**FUTURE TRENDS IN DNA MICROARRAY TECHNOLOGY**

**MS. NIDHI N. PATEL, MS. JANKI THAKKAR, JANKI B. PATEL, TRUPAL BHALALA, KRUTIKKUMAR SHAH, ZUVA LAETITIVA.**

**Department of pharmaceutics, Parul institute of pharmacy & research, Parul university, limda, Waghodia,**

**E-mail:** [**nidhipatel050499@gmail.com**](mailto:nidhipatel050499@gmail.com)

**ABSTRACT**

This article examines recent advancements in DNA microarray technology as well as applications for it. The many kinds of DNA microarray or DNA chip systems, as well as their methods of production and uses, are covered in detail. This includes both high-density microarrays for high-throughput screening applications and low-density microarrays for various diagnostic purposes. The microarray fabrication methods described include a variety of inkjet and microjet deposition or spotting techniques, in situ or on-chip photolithographic oligonucleotide synthesis, and electronic DNA probe addressing approaches. The DNA microarray hybridization applications discussed encompass the critical fields of gene expression analysis and genotyping for point mutations, single nucleotide polymorphisms (SNPs), and short tandem repeats (STRs). In addition to the aforementioned molecular biology and genomic research purposes, this study contains applications of microarray devices and systems for pharmacogenomic research and medication development, infectious and genetic illness and cancer diagnostics, and forensic and genetic identification. The development and application of microarray technology in fresh proteomic and cellular inquiry sectors is also reviewed.

Key Words: DNA arrays, DNA chips, DNA microchips, DNA devices, DNA hybridization

**INTRODUCTION**

Now, several DNA microarray and DNA chip gadgets and systems have been created and put on the market. These tools make it possible to do DNA and/or RNA hybridization analysis in highly parallelized microminiaturized forms. Applications for DNA microarray hybridization often focus on gene expression analysis or sample screening for single nucleotide polymorphisms (SNPs). [[[1]](#endnote-1)]

Such microarray systems are being utilized for pharmacogenomic research, infectious and genetic illness and cancer diagnostics, forensic and genetic identification, in addition to molecular physiologically linked studies and genomic research applications. The sensitivity and selectivity of microarray technology continues to increase, and it is also becoming a more practical research tool. Genetic analysis and several crucial diagnostic fields will continue to undergo a revolution thanks to the usage of DNA microarrays. Additionally, new areas of proteomic and cellular investigation are also being conducted using microarray technology, which was originally designed for DNA analysis.

Gene expression provides a special approach to describe how cells and organisms adapt to changes in the external environment since it is a sensitive indication of toxicant exposure, disease status, and cellular metabolism. The pattern of gene expression variations that a chemical induces both in vitro and in vivo may be used to determine the mechanism of action of toxicants and to create a type of "genetic signature" through the measurement of gene expression levels. By comparing unknown or suspected toxicants to recognized toxicants, these gene expression profiles would enable quick screening of unknown or suspected toxicants. The area of toxicogenomic has grown as a result of the ability to examine the impact of substances and environmental stressors on a significant number of genes in a single experiment. Toxicogenomic proponents want to use mRNA and protein expression technologies to investigate chemical impacts in biological systems.

Microarray is a standard laboratory method for quickly detecting gene expression or mutations. Gene chips or DNA chips are other names for these slides. Thousands of probes are mounted on microscope slides or nylon membranes, each containing thousands of small spots with a known DNA sequence or gene. With the development of DNA sequencing technology, it is now possible to find out more about a person genetic. [[[2]](#endnote-2)]

The technology that are utilized to conduct molecular biology research evolve with time. Traditional approaches cannot be used to study a large number of genes. (GS, LAMP). In a typical microarray experiment, an mRNA molecule is hybridized to the DNA template from which it was derived. An array is made up of many different DNA samples. The amount of mRNA coupled to each spot on the array represents the individual genes' expression levels. This number might be in the thousands. All of the information is gathered, and a gene expression profile for the cell is created. [[[3]](#endnote-3)]

Microarray technology has a wide range of applications, including large-scale genotyping, gene expression profiling, comparative genomic hybridization, and resequencing. Microarray technology is a complex synthesis of numerous technologies and research fields, including mechanics, microfabrication, chemistry, DNA behavior, microfluidics, enzymology, optics and bioinformatics. [[[4]](#endnote-4)]

The successful implementation of microarray technologies has required the development of many methods and techniques for fabricating the microarrays and spotting the probes, for carrying out and detecting the hybridization reactions, and informatics for analyzing the data. DNA hybridization analysis on microarrays usually involves detecting the signal generated by the binding of a reporter probe (fluorescent, chemiluminescent, colorimetric, radioisotope, etc.) to the target DNA sequence. The microarray patterns. Fluorescence scanning/imaging or mass spectroscopy are two of the more common methods used for the “reading” of the microarrays. For high-density type microarrays, a variety of bioinformatic tools have been used to reduce the complex data into useful information. The automation of DNA microarray systems greatly facilitates their use and ease of operation and helps to eliminate many of the human errors that would be involved in manually carrying out the multiplex hybridization analyses. The development of microarray technology has depended on the integration of many different disciplines such as molecular biology, genetics, advanced microfabrication and micromachining technologies, nucleic acid chemistry, surface chemistry, analytical chemistry, software, and robotics and automation. Microarray technology represents a truly successful synergy of these many different scientific and engineering fields. The following sections include a composite of recent general reviews and comments on microarray technologies and their applications; an overview of the important micro arraying technologies, with selected examples of microarray technologies that have utilized techniques from the microelectronics industry; and a final overview of the numerous applications of DNA microarrays in research and diagnostics.[[[5]](#endnote-5)]

**THE EARLY HISTORY OF DNA ARRAYS**

One could argue that the original DNA array was created with the colony hybridization method of Grunstein and Hogness (1975). In this procedure, DNA of interest was randomly cloned into E. coli plasmids that were used to transform bacteria which were subsequently plated onto agar petri plates covered with nitrocellulose filters. Replica plating was used to produce additional agar plates. The colonies on the filters were lysed and their DNA was denatured and fixed to the filter to produce a random and unordered collection of DNA spots that represented the cloned fragments. Hybridization of a radiolabeled probe of an DNA or RNA of interest was used to rapidly screen thousands of colonies to identify clones containing DNA that was complementary to the probe. [[[6]](#endnote-6)]

In 1979, this approach was adapted to create ordered arrays by Gergen et al. (1979), who picked colonies into 144-well microplates. They created a mechanical 144-pin device and a jig that allowed them to replicate multiple microtiter plates on agar and produce arrays of 1728 different colonies in a 26 × 38–cm region. An additional transfer of colonies to squares of Whatman filter paper followed by growth, lysis, denaturation, and fixing of the DNA to the filter allowed the production of DNA arrays on filters that could be re-used multiple times. During the next decade, filterbased arrays and protocols similar to these were used in a variety of applications including cloning genes of specific interest, identifying SNPs, cloning genes that are differentially expressed between two samples, and physical mapping. [[[7]](#endnote-7)]

