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Research Article

Microarray: A Commanding Approach to Study Gene Expression in The Prevailing Scientific Era

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ABSTRACT

Microarrays with biomolecules, cells and tissues arrested on compact substrates are noteworthy tools for biological exploration, counting on genomics and proteomics as well as cell analysis. The demand of microarray tools is the possibility of large-scale corresponding determination of a diversity of variables concurrently. Henceforth, microarray technologies fascinate the concernequally of the scientific and professionaldomains alike. High-throughput screening has been the foremost focus of the exploitation of microarray technologies in modern years, and has delivered the resilient driving force for expansions in this arena. DNA chip and biochip skills have been established as a magnitude of wide-reaching activity in genome exploration. In this review, the current state of microarray fabrication is reviewed and also on microarray-based analysis, microarray stages, techniques and applications.

Keywords: Microarrays, biomolecules, genomics, proteomics, stages, techniques, applications.

INTRODUCTION

Amongst the genomic projects conducted, are novel and commanding tools known to be as the genome-wide devices experiencing hybridization techniques conferred as microarrays. DNA microarray proficiencies originally were considered to measure the transcriptional levels of RNA transcripts consequential from thousands of genes inside a genome at a single stretch, in a single experiment.Primarily these were intended to extent levels of gene transcription, data retrieved from microarray expertise's are currently cast-off for associating further genome features among the tissues and cells of an individual organism. Outcomes, so obtained provides vital information on diseases subdivisions, prognosis and also on treatments upshot. This technology has made it conceivable to relate biological cell states to gene expression patterns for studying tumor genesis, progression of diseases, cellular response, and identification of drug targets.

For example, subsets of genes with amplified and declined activities have been recognized for acute lymphoblast leukemia [15,34], tumor genesis[6], prostate cancer [27], apoptosis induction [8], colon cancer [2], breast cancer [36], drug response [8], multiple tumor types [23] and lung cancer [40].Similarly, microarrays disclose alterations in genetic makeup of an individual, its supervisory mechanisms and refined variations and might direct towards the timeline of adapted medicine to cure the diseases causing hindrance in the treatments.

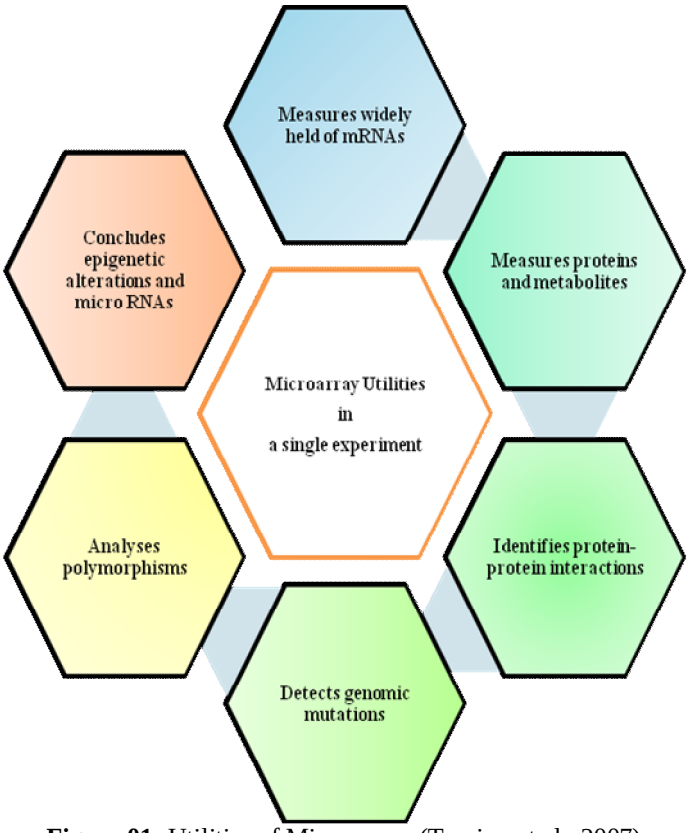

Figure 01: Utilities of Microarrays (Trevino et al., 2007)

Figure 01, establishes the utilities of microarrays in a single experiment, which was not even imagined few years back but now has been made possible with the chip technology. The data generated is so vast that some hidden facts are also revealed with this and also to manage such huge amount of data is a challenging task.

Current uses of DNA microarrays in research related to biomedical discipline are not limited to gene expression, but have expanded beyond its edges. DNA microarrays are being used to identify SNPs i.e. single nucleotide polymorphisms of our genome [12], aberrations/abnormalities in methylation arrangements [41], variations in copy number (gene copy number) [22], RNA splicing (alternative) [24], and detection of pathogens [11,38].

From past 10-15 years, arrays of high excellence, hybridization protocols that are being standardized precisely, exact scanning techniques, and vigorous computational methods have been established for the upcoming DNA microarray techniques for gene expression as a commanding, mature, and potent genomic tool.

