Physics of Biological Systems
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Lecture – 06
Timescales in Biological Systems

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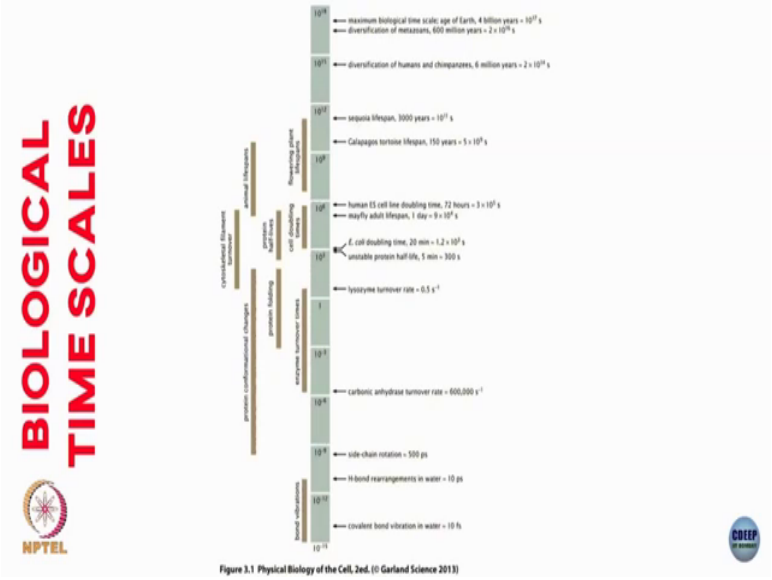

All right so, moving on from spatial scales, let us just quickly take a look at temporal scales. So, let us see. Again I cannot read most of these things. Over here is evolutionary timescale so, 10 to the power 15, 10 to the power of 18. So, this is diversification of humans and chimpanzees over there. You come down, this is 72 hours which is the cell line doubling time. This is an E coli doubling time of 20 minutes.

So, when that is basically the cell division time or the cell lifetime, protein half life sort of the order of minutes. This over here is the scale of around protein foldings. Let us see, these are

enzyme turnover rates which go from milliseconds to seconds and over here are very sort of chemical timescales sidechain rotation, hydrogen bond rearrangements and so on, covalent bond vibrations which occur in the scale of nanoseconds to pico seconds even femtoseconds I guess.

So, all of in principle all of these timescales taken together would constitute. Well, let us forget about evolution, but at least as far if I cut it off as the level of a cell this whole range of timescales constitute processes that are integral to the proper functioning of the cell. So, if the cell takes is in non equilibrium at some time scale over here and you are looking at processes which happen over nanoseconds and so on, we could use equilibrium approximations to deal with those processes.

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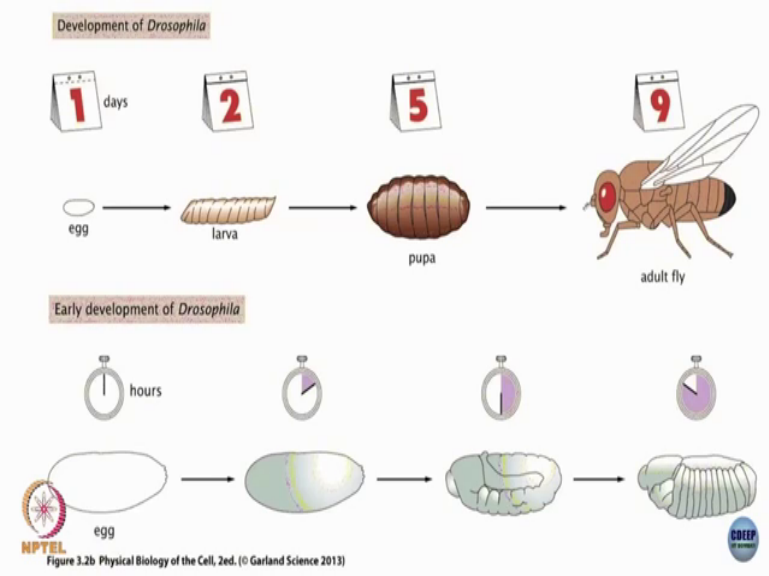

So, here are some examples of different time scales again taken from a random assortment of systems. So, here is drosophila development. Drosophila is the common fruit fly. It is again it is a model system in biology just like E coli; drosophila is another model system. So, you start from an egg, you go to a larva to a pupa to an adult fly. This whole process takes around 9 days, 9 to 10 days.

