Introduction to Dynamical Models in Biology

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Lecture 22
Modeling Transcriptional Circuits - 1

Hello, welcome to module 4 of 4th week of our course on Interaction to dynamical models in biology. In this module we will try to make a mathematical model using ordinary differential equation for a small genetic circuit. Let us first look into the genetic model that we will look today.

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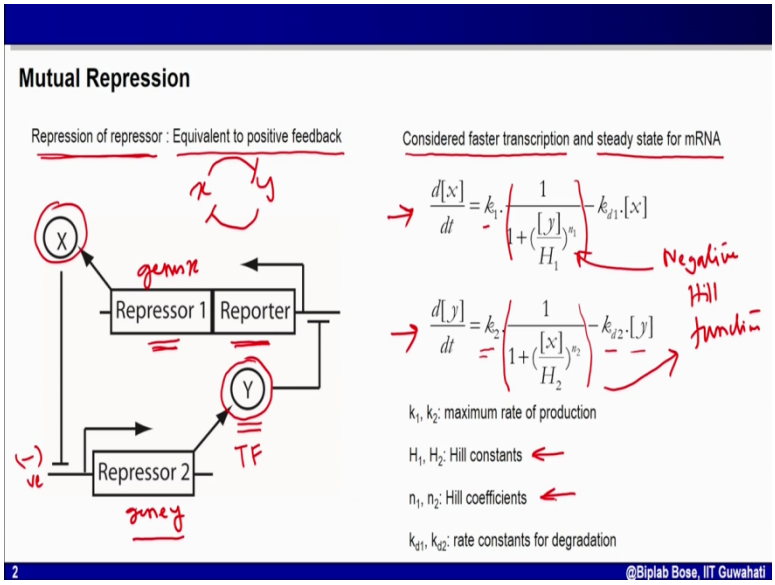

Here this circuit is made of 2 genes, suppose the first gene is the Gene X and the other gene is Gene Y. Gene X give rise to protein X shown in the circle and these X itself is a transcription factor and that transcription factor X controls expression of protein Y from gene Y and the control is negative as you can see we (())(1:23). So essentially X inhibits expression of Y. Y itself is a transcription factor, which inhibits expression of X. It goes and buy the promoters of X and inhibits expression of X.

So what we have we have two transcription factor X and Y each of them have their independent promoters and each of them inhibits each other, so each I simply write it down essentially if I

have X and Y. Y inhibits X and X inhibits Y. In a diagram shown here, if you notice we have shown a reporter gene fused with repressor 1. Repressor 1 is nothing but gene X. Now many time to do an experiment based on genetic network we require reported network like GAP to give us an estimate of level explanation.

So the small network that I have drawn here has been actually tried and equalize and those people who have created this synthetic network equally they had a reporter fuse with protein X or gene X, so X is expressed as a GFP type protein, so that they can track how much X have produced by imaging of (())(2:49). Even if we forget about this GFP we can still understand and analyze the behavior of the system.

In essence this system is made up of mutual repression, X is repressing Y and Y is repressing X, so in other words as there is mutual repression so there is repressor of repression. Y is repressor of X and X is repressor of Y, so it is equivalent to have a positive feedback. So now we want to understand the dynamic behavior of this system and we will create a ODE base model. And if you remember we have create a simple ODE base model. One assumption that I will make here to simplify your model is that the transcription rate I very fast and that's why the mRNA reaches the steady state much before the protein can reach steady state.

So the assumption that I am making is I am coinsuring fastest transcription and that's leads to steady state for mRNA. Once I have made this assumptions that means I don't have to write an ODE for mRNA for X and mRNA of Y because mRNA of X and mRNA of Y has all already reached the steady state at very early time point.

So I will have only two ordinary differential equation one for protein X and I have another ODE for Y. So if you remember we discussed in a particular module how to create ODE for transcriptional circuit, we have discussed this aspect that many a times we can consider transcription to be very fast and we can simply delete the ODE for that. And we can combine both transcription and transmission together to make a clubbed equation that's what I am doing here. So DXDT the first ODE that I have that is the rate of change of protein X concentration is equal to K1 into 1 by 1 plus Y divided by H1 to the power n.

So what I have considered here I have considered a negative Hill function. Because Y is inhibiting X and usually these type of inhibitions are non linear and follow sigmoid behavior and

if you remember the negative or inverse Hill function is very good option to model this type of system. So what I have used here I have used a inverse Hill function to represent the inhibitory effect of Y. Next term in the ODE is minus KD1 into X. KD1 is rate constant to degradation of X.

So what I have in general for DXDT the first term is production K1 into the Hill from negative Hill function minus KD1 into X. the same thing is for Y I have DYDT, rate of change in concentration in protein Y, remember I am not writing down a ODE for mRNA for Y separately I am simply writing the ODE for protein Y. So rate of concentration of Y protein is K2 the maximum rate constant for production into a Hill function which is again a negative hill function with X as a controller. So what I have 1 by 1 plus X divided H2 to the power of n2. So that will control the rate of production of K1 in a sigmoidal fashion or a inverse sig model fashion minus KD2 into Y. So if I just brief what I have used I have used inverse Hill function for both the ODE so that I can have negative control over the production of X and Y in a non linear sigmoidal fashion and the second term in each ODE is nothing but fast forward degradation, here H1 and H2 are Hill constant and N1 and N2 are hill coefficient. So this is my model and I want to analyze this model to understand the behavior of the system. Before I jump to it let us simplify the model a bit further so it will be easy for us to analyze in this class.