TABLE 01: MICROARRAY DATA ANALYSIS

WET LAB	DRY LAB
1. RNA Extraction	1. Image Analysis
2. Labeling	2. Normalization
3. Hybridization	3. Filtering
4. Scanning	4. Transformation
	5. Statistical Analysis

A TYPICAL MICROARRAY EXPERIMENT

- **RNA Extraction**

RNA extraction from the tissues or cultured cells can be done using molecular biology procedures. The quantity of messenger RNA required will be about 2.5 % (0.5/µ/g) which will be comparable to 20/µ/g of total RNA (mRNA, tRNA and rRNA),

though there are some variations that is reliant on this microarray chip technology[39].

- **Labeling**

Complementary DNA (cDNA) is being generated using reverse transcriptase enzyme when mRNA experiences retro-transcription. Modified fluorescent nucleotides are included to achieve the process of labeling by the excitation process at proper wavelengths. Commonest dyes utilized are Cy3 (green) and Cy5 (red) [25,44]. Un-incorporated dyes during the procedure typically are detached by chromatographic techniques specifically; column chromatography further ethanol precipitation can also be used.

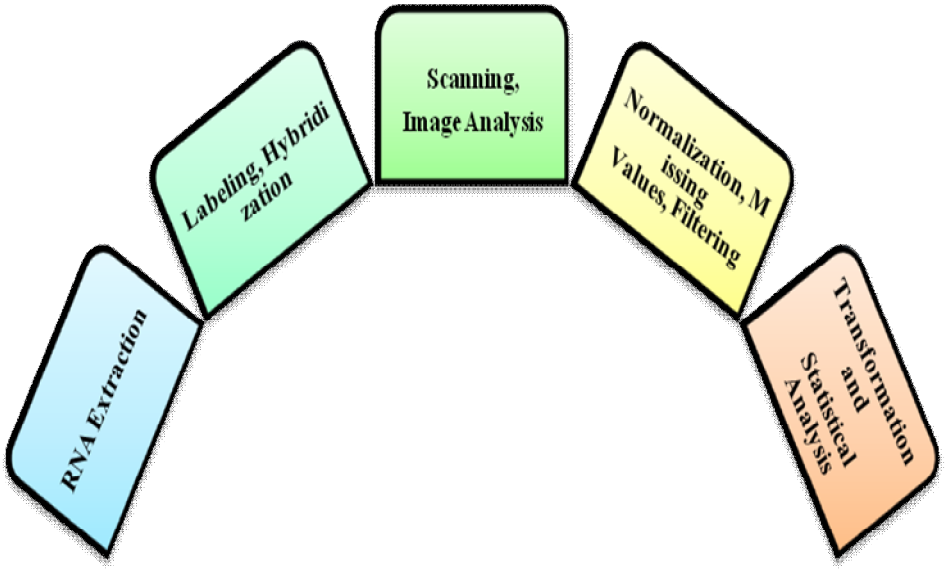

Figure 02: Microarray experiment

- **Hybridization**

Conventional protocols are being utilized for hybridization technique.

TABLE 02: HYBRIDIZATION SOLUTIONS (Cheung et al., 1999)	
Solution A (used at 42 °C) 6´SSC	0.5% SDS 5´Denhardt's reagent (0.5 g Ficoll, 0.5 g polyvinylpyrrolidone, 0.5 g bovine serum albumin) 50% formamide
Solution B (used at 65 °C) 6´SSC	5´Denhardt's reagent 0.5% SDS
Solution C (used at 65 °C) 10% SDS	7% PEG-8000

The solution for hybridization contains saline sodium citrate, sodium dodecyl sulphate (SDS) or sodium lauryl sulfate (SDS is an organic compound used as an anionic surfactant/detergent), non-specific DNA, obstructive reagents like bovine serum albumin (BSA) and labeled cDNA from the tissue or cultured cell samples. Temperatures for hybridization, ranges from 42°C to 50°C for oligo-based microarrays and 42°C to 45°C for cDNA-based microarrays[10]. Moreover, a hybridization compartment is generally desirable to keep temperature and moistness/ humidity constant.

TABLE 03. PROTOCOL FOR HYBRIDIZATION (Cheung et al., 1999)

1.	Moisten array prior to UV-cross linking
2.	Cross-link at 0.25 J/cm2 to 0.35 J/cm2
3.	Air dry
4.	Pre-hybridize array with hybridization solution containing blocking agent for 30 min
5.	Rinse in water for 1 min
6.	Wash the array in 0.1% SDS, 0.2´SSC for 5 min at RT, then in 0.2´SSC for 5 min at RT
7.	Moisten array again and heat snap for 3 s
8.	Wash in 0.1% SDS for 30 s
9.	Dry by centrifugation at 2000 rpm for 2 min
10.	Denature by placing array in 95 °C water for 3 min
11.	Prepare targets and reconstitute in 15 mlhybridization solution.
12.	Immediately transfer to ice-cold ethanol
13.	Incubate probes with the array for 8–24 h

- **Scanning**

Followed by hybridization, the microarray chip is washed in buffers and desiccated by centrifugation or by propelling air after dipping in alcohol. This chip is then read through a scanner which contains of a device equally fluorescence microscope fixed by a laser, and digital camera to record the fluorescent excitation of the gene expression captured till currently. This scanner contains a robotics similarly that focuses on the lens, slide, camera and laser alike to a desktop scanner used in common.

