Computational Systems Biology
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Lecture - 33
Reconstruction of Signalling Networks

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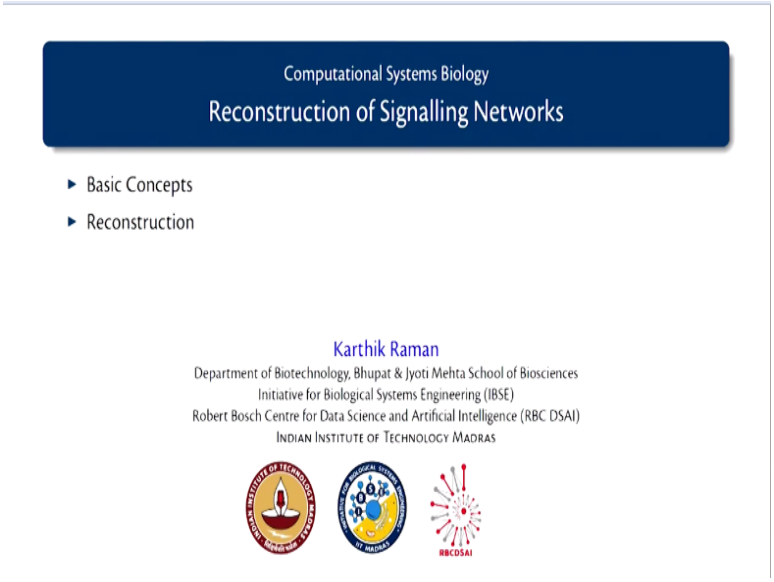

In today's video let us switch to signaling networks from regulatory networks and overview some of the basic concepts of what is the Signalling network and how one tries to go about building these interactions and reconstruct signalling network itself.

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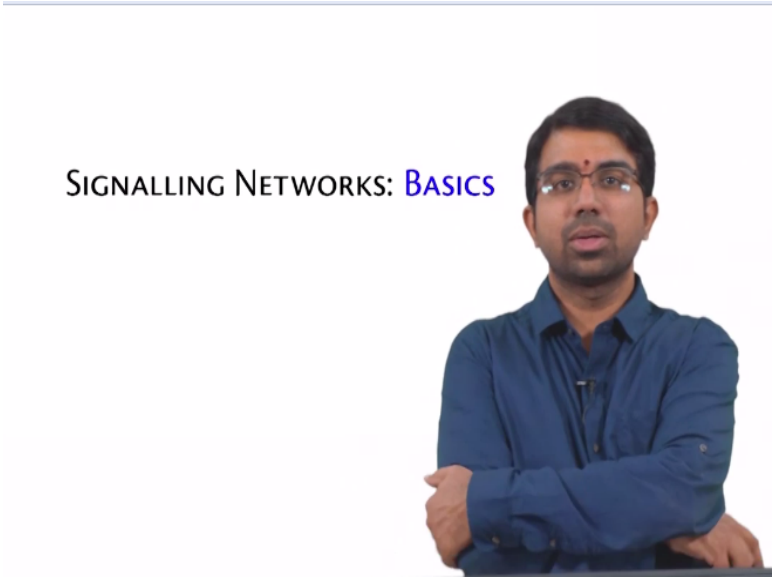

So welcome back. Let us look at Signalling Networks. So, what is the Signalling network? What is signal transduction? So it is usually signalling involves the sensing of something happens outside the cell, some extracellular thing leading to some intercellular response, this is what signalling normally is.

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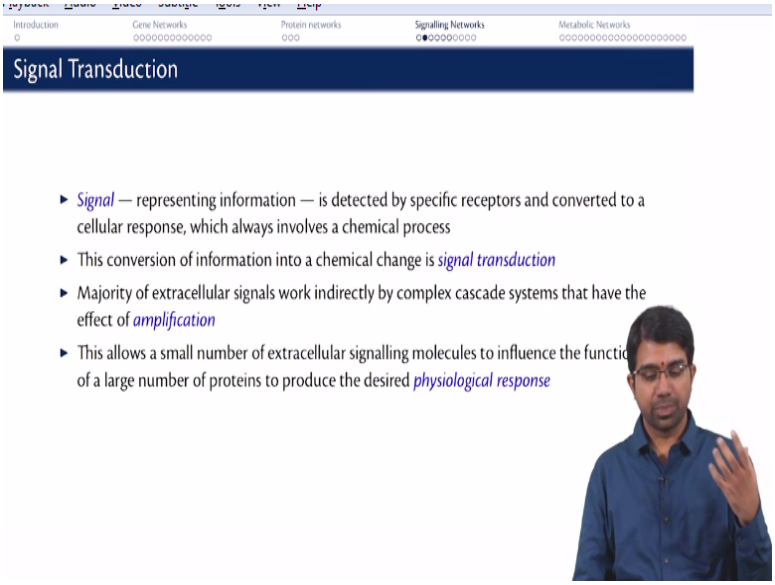

