Bioengineering: An Interface with Biology and Medicine
Prof. Sanjeeva Srivastava
Department of Biosciences and Bioengineering
Indian Institute of Technology- Bombay

Lecture – 32
Proteins & Proteomics

Welcome to MOOC NPTEL course on bioengineering, an interface with biology and medicine, in the last lecture we discussed some basic concepts of amino acids and proteins. Today, we are going to talk about fascinating words of proteins and proteome technologies.

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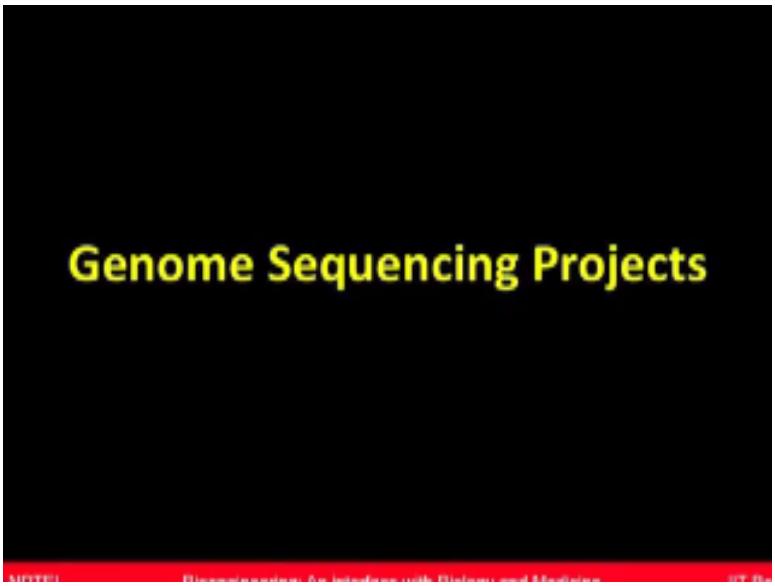

Let us first start with the genome sequencing projects.

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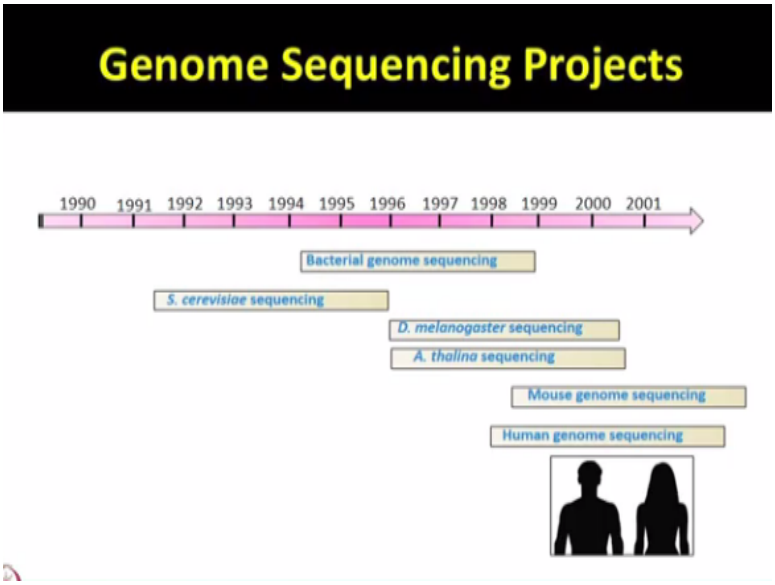

So, the human quest to try to understand and analyse all the genes present in human and various other organism really got materialized during the timeframe of 1990's to 2002, many genome sequencing projects especially looking at bacterial genome sequencing, yeast or Saccharomyces cerevisiae, drosophila melanogaster or fruit fly, Arabidopsis thaliana, mouse has the human genome sequencing projects when progressed during that time frame.

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In 2001, the first draft of human genome was reported in general Nature and Science, the molecular medicine is progressing beyond classical genetics to genomics and proteomics and after the completion of human genome project, the success of human genome project gave rise to the new field which is aiming towards studying all the human protein under proteomics. Let us first look at what we obtain after doing the genome sequencing projects.

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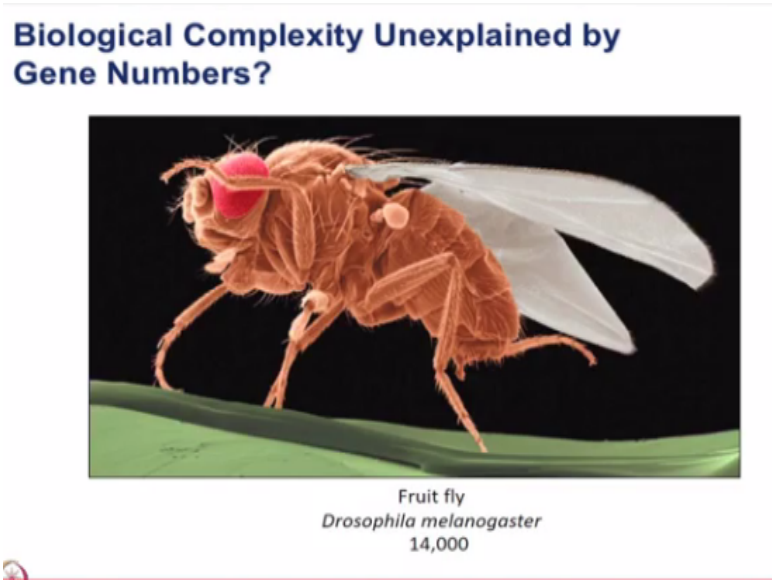

If you look at on the screen, the fruit fly or Drosophila melanogaster, it has around 40,000 genes.

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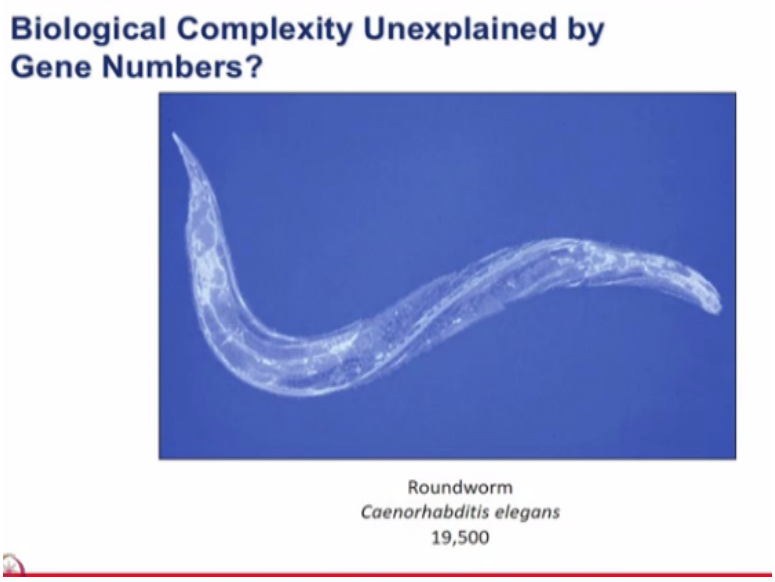

Roundworm, C. elegans has around 19,500 genes.

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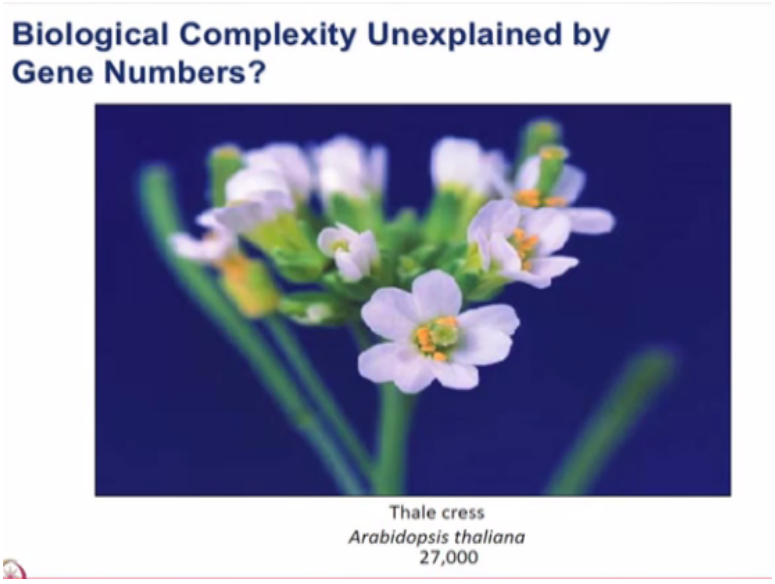

Arabidopsis thaliana or Thale cress has around 27,000 genes.

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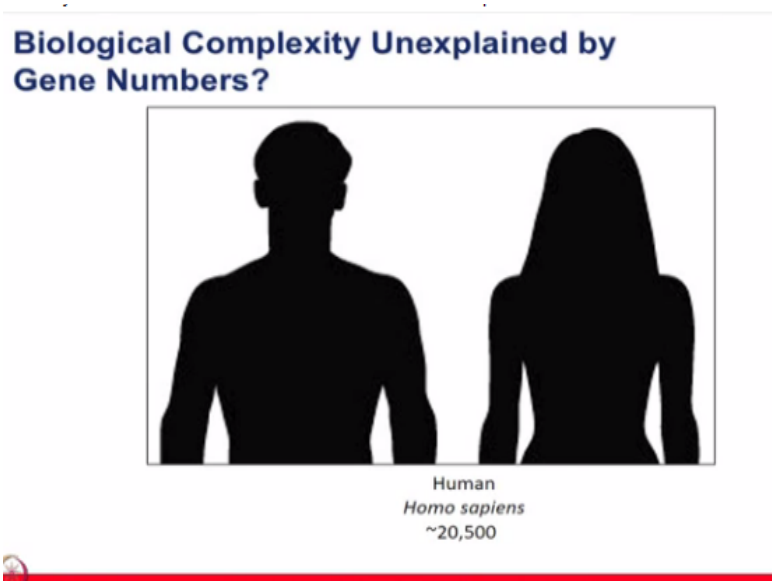

And human has around 20,500 genes, so if you look at velasco complexity from the fruit fly to round worm to the plant as well as the human, the gene numbers does not proportionate with the velasco complexity, so then it was really unexplained that how 20,00 genes are governing such a complex physiology of human, so immediately the new field of proteomics is started getting attention that it is not gene.

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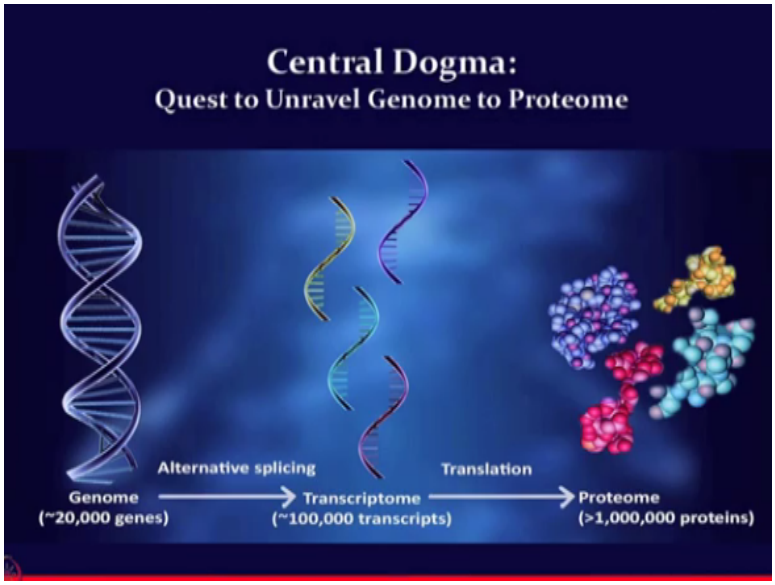

But probably, the proteins which are formed from the transcription and translation processes, they are probably governing many of the functions which is much more important for us to learn and therefore, you know we had gone back to the central dogma concept where the quest was to unravel genome and then further proteome, just to remind you about the central dogma from the genes after the process of alternative splicing, the transcripts are being formed.