The amount of signal representedby the help of color, detected is supposed to be proportional to the number of dye at each spot on microarray chip and henceforth proportional to the RNA concentration of the complementary sequence of nucleotides in the samples [18,33].

TIFF format files are actuality generated for every fluorescent dye, a mono-chromatic (non-colored) digital image. False color images are equally being obtained for visualization purposes.

- **Image Analysis**

The aim of this step is to identify the spots produced on to the microarray chip. Study of the microarray image, quantification of the signal, and recording the quality of the each and every spot meanwhile it will represent the gene expression. The images are loaded in the desired software with a pre-loaded design of chip that will be used to teach the software to consider position, dimension, number and shape of each spot. The grid is then lodged to the genuine image automatically. Fine tuning will also be conducted.

Certain image processing is essential prior to measuring intensity. Maximum is quite standard and need not be labelled here. For instance, the image needs to be segmented into target patches, however this job is straightforward since the robot locations the cDNA targets in a predetermined method. Since the number of pixels in the aim site is together smoothing, limited, and sharpening filters necessary to be avoided [3,9].Human participation is required to mark the errors and false spots, indicating the false alarms of artifacts. Lastly, an integration purposemechanically is accomplished consuming the software efficacies to convert the readings of real spot to numeric.

The automaticaddition considers the signal and background noise for each and every spot. Certain image analysis software includes:

1. GenePix (Axon), (Molecular Devices Corporation, Union City, CA, USA)
2. GeneChip (Affymetrix, Santa Clara, CA, USA)
3. ScanArray (PerkinElmer, Waltham, MA, USA), and

4. TIGR-SpotFinder/TM4 (The Institute for Genomic Research, Rockville, MD, USA)

- **Normalization**

Systematic errors are introduced in the stepssimilarhybridization, scanning procedures, and also labeling. The main objective of normalization is application of correction for these errors conserving the biological information and to producestandards that can be associated between the experiments [43].

Two types of normalization approaches are here, "within" and "between" array normalization methods. "Within" array normalization mentions the normalization applied in the similar slide and it is connected, usually, to two-dye know-hows.

"Between" normalization is necessary when minimum two slides are examined to assure that together slides are measured in the identical scale and that its standards are independent from the strictures, parameters used. The aim is to alter the facts and figures in the process of data in such a technique that all microarrays have the related distribution of values[42].

- **Filtering**

The chip technology not only contains few genes or spots;however, it has the efficacy to hold entire thousands of genes. These genes are actually calculated as spots, or probes. Dealing by this much amount of data may want some specialized technological aspects and these aspects needs computational and informatics approaches and large processing periods.

Usually, the genes that are not able to show significant changes through the samples, missing data or low expression or those having average are removed. This happens since low expressions of genes are susceptible to noise that is meant to be removed.

- **Transformation**

Numerical values retrieved after image analyses are integer numbers between 1 and 32,000 for both background and signal of the genes held on to the microarray chips. Generally the background is being subtracted from the signal values. These values are transformed into logarithms ($base_2$).

- **Statistical Analysis**

The technique after image examination and data processing depends primarily on the specific biological concern and data available [37].

SKETCH OF MICROARRAY TECHNOLOGY

Double stranded hybrids are formed from complementary single stranded sequences of nucleic acids. This has been a base for not only molecular biology techniques but is also useful for many other tools and techniques. Molecular biology techniques that deal with this knowledge of complementarity are in situ hybridization, Southern and Northern blots and Polymerase Chain Reaction.

The aim of the technology nevertheless, is not basically to identify but also to quantitate the expression levels of thousands of genes in a single experiment. For this purpose, n-number of ss-sequences that are complementary to the preferred sequence are synthesized, or marked to a glass chip or support whose size is in realrelated to that of a glass slide.

Commonly, there are two types of DNA arrays, depending on the probes that are spotted on to the glass slide. One of the types uses small ss-oligonucleotides approximately equal to 22 nt base pairs.

Second type of array uses cDNA that is achieved via reverse transcription methodology [14].

The open reading frames of the sequences experiences chain reaction amplification. Variations in the optimal melting temperature of the cDNA sequences also known as ORF's is one of the major limitation that is caused by the GC-content of the paired nucleotides also by the differences in the size of the sequences. Second limitation is the occurrence of cross hybridization of closely related sequences, genes that are overlapped and spliced sequences.

A second problem is cross-hybridization of overlapped genes, closely related sequences and splicing variants. The oligonucleotides are designed to ignore the drawbacks of the complementary DNA probe in turn to exploit the specificity for the favorite target gens. Earlier DNA microarrays are used as nylon members who are still dealt equally.