If you look at the early development when this egg is just sort of starting to differentiate, you are starting to get all these wings and this vertebrae divisions forming that takes place over a timescale of hours. So, this thing forms roughly over 10-11 hours and this whole development from the egg to the adult fly takes place over a period of days. So, these are completely different timescales and again the physics that you would use to describe these sort of processes would again be tend to be very different.

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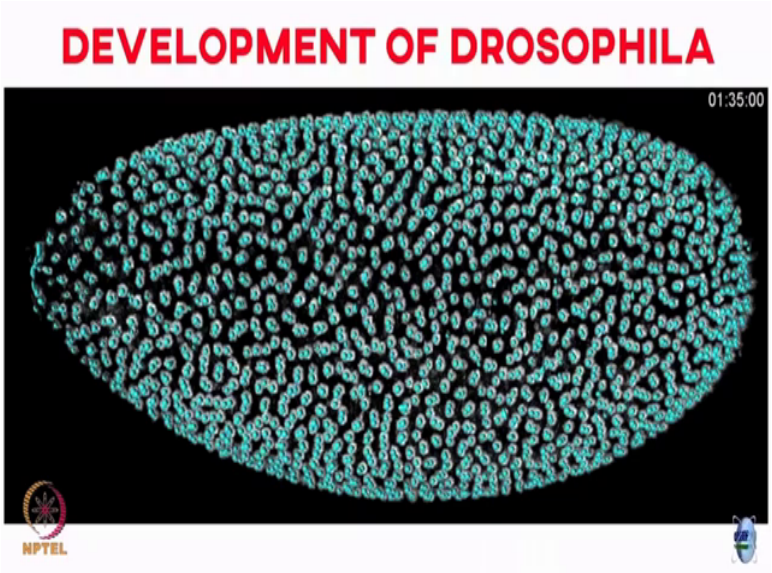

Here is a nice experimental movie which shows the development of drosophila. This particular one shows the early development. So, this is in this stage over here where you so, drosophila is slightly special in that. In this initial stage, you do not have cell divisions; you just have nuclei which are not separated by cell membranes. So, here is my drosophila embryo.

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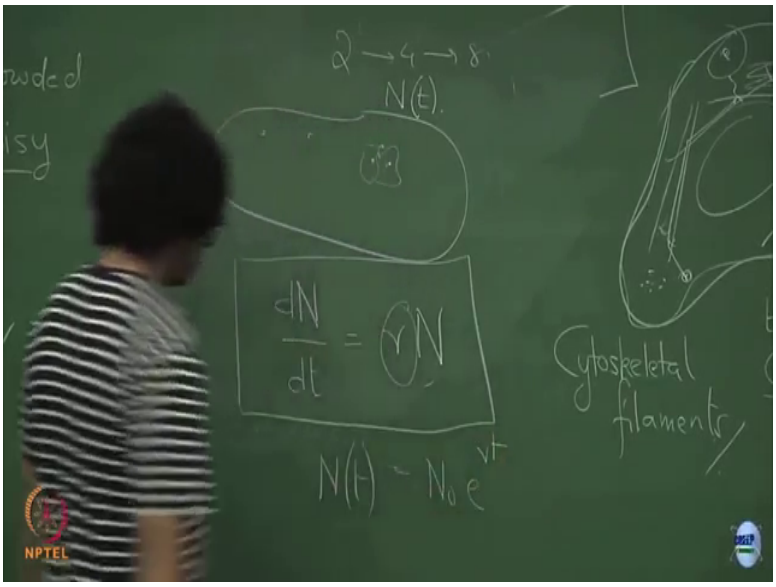

You have nuclei over here and these nuclei sort of divide. So, this one nuclei maybe becomes two nuclei, but there is no cell membrane surrounding this nuclear initially. After some point the cell membrane forms and you get cellularization.

