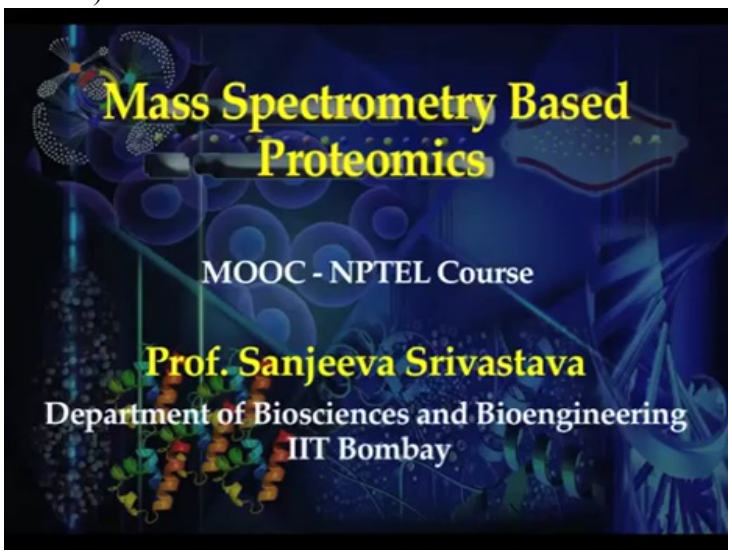
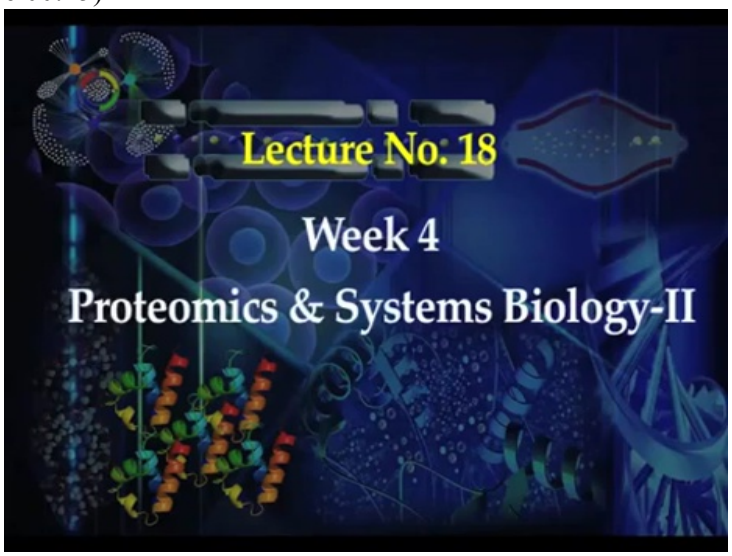
Mass Spectrometry Based Proteomics
Professor Sanjeeva Srivastava
Department of Biosciences and Bioengineering
Indian Institute of Technology, Bombay
Mod 04 Lecture Number 18

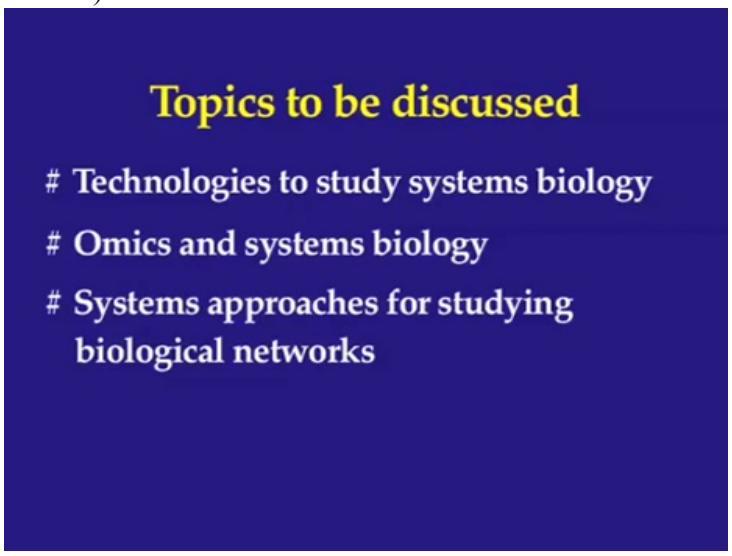
(Refer Slide Time 00:10)



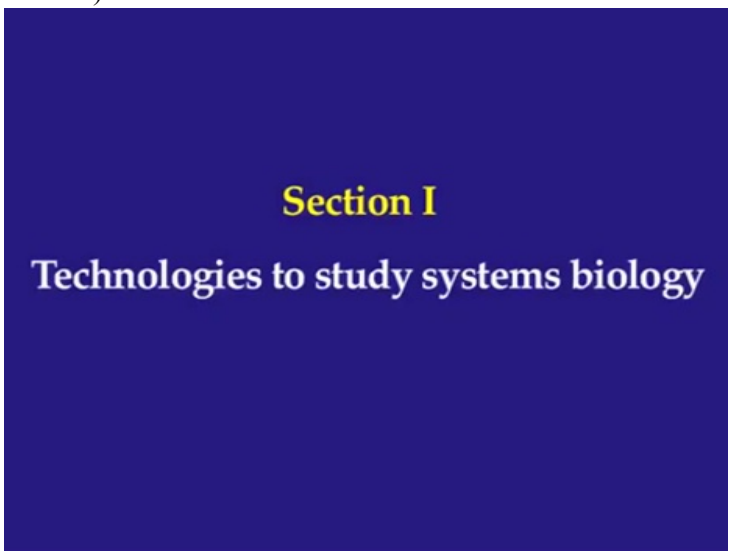
(Refer Slide Time 00:15)



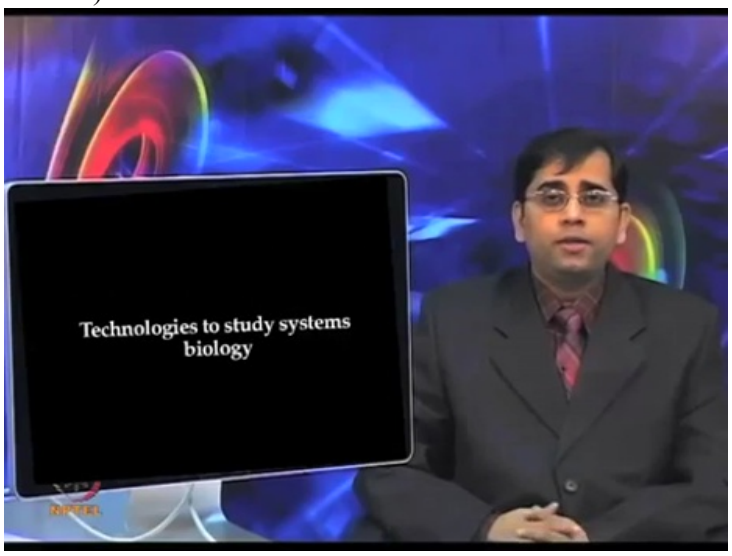
(Refer Slide Time 00:20)



(Refer Slide Time 00:27)

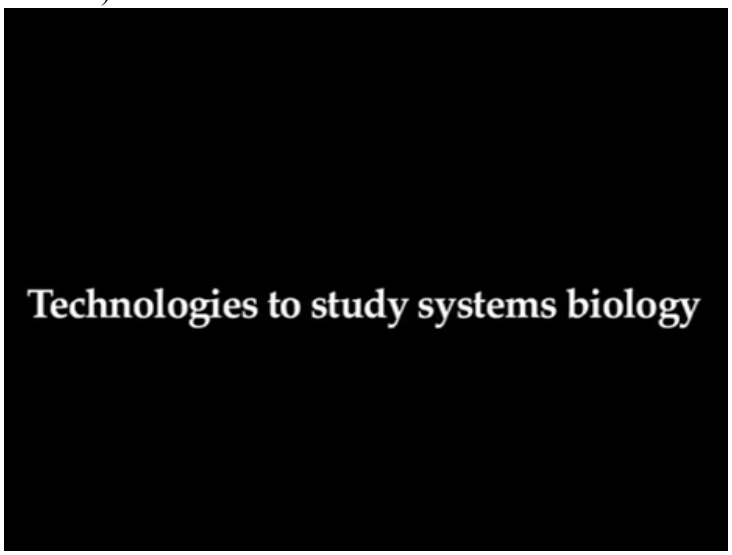


(Refer Slide Time 00:31)



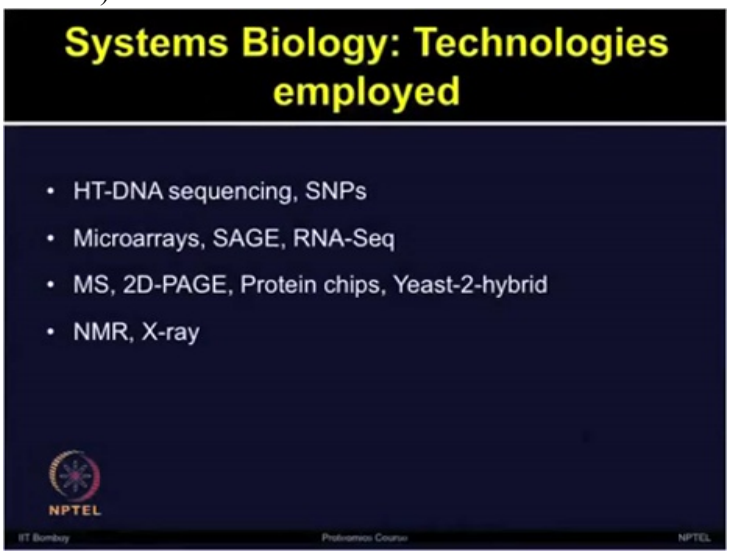
So there are different technologies which have been employed to study the systems biology.