Although, glass slides provides tremendous support to n-number of genes for the attachments of nucleotide bases, which is also beneficial since the glass structures are less sensitive to light than the membranes that show somewhat specificity for the light. The glass slides are not sensitive towards light but are also nonporous, that does not allow much sample to pass, which in turn is beneficiary for the experiment.

These types of arrays are usually utilized for methylation, copy-number measurements, detecting loss of hetero zygosity, genotyping, and allele specific expression. Usually these arrays are delivered by Illumina [1,14].

Followed by the above description is the process of labeling, in which, fluorescent dyes are used so as to tag the extracted messenger RNA or cDNA (amplified) from the cultured cell samples that are left to be examined.

The array is formerly hybridized with the samples labeled previously in the experiment, providing overnight incubation and then washing to eliminate non-conjugated hybrids.

The laser connected (by the confocal scanner) to the device then excites the fluorescent dyes to produce light.

The confocal scanner produces a digital image from the excited microarray chip. This image is formerly further processed on to particular software to transform the image retrieved of each and every spot to a numeric value. At first, particular location and shape of each spot is detected that is followed by the summation of the intensities inside the defined spot, and concluding the estimation of the background noise generated. This noise is subtracted after the signal that is integrated. This concluding remark is an integer value.

The reading retrieved is formerly transformed to a ratio between reference sample (sequence labeled with one form of fluorochrome) and the preferred sample (sequence labeled with another form of fluorochrome). Overall, when merely a marginal number of the genes are projected to change a two-dye or reference proposal is more appropriate, otherwise a one-dye technology may be more appropriate.

Finally, an improvement question is being raised in an effort to control false positives, must be accomplished. Mutual correction methods are the False Discovery Rate projected originally by Benjamini and Hochberg (Benjamini & Hochberg, 1995) [5] and stretched by Storey and Tibshirani(Storey & Tibshirani, 2003) [29].

TABLE 04 : Software For Microarray Data Analysis("Stanford Microarray Software," 2015)

STANFORD SOFTWARE			
Program	Description	Author	Platform
CaryoScope	Viewing aCGH or expression data in a whole-genome context.	IhabAwad	Java
CGH-Miner	Calling Gains and losses in Array CGH data using the CLAC Method.	Wang et al.	Excel Add-in/ R package
Cluster	Perform hierarchical clustering, self-organizing maps	Michael Eisen	Windows
Correlate	A method for the integrative analysis of 2 genomic data sets	Gross/Narasimhan/Tibshirani/Witten	Excel- Add-In
GeneXplorer	Web-visualization of microarray datasets	Rees/Demeter/Matese	Perl
GO-TermFinder	Finds GO terms significantly associated with a list of genes	Gavin Sherlock	Perl
HeatMap Builder	Generates customizable heatmaps from microarray data	Euan Ashley, Josh Spin, Clifton Watt	Windows
Java Treeview	View Results of Clustering	AlokSaldhana	Java
KNNimpute	Estimation of missing microarray values	Olga Troyanskaya	UNIX Linux
PAM	Prediction Analysis for Microarrays	Hastie/Naras/Tibshirani	Excel /R under Windows/Unix

SAM	Significance Analysis of Microarrays : Supervised learning software for genomic expression data mining	Rob Tibshirani	Excel Add-in
ScanAlyze	Processes fluorescent images of microarrays	Michael Eisen	Windows
SLCView	Creates images in many different formats from cdt and gtr files, from the unix command-line	Swaine Lin Chen	UNIX/Linux
SMD Package	Full source code for the Stanford Microarray Database	SMD Staff	UNIX + Oracle
SuperPC	Survival and regression analysis for microarrays	Bair/Tibshirani	R package
TreeView	Graphically browse results of clustering and other analyses from Cluster	Michael Eisen	Windows
XCluster	Perform hierarchical clustering, self-organizing maps	Gavin Sherlock	UNIX Linux MacOS Windows

TABLE 05: Other Softwares For Microarray Data Analysis ("Stanford Microarray Software," 2015)