So, this first video is in this stage where you just have these different nucleis which are dividing. So, this is at that stage. So, this is I think 1 hour 35 minutes past the fertilization of embroil. These blue things are individual nuclei. You that was a cell division cycle and you

will see that the number of nuclei has increased, the system gets denser and denser right. Also very interestingly you see that this cell division sort of propagates as a wave.

So, the color so, the colored the cells depending on when cell division was happening. So, at the time of cell division, they colored the cells by this magenta color and you will see that the cell division sort of progresses. So, this is one end this is called the anterior end of the embryo, that is the posterior end of the embryo. So, the cell divisions are wave sort of progresses from this anterior end to the posterior end and this every time the cell division happens, the number of nuclei is becomes twice what it was earlier.

So, this is one very nice example of what I meant when I said that this whole field of mathematical or quantitative biology has become possible due to this extremely difficult sophisticated and yet very illuminating experiments. So, here you can track each individual nuclei of this embryo right. This whole, this will become the whole organism. You have the positions; you have the velocities of each individual nuclei.

So, you could do a very microscopic level modeling in trying to understand what sort of processes are causing this cell division to happen oh sorry this development of the drosophila embryo to happen. So, that is the clock over there.

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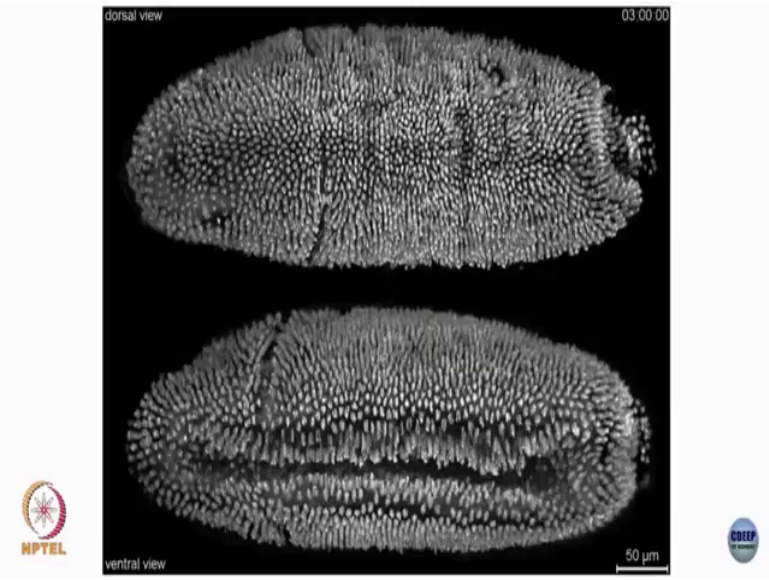

So, this is very early times. If you go to slightly later times, this is again I cannot see this is around the 3 hour mark I think and these are two different views the dorsal view and the ventral view of the same organism as a different shapes.

So, here is here, at this stage the cells have already formed these. Now these individual dots are the cells, they are no longer than nuclei. You have formed the cell membrane and as time progresses, you will see different features sort of starting to become clear within this embryo. So, you can see the segmentation patterns starting to form in this ventral view right.

So, over here this let it be play. This is the other ventral this is the dorsal view sorry where you see from the bottom and if you let it play go on to develop more. So, again in this case, you have exact information about each individual cell of this whole organism; the positions

the velocities is a function of time. You can see how these different cells flow from one point to another.

So, this is basically at roughly this larva this pupal stage rather no, not the pupal stage the larva stage. This is a very fascinating experiments relatively recent over the last 5-6 years where has been possible to sort of image each individual cell or each individual nuclei at that resolution and trying to understand what sort of processes are going on alright.

