Computational Systems Biology
Karthik Raman
Department of Biotechnology
Indian Institute of Technology – Madras

Lecture - 86
Modelling Gene Regulatory Networks

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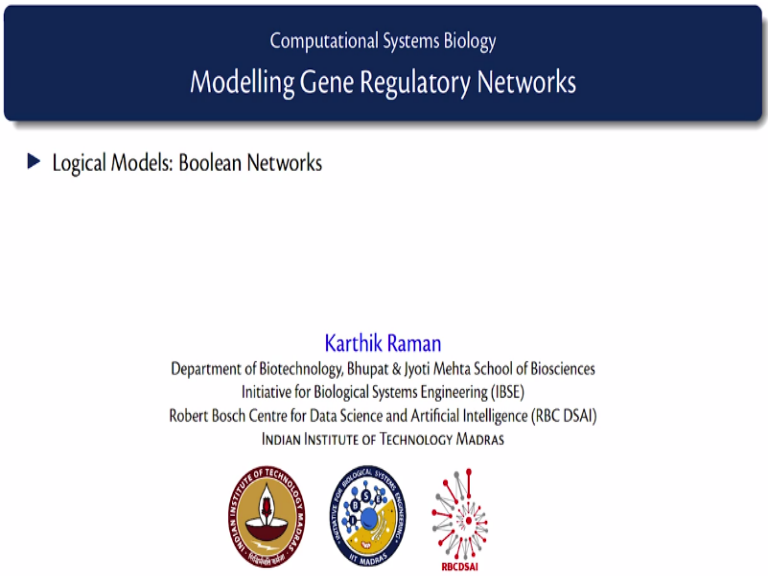

So after a long series of lectures on constraints-based modelling and metabolic networks we will now move towards gene regulatory networks. We will particularly look at logical models or Boolean networks in today's video. So welcome back. Today we will look at modelling gene regulatory networks. There are many ways to model gene regulatory networks or how metabolism is regulated and one of the examples we already saw was regulated flux balance analysis. Today we look particularly at Boolean network modeling.

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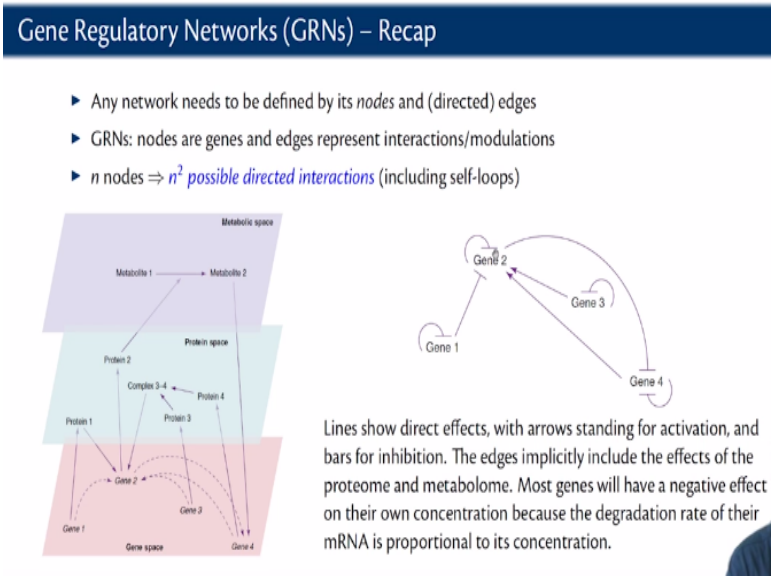

So to recap any network needs to be defined by its nodes and edges. In this case, we will have a directed network. So in a gene regulatory network, the nodes are genes and the edges represent interactions or modulations and you have directed interactions because you have a gene can represent another gene or a gene can activate another gene and so on and you can also have self loops. So you can also have self-loops in gene regulatory networks.

So this is how a gene regulatory network is usually derived so you have some interactions happening in the metabolics phase. Some interactions happening in the protein phase. So you have a protein that complexes with another protein and then you know may be access a transcription factor for another gene and so on and so forth. Finally, this is how the gene regulatory network looks like. If you project all the interactions to the gene space, you say that gene 1 inhibits gene 2 or represents gene 2.

Gene 2 inhibits gene 4. Gene 4 and gene 3 activate gene 2 and so on and so forth. So how do you model these kinds of systems?

