Introduction to Dynamical Models in Biology
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Lecture 20
Modeling A Positive Feedback Circuit

Hello! Welcome to module 2 of last week of our course. In the last module we have learnt how to make a module for a negative feedback circuit. Now in this module, we will try to model a small positive feedback circuit and try to understand the behavior of the circuit using simulation of that model.

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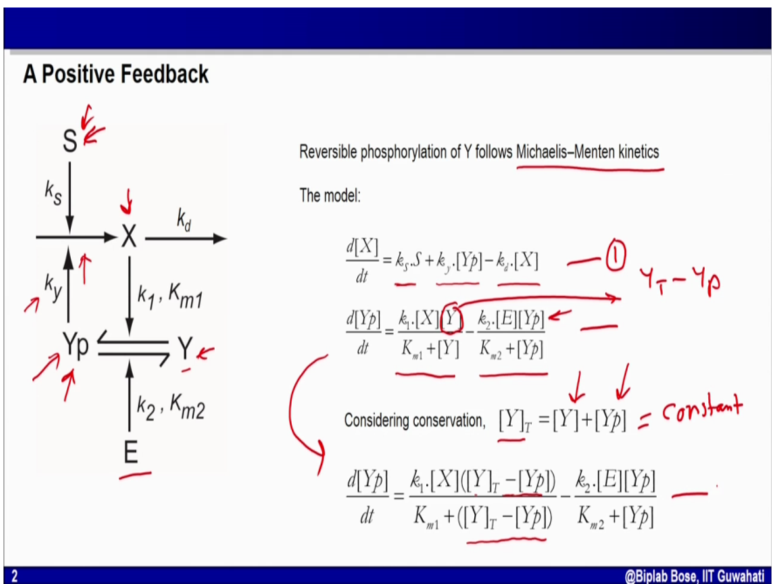

So let us start. So if you remember the last module, we have simple negative feedback, we have just rearranged the molecules to get a positive feedback out of it. So let us look at the graphical model of this positive feedbacK. S is my input signal which shows production of X. X get degraded, X is an enzyme, it's a kinase so X phosphorylate Y to YP and interestingly YP activates production of X so what is happening?

X is produced and the production is triggered by external signal S. X act as an enzyme, it phosphorylates Y to YP. YP in a positive feedback produces more and more X and as we know that this phosphorylation and dephosphorylation are reversible processes in a phosphorylate signaling cascade. YP also get dephosphorylated to Y by a phosphate as E which you can say is present as a constitutively in the system so that's my positive feedback. It involves x, the kinase, Y which gets phosphorylated by X and trigger more and more production of X. S is the input signal which is triggering the production of X and I have a constitutive phosphate as E which dephosphorylate YP to Y.

So let us now try to write a mathematical model for this simple positive feedback circuit. We will consider here this Y to YP inter conversion by reversible kinase and phosphatase activity is actually following Michaelis Menten kinetics. If you remember we are discussing earlier modules that if I have reversible reactions both following Michaelis Menten kinetics then this can have an ultra minus sensitive switch like behavior. So we will take advantage of that type of behavior in this system. So let us start writing the ODE. First for X, so X is produced only when you have the input signals.

One is S and the other one is YP, so the equation for ODE is DXDT equal to K1 KS into S. This is the production by external signal. KS is the rate constant plus KY into YP concentration, so KY is another rate constant minus KD into X. X is getting degraded by fast forwarding K. Now for the YP, YP DYPDT equal to combination of two Michaelis Menten in kinetics formulation. The first one K1 into X into y, X is the enzyme, Y is the substrate which is getting phosphorylated to YP so I have K1 into X into Y by K1. The Michaelis Menten constant for this phosphorylation reaction plus Y the substrate minus the second Michaelis Menten reaction that is reverse reaction from YP to Y that is K2 into E. E is the phosphates or enzyme involved here.

