Introduction to Dynamical Models in Biology

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Lecture 15

Modeling Molecular Processes in Cell

Hello, welcome to module 3 of this week's lectures. Till now we have discussed different generalised aspects of ordinary differential equation base models, we have discussed how to solve the ordinary differential equation base model using analytical method by integrating it the equations, we have discussed how to numerically solve them, along with that we have discussed different algorithm of numerical solutions of ODE's, we have discussed how to graphically analyse using direction field or fixed plane plot. If I have a system of ODE for example, we have also discussed how to create model and simulate them using Jsim. If you have noticed in all these models we have discussed about population growth model, we have discussed about spread of infectious diseases, we have discussed how fish growing in a tank and then sold can be modelled using ODE's, all these models are actually macroscopic processes involving population, individual fish, individual human being or microorganism something like that.

Now we will enter into another aspect of dynamics in biology that is the molecular cellular processes. Every cell undergoes, every living cells continuously undergoes different molecular processes for example a cell may be white, it may go through a cell cycle as you remember. Continuously as a cell is living it requires new protein, so it transcribing and translating proteins, those transcription and translation are again controlled by transcriptional network. Then you have cell signalling by which a external signal comes and the cell responds, obviously there is metabolic processes going on, metabolism of sugar, metabolism of liquid, metabolism of proteins, amino acids, so continuously there are many processes going on in a living cell and all these processes are dynamic processes and we want to create mathematical model for those dynamic processes if you remember and particularly we want to create ordinary differential equation based model for it.

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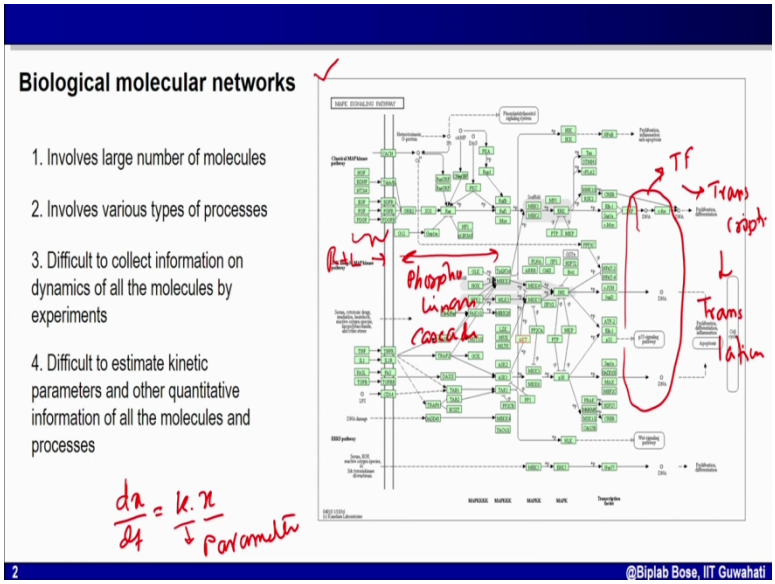

So if you open any cell biology text book you may find the type of figure I have shown here, the figure I have taken from cake database, it is showing a simplified and a reduced model or rather I will say it is a graphical model of MAP kinase pathway. MAP kinase pathway is one of the pathway which controls multiple processes for example cell cycle it control metabolism inside the cell, and multiple signalling molecule like growth factor or growth hormones they give signals, input signal to this MAP kinase pathway and as you can see in this figure these pathway even when we have made it a reduced form in the multiple molecules. So if you know open you biochemistry or cell biology book you will find many such cell signalling pathways, you will find large in chart or maps or graphical model for metabolisms or metabolic circuits and we want to create models for them and I want to understand the dynamics of the processes in alternative.

Now there are certain issues when you are trying to model this type of cellular processes, let us look into those issues and some of the tissues are issues are actually will cause a difficulty in creating mathematical models. The first important issue in this type of molecular cellular processes is that these processes involve large number of molecules in 100's sometime. So if you have large number of molecule and if you want to consider each of these molecule as a their concentration as a dependent variable those are changing with time then you have so many ordinary differential equation. If I have three molecules then I will have three ordinary differential equation, if I have four, I will have four ordinary differential equations representing rate of change of concentration of each of these molecules.