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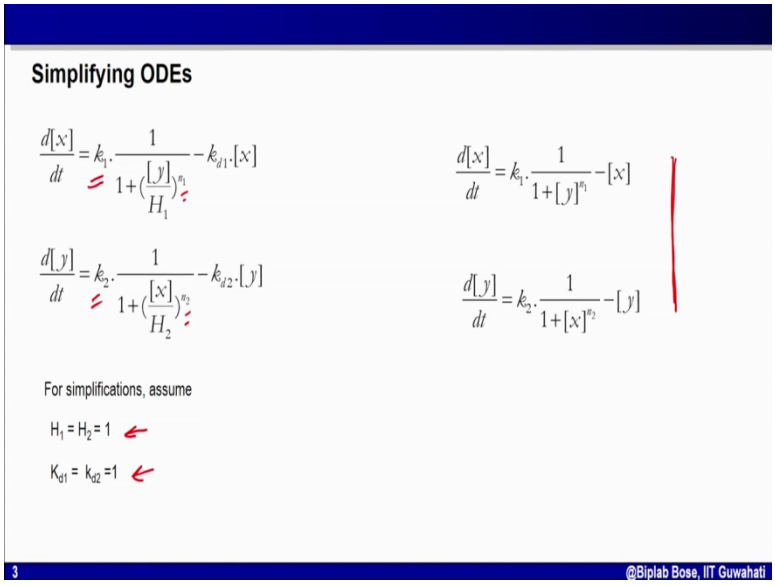

See I want to understand the effect of rate of production K1 and K2, there is maximum rate of production to protein and effect of a Hill coefficient like N1 and N2. So what I have considered to simplify this problem that I have considered H1 and h2 both equal to one and KD1 and KD2 both equal to 1, essentially you can normalize all your equation with respect to degradation and Hill constant that will simplify your problem.

So if I consider the H the Hill constant equal to 1 and K1 and KD 2 equal to 1, I get the equations here. You may have considered some other value of H1 and H2 and KD1, KD2. That will not affect the way we analyze the system, the techniques that we use will remain same only thing you have to do more is numerical calculation nothing more than that. So I have removed H1, H2 and KD1 and KD2 considering 1 and high up this two simplifying ODE 1 and 2.

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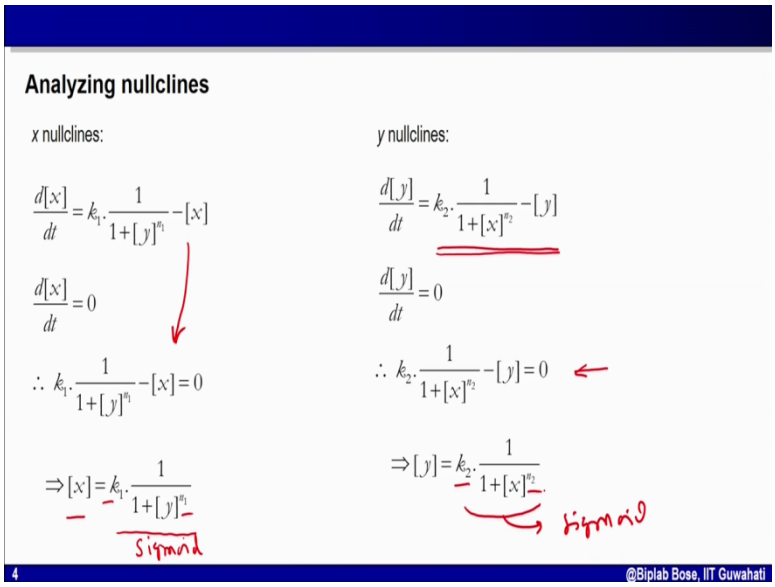

Now I want to analyze this system of ODE. If you remember we can analyze the system of ODE manually the first thing I will do here I will try to understand the behavior of this system, this system using phase plane analysis. To start a phase plane analysis you should have a phase plane drawn so here I have two variables X and Y and then I will plot the nullclines. So let us first analyze the nullclines of this system, so first get the X nullcline, how do I get the X nullclines? The ODE for X is DXDT equal to K1 into 1 by 1 plus Y to the power N1 minus X. This is the ODE for X, so I will put DXDT is equal to 0 to get the nullcline once DXDT is equal to 0 then I that K1 into 1 plus Y to the power N1 minus X equal to 0 from this I am getting this one.

So once I have this then I can separate out the X and Y on the both side of the equal to sign that's what I have done here, so I have X equal to K1 into 1 by 1 plus Y to the power N1, obviously this is a sigmoid function you can easily understand this is a negative sigmoid function. So now I will look at Y nullclines, for getting Y nullclines what I have to do? I will take that ODE for Y so that's what I have taken here the second ODE, then I have to make DYDT is equal to 0 that's what I have done I make DYDT is equal to 0 then this terms will be equal to 0, so K2 into 1 by 1 plus X to the power N2 minus Y equal to 0.

