Proteomics : Principles And Techniques

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Lecture No. # 03
Genomics and Transcriptomics: Why proteomics?

Welcome to the proteomics course. Today, we will talk about genomics and transcriptomics and then, we talk about why to study proteomics. So lecture outline, we will talk about genomics, transcriptomics and need to study the proteome by using proteomics. Understanding biological system is very challenging task. During the last decade, we have witnessed the revolution in biological research asthis discipline has fully embraced genome technologies. The emergence of genome wide analysis to understand DNA, RNA and protein by employing genomics, transcriptomics and proteomics has revolutionised the study of control networks that may relate cellular homeostasis.

So, let us talk about genomics. It has been only 60 years since the 1953 landmark in the study of Watson and Crick deduced the double helix. Structure of DNA and biological cells research has witnessed a great progress in genomic research during the last decade. The simultaneous effort of human genome and cellular genomics completed the sequencing of human genome in 2011.So,let us look at some other definitions; genome that is the entire sequence of an organism's hereditary information including both coding and non coding regions encoded in DNA which is known as genome. Studying genome of an organism by employing, sequencing and genome mapping techniques is known as genomics. The genome sequencing projects produced massive amount of information on DNA sequences for many species. The genomic research is also providing information for mutations, deletions and epigenetic alterations which modulate gene expression.

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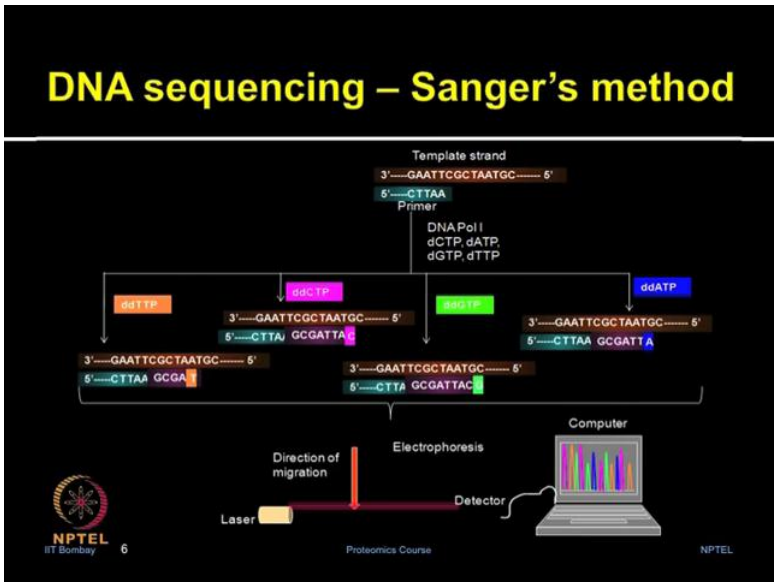

The various sequencing methods have been employed for genome sequencing. Let us first discuss the traditional methods. The traditional DNA sequencing was done by using Sanger's method. As you can see in this image here, the genomic DNA is fragmented, cloned into a plasmid vector and used to transform e colloid. The flow sense enabled dideoxinucleotides or ddNTP'st erminate DNA extension reaction in a single tube. Four labelled ddNTP's are added and in an capillary based electrophoretic gel, the colour DNA fragments are separated then, a laser beam is applied which detects colour and determine the sequences.

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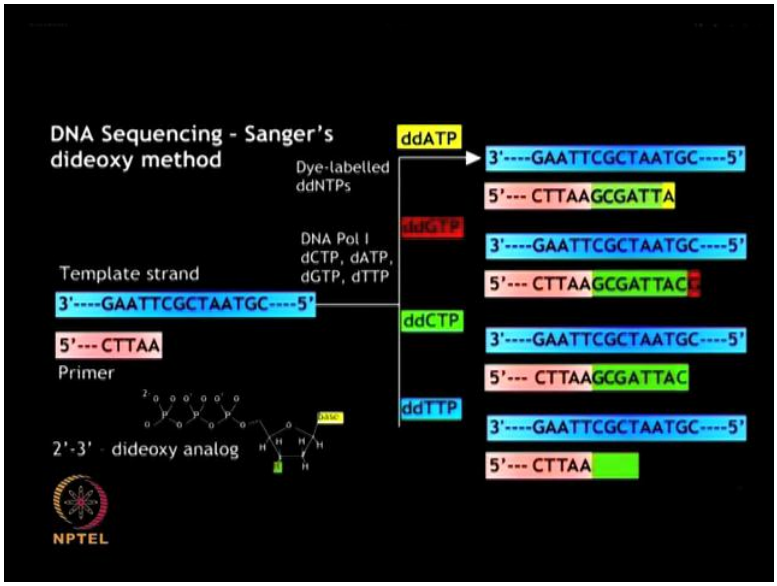

A simple and elegant method for DNA sequencing was devised by Frederick Sanger, where collection of DNA fragments are synthesised by means of controlled interruption of enzymatic replication. Four DNA synthesis reactions are carried out simultaneously with this strand, whose cycrosis is to be determined being used as the template. The reaction mixture consist of regular deoxynucleotides, and DNA polymer is along with a small amount of one labelled did eoxynucleotide analog being added to each of the four reaction mixture. A primer is added to begin the DNA synthesis and a strand elongation continues until a dioxy analog gets added instead of the regular dNTP. The chain termination occurs at this stage due to the absence of the three prime hydroxyl group for the formation of next phosphodiester bond.

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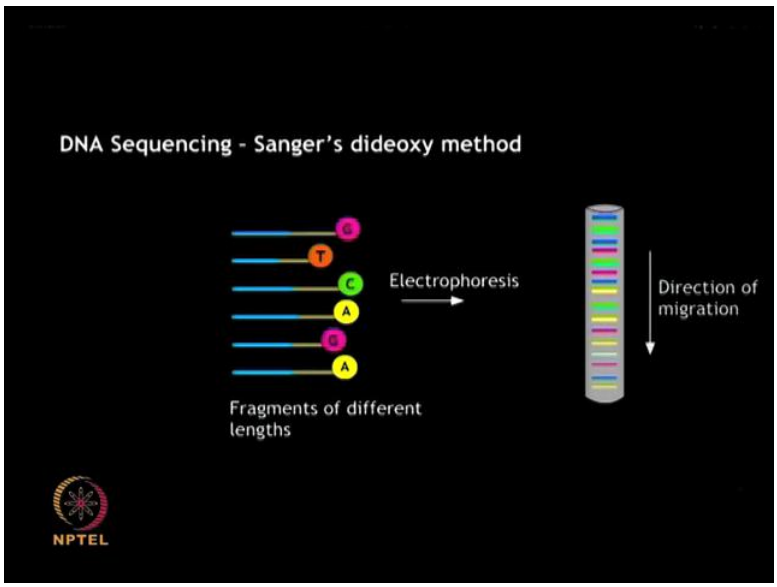

The synthesized strands are separated from each other after which, the differentially labelled strands of various length are separated by electrophoresis; the smallest fragment move further in the gel, while the larger fragments remain close to the point of application.

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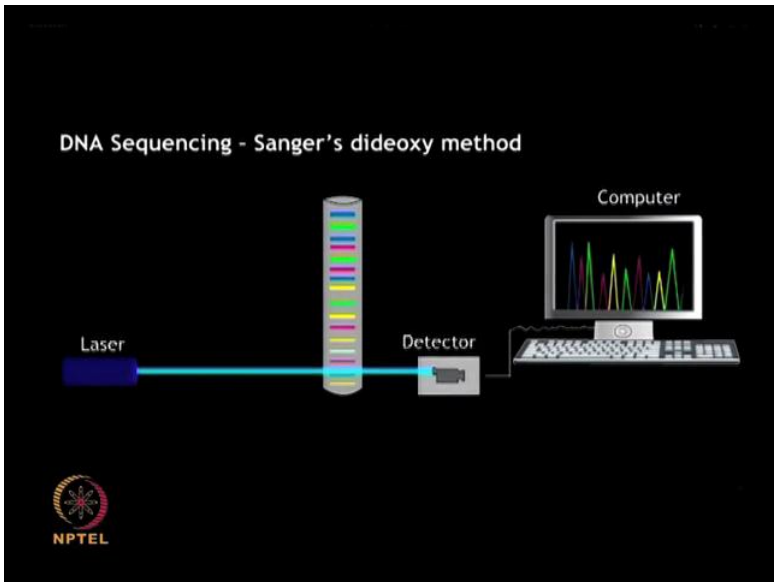

The different fluorescent levels of each dtNTP can then be detected by stranding the gel with a beam of laser. The output sequence obtained is complimentary to the template strand which can be used to deduce the original desired template sequence. To obtain the human genome sequence, the human genome project employed strategy of short gun sequencing.

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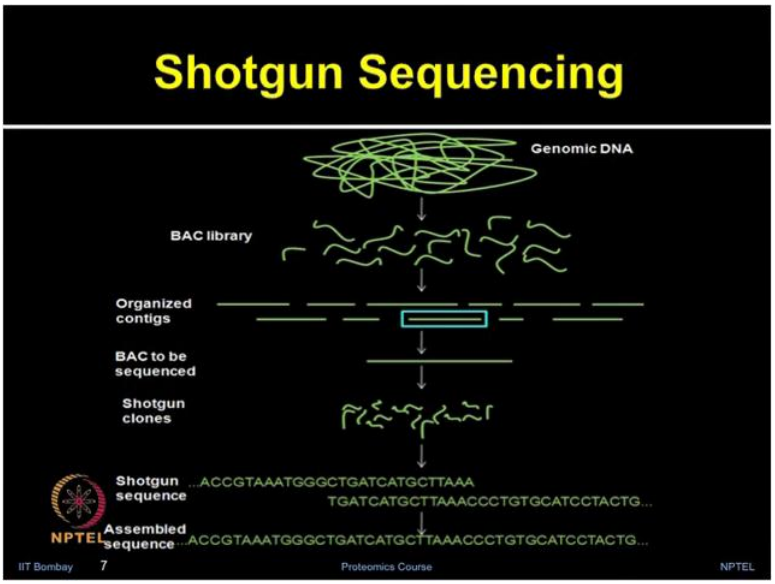

So, from genomic library clones were isolated and altered into a detailed physical map. Further the individual clones were sequenced by short gun sequencing. The human genome

project group produced a working draft of human genome by a map based strategy, while cellular genomics sequence the human genome by whole genome short gun method.

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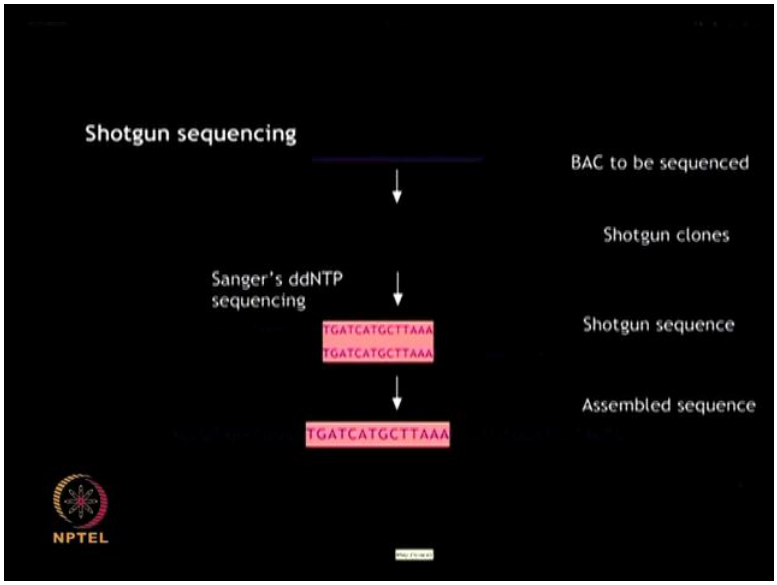

Genomic DNA is cleaved using a suitable restriction endonuclease and to fragments insert it into bacterial artificial chromosomal vectors. These vectors enable the DNA fragments to be amplified. The genomic DNA fragments of the library are then organised into a physical map after which individual clones are selected for sequencing. The selected back is amplified, and these clones are sequenced using Sanger's chain termination method. The sequence of the clone is then deduced by aligning them based on their overlapping regions. The entire genomic sequence is then obtained once each back is sequenced in this manner.