In the late 1980s and early 1990s Hans Lehrach’s group automated these processes by using robotic systems to rapidly array clones from microtiter plates onto filters. The concomitant development of cDNA cloning in the late 1970s and early 1980s combined with international programs to fully sequence both the human genome and the human transcriptome, led to efforts to create reference sets of cDNAs and cDNA filter arrays for human and other genomes. By the late 1990s and early 2000s, sets of nonredundant cDNAs became widely available, and the complete genome sequences of some organisms allowed for creation of sets of PCR products representing all the known open reading frames (ORFs) in small genomes. These sets, combined with readily available robotics, allowed individual labs to make their own cDNA or ORF arrays containing the vast majority of genes in a genome. [[[8]](#endnote-8)]

**THE BIRTH OF THE MODERN DNA ARRAY**

In the late 1990s and 2000s, DNA array technology progressed rapidly as new methods of production and fluorescent detection were adapted to the task. In addition, increases in knowledge of the DNA sequences of multiple genomes provided the raw information necessary to ensure that arrays could be made that fully represented the genes in a genome, all the sequence in a genome, or a large fraction of the sequence variation in a genome. It should also be noted that during this time there was a gradual transition from spotting relatively long DNAs on arrays to producing arrays using 25- to 60-bp oligos. The transition to oligo arrays was made possible by the increasing amounts of publicly available DNA sequence information. The use of oligos (as opposed to longer sequences) also provided an increase in specificity for the intended binding target, as oligos could be designed to target regions of genes or the genome that were most dissimilar from other genes or regions. Three basic types of arrays came into play during this time frame, spotted arrays on glass, in-situ synthesized arrays, and self-assembled arrays. [[[9]](#endnote-9)]

**ADVANTAGES**

* Data for thousands of genes is provided.
* Instead of conducting numerous experiments, conduct just one.
* Results are obtained quickly and easily.
* A huge step forward in the discovery of cures for diseases and cancer.
* Various parts of DNA can be used to study genes.

**DISADVANTAGES**

* The most significant disadvantage of DNA chips is their high cost of production.
* The production of too many results at once necessitates a lengthy analysis, which is quite complex in nature.
* Another major disadvantage of the technology is that the DNA chips do not have a very long shelf life.

**MICROARRAY DEVICES AND SYSTEMS**

In the past several years, many different microarray technologies, devices, and instrument systems have been developed and are now commercially available for producing DNA microarrays. These microarrays and systems are being used for gene expression, genotyping, and other applications. A number of different methods have been developed for creating microarrays, including various techniques for using them. [[[10]](#endnote-10)] Many microarray spotting technologies and techniques now exist. Two of the more important spotting techniques used are the pin-based fluid transfer systems and the piezo-based inkjet dispenser systems. [[[11]](#endnote-11)] Other methods for preparing DNA arrays include the use of photolithography for the in-situ synthesis of high-density DNA microarrays, developed by Affymetrix, as well as the electronic-based addressing of microarrays developed by Nanogel. Both of these methods are discussed below. For further reviews and discussions on other methods for preparing microarrays and the associated techniques and technologies. [[[12]](#endnote-12)]

**Spotted Arrays**

In 1996 DeRisi et al. published a method which allowed very high-density DNA arrays to be made on glass substrates. Poly-lysine-coated glass microscope slides provided good binding of DNA, and a robotic spotter was designed to spot multiple glass slide arrays from DNA stored in crotiter dishes. By using slotted pins (similar to fountain pens in design), a single dip of a pin in DNA solution could spot multiple slides. Spotting onto glass also allowed fluorescent labeling of the sample. Fluorescence detection provided several advantages relative to the radioactive or chemiluminescent labels common to filter-based arrays. First, fluorescence detection is quite sensitive and has a fairly large dynamic range. Second, fluorescent labelling is generally less expensive and less complicated than radioactive or chemiluminescent labeling. Third, fluorescent labeling allowed labeling of two (or potentially more) samples in different colors and hybridization of the samples to the same array. As it was very difficult to reproducibly produce spotted arrays, comparisons of individually hybridized samples to ostensibly identical arrays would result in false differences due to array-to-array variation. However, a two-color approach in which the ratio of signals on the same array is measured is much more reproducible. [[[13]](#endnote-13)]

**In-Situ Synthesized Arrays**

In 1991, Fodor and coworkers published a method for light-directed, spatially addressable chemical synthesis which combined photolabile protecting groups with photolithography to perform chemical synthesis on a solid substrate. In this initial work, the authors demonstrated the production of arrays of 10-amino-acid peptides and, separately, arrays of di-nucleotides. In 1994, Fodor and coworkers at the recently formed company Affymetrix demonstrated the ability to use this technology to generate DNA arrays consisting of 256 different octa-nucleotides. By 1995 to 1996, Affymetrix arrays were being used to detect mutations in the reverse transcriptase and protease genes of the highly polymorphic HIV-1 genome and to measure variation in the human mitochondrial genome. Eventually, Affymetrix used this technology to develop a wide catalog of DNA arrays for use in expression analysis, genotyping, and sequencing. [[[14]](#endnote-14)]

In 1996, Blanchard and coworkers proposed a method using inkjet printing technology and standard oligonucleotide synthesis chemistry to produce oligo arrays. In brief, inkjet printer heads were adapted to deliver the four different nucleotide phosphonamidites to a glass slide that was pre-patterned to contain hydrophilic regions (with exposed hydroxyl groups) surrounded by hydrophobic regions. The hydroxylated regions provided a surface to which the phosphonamidites could couple, while the surrounding hydrophobic regions contained the droplet(s) emitted by the inkjets in defined regions. This technology was eventually commercialized by Rosetta in pharma tics and licensed to Agilent Technologies, which produces these arrays at present. The inkjet array approach shares the advantage of the Affymetrix/Nimblegen approach in that only a small number of reagents are necessary to produce an array. In addition, similar to the Nimblegen approach, the production of a new type of array only requires that a different set of sequence information be delivered to the printer. Hence, the inkjet array technology has been particularly useful for the design of custom arrays that are produced in low volume. [[[15]](#endnote-15)]

**Self-Assembled Arrays**

An alternative approach to the construction of arrays was created by the group of David Walt at Tufts University and ultimately licensed to Illumina. Their method involved synthesizing DNA on small polystyrene beads and depositing those beads on the end of a fiber-optic array in which the ends of the fibers were etched to provide a well that is slightly larger than one bead. Different types of DNA would be synthesized on different beads, and applying a mixture of beads to the fiber-optic cable would result in a randomly assembled array. In early versions of these arrays, the beads were optically encoded with different fluorophore combinations to allow one to determine which oligo was in which position on the array. Optical decoding by fluorescent labeling limited the total number of unique beads that could be distinguished. Hence, the later and present-day methods for decoding the beads involve a series of steps for hybridizing and detecting a number of short, fluorescently labeled oligos. This not only allows for an extremely large number of different types of beads to be used on a single array, but also functionally tests the array prior to its use in a biological assay. Later versions of the Illumina arrays used a pitted glass surface to contain the beads instead of fiber-optic arrays. [[[16]](#endnote-16)]

The above is not intended to be a comprehensive history or survey of all DNA microarray technologies. However, it does cover the major advances in the field and the predominant methods of manufacture of arrays. [[[17]](#endnote-17)]