So again I will separate out X and Y on both side of the equal to sign so I get the Y equal to K2 into 1 by 1 plus X to the power N2, again this one is a sigmoid function. So now I have two equations X equal to something and Y equal to something this is X nullcline and Y nullcline so I will draw the phase plane plot. Now remember in this two equations K1 and N1, K2 and N2 are parameters that means to draw this plot I should have some numerical values for K1, K2 and N1, N2.

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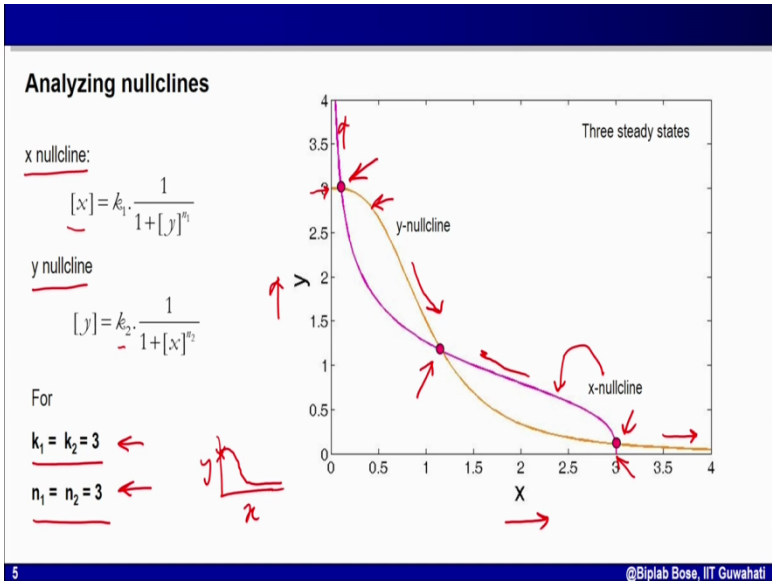

Let us try this, what I have drawn here in this screen X on the horizontal axis Y on the vertical axis so this is my phase plane in this plane I will draw the nullcline for X and Y. As I have said I have to take a numerical value for K1, K2 and N1, N2. I have taken that value. K1, K2 I have taken is equal to 3, N1 and N2 also I have taken as 3. My nullclines are given here my X nullclines are given here my Y nullclines are this one. Let us try with Y nullcline, Y nullcline is

equal to K2 into 1 by 1 plus X to the power so obviously it is a negative sigmoid function having a behavior like this X versus Y if I plot it should fall like this. So it will be negative sigmoid or inverse sigmoid and here it will intersect the Y axis.

So when X is equal to 0, Y is equal to K2, so here K2 is 3 so I can see here this yellow line, this yellow line is my Y nullcline and that is intersecting the vertical axis at 3. So that point X equal to 0 and value of Y is 3. And then this nullcline follows a sigmoid fall with accentor here at the end. For X nullcline the graph the plot will be just opposite, when Y equal to 0, the X equal to K1 and in k1 is equal to 3. So that means this pink line I have drawn here is the X nullcline and that intersects the horizontal axis at K1 equal to 3 and then it goes sigmoidually and here I have the accentors.

So I have two sigmoidal thing both are in inverse but in opposite direction and you can see they are intersecting at 3 position as I have marked by red dot. If you remember intersection of two nullcline that is intersection of X and Y nullcline are nothing but the steady states so that means when K1 and K2 is equal to 3 and N1, N2 is equal to 3 I have three steady states because the nullcline have intersected at three position shown by this red dots. Now let us change the value of K1, K2 and N1 and N2 to see what happen to the steady states.

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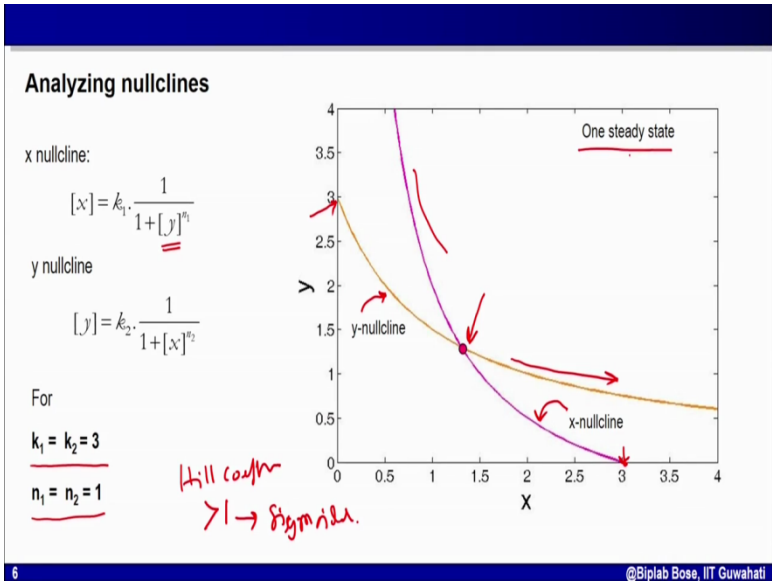