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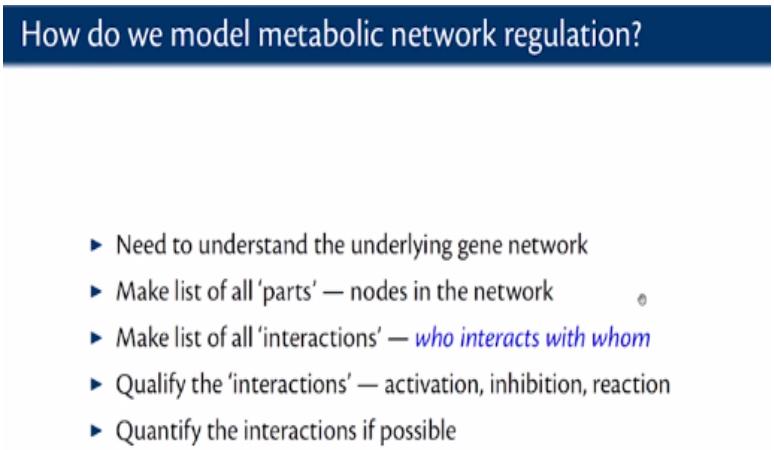

So you need to first understand all the underlying parts. So make a list of all the parts of the network and make a list of all the interactions of the network and then qualify and if possible quantify the interactions. This is almost like filing out an adjacency matrix. So if you just fill 1s and 0s it is sort of qualitative. If you can actually say this is going to be like 0.99 this is going to be - 0.3, it will end up being quantitative and you have to reconstruct this from literature and from experiments and so on and so forth.

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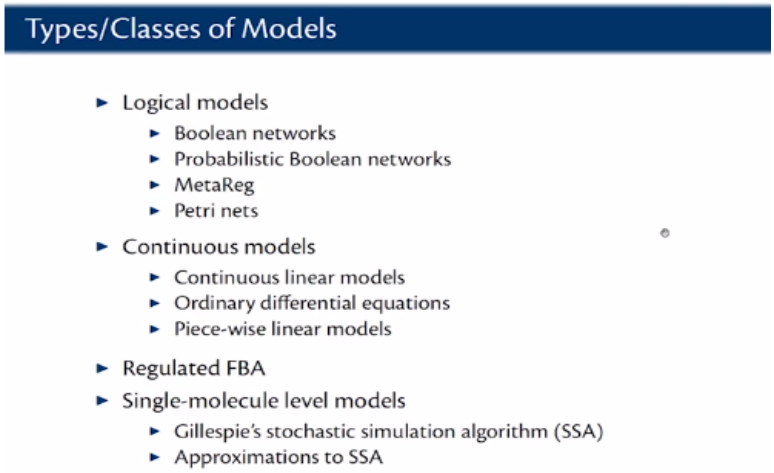

So there are many different classes of models that can be used so this in this slide I tried to list many of them so the most useful paradigm is that of logical modeling where are Boolean networks, probabilistic Boolean networks then tool such as MetaReg and there are also Petri nets

which have been used in the past and continuous models are something that you already know. So you can have continuous linear models, ordinary differential equations, piece-wise linear models and so on.

Regulatory flux balance analysis something we have done in a previous class and you can also have stochastic algorithms so as Gillespie's stochastic simulation algorithm which is very popular and there are approximations to Gillespie's algorithm. So we are not really looking at stochastic because most stochastic models are very small. Stochastic itself becomes important when we have very few numbers of interacting molecules. So when the probabilities of interaction or the numbers of molecules becomes more important than concentrations and rates.

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So what are logical models? So, logical models actually belong in a discrete modelling framework.

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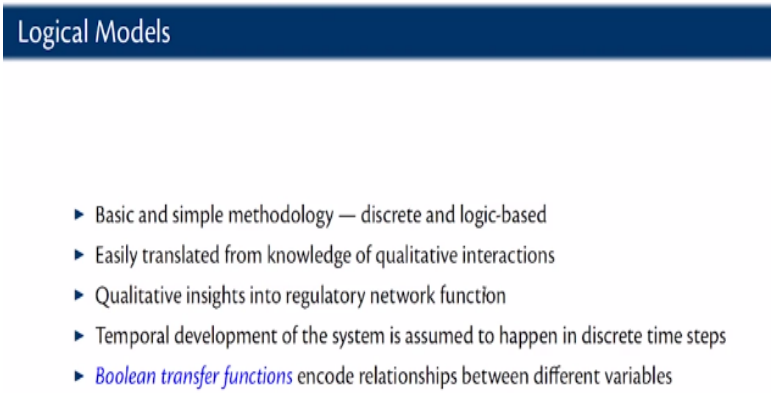