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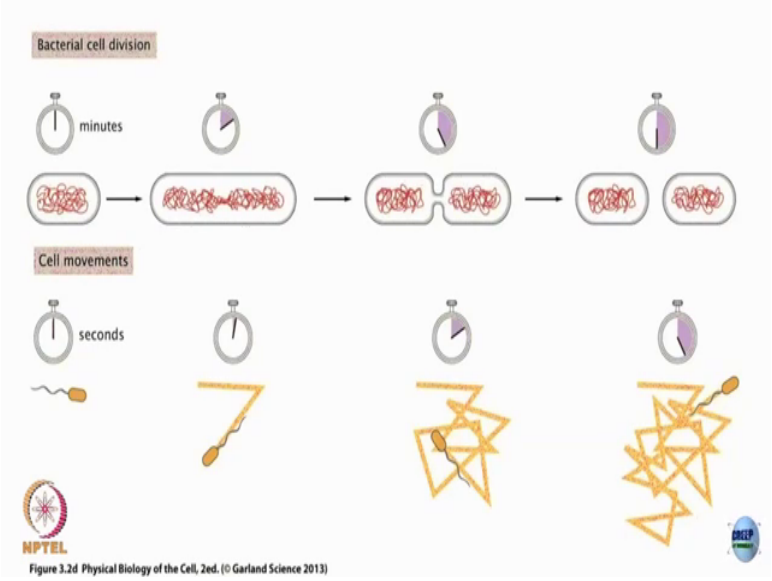

Coming back to this array of timescales: so, if you look at cell division, what time were you asking about, Samarth?

Student: Self assembly.

Self assembly, we will come to that. So, if you think about cell division like E coli cell division that takes place over a timescale of minutes. So, around 30 minutes is when the mother cell is going to divide into two daughter cells. If you look at cell movements, this E coli moving with the help of its flagella and this is what a typical trajectory of an E coli would look like that happens over a timescale of seconds.

So, it moves when it moves like this in a directed fashion, all the flagella are bunched up together. They move beating and synchronously, the cell moves. It reaches one point the flagella sort of let go of one another, it is sort of tumbles around for a bit until it chooses a new direction and again it moves in that direction. If we look at the tracks, it just looks like random walk trajectories and this happens this process happens over a time scale of seconds.

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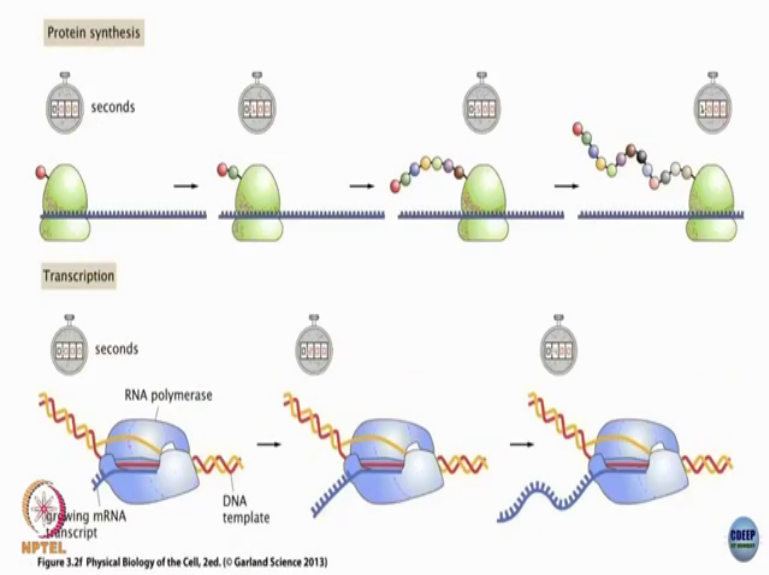

If you look at protein synthesis, that takes place over roughly a second. So, this is 0.1 seconds, 0.5 seconds one. So, this is the ribosome which comes and attaches to the mRNA. The transfer RNAs come and feed in the correct amino acids as the amino acids get fed in the protein gets better spit out and that happens over time scale of around a second rockly.

If you look at transcription, so RNA polymerase coming on to the DNA and producing the same RNA. This growing mRNA transcript that happens over point tenths of a second so, 0.4 seconds is what is given here, but roughly of that order.