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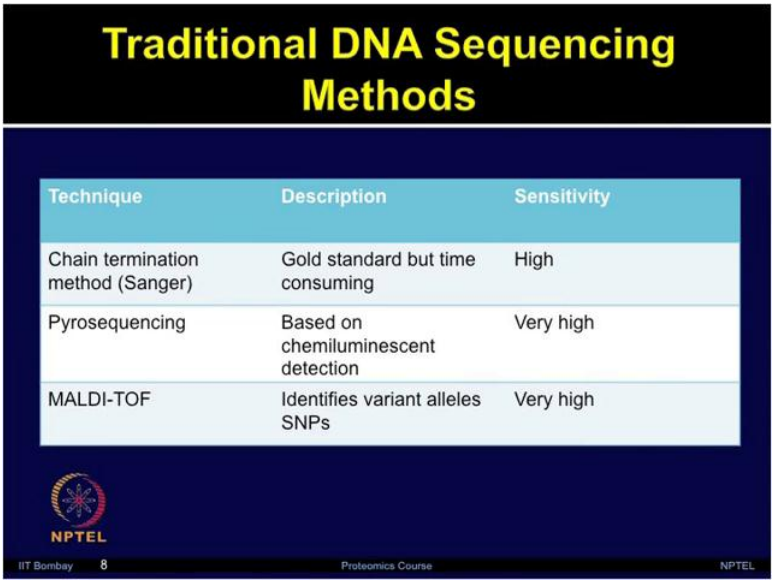

Let us compare some of the traditional DNA sequencing methods. As you can see here, the chain termination method or Sanger method that is the gold standard, but it is very time consuming; sensitivity is high, but in pyro sequencing which is based on chemiluminescent detection system the sensitivity is very high. Even MALDI-TOF can also be employed if your aim is to identify variations in SNP's and sensitivity is very high. So, we discuss about the genome sequencing projects. The genome sequencing projects aim to decipher a complete genome sequence of all chromosomes of an organism. Several such projects were initiated and successfully accomplished.

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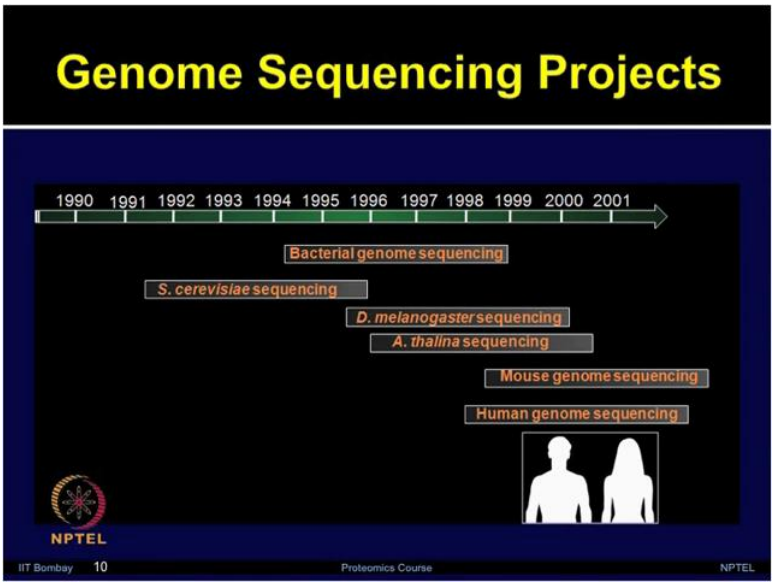

Sequencing a genome of higher organisms such as human was very challenging, but researchers have shown very good team effort, and successfully completed the draft sequence in 2001 and complete sequence in 2003. Here and there time scale, you can see the sequencing of various organism which was progressed from 1990 to 2001.The human genome project provided insights for various details.

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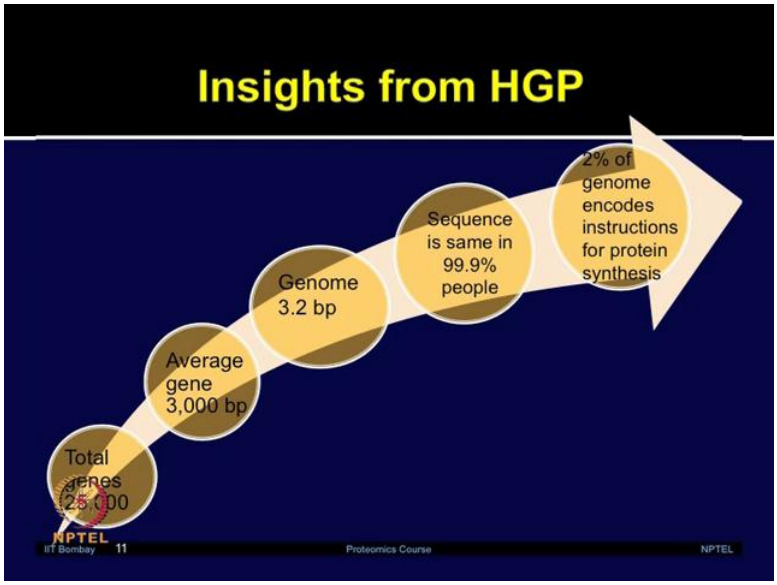

Such as, the total number of genes are estimated to be around 25000.The average gene consist of 3000 base pairs; the human genome consist of 3.2 million base pairs; human genome sequence is exactly the same almost 99percent in all the paper. And about 2 percent of the genome encode instruction for the synthesis of proteins; the various potential benefit of human genome project.

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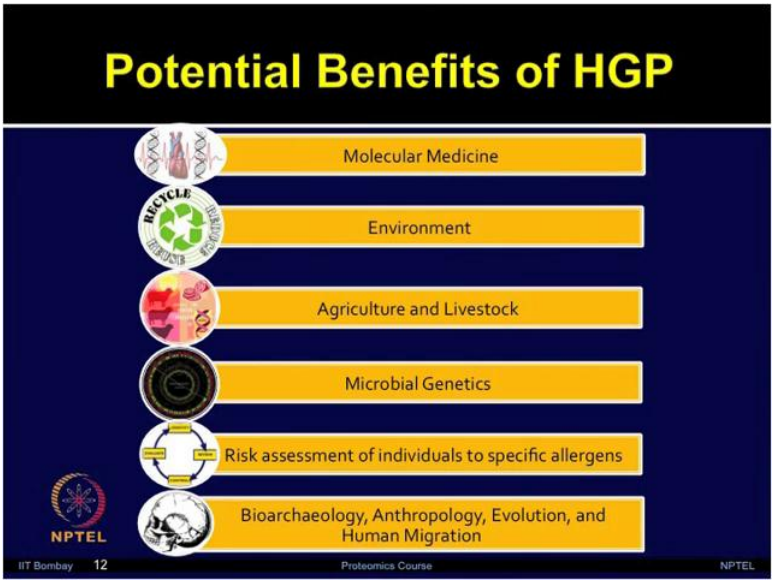

The information was useful for molecular medicine, environment, agriculture and livestock, microbial genetics, risk assessment of individuals for a specific allergens as well as, in other fields such as anthropology, evolution and human migration.

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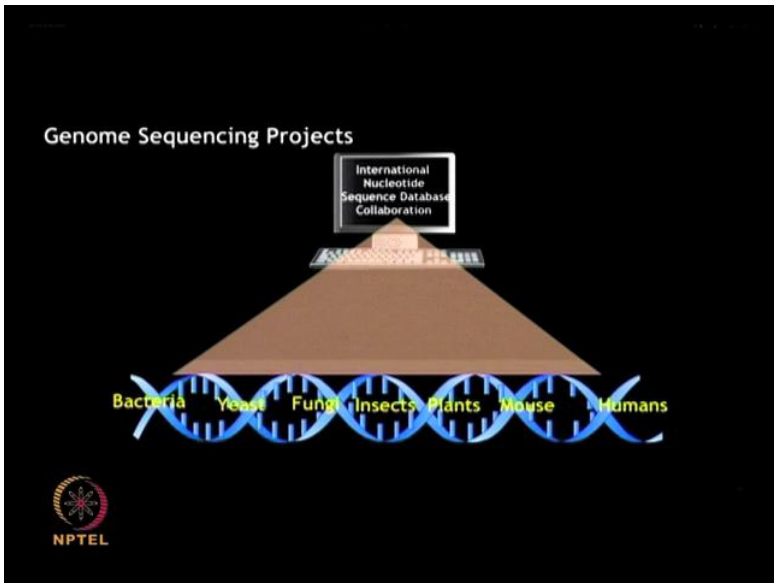

Several genome sequencing projects that aim to elucidate the complete genome sequence of organism have been undertaken by several research groups all over the world. The DNA sequences are identified by the short gun sequencing technique, and then aligned using

suitable software to provide the complete genome sequence; the genome sequence of a large number of prokaryotic.

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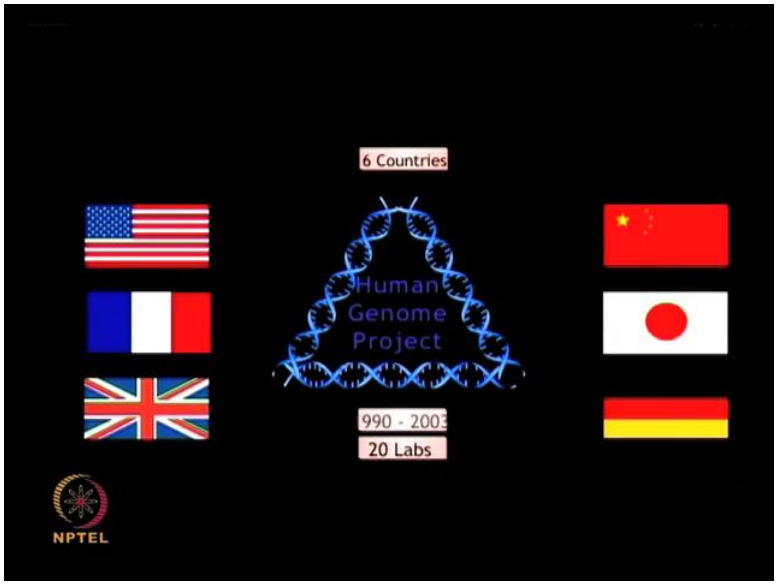

And eukaryotic organisms have been successfully deduced; the immense amount of information held by the human genome motivated researchers to understand the nature and content of genetic material in great detail. A collaborative effort between such countries and 20 laboratories was undertaken in 1990 to produce a draft of human genome sequence were procedure rapidly that the draft covering most of the genome being completed by 2000.

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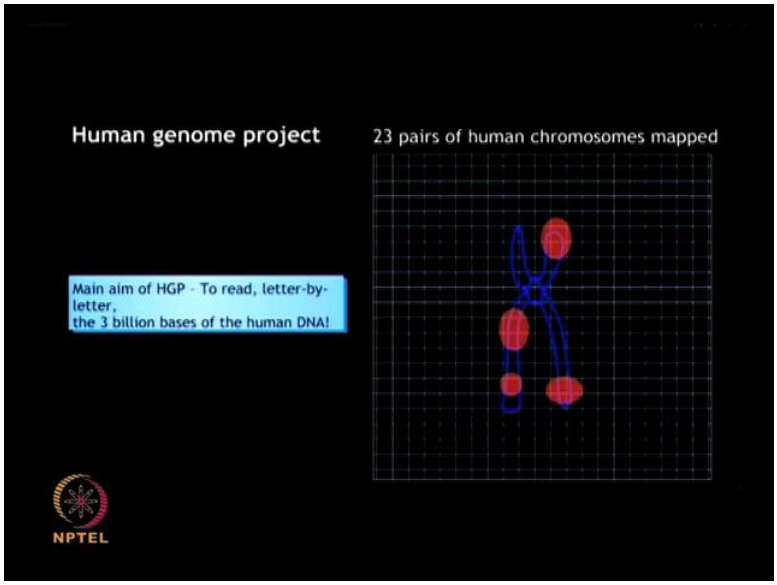

And a greater coverage being achieved by 2003.Before sequencing the entire genome, physical maps of the chromosomes were made. This helped to provide key tool for identification of disease genes.

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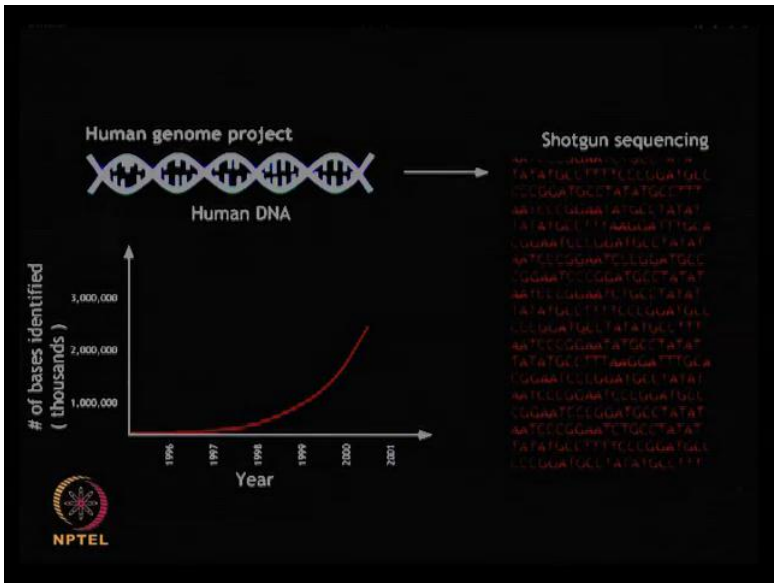

And encoding points in genome sequence. Private projects were then launched to create a draft of the genome sequence. The short gun approach was fundamental technique which was used for large scale sequencing of human genome, which also make use of Sanger sequencing. The collaborative effort to sequence the entire genome was challenged in 1998 by a privately funded organisation which aimed to finish the sequencing before the publicly funded group. Progress made in sequencing was very rapid and by 2001, a draft of this sequence was ready covering around 83percent of the genome.