If I have 100's of them then I have 100's of ordinary differential equations for each of them and that's obviously a trouble when you want to simulate them. Then apart from molecules there many types of processes involved in a particular network, for example the network I have shown here, initially if you notice this is the cell membrane and you have here receptor ligand interaction, receptor ligand interaction. Then what the process is going on this part are essentially cascades of kinase enzymes, so in a phosphokinase pathways where one molecules get activated then it becomes a kinase enzyme, it goes and phosphorylate another molecule, that molecule becomes phosphorylated again and its an active kinase.

Now, so you have a casket of events happening, so this is a phosphokinase, phosphokinase cascades if I say it simply. Then in this part, in this part they are showing how transcription factors are working so that transcriptions happening followed by translation. So if you look it simply in this reduced model of map kind in its pathway there are multiple processes, some are ligand receptor binary, some are phosphokinase cascade of reaction one after another and then at the end there is transcription and translation, apart from there are obviously degradation of proteins using a particular pathway.

So a molecular network which eventually may control suppose cell cycle or growth of the cell is in made up of multiple molecules involved in multiple processes. So when you are doing a mathematical model you have to take consideration of all these processes, so all these processes should be reflected in your model. One third problem that you will always face where while working with large network or molecular process is that dearth of experimental data, till now the type of experimental system that we have, it is very difficult to collect dynamical data, means I want to collect the change in concentration of each molecule with respect to time for all the molecules in this network.

So it is very difficult to collect information on dynamics of all molecules by experiments and that is very rare actually. Then another important problem and rather a big offset in creating ordinary differential equation based model for this type of large network is that you require kinetic parameters. If you remember, if I write a simple ordinary differential equation like $\frac{dx}{dt} = k.x$ so x is the dependant variable, k is the constant which is parameter, so I require numerical help for this parameters if I have to model and understand the dynamics of x, so similarly in

these large bimolecular network I want to know the parameter value for each of the parameter involving the processes like if I write constants and that is very difficult to calculate experimentally and for most of the cases it is actually not known.

So there is a dearth of quantity information that I can pluck in my model and that is a bigger obstacle for us when we want to create a model for ordinary differential equation based model for a large molecular network. Now if I have these troubles, if I know these are the issues there, can I circumvent them and try to break down the problem in a simper fashion and that is what someone watching an electronics or electrical engineering will do.

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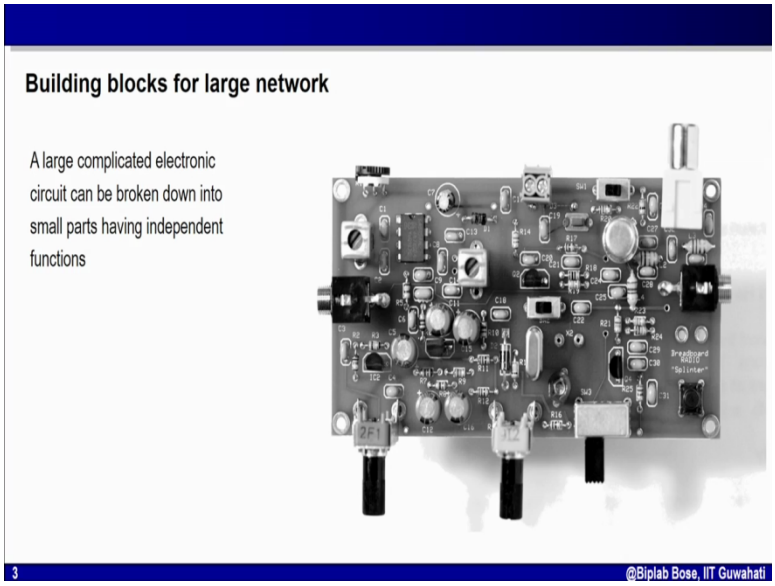

Suppose I have opened a radio and show I can see a electronic circuit board with lots of things attached there, so if you look into the electronic circuit of radio, it is a large circuit involving multiple things but you can jot down few things a part you can break down this whole circuit in small part and each part will have different function. For example one part of the whole circuit maybe essentially a circuit for receiver which receives signals then there maybe one part of the circuit which is independently is nothing but a amplifier, then there maybe another part which is converting this electrical signal into mechanical motion which gives that sound in the speaker.