YP is the substrate divided by K. into that is my Michaelis Menten constant for the second reversible reaction which is dephosphorylation reaction plus Y be the substitute. Now we know we can assume that the total amount of Y that is free Y and phosphorylated Y sum together is the total Y and that remains constant. So if I consider this conservation then this second ODE, this is the first ODE for x, the second is for DYDT. Second ODE gets rearranged where Y is replaced by YT minus YP so that's what I have done. DYPDT equal to K1X into YT minus YP so I have replaced Y by YT minus YP divided by K1 plus YT minus YP that is again I have replaced Y by YT minus YP.

Second Michaelis Menten is minus K2EYP divided by K into plus YP remains as same as. So this will not be my second ODE, this will be my second Ode so I have two ODEs, the first one for X, the second one for YP and I have replaced Y in terms of YP and YT so I don't require to write this ODE for Y so these two ODE represent the mod for this simple positive feedback circuit of a phosphorylated system that I have shown in the graphical model. So now we will try to analyze the behavior of this system and when I say I want to analyze the system, primarily I want to study the steady state behavior. So if you remember steady state behavior, one starting point can be to look into nullclines.

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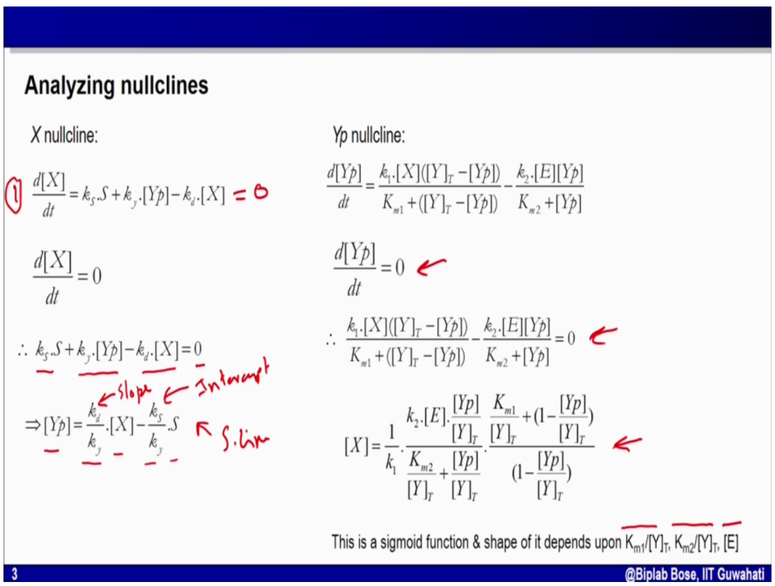

So let us look into the nullclines here. First the X nullcline, if I have to write down the X nullcline, I have to take the ODE for X that is the first ODE I am taking. This is the first ODE. DXDT equal to KS into s plus KY into YP minus KDX. Here to calculate the X nullcline I will consider DXDT equal to 0. DXDT equal to 0 then this first ODE becomes 0 and by simple algebra I get KS into s plus KY into YP minus KD into X equal to 0. So I now rearrange term so I get YP on my left hand one side of the equal to sign and X on the other side and its very simple, you can see rearrangement here is very simple so I get YP on one side that is YP equal to KD by KY into X minus KS by KY into S.

It is simple straight line equation where this part that is KS by KY into s is essentially representing the intersect and this whole term that is KD by KY is actually the slope. YP versus

X is a straight line having intersect KS by KY into S and the slope is KD by KY. Now one thing we should keep it mine here that means this nullcline depends upon input signal S because this nullcine has in its intersect. Now looking into Y nullcline, the DYPDT, the ODE for YP is exactly the same as you have done in negative feedback in the earlier module so I am not going into details of it. You can simply consider for Y nullcline, DYPDT equal to 0 then you can do algebraic rearrangement so that you get ODE equal to 0.

Now, I want to keep YP and X on one side so here it will be easier if we keep X on one side and everything else on the other side. This you must have seen in the earlier module so here X and YP has sigmoid elimination and the sigmoidal function depends upon the shape of sigmoid, depends upon KM1 by YT that is the ratio of Michaelis Menten constant and total Y and KM2YT that is second Michaelis Menten constant and the substrate and obviously E, concentration of E that is the phosphorylate concentration. This we have dealt in earlier module. Now, I have two nullclines and I will plot these nullclines on this phase plane of X versus YP and try to find out the intersect because the point of intersection will be my steady state.

