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An Insight Into Microarray Technology

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ABSTRACT

Genome project generate a large volume of sequence data. Due to that, research in genomics is increasingly focusing on deducing functional knowledge from recently identified genes. By supplying the knowledge needed for microarray manufacturing, "structural genomics" overlay the existing way to a novel field known as "functional genomics". In an identification of differential gene expression, microarray know-how is the product of miniaturization & automation. Using this technology, thousands of genes can be analyzed in tandem for RNA abundance and DNA homology in a sole trial. For past few duration, this distinctive technique is being used to study hundreds of transcriptional patterns & gene dissimilarity in a variety of microbial species. Environmental control, biotechnology , pharmacology, toxicology, and diagnostics are only a few of the fields where microarrays are included. We discuss the broad scope of DNA microarray technique, with a focus on DNA microarray manufacture and implementation in biological systems, with a particular focus on microbial systems.

Key words: *Gene expression,Profiling, Microarray*

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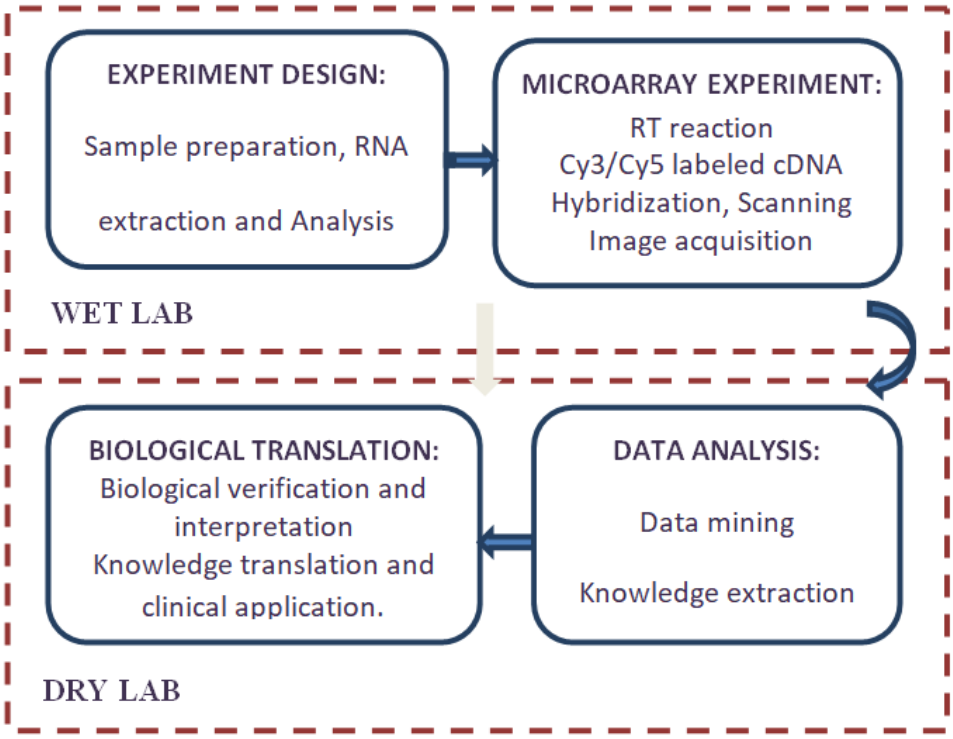
INTRODUCTION

In the late twentieth century, researchers could only look at one or a few genes at a time while investigating gene expression and regulation. Gene expression mapping, Protein expression, whole genome mutation analysis, SNP analysis ,CGH were all made possible by the multiple successful genome projects. This cutting-edge practical molecular biology technologies are incredible instruments for controlling multiple alterations in the genome, tracking all the gene events in a single experimentation, and comparing protein expression variations among various bio-samples at multiple stages: transcriptome, genome and proteome.[1] The microarray technique, which have turn into an important gizmo for a modern field researching the gene expression of in a genome at the same time, is one of the most effective and widely used high throughput technologies. This technology has been used in a variety of experiments, including transcriptome processing, characterization and recognition of genetic variants.[2]

Microarray is a high-density matrix assembly of biologically active molecules. A molecule with a high concentration is immobilized in one location of a microarray and may have a particular interaction with its target. Thousands or millions of individual spots may be immobilized on a single microarray, allowing for the study of an organism's whole genome, proteome, transcriptome at a certain point in time. The concept of DNA microarray is shown in Fig.1.[3]



[Fig:1 Concept of DNA Microarray technology]

DNA MICROARRAYS CONSTRUCTION:

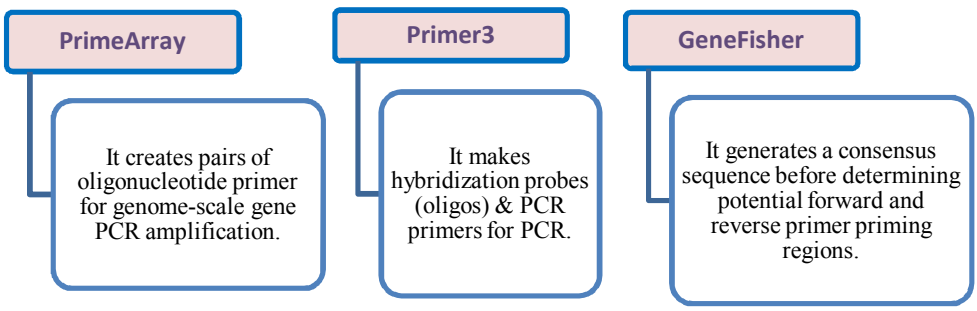
Obtaining DNA sequences, designing primers or oligonucleotides to generate probe DNA, choosing, preparing the appropriate glass base, and place the DNA probe onto the surface are all steps in construction of DNA microarrays. The formation of spotted oligoarrays requires multiple phases that are similar. Crucial variations shall be addressed in depth below.(Fig:4)

PREPARATION OF PROBE DNA:

The choice of probes, which is to be printed on an array is the first step in its production. These are characteristically chosen from GenBank, dbEST, and UniGene databases, which serve as the resource backbones for array technologies. Full-length cDNAs, partly sequenced ESTs/cDNAs, or arbitrarily chosen DNAs/cDNAs from some library of interest, found to be the global options. Probes for yeast and prokaryotes are produced using amplified genomic DNA through gene specific primers, while arrays of superior eukaryotes depends on ESTs.[4]

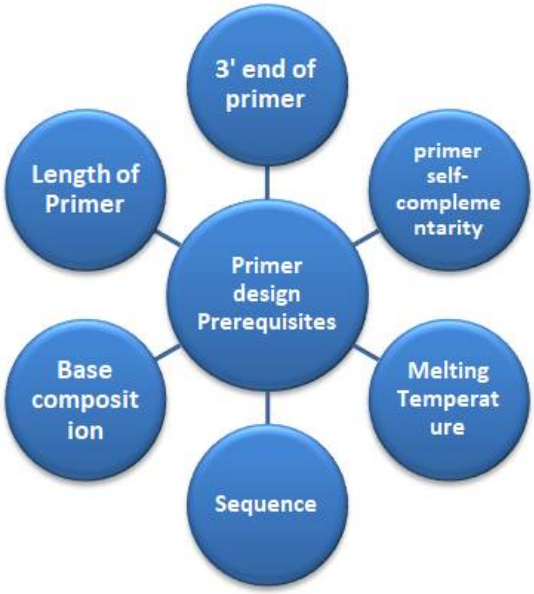
DESIGN A PRIMER:

The first step in the construction of a DNA microarray is to construct primers focusing interested region by amplification. Although majority of existing 'PCR product based arrays' include only ORFs, an optimal array will have both ORFs and intergenic areas. Whole genome primer architecture can be done using freely accessible computer program like PrimeArray, Primer3, GeneFisher, or Primer Premier.(Fig:2)[5]



[Fig: 2 Primer Design]

In the primer creation process, there are a few things to keep in mind.(Fg:3)



[Fig:3 Prerequisites for Primer design]

DESIGN OF OLIGONUCLEOTIDES:

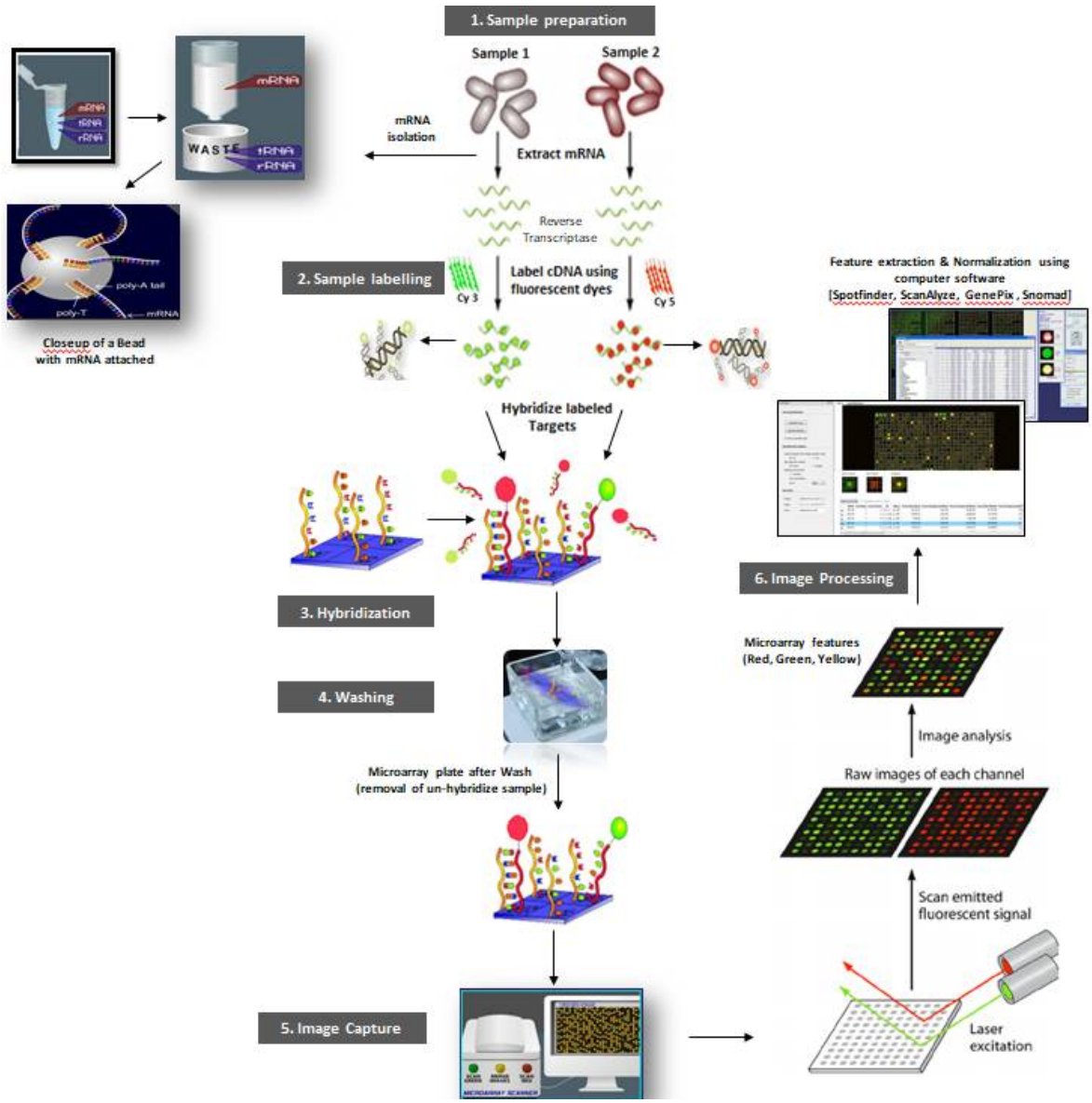
To make oligonucleotide microarrays, photolithography is used, one by 'spotting prefabricated oligos on a glass plate' or second by the use of sophisticate method 'direct in situ oligo synthesis on the glass side'. This method's strength is their ability to isolate molecules of DNA dependent on a gap of single base pair. To create a large number of distinctive oligos, photolithography manufacturing of oligonucleotide chips requires just 4n cycles (n = length of oligonucleotide in bases), the total amount of that is constrained only from the intricacy of photolithographic mask & the chip scale.

For Spotted oligoarrays, the oligonucleotide architecture takes the similar steps the same as primer architecture. 50 to70 bp oligonucleotides or small oligonucleotides in the 20 to 30 bprange, are recently in use for studying gene expression. The best choice for retaining high signal strength and specificity is to use 50-mer probes, but 70-mers helps differentiate between overlapping genes and limits cross hybridization. In general, as the genome becomes larger, the probe's size can increase. A perfect oligonucleotide must be able to tell the difference between its desired target and the rest of the array's targets.[6]

OligoArray, ProbeSelect, OligoWiz, NetPrimer, ROSO, and OligoPicker are some of the available software methods for designing oligonucleotides for spotted oligoarray.

PRINTING PROBE DNA:

In a serial operation, number of matrices are spotted by a robot for the sample of each gene product, which are then written. Touch printing with a mechanism similar to a fountain pen was used for the first spotting robots. There are now several variants on this pattern, including a 'spotter'. Basically, it's a capillary tube onto which constant low pressure is imparted. Non-contact printing types, such as piezo or inkjet printing, are also being investigated.[7]



[Fig:4 Methodology of Microarray]

TECHNOLOGIES FOR MAKING MICROARRAY:

There are currently two DNA microarray platforms / types available for commercial use.