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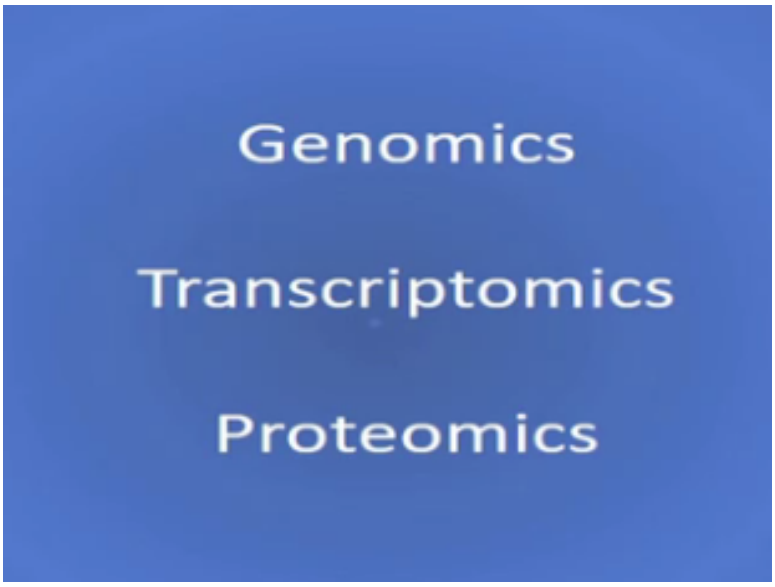

And then the process of translation, proteins are being formed, so if we think about all the genes of the system that is genome, all the transcript of the system that is transcriptome, all the proteins of a system that is proteome, so while if we have around 20,000 genes, the transcript number could be even 100,000, the proteome number could be even 1 million, we have literally no idea exactly how many proteins are present.

Because even after protein synthesis, there are many modifications happens, which are known as post translational modification, so while the genome provides these static snapshot of total information which is encoded in a cell, the biological processes are very dynamic and complex and probably, better explained by the process of transcriptomics as well as proteomics.

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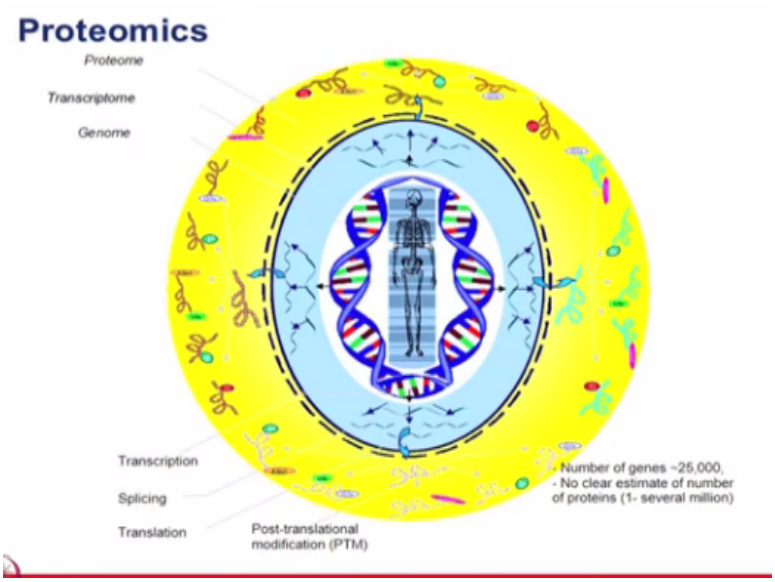

So, this figure illustrates different circles and different level of complexity for example, the inner circle shows all the human genes which could be studied under genomics, now from the same gene different type of functional RNA molecules could be formed in the process of alternative splicing and that blue sphere, one could study under transcriptomics and then each of the transcript can now give rise to the protein forms which could be further modified in the process of post translational modification.

And the yellow circle shows the complex world of proteome, so proteome is set of all the proteins which are expressed by a genome.

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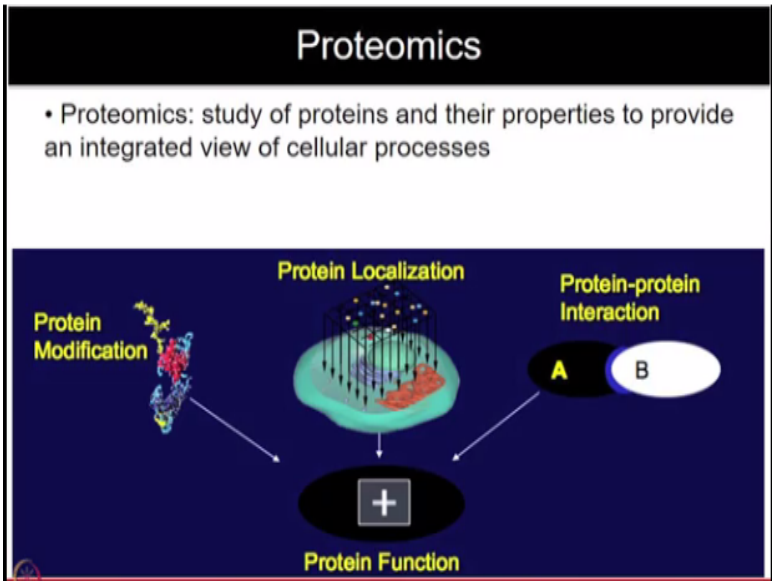

And the field of proteomics aims to study the proteins and their properties to provide an integrated view of all the cellular processes, whether it is protein modification, localization or protein, protein interactions.

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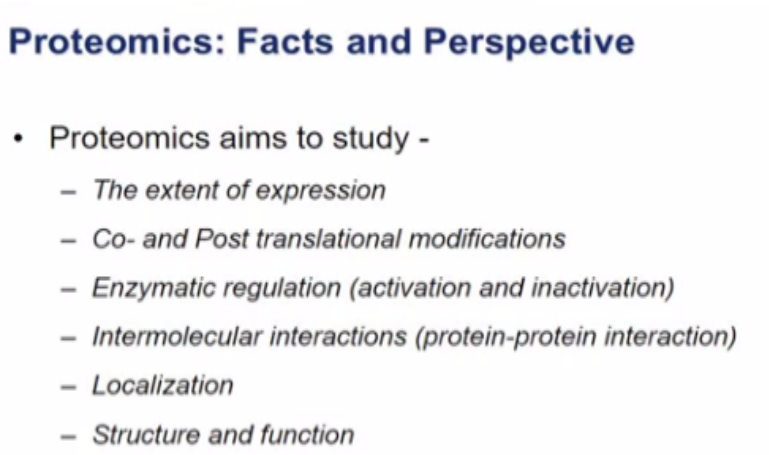

So, proteomics broadly aims to study the extent of protein expression, how the Co and post translation modifications occur, how the enzymatic regulation happens whether its activation or inactivation, how the intermolecular interactions happens especially, protein interactions, where the proteins are localized, what is the structure and function of these proteins?

So, broadly if you see proteomics have very ambitious goals and much more complex goals and objective to achieve as compared to the genomics.

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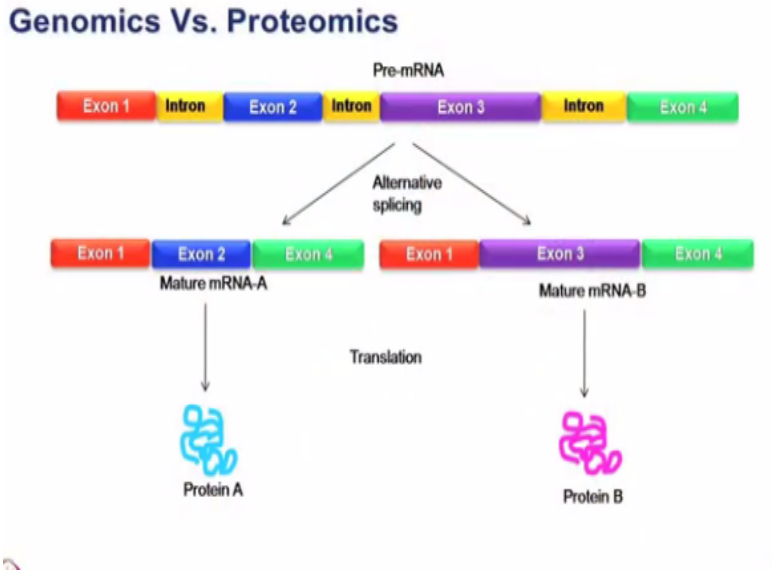

It is kind of the conceptualise the comparison of genome versus proteome, so if we go back to the basics looking at the pre mRNA structure, there is different exons and introns and now, after the process of alternative splicing, same pre mRNA can now give rise to 2 different type of

mature mRNAs, as you can see mature mRNA-A and mature mRNA – B. Mature mRNA - A has exon 1, 2 and 4.

Mature mRNA- B has exon 1, 3 and 4, so alternative splicing is a process by which exons or the coding sequences of the pre mRNA produced by the transcription of a gene is combined in different ways during the RNA splicing. The resulting mature mRNAs can now give rise to different protein products for example, mature mRNA - A will give rise to protein A, whereas mature mRNA- B will give rise to protein B.

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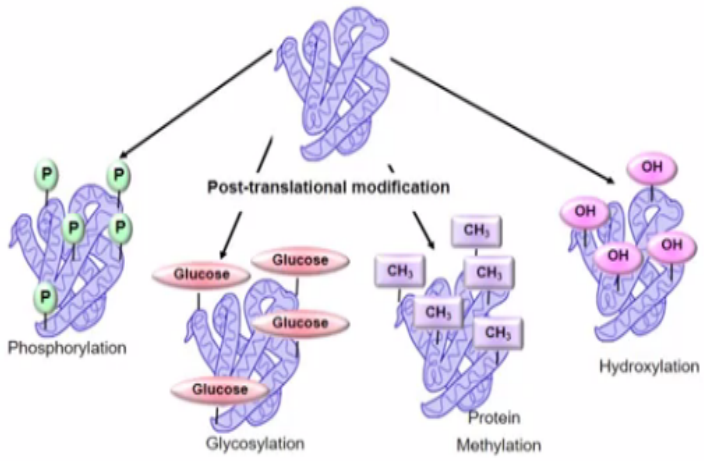

So, therefore a single gene can give rise to the multiple protein products, if you further continue on the complexity of the proteins, proteins can further get modified in the process of post translational modification and here we can see, if the phosphate residue were attached that process is known as phosphorylation, if sugar moieties like glucose are attached that is process of glycosylation.

If methyl groups are attached that is protein methylation and if hydroxyl groups are attached that is known as hydroxylation, so many proteins undergo post translational modification at some of their amino acid residues after the synthesis processes have already happened and some of those examples are shown on the screen but there is still many other type of PTMS happen which further governed the complexity of the proteins.

These PTMS are also highly relevant for various physiological processes for example, many signal transaction cascades, they are governed with the phosphorylation processes, so 20001 to

2003 was a time frame when human genome projects were getting completed but considering the complicity of the proteome and overall proteins present in the human, the process of identifying the protein took longer time.

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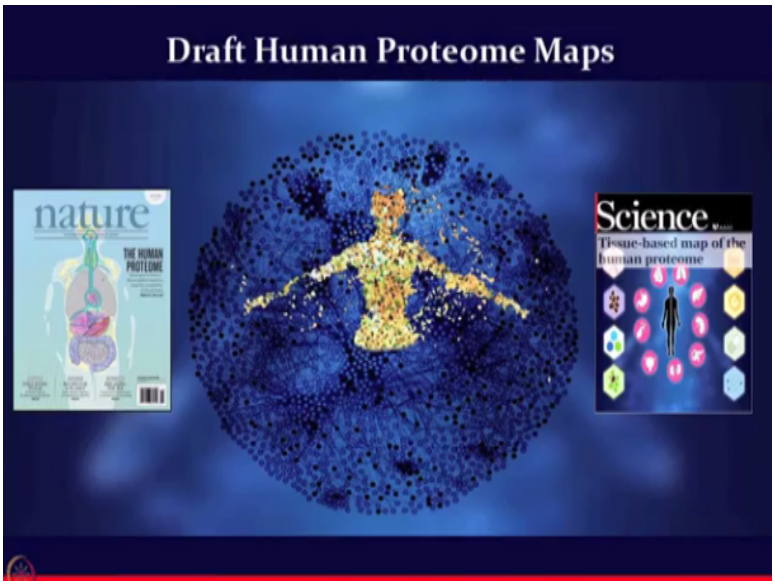

And only 2014 and 2015, the first draft of human proteome Maps was reported, now still aim was to only first try to report all the protein coding genes, so it means we are not talking about millions of proteins but only that many proteins which are coded by the genes can we at least detect those 20,500 proteins in the human body and of course, we need the experimental evidence for detecting those peptides and proteins.