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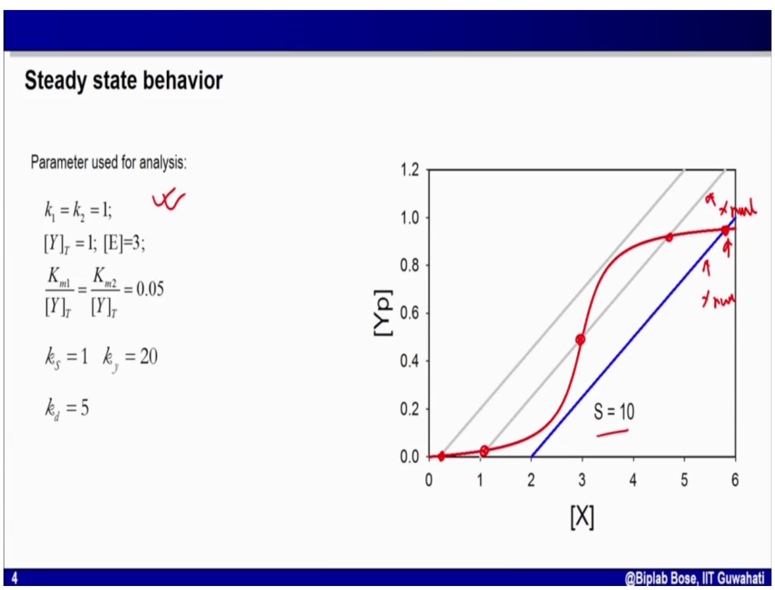

Let us do that. I have plotted first the YP nullcline; you remember just now I said from the YP nullclines equation, X versus Y will be sigmoidal behavior so I have a sigmoid behavior here. Now remember X versus YP relation for YP nullcline does not have any input signal at start so that means this YP nullcline does not depend upon input signal but X nullcine has a start that input signal so X nullcline will change with my input signal. Let us consider first S equal to Y. If you consider input signal S equal to1, then you get this straight line shown in this blue color and that is by X nullcline. Let's clean a bit.

Now what I will do, I will change S from 1 to 5. Before I change you notice here when S equal to 1 for this parameter that I have used to draw this plot, there is only one point of intersection here so I have only one steady state. If I increase S from 1 to 5, obviously my straight line moves right hand side, so now I have this new blue line as my X nullcline and you can easily see now I have three points of intersection between X and Y nullcline that means I have three steady states. Let us increase S further. Double S to S equal to 10, now this blue line is my X nullcline. Now I have only one point of intersection, there so that means that is my steady state.

What is happening here, as I change S my Y nullcline doesn't change because Y nullcine doesn't has any S term in that equation whereas X nullcine has S term, X nullclines is a straight line and the intersect of that has S term so if I keep on changing S, as I increase S, my X nullcine shift right hand side and number of intersection between X and Y nullcine changes. When S is low, for example S equal to1, I have only one intersection that means I have only one steady state. When I have higher value of S, for example 10 the way I have shown here, I have again one point of intersection that means I have one steady state. When I have S in between for example S equal to 5, I have 3 points of intersection that means I gave three steady states.