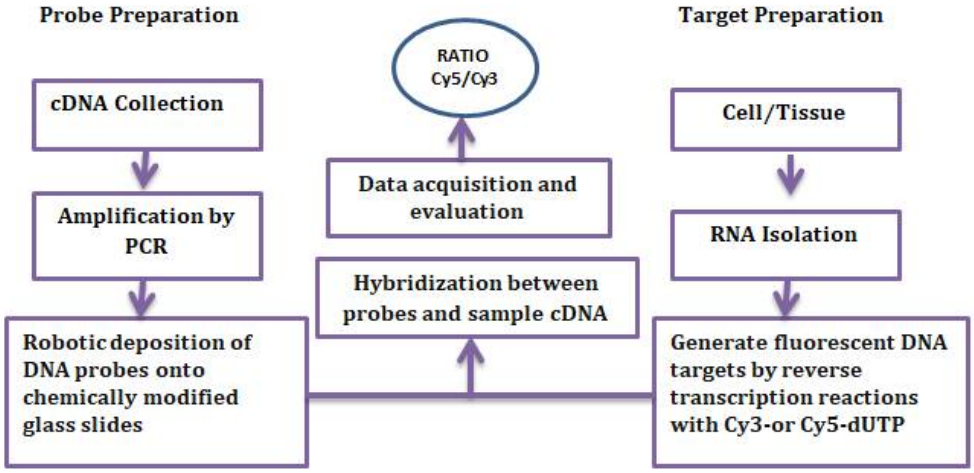
DNA MICROARRAYS MADE OF GLASS: Spotted microarrays or Robotic spotting are the micro spotting of prefabricated cDNA fragments on a glass slide. The most popular glass arrays are prepared on microscope slides that have been encrusted with poly-lysine, amino silans, or amino-reactive silans, that increase slide hydrophobicity & DNA adherence while also reducing spotted DNA droplet distribution.

Robots are used in this technique to position (or array) a large number of probes on slides. The robot is created to obtain samples, from 96 or 384 well microtitre surfaces using upto 12 pens at the same time. Wash stations, which are permanent basins comprising purified water, are used to replace any two microtitre panels. To optimize washing, the robot quake the assembly of pen, back & forth (about 5 Hz). The dryer consists of a Wet/dry vacuum cleaner with computer power and a pen tip connector with limiting inlet holes. The fast flow of air through the ends creates a partial vacuum, which is used to dry the product.[8]

In cDNA technique, cDNA arranged in the multi-well configuration & amplified by the polymerase chain reaction. The amplified clones are then spotted on firm support representing specific genes using high-speed robotics. Spotting on a glass substrate can yield microarrays of up to 10,000 clones. Microarrays include the use of fluorescent or radioactive nucleotide-labeled probes to identify samples on glass.[9]

Monitor and test RNA samples are used to make fluorescent cDNA probes in single-round reverse transcription reactions with fluorescently labeled dUTP by Cy3 and Cy5, resulting in fluorescently labeled

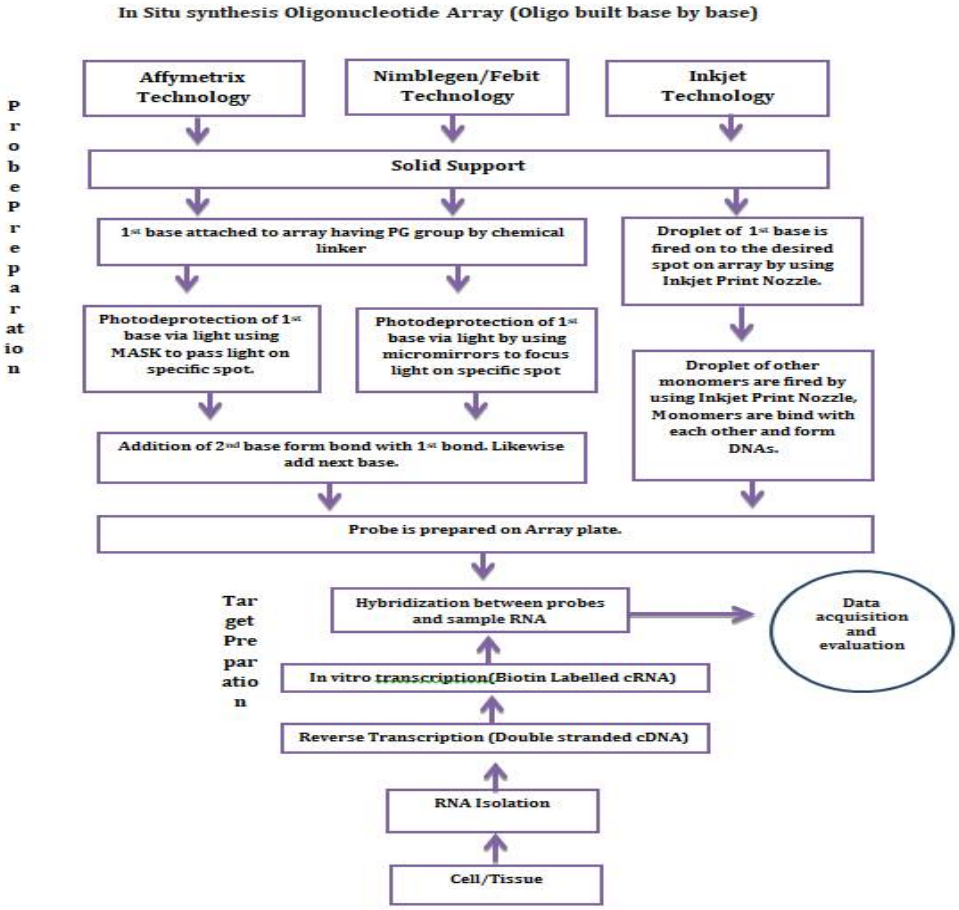
control and test products. Under the cover slip of glass, the cDNAs created from these two populations, collectively referred to as "probe," fused and hybridized with the collection.(Fig:5)[10,11]