So in large electronic circuit which as a whole is a radio can be broken down in different parts. So can I use that concept to breakdown a large molecular network into small independent part that would help us to create a simplified version of the large thing. That means what I am saying

here let us breakdown in large network the way engineer breakdown electronic circuit into a smaller one, let us breakdown in large network, molecular network into small parts.

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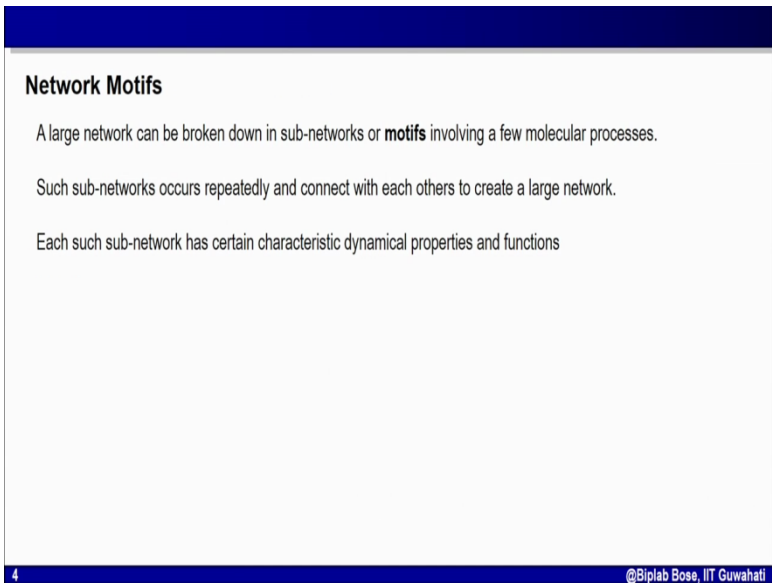

So if we do that what do we get, if I break a large molecular network in the short part we get sharp networks right and we call them network motifs and these motifs are not just made up of one molecule, they are molecules (oh) they involve multiple molecules and involve multiple molecular processes, so they involve few molecular processes and molecules and one interesting thing of these motifs are that if you analyse multiple large network, for example you take each transcriptional control network, human particular cell lines transcriptional network, you look into transcriptional network in *E.coli* and then if you break down all these transcriptional network which are quite large involving thousands of molecule and if you break them in sub network you will find that most of the sub networks they are hand fully numbers but they keep on repeating, so these network motifs or sub networks are actually repeated and connected together to create a large network. So if I can break down a large network into small repeating subunits then what I will do, I will look into whether these subunits or network motifs has specific characteristic dynamical properties or not or functions or not.

So if I can identify certain handful network motifs which involves a hand full of molecules and processes and if each of these network motif has a particular dynamical characteristic and if each of them has a particular function, then I am in a advantages position, then I can study them

separately, I can model them separately and then I can connect them together to create a large model of the large real network, so that's what is impetus behind looking for network motifs and many scientists are actually working on identifying and characterising at rising this network motif in large network.

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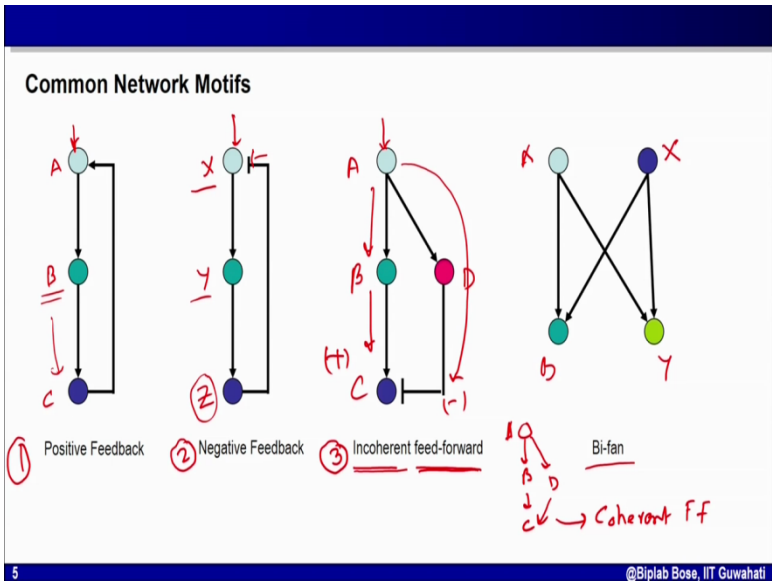

