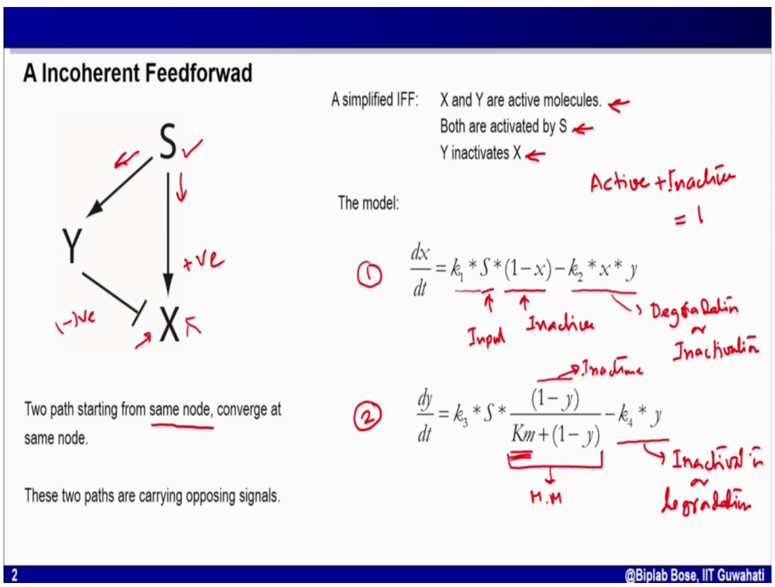
Introduction to Dynamical Models in Biology
Dr. Biplab Bose
Associate Professor
Department of Biosciences & Bioengineering
Indian Institute of Technology, Guwahati
Lecture 21
Modeling An Incoherent Feedforward Motif

Hello, welcome to the third module of this last week of our course. Till now in this week we have discussed about a Positive Feedback Motif. We have discussed Negative Feedback Motif and this video or in this module I'll discuss about a new motif called Incoherent Feed Forward.

(Refer Slide Time: 1:01)



Let's first look into the structure of this motif. In Incoherent Feed Forward you have feed forward, that means from one or two path starts and those two path eventually converge to the same node, for example in this figure you can see the signal is starting from S. S is my input signal. It is converging in two path and then these two path again converge at X. So it is a feed forward. The path is diverging from a node and they again converging at the forward node.

But it is called incoherent because if you can see from S to X, it is a positive path whereas Y to X, it is a negative path because Y is inhibiting X. So through one path S is telling X to grow, to get activated or to do something positive whereas through the other path where we have Y. Y is telling S is telling through Y to X that you have to invite or stop or do something opposite. So two path are not coherent, they are incoherent. So this is my structure of incoherent feed forward motif.

This motif can have different variations but eventually it will have diverted from one node and again converges in on node and two paths will have opposite properties. So we'll try to model this later, this motif. So we will simplify this one. This motif can be seen as a combination of multiple Michaelis Menten and processes but I have simplified this one so that we can understand the basic principles of this motif, basic dynamics of this motif. So what have considered, I have considered that both X and Y are acting molecules. I have not separately shown the inactive state of X and Y. Both X and Y are activated by S that is what shown in the figure also and Y inactive X.

So if this is my basic assumptions then the model that I have written in terms of ordinary differentially equation is like this, the first ODE, DXGT there is a rate of change of X with respective to the time is equal to K1 into S. That is S is the input signal and into one minus X. This one minus X is actually amount of inactive X. So I have active X plus inactive X. The total is equal to 1. So you can consider X as a fraction of total X which is active.