After successfully sequencing the human genome, the technology of sequencing got advanced and now, there are next generation sequencing methods are available. See, human genome sequence project was completed in almost 12 years at a cost of around 3 billion US dollars. Very recently, the next generation sequencing strategies have dramatically increased the pace of sequencing by several order of magnitudes, and also reduced the per based cost of raw sequence significantly. The individual genome sequencing, metagenomic studies and SNP's and mutant analysis is also possible due to the next generation sequencing methods.

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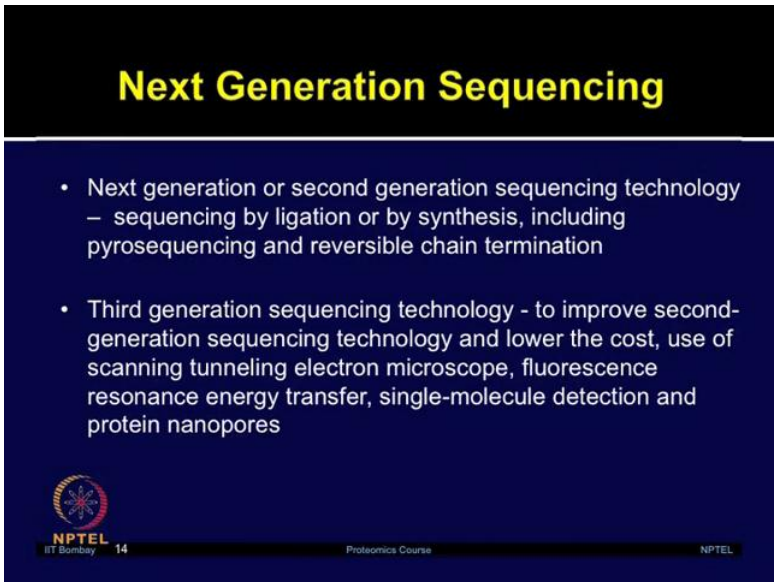

So, traditional sequencing which we discussed earlier including the Sanger's method of chain termination method; as well as chemical method Maxxam and Gilbert in 1976,those can be termed as the first generation sequencing methods. The next generation or second generation sequencing technology it includes sequencing by ligation or by synthesis including the pyro sequencing and reversible chain termination. Even more advanced form, the third generation sequencing technology is also in progress, which is aiming to further improve the second generation sequencing technology, and lowering the cost per base by using stand tunnel electron microscope, fluorescence resonance energy transfer, single molecule detection and protein nanopores.

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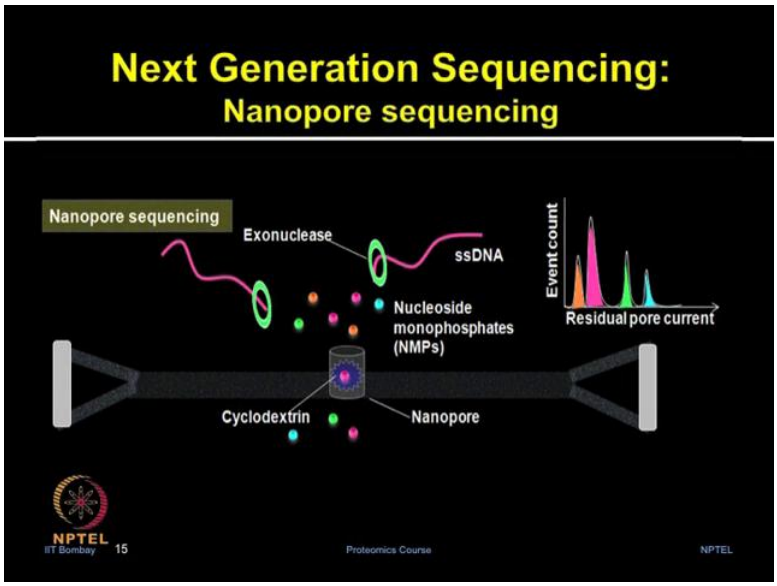

The next generation sequencing based on nanopore structures is known as nanopore sequencing which is shown in the slide. This is a single molecule DNA sequencing technology that does not require any fluorescent labelling, and makes use of any changes in electrical current produced by single nucleotides passed through the nanopores. The individual base detection is achieved through the measurement of conductivity either across or through a membrane via a nanoscale pore.

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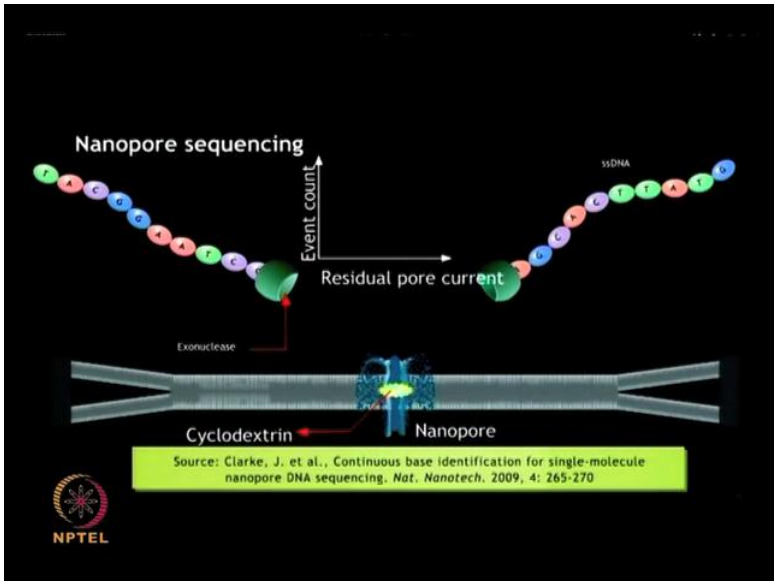

This innovative method offers a level free approach for DNA sequencing. An exo nucleus cleaves the single stranded DNA one base at a time to elise

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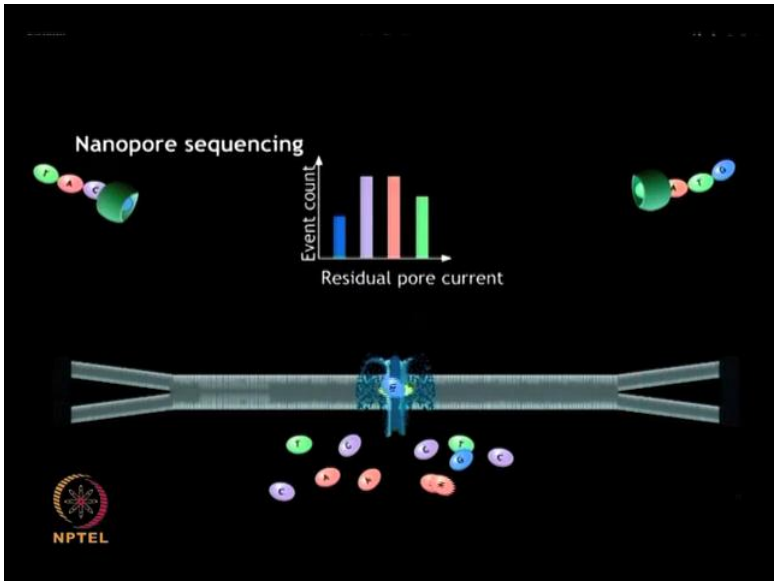

a nucleoside monophosphate. These MNP pass through the nanopore under an applied potential which is covalently coupled to an adapter molecule. The continuous movement of MNP's through the nanopore results in characteristic fluctuation of electric current which enables detection of various nucleotide bases.

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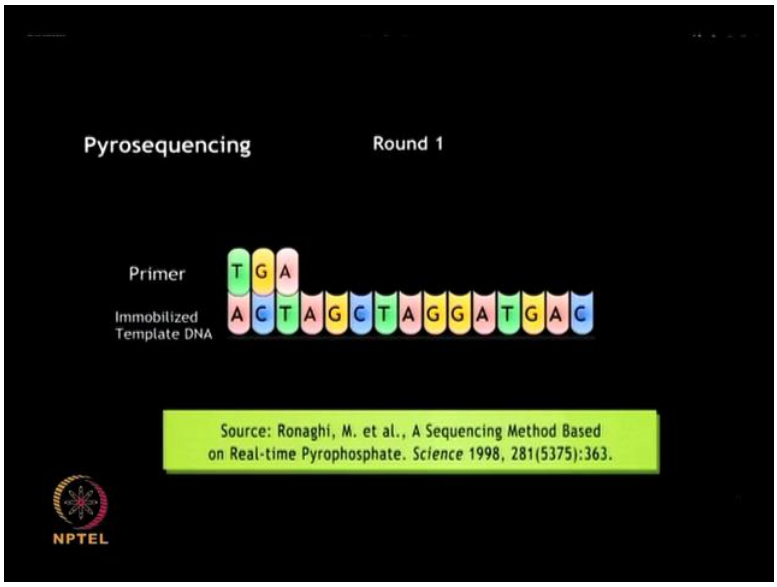

Multiple round of nucleotide addition are carried out on the immobilised template DNA by using DNA polymerase in the presence of ATP, sulfurylase ,luciferase.

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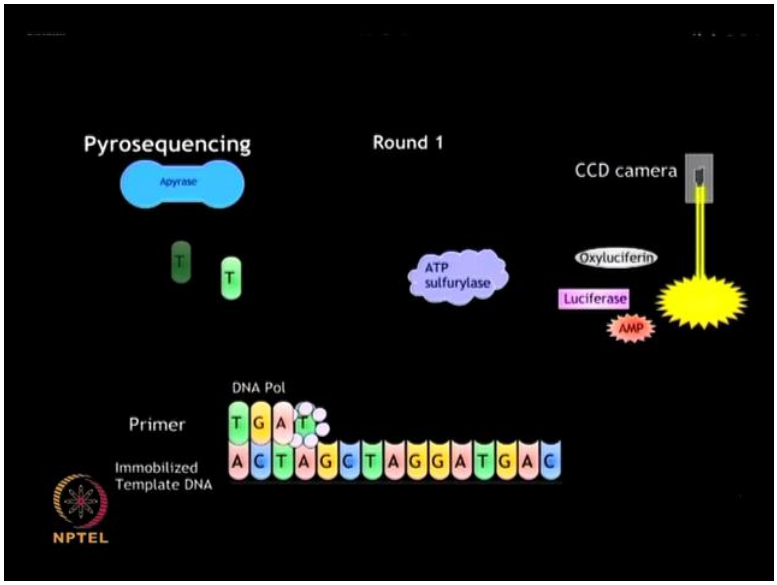

And the nucleotide degrading enzyme imperils. The release of an equal amount of pyrophosphate is determined by its convergent to ATP by ATP sulfurylase, which in turn is determined by the release of light on reaction with luciferase.

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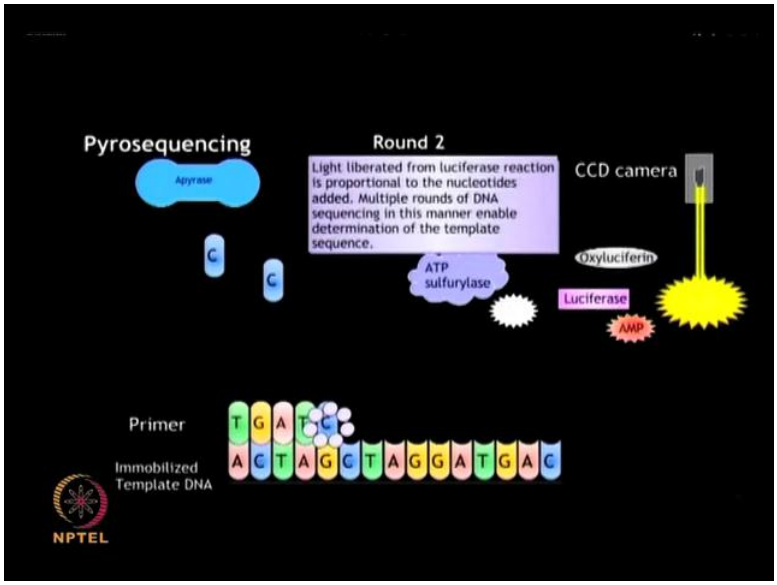

The amount of light produced is determined by means of a CCD camera, which is used to determine the nucleotide added and therefore, the sequence of the template DNA.The

various next generation sequencing commercial platforms currently available; we will briefly talk about the pros and cons of each of these methods.