So there is some signals which is essentially some information, it could be the presents of light, it could be the presents of a nutrient, it could be some present of a danger; if you are looking at larger organisms which represents information essentially, which is dedicated by specific receptors within the cell. There are certain receptors within the cell on the cell and this is converted to an intercellular response which invariably involves a chemical process.

This chemical process could involve changes in metabolism, in regulation, in mortality, in gene expression, in so many different things, right. But the key ingredient is something is that outside the cell is causing something inside the cell, right. So this conversion of some sort of information extracellular information which is transduced inside the cell to produce an intracellular response is called signal transduction.

So a lot of extracellular signals work by complex cascade systems that have the effect of amplification as I was mentioning earlier. If you have a long chain of interactions which finally lead to an amplified signal. You may have one photon that is incident on your eye which produces 10 to the 5 proteins or 10 to the 5 of some other metabolize which respond to that one photon right.

So this allows basically for a small number of extracellular signalling molecules to influence the function of a very large signalling pathway or a very large way of set of proteins within a cell to finally culminate in the desired physiological response which might be mortality you now moving chemotaxis moving towards the presence of some glucose, right. Or it could be the change in gene expression, right turning off something I no longer seeing lactose; I am turning out my lactose machinery, things like that.

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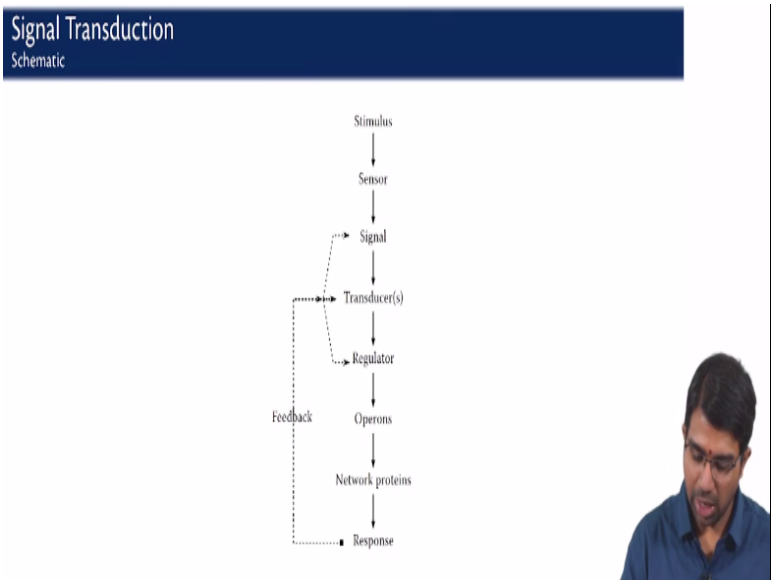

So these are Schematic for a signalling pathway. So does it look? So you have an extracellular stimulus which is sensed you need a sensor protein to first sense it receptor which produces a signal which is then transduced, there is a regulator there are multiple Operons that maybe involved, network of interacting proteins maybe involved finally giving a response. Is it good enough? You need also some feedback. Why? You do not want the response to keep firing, right.

So what happens when you sense a danger maybe you see a snake your (()) (03:21) starts pumping, you know you maybe start taking up more oxygen because you want to create some energy to run or whatever. But you just want to and maybe once you just now wanted to keep firing, firing, firing right. For example, when you walk up of a dark room into a brightly light room, right your eyes start something happens, right.

You people start contracting, contracting-- it has a stop, right it has to adapt it should not be firing, firing, firing because the response is -- you have to reach a new steady state, right. So this is called desensitization of the signal you become desensitized to the perturbing initial signal. This is a very important aspect signal transduction, right.