SOFTWARE FROM OTHER SOURCES			
Program	**Description**	**Provider**	**Platform**
Array Designer	Tool assisting in primer design for microarray construction	Premier Biosoft International	JAVA
ArrayMiner®	Set of analysis tools using advanced algorithms to reveal the true structure of gene expression data.	Optimal Design, Sprl.	Windows MacOS
ArrayViewer	Identification of statistically significant hybridization signals	National Human Genome Research Institute	JAVA
ArrayVision	Automated analysis of macro & microarrays	Imaging Research Inc.	Windows
BAGEL	Bayesian Analysis of Gene Expression Levels: a program for the statistical analysis of spotted microarray data.	University of Connecticut	MacOS, Windows, Linux
BAMarray	Bayesian Analysis of Variance for Microarrays - detect differentially expressed genes from multigroup microarray data	Case University	Windows, Linux
BASE	Microarray database and analysis platform	Lund University	Web
Cluster 3.0	An enhanced version of Mike Eisen's Cluster	University of Tokyo, Japan	UNIX Linux MacOS Windows
DNA arrays analysis tools	Hierarchical clustering, Self Organizing Maps and more	Spanish National Cancer Center, Bioinformatics Unit	Web
Expression Profiler	Analysis & clustering of gene expression data	European Bioinformatics Institute (EBI)	Web
ExpressionSieve	Microarray data analysis package, strong in linking biological significance to expression patterns, data and analysis process management, signature gene discovery and class discovery & prediction.	BioSieve	Java
GEDA	Gene expression data analysis and simulation tools, offering a variety of options for processing and analyzing results.	University of Pittsburgh and UPMC	Web
GeneCluster	Self-organizing maps	Whitehead Institute/MIT Center for Genome Research	JAVA Windows NT
GenMAPP	Tools for visualizing data from gene expression experiments in the context of biological pathways.	Conklin lab; Gladstone Institute & the UCSF	Windows
GeneSifter	The GeneSifter microarray data analysis system provides access to powerful statistical tools through a web interface, with integrated features for determining the biological significance of the data. GeneSifter works with any array format and is especially optimized for AffymetrixGeneChip users. Free trial accounts available.	GeneSifter	Web
GeneX	Gene Expression Database : integrated toolset for data analysis and comparison	National Center for Genome Resources	Windows Linux SunOS/Solaris

GenMaths	Analysis of high density microarrays and gene chips	Applied Maths	Windows
Genowiz™	A Gene Expression Data Analysis and Management Tool.	OcimumBiosolutions	Windows Macintosh Unix Linux Solaris
MicroArraySuite	Extracting and visualizing DNA microarray data	ScanalyticsInc.	MacOS
Partek Pattern Recognition	Extracting and visualizing patterns in large multivariate data	Partek Incorporated	Linux, Unix, Windows
TIGR MultiExperiment Viewer	Analysis and Visualization of Microarray Data	TIGR	JAVA
TreeArrange and Treeps	Software for displaying and manipulating hierarchical clustered data	University of Waterloo, Canada	Linux Unix Windows

MICROARRAYS AND ITS APPLICATIONS

The major objective of the microarray procedure is to provide a base of measurement for each and every gene that is functional in an organism's nucleic acid content.

The common applications of the microarray technique whether at the laboratory level or at the bioinformatics level falls under biomedical research and development, in turn the data derived after the analyzation of chips can be subjected to clinical studies irrespective of the technology engaged.

- **Biomarker Detection**

Diseases are more often difficult to diagnose, but once diagnosed its type and the extent of severity are explained by the people having expertise as physicians based on the symptoms of the diseased part acquired from the patient with the help of biopsy. With this view, molecular markers get its association with the clinical outcomes of the disease in turn allowing the monitoring of the diseased tissue at an early stage.

Recently it has been predicted that more advanced biomarkers should be developed so that they may act not only on one gene but should have multi gene specialty so that number of diseases can be diagnosed. These markers should have multi gene signatures.

Biomarker detection is the identification of the gene expression called as signatures of the gene that is associated with the diseases. These biomarkers are to be developed in terms of sensitivity and specificity, which predicts the accurateness of the biomarker. These types of studies need large number of samples.

For the biomarkers accuracy that is its prediction almost the diseases should be unlike differential expression, it should depend on rule that is formed by a classifier, a statistical model established on gene expressions values generated.

Taking an example, a classifier is said univariate, when basically one variable is measured that is sugar levels in the disease diabetes. However, inculcating the conception of DNA microarrays, it is capable to obtain large set genes since multiple gene analysisdelivers robustness to the data produced and result concluded. So, multivariate classifiers are better to be used. As an example, diabetes is caused due to sugar level raise in the stream but along through it, parental predisposition and obesity are the two main issues that aid in its cure. Multivariate classifier can be premeditated by means of genes nominated by a univariateprocedure (Golub's centroid [15], ANOVA, t-test, PAM [32], Wilcoxon) or by a multivariate method [17,20,26,35].

- **Detection of foreign microbes i.e. pathogens**

Characteristically, pathogen exposure is accomplished over successions of clinical examinations which commonly, identify, single pathogens. A fundamental present methodology uses DNA microarrays to examine for the existence of hundreds of pathogens in a dissimilar research [11,38] of particular experiment. For this,

acknowledged sequences from each pathogen are unruffled and those existence pathogen-specific are selected. The collection of specific sequences is castoff to build a favored microarray. After this, the genomic DNA from a patient biopsy is taken, or from a food sample alleged to be sick, is removed and hybridized to the microarray. Spot intensity exposes the occurrence of the pathogen.

- **Genetic Disorders**

Characteristics and traits are inherited from the parents to the offspring. These characteristics and traits are faced in the genes of an organism. Moreover these, genetic rearrangements like addition, duplication, translocation, deletions andsubstitution of genes cause diseases that are inherited from one generation to another. To detect these abnormalities, a specific type of technique known as microarray discovery is being developed. This technique when focused implements a single experiment of hybridization known as Comparative Genomic Hybridization (CGH) that was deliberated by Pollack, 1999 [22].