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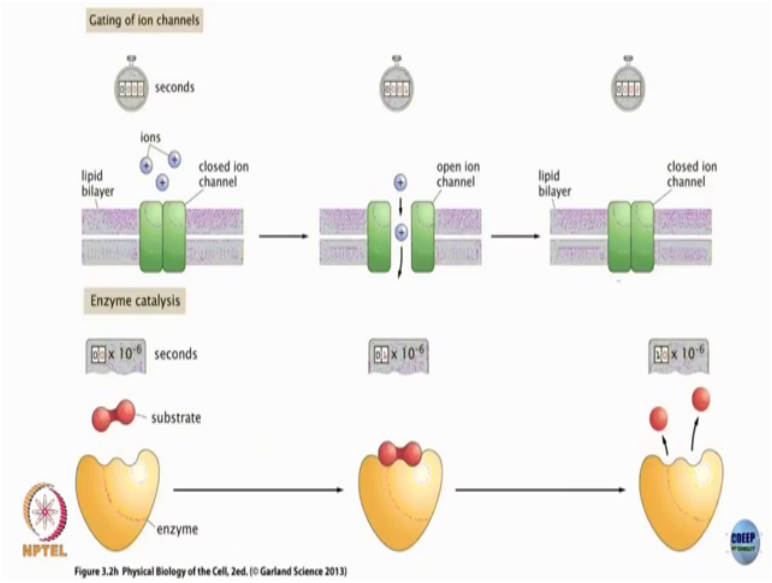

If you look at ion channels, remember ion channels are these objects which are embedded within this lipid bilayer. They open and close and when they are opened they allow ions to pass through that happens over a timescale of milliseconds; 0.001 seconds. So, this is very

fast process compared to these slower scale processes of synthesis and so on that we are talking about.

You could also talk about faster processes where you are leaving more getting more into the chemistry aspect of it. For example, enzyme catalysis that takes place over a time scale of around microseconds. So, both of these are proteins substrate and enzyme they come together to do whatever they are supposed to do and this process takes place roughly around microseconds.

It turns out, I do not have capsid assembly over here. I think capsid assembly typical time scales is roughly of the order of minutes. If I am not mistaken, I will check once more, but roughly I think of order of minutes of I thought I had it over here, but apparently I do not. And in fact, you can show that if you just took this protein subunits which make up this viral capsid and you let them be.

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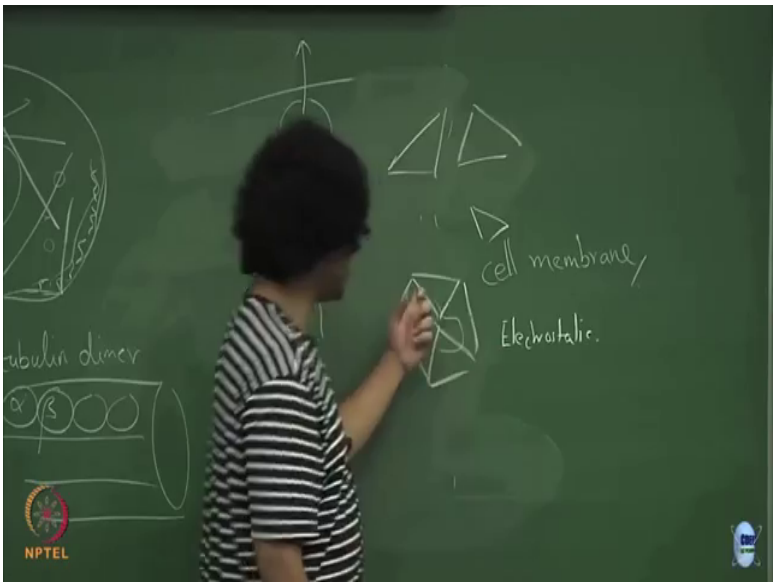

So, you take these protein subunits and you let you just put them together and you let they will also self assemble actually into and they will form whatever like a nice capsid like this. Turns out that the timescales of that are much slower and in order to get it to the biologically relevant timescales, you have to introduce this electrostatic forces.

