Physics of Biological Systems
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Lecture - 58
Some common spatial patterns in biology

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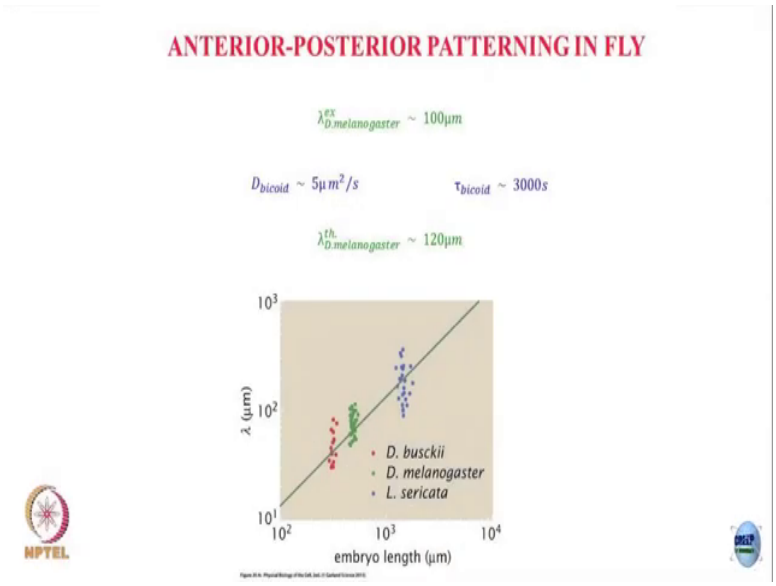

So, I this is sort of the source strength. So, that is the flux. So, it is like del c.

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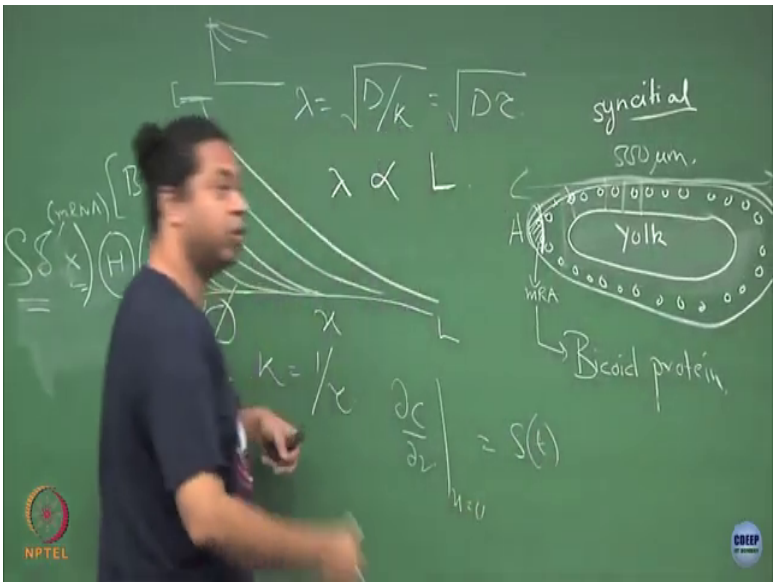

Student: Current.

Current; act at x equal to 0 yes. So, you are saying that you want to vary this current?

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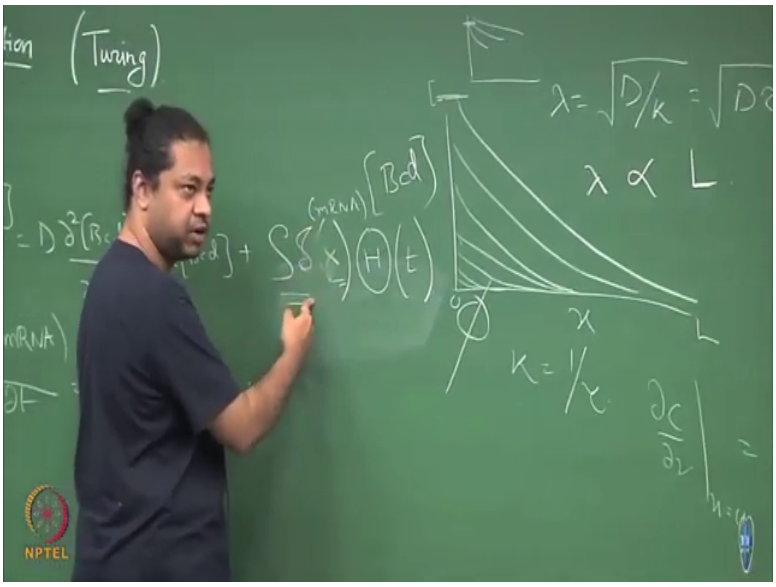