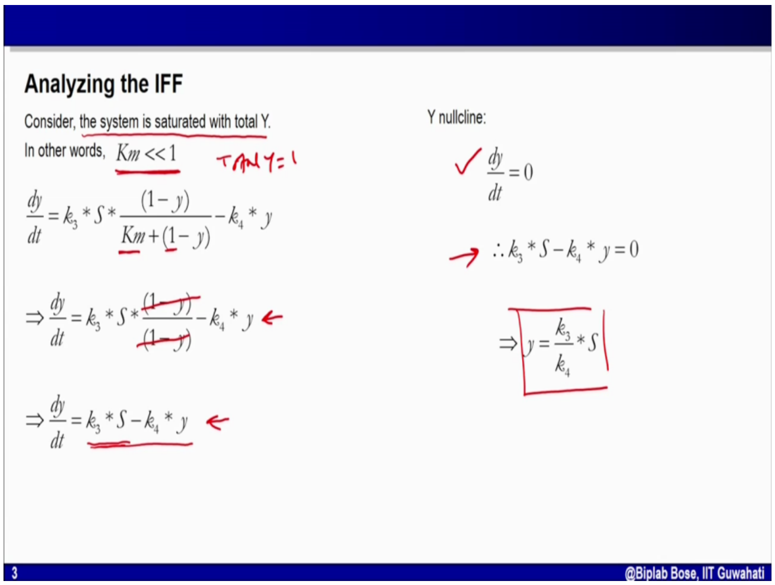
The same thing I have considered for Y also here. So one minus X is actually inactive X. S I the input signal. S work on inactive X to give rise to active X that is represented by X. And the last thing in my ODE is K2 into X into Y that is degradation or inactivation. So Y is either promoting degradation of active X or Y is promoting inactivation of X. So that is my fast ODE.

The second ODE of my model is for Y. So I have DYDT is equal to K3 into S into a term involving one minus Y, that is again the inactive one inactive Y, just like one minus X was inactive X and this whole thing. One minus Y divided by KM, that Michaelis Menten and constant. Plus one minus Y, this is coming from my assumption that this activation of Y by S is Michaelis Menten process. Note that for X, I have not consider any Michaelis Menten formulation. I have could have considered Michaelis Menten in formulation there but to simply the model, I have simply considered that one minus X is, that is the inactive X is reacting with S, as simple as that.

In this case I have considered a explicit Michaelis Menten and formulation because I have to study or I want to explain the importance of KM here, the Michaelis Menten and constant here.

Otherwise I could have simply considered just like DXDT I have considered it is S into one minus X. I could have considered here X into one minus Y or something like that. And the second term in the second ODE is K4 into Y that is this part is inactivation or degradation of Y or degradation of Y. So these two are my ODEs and I want to study the behavior of this motif based this model, this ODE based model.

(Refer Slide Time: 6:38)



So let us look into the issues. As we have discussed earlier. I will initially study this system based nullcline, so let us look into that. I'll first look into the Y nullcline but before I go into that let us make a assumption. Let us configure the system is saturated with total Y. There is inactive and active Y. So I am considering the amount of Y, both inactive and active mixed together is huge so that the KM is much less than one, remember one is the total amount of Y. For me totally is equal to 1 and that is made of both inactive and active Y.

So I am considering the system is completely saturated with Y. In other word that means the KM with respect to total Y is very small. So here the total Y is equal to 1 that's why KM has to be much smaller than one. So if this is the situation and that can happen in many cellular system, if that is the situation then I can rewrite the second OD for Y. This is a second ODE for Y. what I have considered; I have considered KM is much smaller than one. So if Km is much smaller than one then I can remove KM from this denominator so that is what I have done. I have removed

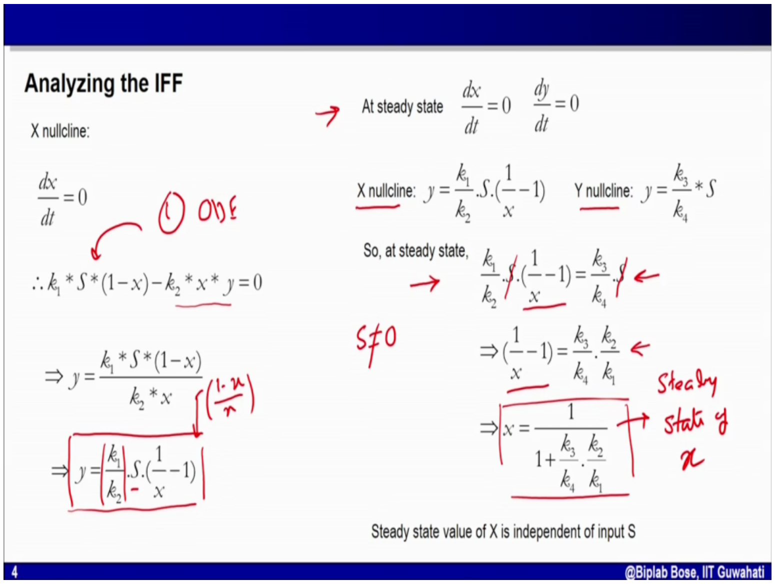
KM from the denominator I get this rearranged ordinary differential equation. Note that here I don't have KM.