So, mass spectrometry based approaches as well as microscopy and tissue based maps of the human proteome were reported during this time frame of 2014 and 15 however, still these are the drops because they had reported almost 17,500 proteins, so still we have not accomplished understanding and knowing about all the proteins present in human or any other given system.

Nevertheless, the advancements in the proteomic technologies have not started showing promise and now there is hope that some of the missing protein which, which we have missed out probably will be screened and will be discovered further.

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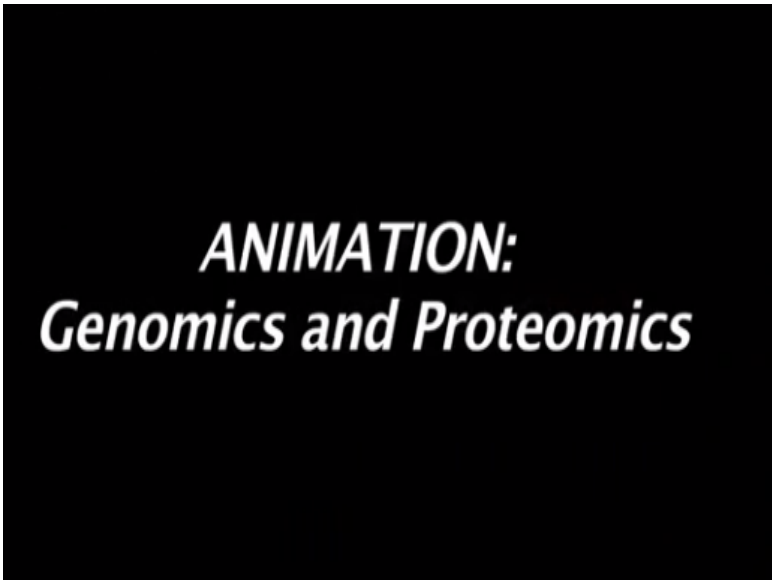

So, let us review the comparison of genomics and proteomics in the following animations.

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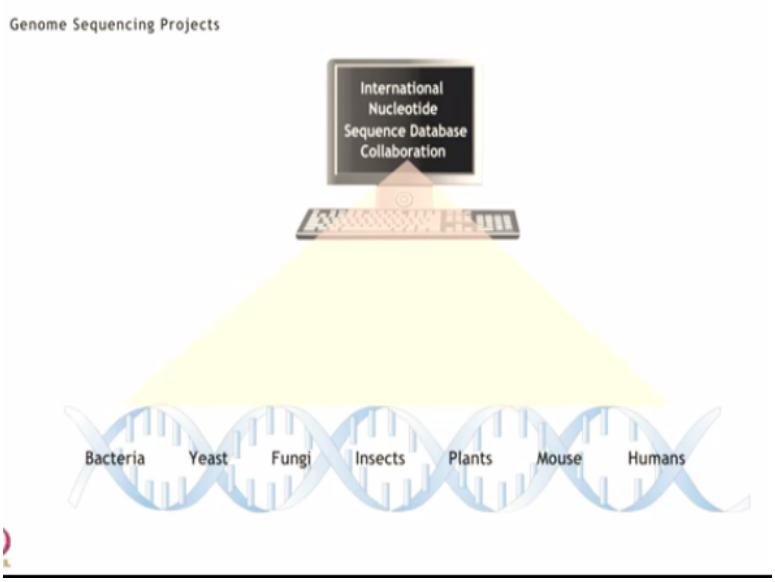

Several genome sequencing projects that aim to elucidate the complete genome sequence of organisms have been undertaken by several research groups all over the world, the DNA sequences are identified by the shotgun sequencing technique and then aligned using suitable software to provide the complete genome sequence. The genome sequence of a large number of prokaryotic and eukaryotic organisms has been successfully Ted used.

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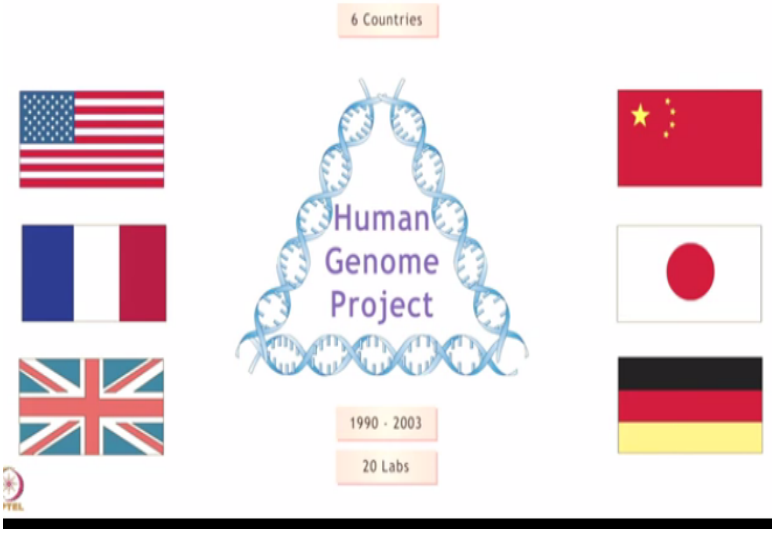

The immense amount of information held by the human genome motivated researchers to understand the nature and content of genetic material in great detail, a collaborative effort between 6 countries and 20 laboratories was undertaken in 1990 to produce a draft of the human genome sequence, work proceeded rapidly with a draft covering most of the genome being completed by 2000.

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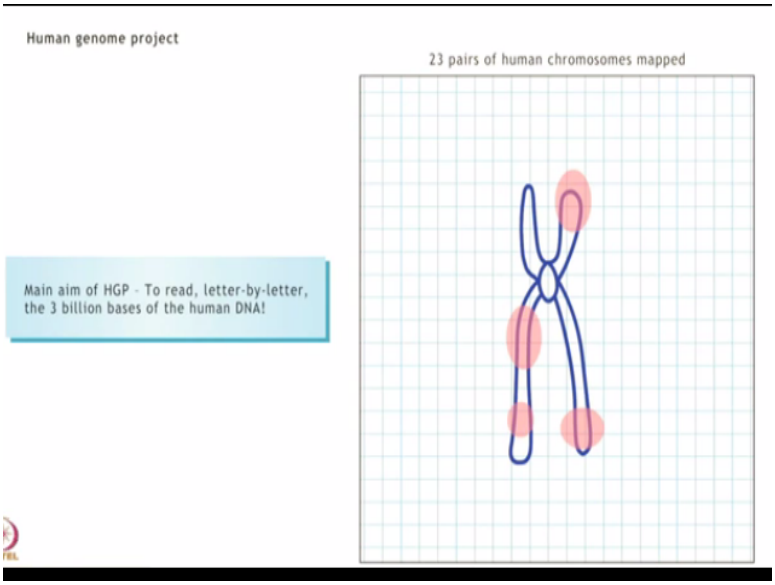

And greater coverage being achieved by 2003, before sequencing the entire genome, physical maps of the chromosomes were made, this helped in providing key tools for identification of disease genes and anchoring points in the genomic sequence, pilot projects were then launched to create a draft of the genome sequence, doubt regarding the potential of available sequencing techniques were overcome in this phase.

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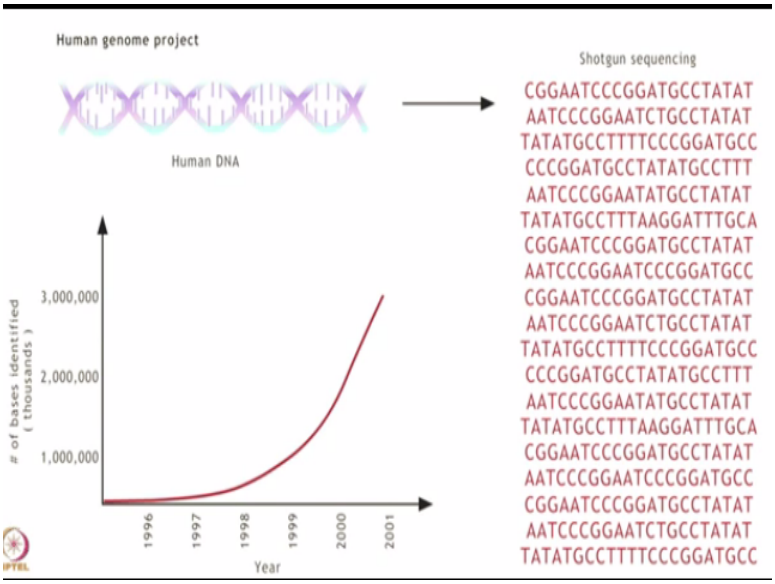

When it was established that they could sequence the genome efficiently, the shotgun approach was a fundamental technique used for large scale sequencing of the human genome which also makes use of sanger's sequencing, the collaborative effort to sequence the entire genome was challenged in 1998 by a privately funded organization, which aimed to reach the target before the publicly funded group.

Progress made in sequencing was very rapid and by 2001, a draft of the sequence was ready covering around 83% of the genome.

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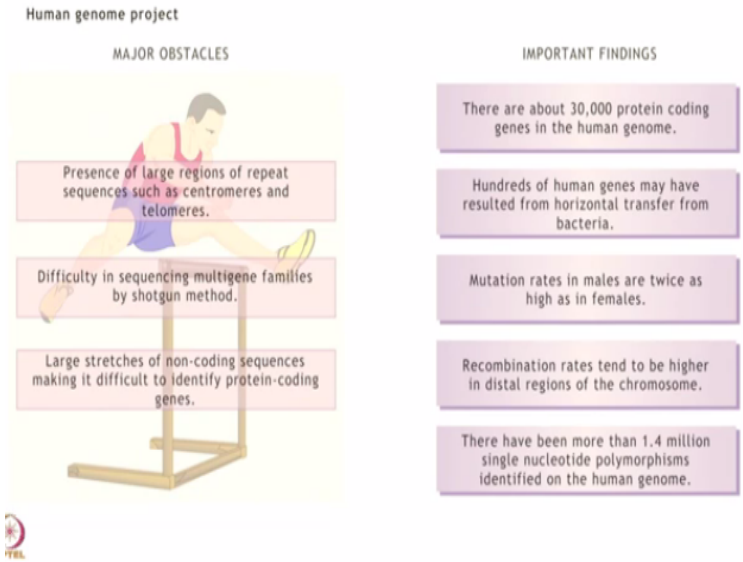

Several hurdles were encountered during sequencing of the human genome, the largest of them being the presence of long stretches of repeating sequences, these repeat regions made it difficult to assemble the genome accurately and the improved drafts published in 2003 covered 92% of the genome with a large part of the remaining 8% being due to the repeat sequences nevertheless, these genome sequencing studies successfully provided many findings about the human genome.

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Genomics Vs Proteomics

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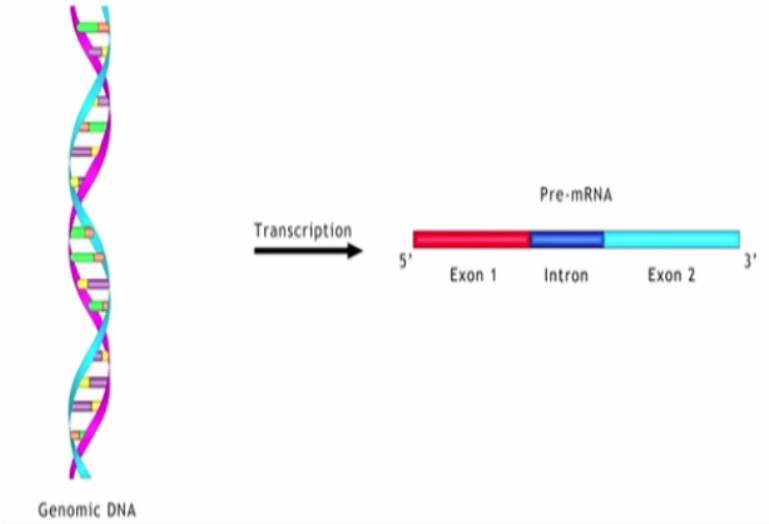

Genomic DNA consisting of introns and exons gets transcribed as such into its pre mRNA.