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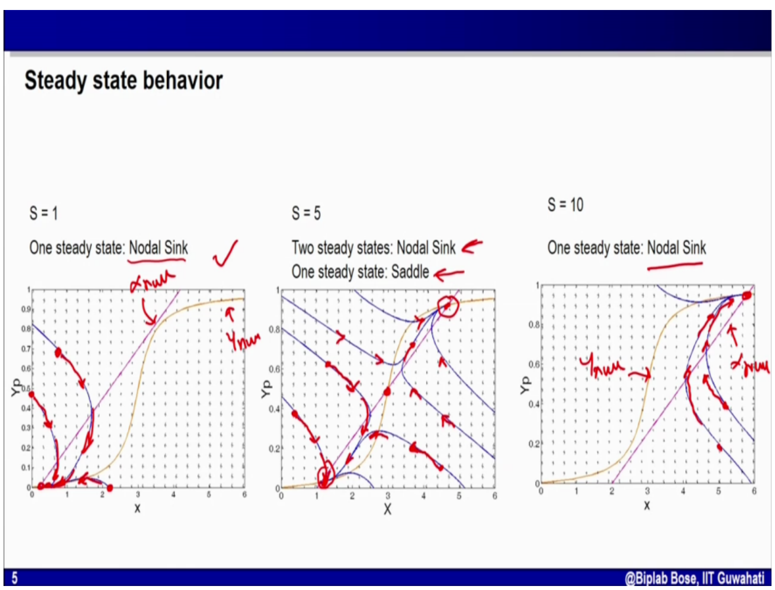

Now we will look into the issue of stability of this steady state. You can take help of drawing the phase plane plot the way we have discussed to draw arrows around the steady state, you can try that but that is with combustion. I have used MATLAB to draw these phase portraits. If you know MATLAB you can try otherwise, let us discuss about it and I will show you some numerical simulation to understand the behavior in different fashion. So when I consider S equal to 1 this is my phase portrait. This is my Y nullcline, this is my X nullcline and I have only one point of intersection that is my steady state if you look into phase portrait, if you start somewhere here, at T equal to 0. The trajectory shows that you will collapse at the steady state here.

If you start somewhere here, at T equal to 0 then following the trajectory in the phase portrait plot, I will collapse here at the steady state. Here if you have started at T equal to 0, then you can collapse on the sensitive state, so this steady state if you do exhaust it which is beyond the scope of this course you will find that this steady state is a Nodal Sink. I have only one steady state at S equal to 1 and that's stable Nodal Sink. What happens if I have higher value of S, S equal to 10 then again this is my one nullcline that X null, this orange null that is my Y nullcline and I have one point of intersection here and phase portrait says that if I start from here suppose T equal to 0 then I move along this blue trajectory and collapse here. If I start somewhere here again I collapse on the single steady state.

Again I have only one steady state and that steady state is a Nodal Sink so it's a stable one. What happens if I have s equal to 5? If you remember what we have, if S equal to 5 then I have three points of intersection and if you look into the trajectories, these trajectory is going and hitting the steady state. This trajectory is again going and hitting this steady state whereas if I start from here, the trajectories are taking me to the other steady state at the lower one. If I start from here I will follow this trajectory and collapse at this lower stead state. If I start somewhere here at T equal to 0, I will follow this blue line and collapse at this stage. Nowhere the trajectory collapsed at the middle steady state so this middle one is a saddle point and I have two lower and higher values of steady state which are Nodal Sink. So you can see easily that depending upon s, not only my number of steady state changing but stability behavior is also changing.

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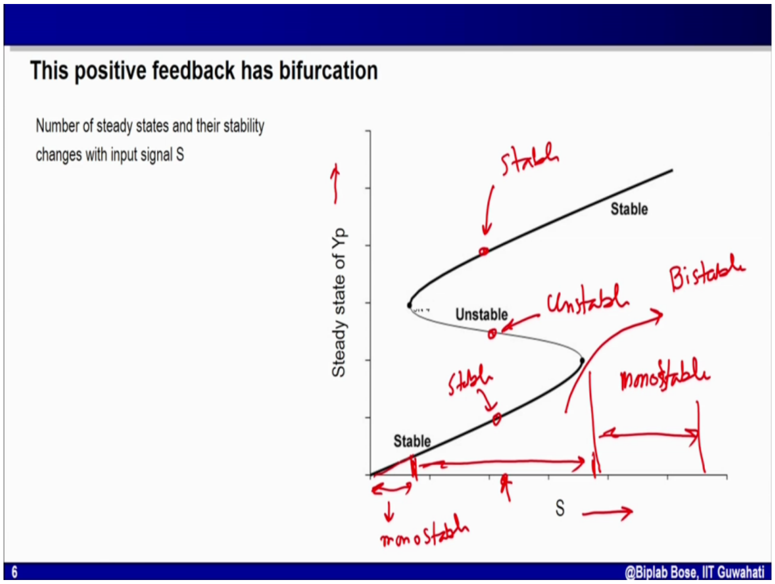