(Refer Slide Time 00:37)



Obviously you need high throughput data sets, which could be derived from microarray platforms, RNA deep sequencing, different configuration of Mass Spectrometry, different type of structural proteomic tools and protein interaction data sets.

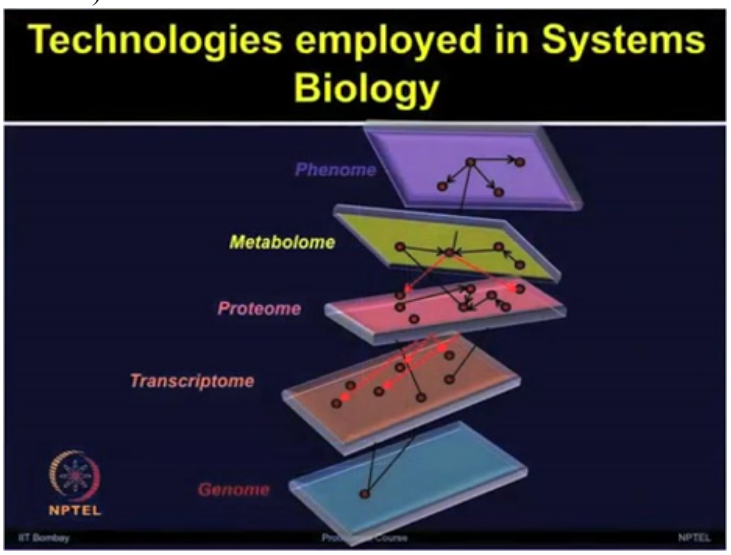
(Refer Slide Time 00:56)



Some of the technologies which are commonly employed in systems biology can be classified broadly under the following techniques: for genomics the high throughput-DNA sequencing methodologies, mutation detection using SNP methods; for transcriptomics, the transcript measurement can include serial analysis of gene expression-SAGE, gene chips, microarrays and RNA sequencing; for proteomics Mass Spectrometry, two-dimensional electrophoresis, protein chips, yeast 2- hybrids

X-ray and NMR are mainly employed for metabolic analysis, the metabolomics

(Refer Slide Time 01:46)

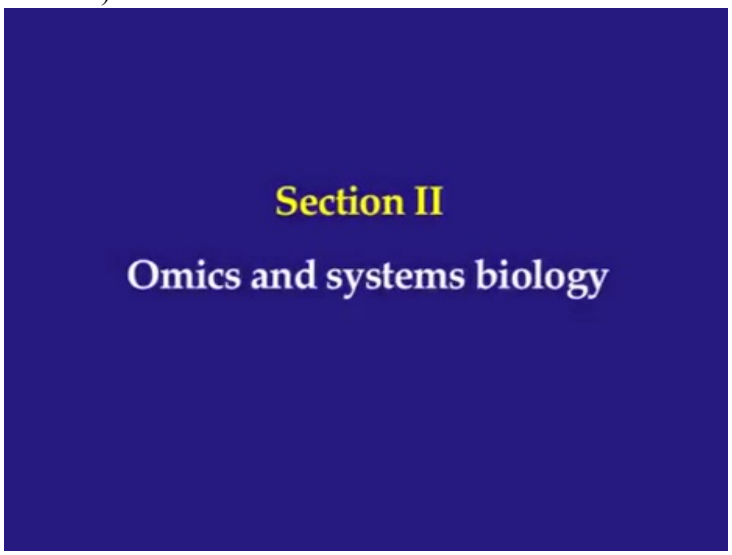


So, as you can see here; to generate the systems level information, the systems study requires different technologies which could be employed in the biological systems.; at genome level

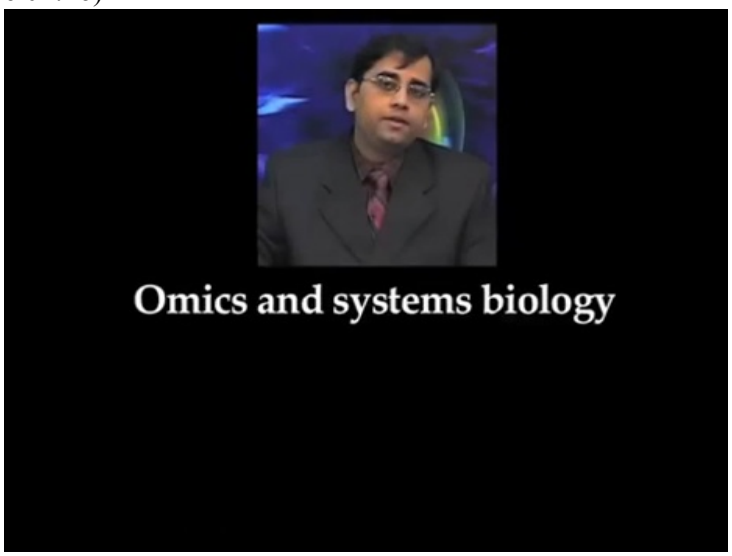
,by studying different type of technologies using high throughput sequencing, High density arrays; transcriptomics, different type of transcriptome analysis using RNA sequencing and microarrays; proteome, we discussed many methodologies; metabolome, could be using either NMR or Mass Spectrometry and then phenome, which is studying about the images by using PET or NMR methods.

So each level of these omic technologies can be useful for studying the systems biology.

(Refer Slide Time 02:41)



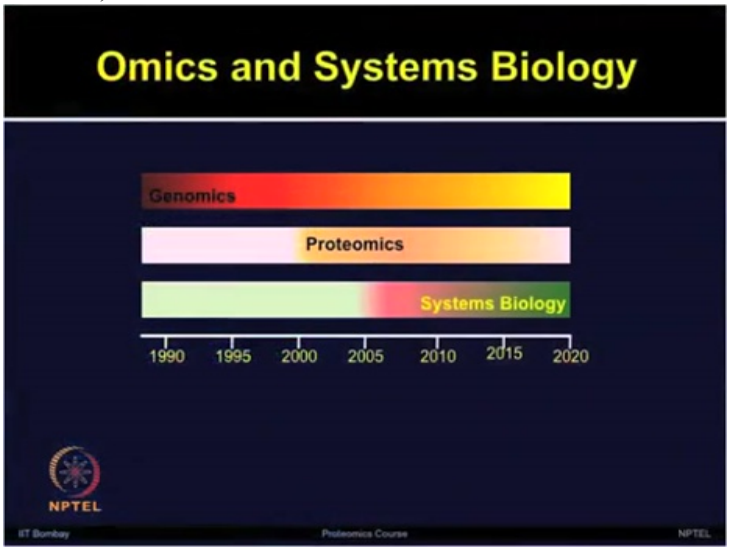
(Refer Slide Time 02:46)



Now let's try to integrate omics approaches with systems biology.

So, genome sequencing projects in genomics era from 1990s to 2000 accelerated the pace of omics research.

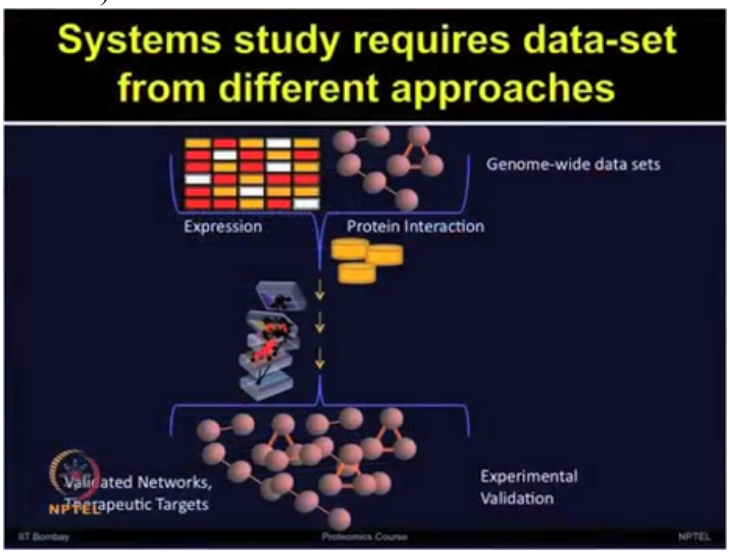
(Refer Slide Time 03:03)



Then from 2000 onwards, proteomics field also got accelerated and new methodologies, new tools came into the place for studying the proteome. And the data derived from genomics, transcriptomics, proteomics, metabolomics and other omics approaches have now brought the integration of these data sets in the systems biology field

The systems study requires obtaining datasets from different approaches and analyzing them. For example, as shown in the slide…

(Refer Slide Time 03:41)

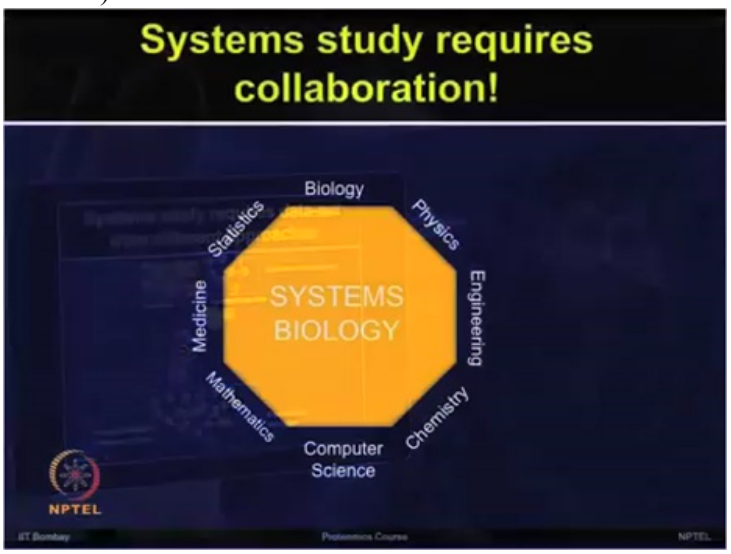


…the genome-wide data sets can be derived at the genome level and looking at the expression of different transcripts or at the proteome level looking at different type of protein interactions

These datasets can be stored in the clinical databases and also it can be mined from the literature, literature manual curation.