So, in one slide I had written. So, the thing is that, this is the correct formulation. This is the current which is why at x equal to 0 also the concentration will rise with time. But if you are just interested in the exponential profile, you could just say that I will normalize everything by the value at x 0; that could be different at different times, but whatever. So, if I normalize everything at 1 at x equal to 0, I would get things like you know, I would get sort of profiles which would evolve, keeping this at 1. It is a different way of seeing, but this is if you think about the physical process, this is the right equation to write down. There is a constant source at x equal to 0.

You would say that well, I could vary the source strength for example, that may be more m RNA is being transcribed at some time and less at some other time. So, the source is strength itself varies that would be a different, that would be an improvement on this model. But yeah it

is as far as I know there is an experimental data on the m RNA sort of transcription rates as a function of time. So, people just take it to be constant.

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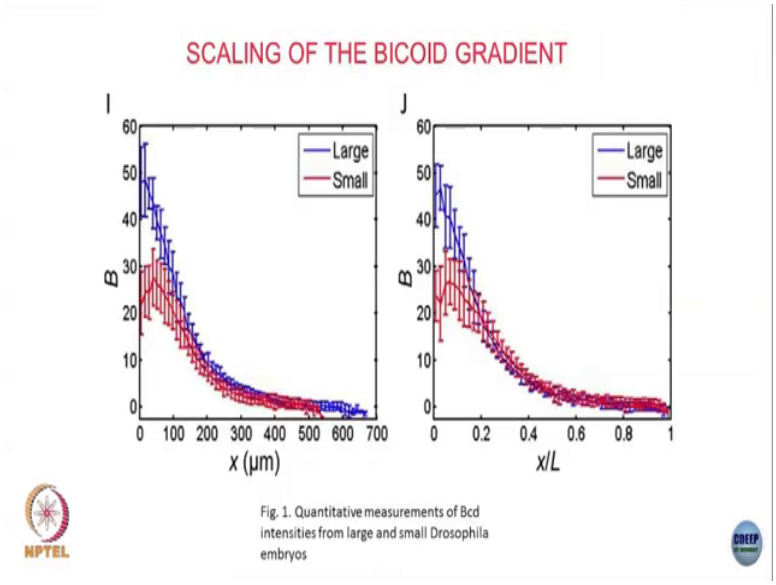

So, here so, that was across different species, three different species. This is the same species, but two embryos; one which has a largest embryo length simply because of random variations and one which have a smaller embryo length and again, you will see that the length the lambda sort of scale with the embryo length So, a larger m. So, if you just plot x. So, one embryo is around 500, the other is around 700. The lengths the lambdas are different which you can see. So, if you scale the x axis by the length of the embryo itself.

So, it goes from 0 to 1, then the two curves fall on each other; collapse on top of each other which basically tells you to this lambda again even within the single species, this lambda is proportional to L ok. So, this Bicoid gradient forms it is an exponential gradient, which we

sort of understand in this context. It scales with the embryo length which we do not understand how it does that ok. But this is the first step to this sort of to the developmental cascade that you get this matter this Bicoid, gradient the constant gradient profile of this Bicoid protein.