Now let us look into it in terms of bifurcation. If you remember what is bifurcation, in bifurcating system I have one or more parameters, depending on the value of parameters, my number of possible steady state changes or the behavior around that steady state, the issue of stability, instability around that steady state changes or both of them change together. In this case as I change S, my number of steady state changes and the stability of those also changes so what I can do is I can bifurcate the plot as shown here, with S in the horizontal axis and steady state of YP in the vertical axis and I can plot different steady state value of YP as I change S and I can see that for some value of S I will have only one steady state that is in this region my system is monostable. In the higher values of S also, in this region my system is monostable because I have only one steady stable state in those cases.

In between I have option for any value of S for example if I take S here I have three steady state, two of them are stable and one is unstable. So this middle region is actually bistable energy. One thing we have to keep in mind that this particular figure I have not drawn based on the exact results from our model. To draw these type of bifurcation plot using ODE based module that we have discussing is not so easy. It requires MATLAB and other tools like expert, those are beyond scope of our discussion here today but in general the behavior will be like this. What we will try to do now is we will use JSim and two numerical simulation and try to draw this type of bifurcation plot and which is very easy and you can use in your desktop. Remember this system has bistability.

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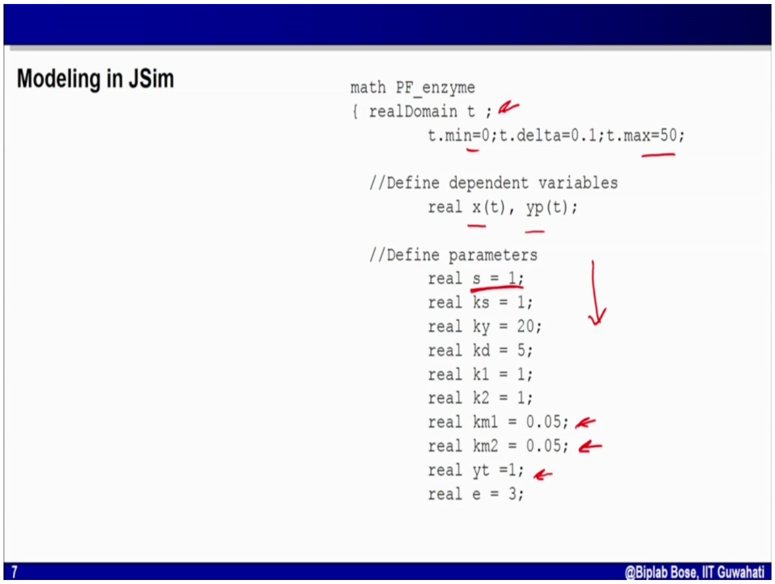

So let us numerically simulate this system. I will use JSim again and JSim code is given here. The code is lengthy so I have broken down into two pages. The first part as you can see obviously it first defines time, initial time as 0 and maximum I have taken as 50. I have two dependent variables X and YP, and I have set up parameters values here. This parameter value we can change, for example we will keep on changing S, and we will keep rest of the parameters as constant. You can easily notice KM1 and KM2 are very small point 0.05 whereas YP is 1 that means the ratio of this KM and YT will be much smaller than Y and that is required so that I get very good sigmoidal YP nullcline.