So let us take few examples of network motifs which are really common in biological molecular processes. The first one I have shown here is positive feedback, you looking to cell signalling pathway, a large cell signalling pathway maybe a MAP kinase pathway or insulin signalling pathway something like that, you will see this kind of positive feedback there. A positive feedback circuit has a particular motif structure, the signal comes from one molecule, this are fist one suppose A, then activates B, B activate C and C in turns active A again, so the signal that is coming from top is processed by intermediate state and then the last state goes back, feedback the information again to the initial, so there is a positive feedback.

This type of architecture of network motif positive feedback you will find in transcriptional networks also, for example A maybe working as a transcription factor and controlling the expression of B, B is again a transcription factor and that controls expression of C and C again is a transcription factor that also controls A's production, that means A will induce production of B, B will induce production of C and C in turn will induce production of A, so it is again a positive feedback.

Let us look in the second very common network motif in molecular processes, negative feedback. Just like positive feedback it is the same thing where a feedback is there but only the signage is changed, so what is happening, maybe this one first is X which is a transcription factor which induces production of Y, suppose Y is another transcription factor and induces production of Z. Now Z is also a transcriptional inhibitor of X, so Z goes back and inhibit transcription of X, so in turn you can see where delay of time X is actually represents its expression.

Now not just in transcription or such, negative feedback are very common in metabolic circuits, they are very common in case of cell signalling, in cell signalling network it can be like this that suppose external signal comes to X that is a information coming to X, X gets activated and it becomes active kinase, so when X becomes activated it work on Y and converts Y into a active enzyme, so once Y is activated it works on Z and converts this Z from inactive form to active form. So now Z becomes a active molecules and it goes inhibit activation of X, it inhibit function of X, so I have a negative feedback.

Let us look into a third network motif which is also very frequent and we will deal with this very frequently in our modelling scheme, this is called incoherent feed-forward. Let us first discuss what is feed-forward and feed-forward network motifs are very common and well known and well-studied in case of metabolic networks but off late we have also found them very regularly in case of transcriptional network studies and case of cell signalling also.

What is feed-forward, feed-forward has a particular motif style where the input starts here at the top, suppose this is A, then the information pass from A to B then B to C but there is another path from A to C which may involve D here, so the information from A can reach C by two path, so it is a feed-forward, it is feeding the information by a another root. Now these two path can have same signage, means they may be doing telling to do the same thing or they may have different signage, where they explain that signage issue in details.

For example the graphic shown here in the motif, A is activating B suppose and B is activating C, I have bifurcation here of the path, A is also activating D but D is inhibiting C, so these path, these path A to C is a positive path, A through B telling C that you get activated, whereas A to D and then eventually C these path is negative path, it is telling no, don’t get activated. So C is controlled by two path originating from A, one is telling it to get activated the other one is telling it to get deactivated, so it is incoherent, that is why it is called incoherent feed-forward.

If I have a situation where A activate B, B activate C whereas A again activate D and D also activates C, this is A, these I will call coherent feed-forward. This type of coherent feed-forward as I said are where you can find in any biochemistry textbook in if you look into the metabolic circuit they are very common and commonly observed in case of cell signalling pathways also and as well as in case of transcriptional networks also. Now look at into another trans motif, network motif which is very commonly shown in observed in case of transcriptional network Bi-fan, this is called Bi-fan as a shape is just like that. So what you have, you have suppose A which is transcription factor maybe controlling expression of B and also Y and you have another transcription factor X which also control expression of B and control expression of Y, so B and Y both are controlled by A and X, so depending upon the dynamics of A and X, B and Y expression will be controlled.