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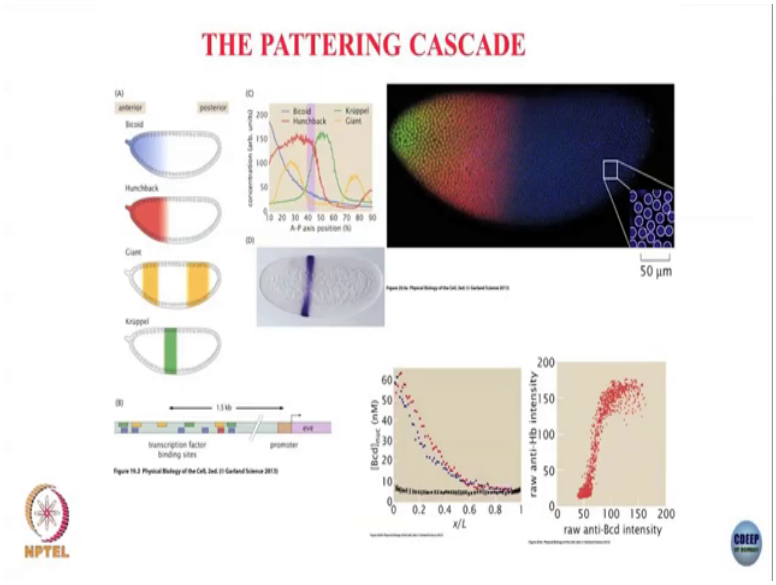

What does that do? Next ok, this is very bad; maybe I can show you. So, here is here is my Bicoid over here the top curve, top figure is Bicoid. It is the highest concentration of the anterior pole, the lowest concentration at the posterior pole. These are different these are these three are different downstream proteins that are expressed. Once the Bicoid concentration has sort of set in.

So, this is one protein called Hunchback, this is one protein called Giant, this is one protein called Kruppel and if you plot the intensities or the concentrations of this protein again along

the A-P axis, you will see that clearly there is a variation. So, this blue curve over here is the Bicoid right, it has an exponential profile. The Hunchback which is the red one over here is roughly constant until the certain level and then, it drops down and becomes 0.

The Kruppel has a peak somewhere in the middle of the embryo; this Giant has sort of two peaks; one here and one here. So, the idea is this that, once you have set in this Bicoid gradient, all of these other proteins respond to the Bicoid gradient and express in a particular way. So, as to give this sort of spatial patterns and then, it responds to these special patterns of these other downstream genes Hunchback, Giant Kruppel whatever. You will get different parts of this fly body developing into different organs; some will be abdominal, some will be wing, some will be head and so on ok.

There is this patterning cascade. So, this I am just showing a few there of course, many other proteins and so on; its a extremely complicated process, but this is the basic idea that once the Bicoid has set in that is the thing that controls all subsequent developmental processes and all other proteins respond to this Bicoid gradient level ok. So, for example, if you look at this so, this is just the Bicoid gradient profile, the two curves being from two sides of the embryo just as a consistently check.

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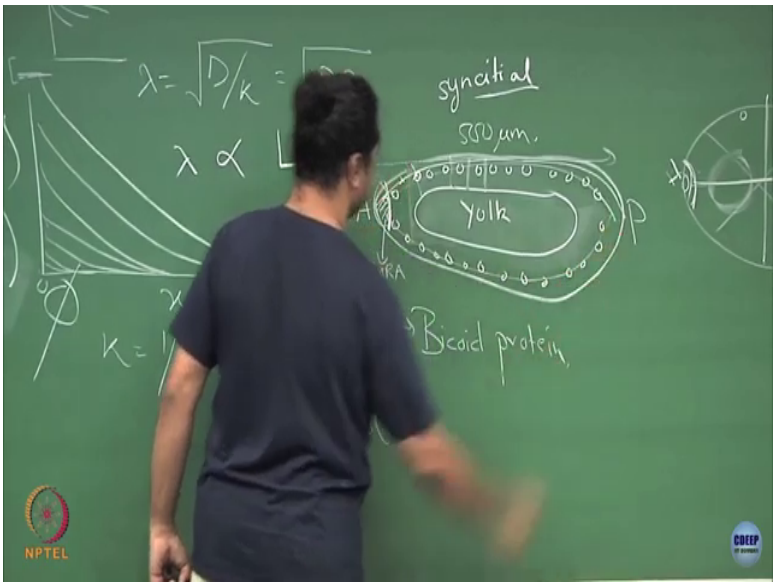

If you draw a line along this, the top half or you will draw a line along the bottom half, you get roughly similar sort of the red and the blue one do that thing ok. So, that is my Bicoid concentration profile as a function of the A-P axis along the A-P axis. So, I will just talk about one of these proteins in particular which is this Hunchback protein ok.