Now obviously as I have one minus Y in the denominator and one minus Y in the numerator and they are not zero I can simply cancel them. So if I can cancel them then I get this ODE. So here DYDT is equal to K3 into S minus K4 into Y. So what I have got, look at the first turn. K3 into S that means the production of Y depends here only upon the input signal. It doesn't depend upon how much inactive Y is there. This is because the amount of total amount of Y is considered so large that my ODE does not depend upon that. It becomes independent of that. It only depends upon the rate of production of Y only depend upon how much signal you give. And that has been achieved because I have considered the system is saturated to the Y. In other word I have considered KM is much smaller than the total amount of Y that is equal to 1 here.

So that's why in my second ODE, at the very beginning I have considered explicit Michaelis Menten in formulation so that I can come back and show you that in this case I am considering that the amount of Y form does not depend upon what is the amount of inactive Y because it is a large amount. It primarily depends upon what is the input signal. The strength of the input signal is S so this is my modified ODE. So I will use this modified or rearranged ODE to calculate the nullcline for Y.

So let us calculate nullcline for Y. To calculate nullcline for Y I have to consider DYDT equal to 0 so that what I have considered. So that means I have to put K3 into S, K3 into S minus K4 into Y equal to 0. So I am putting using this ODE here, the modified second ODE is here. So now I will rearrange term so that I get Y one side of equal to sign and rest of the thing on other side. You do not have X in this equation. So if I rearrange I get this thing, Y is equal to K3 divided by K4, K3 divided by K4 are ratio of two parameters so it is constant into S. S is my input signal. So you can easily see Y is linearly dependent upon S, nothing else, right.

(Refer Slide Time: 11:01)



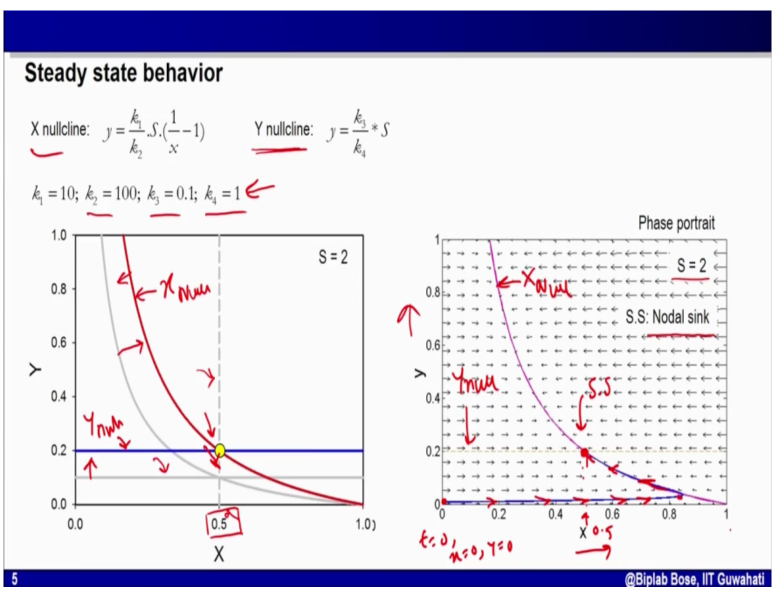
So let us into the X nullcline to get that I have to take the first ODE and make DXDT equal to 0 so my first ODE I get K1 into S into one minus X is equal to K2XY equal to 0. I am getting it from the first ODE. That we have written as our model. Again I will rearrange X and Y. I will put Y on one side, X on the other side to get a relation between X and Y. So here I rearrange the term so I get Y equal K1 into S into one minus X divided by K2 into X. I separate out the constant term, so I get K1 by K2 as one ratio in to S the input signal into one by X minus one. This is nothing but distant 1 minus X by X is nothing but one by X minus one. So I have got this relation here. So this my X nullcline.

And remember here X nullcline also depend upon S but the relation between Y and X is non linear, so if I have got X nullcline and Y nullcline client I can look into the steady state. So I can do that graphically. Before I move into graphically showing X nullcline and Y nullcline let us do some algebra. We know at steady state both DXDT and DIDT has to be zero and that is the intersection point of X nullcline and Y nullcline client. So let us look into the algebraically what will be the value of X at this intersection of X and Y nullcline.