**PRINCIPLE**

Southern blotting, which involves bonding fragmented DNA to a substrate and then probing it with a known DNA sequence, gave rise to DNA microarray technology. The concept of nucleic acid strand hybridization underpins the DNA microarray. Complementary nucleic acid sequences can form hydrogen bonds with one another, allowing them to complement nucleotide sequences. Fluorescent dyes are used for labelling the samples and at least 2 samples are hybridized to the chip. The presence of a large number of complementary base pairs in the nucleotide sequence suggests that the two strands have stronger non-covalent bonds. Only strongly paired strands will remain hybridized after non-specific bonding sequences are washed away. [[[18]](#endnote-18)]

The fundamental principle underlying microarrays is hybridization between two DNA strands, the ability of complementary nucleic acid sequences to specifically pair with each other by forming hydrogen bonds between complementary trinucleotide base pair and complementary trinucleotide base pair and complementary trinucleotide base pair and complementary trinucleotide base pair and complementary trinucleotide base pair and complementary trinucleotide base pair and complementary tri A nucleotide sequence with many complementary base pairs has a stronger non-covalent connection between the two strands.[[[19]](#endnote-19)]

The signal is influenced by hybridization conditions (such as temperature, washing after hybridization, and so on), whereas the overall strength of the signal is determined by the amount of target sample present. [[[20]](#endnote-20)]

**Steps for preparing microarray experiment**

1. Sample collection
2. mRNA isolation
3. The production of labelled cDNA
4. Hybridization of DNA
5. Data gathering and analysis

**1.Sample collection**

Any cell or tissue that we want to research can be used as a sample. In most cases, two types of tests, namely infected and non - infected cells, are collected in order to evaluate and obtain the final.

**2.mRNA isolation**

To extract RNA from a sample, a column or a diluent such as phenol-chloroform are used. The extracted RNA is divided into mRNA, messenger RNA, and transfer RNA. Poly-T tail column beads are used to bind mRNA because it has a poly-A tail. The column is washed with buffer that after extraction to isolate mRNA from the beads.

**3.production of labelled DNA**

Reverse transcription of mRNA results in the production of cDNA. Both samples are then mixed with different fluorescent probes to make fluorescent cDNA strands, allowing the different sampling class of the cDNAs to be determined.

**4.hybridization of DNA**

A labelled cDNA from both samples is hybridized with their counterpart strands on a DNA microarray. Following that, they are thoroughly cleaned to remove any unpaired sequences.

**5.Data gathering and analysis**

The data is being collected using a microarray scanner. The scanner includes a laser, a computer, and a camera. The laser generates signals by stimulating the fluorescence of the cDNA. The images created by the laser scanning the array are captured by the camera. The computer then saves the information and produces fast results. The information is now being evaluated. The distinct intensity of the colors for each spot determines the nature of the gene in that particular spot. [[[21]](#endnote-21)]

**Photolithography**

Photolithography in Greek means light stone it is a process in which patterns in a semiconductor material can be identified using light. Photolithography is the process of defining and transferring a pattern to each layer. The process is created on a silicon wafer which act as a photolithography substrate it is a means of transferring patterns into a substrate, it is a binary pattern there is no color, depth and grey scale Within a microsystem, each layer has its own pattern. This design is transferred from a mask to a photosensitive layer via photolithography. Another phase in the process involves transferring the pattern from the photosensitive material to the non-photosensitive material. A new layer on top of an existing one the resist is stripped after the pattern transfer.[[[22]](#endnote-22)]

**Three Steps of Photolithography**

1. Coat
2. Expose
3. Develop

**1. Coating Step: Surface Preparation**

1.Surface conditioning comes before the photoresist in most cases. Wafer surface conditioning prepares it for implantation. By providing a clean surface, photoresist can be achieved. It uses a chemical to cover the wafer and improve adherence.

2. After the wafer surface has been baked to remove the water molecules, HMDS is applied (prime) to create a hydrophobic surface.

3. Cool the wafer to room temperature.

The wafer is held in place by a vacuum chuck. A vacuum holds the wafer in place. Chuck accelerates until the desired thickness is reached and continues to spin until the film is dry.

Photoresist ants the technology was inspired by the photography business. Resists for general use and resists for specific purposes are available. Typically, they are tuned to a given wavelength. A photoresist's components include

1. **Polymer** - a light-sensitive polymer with a changing structure when exposed to light. Typically, the desired feature is a change in solubility in a particular solvent.

**2. Solvent -** A solvent is used to thin the resist before applying it.

a spin-on procedure on the wafer Typically, the solvent is eliminated by the soft bake procedure involves heating to roughly 100 degrees Celsius.

3. **Sensitizers** - these are chemicals that are used to control the chemical reaction during the process exposure.

**4. Additives** are chemicals that are added to a process to achieve a specific result. Optical resists, which are photoresists that react to UV or visible light, are also known as photoresists. Other types of radiation, such as x-ray and e-beam, have special resistance.

Photoresists are classified into two categories.

1. Positive resists - these become more soluble when exposed to UV light.

2. Negative resists - these resists become less effective when exposed to UV light.

**Softback**

A softback procedure is used after the photoresist has been applied to the desired thickness. A term "softback" refers to the process of removing a layer of fat from the solvents that are left behind during the cleaning process photoresist. The wafer is baked after the softback and cooled to room temperature

**Alignment**

The design is transferred from the mask to the photoresist on the wafers during the alignment and exposure process. The mask is aligned using alignment markers. "Alignment" is a critical component of the microsystem fabrication process. An imbalance of one micrometer or less can cause the device or all the other devices on the wafer to fail. According to standards, each layer must be properly aligned with the preceding and subsequent levels.

**2. Expose**

ultraviolet light from the light source passes it through mask and reacts chemically with the resist. Only the parts of a face that aren't covered by the mask are subjected to the procedure.

**3. Developing**

After being exposed and aligned, the wafers need to be developed. A substance (developer) is applied to the wafers, where it interacts with the exposed photoresist. The resist determines which developer to employ. Positive photoresists have their exposed portions removed, which makes them more soluble, whereas negative photoresists have their unexposed parts removed, which makes them less soluble. A moist chemical process is what developing is most frequently. Until all of the resist has been removed, the wafers are submerged in the developing solution for a predetermined period of time. Bake it (do a "hard bake") at 250 degrees Celsius to set the remaining resist. The procedure is still in its infancy. The resist shields the wafer underneath from damage. When the final design is produced on the wafer, the remaining resist is eliminated by a procedure called resist stripping. This can be done either wetly using an acid mixture or dryly using a solvent. oxygen plasma etching using a dry process. The wafers are then washed and dried. [[[23]](#endnote-23)]

**DNA microarray types:**

1.Microarrays based on cDNA

2.Microarrays based on Oligonucleotide

**1.Microarrays based on cDNA**

Target DNA microarrays are based on the mechanical or ink jet micro spotting printing of cDNA clones with sizes ranging from a few hundred DNA strands to several kilobases on a glass surface. Reverse transcriptase is used to label the sample and rRNA with fluorescent Cy5 or Cy3 dyes. The cDNAs are then nighttime hybridized to the arrays. A fluorescence laser scanner is used to scan the slides after they have been washed. The red/green ratio of each spotted array element may be used to determine the relative quantity of transcripts in the samples. chips with oligonucleotide bases.