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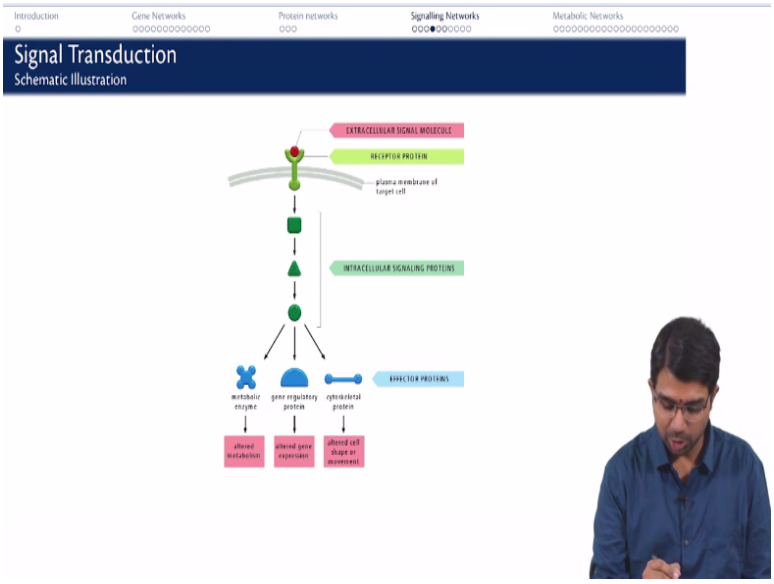

So what you have an extracellular signal molecule, a receptor protein will usually outside the cell which may have an internal domain as you see here then a bunch of internal signalling proteins, finally controlling either a metabolic enzyme or a gene regulatory protein or something

cytoskeletal which will involve mortality and so on. This is a classic canonical representation of any signalling pathway in any cell typically.

So what do we mean by signalling network. This is whole as a signalling network right. You do not have just this you have a bunch of proteins here then a bunch of downstream things and have several allied signalling proteins, right.

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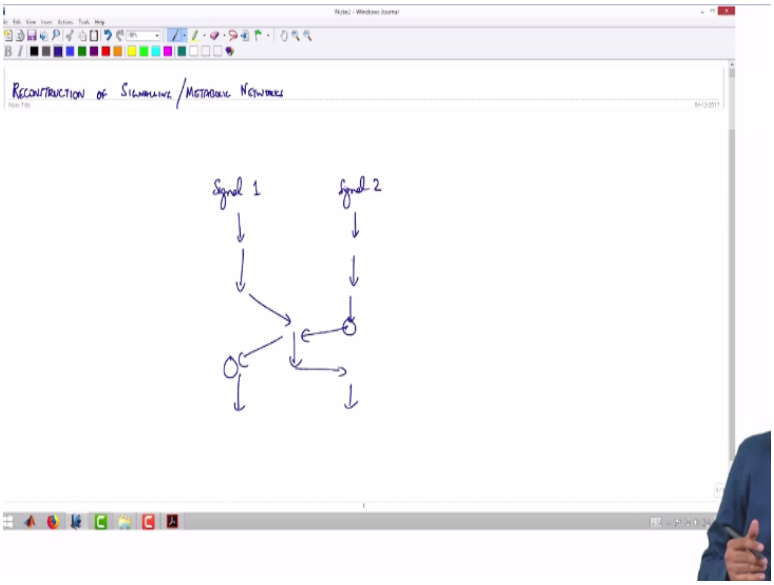

So you may also typically you integrate the two signals, right. So there is some independent pathway, we have a lot of cross-talk, this would independently take a particular route, this would independently take another route, but when the two are present you may have a lot of crosstalk between a signalling pathways, maybe this protein can also bind the protein here and so on. So you basically have a complex network of interactions whenever there is signalling.