So it is easily translated from the knowledge of qualitative interactions and of course you will get qualitative insights in the regulatory network function and the temporal development of a system is assumed to happen in discrete time intervals. So meaning you have a snap shot of the systems at t = 0, then t = 1, at t = 2 and so on and you can sort of make a relationship between what is how the state of the system at t = 1 or 2 depends on the state of the system at t = 0 or 1 and so on and so forth.

So there are what are known as Boolean transfer functions that encode relationships between the different variables or the different states.

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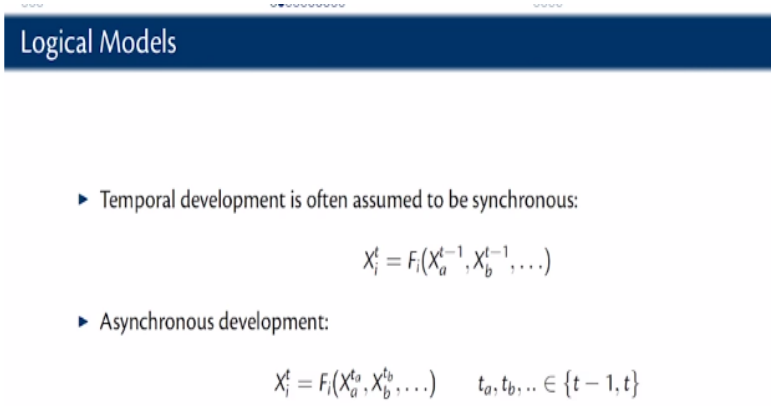

So the temporal development is often assumed to be synchronous or asynchronous. Let us just see what this is.

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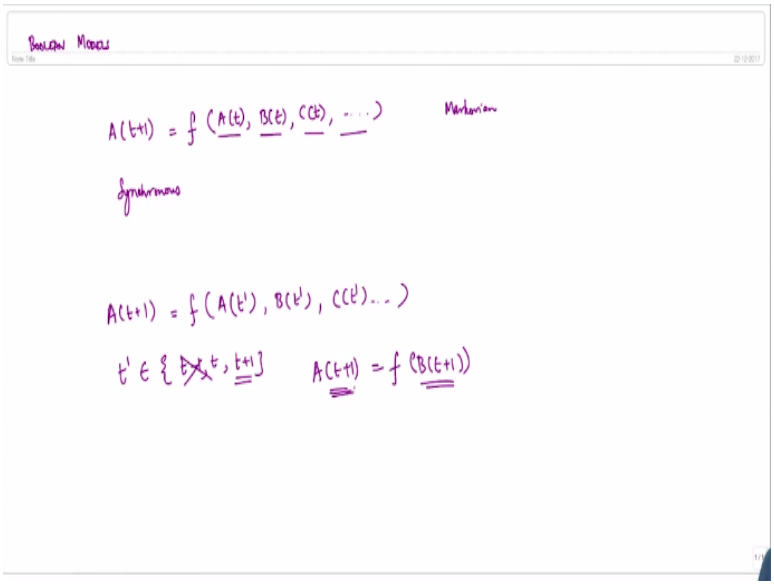

So you basically have A(t) or you can say A(t + 1) = f(A(t), B(t), C(t)) and so on. So this is almost like a Markovian. I have just 1 step 1 piece of memory, 1-time step that you are talking about. So A(t), A(t + 1) directly depends on A(t). So this is called synchronous. You can also have asynchronous where A(t + 1) is dependent on f(A(t dash) where t dash belongs to t - 1 or t or even t + 1).

Usually we only look at t or t + 1 meaning so what does this mean when I say A(t + 1) or A(t + 1) depends on let us say A(t + 1) what does this mean? The effect of Beach, the change in B is instantaneous whereas in this case, you always have 1-time step for anything to take effect. So whenever B has changed so the B(t + 1) immediately affects A(t + 1). So the effect of change in B is instantaneous for A and so on.

