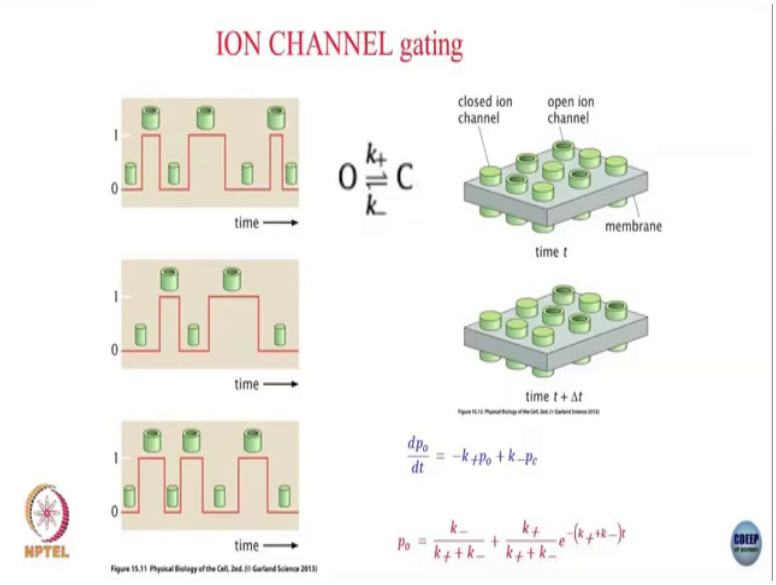

So, these are things that we have looked at earlier using a different sort of language, two state language this ligand receptor complexes or these ion channels; but we could equivalently frame these in terms of this kinetics. So, for example, this is an ion channel gating, which again exists in two states; an open state or a closed state and there is some rate of conversion from the open state to the closed state and the closed state to the open back to the open state with rate constants k plus and k minus.

And again you could write down what is the probability to find an ion channel in the open state p 0 d t that is. So, it goes from the open to the closed state with this rate k plus. So, it minus k plus p 0 plus k minus p c, ok. And so, this is minus k plus p 0 plus k minus p c this is the probability of the ion channel being in the open state, this is the probability of the ion channel being in the closed state.

And again you can solve this equation simply by saying that this p c is nothing, but 1 minus p 0; this ion channel can only exist in either an open state or a closed state and then it just becomes the one variable equation and you can solve that and that will give you some answers. So, the probability to find the ion channel in the open state goes like this; this k minus divided by k plus plus k minus plus this term which decays is a function of time.

So, if you waited long enough, you would see this sort of a probability. But what this sort of framework allows you to do is that, it allows you to sort of say what is the full time dependence, so you do not need to make steady state approximation which is just this. But you could write down the full time dependence of this probability of the open state, provided you give me the initial conditions.

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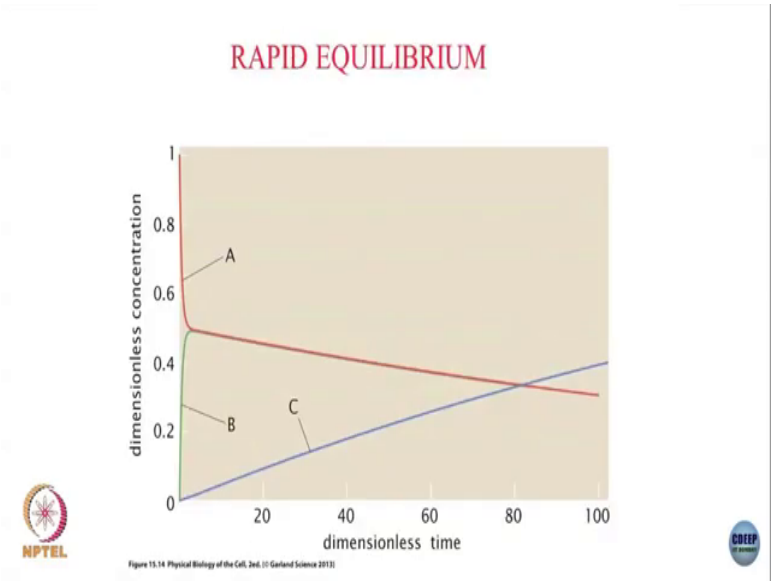

Another thing that we had looked at initially when we are talking about this equilibrium versus non-equilibrium was this sort of equilibrium in subsystem sort of a thing. So, let me just. So, if you recall we had this, we had looked at this sort of equation A going to B going to C with some rates say k plus and k minus some rate r.