Genomic DNA is used in the process of hybridization for the comparative examination of genomic DNA from a healthy individual to a sick individual genomic DNA. For healthy samples, the signal intensity is considered to be similar throughout so that modifications in gene copy number can be simplynoticed.

Zhao *et al.,* used this technology in 2005 to describe the variations in the gene copy number in many cell lines. These cell lines were taken from the tissue of prostate cancer [45]. Equally, Braude*et al.,* detected alterations in CML cells i.e. confirmed variations in chronic myeloid leukemia [45].

- **Polymorphism: Geneand Nucleotide level**

There are as a minimum ten million nucleotide positions in human genome, and it has established important to identify them and recognize their genetic loci linked to complex disorders [21]. Though there are commercially manageable microarrays to recognize SNP, these tools are still in their starts.

Number of SNP's kept in the public databases is more than a million, and the available microarrays for them basically cover few thousands SNP's. The three importantapproaches for SNP genotyping using microarrays all based on primer extension techniques.

The first approach comprises of mini-sequencing the primer exact for each polymorphism arrested in the microarray glass support. In this the genotype is recognized by color amalgamations. Second strategy practices the notion of similar primer-specific hybridization, however combined with more than one base extension and with one dye only.

Genotype achieved is revealed by strength of the signal. Third and the last strategy create one base extension lead in solution in arrangement with dissimilar color fluorescent-labeled nucleotides. Genotype is recognized by color blends. Present readings have fashioned genome-wide SNP classification for a quantity of tumor types [16,30,31].

- **Regulation at Transcriptional level**

To control the level of gene expression regulatory proteins that are Transcription factors can bind particular DNA sequences (promoters) so as to carry out the procedure. Mutations in the expression of transcription factors are recognized in numerous diseases [13].

For example, abnormal over-expression of the transcription factors (c-Myc) is originate in 90 % of gynecological cancers, 70 % of colon cancers, 80 % of breast cancers, and 50 % of liver carcinomas [19].

Therefore, instituting the connection between transcription factors and their aims is vital to characterize and design improved cancer cures. To identify targets, genomic DNA fragments are incubated with selected transcription factors. The complex DNA transcription factors are precipitated by a quite specific antibody in contradiction of the tagged proteins. Precipitated DNA is formerly labeled and hybridized in DNA microarrays.

SIGNIFICANCE

Microarray technologies will play anessential role in the detection of large high-throughput data derived simultaneously when diseased and non-diseased gene expression will be studied. These cannot help in innovation the gene expression but will also discover the similarities between species and organisms on the basis of their metabolic achievements. Examination of SNP's, entering of major histocompatibility complexes will be one of the mainadvantageaccomplished with the support of this technology. Tumor identification and Pathogen identification are the additives to the major utilization of the technology so far.

CONCLUSION

DNA Microarray is that technology that aids the scientists to examine and discourse issues which were supposed to be non-traceable. Analyzation of many genes in a single stretch is made possible because of this technology.Microarray presents anapproach that can detect metabolic pathways and the genes involved, for novel and distinctive prospective drug targets, predict drug receptiveness for discrete patients, and, in due course, initiate prevention approaches.This has endowed the scientific community to comprehend the vital aspects highlighting the progress and enlargement of existence as well as to explore the arena of genomics specifically chromosomal reasons of anomalies taking place in any operational human body.

FUTURE PROSPECTS

- ✓ *Pharmacogenomics* is the study of links between therapeutic reactions to drugs and the genetic profiles of the patients.
- ✓ Gene discovery
- ✓ Toxico-genomics–microarray technology permits us to research the effect of toxins on cells. Some toxins can change the genetic profiles of cells, which can be approved on to cell progeny.
- ✓ Disease diagnosis: classify the types of cancer/diseases on the basis of the patterns of gene movement in the tumor cells.

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REFERENCES

1. (2015)., from https://www.illumina.com/(Accession Date: 25 December 2015)
2. Alon, U., Barkai, N., Notterman, D. A., Gish, K., Ybarra, S., Mack, D., & Levine, A. J. (1999). Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucleotide arrays. *Proceedings of the National Academy of Sciences, 96*(12), 6745-6750.
3. Aziz, R., Verma, C. K., & Srivastava, N. (2015a). T-Independent Component Analysis For Svm Classification of Dna- Microarray Data. *International Journal of Bioinformatics Research, 6*(1), 305-312.
4. Aziz, R., Verma, C. K., & Srivastava, N. (2015b). A Weighted-SNR Feature Selection from Independent Component Subspace for NB Classification of Microarray Data. *International Journal of Advanced Biotechnology and Research(IJBR), 6*(2), 245-255.
5. Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 289-300.
6. Bonner, A., Lemon, W., & You, M. (2003). Gene expression signatures identify novel regulatory pathways during murine lung development: implications for lung

tumorigenesis. *Journal of medical genetics, 40*(6), 408-417.