**2.Microarrays based on Oligonucleotide**

The most popular technique is in situ synthesis on glass using a mix of photolithography and oligonucleotide chemistry, however some manufacturers build their arrays by spotting routinely produced oligonucleotides. This particular style of spotted probe has 20–25 short, chemically produced sequences per gene. Reduced probe synthesis errors and the ability to analyse polymorphisms and tiny genomic regions are two benefits of shortened probe lengths. [[[24]](#endnote-24)] Covalent linkage is utilized to attach probes to glass slides since electromagnetic immobilization and inter-linking might cause significant probe loss during washing procedures due to its low weight. On functionally group-coated slides, probes are connected to the microarray ground using modified 5′ to 3′ ends. [[[25]](#endnote-25)]

**Application**

Tumor formation necessitates simultaneous changes in hundreds of cells as well as gene variations. The DNA chip can be useful to researchers because it allows them to examine large numbers of genetic samples at the same time. It specifically aids in the identification of single nucleotide polymorphisms (SNPs) and mutations, tumor classification, tumor suppressor target gene identification, cancer biomarker identification, and tumor suppressor gene identification. Drug discovery, chemical resistance, and gene associations for example, we can compare different patterns of gene expression in cancer patients and normal patients to identify the gene associated with that specific cancer. [[[26]](#endnote-26)]

Gene microarrays have been used to do comparative genome hybridization. This method uses chemically synthesized genomic DNA to detect gene loss or amplification. Mapping genetic anomalies in a variety of tumor types, such as breast carcinoma, bladder carcinoma and ductal carcinoma, fallopian tubes, gastric carcinoma, melanoma, and lymphoma, has been done using the matrix-based comparative gene hybridization (aCGH) technique. [[[27]](#endnote-27)]

It's important to look into how non-invasive tumours might develop into invasive tumours. A gene known as RhoC was found to be higher expressed in metastatic cells compared to non-metastatic melanoma cells when Clark et al. looked at the genetic makeup of metastatic melanoma cells. We can recognise gene families and significant cellular and molecular events that may be involved in intricate processes like metastasis thanks to microarray-based expression profiling. The management of patient prognosis, diagnosis, and care are future practical applications. Clinicians will be able to validate pharmacological mechanisms of action and evaluate drug sensitivity and toxicity using DNA microchips during therapy trials. By dividing malignancies into prognostic categories based on gene expression patterns, for example, they can create a new molecular classification for cancer. Microarray technology may be used to research the categorization of diseases, molecular phenotype profiling, gene function in relation to gene regulatory networks, and functional genomes. Research is done in the fields of developmental biology and pharmacology. [[[28]](#endnote-28)]

**Gene Expression Analysis**

Measurement of gene expression levels has been the primary use of DNA microarrays. In this application, RNA is isolated from the target cells and either labelled directly, transformed into a labelled cDNA, or transformed into a T7 RNA promoter-tailed cDNA that is then transformed into cRNA through the Eberwine amplification procedure. For labelling the cDNA or cRNA, a wide range of techniques have been developed, including incorporating fluorescently labelled nucleotides during the synthesis, incorporating biotin-labeled nucleotides that are then stained with fluorescently labelled streptavidin, incorporating a modified reactive nucleotide to which a fluorescent tag is added later, and a variety of signal-amplification techniques. An early overview of several labelling techniques is given. The inclusion of fluorescently labelled nucleotides in the cRNA or cDNA synthesis stage and the incorporation of a biotin-labeled nucleotide in the cRNA synthesis step (as done by Affymetrix) are the two techniques that are most often employed. The microarray is then rinsed, the labelled cRNA or cDNA is hybridised to it, and the signal is identified by measuring the fluorescence at each place. After hybridization, fluorescently labelled streptavidin is used to stain the array in the case of biotin-labeled materials. A scanning confocal microscope is generally used to measure laser-induced fluorescence. Each spot's signal intensity is used to calculate the degree of gene expression for that particular location. [[[29]](#endnote-29)]

**Transcription Factor Binding Analysis**

Using chromatin immunoprecipitation and microarrays, it has been possible to identify the binding locations of transcription factors. In essence, DNA Microarray Overview 22.1.6 Supplement 101 Transcriptional factors (TFs) are cross-linked to DNA using formaldehyde and the DNA is broken apart, according to Current Protocols in Molecular Biology. Either a TF-specific antibody or tagging the transcription factor with a peptide compatible with affinity chromatography are used to affinity purify the desired TF(s) (while leaving the DNA to which they were bound still attached). The DNA is released from the TF after purification, amplified, labelled, and hybridized to the array.  [[[30]](#endnote-30)]

The design of the array and the size distribution of the fragment length are connected because TFs frequently bind quite a distance from the genes they control. For instance, the array has to include probes that can examine the area of DNA that the TF has attached to it. Since the intergenic regions in bacteria or yeast are very tiny, ChIP-chip may be performed using the same arrays as gene expression research. The intergenic regions of mammalian genomes are vast, and the TF frequently binds thousands of base pairs away from the gene of interest. So, for ChIP-chip investigations, oligo arrays with oligos equally spaced over the whole genome are commonly employed for mammalian genomes. [[[31]](#endnote-31)]

**Genotyping**

Single nucleotide polymorphism (SNP) genotyping systems have frequently utilised microarrays. Affymetrix's allele discrimination by hybridization, allele-specific extension and ligation to a "bar-code" oligo hybridised to a universal array, or methods in which the arrayed DNA is extended across the SNP in a single nucleotide extension reaction are the most widely used alternative methods for finding SNPs. Due to nonspecific hybridization in complicated genomes, allelic discrimination via hybridization suffers from background. SNP genotyping techniques from Affymetrix and Illumina have both achieved great success and are often employed. Both companies now provide SNP arrays that are capable of identifying more than one million distinct human SNPs. SNP calls are reproducible and have call rates (the percentage of SNPs on the array that can be reliably called) above 99.5 percent. Additionally, copy-number variants can be found using the same arrays or variants of them. [[[32]](#endnote-32)]

**Data Standards and Data Exchange**

Microarrays were maybe the first piece of technology that allowed scientists to produce enormous volumes of sophisticated digital data, predating DNA sequencing. The adoption of the technology made it quickly clear that a thorough explanation of the array, the sample, the protocols, and the data processing techniques was required in order for others to be able to replicate a specific microarray experiment. It also became clear that others would be able to do studies and meta-analysis (on combinations of data) that the original data creators had not thought of with access to the raw and processed data. Members of the Microarray Gene Expression Data Society (now the Functional Genomics Data Society; http://www.FGED.org) developed the MIAME (Minimum Information About a Microarray Experiment) standards for the description of microarray experiments and for the exchange of microarray data in order to address these issues of reproducible science and data exchange. These initiatives had an impact on following standardization initiatives in other fields as well as the development of open databases for microarray data. [[[33]](#endnote-33)]