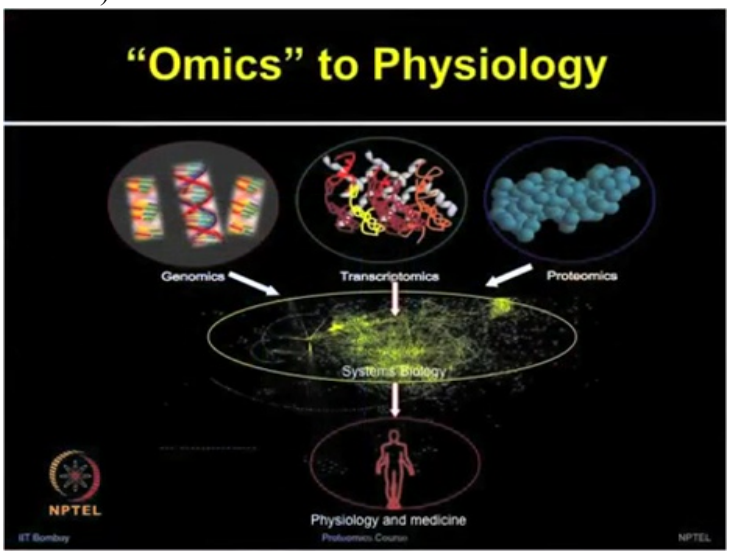
Then integration of orthogonal datasets further can be used for validating the networks and deriving, identifying therapeutic targets. Further, it can be used for experimental validation.

(Refer Slide Time 04:23)



Studying systems cannot be done in isolation individual labs. It requires different expertise and collaborations from scientists from different disciplines of biology, physics, engineering, chemistry, computer science, mathematics, medicine, statistics and many more.

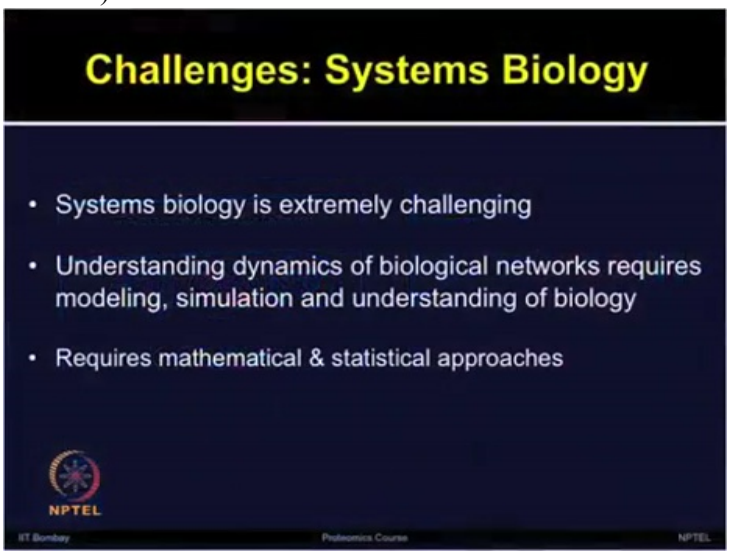
(Refer Slide Time 04:46)



So eventual aim of, the goal of this current systems biology field is to employ the omics level information obtained from different levels; from genome, transcriptome and proteome; derive that information at the systems level; integrate, quantitate some models and then propose and use it for the understanding the physiology and apply that in medicine.

So this omics to physiology, this flow can be well-maintained by employing systems biology tools.

(Refer Slide Time 05:25)

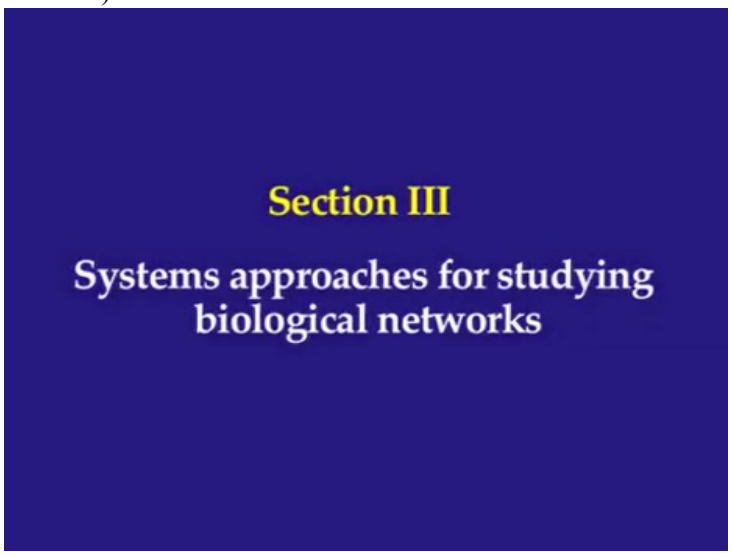


What are the challenges of systems biology?

Systems biology is extremely challenging. The emphasis is to understand a system. Understanding dynamics of even simplest biological networks not only requires only the understanding of biology but also its modeling and simulation.

The disintegrative study can be used for studying from cells to proteins to gene; or integrative study could be used for putting these pieces back together again and then understanding and doing the prediction and control of functional biological processes. All of these are very challenging but currently being addressed by applying various systems levels tools.

(Refer Slide Time 06:21)



(Refer Slide Time 06:26)

(Refer Slide Time 06:34)

Professor- Expert conversation starts

Professor: This is my pleasure to introduce Doctor Sarath Chandra Janga from Indiana University and Purdue University, Indianapolis. He is in the School of Informatics and School of Medicine.

So as we have been discussing about...need for studying proteomics and Systems Biology, there is lot of information available at the transcription and translation level and often there is not good correlation between RNA level and protein level.

So today it would be interesting to talk about systems approaches for a study of biological networks from post-transcriptional control towards the drug discovery. So I have invited professor Sarath for having a discussion and a short talk on this topic.

Refer Slide Time 07:28)

Expert: Thank you Doctor Srivastava. It is my pleasure to be here to talk about some of the work that we have been doing and more generally the principles of regulation and how you can use systems approaches for understanding biological networks more generally.

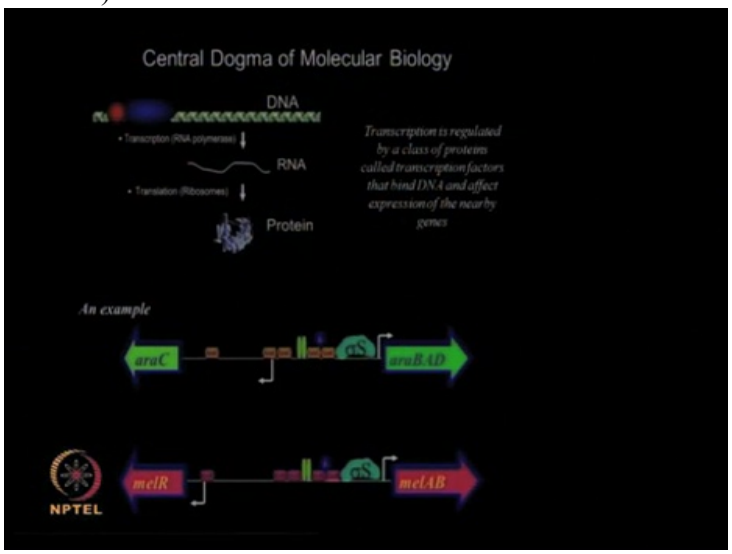
As some of you might be familiar with the use of the concept of networks is increasingly becoming prominent in not just proteomics but also in genomics data and all kinds of high throughput data.

So, today what we will be talking about is some basic introduction to the application of networks and biological systems, and how it can be applied to understanding transcription regulation, post-transcription regulation and as well as to the proteomics data, and at large how this can be used to understand the drug discovery, how can how it can be applied to the drug discovery concept.

(Refer Slide Time 08:21)

Expert: According to the central dogma of molecular biology, DNA gives rise to RNA through the process of transcription, and

(Refer Slide Time 08:31)

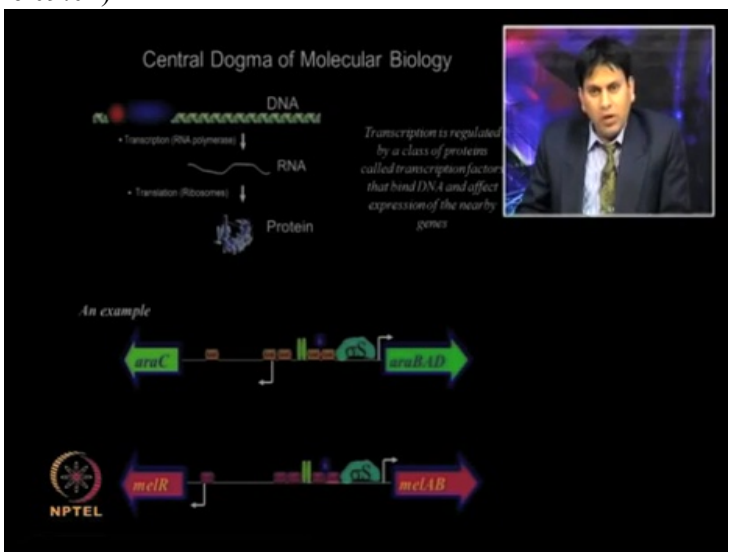


Expert: this process is facilitated by the binding of the RNA polymerase as well as a number of other transcription factors which bind to the upstream regions of the DNA, as we can see, and control the expression.

And RNA can give rise to protein through the process of translation, and this happens through the process of translation with the help of ribosomes.