What I have done I have K1, K2 is equal to 3 but I have changed N1 and N2 to 1, if you remember in Hill function N1 is the Hill function and N2 is the Hill coefficient. If I have Hill coefficient bigger than Hill coefficient bigger than 1 then only I will get sigmoidal behavior, otherwise I will get a hyperbolic behavior. So here N1 and N2 the Hill coefficients are not bigger than 1 that means I will not get a sigmoidal behavior rather it will be the hyperbolic behavior and when X is equal to 0 Y will be equal to K2 that means this is my Y nullcline the yellow one, so when X is equal to 0 it is intersecting at Y equal to 3 and as you can see this is not a sigmoid this is a Y nullcline in a hyperbolic one.

Similarly X nullcline is pink on and it is also hyperbolic and it is intersecting the horizontal axis at 3 because when y is equal to 0, X is equal to K1. So K1 is 3 this will intersect at this position. So I have two hyperbolic cars and you can see they are intersecting only at one position so that is my steady state for this system that means when N1 and N2 is equal to 1 this system has only one steady states.

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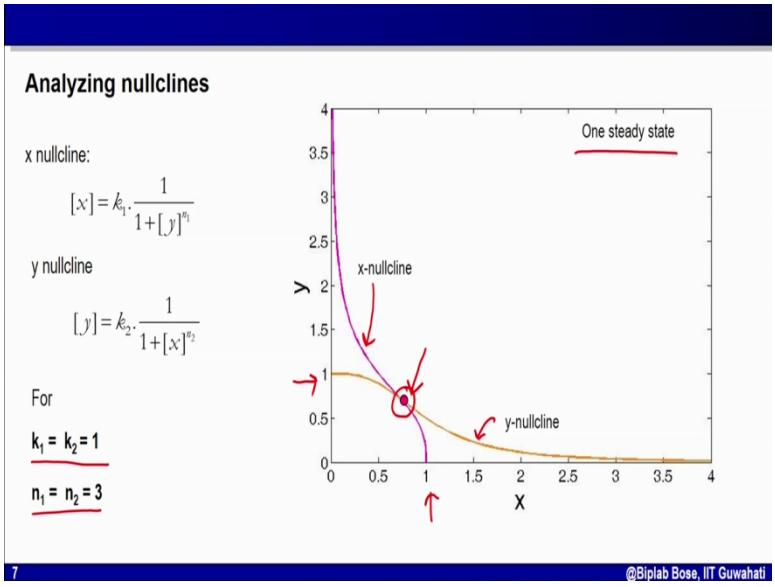

Let us change the value further, now I have kept N1 and N2 equal to 3 that means I will get sigmoidal cars for nullcline but we have change K1 and K2 equal to 1 that means the rate of production has been reduce, so when you change the rate of production of the system what will happen the intersection point on horizontal and vertical axis will change so, now they are one not

3 anymore but Y nullcline is still sigmoidal one negative sigmoid one and x nullcline is inverse sigmoid one.

And as you can see in the car they graph they are intersecting at only at one point shown by these red dots that means these systems has only one steady states, so if I in the last stage I have shown if I reduce the system for non linearity for a sigmoid to the hyperbolic one I get one steady state, if I reduce the rate of production of proteins then also I get one steady state. When both the rate of the production of the protein and the sigmoid lace of non linearity of the system throughout the promoter's matches I get three intersections or three steady states.

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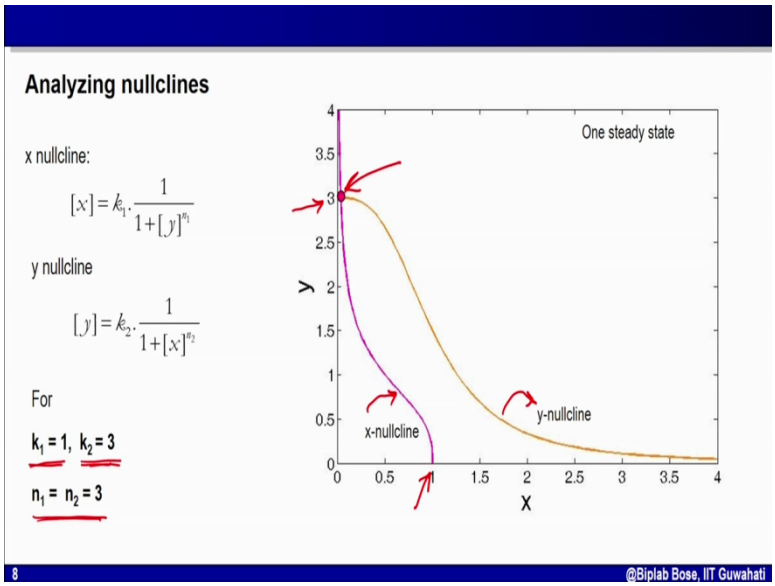

Let us consider a situation where one promoter is more active or one protein is produce more than other, so in that case K1 and K2 should not be equal, so I consider K1 equal to 1 and K2 equal to 3 that means Y is producing more than X and I have considered the non linearity of the promoters as sigmoidal one with N1 and N2 equal to 3, so if I do the nullcline this is my Y nullcline the yellow one it is a sigmoidal with a intersection on the vertical axis at 3 because K2 is equal to 3. For the X nullcline the pink line that is the sigmoidal one but it will intersect at 1 with the horizontal axis.