**LIMITATIONS OF DNA MICROARRAYS**

Microarrays are really just instruments for measuring the relative concentrations of several distinct DNA or RNA sequences concurrently. They have a lot of shortcomings while being highly helpful in a wide range of applications. First, arrays give a measure of relative concentration that is indirect. In other words, it is common to assume that the signal detected at a certain site on a microarray is related to the concentration of a single, presumptive species in solution that may hybridize to that spot. [[[34]](#endnote-34)]The array will become saturated at high doses, whereas equilibrium favors no binding at low values. As a result, the signal is linear only within a certain range of solution concentrations. Second, it is frequently difficult (if not impossible) to build arrays in which numerous related DNA/RNA sequences will not bind to the same probe on the array, especially for complex mammalian genomes. If genes B, C, and D have Significant sequence similarity with gene A, a sequence on an array intended to detect gene A may also detect those genes. In the case of gene families and genes with several splice variants, this can be particularly difficult. It should be emphasized that array probes may be made for each exon in the genome or for exon junctions in order to precisely create arrays to detect splice variants. In genomes with many linked genes, it is challenging to create arrays that will accurately identify every exon or gene. [[[35]](#endnote-35)]

Finally, a DNA array can only identify sequences that it was built to recognize. In other words, species of RNA or DNA for which there is no complimentary sequence on the array but which are present in the solution being hybridized to the array will not be identified. For the purposes of gene expression analysis, this often means that genes that have not yet been identified in a genome will not be represented on the array. Non-coding RNAs that have not yet been identified as expressed are also frequently absent from an array. Furthermore, arrays are often created utilizing data from a reference strain's genome for highly varied genomes, such those seen in bacteria. A significant portion of the genes present in a specific isolate of the same species may be absent from such arrays. For instance, the gene content of any two isolates of the bacterial species Aggregatibacter actinomycetemcomitans might vary by as much as 20%. As a result, many of the genes identified in other isolates will not be present in an array created using gene annotation from a reference isolate. [[[36]](#endnote-36)]

**THE FUTURE OF DNA ARRAYS**

It would be much ideal to have an impartial way to directly quantify every DNA or RNA species present in a specific sample, given the limitations of arrays outlined above. With the probable exception of genotyping, next-generation sequencing technologies have now rendered sequencing cost-competitive with microarrays for all tests. This was not always the case. Sequencing provides numerous benefits over microarrays when the cost is comparable. The nucleic acids that are present in solution may be directly measured by sequencing. To determine the abundance of a certain sort of sequence, one need merely count the number of such sequences. The signal to noise ratio that may be produced by sequencing is solely constrained by the number of reads utilized for each sample, and counting sequences is linear with respect to concentration. [37] Using sequencing, one may fairly objectively determine which nucleic acids are present in solution. Sequencing is not dependent on knowledge of the possible nucleic acids present, unlike DNA arrays, even though sample preparation or different enzymes may bias the sequencing results. RNA editing, new splice forms, and closely similar gene sequences that may have gone undetected on DNA microarrays owing to cross hybridization can also be found independently by sequencing. These benefits, together with a drop in sequencing costs, have caused DNA arrays to be quickly replaced by sequencing for almost all analyses that were previously conducted on microarrays. Within the next five to ten years, sequencing techniques are projected to completely replace DNA arrays since the cost of sequencing is currently decreasing by a factor of two every five months. [[[37]](#endnote-37)]

**CONCLUSION**

This review has shed some light on the various steps of the microarray approach. Although there are now just a few commercial items available because of cost considerations, this technique's potential might grow as more commercial products become accessible. Understanding the notion of molecular biology is aided by the capability of gathering a huge number of historical samples and examining them for distinct genetic variants. The examination of illnesses of the mouth cavity has a lot of potential for DNA microchips. Our capacity to identify, stop, monitor, and treat patients will be significantly improved by the classifying oral disorders based on DNA, RNA, or protein profiles. Currently, research is the main usage of the DNA chip. Future dental practices will be significantly impacted by DNA microchips, which promise to deliver oral treatment that is considerably better, personalized, and bio-based.

**REFERENCE**

1. Ulyashova CE, Khalilova YI, Rubtsova CE, Edelstein CE, Alexandrova IА, Egorov CA.Acta Naturae. 2010 Jul;2(3):101-9.

2. Yu W, Ballif B C, Kashork C D, et al. Development of a comparative genomic hybridization microarray and demonstration of its utility with 25 well-characterized 1p36 deletions. Human Molecular Genetics, 2003, 12(17): 2145-2152.

3.Theisen A. Microarray-based comparative genomic hybridization (aCGH). Nature Education, 2008, 1(1): 45.

4. 4. Schena, M., Shalon, D., Davis, R.W. and Brown, P.O. (1995) Quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science*, **270**, 467–470

5.Zammatteo, N., Jeanmart, L., Hamels, S., Courtois, S., Louette, P., Hevesi, L. and Remacle, J. (2000) Comparison between different strategies of covalent attachment of DNA to glass surfaces to build DNA microarrays. *Anal Biochem*, **280**, 143–150.

6.Ishkanian, A.S., Malloff, C.A., Watson, S.K., DeLeeuw, R.J., Chi, B., Coe, B.P., Snijders, A., Albertson, D.G., Pinkel, D., Marra, M.A. et al. (2004) A tiling resolution DNA microarray with complete coverage of the human genome. *Nat Genet*, **36**, 299–303.

7.Lueking, A., Horn, M., Eickhoff, H., Bussow, K., Lehrach, H. and Walter, G. (1999) Protein microarrays for gene expression and antibody screening. *Anal Biochem*, **270**, 103–111.

8.Huang, R.P. (2001) Detection of multiple proteins in an antibody-based protein microarray system. *J Immunol Methods*, **255**, 1–13.

9.Huang, R.P., Huang, R., Fan, Y. and Lin, Y. (2001) Simultaneous detection of multiple cytokines from conditioned media and patient's sera by an antibody-based protein array system. *Anal Biochem*, **294**, 55–62.

10.Li, Y., Lee, H.J. and Corn, R.M. (2006) Fabrication and characterization of RNA aptamer microarrays for the study of protein-aptamer interactions with SPR imaging. *Nucleic Acids Res*, **34**, 6416–6424.

11.Lee, M. and Walt, D.R. (2000) A fiber-optic microarray biosensor using aptamers as receptors. *Anal Biochem*, **282**, 142–146.

12.Bradner, J.E., McPherson, O.M., Mazitschek, R., Barnes-Seeman, D., Shen, J.P., Dhaliwal, J., Stevenson, K.E., Duffner, J.L., Park, S.B., Neuberg, D.S. et al. (2006) A robust small-molecule microarray platform for screening cell lysates. *Chem Biol*, **13**, 493–504.

13.Wang, D., Liu, S., Trummer, B.J., Deng, C. and Wang, A. (2002) Carbohydrate microarrays for the recognition of cross-reactive molecular markers of microbes and host cells. *Nat Biotechnol*, **20**, 275–281.

14.Horlacher, T. and Seeberger, P.H. (2006) The utility of carbohydrate microarrays in glycomics. *Omics*, **10**, 490–498.

15.Velculescu, V.E., Zhang, L., Vogelstein, B. and Kinzler, K.W. (1995) Serial analysis of gene expression. *Science*, **270**, 484–487.

16.Ekins, R., Chu, F. and Biggart, E. (1990) Fluorescence spectroscopy and its application to a new generation of high sensitivity, multi-microspot, multianalyte, immunoassay. *Clin Chim Acta*, **194**, 91–114.