So, if you plot the Hunchback intensity against the Bicoid intensity, what it shows is that there is some sort of sigmoid response, in a very sharp sigmoidal response. When the Bicoid intensity is low, the Hunchback is low. Once the Bicoid intensity crosses some sort of a critical threshold, the Hunchback level sort of jumps up ok.

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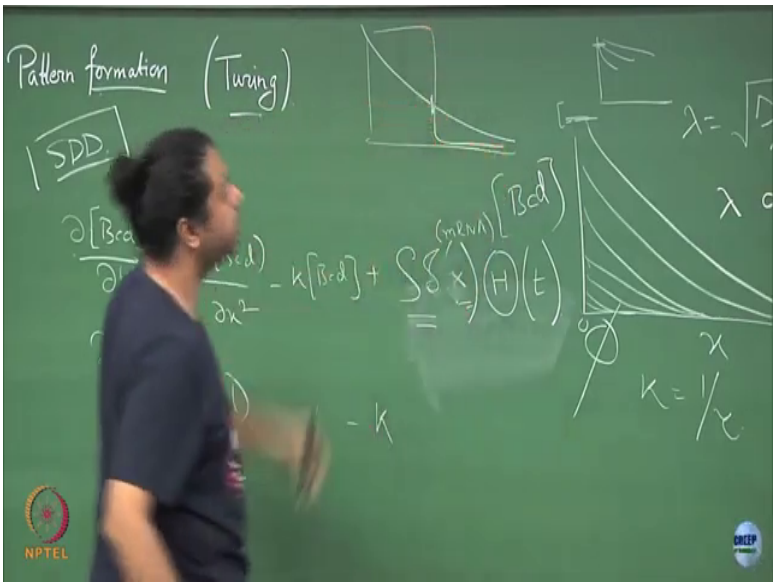

So, you can imagine that when I have a Bicoid gradient like this and let us say the critical threshold is somewhere over here, the Hunchback can respond to this. So, on this side the Bicoid intensity is greater than the critical density. So, I will have a high Hunchback; on this side the Bicoid intensity is lower than this critical intensity.

So, I will have a low Hunchback profile right and I will get a concentration which looks something like this. It is high on this anterior half; then, it sort of falls sharply and its low in the posterior half. How does how does this happen; how does this sort of control happen so that people have understood to a certain extent.

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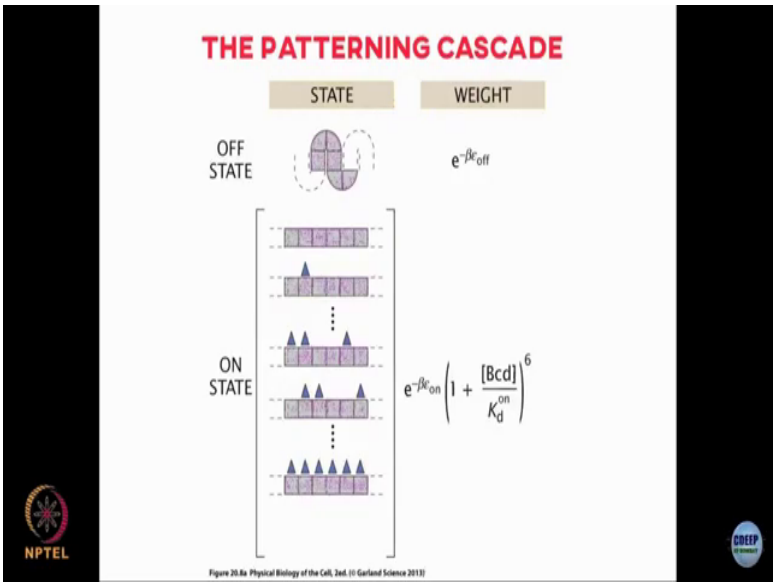

What Bicoid does is that, so you have the fly DNA right. So, you have the fly genome which has all these base pairs, let us say here is the gene that codes for Hunchback starting from here ok.