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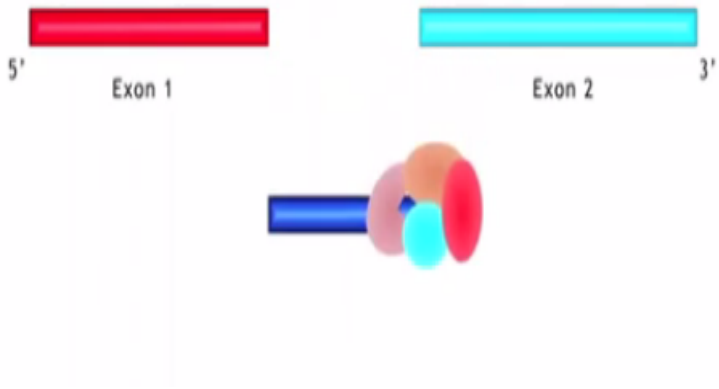

Specific recognition sequences within the intron employ the spliceosome assembly to it which cleaves the intron out of the pre mRNA.

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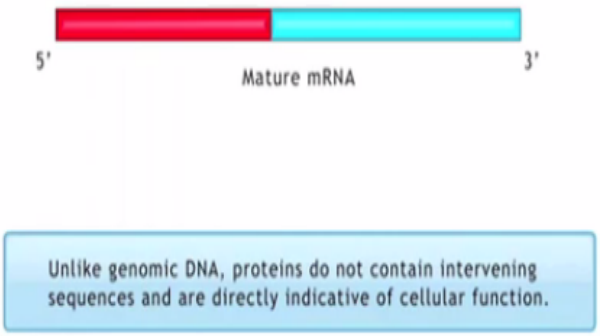

The resulting sequence consisting of only the coding exons is known as immature mRNA and is ready for translation into the corresponding protein.

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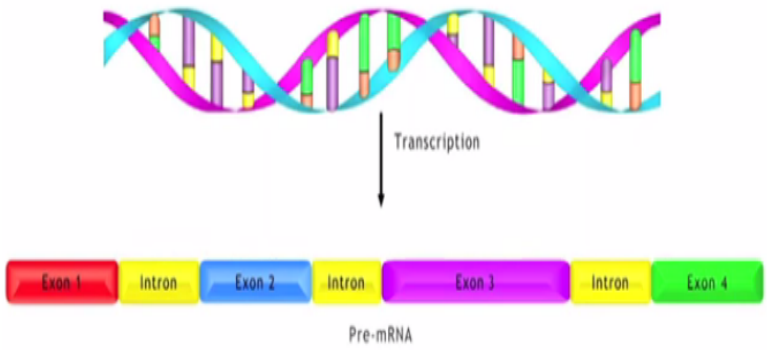

And from genomic DNA is often made up of several coding exons in dispersed by non-coding introns.

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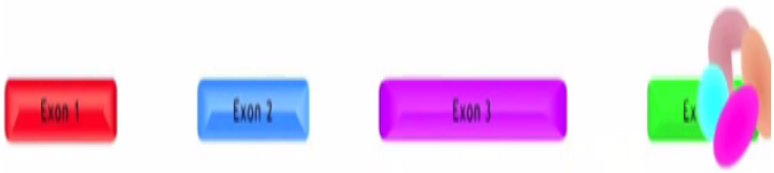

Alternative splicing, a common phenomenon observed in eukaryotes, allows the exons to be reconnected in multiple ways by several different mechanisms.

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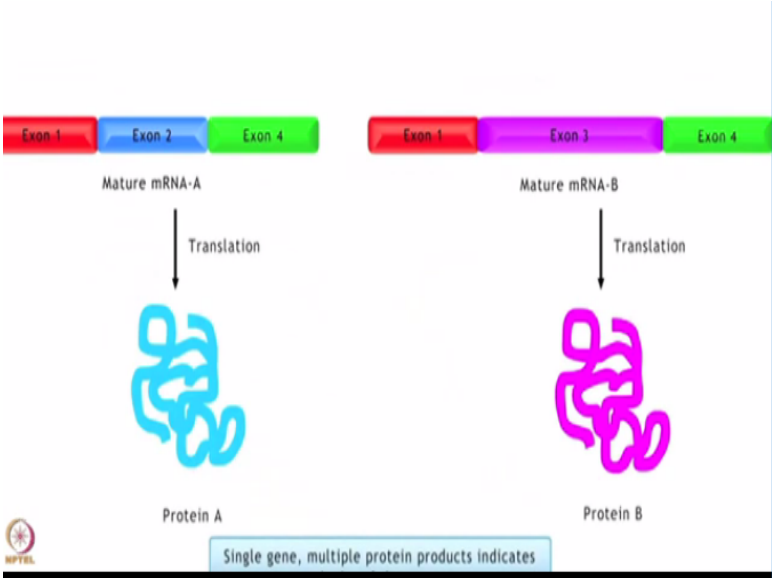

The diversity of proteins encoded by a genome is greatly increased due to alternative splicing, each mature mRNA formed gives rise to different protein products upon translation. Let us now talk about history of proteomics, is this feel very new, as I mentioned maybe after genomics, the new field of proteomics was really got attention however, the development of proteomics actually spans from very long time scale.

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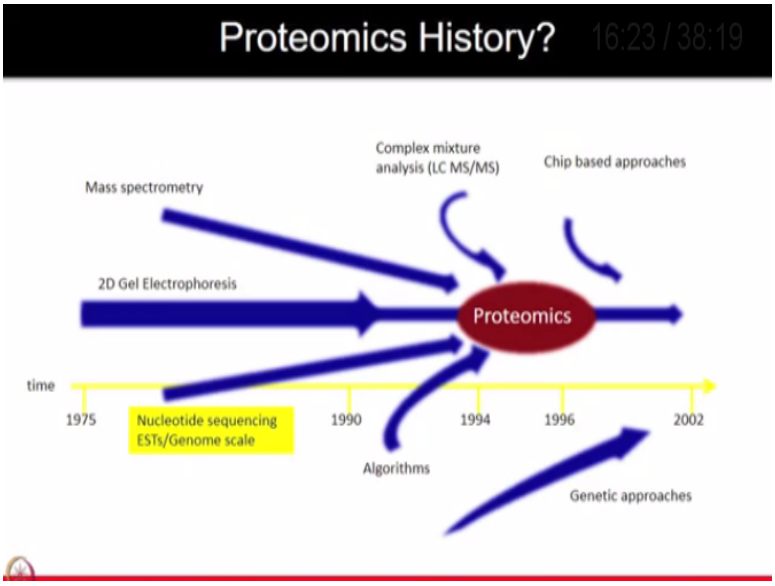

If you think on the you know, various developments which are happening over the period, even from 1970's, the 2 dimensional electrophoresis or how to separate proteins based on their different properties of molecular weight and isoelectric point was used by (()) (16:07) in 1975, simultaneously different advancements are happening in the field of mass spectrometry, various type of nucleotide sequencing ESTs, genome scales were actually under development during the timeframe of 1980's to 1990's.

And then, over the period advancement in the mass spectrometry especially, the soft ionization techniques like ESI and MALDI, they started giving now in a much better understanding of the proteins and good capability of performing the large scale protein analysis, so all these developments are happening parallel and along with the genome sequencing projects which we are giving rise to lot of data.

Now, people started realizing the need for developing the new algorithms, new databases and new ways of searching the genes and proteins simultaneously, different type of chip based approaches, a different type of microarray chips and various genetic approaches were all under development but only after completion of you know genomics project, the scientists started realizing the need for studying proteomics or studying the proteins comprehensively under the field of proteomics.

And Mark Wilkinson gave the term proteome in 1995 and then over the period after completion of genome sequencing project the whole field of proteomics really got into the limelight and now that you know from 2003 onwards, lot of new developments is happening in the area of proteomics.

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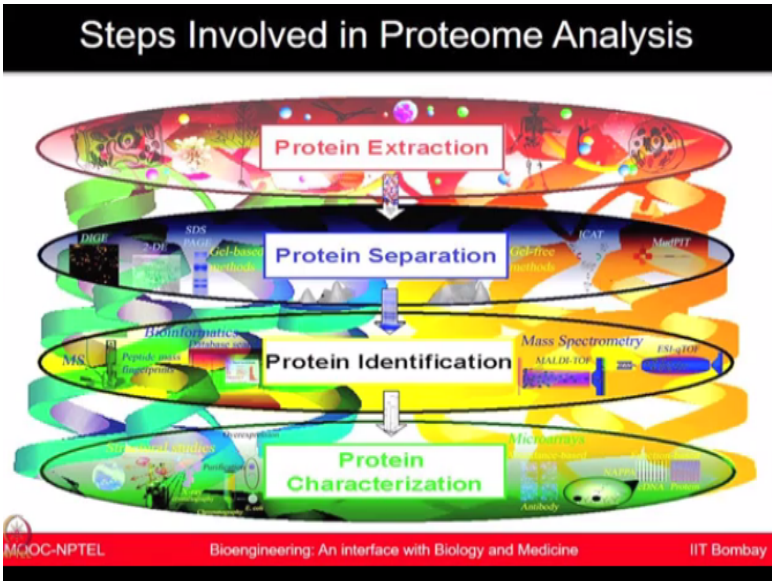

For any kind of complex proteome analysis, there are certain major steps involved whether we talk about human, bacteria, plant, any kind of sample, first thing is for studying protein you have to extract the protein out of that complex system, you want to you know rupture all the

membranes you want to get all the cellular contents out and only you want to get the proteins extracted whereas, nucleic acid, lipids, carbohydrates, etc. you want to get rid of them.

Then you want to separate the proteins and the protein separation could be based on the chromatography, could be based on the electrophoretic techniques, there are many different ways of protein separation, then further you want to identify those proteins and different type of mass spectrometry based approaches like MALDI-TOF TOF or ESI Q TOF or ESI orbitrap, those kind of platforms could be very helpful for both protein identification.

And if you want to compare the control versus disease condition, then protein quantification and in the process now, the bioinformatics, different algorithm, software's they become very crucial because without them you cannot do the proper identification as well as quantification and then, if now you are interested biologically for a given protein, then doing the structure and functional studies under the protein characterization can be very important.

And different type of technologies including various type of you know, structural studies, CD and MR etc. and microarrays technologies they are all helpful for the protein characterization.

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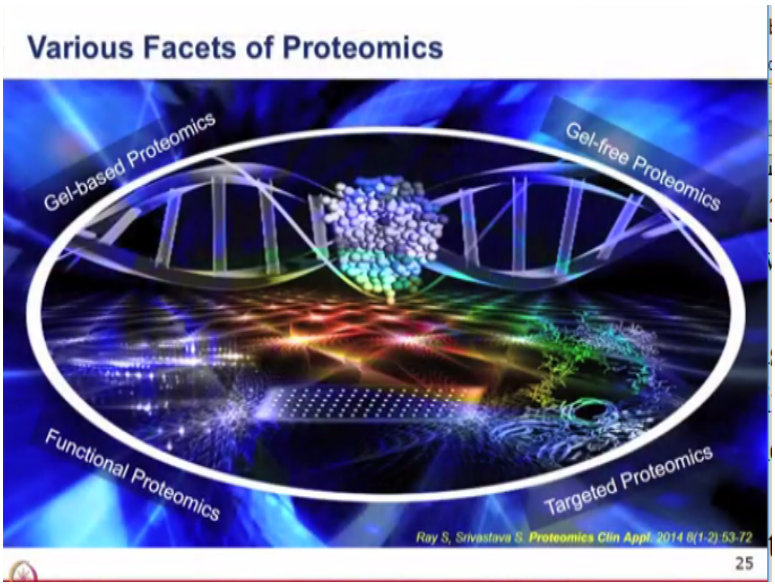

So, looking at these kind of you know, various technological approaches which are trying to understand the proteome, one could term; one could broadly classify the whole field into gel based proteomics which looks into the protein analysis using the gels like SDS page or 2d gel or dye gels or gel free proteomics which essentially looks into direct protein analysis using shotgun approaches especially, mass spectrometry based approaches.