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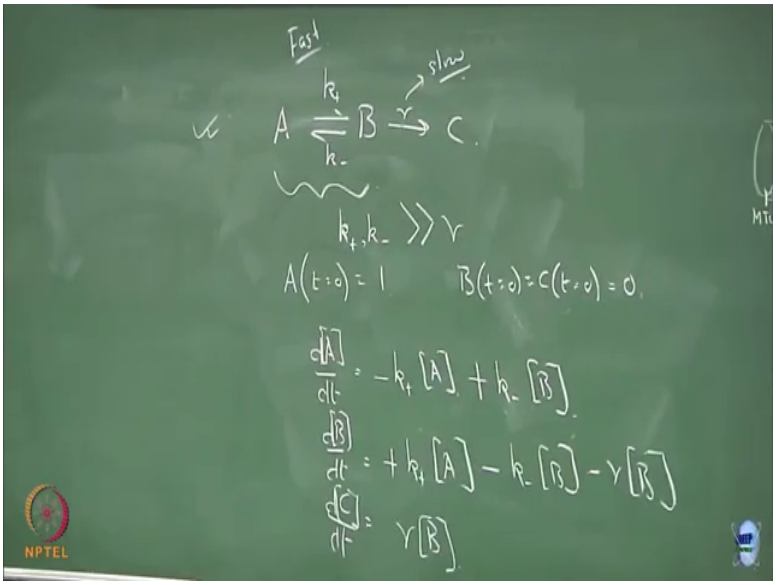

And we had said that, if these if this part of the equation was happened very fast, so if this was a fast time scale process; whereas, this was a slow time scale process, then you could see that this A B sort of achieve an equilibrium amongst themselves. Whereas so, this A and B achieve an equilibrium amongst themselves and then they sort and then they evolve to their final steady state, ok. So, I will just try to. So, this I had just stated at that time.

So, if I try to look at an equation like this and sort of work out, write down the rate equations for these three species and try to work out what this condition for rapid equilibrium means in

this context, ok. So, again just to say that this equation these reactions are happen on a fast time scale which means that these rate constants k plus and k minus are much much greater than this slow time scale rate constant the r, ok.

So, I have a separation of time scales. So, 1 by k plus 1 by k minus are much smaller than 1 over r, ok. And let us say I mean if I need to start from an initial condition. So, let me say that at time t equal to 0, I simply had A and I did not have anything else so, B and C will 0, ok. I start with simply A and that I have just normalized to 1. So, then I can write down the rate equations for these three species. So, d A d t, d B d t and d C d t and I just writing A think of these as concentrations, ok.

So, these are the concentrations of these three species and I can write down the rate equations for each of these. So, for example, for A what would it be, it would. So, A decays to B with a rate k plus, right, so it is minus k plus concentration of A right. And then B decays to A with a rate k minus, so plus k minus concentration of B.

Similarly, for B, I have a growth term from A k plus A; I have a decay term which is like this k minus B and then there is a further decay which is to C. So, minus r times C and the C simply grows like r times, right. So, for B I have these two decay processes; one to A and one to C; this one with a rate k minus, the other one with the rate r; and this C I assume just simply grows, there is no decay. So, that grows with a rate r.

So, these are my equations that describe this sort of a process, where I have the separation of time scales. So, before I do anything, let me just define dimensionless scaled time.

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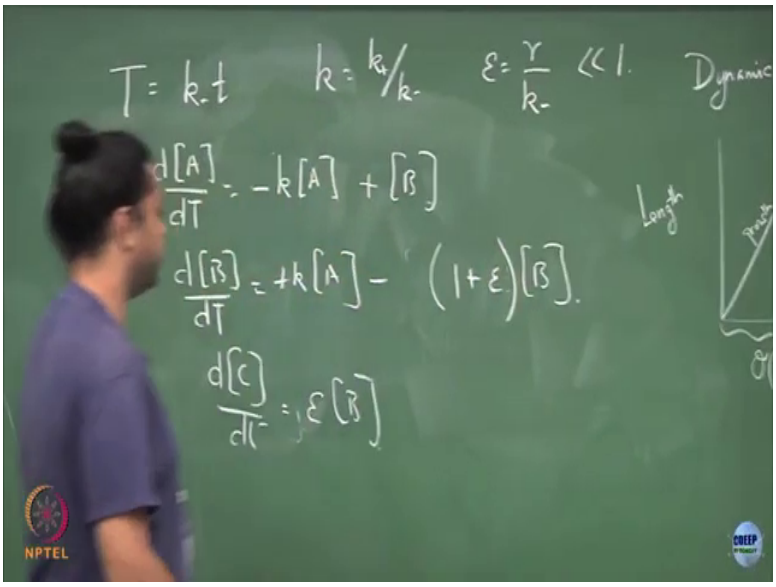