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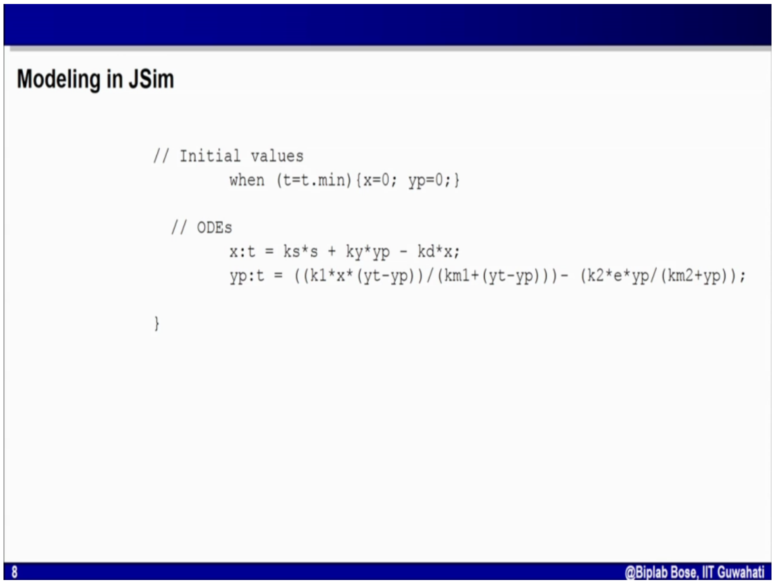

Now rest of the part of the code I have to define the initial value, here I have shown X equal to 0, YP equal to 0. This part we will keep on changing during our simulation to see the change in behavior and rest of the things are the same for ODEs. This code you can write in your JSim model and try to simulate the way I have shown the simulation.

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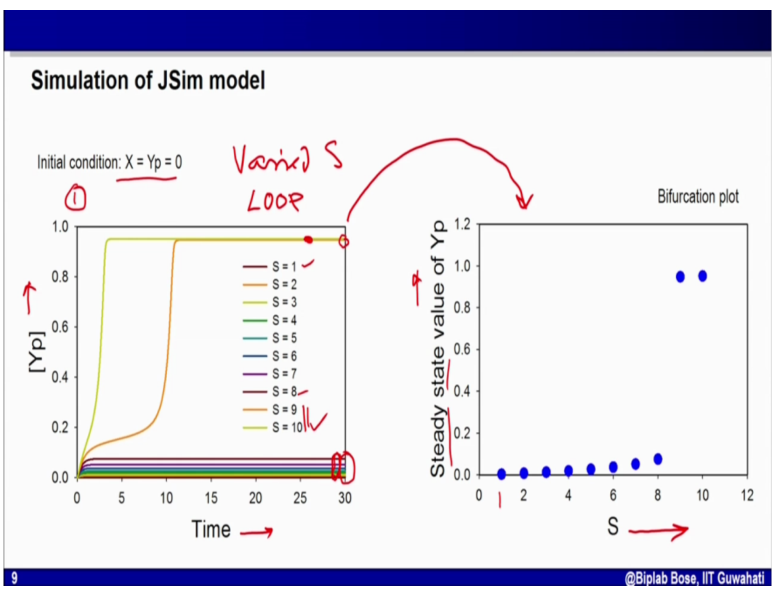

Now what I have done first, I have done the simulation of this model with initial condition where both X and YP are equal to 0 and I have varied s using the loop option, if you remember JSim has loop option, and I have plotted the data. Look at figure 1. I have got a time T here and YP in the vertical axis. Only for two higher values I am having s from 1 to 10, only for these two higher values 9 and 10, the steady state is a near1 that is higher value whereas for rest of the other value of S starting from 1 to 8, you can see the steady state are near point 1 so lower value so you can easily see, depending upon the input signal S I am getting two different regimes.

Till S equal to 8 I have got steady state which are very close to each other and the lower value of Y whereas when I increase S to 9 or 10 they bunch together and they are giving me higher steady state. I can use these data and plot a second plot where I will put S in my horizontal axis and steady state value. Remember the steady state value for YP in vertical axis, how do I get the steady state value? I take the value of YP at the T equal to 30 or at the end of the simulation. By that time the system has steady state so I have plotted those values and you can easily see when S is higher around 9 or 10 I have a steady state which is a higher value near 1 whereas in these regions from 1 to 8, my steady states are low and close to 0.1 so that means you an easily see, this system has interesting jumping steady state.