Functional proteomics aims to try to understand the function of the given protein and different type of functional technologies including microarrays, surface plasmon resonance etc. have been very helpful for the functional proteomic analysis, then it comes the target proteomics where now you have identified the given peptides or given protein sequences and now, you want to only look into those targets, you want to know further ignore all the remaining you know millions of peptides.

So, how to selectively analyse those peptides from the complex sample can be a studied now under the new field of target proteomics.

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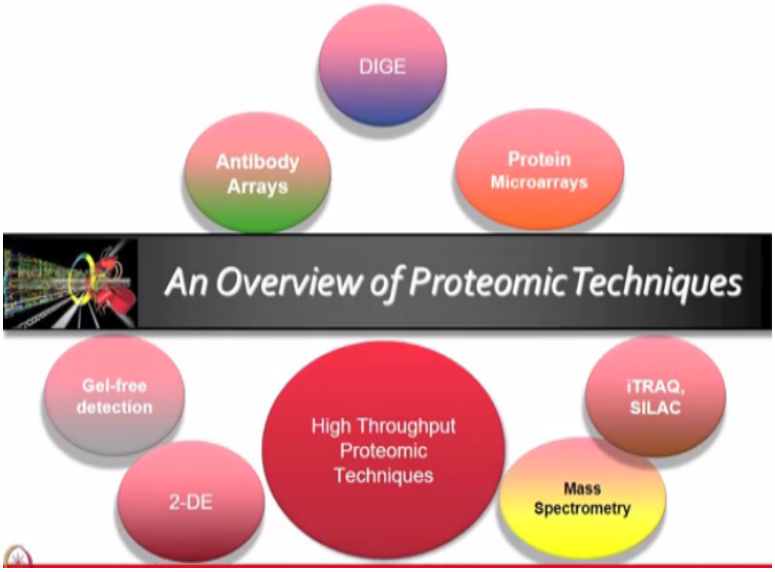

So, very briefly let us kind of you know, glass through different type of proteomic technologies which are currently being used. There are you know, gel based platform as I mentioned which includes 2D gel and difference in gel electrophoresis, there are different type of protein microarray platforms including the protein arrays and antibody arrays, there are gel free approaches which are essentially mass spectrometry based approaches which also include the quantitative proteomics using iTRAQ, SILAC TMT etc.

So then, many technologies which are currently under development which are currently advancing the field of proteomics, in the subsequent lectures we are going to talk about various protein technologies in much more detail, however, let me kind of you know give you the the glimpse of different proteomic technologies which are currently being used for many biological applications.

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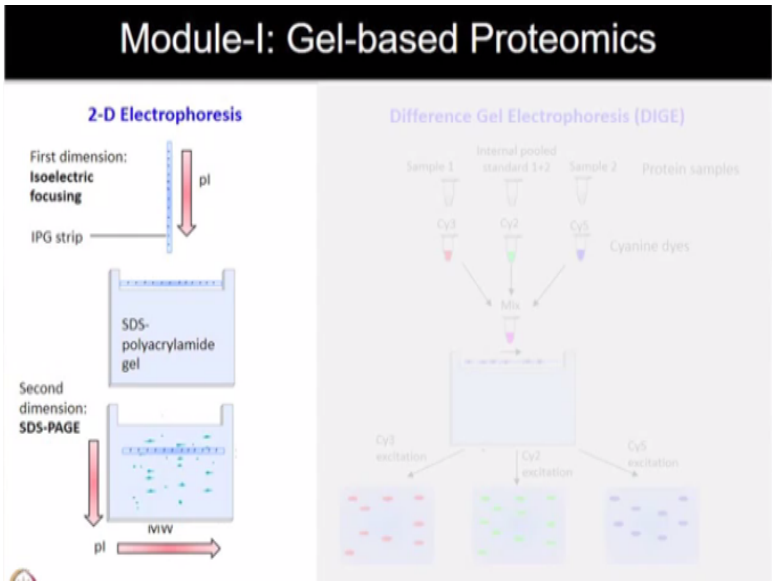

For example, the gel based proteomics, as I mentioned you can separate the proteins based on their molecular weight, in the SDS page or you can separate proteins based on their molecular weight as well as isoelectric point in the process of 2 dimensional gel electrophoresis.

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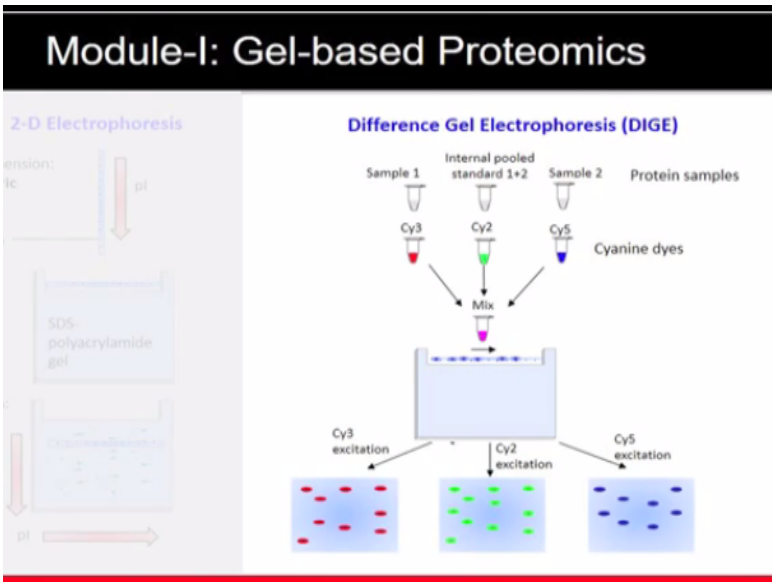

Or if your intention is to quantitate the proteins from the control and the test conditions then you can use a new technology which is difference gel electrophoresis or DIGE alright, so now let us talk about mass spectrometry, so mass spectrometers have increasingly become the method of choice for analysis of complex protein samples in proteomic studies because of their ability to identify as well as quantify thousands of protein.

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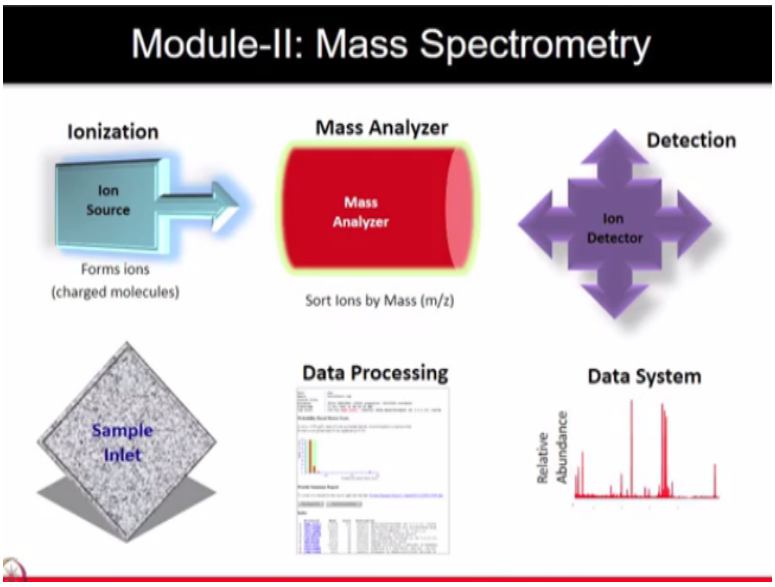

Broadly, any mass spec has ionization sources, mass analysers and detector, there could be a different type of ionisation sources, the popular ones are electro spray ionization or matrix assisted laser desorption ionization or MALDI, a different type of mass analysers, again some of the popular configurations include TOF; time of flight quadruples, orbit raps ion traps etc.

This slide shows you the kind of various major steps involved in doing mass spectrometry based proteomics where you have a sample inlet especially liquid chromatography, now the peptides are coming to the mass spec in the ionisation source, now they are entering into the mass analysers where you want to solve these ions based on the mass to charge ratio, then they are being detected on the detector and then the data could be analysed using databases.

And we can also look at the their identification as well as relative abundance or quantitation, let us now watch this animation to get an overview of mass spectrometry based proteomics.

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Tandem Mass Spectrometry

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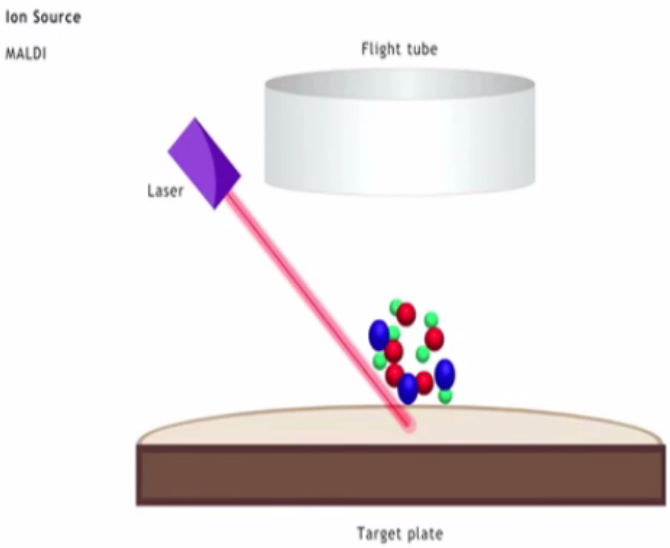

The ionization cells is responsible for converting analyte molecules into gas phase ions in vacuum, this has been made possible by the development of soft ionization techniques like matrix assisted laser desorption ionization and electrospray ionization which ensure that the non-volatile protein sample is ionized without completely fragmenting it.

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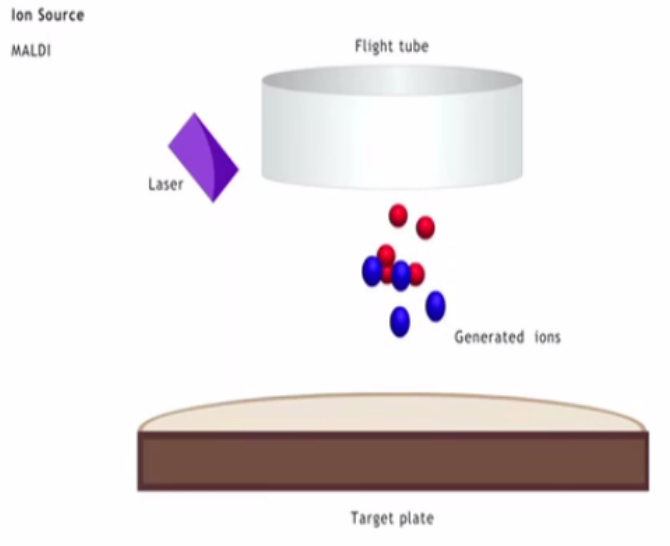

MALDI; the analyte of interest is mixed with an aromatic matrix and bombarded with short pulses of laser. The laser energy is transferred to the analyte molecules which undergo rapid sublimation into gas phase ions.