So what I have shown here just 4 few examples of very recurrently occurring network motifs which you may observe in your transcriptional network in case of cell signalling network as well as in case of metabolic networks. That does not mean that this network motifs are limited to only this four, there are many more but all of them have this common property, they made up of handful of molecules, maybe 3, 4 and a handful of processes, 3, 4 processes or 2 processes, they occur repeatedly in large network, each of these motif has a particular dynamical properties as well as they based on the dynamical property they may have particular type of functions. We will in our future discussion we will try to model using ODE's for this type of network motifs and I will try to understand the dynamics of these type of network motifs in details.

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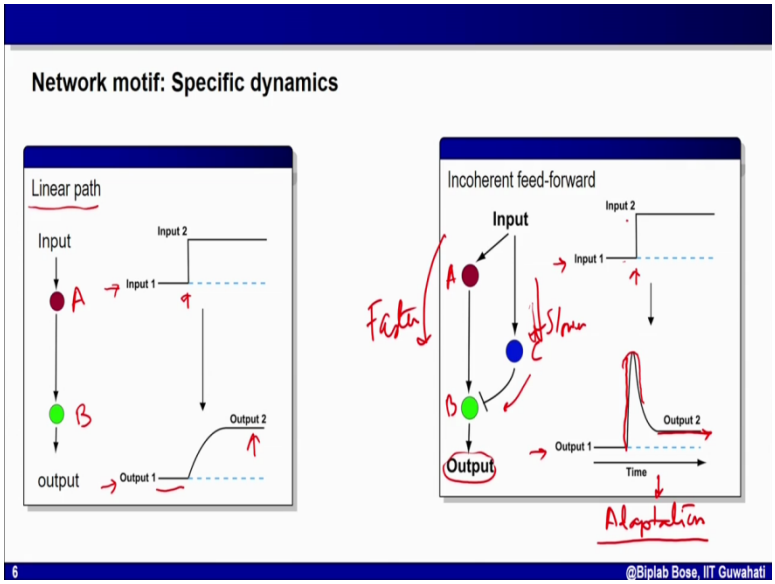

Now as I say, these network motifs has a particular types of dynamic, what do I mean by that? Let us take a example to understand that issue of dynamics for a network model. Let us first look into a simple linear path, what is happening here, you are giving a input signal to suppose A, A controls B that means A is activating B, it maybe enzymatic cascade, A is a enzyme which get activated when it input signal comes and when A is active, A work on B to make it more active and so I get a output.

So suppose initially input was at input 1, a particular value maybe 10 or something like that and the output you have measured is actually at this particular value say 200 or something like that. Now if I all of a sudden increase the input to input 2 which is higher value than 1, so I am doing a straight jump for the input then for these type of linear path I can show by making ODE based model or even by experiment many a time is that the output will also increase, so output was initially like this but then output will increase. So as the input increases output also increases and stabilizes at a higher value, so that means input outputs are matching changing equally.

Now what is the, this is a dynamics of a linear path, this are dynamic characteristic of a linear path A to B. Not let us look into the dynamic property that a incoherent feed-forward will have that does not mean that all incoherent feed-forward will have that type of dynamics that I will show here but it can have under certain constant it can have this type of behaviour that I will discuss. So let us look into incoherent feed-forward, I have input which activates A that activates

B, the same input activate C also, this is the feed-forward path but C inhibits B and I get a output, so again if I have kept input at input 1 in lower value suppose I get a output, output 1, now all of a sudden if you increase input to input 2 what will happen. See if I look into without going in the model, if I look into the structure of the network, I can easily intuitively guess what can happen here.

So as you increase input, input goes through A to B and output should increase but at the same time input is also going to C and it is telling B not to increase and that as you increase input that path, this negative path is also getting activated, so as I increase input 1 path is telling more B to B getting activated, whereas the other path is also telling don't do, reduce the amount of B, so there must be a balance between this. Now imagine if this path is faster than this path which is slower than what will happen, as you jump input from input 1 to input 2, these faster path will increase the output but after it has reached certain level by that time these negative path will catch up and it will try to inhibit the process, so output will drop and then eventually it will set at a lower value.