So in other word I want to know algebraically what will be the steady state value of X, so that calculation I am doing here so at steady state DXDT and DYDT both as zero. My nullcline are given X nullcline is this one, Y equal to K1 by K2S into one minus X minus one. And Y nullcline is Y equal to K3 by K4 into S so I can solve this by equating these two nullcline because I want to find out the X and Y value at the intersection of these two nullcline so I can write one by K1 by K2 into S into one minus one by X minus one is equal to K3 by K4 into S, this is coming from because X and Y nullcline are intersecting so I am putting Y value for both of them. So now I can algebraically separate out X. So if I rearrange I kept this one minus X on the left hand side and arranged everything S on the other side. Remember if S is not equal to 0 then I can cancel this S so by rearrangement I get one by X minus one is equal to K3 by K4 into K2 by K1.

So one minus X one by X minus one is nothing but a ratio of multiple parameter constants. So if I rearrange the term again I take one on the other side. One by X on the other side and then invert I get this relation. X is equal to 1 by one plus K3 into K2 divided by K4 into K1. Now this is my steady state value of X. Note one interesting thing in this steady state value of X. This steady state value of X does not have Y obviously and that is obvious because we are separating out Y and X but it also does not have S, the input signal. That means irrespective of value of S where steady state value of X will remain same, which will only depend upon K3, K2, K4 and K1 which are constant in my system. That means the steady state value of X is insensate to S as long as S is not equal to 0 that is the condition we have given here.

(Refer Slide Time: 15:55)



So now look into the whole thing graphically. So this is my X nullcline this is my Y nullcline client we have calculated. I have taken some numerical values for K1, K2, K3 and K4 because I have to draw the nullcline plots. And I have considered S equal to 1 to draw this nullcline. So this red line is my X nullcline this blue one is my Y nullcline you can easily see Y nullcline is a straight line or horizontal straight line and it will vary with S.

And Y has a hyperbolic relation with X so it is decreasing with X. And the intersection point here is shown by this yellow dot and you can easily calculate the value of the intersection point from the previous calculation that we have done. Remember X is equal to 1 divided by one plus K3 into K2 by K4 into K1 so you can put the value of K3, K2, K4 and K1 and it will come that the steady state value of X equal to point 5. So that is what this dotted line is showing. So here I have steady state value of X at point 5. Now what will happen if I change S from one to two that means I am doubling the input signal, what will happen to the steady state?

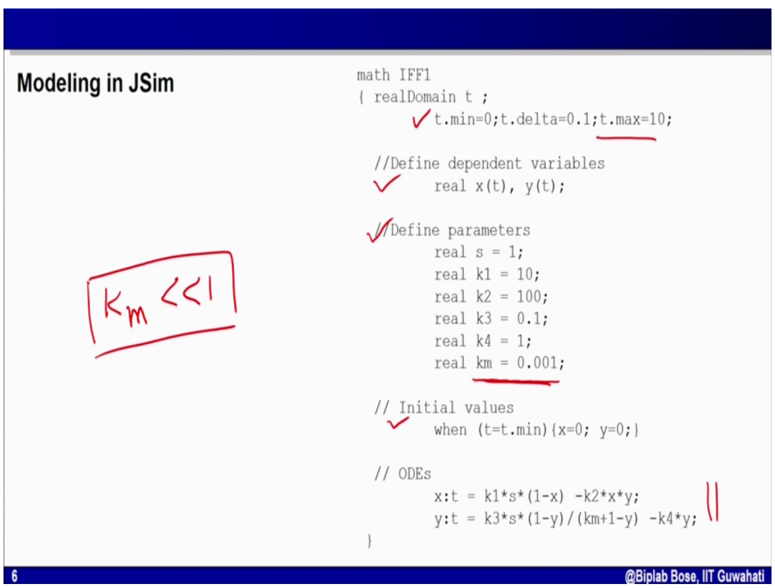
From the algebraic calculation I know that the steady value of X does not depend upon S, it remains constant. So as long as the parameter value K1, K2, K3, K4 does not change my steady state value of X will not change. Let us see what is happening here. So I change S equal to 2 my X nullcline is this one and Y nullcline is this blue one. And you can see the grey lines are the older nullcline. I have shown in the same plot. Both Y nullcline Y nullcline client has moved from this grey to this one X nullcline has moved from this grey line to this one. Both of them has changed because both them has S the input signal term in their equation but their intersection point is shown this yellow point and you can easily see at that intersection point the value of X is 0.5 same that we have got in the previous nullclines intersection.