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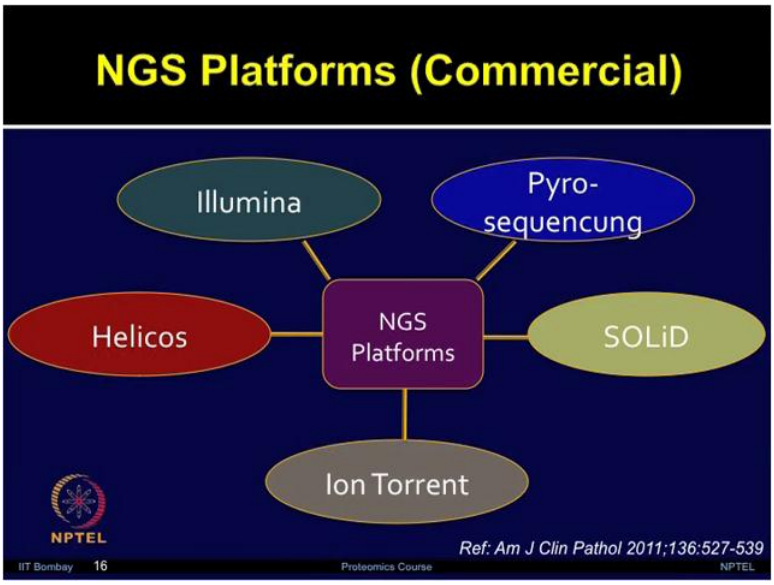

The alumina method which is a flowcell based method is implied reversible dye termination, and uses four colour optical imaging. It is used for whole genome sequencing and will widely used, but one of the limitation is low multiplexing capability. The pyro sequencing or 454 pyro sequencing is based on bead based method with emulsion PCR and CCD light imaging; it is used for targeted (( )). However, the contamination risk due to the emulsion PCR is one of the limitations.

Helicos; here oligoDT captured polyated DNA fragments and optical imaging is used. The method is used for whole genome and single molecule sequencing. High NTP incorporation error is one of the limitation supported oligo nucleotide ligation and detection known as solid is based on sequential dinucleotide ligation and optical imaging; it is used for whole genome sequencing and SNP detection limitation is longer in time.

Last method is ion torrent method, which is a standard DNA polymerase chemistry based method where semiconductor based non optical detection method is used. It is used for targeted sequencing. These are only few representative platforms which are described here, but there are many exciting commercial platforms are also available currently for next generation sequencing.

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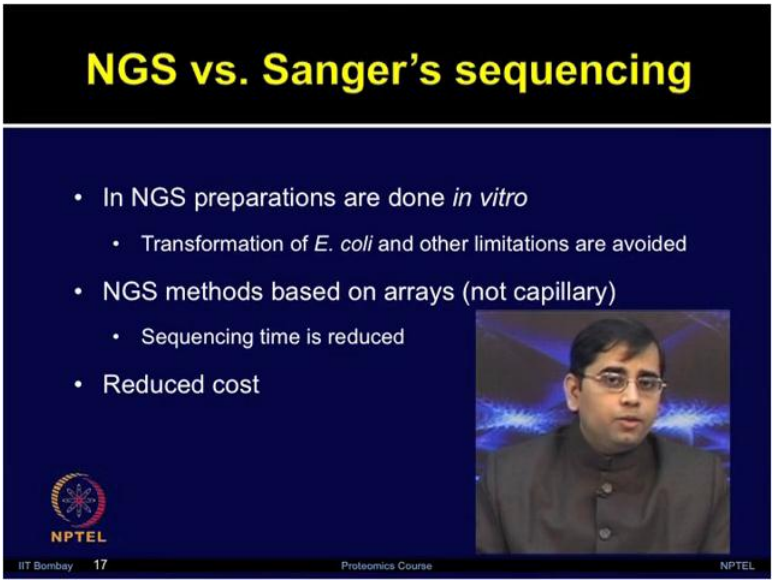

So, let us discuss the advantage and disadvantage of next generation sequencing versus the traditional Sanger's based sequencing. In next generation sequencing, the preparations are done in vitro whereas, in Sanger's method as we discussed the transformation of E coli is done. So these type of limitations can be avoided by using NGS method. NGS method is based on arrays not the capillary gel based method, which is employed in Sanger's method so sequencing time is reduced in NGS method. The cost is reduced in NGS method because, all polonies can be treated with single reaction volume which reduces the overall cost. The next generation sequencing methods can detect deletion, translocation, copy number alterations, etcetera with very high frequency. However, very sophisticated bioinformatic tools are required for data analysis of next generation sequencing, and data interpretation is a still remain challenging. Some of these are a still limitation of next generation sequencing platforms.

Now, let us talk about another interesting technology commonly employed in genomics as well as in transcriptomics, the DNA microarrays. The DNA microarrays can be prepared from any DNA sequence by chemical synthesis or polymerase chain reaction. The DNA is printed on the glass slide or other substrates; DNA can be cross linked by UV light or employing other immobilisation chemistries. Once ready, these microarray slides can be used for various applications.

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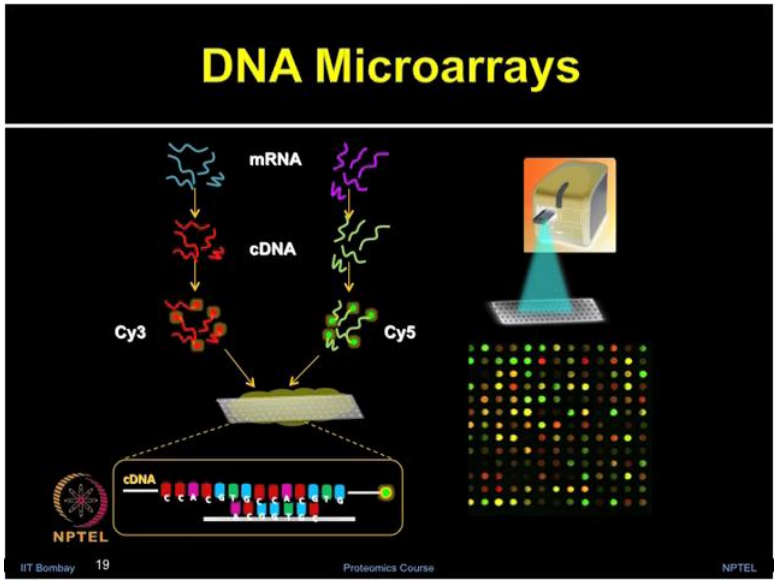

So, let us talk about a typical microarray experiment, where aim is to compare an healthy sample with the a disease treated sample. So from both the populations, the mRNA has to be extracted then mRNA should be converted to cDNA by enzyme reverse transcriptase, as you can see the second step here in the slide. During this step label samples using the fluorescently labelled deoxyribonucleotide triphosphate on a microarray side incubate labelled DNA which have complimentary sequences on the microarray. Perform washing steps and remove the unhybridized probe and then, scan the gel to look for the changes in the gene expression. In this manner, expression level of thousands of gene can be measured and analysed by using DNA microarray platform simultaneously. After discussing some of the technologies used in genomics, let us now move on to transcriptomics. So MRA translation is a very intricate process which takes place on ribosome's, a study of all them RNA molecules expressed by a particular cell type of an individual is known as transcriptomics. The transcriptomic analysis measures the genes that are been actively expressed or modulated at any given time, and varies significantly with external environmental conditions, development conditions or different type of environmental tools.

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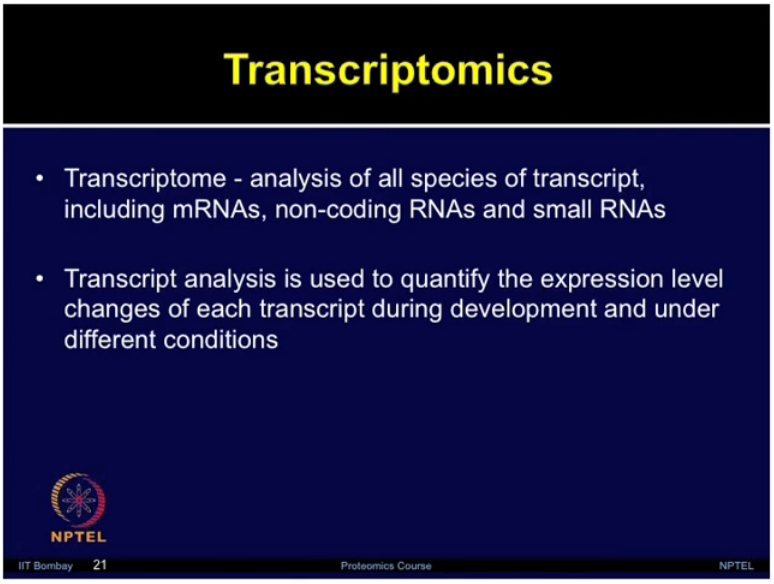

Lets look at some of the definition; a transcriptome is analysis of all species of transcript including mRNA's,non coding RNA'sand a small RNA's. The transcript analysis is used to quantify the expression level changes of each transcript during development and under different conditions. The transcript analysis is also very important for understanding the functional elements of genome and also the molecular constituency of cell and tissue.

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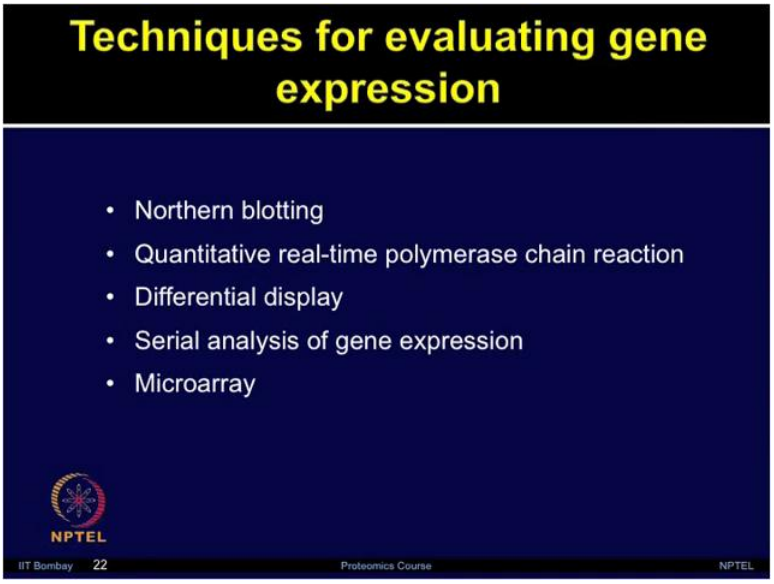

The various techniques which have been used for evaluating gene expression changes such as, northern blotting, the more traditional method and some of the newer methods

involved quantitative real time polymerase chain reaction q r t PCR or q PCR, differential display method, serial analysis of gene expression or sage and microarrays. Let us talk some of these techniques in some more detail. Reverse transcription PCR; RTPCR is a variation of regular polymerase chain reaction of PCR that is used to generate multiple copies of DNA starting from a molecule of RNA.

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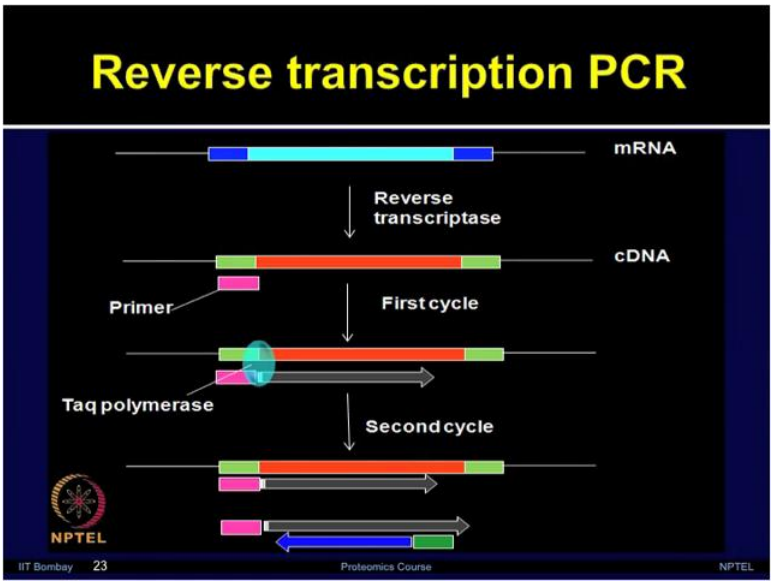

As you can see in the slide, the technique first requires the template RNS strand to be reverse transcribed into corresponding complimentary cDNA which will then amplify by using traditional PCR and multiple copies can be generated. Reverse transcription PCR is used to generate multiple copies of DNA with RNA as the starting material.

