Review of dna and protein microarray for biomems technology

In recent years increase in genetically caused diseases is one of the major threat to mankind. Some of the genetically caused diseases are down syndrome, diabetes, obesity, sickle cell anemia, cystic fibrosis. This review paper explains how BioMEMS (Biological MicroElectroMechanicalSystem) technology used in microarrays and finding of gene expression which leads to medicine for particular diseases. BioMEMS research has been acquiring importance, due to the possibility of exploiting miniaturization to create new opportunities in medicine. BioMEMS systems in general have more diversity of materials and function than conventional MEMS devices. In BioMEMS ink-jet printing, photolithography techniques were introduced to deposit protein and DNA in array. DNA and protein micro-arrays based BioMEMS could be very extensively for rapid detection, drug discovery, and screening, especially when combined with integrated micro-fluidics and sensitive detection technologies. The techniques used to define patterns on semiconductor surfaces were utilized to construct arrays of single-stranded DNA. Once single strands of known sequences (capture probes) are placed at specific known sites on a chip surface, hybridization with molecules of unknown sequence (target probes) can reveal the sequence. Microarray-based gene expression profiling can be used to identify genes whose expression is changed in response to disease caused genetically by comparing gene expression in infected to that in uninfected cells or tissues. Protein and antibody arrays can play a key role in search for disease-specific proteins that have medical, diagnostic, prognostic, and commercial potential as disease markers or as drug targets and for determination of predisposition to specific disease via genotypic screening. Array-based integrated chips and micro-fluidics hold a great potential for the development of high-throughput

approaches to systematically analyze these proteins and to assign a biological function, determine protein-protein and protein-DNA interactions. This paper tells about varies applications of BioMEMS to detect the defective gene the causes diseases and the fabrication methods used in microarrays chip production.

Keywords: LOC ‘ Lab-on-a-chip’, BioMEMS (Biological MicroElectroMechanicalSystem), Î¼TAS (Micro Total Analysis System), Oligonucleotide, Microdroplets , Electrospray.

1. Introduction

Microarray technology has been applied to study of gene expression to study mechanisms of diseases and to accelerate the drug discovery process. There is a definite trend towards increasing the use of molecular diagnostic methods, and biochip technologies, along with bioinformatics techniques. Classification of human disease using microarrays is considered to be important. The emphasis is not only on diagnosis but also on disease management, including monitoring the effect of treatment and determining prognosis [1]. Microarray and lab-on-a-chip systems are going to fulfill these new requirements, including the miniaturization of biological assays as well as the parallelization of analysis. Although the concept has been performed by miniaturizing the analytical equipments, the technology comes from the microeletromechanical and microelectronics industries [2]. ‘ Lab-on-a-chip’ technology is the method of choice to integrate processes and reaction and scale them down from conventional glassware to microfluidics, involving micro-sized channels in glass or polymer chips [3]. DNA microarray also knows as DNA chips, comprise a new technology emerging at a tremendous

pace because of its power, flexibility, sensitivity and relative simplicity [4]. BioMEMS for proteomics can be divided into LOC device for specific tasks such as protein isolation, purification, digestion, and separation; and microarray device for high throughput study of protein abundance and function. An emergence of DNA, protein microarray has emerged over the last few years with commercial potential beyond the confines of the research laboratory [5]. In this paper we start our discussion with the history of microarray; subsequently we go into the details of general techniques used in DNA and protein microarray followed by fabrication and the application and future of microarray.

2. History of Microarray

Microarray technology evolved from Southern blotting, where fragmented DNA is attached to a substrate and then probed with a known gene or fragment [6]. The first reported use of this approach was the analysis of 378 arrayed lysed bacterial colonies each harboring a different sequence which were assayed in multiple replicas for expression of the genes in multiple normal and tumor tissue [7]. These early gene arrays were made by spotting cDNA onto filter paper with a pin-spotting device. The use of miniaturized microarray for gene expression profiling was first reported in 1995 [8]. This technology allowed scientists to analyze thousands of mRNAs in a single experiment to determine whether expression is different in disease state. Unfortunately, mRNA levels within a cell are often poorly correlated with actual protein abundance [9]. A complete eukaryotic genome on a microarray was published in 1997[10]. The development of biochip has a long history, starting with early work on the underlying sensor technology. In