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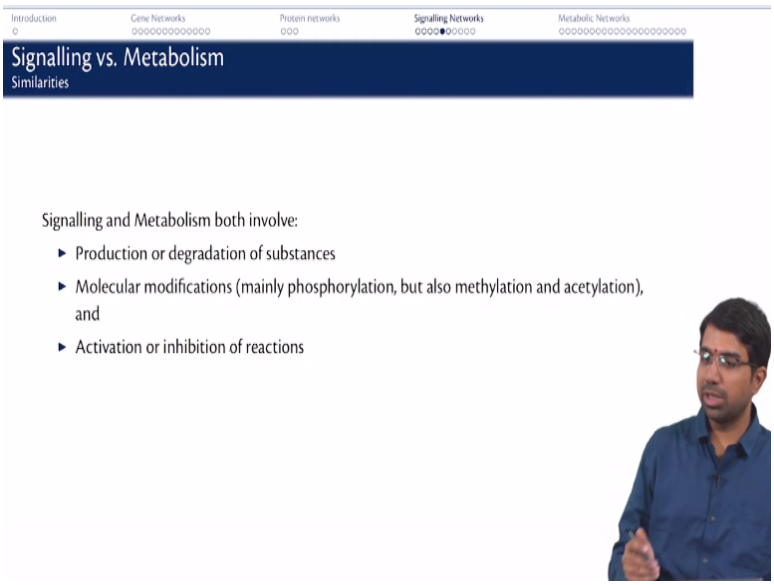

So let us look at signalling and metabolism, right. We did do a little bit of metabolic networks earlier on. Will again do some more metabolisms today. Both signalling and metabolism involve production or degradation of substances. In one case, it is small molecules in the other case it is some it could be small molecular again in signalling but often it is larger molecules or protein themselves is turned off and turned on. They may not be degraded they maybe just switched off.

And then lots of Molecular modifications. Now here in signalling it is mostly phosphorylation, methylation and acetylation. In metabolism, you have many more complex types of modification. You could have activation or inhibition of various reactions, same thing that holds for signalling.

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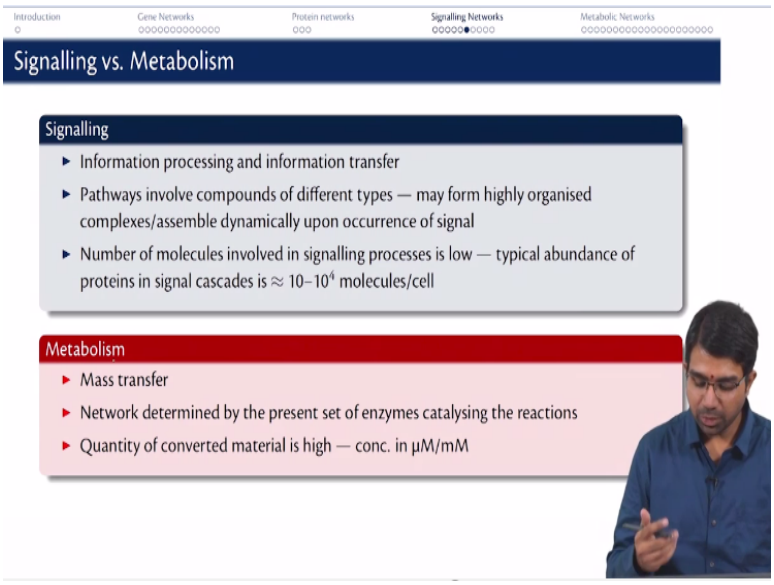

What are the differences? In metabolism you have a lot of mass transfer, in signalling it is mostly information processing and transfer. So in metabolism the network is determined by the current present set of enzymes catalyzing the reactions whereas in signalling there are compounds of different types and there is a lot of complexity possibility you can have sub-networks, modules all operating in different ways.

You do not have pathways here but here in signalling the organization is the lot more important. Because one module might fire under one condition the other module might fire under another condition so on and so forth. And in metabolism you have lots of reaction happening, right. You have nanomolar, micromolar, millimolar concentrations, whereas in signalling you are talking about few molecules you are not talking about few moles or micro moles you are talking about a few molecules, right.

So still in many cases you have enough molecules so that you can go in for regular dynamic modelling but some cases you may have to resort to stochastic modelling.