7. Brachat, A., Pierrat, B., Brungger, A., & Heim, J. (2000). Comparative microarray analysis of gene expression during apoptosis-induction by growth factor deprivation or protein kinase C inhibition. *Oncogene, 19*(44), 5073-5082.
8. Brachat, A., Pierrat, B., Xynos, A., Brecht, K., Simonen, M., Brungger, A., & Heim, J. (2002). ONCOGENOMICS. *Oncogene, 21*, 8361-8371.
9. Chen, Y., Dougherty, E. R., & Bittner, M. L. (1997). Ratio-based decisions and the quantitative analysis of cDNA microarray images. *Journal of Biomedical optics, 2*(4), 364-374.
10. Cheung, V. G., Morley, M., Aguilar, F., Massimi, A., Kucherlapati, R., & Childs, G. (1999). Making and reading microarrays. *Nature genetics, 21*, 15-19.
11. Conejero-Goldberg, C., Wang, E., Yi, C., Goldberg, T. E., Jones-Brando, L., Marincola, F. M., . . . Torrey, E. F. (2005). Infectious pathogen detection arrays: viral detection in cell lines and postmortem brain tissue. *Biotechniques, 39*(5), 741.
12. Cutler, D. J., Zwick, M. E., Carrasquillo, M. M., Yohn, C. T., Tobin, K. P., Kashuk, C., . . . Warrington, J. A. (2001). High-throughput variation detection and genotyping using microarrays. *Genome research, 11*(11), 1913-1925.
13. Dumur, C. I., Dechsukhum, C., Ware, J. L., Cofield, S. S., Best, A. M., Wilkinson, D. S., . . . Ferreira-Gonzalez, A. (2003). Genome-wide detection of LOH in prostate cancer using human SNP microarray technology. *Genomics, 81*(3), 260-269.
14. Fan, J.-B., Chee, M. S., & Gunderson, K. L. (2006). Highly parallel genomic assays. *Nature Reviews Genetics, 7*(8), 632-644.
15. Golub, T. R., Slonim, D. K., Tamayo, P., Huard, C., Gaasenbeek, M., Mesirov, J. P., . . . Caligiuri, M. A. (1999). Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *science, 286*(5439), 531-537.
16. Hoque, M. O., Lee, C.-C. R., Cairns, P., Schoenberg, M., & Sidransky, D. (2003). Genome-Wide Genetic Characterization of Bladder Cancer A Comparison of High-Density Single-Nucleotide Polymorphism Arrays and PCR-based Microsatellite Analysis. *Cancer Research, 63*(9), 2216-2222.
17. Li, L., Weinberg, C. R., Darden, T. A., & Pedersen, L. G. (2001). Gene selection for sample classification based on gene expression data: study of sensitivity to choice of parameters of the GA/KNN method. *Bioinformatics, 17*(12), 1131-1142.
18. Loy, A., Lehner, A., Lee, N., Adamczyk, J., Meier, H., Ernst, J., . . . Wagner, M. (2002). Oligonucleotide microarray for 16S rRNA gene-based detection of all recognized lineages of sulfate-reducing prokaryotes in the environment. *Applied and Environmental Microbiology, 68*(10), 5064-5081.
19. Moreno, R. J., Revol, d. M. A., & Barrera, S. H. (1998). [Genetic transcription in eukaryotes: from transcriptional factors to disease]. *Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion, 51*(6), 375-384.
20. Ooi, C., & Tan, P. (2003). Genetic algorithms applied to multi-class prediction for the analysis of gene expression data. *Bioinformatics, 19*(1), 37-44.
21. Piotrowski, A., Benetkiewicz, M., Menzel, U., de Ståhl, T. D., Mantripragada, K., Grigelionis, G., . . . Bała, D. (2006). Microarray-based survey of CpG islands identifies concurrent hyper-and hypomethylation patterns in tissues derived from patients with breast cancer. *Genes, Chromosomes and Cancer, 45*(7), 656-667.