So, if you introduce electrostatic forces between these charged proteins in this viral capsid proteins and the DNA that this capsid is going to encapsulate which is negatively charged. You can show that you will get to the right timescales roughly; this process of cell division.

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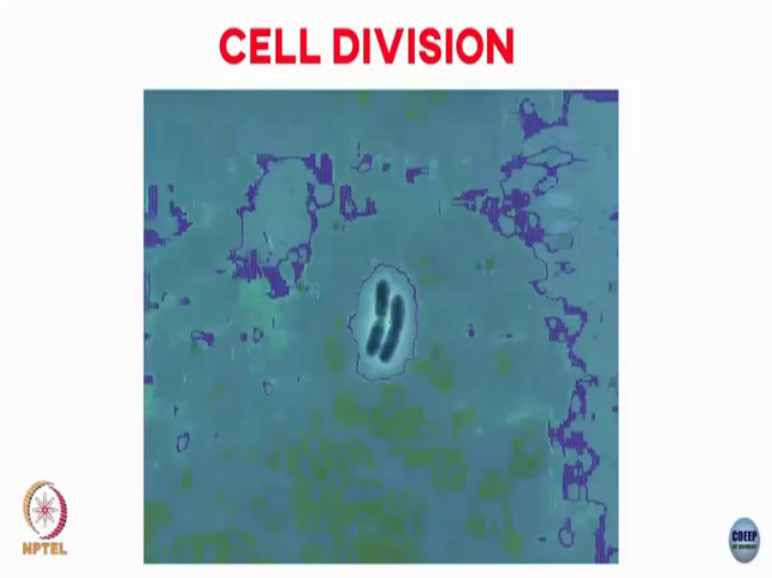

So, here is a movie again forgive the poor. So, here is a process colony of E coli cells dividing. It started off from two cells; they divide and divide and divide until it sort of fills the petri dish that you had.

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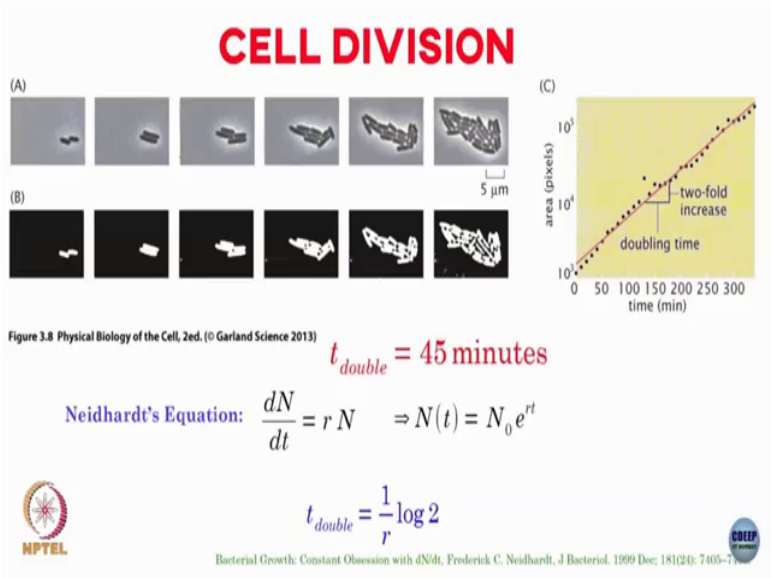

You can take the frames of this movie and you can analyze that and you can plot the area that is covered as a function of time. So, this is the; this is the frames of that movie, you sort of calculate what area is covered by these cells and you plot that area as a function of time. This x axis is time in minutes and here is the sort of plot that you get. You can calculate roughly a doubling time which is that how fast does this area dub double and from this plot, it comes to roughly around 45 minutes.

So, this is a sort of geometric growth right. You get you started off with 2 2 bacteria that becomes 4 that becomes 8 and so on. So, I could write if I would write an evolution equation for the number of bacteria, how that changes as a function of time. So, I have n number of bacteria and some time. Again I will try to be very naive and try to write the simplest thing

that I can and I will say that well let me say that dN dt will grow depending on how many bacteria you have to start off with right because its doubling.