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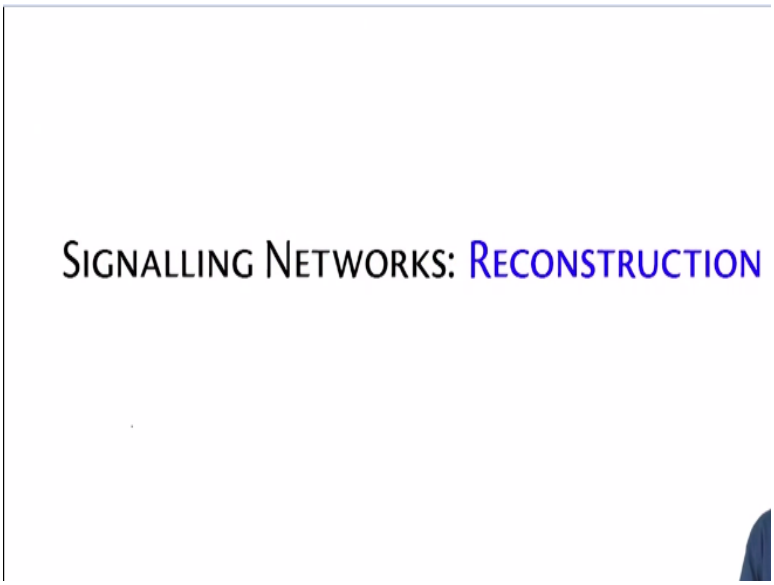

So how do you reconstruct signal networks? What is mean by reconstructing a signalling network?

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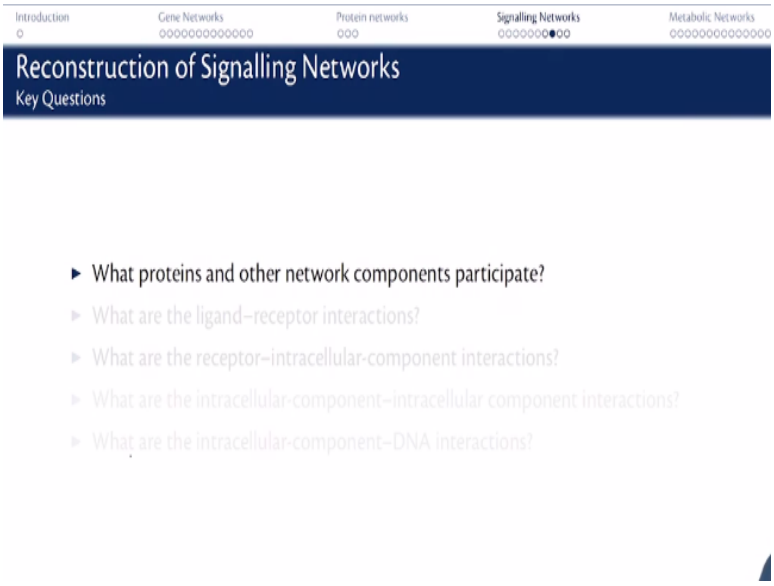

First question is what are the proteins that are involved and what other components participate? So any signalling network has, what are the components of any signalling networks?

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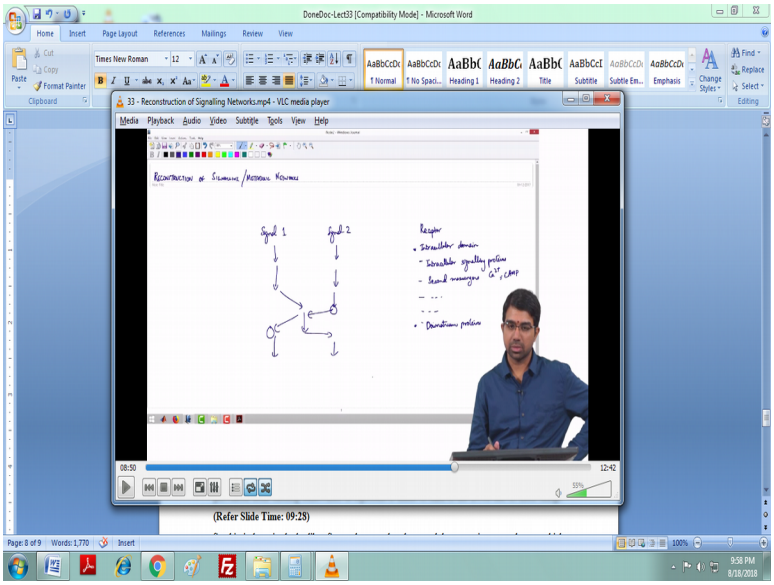

You have a receptor or sensor whatever where a signal comes and binds. Then you have Intracellular domain typically but then you have bunch of Intracellular signalling proteins and what are known as Second messengers. This could be something like and so on. Small molecules that usually carry some information from one protein to another and so on and so on till finally your downstream proteins. This whole thing is your network, right.