[Fig:5 Microarray on Glass slide]

HIGH-DENSITY OLIGONUCLEOTIDE MICROARRAYS, also known as "chips," are characterized by in-situ oligonucleotide synthesis.

- ***In-situ*** **synthesized microarrays:** These arrays are mediated either by photo-deprotection or chemical deprotection. The photo-deprotection stage is performed by means of micro-mirrors to focus light on the array at the pixels, according to authors from Nimblegen Systems Inc. in 2002. Blanchard et al. introduced a method for producing oligo arrays using inkjet printing technologies and normal oligo synthesis chemistry in 1996.[12]



[Fig:6 In situ synthesized Microarray]

- Affymetrix used the technology to create a variety of DNA arrays for expression synthesis, genotyping, and sequencing. Since the DNA sequences are directly synthesized on the surface, only a few reagents are needed to create an arbitrarily complex series (the four modified nucleotides plus a small handful of reagents for the de-blocking and coupling steps). Since each type of array required the construction of a separate series of photolithographic masks to focus the light to the array at each stage of the synthesis process, the flexibility of the original Affymetrix technology was reduced. Traditional photolithographic methods that use masks to concentrate light allow for the production of custom arrays in small amounts at a much lower cost than the Nimblegen Systems approach (cheaper for large volume manufacture). The total number of addressable pixels is constrained by the number of addressable positions in the micro-mirror unit, which is a disadvantage of this technique. The four nucleotide phosphoramidites were shipped to a glass slide that had been pre-patterned with inkjet printer heads to include regions with hydrophilic (exposed hydroxyl groups) regions surrounded by hydrophobic regions. The adjacent hydrophobic regions contained the droplet(s) released by the inkjets, while the hydroxylated regions provided a surface for the phosphoramidites to pair with. Inkjet array technology has proved to be particularly useful for creating custom arrays in limited amounts.(Fig:6)[13]

TARGET DNA PREPARATION (SAMPLE PREPARATION &LABELLING)

The labeled DNA added to the microarray, hybridizes to the slide's surface with the additional probe DNA attached is known as target DNA. The target DNA is usually generated by incorporating a fluorescent nucleotide into cDNA during reverse transcription of RNA into cDNA. Extracting RNA from tissue or cells, converting it to cDNA, and marking it are all steps in the target DNA preparation process.[14]

ISOLATION OF RNA

Researchers have devised a process for polyadenylatingE.coli mRNA in crude cell extracts using E.coli poly-A polymerase I and purifying it using oligo-dT chromatography.After RNA separation, RNAase-free DNAase therapy may be used to purify RNA.[15]

RNA/cDNA LABELING:

The test and reference samples RNA is transformed to cDNA by reverse transcription (RT) with reverse transcriptase and labeled with two separate fluorescent dyes. Oligo-dT primers are required for the synthesis of cDNA by reverse transcriptase, which anneals to a poly-A tail at the 3' end of the majority of mammalian mRNAs. For this method a high amount of starting RNA is required. The starting material should be amplified to solve these issues.[16]

It's also important to use the right fluorescent dyes when marking. The cyanine-based fluorescent dyes Cy3 and Cy5 are the most widely used in a specific microarray assay. The synthetic polymethine dyes Cy3(green fluorescent) and Cy5 (red fluorescent) are included in this category. [17]

Labeling methods are of two types: Direct and indirect.The fluorescent dyes, called direct labelling, are spectrally well-separated and can be integrated directly into synthesized cDNA during reverse transcription. Additionally they provide enough visibility for processing image acquisition.Indirectlabeling, is a two-step technique based on aminoallyl-dUTP, is securing a recognition due to augmented labeling performance, decreased bias, and lower dyeing costs. Main aliphatic amino groups inserted for the first time through cDNA synthesis. In the second cycle, a chemical process involving amino functional groups couples the'monofunctional N-hydroxysuccinimide-activated fluorescent dye'(Cy5,Cy3) to cDNA. Both indirect & direct labeling technique depend on utility of mixing modified nucleotide and clone sequence itself for an amount of inserted symbol.[18]

TARGET PURIFICATION:

After labeling, unincorporated dyes must be removed to minimize the context. This can be done by traditional methods of 'DNA purification' like the QIAquick PCR Purification Kit, Telechem Fluorescent Probe Purification Kit and Amersham Cy-Scribe GFX Purification Kit.[19]

HYBRIDIZATION:

Hybridization is a method to mix the labeled DNA target with the DNA probe on the microarray plate. Before hybridization, nonspecific binding sites on most glass slides must be blocked or inactivated. Prehybridization is based on the spotting chemistry & the form of slide. A pre-hybridization solution of 0.1% SDS, 5% SSC, and 1% BSA, performed well with aminosilane-coated slides. The microarray is washed and dried after hybridization. Once the fluorescent target DNA hybridizes with the cDNA probe on slide, the volume of radioactivity or immobilized fluorescence could be measured.