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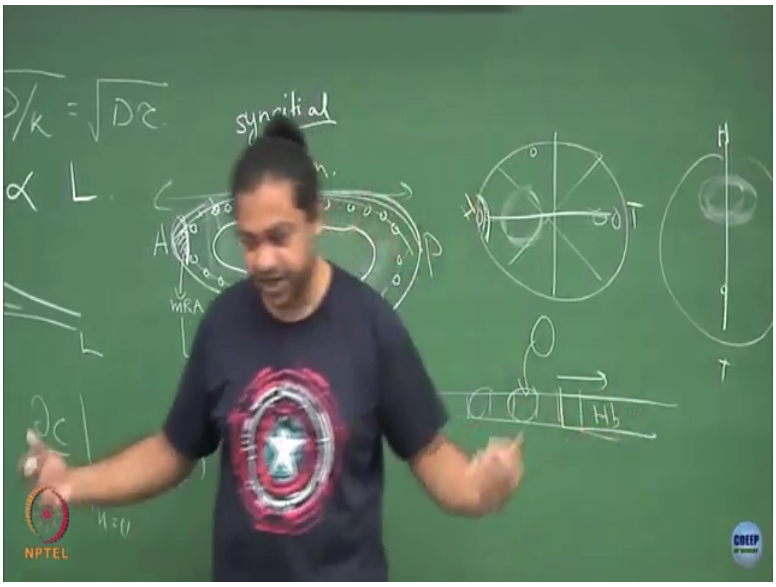

What Bicoid can do is that, it can come and bind to these sites upstream of the Hunchback gene and it regulates a transcription of this Hunchback gene itself. So, in particular its known that Bicoid has 6 binding sites, upstream of this Hunchback gene. So, 6 Bicoid proteins can come and bind and once it binds, the Hunchback starts expressing ok.

So, you can think of this if you go back, you can think of this in terms of the MWC, if you remember the Monod Wyman Changeux model. So, in the states and we it is a sort of a thing that when this DNA is in the off state, the Bicoid cannot bind and it has some particular weight, let us say if I some energy e naught epsilon naught.

In the on state, the Bicoids can come and bind and in particular there are 6 sort of binding sites. So, you can get any of these confirmations, no Bicoid bind bound 1 Bicoid bound, 3 2 bounds, 3 bound till all 6 bound and let us say this on state where this DNA is accessible to the

Bicoid that is some energy let us say epsilon on and then, you can write down those weights corresponding to this state the off state of these on states.

So, for example, if this is an energy epsilon off, this is the weight e to the power of minus beta epsilon off. If this has an energy epsilon on, this on state, it has as e to the power of minus beta epsilon on. And then because there are 6 sites, remember this was the concentration went as if you remember k d sort of hill function a first order.

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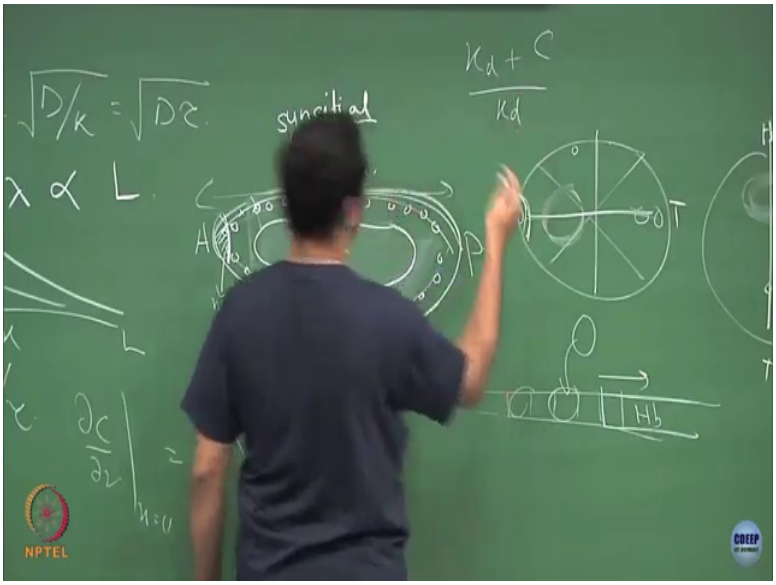