Now as you can see in this plot there is only one point of intersection between X and Y nullcline and that is shown by this red dot, that means I have a unbalanced system both the promoters are

following a sigmoidal inhibition, non linear inhibition but one protein is producing more because may be of the promoter activity ribosome binding activity, so one protein Y is producing more than the other t a higher rate than the other one. Then gain I don't get the three steady case but rather I get only one stead state.

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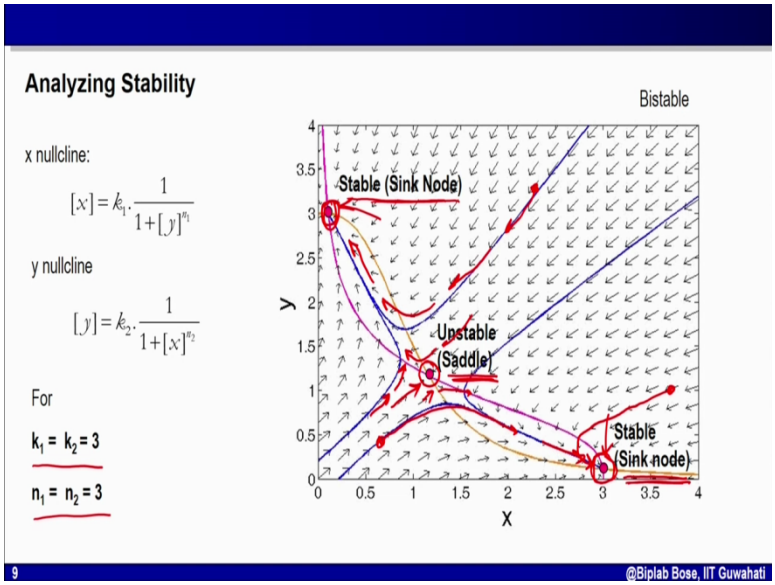

Now till now I have drawn only the nullclines, obviously in phase plane analysis I have to draw the tragic trees and portraits and that's what I have already done here. So this one is for the phase portrait for the system when your K1, K2 or 3 your both are equally producing the higher rate and N1 and N3 are 3 that means both of them have the sigmoidal control. I have three intersection point shown by this red dots, if you follow this arrow you can easily see if I start somewhere here I will follow this arrow and eventually collapse on this steady states. So all arrows near these steady states near 3 is actually collapsing at that point so that's why it is a Stable Sink Node.

Same behavior happen where I have another steady state near X equal to 3 as shown here by red dot, if you start from anywhere suppose here and then you follow this and then you collapse here, if you start somewhere here then you follow this and collapse somewhere here on the steady state. So again this steady state is a stable one and Sink Node. So I have three steady state two of them is stable Sink Node, what about the third one? This is my third steady step and as you can see these have the saddle structure because the trajectories here goes towards it and then

move away. Trajectories here goes towards it and then move away. If you start from here you go towards it and then move away. So that means this one is a saddle point. This one is a saddle point. So I have two Sink Node and one saddle points which are unstable.

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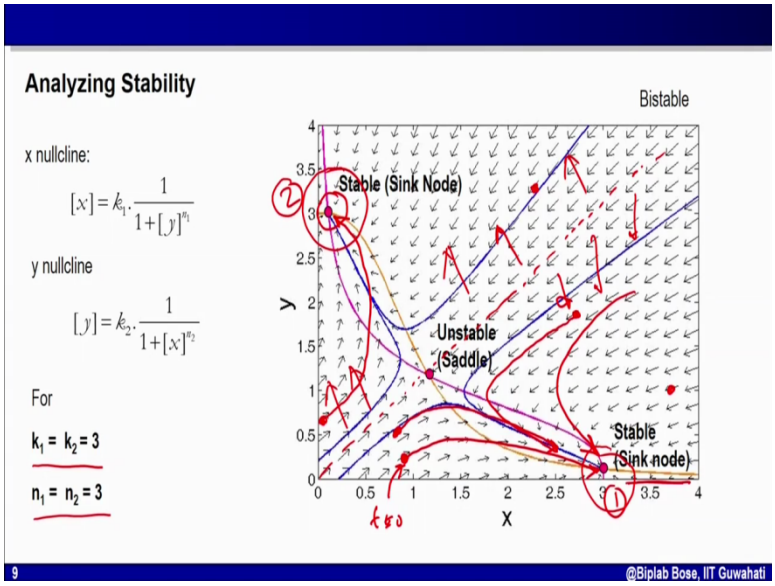

Now if you have this type of system then what will be the behavior of the population of cell, let us is analyzes that. So if I have a population of sale with some sale having X and Y at T equal to 0 this is T equal to 0 this is my position of some cell. So as time will progress this cells will move towards this steady stage. I may have another few cells at T equal to 0 they were here, they will also with time collapse here. You may have some cells T equal to 0 with initial condition where X and Y values are like this at T equal to 0 they will follow this path and they will collapse. Whereas if you have some cells with T equal to 0 here they will follow this path and collapse with the other steady state.