Now, in this process the proteins which are produced, some of them can be classified as transcription factors which bind to the DNA, and some others are classified as RNA binding proteins

(Refer Slide Time 09:04)



Expert: which can bind to the RNA and control the expression at the post-transcriptional level as oppose to at the transcriptional level where transcription factors bind to the DNA.

Now, as an example, let see that case of Ara c transcription factor in a bacterial genome such as E coli.

This particular transcriptional factor binds to the upstream reasons of Ara b a d operon which encodes for the enzyme and the transporter responsible for uptake of arabinose from the environment.

Now the transcription factor Ara c not only binds to the upstream of Ara b a d, but it can also binds to itself and control the expression, as you can see from the small orange boxes which are shown as representation for the binding sights

Now, what this suggests is, transcription factor can auto-regulate, bind and regulate it is own expression or it can also bind to other genes controlling their expression.

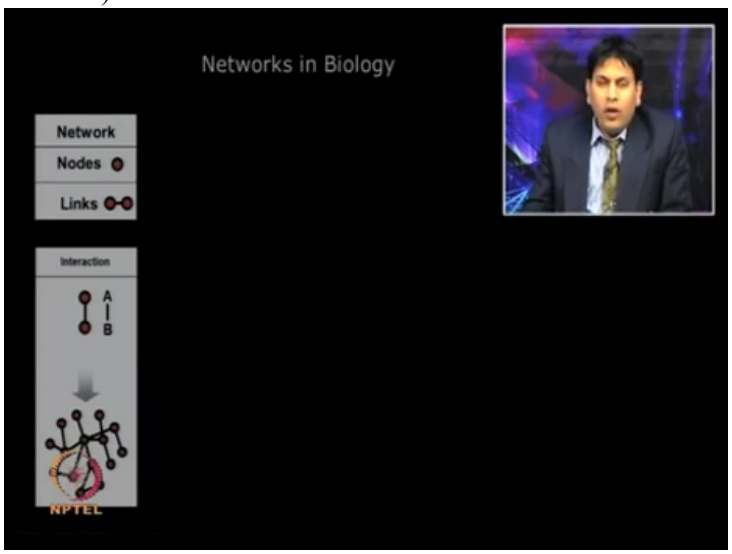
There are also cases; there are many cases actually, where transcription factor, multiple transcription factors bind to the upstream regions. As you can see in the case, in this case,

represented with the orange box as well as the blue box.... blue circle, where other transcription factors bind

Now in addition to this binding of transcription factors, as I mentioned earlier polymerase, RNA polymerase, also binds shown in with the with the green box, a green circle, green oval box out there so that they can control the expression

Now there are other examples I have also shown in this figure with mel r regulator also doing something similar.

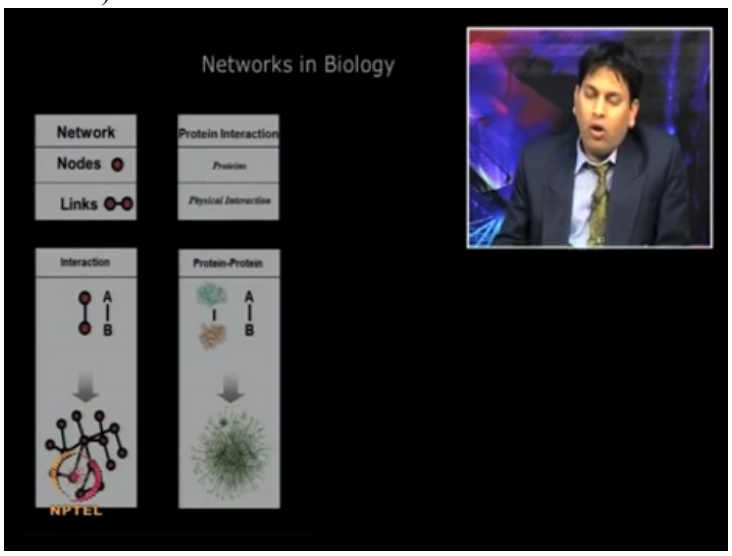
(Refer Slide Time 10:39)



Expert: Now, this is what we just discussed is an idea of how regulation happens from a biological view point. Now an increasing thing, increasing amount of literature, now supports the ideas of networks in biology. So, what exactly are networks?

Networks simply represent, are represented, as nodes and links or edges. These nodes can be biological entities and the links or edges are actually the association between these entities. Now there are number of ways you can talk about the nodes or the entities.

(Refer Slide Time 11:08)

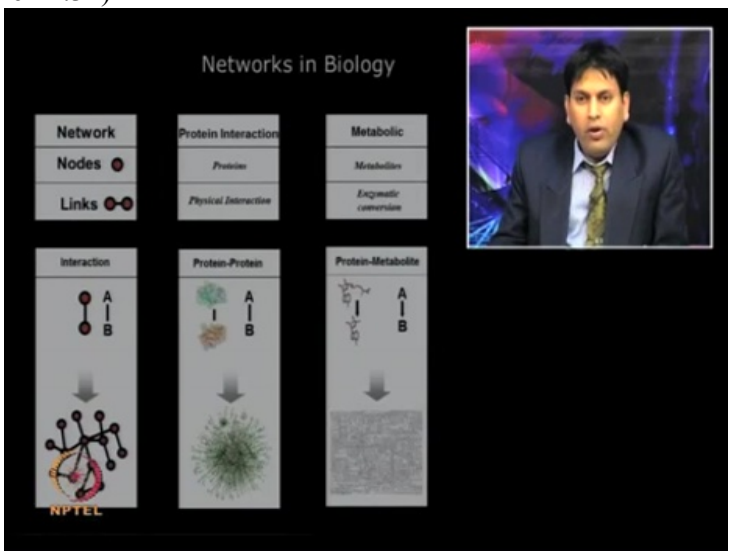


Expert: Now there are number of ways you can talk about the nodes or the entities.

So one form, one common form of representation are protein interaction networks, where the proteins form the nodes and the physical interaction between this proteins forms the edge as you can see in this in the figure below.

There, you can have a representation of this networks in a, in a fashion that is shown in this figure below.

(Refer Slide Time 11:32)

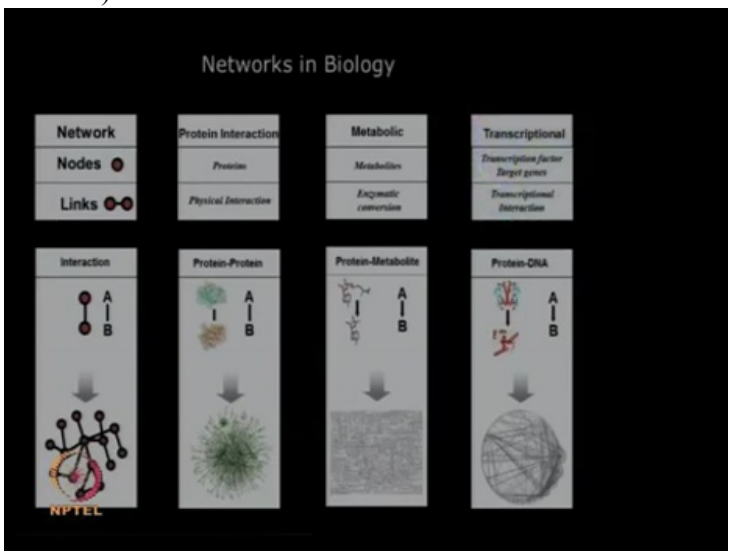


Expert: Now an alternate kind of network which is also studied in the literature over the last 10 years or so are metabolic networks.

In metabolic networks, the metabolites form the nodes and the conversion of one metabolite to other forms the edge in this case. Now as you can imagine the conversion of one metabolite to the other is actually facilitated by the enzyme.

So the particular protein enzyme converts a metabolite a to b, and when you look at on a global scale and when you looking at the conversion number of metabolites one to the another, and sometime one metabolite can give rise to more than one set of a metabolites; such complex set of associations can be called as a metabolic network.

(Refer Slide Time 12:14)



Expert: Now, the third kind of networks, which I will be elaborating in more detail in the next slides are transcriptional networks.

In transcriptional networks, transcription factors form one set of nodes. And the target genes form other set of nodes.

So, as you can imagine, what here actually looking at in this case from a biological viewpoint is the interaction of the transcription factor with the DNA and controlling of the expression of the downstream genes.

But in the context of the networks, what we are showing here, what we are showing is the transcription factor and the target gene or operon whose expression is control

(Refer Slide Time 12:50)

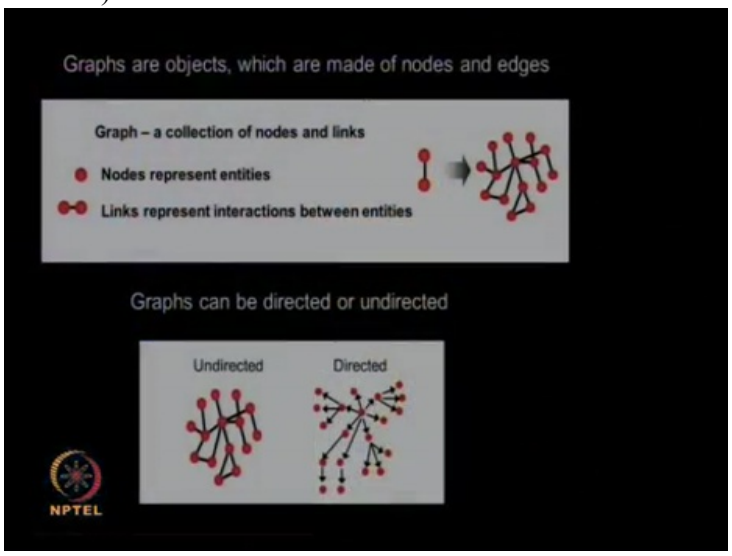
Expert: Again, in this case, you can see that the, "a" protein "a", which is transcription factor, controls "b". But it may or may not be that "b" is transcription factor and it also controls "a". So that might be a case-to-case specific and may or may not be having reciprocal interaction.