These reactions are governed by Wetmur's (1991) melting temperature equation for polynucleotides. The temperature at which complementary nucleotides bind determines hybridization temperature. Lower temperatures (37-45 ° C) should be used for 20-40nt long oligonucleotides, while higher temperatures (45-60 ° C) are used for longer complementary nucleotides to achieve better rigidity and stable results. By

selecting the proper hybridization temperature and wash step stringency after hybridization, we may exclude signals from weak or non-specific bonding.[20]

The duplex's melting point gets low down by fluorescent dyes, that allows for more flexible hybridization and washing conditions than with non-fluorescent probes. The solution of hybridizationis usually placed on an array, sealed by a cover slip. After that, the slide is either passively hybridized or the hybridization reaction is mixed and recirculate to maintain a uniform probe concentration.[21]

WASHING:

The array is then washed to remove any unbound labelled target cDNAs after hybridization. Washing is a crucial phase in reliably delivering low histories. As a result of insufficient washing, salts or fluorescent materials may be treated, masking the entire array or parts of it. Wash buffers must be of the best possible standard and free of contamination. During this procedure, the whole package have to be soaked in the washing solutions. At the time of washing, it is significant not to let the arrays gets dry, since that can consequence in elevated backgrounds. If required, the length and number of washing steps be increased.[22]

IMAGE CAPTURE:

A specially made microscope (laser confocal) having a scanning stage of 70 to 90 cm/s and PMT(Photomultiplier tube)detector is used to test the fluorescence intensities at the immobilized probes. The intensity data is recorded at 16 bits and is integrated over a 1520 micron square pixel. "Two fluorescent images: Cy3 and Cy5" were achieved by a software (DeArray) to determine differential gene expression ratio values.[23]

In a standard microarray experimentation, the scanner generates two "16-bit TIFF files", individually for separate fluorescent dye, that monitors the intensities of pixels in a large number within the array's scanning region. The PMT detector is normally set such that the brighter pixels are only below saturation (i.e. 216), which improves image processing accuracy for the fewer bright pixels.[4]

ANALYSIS OF DATA

Picture processing is the first step in the data analysis process. A microarray scanner produces images that reflect any microarray experiment's raw data. The picture is converted into numeric knowledge that measure gene abundance using computer algorithms. The second transition, known as normalization, eliminates non-biological effects from biological results, such as uneven amounts of starting RNA, variations in marking, and detection ability.One of the main aims of microarray research is to determine which genes are differentially expressed, which is the third and final component of data analysis. Statistical approaches may be used to find these genes and calculate their expression rates. Genes that expresses themselves in a similar way are then grouped and analyzed in a dynamic fashion using clustering techniques.[24]

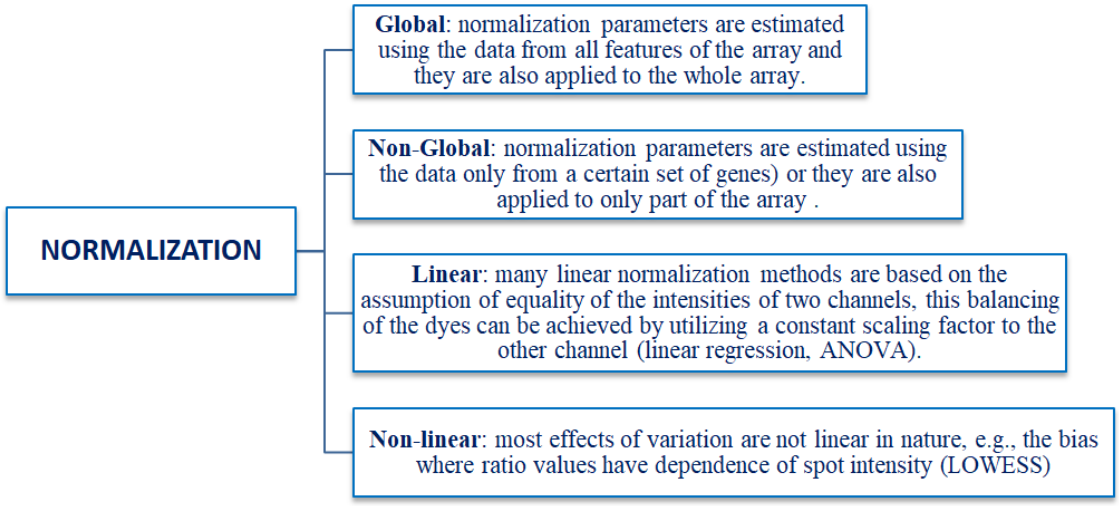
IMAGE PROCESSING:

Background intensities are used to adjust the foreground intensities for local dissimilarity on the surface of an array, yielding accurate channel intensities for each position. The three fundamental stages in the processing of array images are position detection, quantification, and context estimation. Many software tools, both free and commercial, have been created for this purpose. Spotfinder (part of TIGR's TM4 package), Quant Spot, Array, ScanAlyze, GenePix (Molecular Devices) are among the most well-known and useful (Perkin-Elmer).[25]

The DNA spots on the collection should ideally be identical in shape and height (circular Spot segmentation and intensity calculation are essential for quantification. Segmentation classifies each pixel in targeted area as background or foreground. The four most popular approaches for segmentation are histogram , set circle, adaptive shape & variable circle, which results in spot mask for a quantitative measurement of foreground pixel power.The removal of error spots, also known as "flagging," is an essential aspect of image processing.[26]

NORMALIZATION:

In mostly all biological research and microarray experimentation, many methodical variables may influence the measurement of mRNA levels, creating exact comparisons hard. Sample management errors, slide to slide inconsistency, hybridization or labeling output variations & image processing differences may all induce variation. These variations aren't caused by alteration in gene expression levels. Normalization is the primary transition introduced to expression results, and it balances the human hybridization intensities to allow for practical biological comparisons.(Fig:7) Normalization is the method of excluding non-biological sources from biological data in order to minimize differences and create a standard basis for reference.[27]

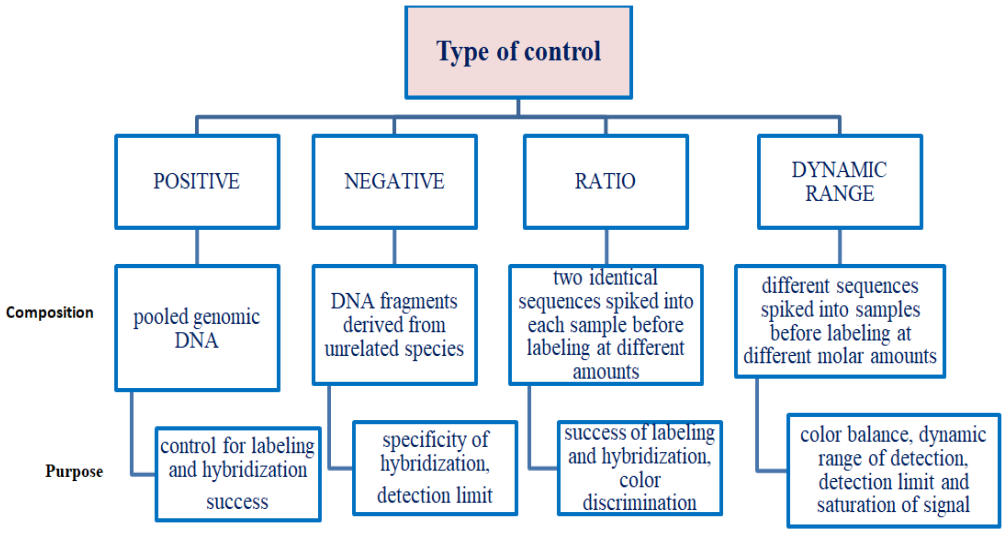


[Fig:7 Parameters of Normalization]

Typically, accessible computer software is used to normalize data. The SNOMAD (Standardization and Normalization of MicroArray Data) tools are an assortment of algorithms for normalizing microarray data that are accessible through a web interface.

MICROARRAY CONTROLS:

It's necessary to specify a series of genes for normalization before determining normalization factors. These genes serve as a starting point for the normalization process. To make sure, the data collected by the arrays is correct, microarrays can have a set of controls. The properties and primary functions of four common control types are listed in the Fig:8. Controls provide valuable information about printing accuracy, goal preparation performance, hybridization specificity and sensitivity, and fluorescence signal dynamic range, as well as serving as "landing lights" for diagnostic software.[24]



[Fig:8 Types of Control]

METHODS OF CLUSTERING AND STATISTICAL ANALYSIS

The most important field of microarray bioinformatics is statistical and clustering approaches, which address there queries about gene expression,connections between gene and categorization of sample using gene expression.[28]