Starting from this protein if you will all the way up to these proteins. So how does it look like?

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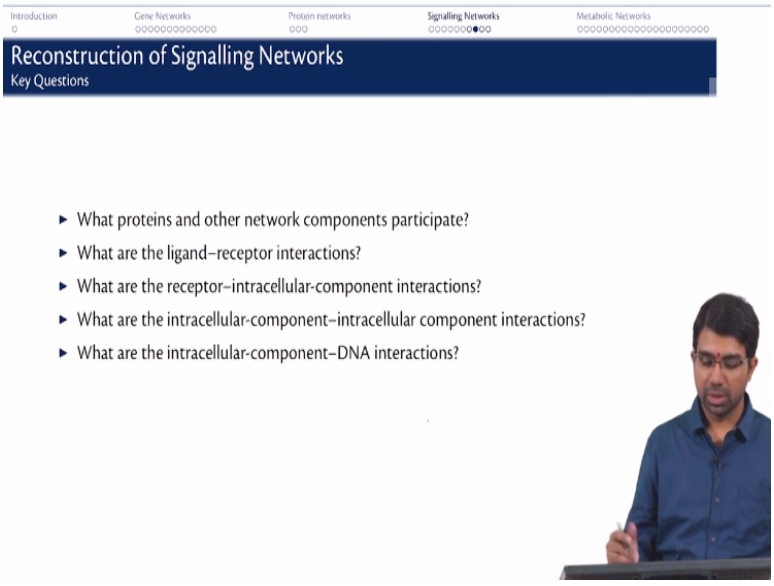

And, the next thing you need to worry about are what are the ligand-receptor interactions. You may have CAMP which is a ligand which will go and bind to some receptor, right. Or what are

the receptor-intracellular-component interactions. What are the intracellular-component-intracellular-component interactions? And finally you know, maybe DNA is involved, right. You have a transcriptional factor that is prevented from binding somewhere or made to bind represses is made to bind to the DNA, one of these things.

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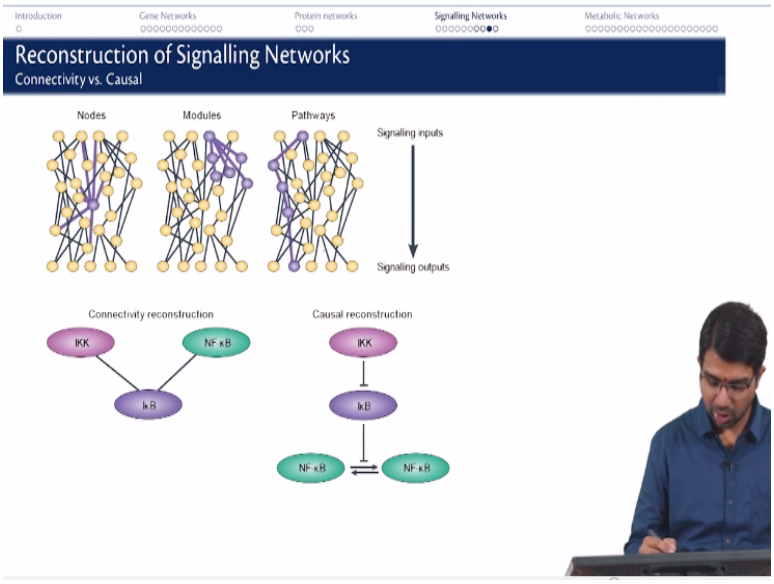

So this is how its looks like. So we have nodes then modules organized into pathways which basically translate the signalling inputs to some signalling outputs, okay. And you can have different types of reconstruction. You can have just simple connectivity based reconstruction. What does this mean? This means that there is an edge in the adjutant cemeteries but you do not know the sign of the edge.