So, K d plus C by sort of k d. So, 1 plus C by K d; the concentration in this case being the concentration of Bicoid and K d being that the source equilibrium constant and because there are 6 sites and if I assume that these 6 sites are sort of independent of each other. So, I do a z to the power of n sort of the thing. So, there is a power of 6. So, given this sort of a thing you

can say that what is then the probability to find this DNA in the on state, what is the probability.

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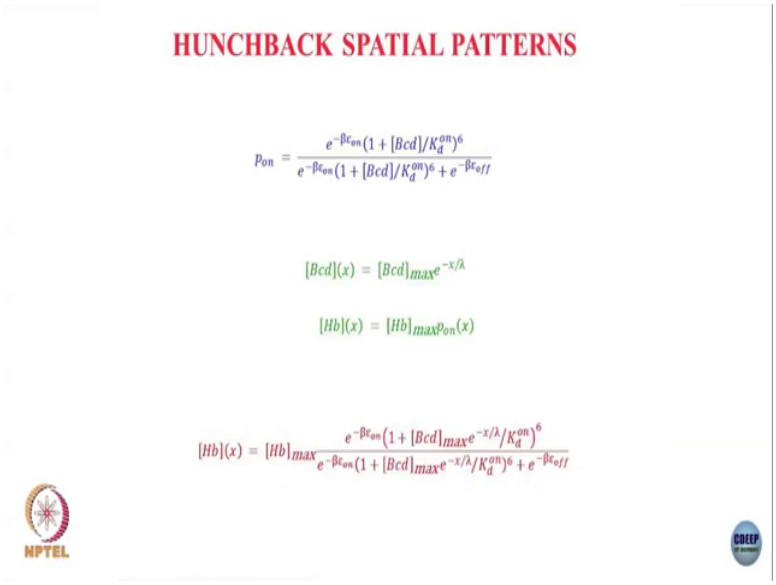

And therefore, the Hunchback to be expressed and then, that probability of being in the on state is just this divided by the whole partition function this on state plus the off state ok. So, this is just the kinetic part of it that given a Bicoid concentration, if I know that there is this sort of a 6 fold interaction of the Bicoid on this DNA, maybe I can write in probability of being in the on state which depends on the Bicoid concentration. If on top of that you say that well the Bicoid concentration I know from this SDD model is a function of position.

So, the Bicoid has this exponential sort of a profile and I put that n over here what I will get is that I will get a profile for this Hunchback protein itself, assuming that the Hunchback concentration is proportional to this on rate ok. So, I have this from the kinetics, I have this

Bicoid profile gradient profile from this SDD sort of a model. It is an exponential profile. If I put them both together, I will get a profile for this Hunchback protein itself and how does that look? So, this is if I just put back plug back everything, I put in the Bicoid exponential profile. So, this is how my Hunchback profile looks like as a function of x; x being the distance along the b axis ok.