So, let me define a new time which is like k minus t. So, what this means is that, I will just write everything in terms of this capital T. So, d A d T is equal to minus k times A plus B. So, I am sort of dividing everything by k minus over here. So, k minus into t is capital T k plus by k minus let me call as k and this is k minus by k minus, so it becomes 1.

Similarly, d B d T over here is plus k A minus B plus let me call this as epsilon minus epsilon B and d C d t is epsilon. So, my k is nothing, but k plus by k minus and my epsilon is r by k minus; this r by k minus I just call it epsilon, and because this r is much much smaller than k minus this epsilon is very small parameter. So, this is much much less than 1. Let me just write this as, let me just group this together. So, let me just write this is 1 plus epsilon.

So, I try to solve this set of equations, this set of coupled equations. To do that the first thing I notice is that, these two equations do not involve this concentration C of the species C, right.

So, I can solve them independently. So, that is what I will try to do, I will just try to solve this A and B thing first.

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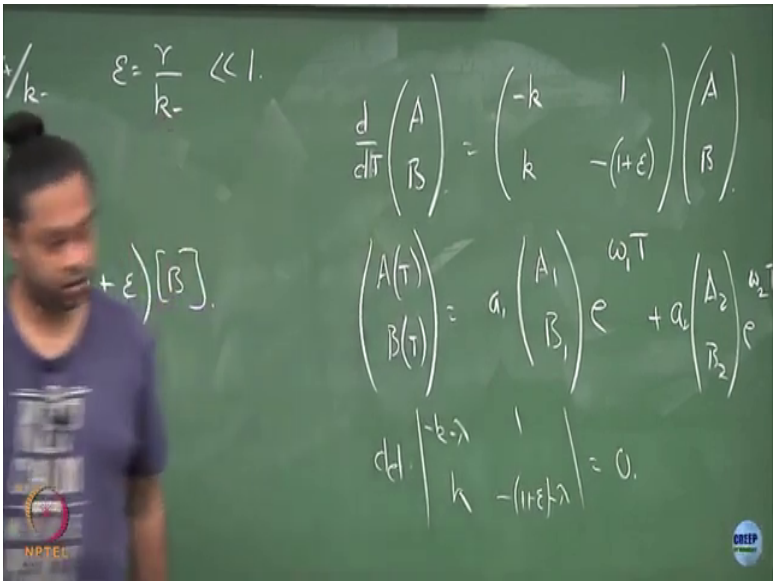

So, let me just write it in sort of a matrix form d d T of this capital T d T of A comma B; this is equal to minus k 1 k minus 1 plus epsilon into A comma A B, ok. So, I have just taken these first two equations and I just wrote it down in a matrix form, ok. So, then I can write down the general solution of this the A as a function of T and B as a function of T, this is a 2 cross 2 matrix. So, it will have two eigenvalues in two eigenvectors.

So, I can just write down in terms of these; let us say some constant into eigen vector 1 A 1 B 1 e to the power of omega 1 T plus some constant A 2 B 2 e to the power of omega right; where omega 1 and omega 2 are my eigenvalues and this A 1 B 1 is one eigenvector, A 2 B 2 is another eigenvector. So, what are the eigenvalues of this matrix? So, I need to solve. So,

this I will not do, you can just do. So, I need to solve the determinant of this minus k minus lambda 1 k minus 1 plus epsilon minus lambda equal to 0 to find out the eigenvalues.