As we just discussed, these networks are actually, the concept of network has been borrowed from physics and computer science where often these kinds of networks are referred to as graphs.

And graphs are objects which are collection of nodes and entities. The nodes are representing the entities. It could be, these entities could be genes, proteins, small molecules, cells, organs or at any level you can represent these entities. The interactions or association between them are the links.

Now as I am just mentioned, there are different kinds of networks. There protein-protein interaction networks, metabolic networks, transcriptional networks. In the case of protein-protein interaction networks, what we are looking at often is no directionality in such interactions

(Refer Slide Time 13:53)

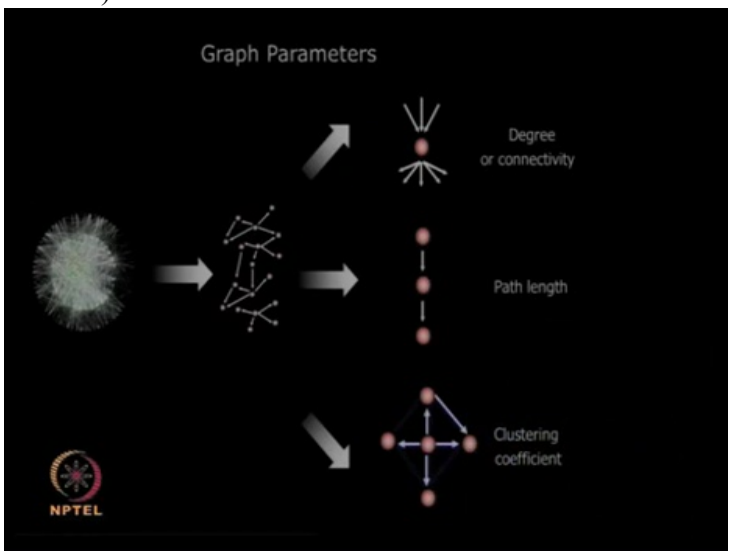


Expert: and these are called as undirected networks.

However, there are also directed networks such as transcription networks or metabolic networks.

In these cases, there is a flow of information i.e. where “a” controls “b”, which should mean “a” is controlling,” a” is regulating “b”. So therefore, there is directionality and these are often commonly studied as regulatory networks.

(Refer Slide Time 14:18)



Expert: And we will be talking in more detail in the next slides.

However, before we get into the more specific observation about the properties of these networks, one set of common properties which are studied when you are looking at biological networks are degree, path length and clustering coefficient.

Now, often when you look into a network as such, you do not have a clear understand of the properties of the different nodes.

But when you look into the specific aspect such as, in this case, shown in this case as degree; what it tells you is, how many connections of particular gene protein or node has in your network?

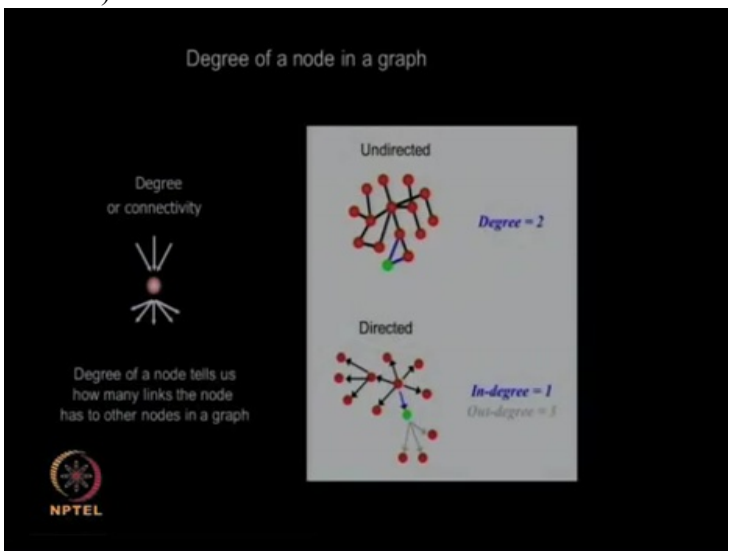
So, what we can say from the first example on the top is the degree of the node is 8. That means it is connected to 8 other proteins.

And the second property is path length. What it is showing in this case, if you, is that, the number of edges that you need to travel from one node to the other. So, if I ask you what is the path length between that first and the bottom node in this figure; you would say the path length is equal to 2.

The third kind of property which often studied is the clustering coefficient. Clustering coefficient tells how often the neighbors of a given node are connected to what you would see in a completely connected graph.

Let us look at more detailed examples. For instance, if you are studying the degree of a node

(Refer Slide Time 15:38)



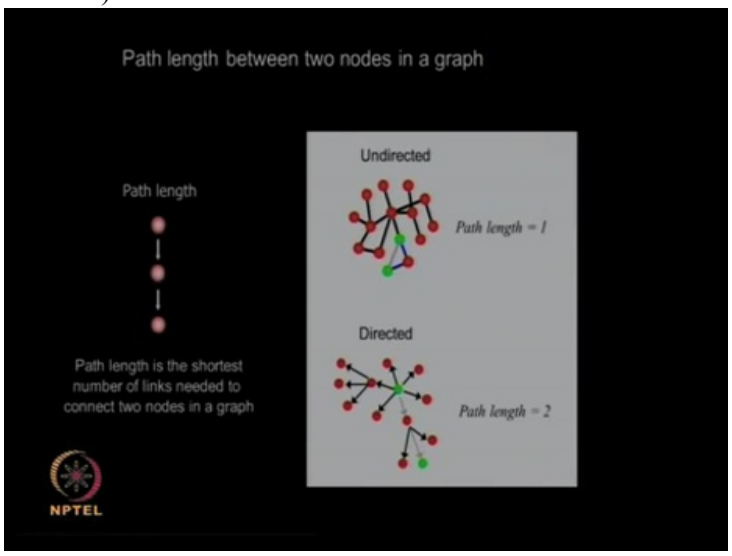
Expert: ….in the case of undirected network, such as in the example shown in the top, the florescence node that shown, florescence color has a degree equal to 2

On the other hand, a directed node example shown at the bottom has a degree equal to 4 because it is connected to 4 other nodes.

However, what you can also say is there is in-degree and out-degree. An in-degree is the number of incoming connections of a particular node. So, the green or florescent node here has in-degree of 1

It also has an out-degree equal to 3 because it is directing 3 other nodes shown in red color out there, so it's out-degree equal to 3.

(Refer Slide Time 16:19)



Expert: Now, you can also extend this idea of undirected and directed graphs and ask what is the path length of a node? Now, as I mentioned the path length is referred to as the number of edges that one needs to travel between two different nodes that you are interested.

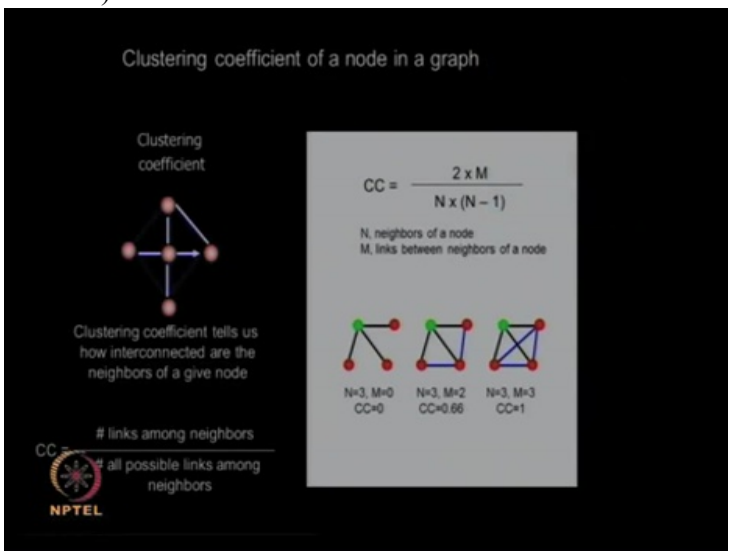
On, in the top, the network that you are seeing, the path length between the 2 green or florescent nodes is equal to 2 as well as equal to 1; because the path that you can take can be different than the shortest path that you looking at.

However, almost often unless otherwise specified, when you are talking about the path length between two nodes, it is the shortest path length. So the two florescent nodes have a path length equals to 1.

However, if you if you are ask what are all the path lengths, you would say they, it has two different paths; one with a path length of 1 the other with a path length of 2.

In the undirected networks your definition of path length essentially does not change. So in the example that you see at the bottom the path length between two florescent nodes is equal to 2.

(Refer Slide Time 17:24)



Expert: The other property that I was referring to previously is the clustering coefficient of node. And clustering coefficient refers to the number of the connection between the neighbors of a given node of interest to what you would see in a completely connected graph.

Now, let us look an example. In this figure that you see, there is, the first example, the florescent node, the green node has 3 connections; 3 red dots are connected to it.

However, if you ask the number of connection between the red dots, it is 0. There are 0 connections between the red dots. But, if they were fully connected you would see that they will have 3 edges between them. So the clustering coefficient of the florescent node right now is 0 upon 3.

Let us look at this second toy network. In the second toy network, the florescent node has a clustering coefficient of 2 upon 3.

In the third case, the clustering coefficient of the florescent node is 3 upon 3, which is completely connected. So the clustering coefficient is equal to 1.