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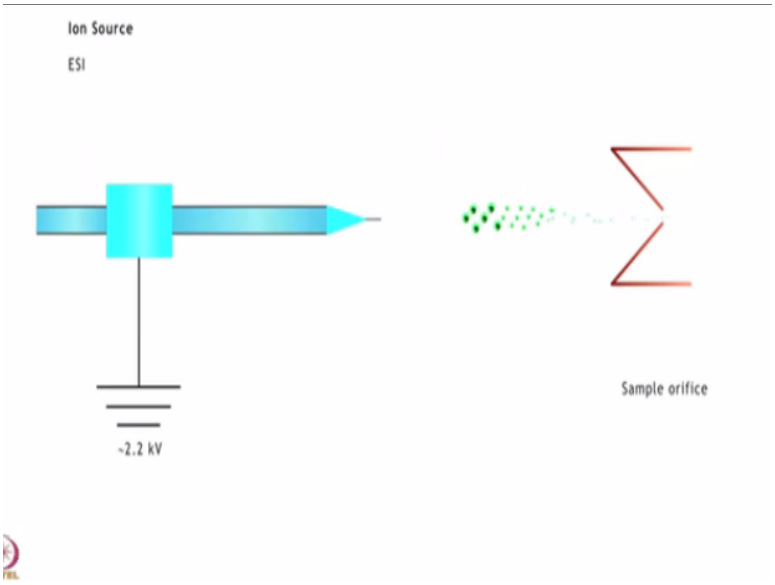

In ESI, the sample is present in the liquid form and ions are created by spraying a dilute solution of the analyte at atmospheric pressure from the tip of a fine metal capillary creating a mist of droplets, these ions are then accelerated towards the mass analyser depending upon their mass and charge.

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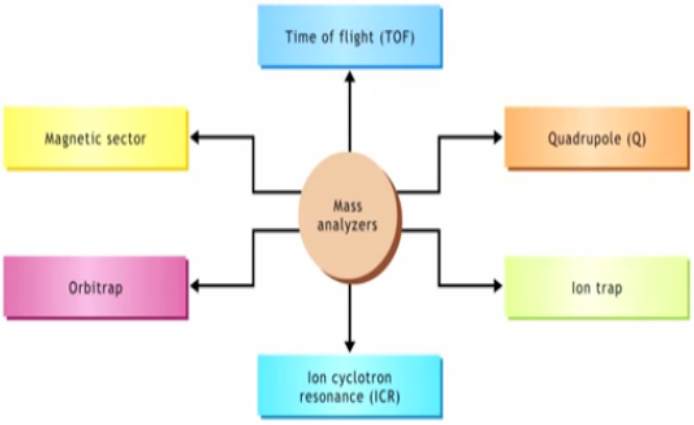

The mass analyser resolves the ions produced by the ionization source on the basis of the mass to charge ratios, various characteristics such as resolving power, accuracy, mass range and speed determine the efficiency of these analysers. Commonly used mass analyser includes time of flight TOF, Quadrupole Q and ion trap. Here, we will focus on TOF and Quadrupole mass analysers.

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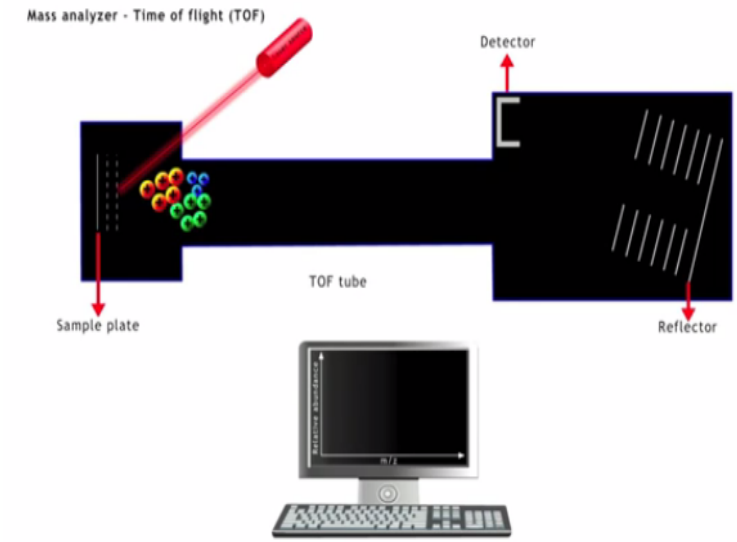

The time of flight analyser accelerates charged ions generated by the ionization source along a long tube known as a flight tube, ions are accelerated at different velocities depending on the mass to charge ratios, ions of lower masses are accelerated to higher velocities.

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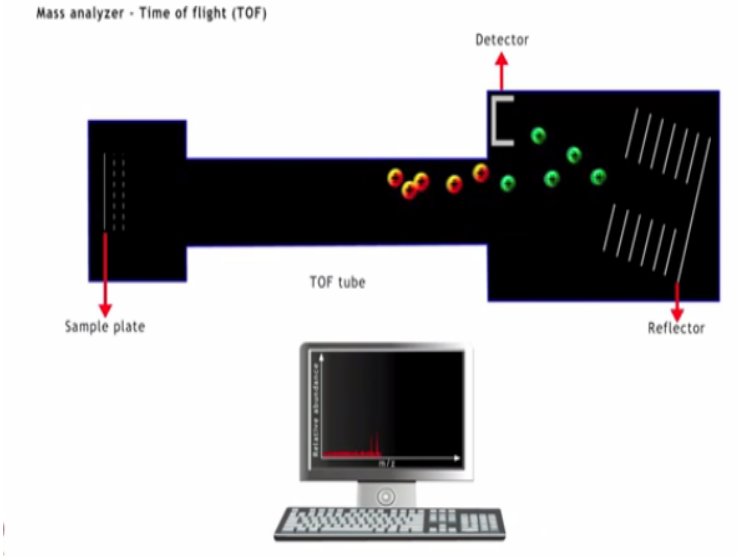

And reach the detector first, the TOF analyser is most commonly used with MALDI ionization source, since MALDI tends to produce singly charged peptide ions.

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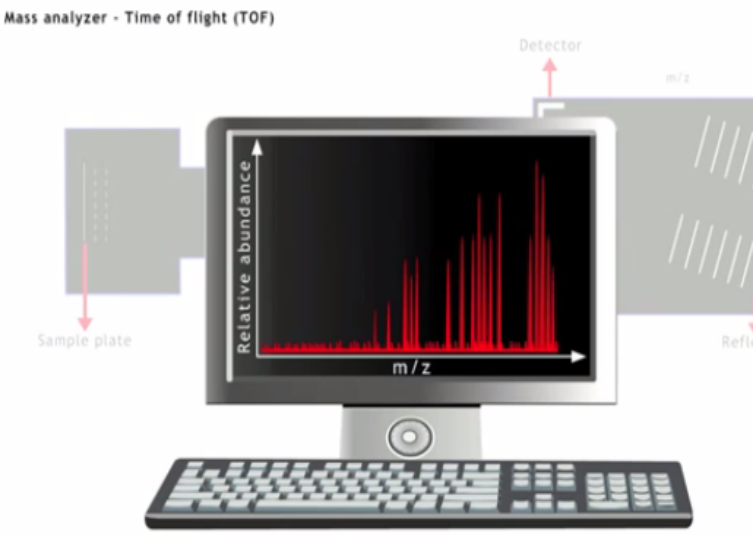

The time of flight under such circumstances is inversely proportional to square root of molecular mass of the ion.

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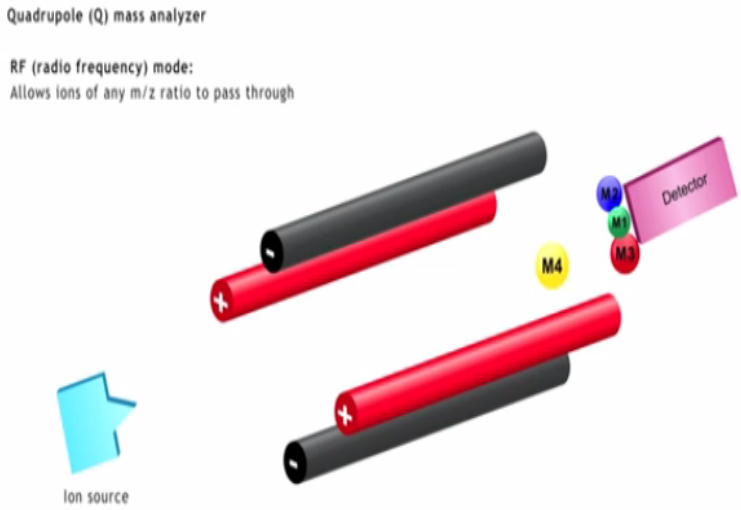

Quadrupole mass analysers use oscillating electrical fields to selectively stabilize or destabilize the parts of ions passing through a radio frequency RF quadrupole field. The quadrupole mass analyser can be operated in either the radio frequency or scanning mode, in the RF mode, ions of all m/z are allowed to pass through which are then detected by the detector.

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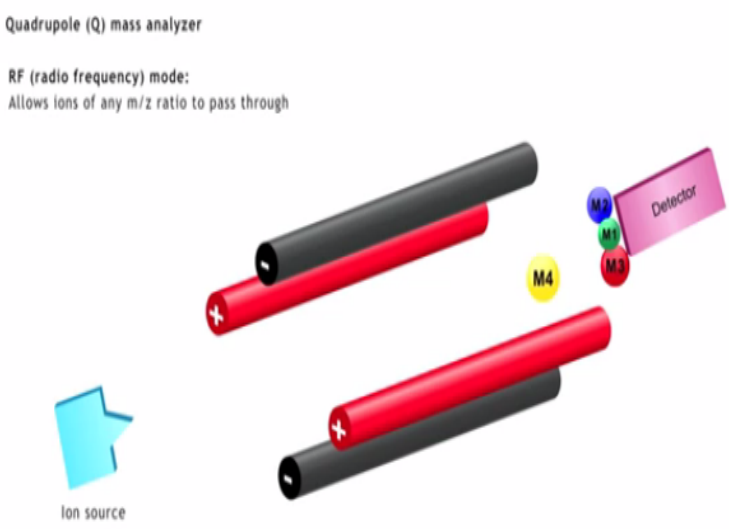

In the scanning mode, the quadrupole analyser selects ions of a specific m/z value, a set by the user, a range can also be entered in which case only those specific ions satisfying the criteria will move towards the detector and the rest are filtered out.

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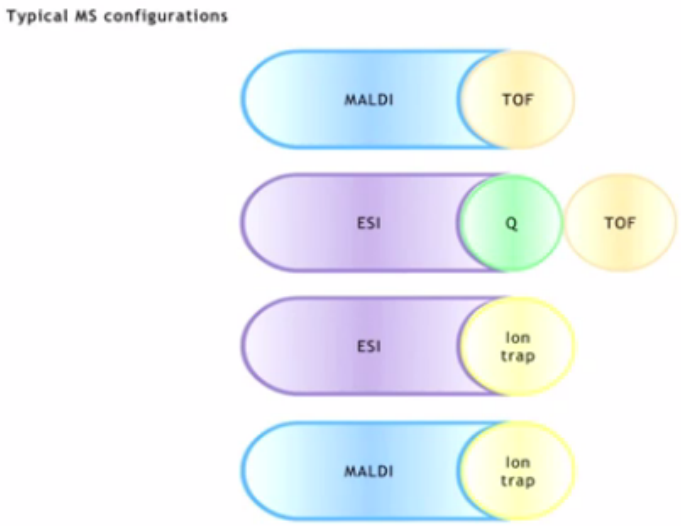

Some of the most commonly used MS configurations are MALDI with TOF or ion trap and ESI with Q, TOF and ion trap, 2 mass analysers can also be connected in series such that the first one separates intact ions while the second one separates the fragmented ion particles, this helps in providing better resolution and allows identification of proteins through peptide fingerprinting.

Hybrid TOF analysers such as Q TOF make it possible to carry out high throughput analysis, so we have discussed about broadly 2 major technology streams, one is the gel based proteomics,

second is gel free or mass spectrometry based proteomics, now let us briefly look into interactomics where intention is to look at protein, protein interaction or various biomolecular interactions and some sort of even functional characterization of known protein functions which you want to identify.

So, for example if you have identified various candidate proteins or biomarkers from a discovery set off either you know 2D gel based approach or ITRAQ or you know various types a quantitative mass spectrometry based methods, then you want to further study their protein of interest.