17.Ekins, R., Chu, F. and Biggart, E. (1990) Multispot, multianalyte, immunoassay. *Ann Biol Clin (Paris)*, **48**, 655–666.

18.Adey, N.B., Lei, M., Howard, M.T., Jensen, J.D., Mayo, D.A., Butel, D.L., Coffin, S.C., Moyer, T.C., Slade, D.E., Spute, M.K. et al. (2002) Gains in sensitivity with a device that mixes microarray hybridization solution in a 25-microm-thick chamber. *Anal Chem*, **74**, 6413–6417.

19.MacBeath, G. and Schreiber, S.L. (2000) Printing proteins as microarrays for high-throughput function determination. *Science*, **289**, 1760–1763.

20.Kafatos, F.C., Jones, C.W. and Efstratiadis, A. (1979) Determination of nucleic acid sequence homologies and relative concentrations by a dot hybridization procedure. *Nucleic Acids Res*, **7**, 1541–1552.

21.DeRisi, J.L., Iyer, V.R. and Brown, P.O. (1997) Exploring the metabolic and genetic control of gene expression on a genomic scale. *Science*, **278**, 680–686.

22.Iyer, V.R., Eisen, M.B., Ross, D.T., Schuler, G., Moore, T., Lee, J.C., Trent, J.M., Staudt, L.M., Hudson, J., Jr., Boguski, M.S. et al. (1999) The transcriptional program in the response of human fibroblasts to serum. *Science*, **283**, 83–87.

23.Cho, R.J., Campbell, M.J., Winzeler, E.A., Steinmetz, L., Conway, A., Wodicka, L., Wolfsberg, T.G., Gabrielian, A.E., Landsman, D., Lockhart, D.J. et al. (1998) A genome-wide transcriptional analysis of the mitotic cell cycle. *Mol Cell*, **2**, 65–73.

24.Spellman, P.T., Sherlock, G., Zhang, M.Q., Iyer, V.R., Anders, K., Eisen, M.B., Brown, P.O., Botstein, D. and Futcher, B. (1998) Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by microarray hybridization. *Mol Biol Cell*, **9**, 3273–3297.

25.Chu, S., DeRisi, J., Eisen, M., Mulholland, J., Botstein, D., Brown, P.O. and Herskowitz, I. (1998) The transcriptional program of sporulation in budding yeast. *Science*, **282**, 699–705.

26.Galitski, T., Saldanha, A.J., Styles, C.A., Lander, E.S. and Fink, G.R. (1999) Ploidy regulation of gene expression. *Science*, **285**, 251–254.

27.Perez-Diez, A., Morgun, A. and Shulzhenko, N. (2007) Microarrays for cancer diagnosis and classification. *Advances in experimental medicine and biology*, **593**, 74–85.

28.Venier, P., De Pitta, C., Pallavicini, A., Marsano, F., Varotto, L., Romualdi, C., Dondero, F., Viarengo, A. and Lanfranchi, G. (2006) Development of mussel mRNA profiling: Can gene expression trends reveal coastal water pollution? *Mutat Res*.

29.Stangegaard, M., Wang, Z., Kutter, J.P., Dufva, M. and Wolff, A. (2006) Whole genome expression profiling using DNA microarray for determining biocompatibility of polymeric surfaces. *Molecular Biosystems*, **2**, 421–428.

30.Stangegaard, M., Petronis, S., Jorgensen, A.M., Christensen, C.B. and Dufva, M. (2006) A biocompatible micro cell culture chamber (microCCC) for the culturing and on-line monitoring of eukaryote cells. *Lab Chip*, **6**, 1045–1051.

31.Tusher, V.G., Tibshirani, R. and Chu, G. (2001) Significance analysis of microarrays applied to the ionizing radiation response. *Proc Natl Acad Sci U S A*, **98**, 5116–5121.

32.Frey, B.J., Mohammad, N., Morris, Q.D., Zhang, W., Robinson, M.D., Mnaimneh, S., Chang, R., Pan, Q., Sat, E., Rossant, J. et al. (2005) Genome-wide analysis of mouse transcripts using exon microarrays and factor graphs. *Nat Genet*, **37**, 991–996.

33.Castoldi, M., Schmidt, S., Benes, V., Noerholm, M., Kulozik, A.E., Hentze, M.W. and Muckenthaler, M.U. (2006) A sensitive array for microRNA expression profiling (miChip) based on locked nucleic acids (LNA). *Rna*, **12**, 913–920.

34.Beuvink, I., Kolb, F.A., Budach, W., Garnier, A., Lange, J., Natt, F., Dengler, U., Hall, J., Filipowicz, W. and Weiler, J. (2007) A novel microarray approach reveals new tissue-specific signatures of known and predicted mammalian microRNAs. *Nucleic Acids Res*.

35.Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O. and Davis, R.W. (1996) Parallel human genome analysis: microarray-based expression monitoring of 1000 genes. *Proc Natl Acad Sci U S A*, **93**, 10614–10619.

36.Loftus, S.K., Chen, Y., Gooden, G., Ryan, J.F., Birznieks, G., Hilliard, M., Baxevanis, A.D., Bittner, M., Meltzer, P., Trent, J. et al. (1999) Informatic selection of a neural crest-melanocyte cDNA set for microarray analysis. *Proc Natl Acad Sci U S A*, **96**, 9277–9280.

37.Matsuzaki, H., Dong, S., Loi, H., Di, X., Liu, G., Hubbell, E., Law, J., Berntsen, T., Chadha, M., Hui, H. et al. (2004) Genotyping over 100,000 SNPs on a pair of oligonucleotide arrays. *Nat Methods*, **1**, 109–111.

38.Gunderson, K.L., Steemers, F.J., Lee, G., Mendoza, L.G. and Chee, M.S. (2005) A genome-wide scalable SNP genotyping assay using microarray technology. *Nat Genet*, **37**, 549–554.

39.Chou, W.H., Yan, F.X., Robbins-Weilert, D.K., Ryder, T.B., Liu, W.W., Perbost, C., Fairchild, M., de Leon, J., Koch, W.H. and Wedlund, P.J. (2003) Comparison of two CYP2D6 genotyping methods and assessment of genotype-phenotype relationships. *Clin Chem*, **49**, 542–551.

40.Gemignani, F., Perra, C., Landi, S., Canzian, F., Kurg, A., Tonisson, N., Galanello, R., Cao, A., Metspalu, A. and Romeo, G. (2002) Reliable detection of beta-thalassemia and G6PD mutations by a DNA microarray. *Clin Chem*, **48**, 2051–2054.

41.Kallioniemi, A., Kallioniemi, O.P., Sudar, D., Rutovitz, D., Gray, J.W., Waldman, F. and Pinkel, D. (1992) Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. *Science*, **258**, 818–821.

42.Fiegler, H., Redon, R., Andrews, D., Scott, C., Andrews, R., Carder, C., Clark, R., Dovey, O., Ellis, P., Feuk, L. et al. (2006) Accurate and reliable high-throughput detection of copy number variation in the human genome. *Genome Res*, **16**, 1566–1574.

43.Pollack, J.R., Perou, C.M., Alizadeh, A.A., Eisen, M.B., Pergamenschikov, A., Williams, C.F., Jeffrey, S.S., Botstein, D. and Brown, P.O. (1999) Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *Nat Genet*, **23**, 41–46.