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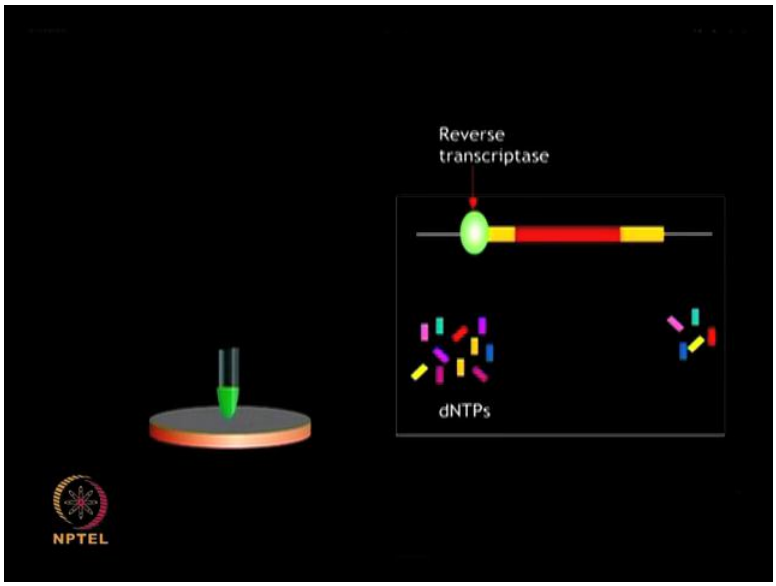

The template RNA molecule is first reverse transcribed into the corresponding cDNA by means of enzyme reverse transcripting; that enzyme which is commonly found in viruses is capable of synthesizing DNA from an RNA template.

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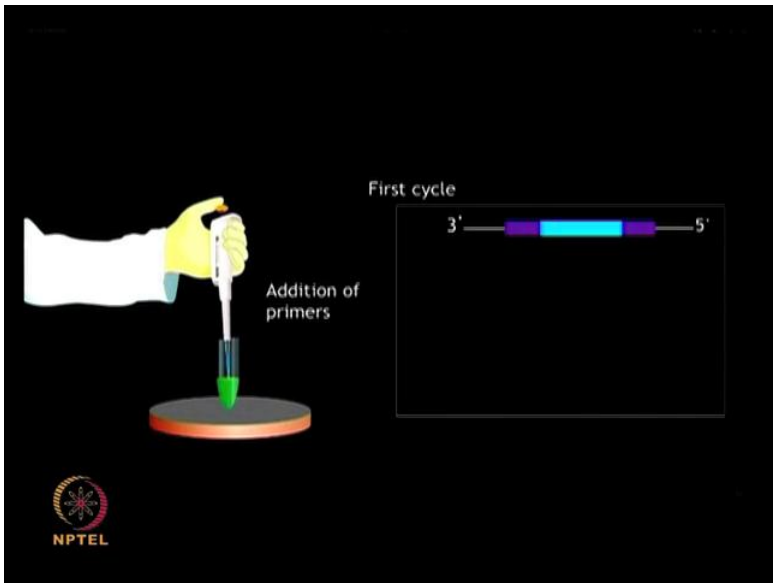

Traditional PCR is the performed on cDNA obtained by addition of primers which are allowed to anneal at 54 degree centigrade. This is followed by addition of nucleotides.

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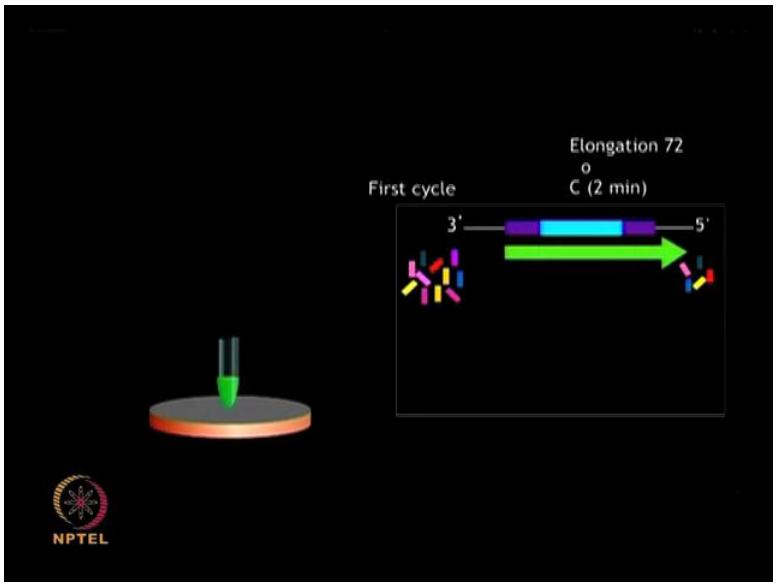

And taq polymerase, which performs elongation of template strand at 72 degree centigrade.

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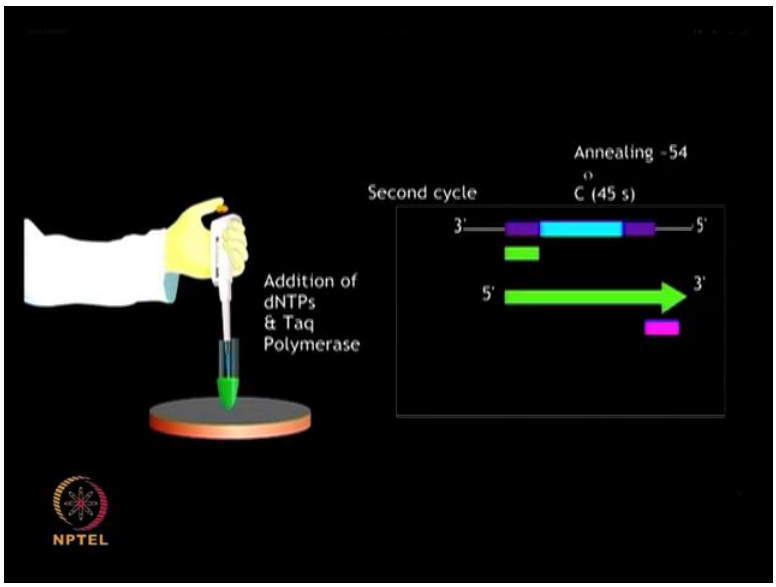

Second and subsequent rounds of PCR result in further amplification of the cDNA of interest. A strand separation is performed at 95 degree centigrade followed by primer annealing and elongation respectively.

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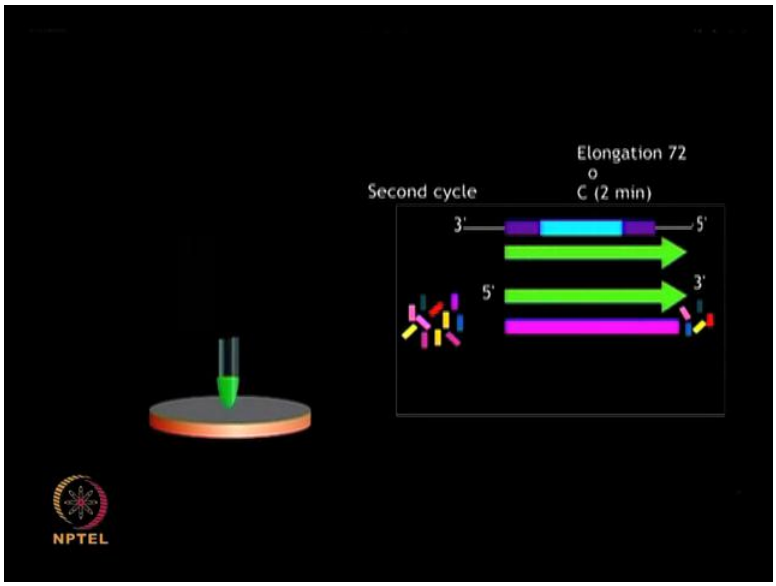

In this way, the mRNA transcript originally used is amplified in form of that corresponding cDNA which can be studied further. A highly sensitive method which is employed to quantify the amount of RNA is known as real time polymerase chain reaction or quantitative PCR.

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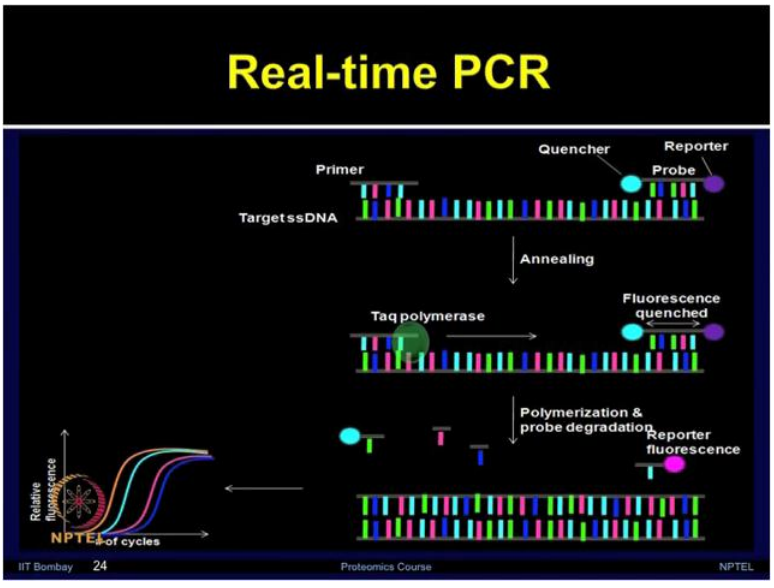

This method requires very little around 5 to 10 nanogram of RNA for detection of transcript changes. It quantifies a target DNA molecule as and when it is amplified by means of a suitable reporter dye that emits florescence every time a PCR cycle is formed.

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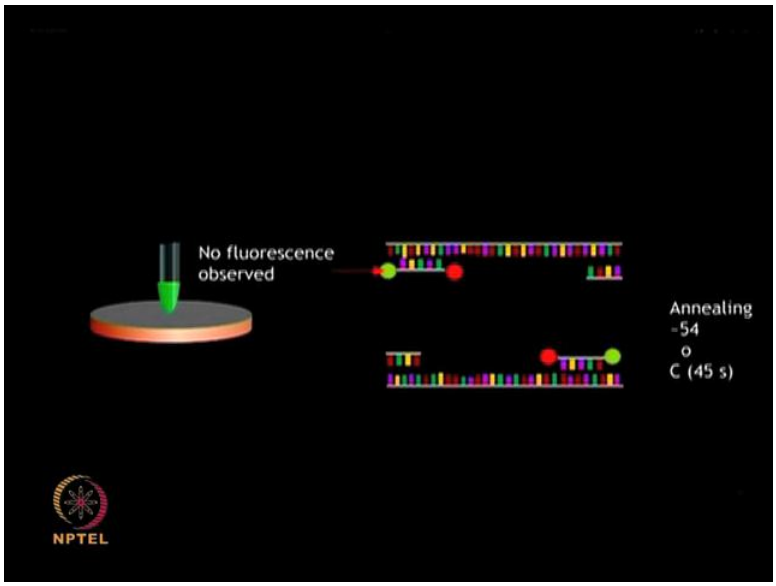

The double standard DNA that needs to be amplified is heated to 95 degree to bring about a strand separation. Once the strand are separated, primers are added along with the probe DNA molecule which have the quencher, and the reporter molecule bound towards end; while these have annealed to the template DNA strands at 54 degree centigrade, taq polymerase and nucleotides are added and temperature is again increased to 72 degrees to carry out a strand elongation.

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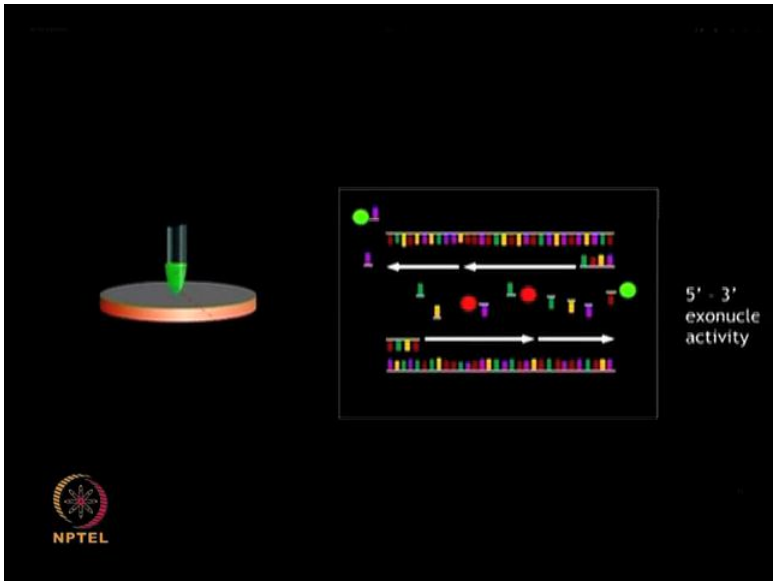

The taq polymerase continues to elongate the DNA strand based on corresponding template DNA; when it reaches the bound probe molecule, the 5 prime to 3 prime exonuc lease activity of taq polymerase degrades the probe into its nucleotide fragments and continues to elongate the DNA strand. The released reported dye thus getsseparated from the crenture molecule.