If I start at X equal to 0, YP equal to 0 and if I keep on changing S, up to S equal to 8 I will remain as a lower steady state. After that if I increase s equal to 9 or 10 I will jump into higher steady state, that's a drastic jump. Now let's do the same simulation but change the initial condition so now I am taking X equal to 5 and YP equal to 0.5 and I am doing the same simulation here.

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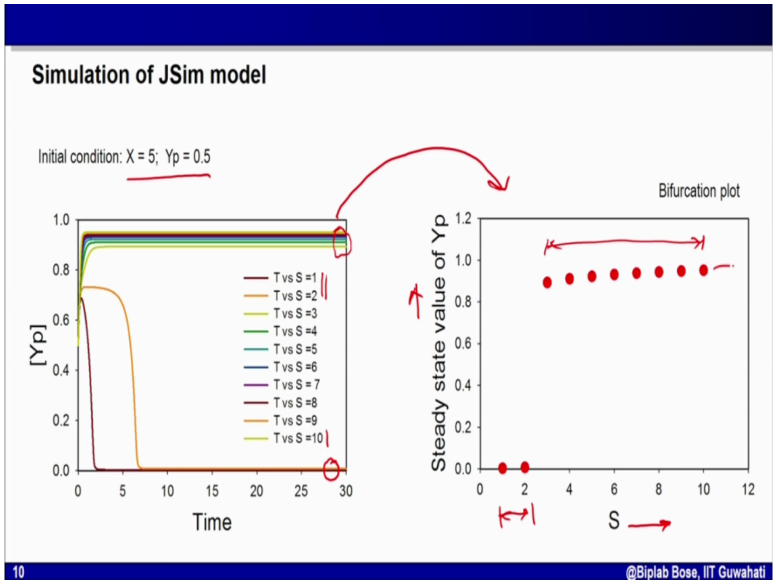

Now you see just the opposite if I have s equal to 1 or 2 then they give me a lower steady state value. For rest of the other value of s starting from 3 to 10, the system converges at a higher steady state. Those values are very close, so if I now got the steady state value from this simulation in a plot which is bifurcation plot essentially with S in my horizontal axis and steady state value of YP in these axis, I get this stage of data so if S is lower value here then I go to this lower steady state which is close to 0 where as if I am on a higher value of S I reach this higher steady state which is close to 1. So you can see there are two regimes, depending upon the value of S, one is higher steady state and one is lower steady state but where you will reach will depend on the initial condition so now let's merge these two data sets and combine in a single plot.

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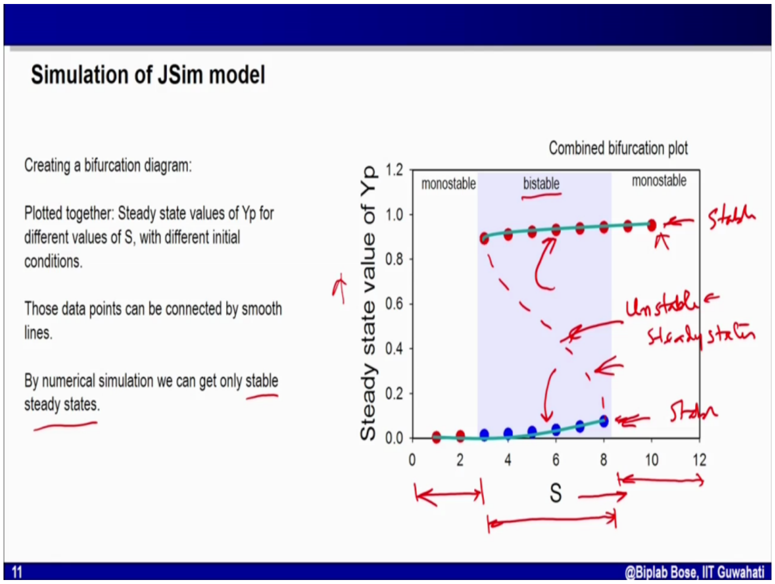

I have merged those two data sets and I have combined single bifurcation plot so this is my complete bifurcation plot that is s in the horizontal axis and the steady state value of YP in the vertical axis. You can easily see up to this region the system irrespective of the steady state, the initial condition have only one option, the lower steady state so the system is mono state whereas for this higher value again, irrespective of the initial condition the system reaches this higher steady states so again here the system is mono state. In between the grey region that I have shown here, the system is bistable because it has two steady states shown by these red dots, the higher steady state and this blue dot the lower steady state.