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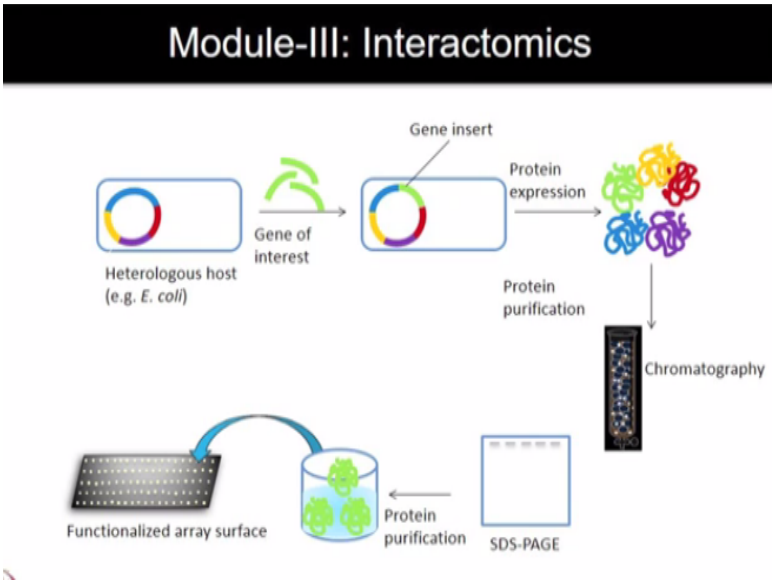

To do that you can use heterologous system, where you can clone the gene, you can express the that particular protein in the bacterial system, purify their protein and now you can study that on the functional array surface or the microarrays to look into that you know this protein interacts with which are the other possible proteins or then you can start doing various type of modifications, various types of structural characterizations to know this protein in much more detail.

Let us watch this animation to learn about how protein microarrays could be used for studying protein, protein interactions interaction.

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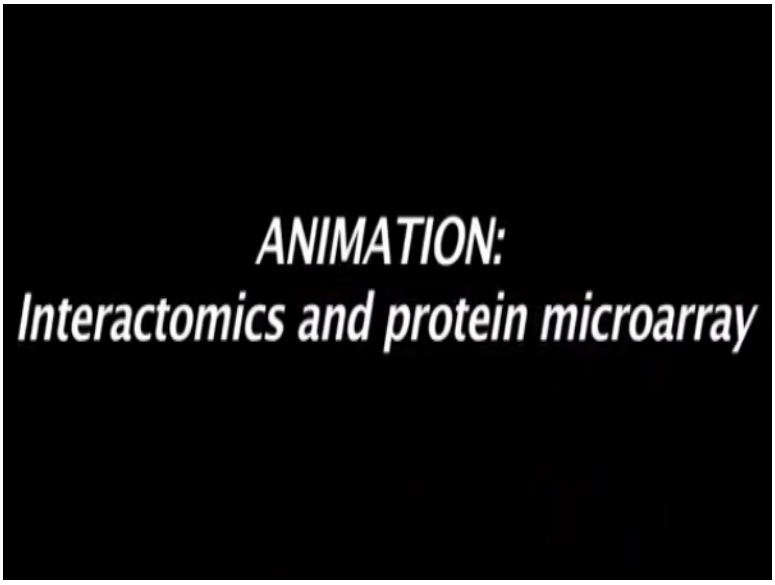

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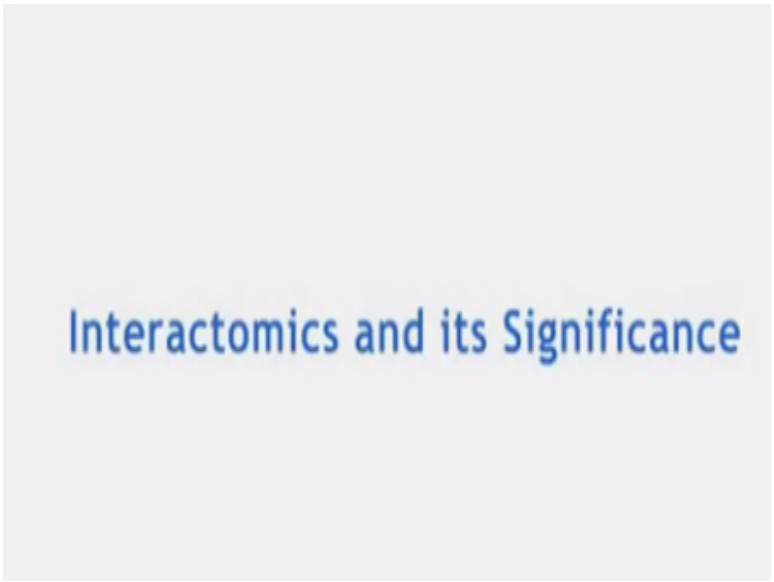

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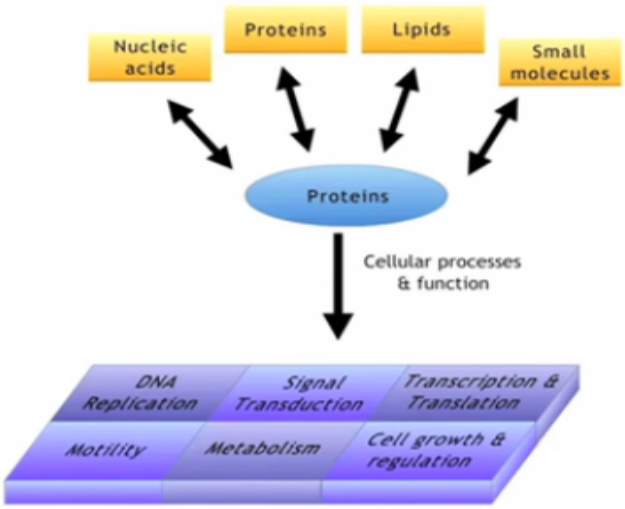

Interaction studies of proteins with various biomolecules help in deciphering and understanding the functions of various proteins in the complex network of cellular pathways, proteins interact with other biomolecules such as nucleic acids, lipids, hormones etc. to execute a multitude of functions in living organisms such as signal transduction, growth and regulation and metabolism to mention a few.

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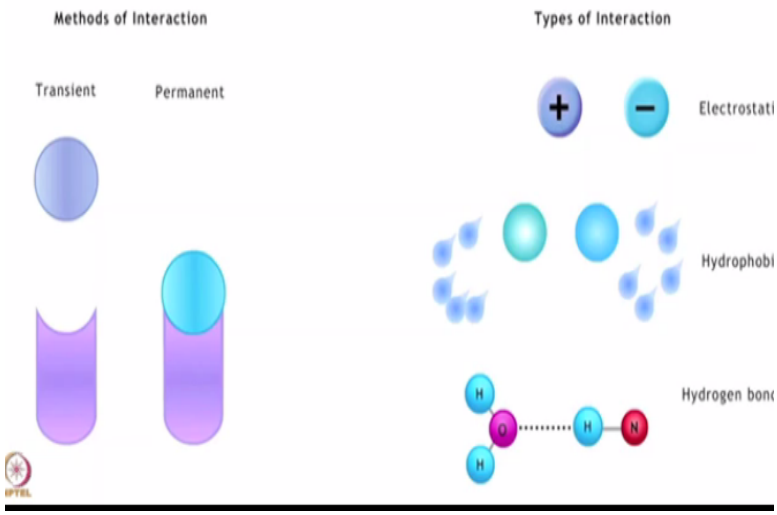

Protein interactions with other biomolecules can be of several different types, they may be weak or strong, obligate or non-obligate, transient or permanent. The physical basis for these interactions include electrostatic, hydrophobic, steric interactions, hydrogen bonds etc.

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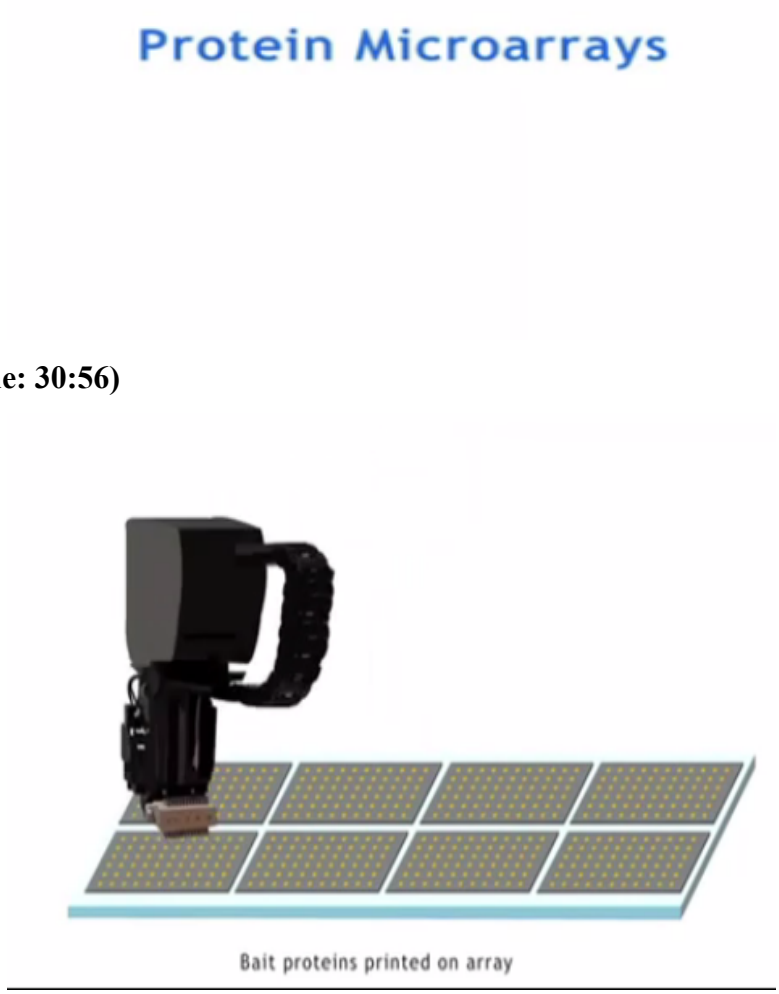

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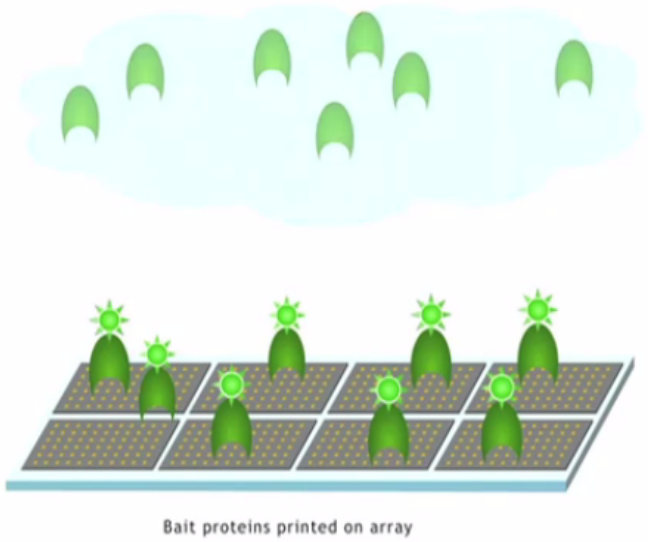

Protein micro arrays are widely used for protein interaction studies, one of the proteins to be analysed is printed onto a microarray surface usually made of glass, the proteins known as bait proteins get immobilized onto the array surface that is functionalized with reagents like nickel or aldehyde compounds that interact with groups present in the protein. This bait protein is then probed for interactions with suitably labelled query or pre proteins.