You can see I can simply draw a simple line like this. Cells in this region will collapse to this steady states. Let us say steady state one, whereas all the cell which are present here in this region at T equal to 0 will collapse at the second steady state here. So that means initially suppose I a unimodal distribution of protein X and Y then if I allow the system to progress eventually the population of sale will divert in two population, one population will go to the stable steady state the Sink Node one and the other population will go to the other stable steady state two. So I will get a bimodal distribution.

That means this simple genetic circuit made up of X and Y who are repressing each other can give rise to bimodal expression of X and Y starting from a unimodel system. Given that the value of K1, K2 and N1, N2 are matching properly.

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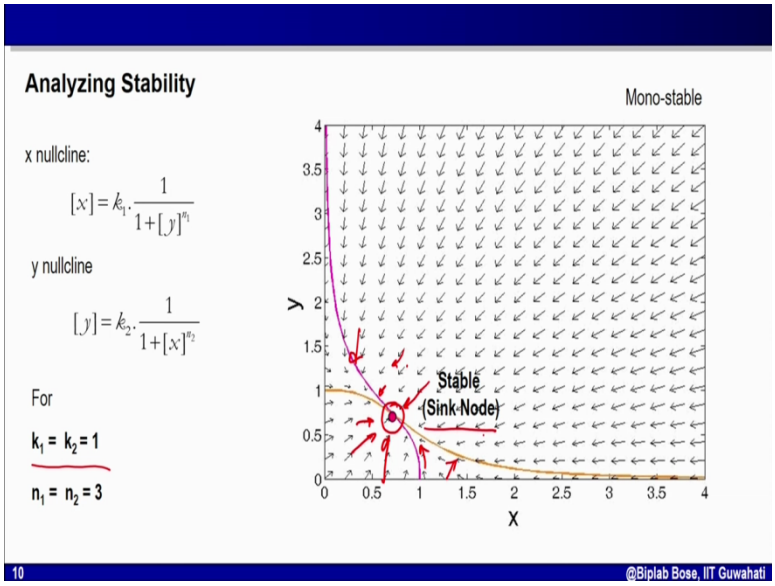

Let's see I have changed K1, K2 what I have done? Now I have reduce the rate of production for both the protein now you can easily see these are the nullcline the pink and yellow line that we have drawn the phase portrait is drawn here with all the arrows, the intersection points the steady states is the red one. You can see that all arrows are actually collapsing at the steady sates. So this steady states is a Sink Node. So in this case if the rate of production of K2 and K1 is equal to 1 which is less than in the previous case where they were three then I get only one steady state and that is a Sink Node and a stable one. That means if I start with a unimodal system I still get a unimodal population of cells.

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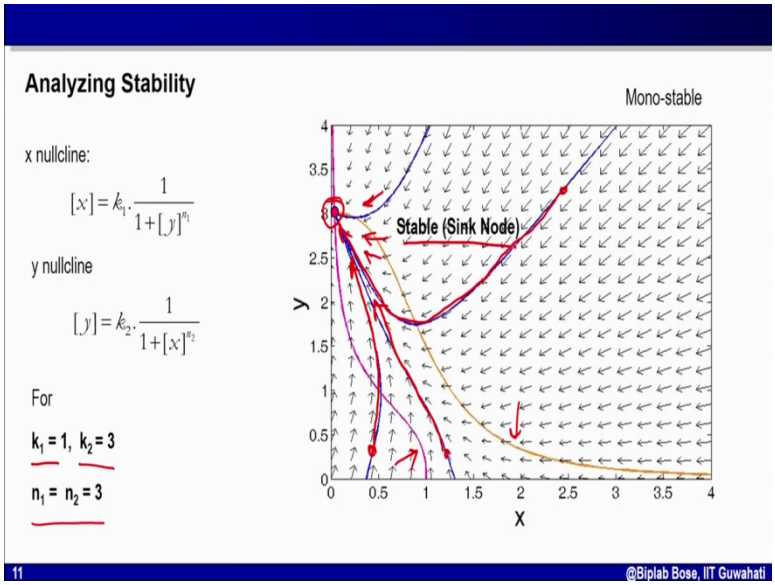

What if there is a imbalance between production, so we have considered K1 equal to 1 and K2 equal to 3 earlier, the sigmoidal method is still retained so I have these yellow and pink line as nullcline that we have drawn earlier and I have only one intersection point near here X where Y equal to 3 and X equal to 0, near that. Now this is the only steady state and if you follow the arrows present in this phase plane plot you can see where ever you start you will actually end up at the steady state. Wherever you start T equal to 0 you will at steady state that means th4ere is a stable Sink Node.