44.Barrett, M.T., Scheffer, A., Ben-Dor, A., Sampas, N., Lipson, D., Kincaid, R., Tsang, P., Curry, B., Baird, K., Meltzer, P.S. et al. (2004) Comparative genomic hybridization using oligonucleotide microarrays and total genomic DNA. *Proc Natl Acad Sci U S A*, **101**, 17765–17770.

45.Pinkel, D. and Albertson, D.G. (2005) Array comparative genomic hybridization and its applications in cancer. *Nat Genet*, **37 Suppl**, S11–17.

46.Redon, R., Ishikawa, S., Fitch, K.R., Feuk, L., Perry, G.H., Andrews, T.D., Fiegler, H., Shapero, M.H., Carson, A.R., Chen, W. et al. (2006) Global variation in copy number in the human genome. *Nature*, **444**, 444–454.

47.Ren, B., Robert, F., Wyrick, J.J., Aparicio, O., Jennings, E.G., Simon, I., Zeitlinger, J., Schreiber, J., Hannett, N., Kanin, E. et al. (2000) Genome-wide location and function of DNA binding proteins. *Science*, **290**, 2306–2309.

48.Malanoski, A.P., Lin, B., Wang, Z., Schnur, J.M. and Stenger, D.A. (2006) Automated identification of multiple micro-organisms from resequencing DNA microarrays. *Nucleic Acids Res*, **34**, 5300–5311.

49.Lin, B., Wang, Z., Vora, G.J., Thornton, J.A., Schnur, J.M., Thach, D.C., Blaney, K.M., Ligler, A.G., Malanoski, A.P., Santiago, J. et al. (2006) Broad-spectrum respiratory tract pathogen identification using resequencing DNA microarrays. *Genome Res*, **16**, 527–535.

50.Lin, B., Blaney, K.M., Malanoski, A.P., Ligler, A.G., Schnur, J.M., Metzgar, D., Russell, K.L. and Stenger, D.A. (2007) Using a resequencing microarray as a multiple respiratory pathogen detection assay. *J Clin Microbiol*, **45**, 443–452.

51.Chee, M., Yang, R., Hubbell, E., Berno, A., Huang, X.C., Stern, D., Winkler, J., Lockhart, D.J., Morris, M.S. and Fodor, S.P. (1996) Accessing genetic information with high-density DNA arrays. *Science*, **274**, 610–614.

52.Wang, D.G., Fan, J.B., Siao, C.J., Berno, A., Young, P., Sapolsky, R., Ghandour, G., Perkins, N., Winchester, E., Spencer, J. et al. (1998) Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome. *Science*, **280**, 1077–1082.

53.Ziauddin, J. and Sabatini, D.M. (2001) Microarrays of cells expressing defined cDNAs. *Nature*, **411**, 107–110.

54.Palmer, E.L., Miller, A.D. and Freeman, T.C. (2006) Identification and characterisation of human apoptosis inducing proteins using cell-based transfection microarrays and expression analysis. *BMC Genomics*, **7**, 145.

55.Ramachandran, N., Hainsworth, E., Bhullar, B., Eisenstein, S., Rosen, B., Lau, A.Y., Walter, J.C. and LaBaer, J. (2004) Self-assembling protein microarrays. *Science*, **305**, 86–90.

56.Bruun, G.M., Wernersson, R., Juncker, A.S., Willenbrock, H. and Nielsen, H.B. (2007) Improving comparability between microarray probe signals by thermodynamic intensity correction. *Nucleic Acids Res*.

57.Dufva, M. (2005) Fabrication of high quality microarrays. *Biomol Eng*, **22**, 173–184.

58.Moorcroft, M.J., Meuleman, W.R., Latham, S.G., Nicholls, T.J., Egeland, R.D. and Southern, E.M. (2005) In situ oligonucleotide synthesis on poly(dimethylsiloxane): a flexible substrate for microarray fabrication. *Nucleic Acids Res*, **33**, e75.

59.Southern, E.M., Case-Green, S.C., Elder, J.K., Johnson, M., Mir, K.U., Wang, L. and Williams, J.C. (1994) Arrays of complementary oligonucleotides for analysing the hybridisation behaviour of nucleic acids. *Nucleic Acids Res*, **22**, 1368–1373.

60.Fodor, S.P., Read, J.L., Pirrung, M.C., Stryer, L., Lu, A.T. and Solas, D. (1991) Light-directed, spatially addressable parallel chemical synthesis. *Science*, **251**, 767–773.

61.Ohyama, H., Zhang, X., Kohno, Y., Alevizos, I., Posner, M., Wong, D.T. and Todd, R. (2000) Laser capture microdissection-generated target sample for high-density oligonucleotide array hybridization. *Biotechniques*, **29**, 530–536.

62.Gilbert, M.T., Haselkorn, T., Bunce, M., Sanchez, J.J., Lucas, S.B., Jewell, L.D., Van Marck, E. and Worobey, M. (2007) The isolation of nucleic acids from fixed, paraffin-embedded tissues-which methods are useful when? *PLoS ONE*, **2**, e537.

63.Chomczynski, P. and Sacchi, N. (1987) Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal Biochem*, **162**, 156–159.