So, let me say it grows as something like this r times N right. If I wrote an equation like this dN dt is equal to rN and I gave you the scurf of this experimental curve which says that my doubling time is roughly around 45 minutes. Could you estimate what sort of an r this implies, this data implies? How would you go about doing that? What is the solution of this equation? What is N of t? Exponential.

So, what is this r then? The doubling time. So, r is basically locked divided by the doubling time. So, you can try even if you do a very simple equation like this, you can try to say that well you can explain this data that I have that I observe in this experiment. If I provided, I take this rate to be locked to over this doubling time that I have observed. This is called line Howard situation, it is in this bacterial growth paper it is of course, a very naive model it is of course, at some point this model will fail. When will this model fail?

Student: Large number of.

When it when the numbers become very large and whatever agar or whatever food that you have put in the petri dish, it cannot sustain an infinitely growing colony. So, at some point this rate of growth must slow down right. So, it cannot keep growing like this.

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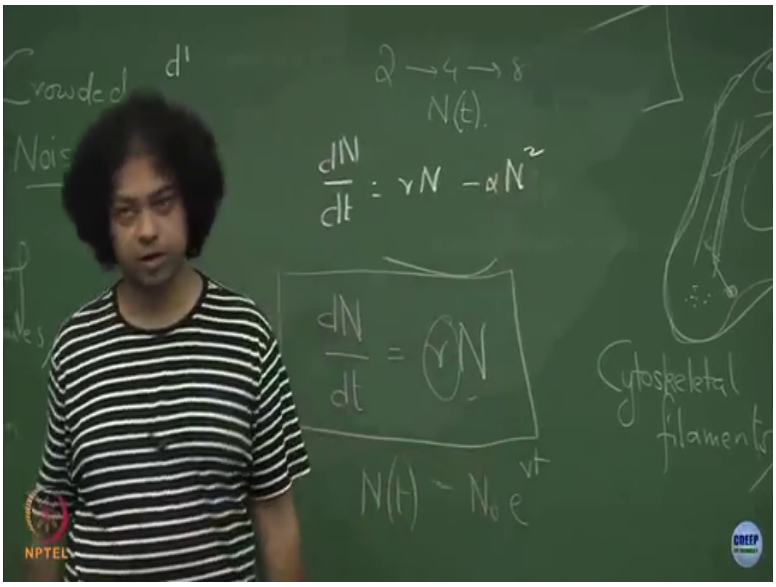

So, initial times it might grow very fast, but as you sort of reach the limits of the population that you can sustain that growth is necessarily has to slow down. Can I write down a simple equation that will correct for that? You have come across an equation like that? Yes, minus N square something, that is about it.

What is this sort of an equation?

Student: Logistic.

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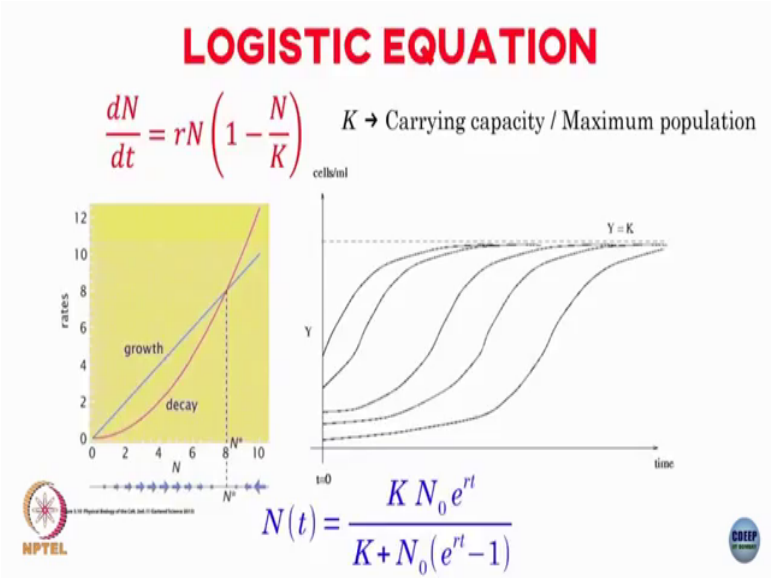