An appropriate statistical analysis shall be conducted for every gene in order to distinguish expressed genes in relation to the specific biological query. To group genes with identical expression patterns, clustering algorithms are often used. Cluster analysis techniques may disclose structure in a slew of array results, combining both identified and unidentified genes in ways so as to propose organized regulation means and roles in typical pathways.[29]

Program for analyzing array data using statistical methods based on the t-test has been described. The study of variance (ANOVA) and its variants are another popular statistical method for comparing data

sets (e.g., MAANOVA). There are several freeware and commercial tools available for microarray clustering and statistical study, such as Gene Publisher, ClustArray and TM4.[30]

DATABASES AND STANDARDS OF MICROARRAY :

In order to make sure the interpretation of experiment observations collected by microarray testing,it is critical to identify the least details which shall be registered. "MIAME: Minimum Information About a Microarray Experiment" has been anticipated as a preliminary point for synchronizing the contextual side of several diverse microarray techniques rather than the scientific arrangement. Enhanced right to use to big electronic data sets, clear and precise characterization, and powerful facts processing techniques are needed to conduct adequate comparative data evaluation. Consequently MIAME has two main divisions:[31]

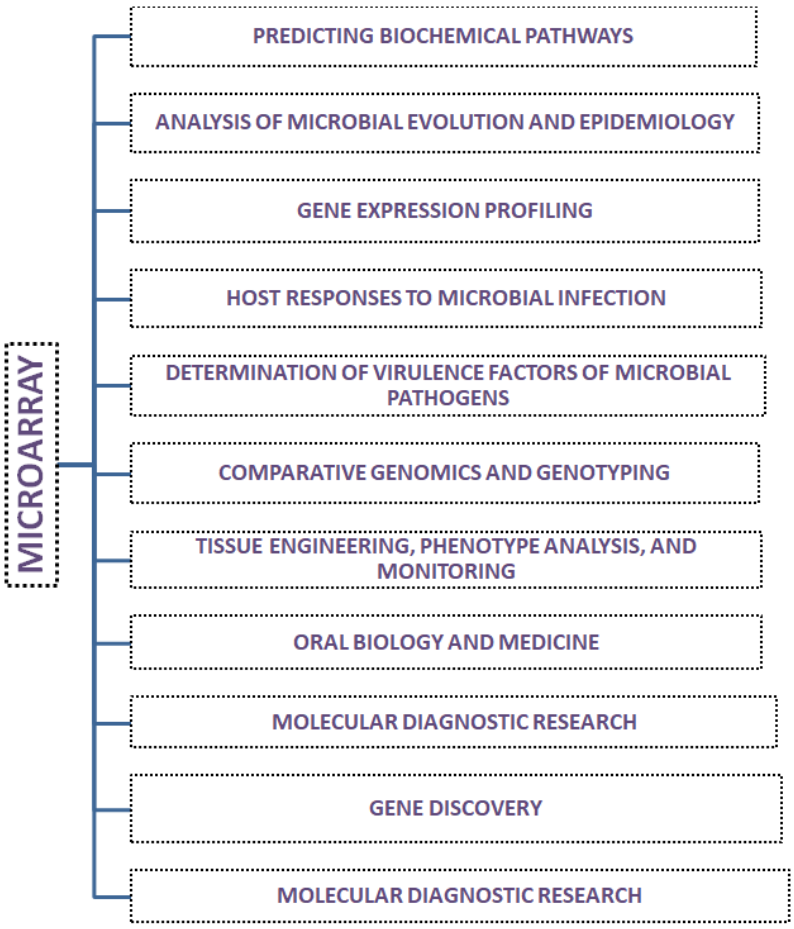
1. design of array and its explanation
2. definition of the experiment

MIAME's scientific implementation, MAGE (MicroArray and Gene Expression), allows applications to be built using MIAME. Individuals pursuing established microarray functionality that is completely compatible with MIAME would be interested in MAGE.

Microarray data must be shared in order to validate reported microarray experimentation information, compare findings with similar experiments, and establish new data analysis techniques. 'ArrayExpress', 'GeneX', , 'Stanford databases', , 'KEGG: Kyoto Encyclopedia of Genes 'GEO:Gene Expression Omnibus' and Genomes', and 'GO:Gene Ontology' are some of the latest databases used for this purpose (Gene Ontology).[32]

APPLICATIONS

The Microarray comprises the broad range of applications as mentioned in Fig:9. [25]



[Fig:9 Applications of Microarray]

CONCLUSION

DNA microarray research is a quick and scalable way to explore genome structure, gene expression scheme, and gene function at both the cellular and organismal levels. It's a multistep procedure that necessitates knowledge of molecular biology, image processing, computing, and statistics, among other areas.

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CONFLICT OF INTEREST

The authors declare that not competing interests exist.

AUTHOR CONTRIBUTIONS

Mr. Nehal Rami has idea of the article. He has collected the recent data of the topic ,Write ,Review and finalized the article.

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