So as I have shown in case of algebraic calculation here also I am getting that the steady state value of X remain constant at a particular value and for this numerical value here it is point 0.5 that means the steady state value of X does not depend upon what is the input signal. Now if I consider input signal S and steady state value of X as output. Then I can say that the output is independent of input signal. I will explain this on further before that let us look into the phase portrait that I have drawn. One can try to draw that manually but it rigorous so I have drawn this using a MATLAB code.

Just let us look in the feature of it. The arrows are obviously showing their direction. Now X is in the horizontal axis. Y is in the vertical axis. I have drawn the phase portrait considering S equal to 2 and this is my X nullclines and this is my this yellow one is my Y nullclines. Let me erase this one. So now the intersection point is here, so this is my steady state and you can easily see that is coming at around 0.5. So now if I start near zero zero that means T equal to 0, X is equal to 0, Y is also equal to 0 something like that. Then my trajectory in my phase portrait showing that, this way I will keep on increasing X and then I will hit upon here and then I will follow this path eventually collapsing here, which is a steady state.

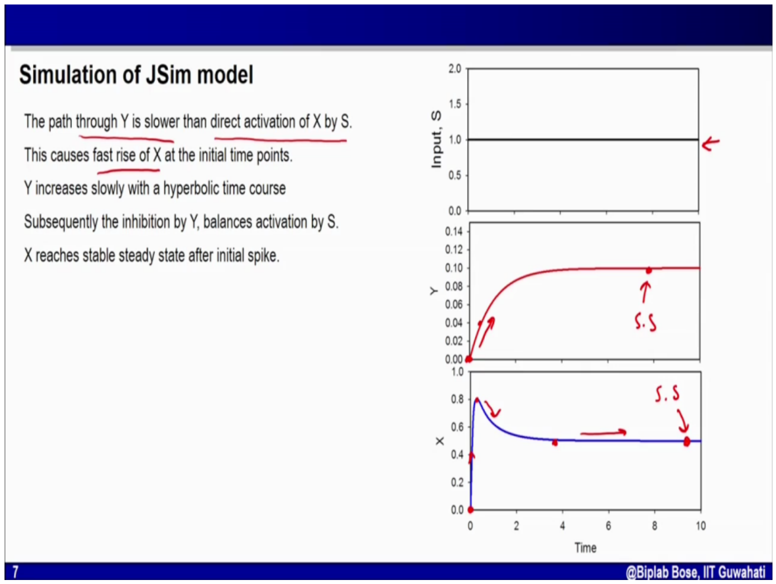
You can start from any point and eventually you will see that you will collapse at the steady state where X equal to 0.5, near 0.5. So in this case, this steady state is actually a Nodal Sink so that means this steady state is a stable one. Keep notice on the behavior of X with time. Initially X is increasing. Y is not increasing much and then X start decreasing and collapse at the steady state so that means if I am starting at zero zero for XY, I have initially a spike of X and then it reaches the steady state. We will get back to this behavior when we will do the numerical simulations using JSim**.**

(Refer Slide Time: 21:11)



So let us look into JSim code. I have given the code here. You can copy and try to run it in your own desktop. I will strongly advise you to run it and play around it to understand the behavior of this particular motif. The code is as usual that we have done earlier. Initially we have decided that define the time. I have kept T max equal to 10 here. You have defined two dependent variable, X and Y in this case, remember my signal input signal is S, output signal is steady state value of X and you have defined the parameter values. Note here I have considered KM is equal to 0.001 if you remember in our calculations. We have considered the simplification where we have considered KM much smaller than one so to satisfy that I have kept KM equal to 0.001. Then you define the initial values and then the ODEs.