1. Aaronson, J.S., Eckman, B., Blevins, R.A., Borkowski, J.A., Myerson, J., Imran, S., and Elliston, K.O. 1996. Toward the development of a gene index to the human genome: An assessment of the nature of high-throughput EST sequence data. Genome Res. 6:829-845. [↑](#endnote-ref-1)
2. Ulyashova CE, Khalilova YI, Rubtsova CE, Edelstein CE, Alexandrova IА, Egorov CA.Acta Naturae. 2010 Jul;2(3):101-9. [↑](#endnote-ref-2)
3. Chrisey, L.A., Lee, G.U., and O’Ferrall, C.E. 1996. Covalent attachment of synthetic DNA to selfassembled monolayer films. Nucleic Acids Res. 24:3031-3039. [↑](#endnote-ref-3)
4. Lashkari, D.A., DeRisi, J.L., McCusker, J.H., Namath, A.F., Gentile, C., Hwang, S.Y., Brown, P.O., and Davis, R.W. 1997. Yeast microarrays for genome wide parallel genetic and gene expression analysis. Proc. Natl. Acad. Sci. U.S.A. 94:13057-13062 [↑](#endnote-ref-4)
5. Pease, A.C., Solas, D., Sullivan, E.J., Cronin, M.T., Holmes, C.P., and Fodor, S.P.A. 1994. Light generated oligonucleotide arrays for rapid DNA sequence analysis. Proc. Natl. Acad. Sci. U.S.A. 91:5022-5026 [↑](#endnote-ref-5)
6. Wallraff, G., Labadie, J.L., Brock, P., Dipietro, R., Nguyen, T., Huynh, T., Hinsberg, W., McGall, G. 1997. DNA sequencing on a chip. Chemtech 27:22-32 [↑](#endnote-ref-6)
7. Miller, J.K. and Barnes, W.M. 1986. Colony probing as an alternative to standard sequencing as a means of direct analysis of chromosomal DNA to determine the spectrum of single-base changes in regions of known sequence. Proc. Natl. Acad. Sci. U.S.A. 83:1026-1030 [↑](#endnote-ref-7)
8. Hacia, J.G., Brody, L.C., Chee, M.S., Fodor, S.P., and Collins, F.S. 1996. Detection of heterozygous mutations in BRCA1 using high density oligonucleotide arrays and two-colour fluorescence analysis. Nat. Genet. 14:441-447. [↑](#endnote-ref-8)
9. Humphries, P., Cochet, M., Krust, A., Gerlinger, P., Kourilsky, P., and Chambon, P. 1977. Molecular cloning of extensive sequences of the in vitro synthesized chicken ovalbumin structural gene. Nucleic Acids Res. 4:2389-2406. [↑](#endnote-ref-9)
10. Schena M, Davis RW. 1999. Genes, genomes, and chips. See Ref. 85, 1:1–15 [↑](#endnote-ref-10)
11. Theriault TP, Winder SC, Gamble RC. 1999. Application of ink-jet printing technology to the manufacture of molecular arrays. See Ref. 85, 6:101–19 [↑](#endnote-ref-11)
12. Zhang N, Tan H, Yeung ES. 1999. Automated and integrated system for highthroughput DNA genotyping directly from blood. Anal. Chem. 71:1138–45. [↑](#endnote-ref-12)
13. Sosnowski R, Tu E, Butler W, O’Connell J, Heller MJ. 1997. Rapid determination of single base mismatch mutations in DNA hybrids by direct electric field control. Proc. Natl. Acad. Sci. 94:1119–23 [↑](#endnote-ref-13)
14. Gunderson KL, Huang XC, Morris MS, Lipshutz RJ, Lockhart DJ, Chee MS. 1998. Mutation detection by ligation to complete n-mer DNA arrays. Genome Res. 8:1142–53 [↑](#endnote-ref-14)
15. Boone TD, Hooper HH, Soane DS. 1998. Integrated chemical analysis on plastic microfluidic devices. Solid State Sens. Actuator Workshop Proc., Hilton Head Island, pp. 87–92 [↑](#endnote-ref-15)
16. Weindruch R, Kayo T, Lee CK, Prolla TA. 2001. Microarray profiling of gene expression in aging and its alteration by caloric restriction in mice. J. Nutr. 131(3): 918S–23 [↑](#endnote-ref-16)
17. Kallioniemi OP. 2001. Biochip technologies in cancer research. Ann. Med. 33(2): 142–47 [↑](#endnote-ref-17)
18. Polyak K, Riggins GJ. 2001. Gene discovery using the serial analysis of gene expression technique: implications for cancer research. J. Clin. Oncol. 19(11):2948– 58. [↑](#endnote-ref-18)
19. Lewohl JM, Dodd PR, Mayfield RD, Harris RA. 2001. Application of DNA microarrays to study human alcoholism. J. Biomed. Sci. 8(1):28–36 [↑](#endnote-ref-19)
20. Benoit GR, Tong JH, Balajthy Z, Lanotte M. 2001. Exploring (novel) gene expression during retinoid-induced maturation and cell death of acute promyelocytic leukemia. Semin. Hematol. 38(1):71–85 [↑](#endnote-ref-20)
21. . Grouse LH, Munson PJ, Nelson PS. 2001. Sequence databases and microarrays as tools for identifying prostate cancer biomarkers. Urology 57(4 Suppl 1):154–59 [↑](#endnote-ref-21)
22. Becich MJ. 2000. The role of the pathologist as tissue refiner and data miner: the impact of functional genomics on the modern pathology laboratory and the critical roles of pathology informatics and bioinformatics. Mol. Diagn. (4):287–99 [↑](#endnote-ref-22)
23. McGall GH, Barone D, Diggelmann M, Fodor SPA, Gentalen E, Ngo N. 1997. The efficiency of light-directed synthesis of DNA arrays on glass substrates. J. Am. Chem. Soc. 119:5081–90 [↑](#endnote-ref-23)
24. Radtkey R, Feng L, Muralhidar M, Duhon M, Canter D, et al. 2000. Rapid high fidelity analysis of simple sequence repeats on an electronically active DNA microchip. Nucleic Acids Res. 28:E17 [↑](#endnote-ref-24)
25. Weedn VW, Hicks JW. 1997. The unrealized potential of DNA testing. Natl. Inst. Justice J. 234:16–23 [↑](#endnote-ref-25)
26. Prosnyak MI, Veselovskaya SI, Efremova EJ, Potapov VK, Limborska SA, Sverdlov ED. 1994. Substitution of 2-aminoadenine and 5-methylcytosine for adenine and cytosine in hybridization probes increases the sensitivity of DNA fingerprinting. Genomics 21:490–94 [↑](#endnote-ref-26)
27. Okamoto T, Suzuki T, Yamamoto N. 2000. Microarray fabrication with covalent attachment of DNA using bubble jet technology. Nat. Biotechnol. 18(4):438– 41 [↑](#endnote-ref-27)
28. Diehl F, Grahlmann S, Beier M, Hoheisel JD. 2001. Manufacturing DNA microarrays of high spot homogeneity and reduced background signal. Nucleic Acids Res. 29(7):E38 [↑](#endnote-ref-28)
29. Fodor SP, Read JL, Pirrung MC, Stryer L, Lu AT, Solas D. 1991. Light-directed, spatially addressable parallel chemical synthesis. Science 251:767–7 [↑](#endnote-ref-29)
30. Lockhart DJ, Solas D, Sullivan EJ, Cronin MT, Holmes CP, Fodor, SA. 1996. Expression monitoring by hybridization to high-density oligonucleotide arrays. Nat. Biotechnol. 14:1675–80 [↑](#endnote-ref-30)
31. Gunderson KL, Huang XC, Morris MS, Lipshutz RJ, Lockhart DJ, Chee MS. 1998. Mutation detection by ligation to complete n-mer DNA arrays. Genome Res. 8:1142–53 [↑](#endnote-ref-31)
32. Diehn M, Relman DA. 2001. Comparing functional genomic datasets: lessons from DNA microarray analyses of host-pathogen interactions. Curr. Opin. Microbiol. 4(1):95–101 [↑](#endnote-ref-32)
33. Weindruch R, Kayo T, Lee CK, Prolla TA. 2001. Microarray profiling of gene expression in aging and its alteration by caloric restriction in mice. J. Nutr. 131(3): 918S–23 [↑](#endnote-ref-33)
34. .Southern, E.M., Case-Green, S.C., Elder, J.K., Johnson, M., Mir, K.U., Wang, L. and Williams, J.C. (1994) Arrays of complementary oligonucleotides for analysing the hybridisation behaviour of nucleic acids. *Nucleic Acids Res*, **22**, 1368–1373. [↑](#endnote-ref-34)
35. Kallioniemi OP. 2001. Biochip technologies in cancer research. Ann. Med. 33(2): 142–47 [↑](#endnote-ref-35)
36. Thompson M, Furtado LM. 1999. High density oligonucleotide and DNA probe arrays for the analysis of target DNA. Analyst 124(8):1133–36 [↑](#endnote-ref-36)
37. Stewart DJ. 2000. Making and using DNA microarrays: a short course at Cold Spring Harbor Laboratory. Genome Res. 10(1):1– 3 [↑](#endnote-ref-37)