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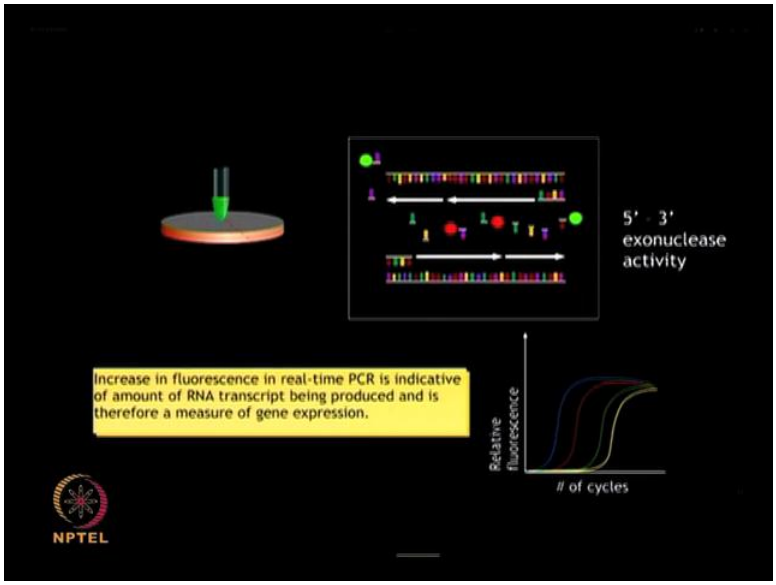

During this process and florescence emitted can be detected by using suitable detective. The increase in florescence in real time PCR is directly indicative of the amount of nucleotide being synthesized and therefore, a useful tool to measure the gene expression. As we have talked earlier, microarrays are a very strong platform for measurement of gene expression changes.

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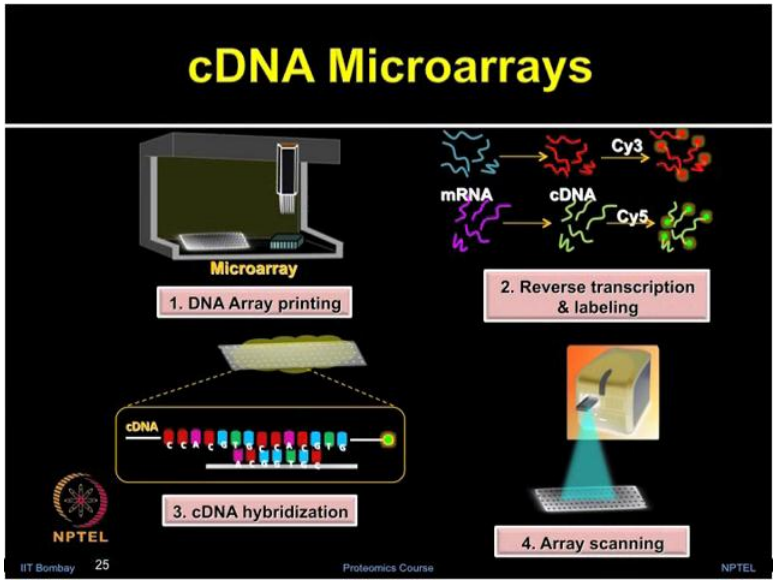

A cDNA arrays measure many thousands of gene specific mRNA in single tissue sample simultaneously. As discussed earlier, the microarray can be used for various application including mRNA stability, identification of short poly a phenotype and studying mRNA association with membranes or cellular organics. The methodology is similar to what we discussed earlier; the larger scale gene expression analysis has also proved to be useful as a validation strategy to validate the proteomic data, and look at the changes at both protein level and correlate with the transcript level.

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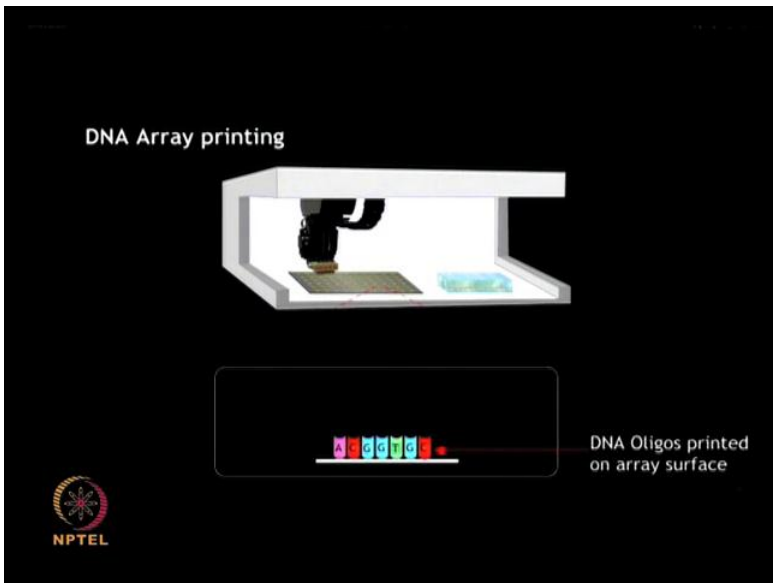

ADNA microarray is printed with oligonucleotide sequences that will serve as probe molecules by providing complimentary strand for binding cDNA of interest. Thousands of such a spot is containing as little as pico more quantity of DNA can be printed on a single slide. Commonly used binding chemistries for printing include covalent attachment via epoxysilane, aminosilane, polyacrylamide etcetera.

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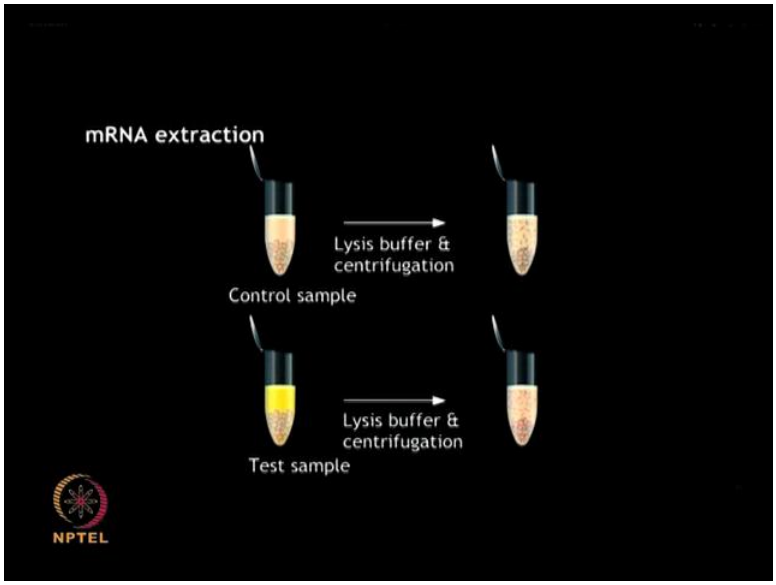

The mRNA present in the control and test sample is distracted by addition of lysis buffer which breaks open the cell.

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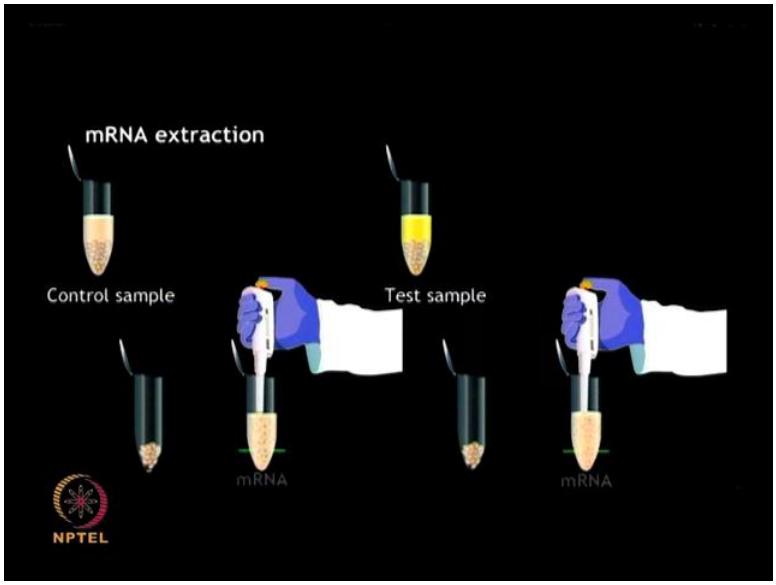

Centrifugation helps in piloting down the cell debris after which, the mRNApresent in the supernatant can be transferred into a fresh tube for further analysis.

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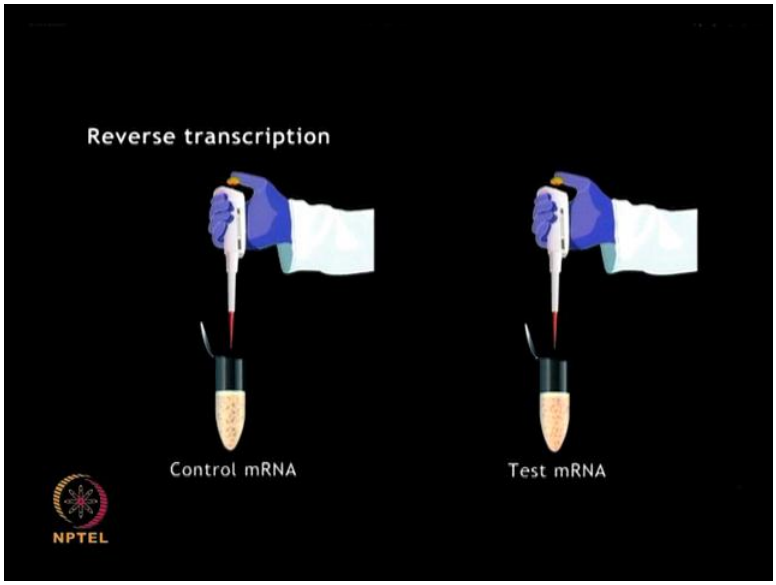

Distractedm RNA is then reverse transcribed into its corresponding cDNA by means of enzyme reverse transcript.

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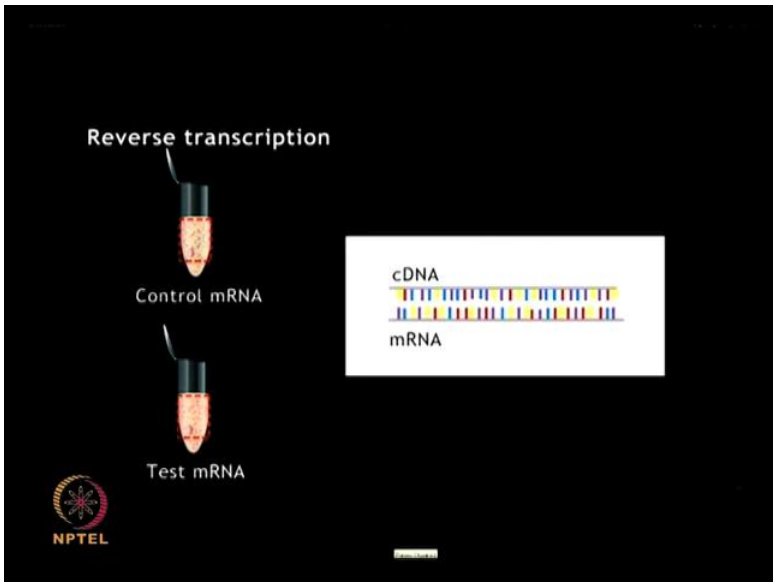

This enzyme which is also known as RNAdependent.DNApolymerase is capable of synthesizing DNAfrom a corresponding RNAtemplate.

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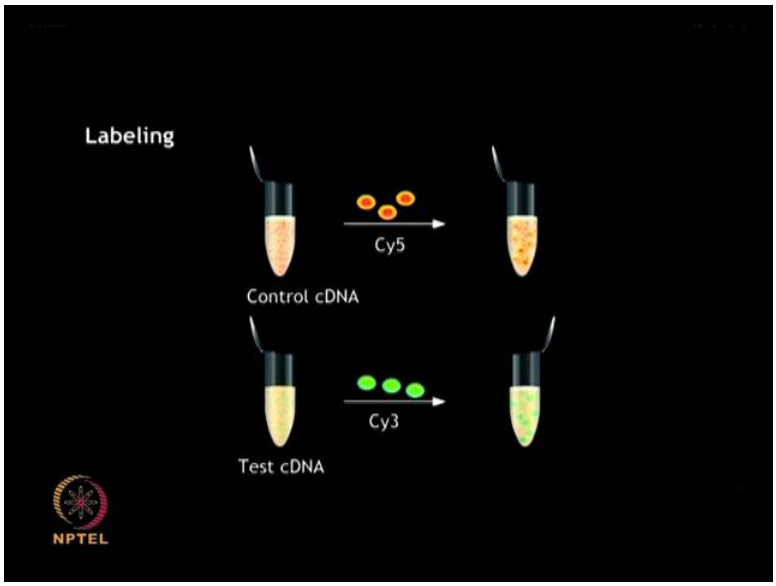

The control and test cDNAsamples obtained are then labelled with Cy5 and Cy3 dice respectively.