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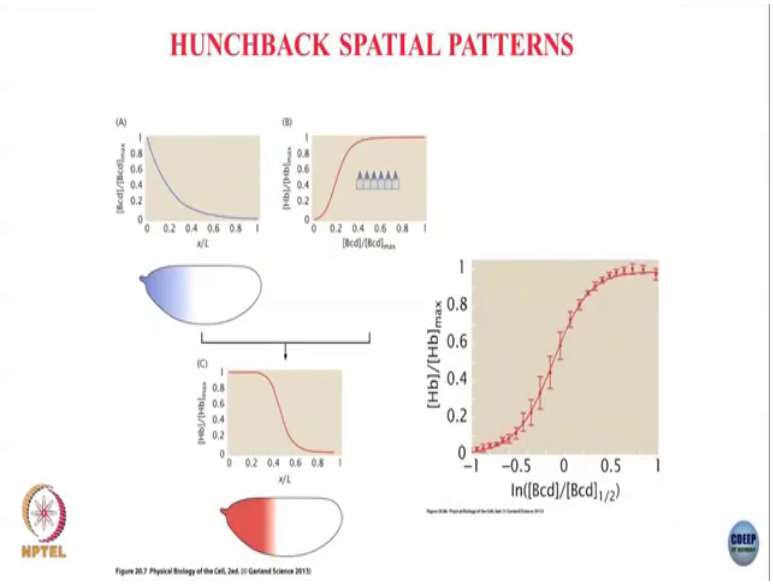

How does this curve look like? So, for example, if I take an exponential profile for the Bicoid, this is what my hunch Hunchback as a function of Bicoid concentration looks like and if; so, if I take this exponential profile here is how my Hunchback profile looks like ok. So, it looks exactly like this sigmoidal function as we expect. The sharpness of the sigmoidal function depends on the fact that you have this to the of power 6 sitting over here right. So, the higher this number, the sharper that sort of sigmoidal curve will appear.

So, this sort of a model which sort of bill takes in this SDD model, then this sort of a MWC model for the Bicoid interaction with the DNA; then, tells you how this Hunchback profile will look like in response to this Bicoid concentration profile and this is precisely well not precisely, but this is roughly what you see in experiments ok. It gets even the transition region sort of correct in that, if you look at these experimental graphs, this Hunchback actually falls Hunchback level falls very precisely at around the midpoint of the embryo.

So, it falls exactly around 50 percent of the embryo. It does not care what the embryo length is; but if you take a large embryo versus a small embryo, the Hunchback this transition will always happen very precisely at around 50 percent forty-nine point some percent. In fact, even that is a puzzle.

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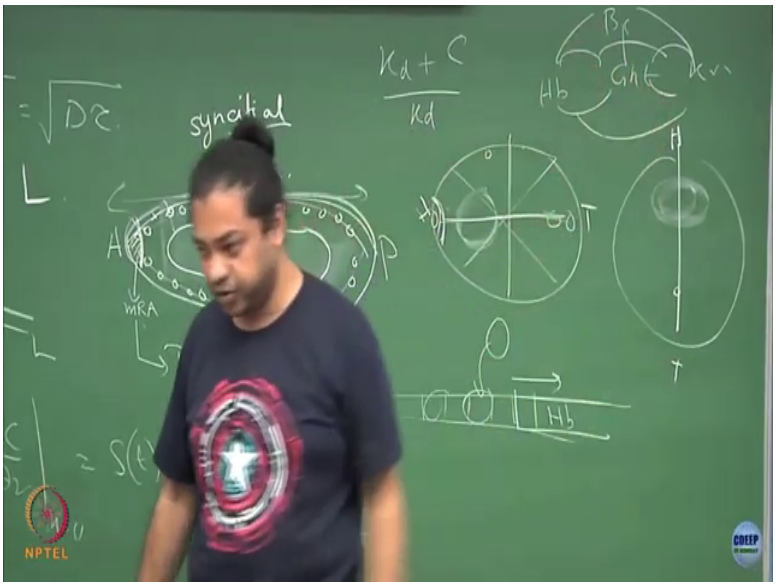

So, for example, if you look at different embryos and you were to plot this Bicoid concentration as a function of x; you get an exponential profile, let us say with some lambda equal to 100 microns on an average. So, different embryos, some will be 110, some will be 90 and so on. So, you will get a spread with a mean of around 100 let us say. But in all of these somehow this regulatory cycle is such that if you look at the Hunchback proof, if you look at the Hunchback concentration, the Hunchback will still precisely happen at 50 percent of the embryo length.