Again this page portrait is shown that if I have a unimodel population where difference expression but I have unimodal behavior at T equal to 0 and at time all cells will move towards the steady sales and again I have a unimodal distribution I will not have bimodal distribution. So these phase portrait analysis is telling one critical point that if I have X and Y repressing each other so there is repression of repression which is equivalent to positive feedback, then if the rate of production of both the protein and the N1 and N2 of Hill coefficient are correctly taken than the system can have the baisbilty and that can give rise to bimodal population behavior. Where as in the same system if I reduce the rate of production of the protein or if I keep an imbalance in these two proteins I will not get the bimodality I will have the mono stable system and my population behavior will be unimodal.

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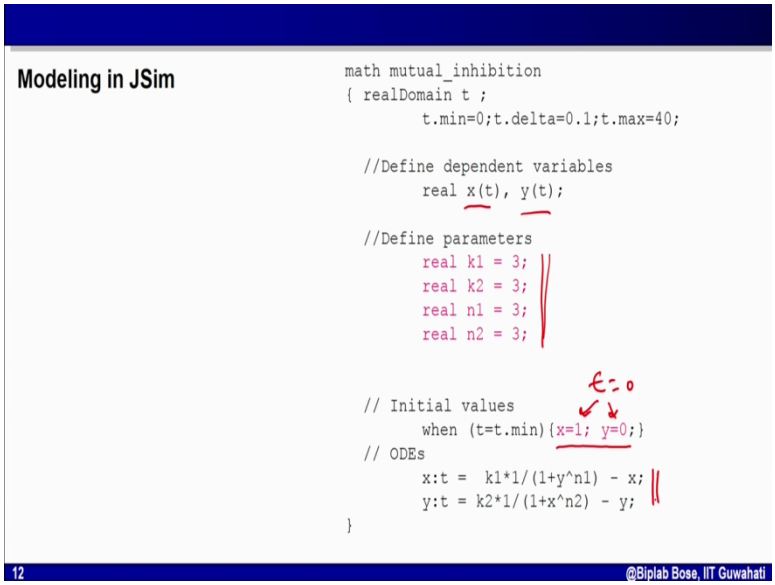

Till now what I have discussed is essential of phase plane analysis which is done graphically suppose I want to analyze it using JSim and I will recommend you use JSim to simulate the behavior of the system I have always shown the code here it is standard JSim code, where I have only two depended variable X and Y and these are the two independent variable and you can play around with this two parameters. I have considered all of them equal to 3 K1, K2 equal to 3 and N1, N2 equal to 3 and I have taken at T equal to 0, at T equal to 0 I have X equal to 1 and Y equal to 0. So I have considered the cells that I am taking have more X than Y at T equal to 0 and this is the ODE as we discussed earlier.

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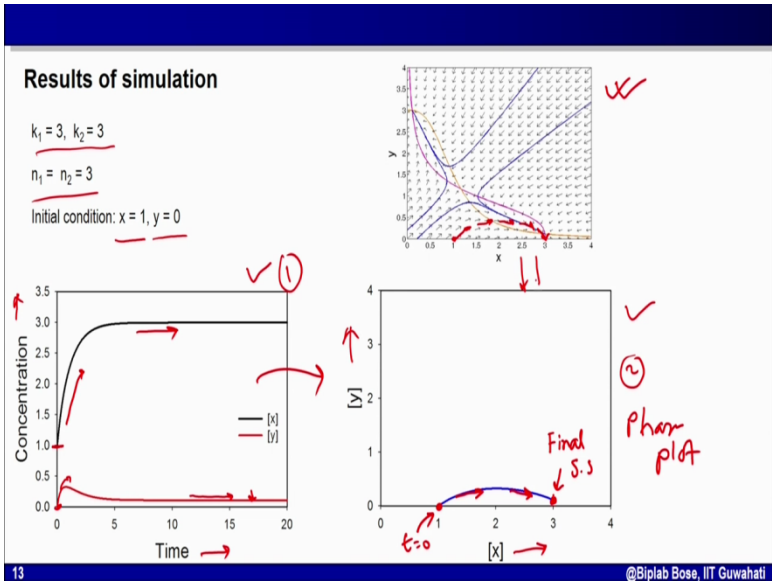

Now if I do the simulation of 3 with K1 and K2 equal to 3, N1 and N2 equal to 3 and as I said the initial equation is X equal to 1, Y equal to 0 then I plot my data after JSim simulation I get this card. So I have time in this and concentration of protein here. So X is starting from here from one and the black line is showing the behavior of X and it is increasing and then reaching the steady state near 3 whereas Y is starting from 0 it is rising slightly and then coming to another steady state. So the steady state of one is higher than steady state 1. If I got the phase plane for the same data, in this plot I have the first plot I have time verses X and Y and in second I am plotting X in the horizontal axis and y on the vertical axis. So the same data is plotted here and the same data is plotted here so I am getting a phase plot.

So if you see a phase plot at T equal to 0 at T equal to 0, I have these positions where X equal to 1 and y equal to 0 then with time ultimatelythe system moves where X equal to 3 and Y is slightly higher than it. This is my final steady state. So this is my phase plot, look at the phase plot that we have drawn just now in the previous slide, which have a phase portrait and graphical method has been used. So you are starting from here if you follow the arrow, if you follow the arrow you will land up in this position so I got same behavior as I got by numerical simulation.