Depending upon the initial value of X and Y there is initial condition, the system will either go into lower steady state or to the higher steady state so that's one my bifurcation concept tells me so what I have got here, I have got partial bifurcation plot. I will say partial because remember both these steady states are actually stable. If you compare the real bifurcation plot the way I have drawn in few slides back you have another dotted line somewhere here which represent unstable steady states. But in numerical simulation your simulation will never reach unstable steady state so you only get steady stable state so this unstable steady state can't be drawn by numerical simulation so we only see that steady stable state.

Whatever it is we are not bothered about unstable steady state because the system in reality will also never reach unstable steady state, it will move away from it so my numerical simulation tells me that this system has bifurcation depending upon the initial value and the value of S, the system can be monostable or bistable and if its bistable regime, which steady state it will go will depend upon the initial condition. You can easily draw this type of bifurcation plot by numerical simulation if in case of other type of networks and circuits.

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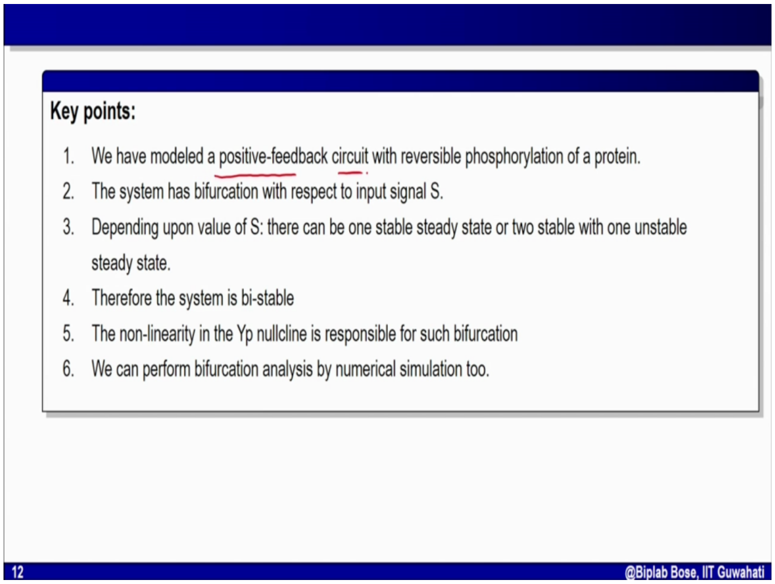

Let us jot down the points so the key points for this module is that we have modeled a positive feedback circuit with reversible phosphorylation of protein and remember this phosphorylation and both the phosphorylation are following Michaelis Menten kinetics. We have shown the system has bifurcation with respect to input signal S, simple nullcline analysis we have shown and numerical analysis we have also shown that. Depending upon the value of S you can have two situations. One you can have one stable steady state or you can have one situation where you have two stable steady states and one unstable steady state, therefore the system is actually bistable in that region and remember these types of situations where number of steady state is changing with S, the input signal is happening because the YP nullcline is nonlinear, sigmoidal.

If it has been linear then we have always only one point of intersection between X and YP nullcline that means we always one only one steady state but here the YP nullcline is nonlinear sigmoidal and X is linear one so I have multiple type of possible intersection depending upon the value of S. so this nonlinearity is crucial to give rise to this bistability and the last one what I have discussed is that you can actually do bifurcation analysis by simple numerical simulation the way I have shown you.

You have to change the parameter, in this case the parameter is S the input signal, I am changing the value from 1 to 10 for S and I am simulating for different initial conditions and then I am getting steady state value from my simulation and I am plotting S versus steady state value of YP from this steady state values and that gives me a partial bifurcation plot which tells me system is monostable in some value of S and is bistable for some value of S. That's all for this module, see you in the next one.