(Refer Slide Time: 22:09)

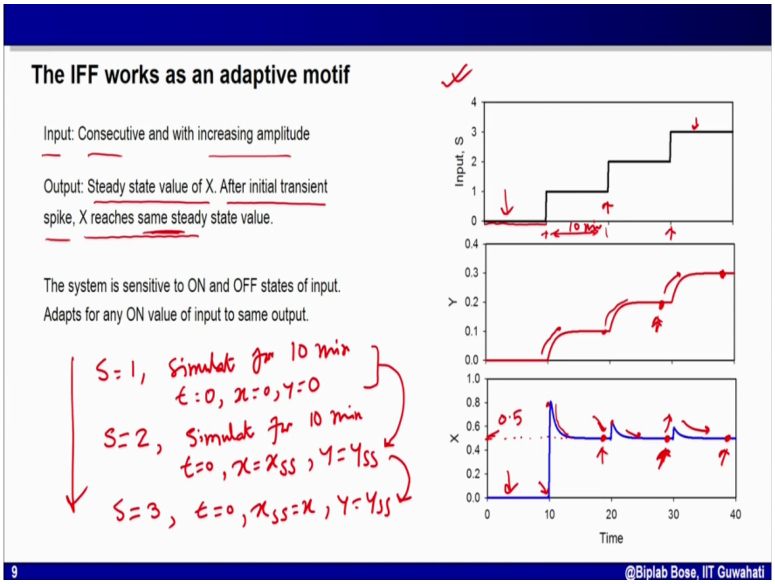


So if you compile this code and then run you will see the behavior of X and Y and that I have shown here. So this is my input signal. Signal of input S equal to 1 so at T equal to 0, both X was at 0 and Y was at 0. As I have given the signal there is sharp rise in X, X rises with time then reaches this peak and then it falls. It falls and reaches the steady state value. So it reaches the steady state here. So initially there is spike and then it reaches the steady state whereas Y increases slowly just like hyperbola and then reaches the steady state. So what is happening here?

Actually in this case I have two path, signal is going to X from S using two path, one in volume Y and one is direct. The path through Y is slower. The direct path is obviously faster so initially there is a sharp rise of X and as Y path is slower. So that is what I have written here. The path trough Y is slower than the directed activation or X by S. And that causes fast rise of X at the initial time points.

But then Y increases slowly and it catches up the progress of X and then you start inactivating X. So once it reaches this peak and Y reaches here. Y become in dominant and it try to inactive or pull down X and eventually it reaches the steady state where their effect of S on X for activation and the inactivating effect of Y balance each other and I get a steady state of X. So the steady state of X reaches after a initial spike. Now remember using algebraic calculation is simplification and the phase portrait we have shown that the steady state value of X is independent of S.

(Refer Slide Time: 24:40)



Let us try to see that using numerical simulation, using this JSim code, what I will do here? I will initially keep S equal to 1 and simulate for 10 minutes. So I keep S equal to 1 and simulate for 10 minutes and this simulation start at T equal to 0 with X equal to 0 and Y equal to 0. So after 10 minutes X reaches the steady state, Y reaches the steady state and note down those steady states value and then I again do another simulation with S equal to 2, again simulate for 10 minutes.

But in this case at initial condition T equal to 0, X is equal to X steady state that I have got earlier and Y equal to Y steady state. These two values are coming from this simulation, the previous simulation. The steady state values of X and Y that I have got in the previous simulation, I used them as initial condition now and increases S to S2. Then what I do? Again I do a simulation which is S equal to 3 and simulate it for 10 - 15 minutes but here T equal to 0 at initial condition X is equal to XSS, the steady state value of X that I got from the previous simulation.

So that's how I keep simulating so that I can show you the effect that how if I switch signal S from zero to one then two, then two to three how the steady state behavior X or the output will change. So I have coupled all these three data set together to create one signal graph here.