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Since the two dice can be excited at different wavelengths, the differentially labelled samples are then mixed together for further analysis.

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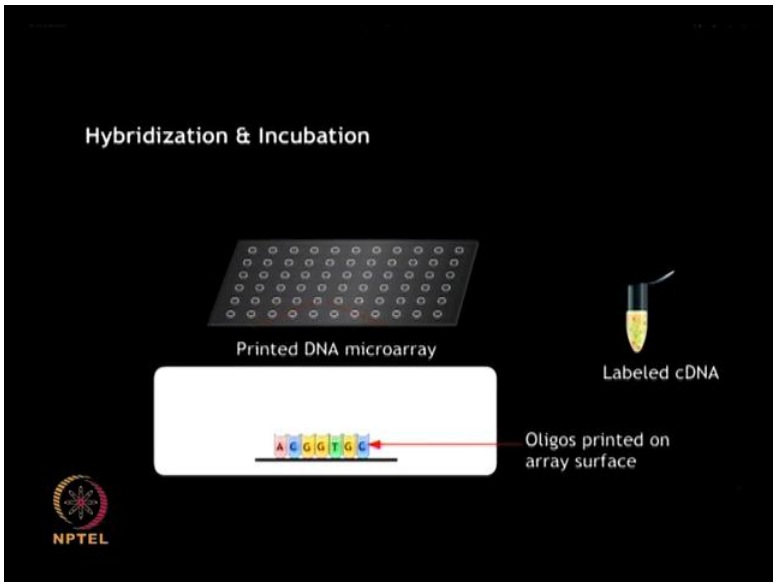

The mixed cDNA sample that is differentially labelled by means of two signing dice is then incubated with printed DNA microarray slide. It allows hybridization to occur between the probeoligonucleotide on the array surface, and a labelled cDNA samples of interest.

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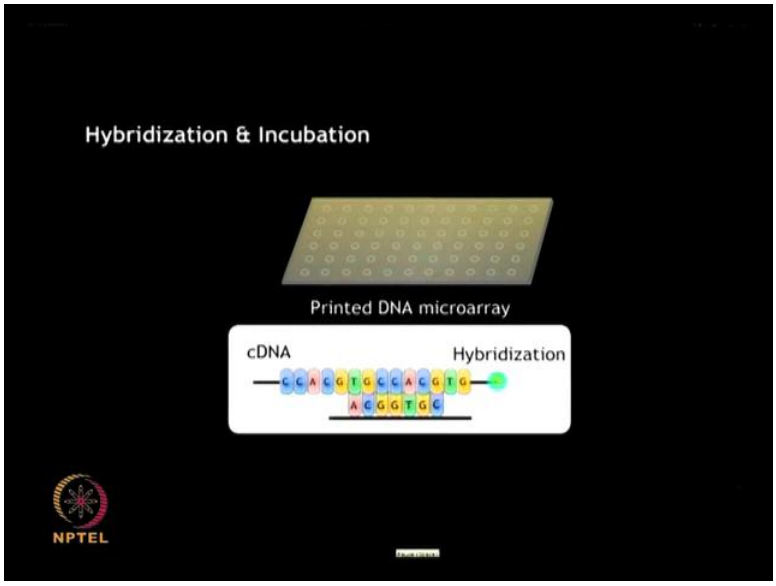

The microarrays is washed to remove any unbound cDNA molecule and then expanded suitable wavelength by means of a microarray scanner .A new advancement in transcriptomics technology is RNA sequencing. RNAseq has been used for transcription

analysis by sequencing cDNA through next generation sequencing. This methodology was initial utilized for identification of transcriptional map of list.

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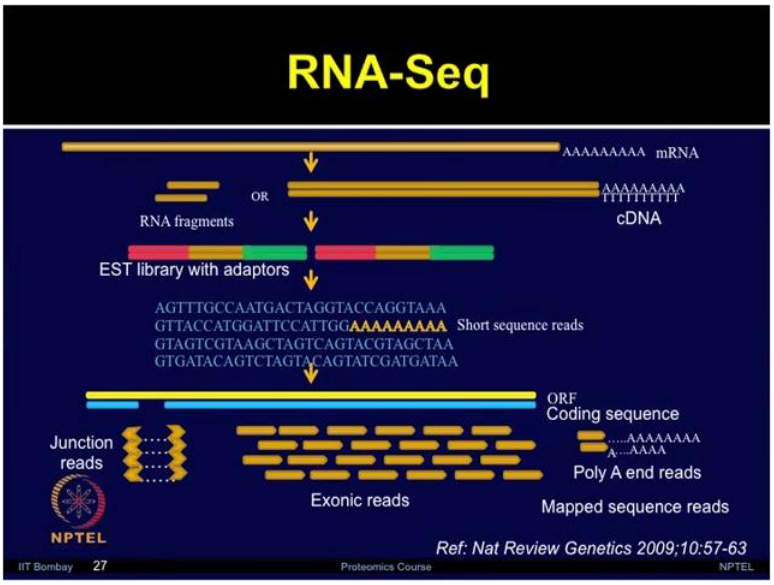

In RNA sequencing, the long RNA are converted into library of cDNA fragments as you can see here, through RNA or DNA fragmentation and to each DNA fragment or cDNA fragment, sequencing adapters are added.

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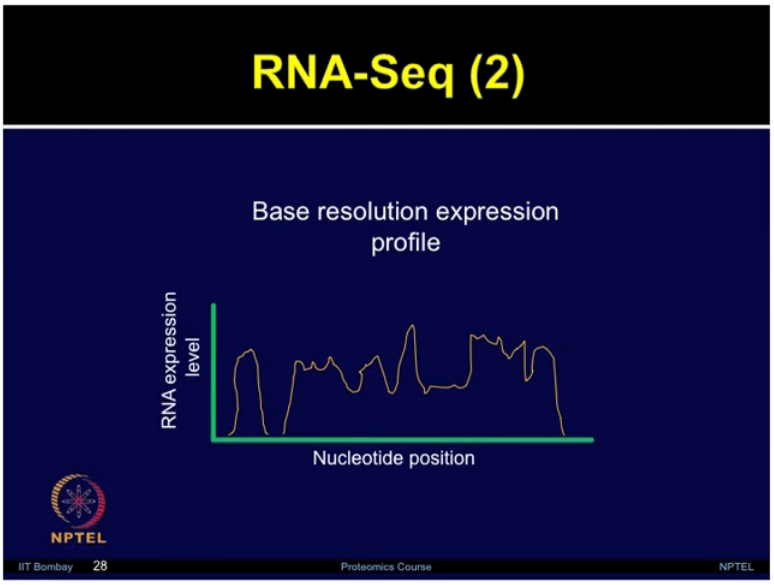

From each cDNA the short sequence is obtained and resulting sequence reads such as exonic, junction and polyandry are aligned with referral genome sequence. So, the

sequence reads exonic rate, junction rate and polyandry rates can be used to generate base resolution expression profile as you can see here, plotted with nucleotide position on x axis and RNA expression level on y axis. The RNA sequence has dynamic range greater than 8004 to quantify gene expression changes. Therefore, the RNA sequencing method is very useful for discovering new transcript, identifying notations, deletions and insertions as well as displacing alternative.

After studying genomics and transcriptomics, let us now move on to, why do we need to study proteomics? So after completion of human genome sequence, we are interfied around 30000 genes which were much less than expected number of 1100 genes. The lower number of genes were surpassed by the estimated number of proteins which is in millions. Therefore, studying large scale study of protein a structural function requires a thorough understanding of protein composition as well as, information at various structural level by employing different type of proteomic tool.

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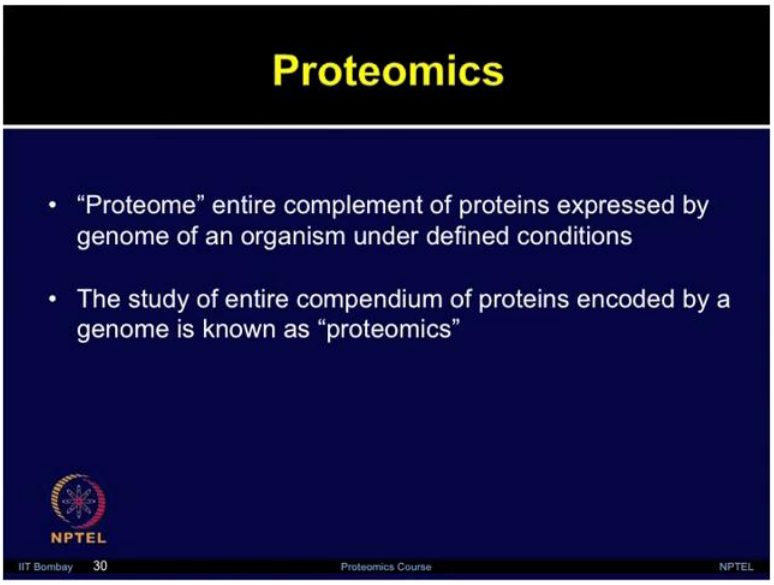

So, let us look at some of the definitions. So proteome is entire complement of proteins expressed by genomes of an organism under defined condition, and a study of entire compendium of proteins encoded by a genome is known as proteomics. So let discuss, why do we need to study proteomics and how it compares with genomics? So there are various reasons.

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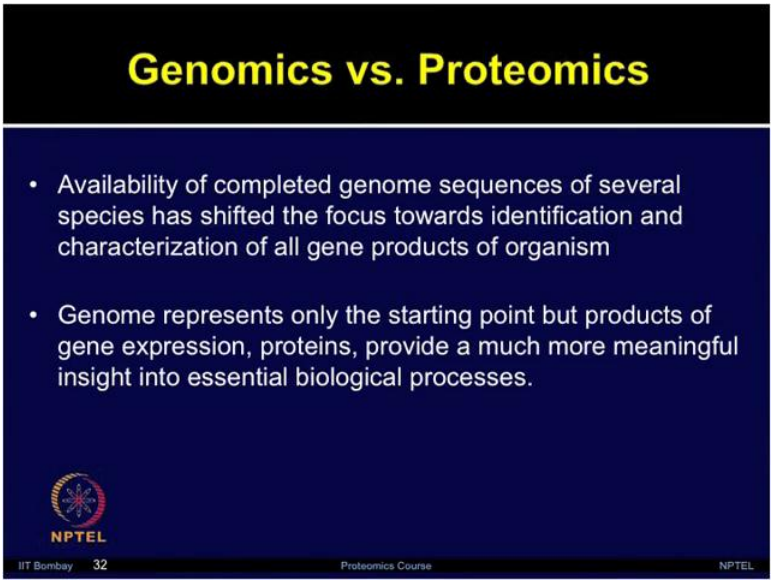

If you compare genomics versus proteomics to look at the advantages and disadvantages of each method, the genome represents only the starting points towards understanding the complexity of biological functions. The proteins provide a much more meaningful insight into the complex biological system and mysteries associated with it to understand the biological processes.

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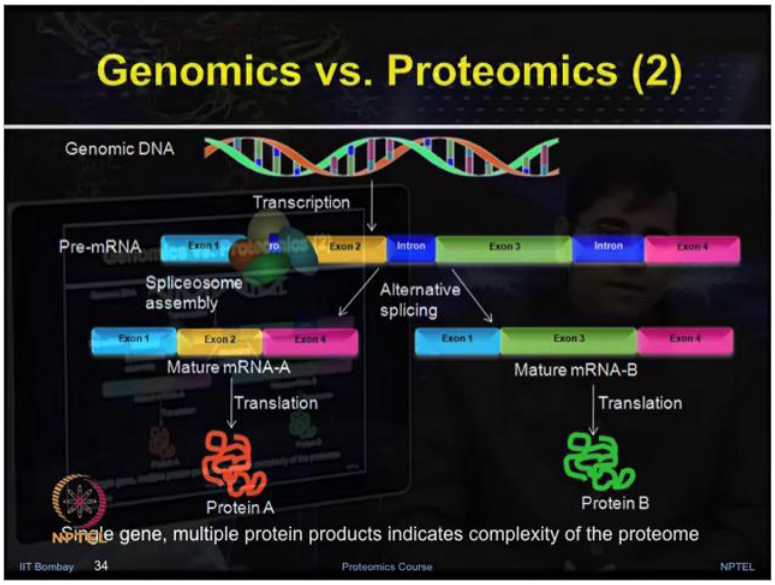

So unlike the genomic DNA, proteins do not contain intervening sequences in a trans and directly indicative of cellular functions alternative slicing. It is a process by which axons

or cording sequence of pre mRNA produced by a transcription of a gene are combined in different methods during RNA slicing. The resulting mature mRNA gives rise to different protein products as you can see in the slide. By the process of translation, most of these are isoforms of one another.