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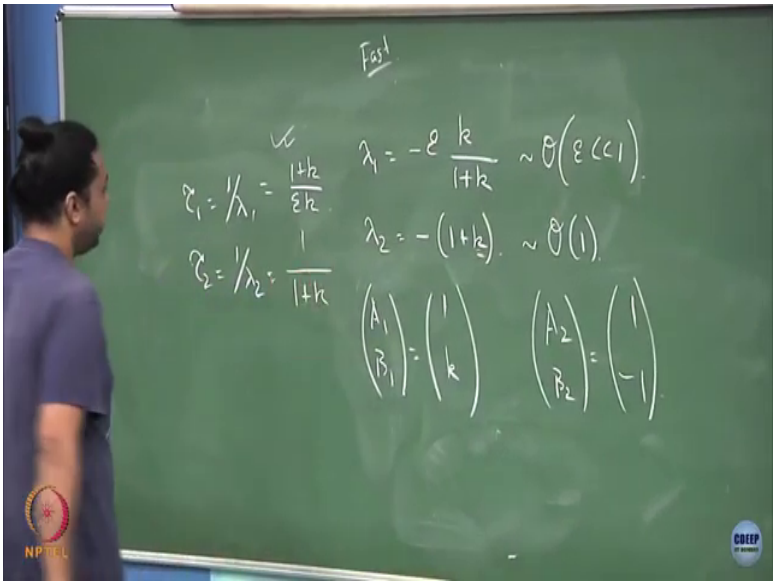

And if you do this, hopefully you will find that the eigenvalues of; so the eigenvalues of this equation are lambda 1 is minus epsilon into k by 1 plus k and lambda 2 is minus 1 plus k. So, this just do and check that you get these eigenvalues out of the 2 cross 2 matrix. So, what this immediately says is that, note that k is roughly of order 1 ok; k let us say k plus and k minus are comparable to each other.

So, this is of order 1, which means that, this eigenvalue lambda 2 is of order 1; whereas, this eigenvalue lambda 1 is of order epsilon which is much much smaller than 1, right. So, therefore, I have a slow rate which is over here corresponding to this lambda 1, and I have a fast rate over here corresponding to this lambda 2 ok, which is what comes out. Once I have

put once I have made this assumption with this epsilon is much much less than 1. I get these two time scales lambda 1 and lambda 2; a fast scaling and a slow scale.

You can now find out also the eigenvectors, there is a 2 cross 2 matrix; again I will not do it, but you can check that eigenvectors are say A 1 B 1 is 1 k and A 2 B 2 is 1 minus 1. So, corresponding to these two eigenvalues you can find eigenvectors and this is what you should get right; one eigenvector is 1 comma k, the other is 1 comma minus 1, ok. So, I can now put all of this back into this equation, so 1 comma k.

So, this is my general solution that, I have a 1 comma k and this is minus k epsilon by 1 plus k minus epsilon k by 1 plus k, this is 1 and minus 1, this is 1 and minus 1 and this is 1 plus k. So, that is my general solution. I still have these unknown coefficients A 1 and A 2; but to determine that I have my initial condition which I have dropped off which was that I started off with all A and B and C's were 0.

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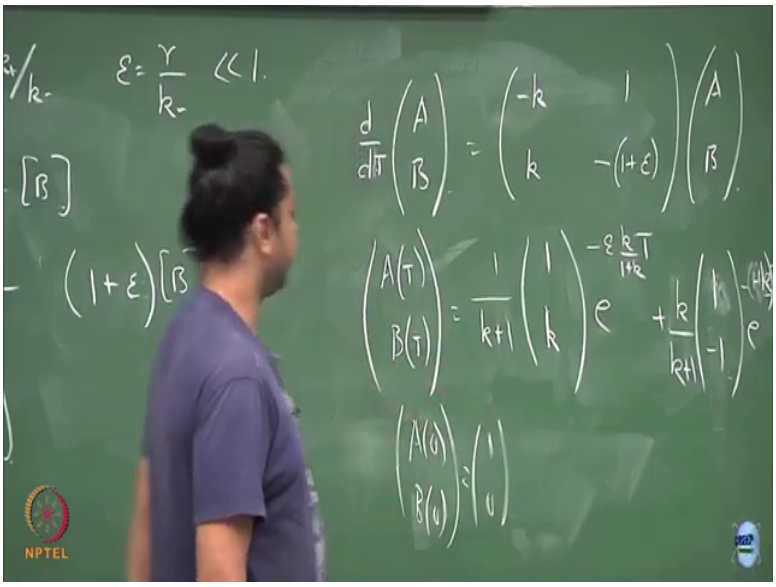
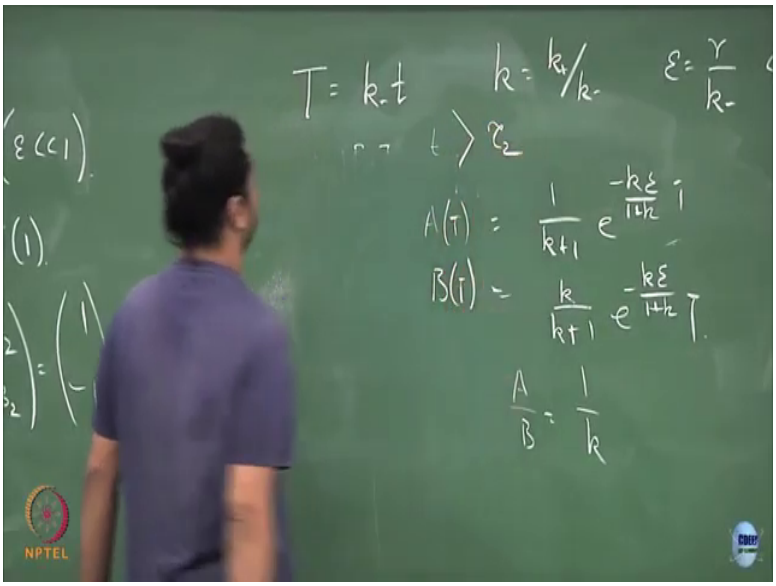