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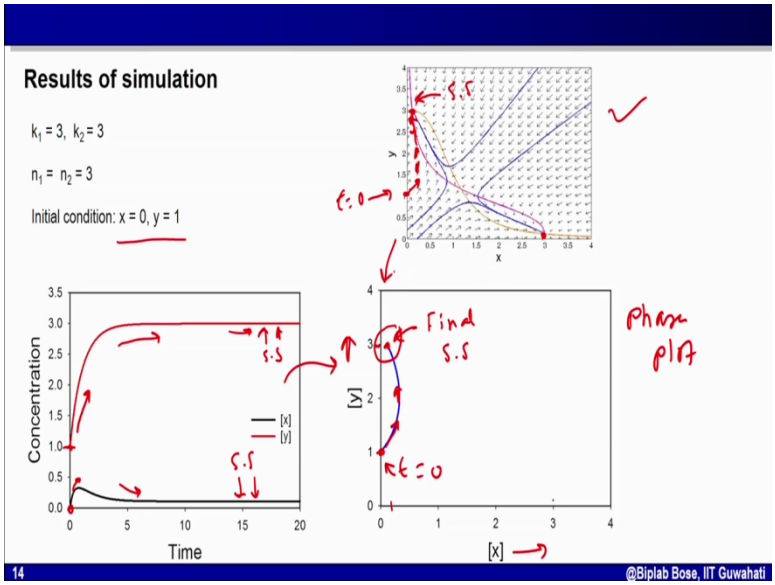

Let us do the same numerical simulation same code but I change the initial condition. Now Y is more if T is 1 X equal to 0 so if I do simulation in JSim what I get Y on the red line start zero at T equal to 0 at one in the start and then it rises and then it saturates at the steady state at the higher value 3. X now starts at 0 rises slightly and then fall back and reaches the steady states which is close to 0. Again I can plot the same data in X and Y axis that will be my phase plot, so at T equal to 0, X equal to 0 and Y equal to 1 as time progresses Y increases X slightly increases and then ultimately reaches the steady states where I have X is close to 0 and Y is equal to 3.

So this is final steady state that we get, if I look at the phase plot that we have drawn just before few slides before so this is my steady state here this is another steady state here. Now I am starting from this position Y equal to 1 and X equal to 0 that is my T equal to 0 position so if I follow that arrows in that trajectories, so I get this trajectories and I reaches this higher steady states where y equal to 3 and X equal to 0 and that's what I have got here also. So that means from numerical solution although I don't get the complete phase plot but I get the same behavior that is expected by the graphical method.

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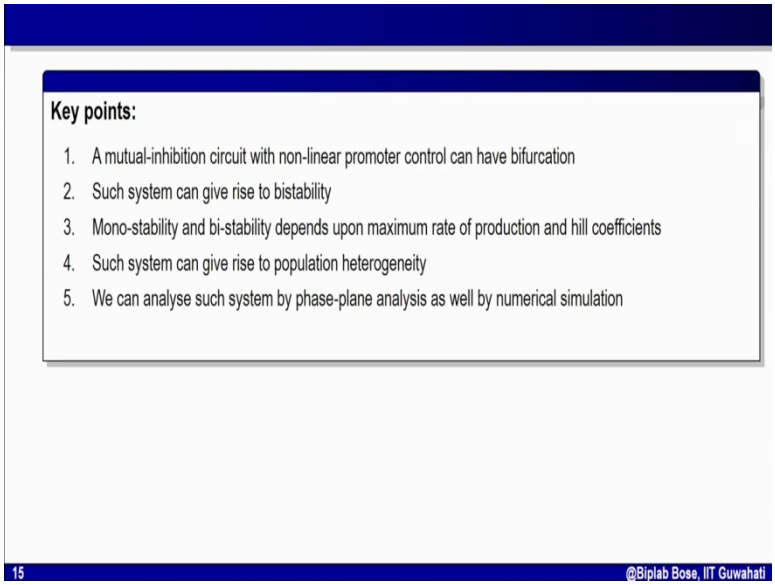

So let us jot down what we have learned in this module. In this module we have shown the two genes based mutual repressor system, so I have mutual inhibition circuit which has a non linear promoter control and this type of circuit is sometimes called Toggle switches. And we have shown if the non linearity of the promoter control and the rate of production of the protein matches then theses systems can have obviously have bistability. If change the rate of production of the protein and the non linearly in the promoter changing the value of Hill coefficient then from bistable system I can have monostable system I mean the system has bifurcation.

And this choice of mono stability and bi stability depends on maximum rate of production and the Hill coefficient. Hill coefficient is process of non linearity in the system and as a bistable system gives rise to bimodal in population behavior so we can expect that such a system can give rise to population heterogeneity. And what I have shown in this module that I can analyze this system by using both graphical method by phase plane analysis as well as simple numerical simulation as in JSim. That's all for this module thank you for watching.