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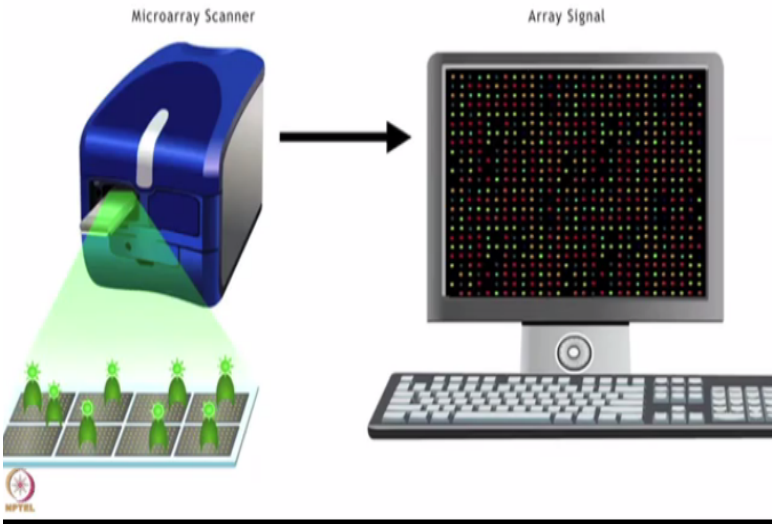

Any unbound proteins are washed off the array surface, once the unbound proteins are washed off the array surface, the protein interactions are detected by means of an array scanner, these protein micro arrays are extremely useful in studying interactions with other proteins as well as small molecules, DNA or RNA. Another major area is label free detection technologies which mainly you know being used by surface plasmon resonance or SPR imaging kind of technologies.

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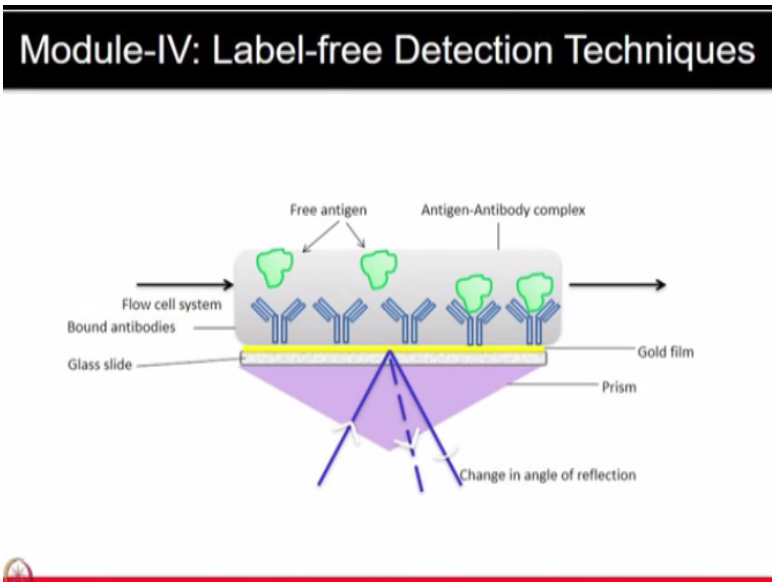

Again the protein of interest which you want to further characterize, let us say an antibody raised against that protein is immobilized on the chip surface and now, you have you want to study the antigen antibody interaction, so you can float that protein and now you can see that whether this antibody is binding this protein of interest or not and if you want to look at you know the protein drug interaction then you can immobilize the protein of interest on the chip surface.

And then float the drug molecules and see whether the drug or inhibitors they are making any complex with this protein of interest or not, so again the various type of label free biosensors which are currently being used for the further characterizing these proteins of interest and they can provide not only the binding information but also the kinetic information about the KD values of how these binding events are governed.

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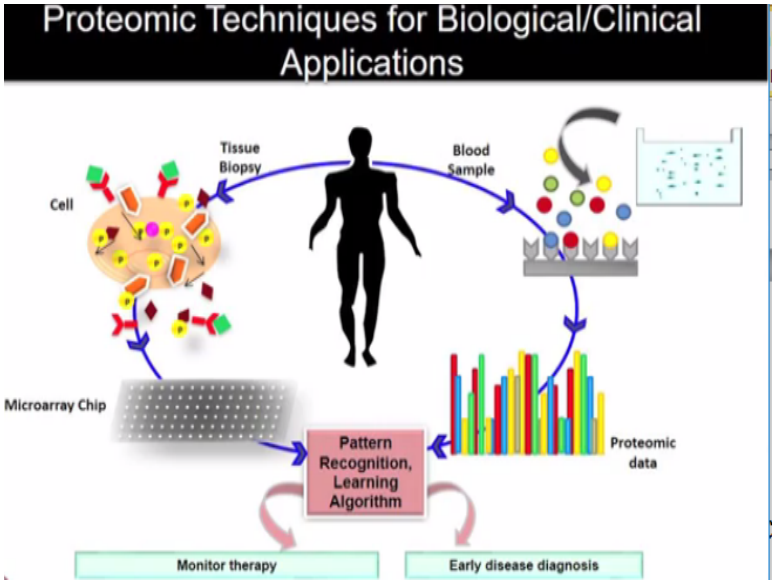

So, if you look at any biological applications and specifically more so about the clinical applications, various proteomic technologies which we are going to discuss in much more detail in the subsequent lectures, they all can fit into you know in various ways to add different type of questions. For example, you know if you are studying let us say some clinical applications you are looking at some disease biomarkers in the human context, you are looking at tissue biopsies.

So, again you are you know, extracting the proteins from them, you can also take the blood samples, you can extract the protein from them either analyse them using the mass spec or analyse using the gel based platforms, you have identified now certain you know characteristic protein which looks very interesting for the pattern analysis point of view from the you know, disease individual as compared to the healthy individuals.

You have also now after looking at these proteins of interest, you see there are many proteins belonging to a given network, they are you know highly (()) (34:20), so now you want to look at their you know interactome or interaction networks, you can use microarray kind of you know platforms, so again many of these technology which we are talking together, they can be used for us to understand a given system much more in detail, much more comprehensively we can study.

Especially, now again if you think about clinical context, these technologies can be used to monitor the therapeutic responses as well as the early disease detection, so many of these applications are not possible without advent and advancements of these kind of proteomic

technologies however, you know while I am mainly discussing about the proteomic technologies.

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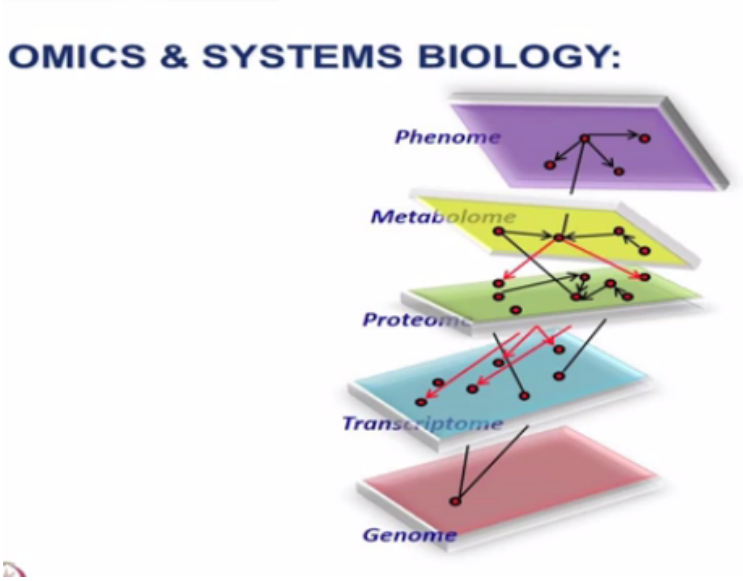

But I would like to highlight here that you know there are different spheres of Omics, if you think about all the gene information at the part of genome or the transcripts in the transcriptome, all the proteins proteome, all the metabolites in the metabolome and the phenotypic behaviour in the phenome, so the balance in complexities are governed with all of these spheres, only studying proteins or only studying genes will not help us to give the full picture of what is happening in that physiological context.

And therefore, a new field of proteogenomics, where intention is to correlate both genome and proteome information is become much more powerful.

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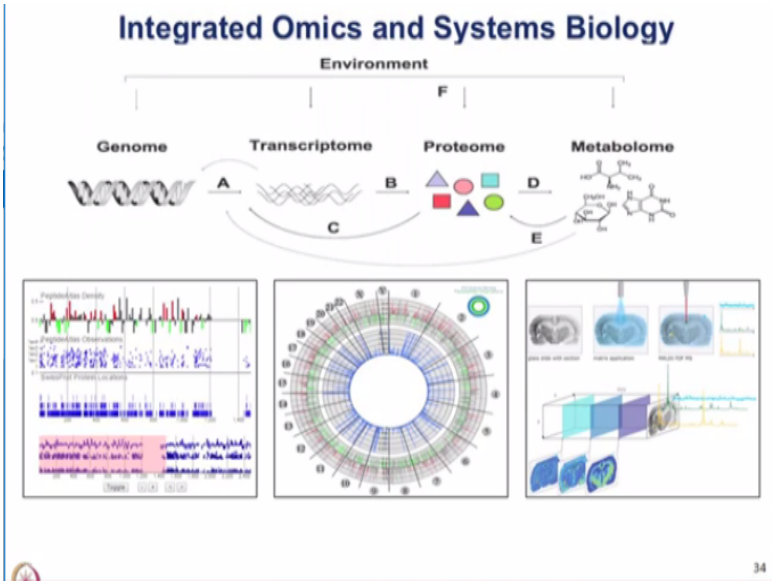

So, as studying all these you know different biomolecule in systems network or cell biology is becoming much more powerful, so while genome provides the static snapshot of the total information which is encoded in the cell, these biological processes are very dynamic governed with the proteins, transcripts, metabolites, so studying all of them together can be comprehensively can be much more powerful for us to know what is exactly happening in the given system.

So, currently you know there is lot of data being generated, the big data is coming from various type of DNA sequencing platform, there are various type of next generation sequencing, technologies which are you know, really advancing fast and they are now able to give us the you know entire whole genome sequence, RNA expression analysis, so whereas you know different type of mass spectrometry based technologies are able to provide you know, very big data set for all the proteome as well as the metabolites or metabolome.

So, now there is system approaches are really required to analyse and interpret these large data sets because if you really want to comprehensively investigate these ballast system, we need to analyse the data together, so this will help us actually to find the molecular mechanisms and therapies for diseases, it could also relate the molecular phenotypes with relevance to the clinical characteristics.

So, in conclusions today we try to, to see the journey of genome to proteome, some brief comparison of what are the key differences from the genome to proteome, we have also looked at there are many technologies which are part of extending the proteome is starting from the gel

based platforms to different type of advent in the mass spectrometry platforms, different protein microarrays, label-free biosensors as well as the emerging field of targeted proteomics.

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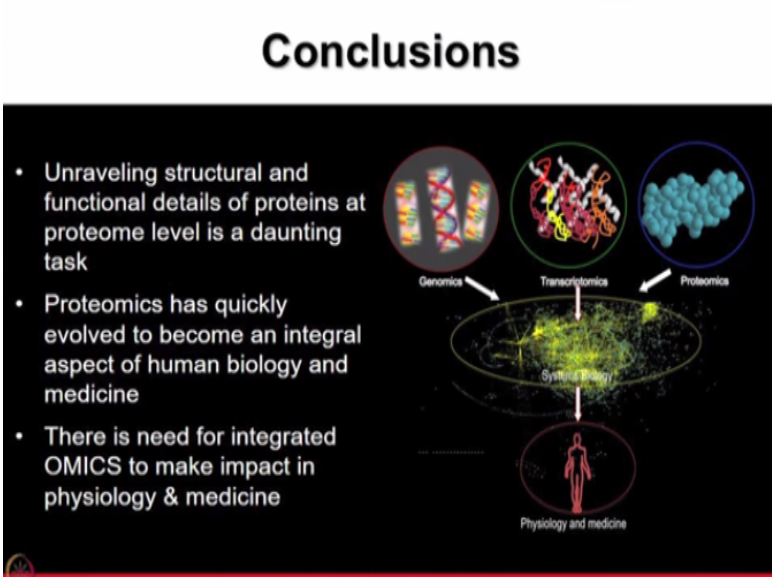

So, unraveling the structural and the functional details of proteins at the proteome level is very daunting task, proteomics has quickly evolved to become an integral aspects of human biology and medicine however, there is still the need to integrate Omics at different level whether we talk about genome, transcriptome, proteome, metabolome and phenome, so that we can make a real impact in physiology and medicine.

I will stop here and in the subsequent lectures, we are going to talk to you about some of these proteomic technologies in much more detail with certain lab sessions, thank you very much.

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