So, I had an initial condition that, A at 0 B at 0, this was 1 comma 0 and if I put that in then I to match with this A 1 and A 2; then I will get some solution for A 1 which is 1 by k plus 1 and something for A 2 which is k by k plus 1, ok. So, that is basically my final solution; once I have taken into account the initial conditions and everything. So, this is my final solution for A and B.

So, I have these two timescales right; let us say tau 1 is 1 by lambda 1 and tau 2 is 1 by lambda 2. So, 1 by 1 plus k, this is 1 plus k by epsilon k. So, when I am in a time regime where this where my time is greater than this tau 2 right; but smaller than this tau 1, in that case I can sort of drop this term, this exponential will not matter so much.



And what I will get for these concentrations of A's and B's is that, A T B T, A of T B of T is simply 1 by k plus 1 e to the power of minus k epsilon by 1 plus k t and k by k plus 1 e to the power minus k epsilon 1 plus k T, ok. So, this says is that very quickly after this time, this A and B come to a fixed ratio of each other.

So, this A T by B T is always this factor k right and then they continue to evolve in this fashion. So, they there is still a time dependence of course; but the relative ratios A divided by B is always fixed to 1 over k. Once your time t is greater than this tau 2 so, very quickly they come to an equilibrium amongst themselves and then they continue to evolve in the in some fashion.

So, that was what gave us this curve. So, this time the time that it takes for this A and B to reach equilibrium amongst themselves is this time tau 2 and after that they could continue in a

fixed ratio. And then to find the full time revolution you can of course, look at this full equation.

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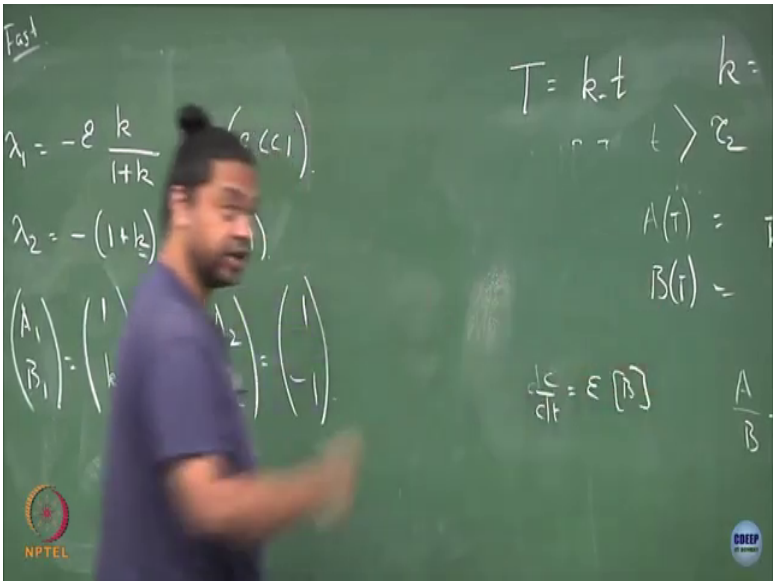

And once we have the time evolution of B you can also of course, solve for this time evolution of C; remember d c d t was nothing, but epsilon times the concentration of B which we have now anyway solved, ok. So, this sort of this gives us a way to quantify this concept of rapid equilibrium that we had. What do we mean by this slow and these fast timescales and after what time can I assume this equilibrium to a big reach; that is given by this time scale 1 by 1 plus k. And after and this long time 1 plus k by epsilon k the system will reach it two steady state.