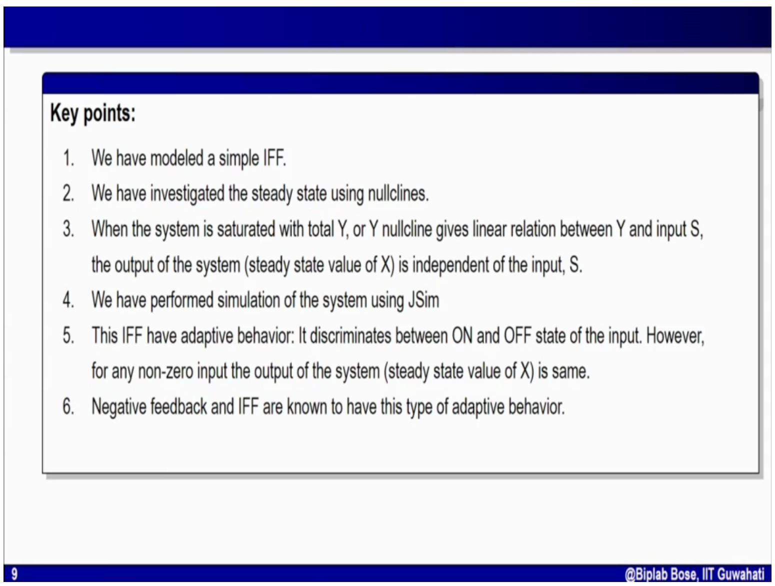
So you can see initially S the input signal was zero, this on level. Here at 10th minute I have increased S equal to 1, so S equal to 1 here and kept it for next 10 minutes. So this is my 10 minute. So when I have given this pulse of S is equal to 1 I got sudden rise of X up to this spike point and then it falls and reaches the steady state. Similarly here Y increases and reaches a steady state here. Now at this 20 minute I give another pulse of S to make S equal to 2 now I double S, the input signal is doubled. You can see Y increases and stabilize at a higher steady state value but X increases with a spike up to this point and then it falls back and reaches another steady state.

Here at this steady state I do the third simulation. I take these two steady states values; this one and this one as initial condition and give another pulse of S. Now S is equal to three so S has higher value here. Here also we consider why this point this steady state value as initial value and this steady state value of X as initial value. You can see Y increases and reaches a higher steady state with time whereas X increases and then falls back and reaches another steady state value. If I look into this steady state, these three steady states, for S equal to 1 S equal to 2 and S equal to three all are actually in the same line and that is near point five.

So in this composite graph I can easily see that as I jump S from one to two, two to three, X increases slightly initially but then it falls back to the same value. It is just like the stabilizer work in your house. If there is a sudden spike in current there is a sudden spike you get and then stabilizer stabilize the current again to the same value. The same thing is happening here. So in this system the motif can differentiate between on and off. When S equal to 0 obviously X is also equal to 0, the steady state value. But once you make S non zero irrespective of the value S so either it one, two, three, four or five I always get a same higher steady state value of X, which is here close to 0.5.

So the system is like this. I have a input which is consecutive on increasing amplitude, I am giving S is changing from zero to one to two, two to three and the output which is nothing but study state value of X has a unique behavior that after initially transient spike, X reaches the steady state value which is same for all values of X. In other words, the system is sensitive to on and off state of the input, for an adapts for on and on values to a same output. That's why this type of motif is adaptive motif. It can differentiate within on and offs state for all on state it reaches to the same steady state the same output irrespective of what is the input signal and this type of behavior this type of adaptive behavior is very crucial in many cellular process where the signal from the outside can fluctuate. But whatever be the signal as long as it is a on signal, it is above basal level, the system will collapse to the same steady state, the same output.

(Refer Slide Time: 30:52)



Let us jot down the key points that we have discussed in this module. We have modeled is simple IFF, Incoherent Feed Forward. WE can make it complicated; we can consider complex dynamics of that to get a understand the basic feature of this system. I have considered very simple IFF. We have investigated the steady state using the nullclines then we have shown even the system is saturated with total Y or Y nullcline give linear relation with Y and S. Then the output of the system, here the steady state value of X is independent of input, that is S. This is the crucial one.

So the output is independent of S and one key assumption to achieve that what we have got is that the system is saturated with Y, in other words KM, the micro segment and the constant for activation of Y was much smaller than total amount of Y so that I get a relation between, leaner relation between Y and S. Then the system is adaptive and I get same output for all values of S. We have performed simulation using JSim and we have tried to understand the IFF behavior here and we have shown that the system can discriminate the, the motif can discriminate between on off state of the input however for any non zero input the output of the system that is the steady state of X is same. So system is adaptive.

And one key point here we have to remember it is not just the IFF, negative feedback in certain cases also can show adaptive behavior in general where modeling, a cellular process we have to keep in mind, depending upon the parameter values both negative feedback and incoherent feed forward can give rise to this type adaptive behavior. That’s all for this module. Thank you for watching.