So this is what we say here. So here instead of t + 1 and t I have t (nt - 1) where it is basically the same and you can also expand this if you want this no real restriction. You can have kind of discrete modeling framework where you can have something that depends on t - 10 for all you want. So if you know that something is very slow it is going to take 10 steps for you to take effect so that can be integrated. So how do you set up these rules?

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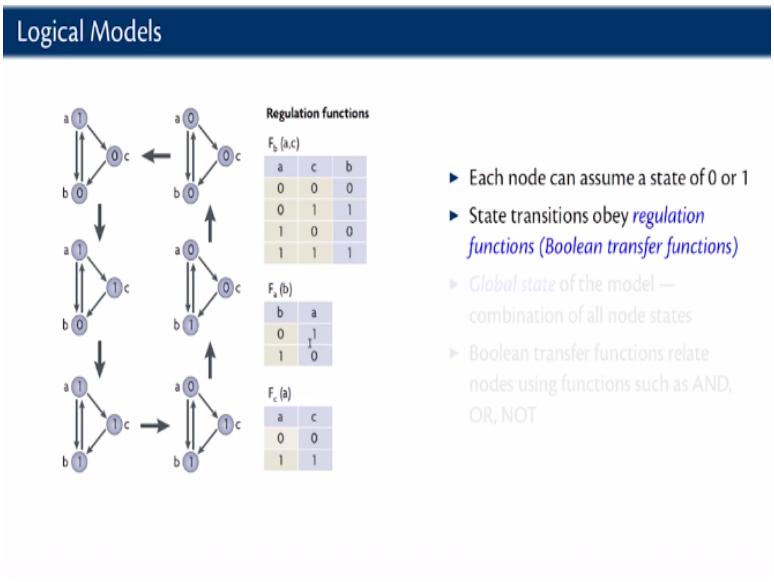

That becomes the next question. Let us look at a simple example. So the first thing we assume is that every node is only in 2 states. It is either on or off. Basically 1 or 0 and all the state transitions obey the Boolean regulation functions are what we translate to Boolean transfer functions. So can you tell me what is this function? So this is basically a truth table which says what happens to be as a function of A and C. So BAC.

So you can essentially write this as we normally try to write down the rules in this fashion. This is to denote the update using A star.

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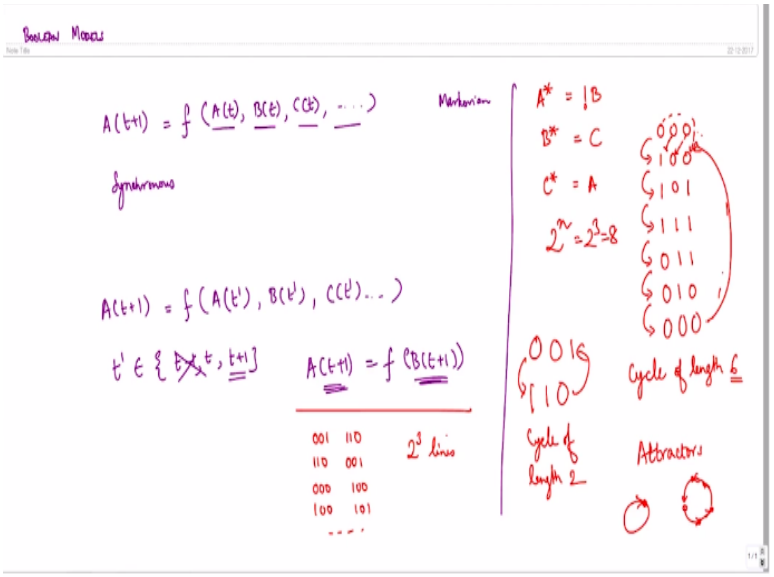

“Professor - student conversation starts” So B star = C and here A star != B and what about C star. So now given this you can immediately figure out how the straight transitions happen. So let us say we started 0, 0, 0. May be I will reorder the rules. It will be easier for us. So A star != B. B star is C and C star is A. So what does 0, 0, 0 transit to? 0, 0. So you basically negate the second one and copy the third and the first and that is what we are doing.

So you take C axis and put here and this you negate and put here and is that right. **“Professor - student conversation ends”** So now let us do the same thing. So it will again become 1, 0, 1. It will now become 1, 1, 1. So this is. Now what is the next step? 0, 1, 1 and the next step would be 0, 1, 0 and the next step would be 0, 0, 0 it is basically the same as this. So you have a cycle of length 6. So what are the things that we do not see here? I think we do not see a 0, 1, 1.