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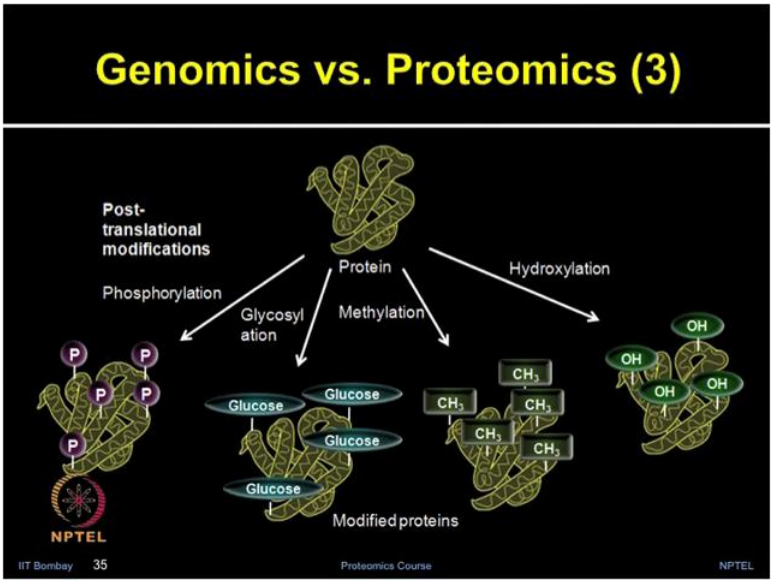

So in this way, a single gene can give rise to multiple protein forms. Another level of information which is only obtained at the proteomic level is post translational modification. Many proteins undergo p t m's at some of their amino acid residues after the synthesis process. These modification include hydroxylation, methylation, alkylation, phosphorylation, glycosylation, etcetera which are some of the most commonly modified p t m's observed. But, there are many other forms of post translation modification which also occurred in proteins. Very briefly, let us touch upon some of the techniques which are employed in proteomics.

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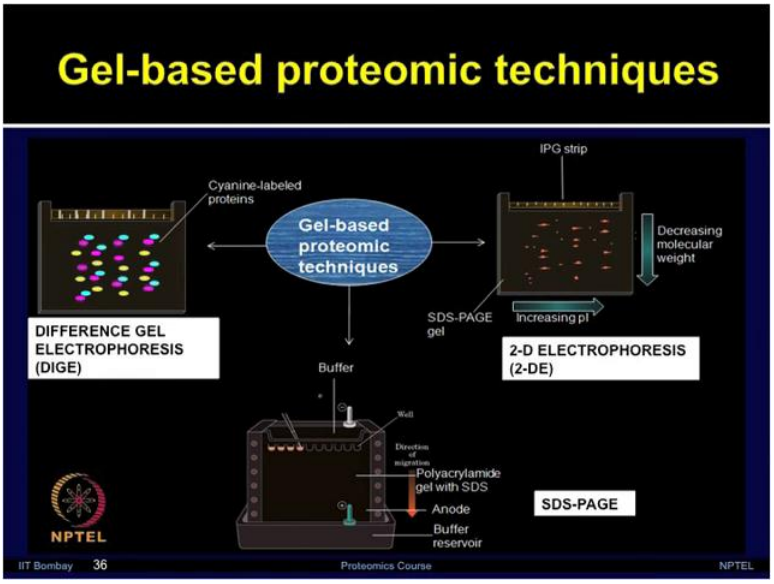

So, different type of proteomic technology which imply gels can be grouped under the gel based proteomics. The protein within a cell are commonly analysed using SDS page and two dimensional gel electrophoresis. Separation in SDS page occurs almost excessively on the bases of molecular weight. Since all the proteins have similar charge to mass ratio and shape after they have bound the SDS. In 2-DE,the complex mixtures can be resolved first by isoelectric focusing followed by the based on size in polyacrylamide gel; some of the limitation of two dimensional electrophoresis were overcome by using two dimensional different gel electrophoresis or dige method.

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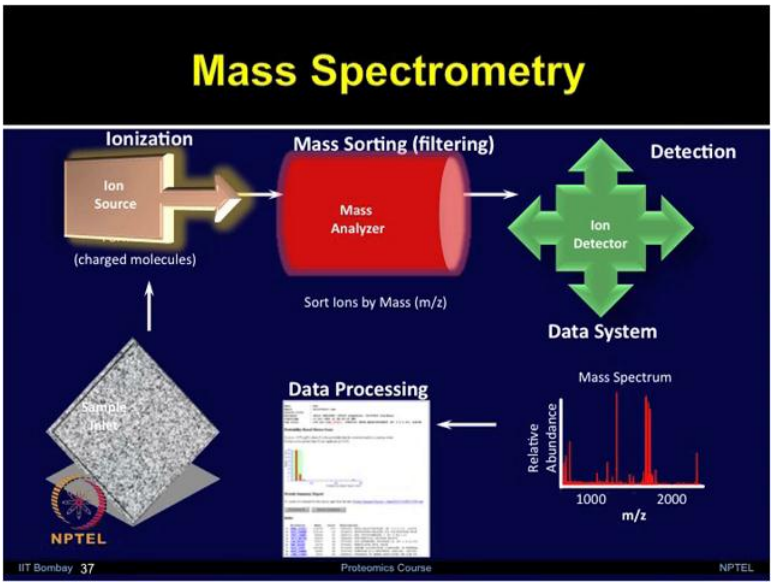

The 2-DE or dige in combination with mass spectrometry has been the standard technique for proteomic analysis. Mass spectrometry, it is another technique for protein identification and analysis by production of charged molecular species in vacuum, and its separation by magnetic and electric field based on m by z ratio. The different components of mass spectrometry, ionization source; it is one of the major components of any mass spec instrument which fragments the sample into ionic forms for further detection. Maldi and electrspray ionization ESI are commonly used for protein sample analysis. Mass analyser, another important component resolvesions which are produced by the ionization source on the basis of m by z ratio.

The various characteristics such as resolving power, accuracy, mass range and speed which determine the efficiency of these mass analysers; the commonly used mass analysers include quadrupole, time of flight, ion trap or b trap etcetera. The mass spectrometry has become the method of choice for analysis of complex protein samples in proteomic study due to its ability to identify as well as, quantify thousands of proteins. Protein microarrays, these are miniaturized arrays which are normally made on a glass slide as well as, other substrateon to which the small quantities of thousands of proteins are immobilized and analyzed.

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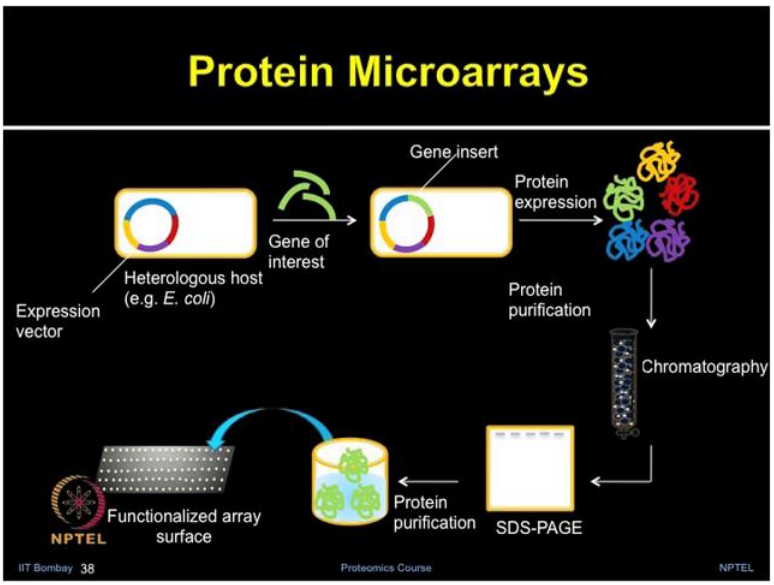

Protein microarrays can be generated either by traditional cell based method, where proteins can be purified and then immobilized or cell free methods, where proteins can

be produced by using invectro transcription and translation system. These protein arrays can be used for various application including protein protein protein DNA as well as, measurement of protein activity and other biological application.

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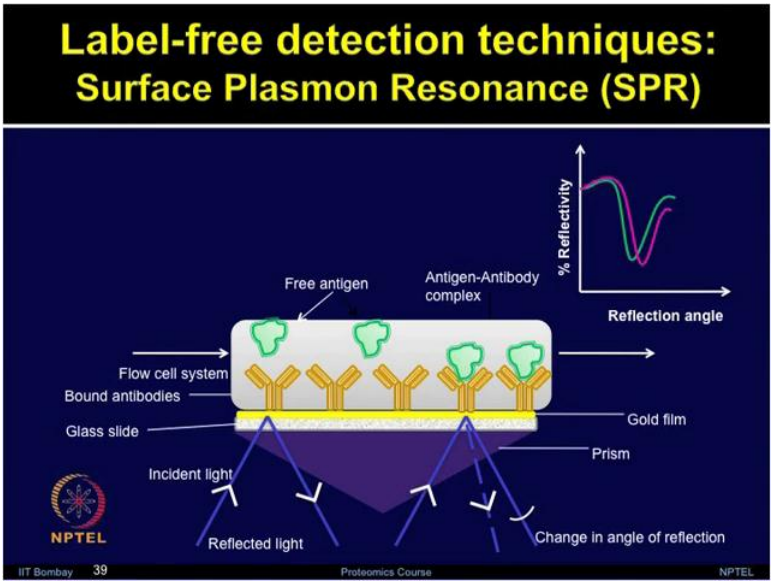

Now very briefly, let us look at the label free detection techniques includes surface plasm on resonance or SPR. The label free detection methods monitor inherent properties of the molecule itself, and overcome many limitation of traditional label based methodology. The various techniques such as SPR, SPR emerging, electrometry, interferometry, etcetera which are commonly used for label free detection system. Now shown here in the slide is, surface plasm on resonance method which detects any change in the refractive index of the medium of the material interface between the metal surface and ambient medium.

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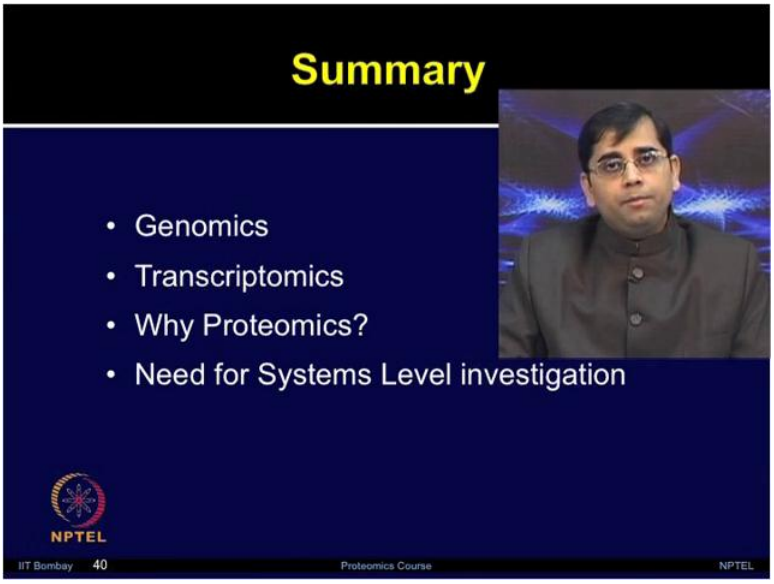

So in summary, today we talked about different techniques which are employed in genomics, transcriptomics and we looked at, why to study the proteomics? So as we know, the biological systems are very complex to understand the genomics, transcriptomics and proteomics can be used in various permutation and combination to address different biological questions, and obtain information at different levels. An ideal approach would involve the systems biology based investigation which we will discuss in the next class thank you.

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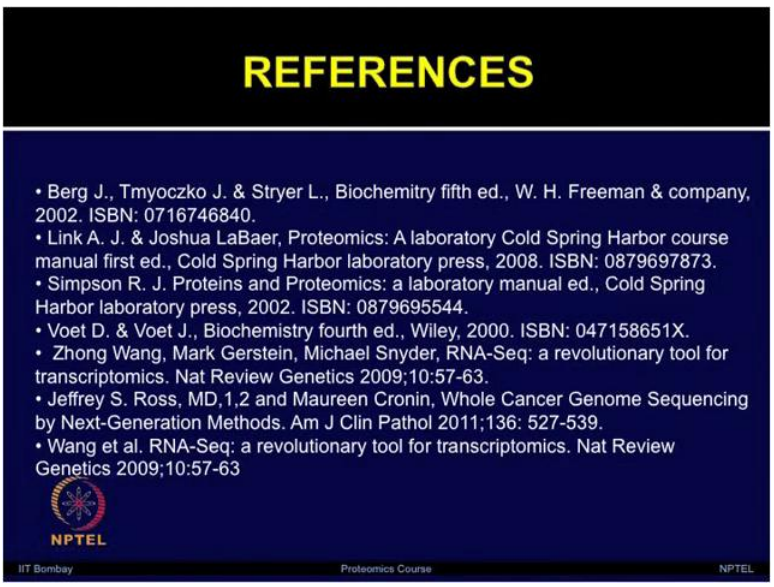

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