So, there is some sort of an error correction built in. The fly can very precisely regulate this domain boundary between the high Hunchback and the low Hunchback and there is a lot of work in trying to explain how this high level of precision of the Hunchback actually comes. So, this is just for one. Of course, you can do this for other proteins as well. In particular all of these proteins talk to one another.

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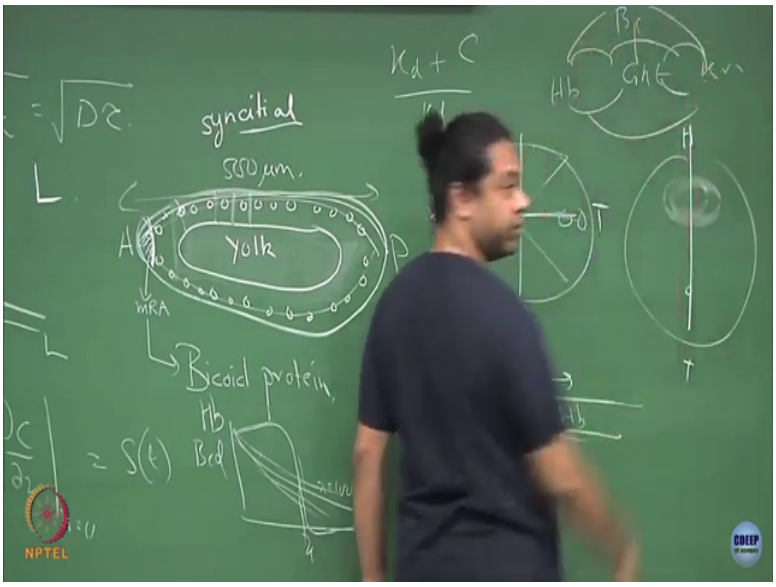

So, all this Hunchback, Giant, Kruppel; they all have they all join Kruppel, Bicoid. So, they all talk to each other and Bicoid talks to every one of them. So, you have this very complicated network of chemical kinetics. So, this is our chemical kinetics networks and on top of these, these things can diffuse to form some sort of the gradients that you see. And there have been models like this which have actually done very well in explaining the observed radiance of all of these or many of these proteins simultaneously.

So, this was for drosophila. Let me now switch gears to a slightly more general model, which is to say that how do I if I have a complex network like this of chemical reactions and then, I imagine that these species themselves are diffusing; how do I generally think about genetically think about patterns that form.

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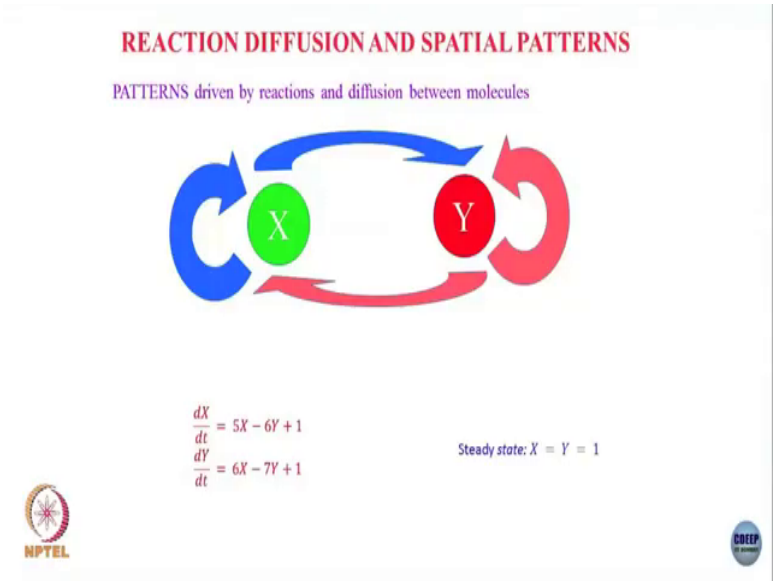

So, this was very simple case of a pattern a high low sort of a thing, but you can have more complicated patterns that form and then, how do I think about cases such as that.