So let us see what happens to 0, 1, 1. 0, 1, 1 would become 0, 1, 1 is there. What is that we do not see here. 0, 0, 1. 0, 0, 1 would become a 1, 1, 0 which will become 0, 0, 1 which is essentially the same as this. So you have a cycle of length 2. You can also call these attractors. You can have a point attractor or a cycle attractor. We do not have 1 more. This would be a point attractor. This would be a cycle attractor. So how many states do we have?

We will have 2 to the n here it is 8 possible states. So we when covered what happens to each of the 8 possible states. What is the next step? So in fact you can visualize this even with something like cytoscape. All you need to do is you just compute the edges like this. So you make a file of this sort. This is 0, 0, 1 1, 1, 0 1, 1, 0, 0, 0, 1 then 0, 0, 0 1, 0, 0 1, 0, 0 1, 0, 1 and so on.

So all we need is to create a file with 2 to the n lines for each initial condition and then you can visualize certain cytoscape you will be able to see all the how the changes are happening and so on can you can immediately see how many point attractors are there or cycle attractors are there and so on. Better way is to find it, but it is just easy to visualize it using cytoscape.

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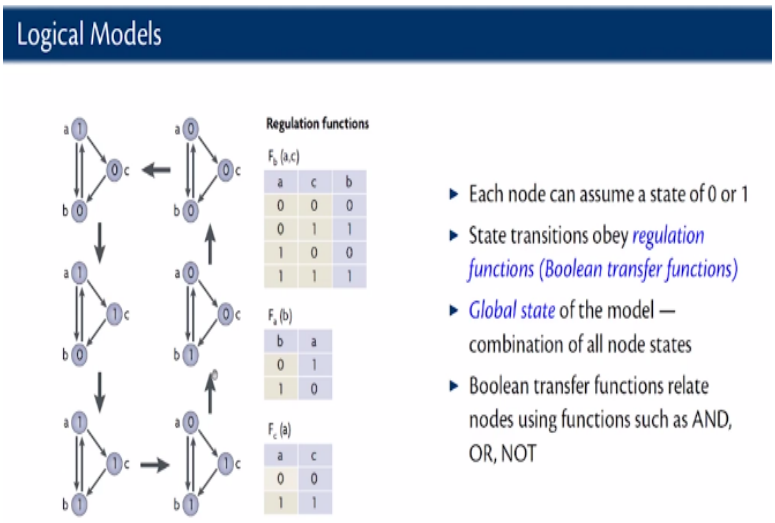

So the global state of the model is the combination of all node states. So this is the state 0, 0 is the state. So you see the same thing here. So 1, 0, 0 goes to 1, 0, 1 and so on exactly what we just calculated. So the Boolean transfer functions can relate the nodes using various Boolean operators like and, or, not. You have AND, NOT whatever you want.

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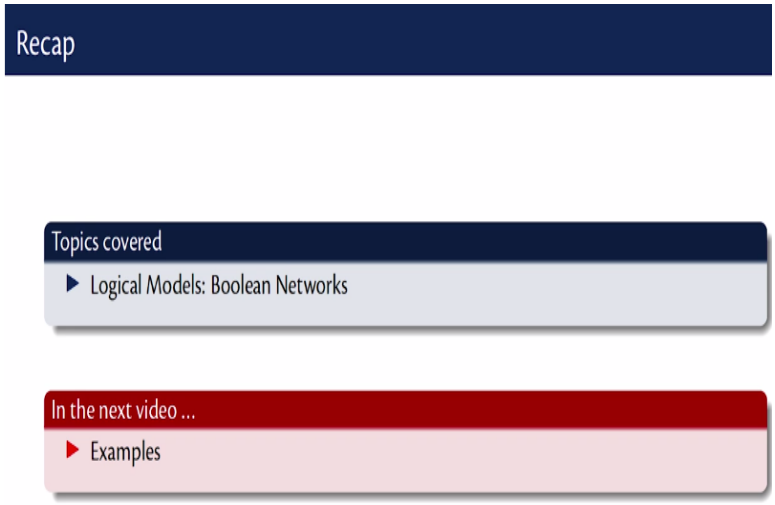

I hope this lecture gave you an overview of logical models particularly Boolean networks. How do you set up Boolean transfer functions and so on to model a simple gene regulatory network? In the next video we look at a few classic examples of Boolean networks.