22. Pollack, J. R., Perou, C. M., Alizadeh, A. A., Eisen, M. B., Pergamenschikov, A., Williams, C. F., . . . Brown, P. O. (1999). Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *Nature genetics, 23*(1), 41-46.
23. Ramaswamy, S., Tamayo, P., Rifkin, R., Mukherjee, S., Yeang, C.-H., Angelo, M., . . . Mesirov, J. P. (2001). Multiclass cancer diagnosis using tumor gene expression signatures. *Proceedings of the National Academy of Sciences, 98*(26), 15149-15154.
24. Relógio, A., Ben-Dov, C., Baum, M., Ruggiu, M., Gemund, C., Benes, V., . . . Valcárcel, J. (2005). Alternative splicing microarrays reveal functional expression of neuron-specific regulators in Hodgkin lymphoma cells. *Journal of Biological Chemistry, 280*(6), 4779-4784.
25. Rosenzweig, B. A., Pine, P. S., Domon, O. E., Morris, S. M., Chen, J. J., & Sistare, F. D. (2004). Dye bias correction in dual-labeled cDNA microarray gene expression measurements. *Environmental health perspectives, 112*(4), 480.
26. Sha, N., Vannucci, M., Tadesse, M. G., Brown, P. J., Dragoni, I., Davies, N., . . . Buckley, C. (2004). Bayesian variable selection in multinomial probit models to identify molecular signatures of disease stage. *Biometrics, 60*(3), 812-819.
27. Singh, D., Febbo, P. G., Ross, K., Jackson, D. G., Manola, J., Ladd, C., . . . Richie, J. P. (2002). Gene expression correlates of clinical prostate cancer behavior. *Cancer cell, 1*(2), 203-209.
28. Stanford Microarray Software. (2015). 2015, from http://smd.princeton.edu/resources/restech.shtml(Accession Date: 20 November 2015)
29. Storey, J. D., & Tibshirani, R. (2003). Statistical significance for genomewide studies. *Proceedings of the National Academy of Sciences, 100*(16), 9440-9445.
30. Syvänen, A.-C. (2005). Toward genome-wide SNP genotyping. *Nature genetics, 37*, S5-S10.
31. Teh, M.-T., Blaydon, D., Chaplin, T., Foot, N. J., Skoulakis, S., Raghavan, M., . . . Young, B. D. (2005). Genomewide single nucleotide polymorphism microarray mapping in basal cell carcinomas unveils uniparental disomy as a key somatic event. *Cancer Research, 65*(19), 8597-8603.
32. Tibshirani, R., Hastie, T., Narasimhan, B., & Chu, G. (2002). Diagnosis of multiple cancer types by shrunken centroids of gene expression. *Proceedings of the National Academy of Sciences, 99*(10), 6567-6572.
33. Timlin, J. A., Haaland, D. M., Sinclair, M. B., Aragon, A. D., Martinez, M. J., & Werner-Washburne, M. (2005). Hyperspectral microarray scanning: impact on the accuracy and reliability of gene expression data. *Bmc Genomics, 6*(1), 72.
34. Trevino, V., & Falciani, F. (2006). GALGO: an R package for multivariate variable selection using genetic algorithms. *Bioinformatics, 22*(9), 1154-1156.
35. Trevino, V., Falciani, F., & Barrera-Saldaña, H. A. (2007). DNA microarrays: a powerful genomic tool for biomedical and clinical research. *Molecular Medicine, 13*(9-10), 527.
36. Van't Veer, L. J., Dai, H., Van De Vijver, M. J., He, Y. D., Hart, A. A., Mao, M., . . . Witteveen, A. T. (2002). Gene expression profiling predicts clinical outcome of breast cancer. *nature, 415*(6871), 530-536.
37. Verma, C., & Srivastava, N. (2012). Study of Gene Regulatory Network Using Polynomial, Rational Polynomial and Circular function. *International Journal of Advanced Science and Technology, 42*, 19-32.
38. Wang, D., Coscoy, L., Zylberberg, M., Avila, P. C., Boushey, H. A., Ganem, D., & DeRisi, J. L. (2002). Microarray-based detection and genotyping of viral pathogens. *Proceedings of*

the National Academy of Sciences, 99(24), 15687-15692.

39. Wang, J., Robinson, J. F., Khan, H. M., Carter, D. E., McKinney, J., Miskie, B. A., & Hegele, R. A. (2004). Optimizing RNA extraction yield from whole blood for microarray gene expression analysis. *Clinical biochemistry, 37*(9), 741-744.
40. Wang, T., Hopkins, D., Schmidt, C., Silva, S., Houghton, R., Takita, H., . . . Reed, S. G. (2000). Identification of genes differentially over-expressed in lung squamous cell carcinoma using combination of cDNA subtraction and microarray analysis. *Oncogene, 19*(12), 1519-1528.
41. Yan, P. S., Chen, C.-M., Shi, H., Rahmatpanah, F., Wei, S. H., Caldwell, C. W., & Huang, T. H.-M. (2001). Dissecting complex epigenetic alterations in breast cancer using CpG island microarrays. *Cancer Research, 61*(23), 8375-8380.
42. Yang, Y. H., Buckley, M. J., Dudoit, S., & Speed, T. P. (2002). Comparison of methods for image analysis on cDNA microarray data. *Journal of computational and graphical statistics, 11*(1), 108-136.
43. Yang, Y. H., Buckley, M. J., & Speed, T. P. (2001). Analysis of cDNA microarray images. *Briefings in bioinformatics, 2*(4), 341-349.
44. Yu, J., Othman, M. I., Farjo, R., Zareparsi, S., MacNee, S. P., Yoshida, S., & Swaroop, A. (2002). Evaluation and optimization of procedures for target labeling and hybridization of cDNA microarrays. *Mol Vis, 8*(17), 130-137.
45. Zhao, H., Kim, Y., Wang, P., Lapointe, J., Tibshirani, R., Pollack, J. R., & Brooks, J. D. (2005). Genome-wide characterization of gene expression variations and DNA copy number changes in prostate cancer cell lines. *The Prostate, 63*(2), 187-197.