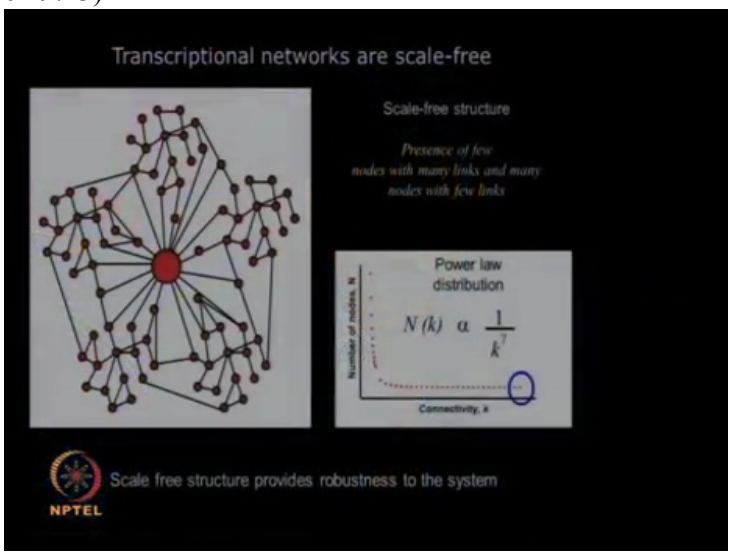
Now, more generally, formula can be brought up and it can be written as; if there are m number of interactions between the neighbors of a node of interest and there are n number of neighbors of a given node of interest, then it can be written as m upon n into n minus 1 by 2.

So that would be defined as a clustering coefficient of that particular node.

And when averaged, the clustering coefficient of a node on a whole network scale, it gives you an essence of modularity of the network. The higher the average clustering coefficient, the more likely is the network clustered, can be decomposed into specific modules.

Another property that is of great interest in understanding biological networks is a scale-free structure.

(Refer Slide Time 19:13)



Expert: And while lot of biological networks are documented and shown to be scale-free, transcriptional networks are also documented to be scale-free structures.

So, what exactly our scale-free networks? Scale-free networks correspond to the structure of a network where there are few nodes which are highly connected.

For instance, in the figure to the left, in the network figure that you see to the left there is a big red dot, big red node which is highly connected.

So, but, there are not many such highly connected nodes And there are many nodes which are very poorly connected.

So, in other words, a scale-free structure refers to a network structure where there are few nodes which are highly connected and most nodes are poorly connected.

Or more mathematically, if you plot the connectivity of a node versus the number of nodes with a given connectivity you should see a power-law distribution.

Otherwise, if you plot the log-log plot of the connectivity versus the number of nodes with a given connectivity, you should see a negative slope of gamma as shown in this figure, where gamma lies between 2 to 3.

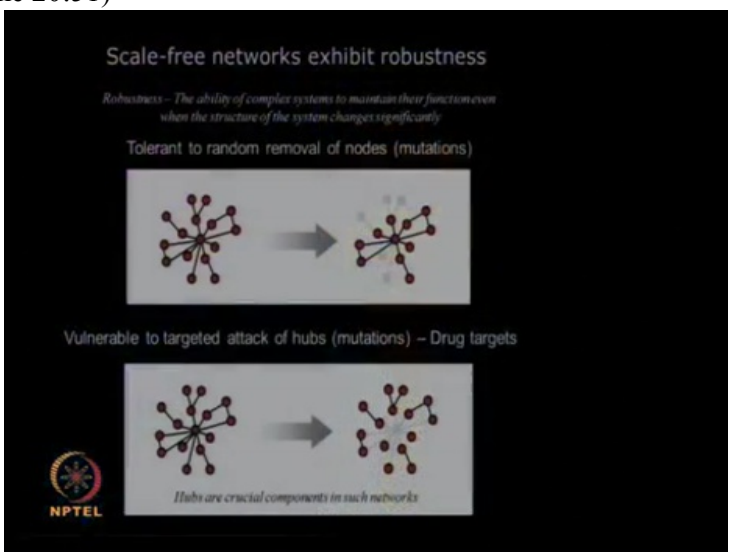
That is when you can call the structure to be scale-free and the, and the distribution to be a power-law distribution

Now, what is so special about this scale-free structure? Scale-free structures have been postulated to provide robustness to the biological system.

Now, what exactly is robustness? So, robustness is the ability of a complex system, a complex system such as a biological system to maintain its function even when the structure of the system changes significantly.

Now, let us look at an example.

(Refer Slide Time 20:51)



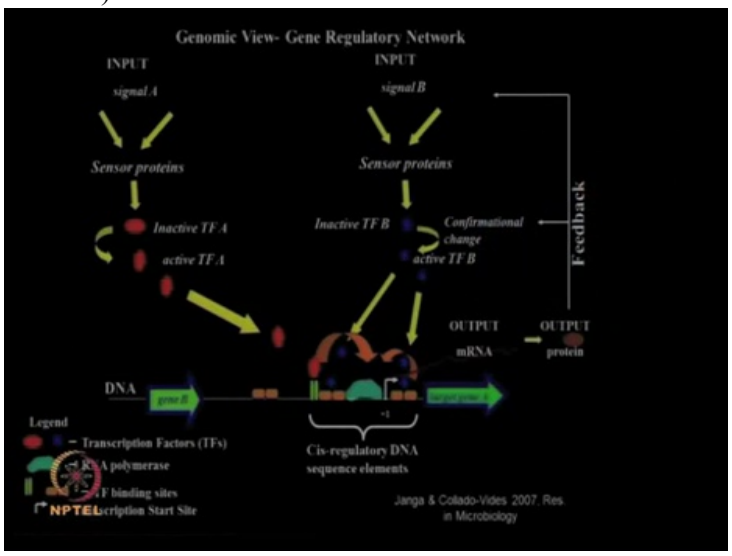
Expert: So, in the network figure that you see, if you randomly perturb any of these nodes you are likely to affect a small fraction of the network.

However, if you target the highly connected node, that is the central node which is highly connected, you are going to disrupt a major fraction of this network suggesting that these highly connected nodes can be vulnerable to be the drug targets.

So, if you are trying to inhibit the growth of a pathogen, you are likely to target these highly connected nodes because you are more likely to be able to crumble the biological system of the pathogen.

So and this has been increasingly gaining attention as a method of targeting drugs to this kind of this class of proteins.

(Refer Slide Time 21:35)



Expert: So, as mentioned earlier, we have been talking about regulation of a single transcription factor.

But in the context of network regulations is much more complex and what we are referring to is a combinatorial regulation by many different transcription factors.

Let us look at a specific scenario. So the slide shown here shows a typical regulatory system in a bacterial organism.

What you usually have is a set of signals which are sensed by the cell and these signals are sensed by sensor proteins.

These sensor proteins could be transcription transporters, or these could also be histidine kinases.

And once these sensor proteins sense the signals from the exterior or even sometimes interior of the cell, they can cascade the information to transcription factors.

The transcription factors, upon receiving the signals, can change from active to inactive or inactive to active state

And when this happens, because of multiple sensor proteins, these transcription factors can change the confirmation and bind to the upstream regions.

And shown at the bottom is a stretch of DNA where these transcription factors can bind in combinatorial fashion often and control the expression of the target gene or operon.

As a rule of thumb, if transcription factors bind to the upstream regions, in the upstream of the transcription start site shown as plus 1; that is where the transcription actually starts; you often are stimulating the polymerase and enhancing the expression.

However, when you bind to the downstream of transcription start site, you typically repress the expression of the target gene, thereby blocking the transcription by the polymerase shown in the oval shaped polymerase symbol in green.

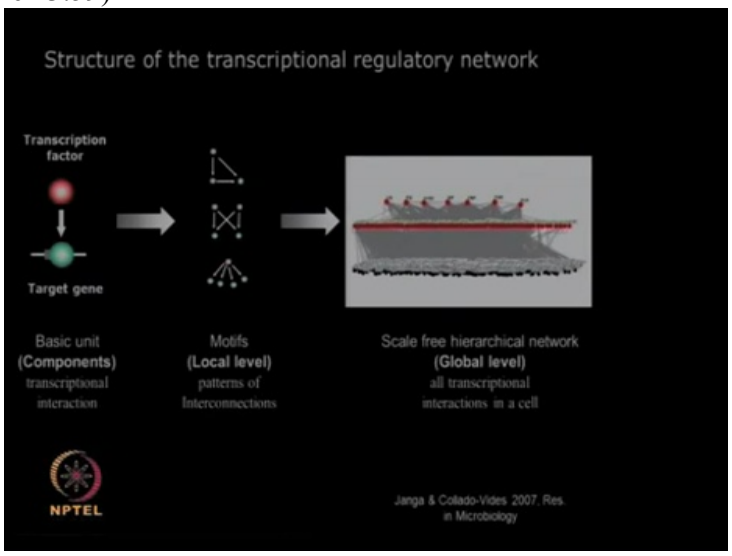
So based on these principles and together with the interplay with the transcription factors and the polymerase your transcript is produced.

And once transcript is produced, you can have mRNA and protein levels regulation which is not what will be talking immediately now.

But all these levels together contribute to provide feedback and this is typically a system, a simple regulatory system that you encounter in bacterial organisms

But more complex systems, more complex eukaryotic gene regulation is much more complex and beyond the scope of our current discussion.

(Refer Slide Time 23:59)



Expert: As discussed in the previous slides, the basic unit of regulation is a transcription factor and a target gene whose expression is being controlled.

Now on a different scale, if you increase, if you put together all the set of regulatory events between transcription factors and the target genes or operons, you construct a global transcription regulatory network.

And as I mentioned earlier, this network is a scale-free structure, scale-free network.

But in addition to this, it is also a hierarchical structure; wherein, what we are actually referring to in a hierarchical structure is there are set of transcription factors which are able to regulate a large number of genes.

And there are set of genes, other transcription factors which are also controlled by this global transcription factors shown at the top of this network structure.