So what is happening here, actually the system is adaptive, you have a input signal for which you have a output signal, all of a sudden you have increase the input signal, if you have a linear path then output will also get increased but you don't want it, you want that the output should remain close to what was earlier, so if you have a incoherent feed-forward then initially there will be spike of output and then the negative path will drag it down and it will settle at a lower steady state value, so this is typically nothing but adaptation. Imagine you require this thing in a electronic circuit, your input current may fluctuate, so the output should not get disturbed, so you will put a incoherent feed-forward there so that if there is a all of sudden spike of current then there will be rise initial output but then it will again fall back to the previous one, so these type of requirement are very common in case of biological cell signalling also, in case of metabolic pathways also.

So incoherent fright forward can have this particular dynamic characteristic that it can work as a adaptive motif. Hope now this clear to you that what do you mean by dynamic characteristic of a particular network motif and each of these network motif under certain constrain, under certain parameter values will have this type of unique characteristic properties.

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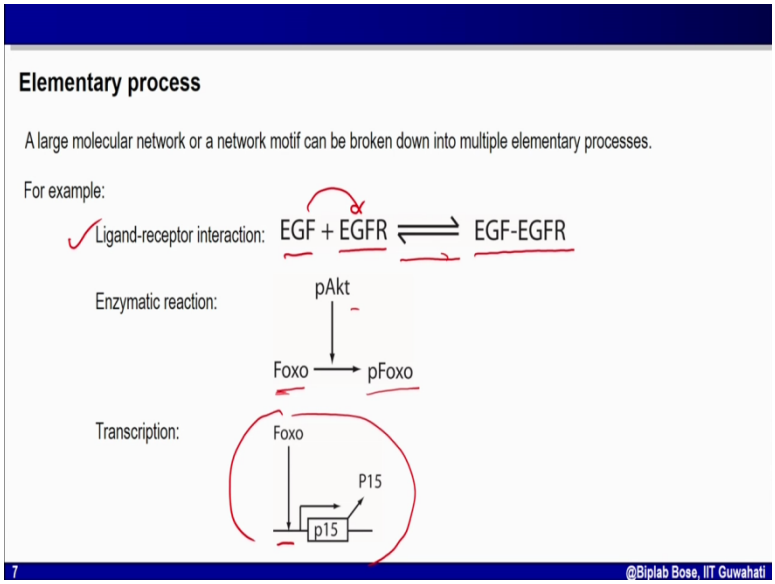

What we have done till now, we have discussed that there are large molecular network which control biological processes, then we have tried to understand what if I break down them in smaller sub-network which we call network motifs. Now network motifs can be again broken down into parts, if you remember I said network motifs are made up of handful of molecular processes, so what are those molecular processes, I can call each of these molecular processes as elementary processes.

Let us take few example of elementary processes, for example ligand receptor interaction on cell surface you have EGFR, receptor for EGF epidermal growth factor, so a EGF molecules comes and bind to the receptor EGF work and forms a complex EGF, EGFR and this complex is auto catalytically activated and some other things activated downstream. So this binding process is a legendary receptor interaction or the binding of ligand to the receptor is actually elementary process.

Then you can have a elementary process involving enzymes, for example if you remember the old example that we had given at the very beginning, FOXO become phosphorylated by pAKT, so pAKT is the enzyme which is a kinase which is activated FOXO related KT and is a kinase and it works on the substrate FOXO and phosphorylate, so this is a unit elementary process. A transcription can also be elementary process for example I have P15, P15 gene which is expressed under the control of FOXO, FOXO accelerate transcription factor and it controls and

activates expression of P15, so this whole thing, this whole transcriptional unit I can consider as a elementary process. Now in large network can be broken down in sub network motif and each of this sub network motif can be again broken down within to this type of elementary processes.