You may know the sign in which case you get more information like this. You have IKK inhibits, IkB which then innovates this enough carba-beta switching on and off, right. So this is more detailed than what you have here, right. So it depends upon the level at which you have data, it depends upon what is the question you want to ask about signalling network typical things. So if you know that you are dealing with very small number of molecules you will have to start worrying about noise.

So Stochastic modelling is you do not no longer talk about concentrations and things like that but you instead start talking about probabilities and numbers. How many enzymes are in phosphor

related state right and yeah expected number of molecules in a particular state, what is the probability of a particular event happening, okay. Usually assume that if there is a x of this there will be point of 1x of something else, no. With some probability you will have the number of molecules which will be in state B will be drawn from a distribution. It is not deterministic.

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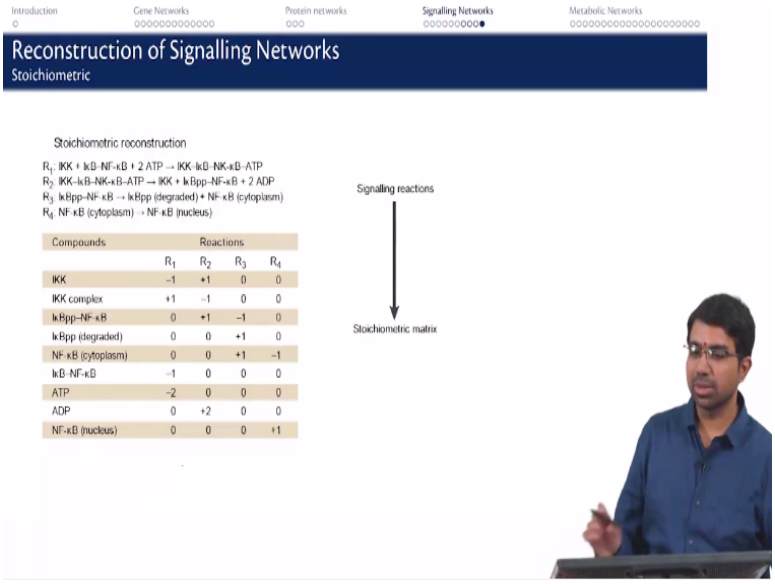

So if you run this-- if you have a simulation you run it many times you will get different outputs. Another way to go about this reconstruction is something known as a Stoichiometric reconstruction. You basically treat all these chemical reaction, okay. You have 1 IKK+ 1 molecule of this protein + 2 molecules of ATP giving some other phosphor related version of this intermediate or something like that.

And then you have this reaction which finally gives you 2 ADP, right. You have chemical modification happening all along. We will see how this Stoichiometric build couple of slides down the line. But basically you start modelling them as reactions instead of networks, right. So this is finally going to represent a network but this is notionally different in the sense, you are looking at individual signalling reactions rather than a network.

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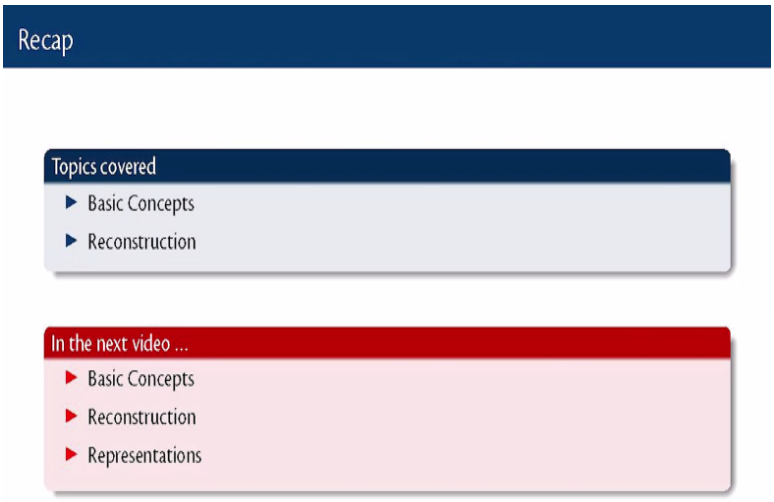

So in today's video we looked at some of the basic concepts underlying signalling networks and how one goes about reconstructing signalling networks. In the next video, we will move over to metabolic networks which has a special emphasis in this course and we will look at some basic concepts of metabolic networks, how does reconstruct metabolic networks and what are the different ways to represent metabolic networks.