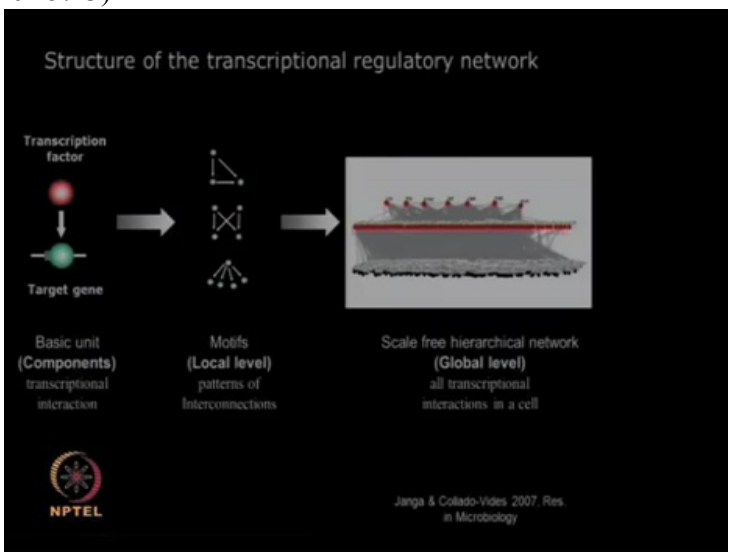
And both, the top layer and the second layer, all of them together regulate the set of genes which are not essentially encoding for the protein coding, which are not essentially encoding for the transcription factors.

So, in a way there are transcription factors which are at the top of the system, there are transcription factors which are controlled by this top layer and there are subsequent layers.

And the number of layers such a hierarchical structure depends on the complexity of the system.

Now in between the top and the bottom layer, the in between the leftmost figure of the basic unit and the rightmost figure

(Refer Slide Time 25:23)



Expert: there are set of sub-structures or sub-graphs within the regulatory network which we call as motifs.

Motifs are the set of sub graphs which occur more often than expected by chance. And there were three kinds of regulatory motifs that are identified in regulatory networks.

One is the feed-forward loop where there is, there are two transcription factors.

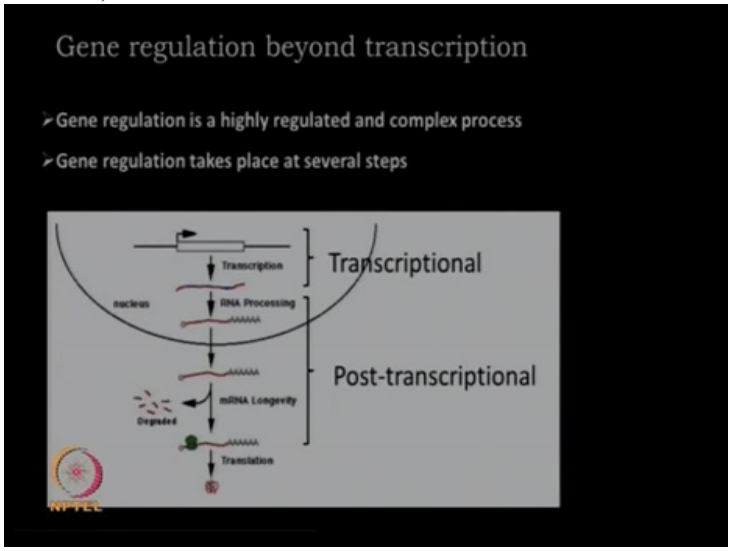
The first transcription factor regulates the other two genes. The second transcription factor regulates the target gene.

The second kind of motif is multiple-input module, where there are two different transcription factors; both of them regulate two different target genes.

The third is a single input module where a single transcription factor regulates a set of target genes.

Now each of this set of regulatory motifs has been shown to have specific functions and which would be beyond the scope of our current discussion.

(Refer Slide Time 26:16)



Expert: Now, although the idea of regulation of gene expression, the level of transcription has been documented for several years and we have extensive understanding, very little is known about the regulation of gene expression beyond transcription.

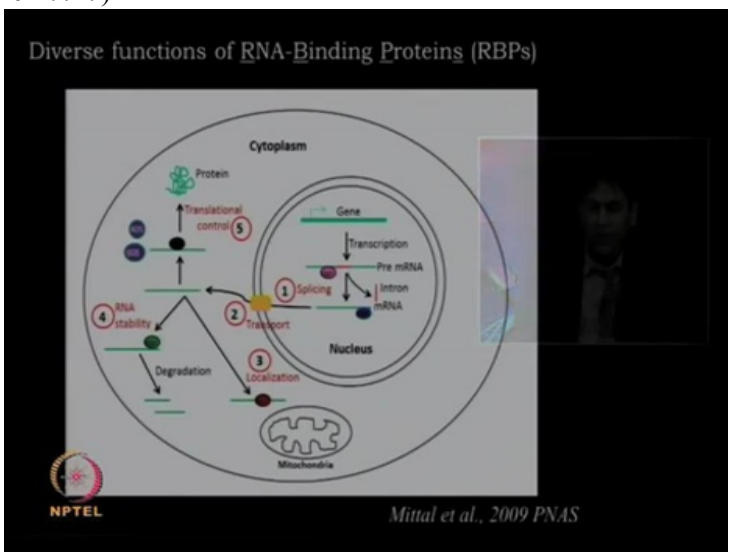
And it has only been recently being appreciated about the role of regulation at the post-transcriptional level.

Now most of this evidence for the reason why post-transcription regulation is becoming important is coming from the lack of correlation between mRNA and protein pools in model systems.

Now, there is now enough evidence to suggest that these post-transcriptional processes are actually controlled by a class of proteins called RNA binding proteins.

Among non-protein coding components such as micro RNAs, non-coding RNAs, so RNA binding proteins are now known to be involved in controlling the RNA processing, RNA longevity as well as in the translation.

(Refer Slide Time 27:17)



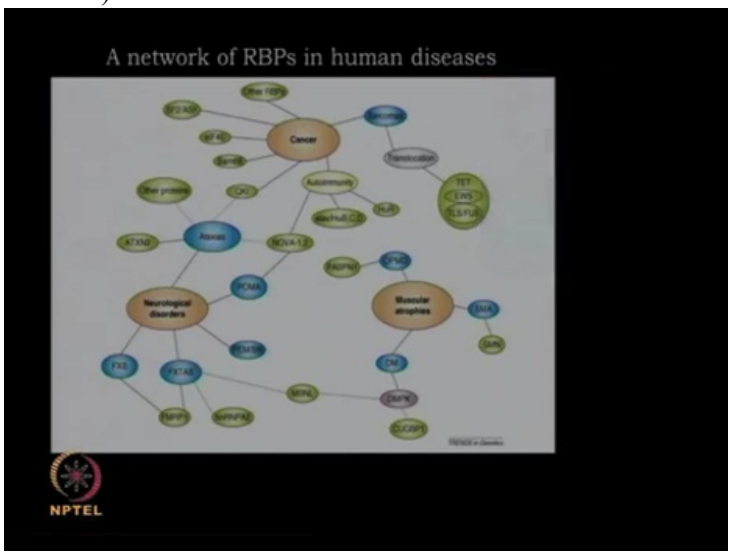
Expert: Now, in particular as soon as the gene is transcribed and pre mRNA is produced, splicing associated RNA binding proteins bind to the pre mRNA and convert into mature mRNA by splicing of the introns.

Now the produced RNA, not necessarily only mRNA is, needs to be exported from the nucleus into to the cytoplasm. And this is carried out by class of RNA binding proteins which can be termed as transport RNA binding proteins shown with number 2 in the figure.

RNA binding proteins have also been implicated in the specific sub-cellular localization of these transcripts. RNA binding proteins are documented also in controlling the stability of the transcripts thereby promoting or degrading the expression of these transcripts.

As is expected, RNA binding proteins, a number of them, are associated with the ribosomal proteins to control the regulation of expression at the translational level.

(Refer Slide Time 28:17)



Expert: Now, other aspect of regulation, understanding regulation at the post-transcriptional level is that number of RNA binding proteins are involved in human diseases, major class of human diseases, such as cancer, muscular atrophies and neurological disorders.

In this network diagram shown here the major class of diseases are shown in orange while the subtypes of diseases which are, which can be sub classified are shown in blue, and the specific RNA binding proteins which have been documented, are implicated in these disorders are shown in green.

Now, let us take it a specific example of, as a muscular atrophy called myotonic dystrophy.
In this particular kind of disorder, a CUG repeat binding protein called CUG B P 1 binds to the 3 prime un-translated region of a D M protein kinase.

And because of the sequestration of this CUG repeat binding protein onto the trinucleotide repeat expansion in the 3 prime un-translated regions, this particular disease phenotype is observed.

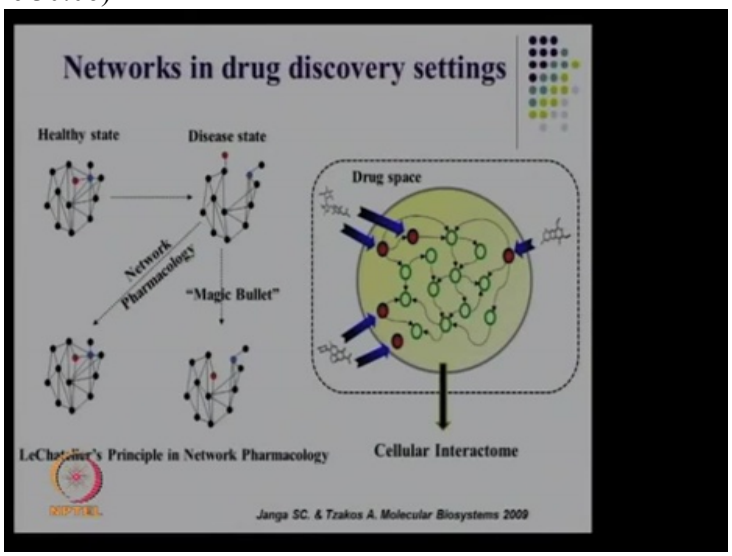
Another example of mis-regulation of an RNA binding protein happens in OPMD which is another kind of muscular atrophy.