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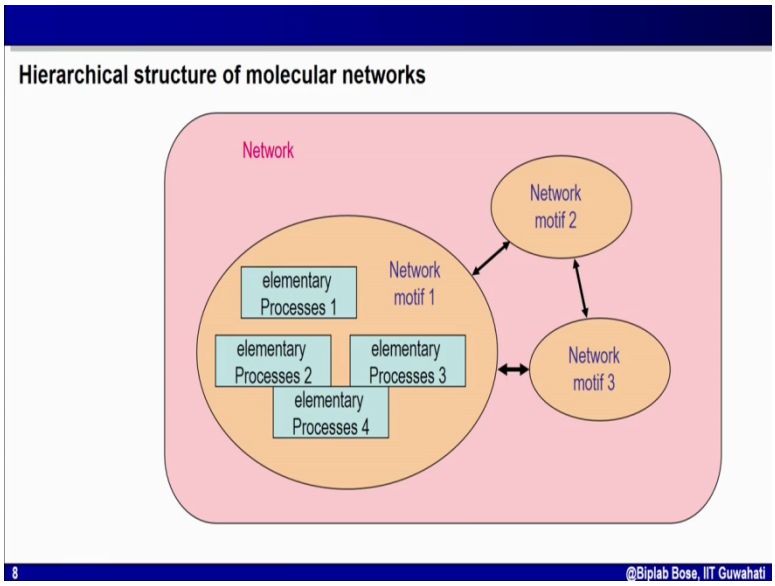

So if you look into the hierarchical structure what do I see, at the lowest level, at the lowest level there are certain elementary processes, for example ligand receptor binding, enzymatic reaction, production of molecules, degradation of molecule, enzymatic control of production of molecule, transcription, translation something like that, so multiple elementary processes come together maybe a handful of them and create a network motif for example a positive feedback, incoherent feed-forward something like that, so I get a network motif, these network motifs are again connected to each other, so I have multiple network motif, 1, 2, 3 for example I have shown here and then all these network motifs they are connected to each other and give rise to a large network.

So if I have to create a mathematical model I should be able first to write down ODE's for this elementary processes because they are the building block of a large network, so what I have to do, I have to first learn how to write it simple ordinary differential equation for each of these co-elementary processes then I will club this ordinary differential equation so that I can create a mathematical model for a network motif and then for multiple models of multiple network motifs can be connected together to create a large model for a large molecular network.

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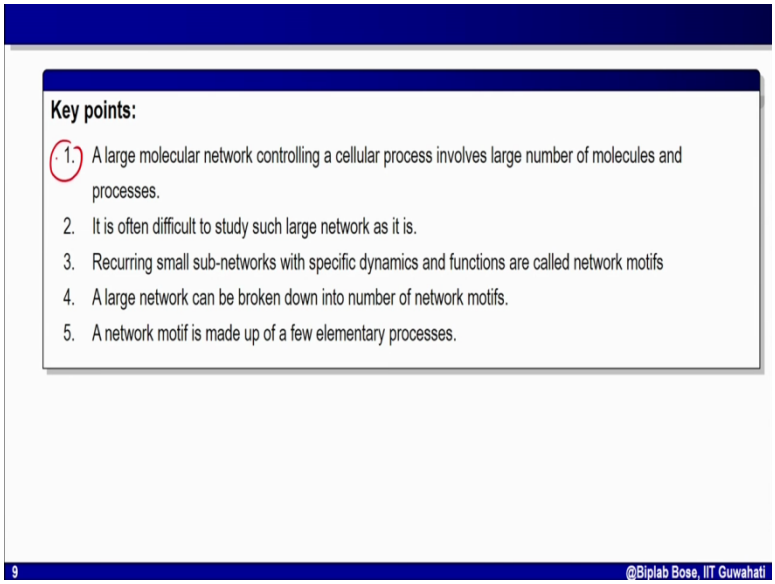

So let us come to the key points that we discussed today, a large molecular network controlling a cellular process involves large number of molecules and processes. It is often difficult to study such large network, as it is, it is difficult to study as it is if you have to do it experimentally as well as if you do it mathematically. Interestingly there are recurring small sub networks which we call network motifs with specific dynamics and functions, so you want to breakdown the large network into small network motif and try to study them or create mathematical model for them.

A large network can be broken down into a number of network motifs on the other hand a network motif is made up of few elementary processes, so if you want to start modelling a large network controlling molecular network, suppose controlling sporulation for something, so it may involve 100 submolecules but first break down into elementary processes and try to find out network motifs so first thing create models for this network motif based on the elementary processes and then connect them together to create a large model for the as a whole process. That is all for today, thank you for watching.