Logistic equation so, I can write down a logistic sort of growth model for this. Typically it is written like r N 1 minus N over K where K is called the carrying capacity or the maximum population that you can sustain right. So, basically when N reaches K, you will see that dN dt goes to 0. It will not grow any more. When N is much much smaller than K, then this dN dt is like rN which goes back to this Neidhardts equation. This is called the logistic equation and then you can see how this equation will look like.

So, if you look plot the number as a function of time, this is what will look like initially it will grow very fast, but then after some time after some time it will as it reaches the carrying capacity, the growth will first slow down and then entirely stop. This N of t will as t goes to infinity. This N will just tend to K. Talking from a non-linear perspective, this equation has

two fixed points. One fixed point is at 0 if you did not start off with any bacteria of course, you would remain at no bacteria.

But provided you started off with something so, there is an unstable fixed point t. The moment you perturb away from this fixed point, it will go to this stable fixed point which is this N star equal to K. So, that is the logistic equation, you can solve the logistic equation we are going to get N as a function of time and then try to see whether that fits your experimental data or not this is roughly. So, the basic idea is. So, this is what we will start off with. We will start off at looking at these biological processes growth, movement and so on.

So, from next class, I think we will start with diffusion and movement and we will try to see what is the sort of simplest model that we can write down. We will try to analyze that model and see what are the shortcomings of that in, what regimes are those model correct in what regimes are they not and then can we do anything better than this.

So, for example, this rN was the simplest possible thing that we could write. It works in a certain regime when number of cells is small, it will fail at a certain regime and the number reaches close to the carrying capacity and then we would need to readjust your model ok. So, that is the sort of spirit and it is a very trivial example of course. We will try to do slightly more complicated things as the course goes on.

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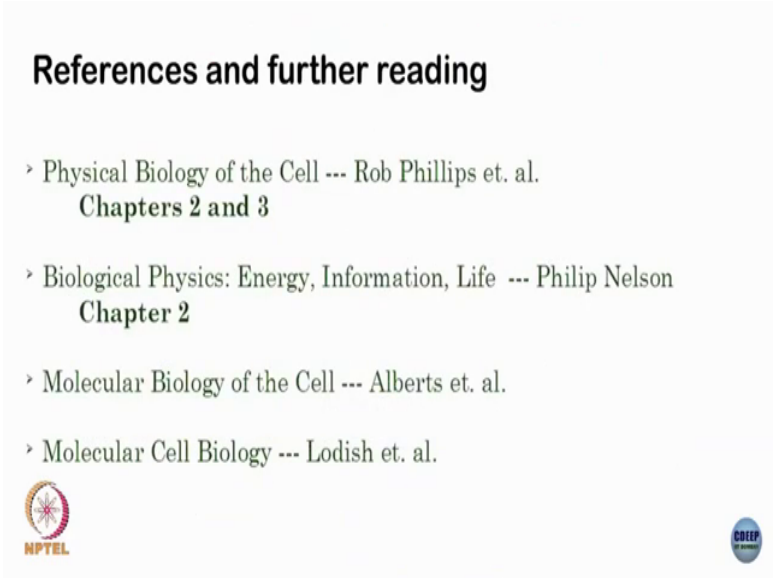

So, this sort of glossary of terms ah; what are the molecules, what are the numbers and so on. Those are roughly taken from these first two references Rob Phillips, chapters 2 and 3 and Nelson's chapter 2. If you are interested even more, these two books Albert's and Lodish; these are sort of the bible for molecular biology. These have all this information in a lot more lot greater detail and depth.

So, for those of you are interested, you can take a look at these books over a long period of time. These are really really thick books. So, I think, I will stop here today. I will start off with movement and diffusion starting with next class and how to do modeling of diffusive processes in biology. Good so, I will see you again on Tuesday then and we will sort of get into it properly.