In this particular kind of disease, there is a GCG repeat expansion in the axon 1 of an RNA binding protein which is a poly a binding protein called pab P N 1.

Another example we can observe, which is, which is heavily documented in the literature is a brain specific splicing factor called nova, whose mis-expression is known to cause a disease called poma which is a subtype of neurological diseases.

So what I am trying to arrive at here is that if there is a change in expression of either RNA binding protein, or any of its targets it can be associated to a disease phenotype.

(Refer Slide Time 30:06)



Expert: And all the studies basically suggest that it is not just the effect of a single gene or protein. It is rather a combination of different set of genes and proteins which contributes to a disease phenotype.

Now while this observation is not very new; while we knew that this is common for a number of complex diseases, what we have still been not able to achieve is the able to cure diseases for these complex diseases.

Now, let me introduce to you the traditional notion of how drug discovery is usually happening in most places.

Let us represent the healthy state of an individual with a network of interactions shown in this figure on to the left.

Now at disease state could be studied as a perturbation in such a network where some of these nodes are actually not properly connected compared to the healthy state.

Now, according to the idea of Paul Ehrlich and others, the magic bullet approach suggest that the conversion of disease state to the healthy state should involve one or, most likely, one particular drug which is non-promiscuous and specific to a particular drug target; so that you have minimal off -target effects.

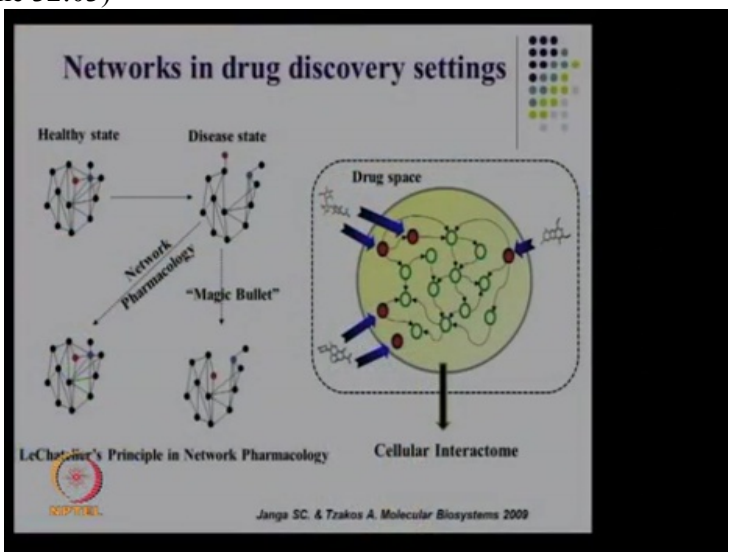
Now, often such magic bullet approach can only yield, only a semi-recovery to the, to the from the disease state.

Now what network pharmacology or network medicine approaches are trying to arrive at is use a combination of perhaps promiscuous drugs, but which do not cause negative side effects, which do not cause side effects with a lethal and can still convert the disease state into healthy state as close as it is to the original one

Now how would you achieve such an approach? To understand the, this particular idea let us look at a network representation of how the different entities in the cell are interacting.

In the figure to the right, you can see that, a number of drugs, each of them, perturbing to different nodes.

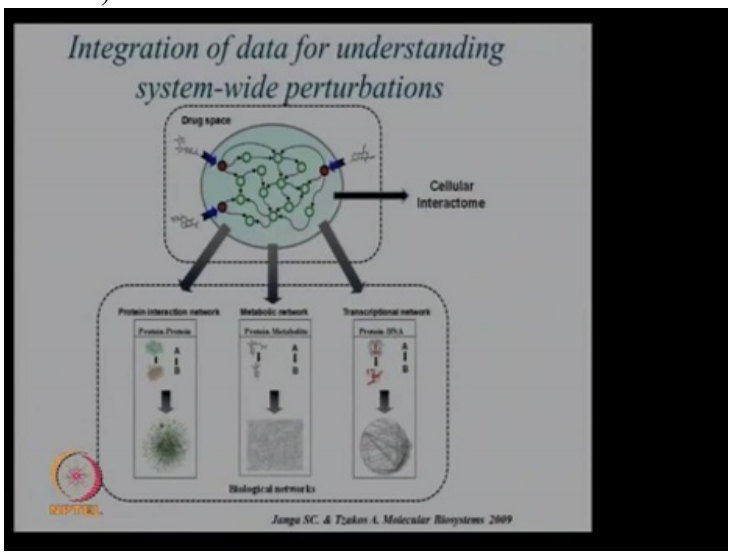
(Refer Slide Time 32:03)



Expert: Now, all of these nodes are actually interconnected to each other because we are looking into the cellular contacts and there are protein-protein interactions; there are metabolic interactions; there are also regulatory interactions

Perturbation of one cannot be seen in isolation. It has to be seen in the context of other perturbations. Now a combination of these perturbations is going to yield a phenotype which, we hope, can be treating the complex disease. That is the concept behind this idea of network pharmacology.

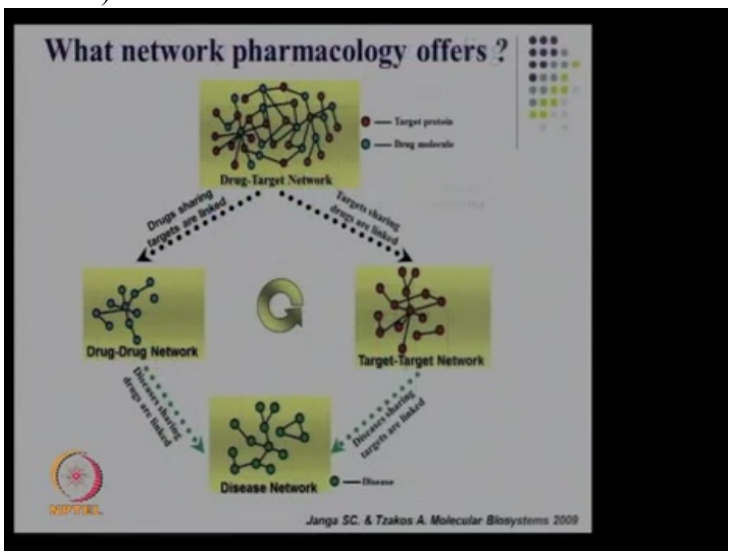
(Refer Slide Time 32:34)



Expert: Now, how do we achieve such bigger goal?

So, usually when you have such kind of complex problem, complex phenotype you have to put together data; such as knowledge on the current metabolic network in the human genome, knowledge on the transcription network, knowledge on the protein-protein interaction network, and knowledge on the post-transcription network, and together with a current knowledge of the drugs and the targets and the target pathways, one can start looking at how these perturbations can be studied in the context of specific diseases, and what particular drugs can be used to identify potential new therapies for existing diseases.

(Refer Slide Time 33:13)



Expert: An alternative set of approaches which are being used in the context of drug discovery is that if you have a target, a drug target network; for all the approved drugs in the literature, one can start understanding, what are the drugs which are sharing the targets?

Can we use the drugs which share the targets as alternatives to existing drugs?

If there is any resistance acquired for a particular drug can you compliment the current drug with another drug which is having the same set of targets?

Or one can start studying the set of drug-drug relations if there are drugs sharing the targets, can we start studying what are the profiles of the two true drugs which are linked?

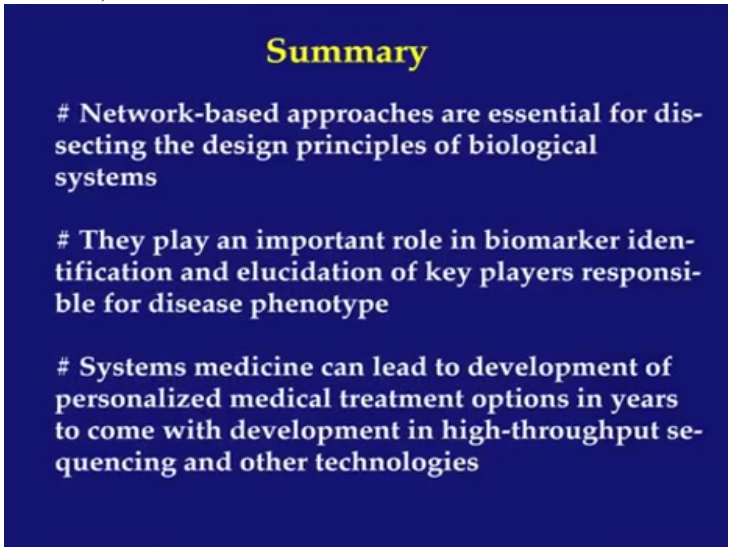
Are they similar in the structure? Are they similar in the final phenotypes or what are the common principles of these drugs which are connected to each other?

Likewise one can also study disease-disease associations by linking any pair of drugs which are working, which are used for the same disease.

Likewise one can study target -target network to construct disease-disease association network.

So, this is, these are some of the ideas which, where the field is moving to understand or to even re-purpose existing drugs for novel therapies.

(Refer Slide Time 34:27)



Expert: So, to conclude what we have tried to cover in the past set of slides is that the network-based approaches are essential and a powerful paradigm for dissecting the design principles of biological systems

They play an important role in biomarker identification and even in the elucidation of key players responsible for the disease phenotype.

Systems medicine can lead to the development of personalized medical treatment options in years to come with developments in high throughput sequencing and other technologies which can yield a lot of data in a very short time, so that clinical relevance can be achieved based on these kind of techniques, based on these applications of these network based approaches in the context of clinical settings.

(Refer Slide Time 35:12)

Professor: Thank you very much Sarath for giving very nice talk and giving some of the basic concepts as well as illustrating how systems level network studies can be employed for illustrating various types of problems including in the drug discovery as well as in pharmacology and it could standard for even by biomarker discovery and many other applications. So thank you very much.

Expert: Thank you.

Professor- Expert conversation end

(Refer Slide Time 35:38)