1953, Watson and Crick announced their discovery of now familiar double helix structure and sequencing techniques by Gilbert and Sanger in 1977 [11, 12]. Two additional developments enable the technology used in modern DNA-based biosensors. First, in 1983 Kary Mullis invented the polymerase chain reaction (PCR) technique, a method for amplifying DNA concentration. This discovery made possible the detection of extremely small quantities of DNA in samples. Second, in 1986 Hood and co-workers devised a method to label DNA molecules with fluorescent tags instead of radiolables, thus enabling hybridization experiments to be observed optically [13]. A big boost in research and commercial interest came in the mid 1990's, when Î¼TAS (Micro Total Analysis System) technology turned out to provide interesting tooling for genomics application, like capillary electrophoresis and DNA microarray [14]. Immunoassays, the precursor to protein chips available since the 1980s, exploit the interactions between antibodies and antigens in order to detect their concentrations in biology sample. Their creation, however, is tedious and expensive. As to this, research at Harvard University combined the technology of immunoassays and DNA microarray to develop the protein chip [15].

3. DNA Microarrays and Fabrication

3. 1 Introduction

Microarray analysis allows simultaneous of gene and gene products, including DNA, mRNA and proteins. There are basically two formats: cDNA microarrays and oligonucleotide microarrays. A cDNA microarray is an orderly arrangement of DNA probe " spot" printed onto a solid matrix such as glass, nylon, or silicon. The substrate is usually less than 4Ã-4 cm, while

the spot size is less than 250Î¼m. A DNA molecular probe is tethered (embedded and immobilized) to each spot on microarray. surface modification of the substrate, such as wit poly-L-lysin or silane, facilitates adhesion of the DNA probes. Hybridization is the base pairing between target and the probe, and is limited by the sensitivity and specificity of the microarray. There are three basic types of oligonucleotide microarrays: gene expression, genotyping (SNPs), and resquencing. Genomic DNA may be used for the study of SNPs, while expressed DNA sequence (cDNA clones, expressed sequence tags or ESTs) are used for gene expression [17].

3. 2 Microarrays for Gene Expression

Gene expression microarrays are tools that tell how much RNA (if any) a gene is making. Since 1977, and prior to microarray, only a few genes could be studied at a time using the northern blot analysis. GeneChip (Fig. 1. 1) microarrays use the natural chemical attraction, or hybridization, between DNA on the array and RNA target molecule from the sample based on complementary base pairs. Only RNA target molecule that have exact complementary base pair bind to the prob. Gene expression detection microarray is that they are able to measure tens of thousands of genes at a time, and it is this quantitative change in the scale of gene measurement that has led to a qualitative change in our ability to understand regulatory processes that occur at the cellular level. It is possible to obtain near comprehensive expression data for individual tissues or organs in various states. Compressions are possible for transcriptional activity across different tissue, and group of patients with and without a particular disease or with two different diseases. Microarray studies are designed in principle to

directly measure the activity of the genes involved in particular mechanism or system rather than their association with a particular biological or clinical feature [18]. Although genes may be thousand of base pairs long, it is only necessary to construct a probe of 25 bases that represent a unique complementary portion of the target gene. In other words, the short probe on the microarray measures the expression of the complete gene by sampling only a small section of the gene. In some instances, as little as one RNA molecule out of 100, 000 different RNAs in an original sample may be detected [19].

Sensitivity is the ability to identify the rarely expressed transcripts in a complex background. Specification is the ability to discern between different family members. The hybridization efficiency of two nucleic acid strand depends on

1) Sequence-dependent factors for length, extent of complementarity, and overall base composition;

2) Sequence independent factors such as the concentration of the probe and target, time, temperature, cation concentration, valency character, pH, dielectric and chaotropic medica, surface characteristics of the solid, and density spacing of the probe molecules; and

3) Sample-dependent complex background signal, which are probes interacting with the wrong complementary sequence [20].

Fig 1. 1 GeneChip probe microarray cartridge (Image courtesy of Affmetrix)

3. 3 Microarray for SNPs

Small difference in a DNA sequence can have major impact on health. Deletions, insertions, and other mutations of as little as a single base pair may result in signification disease. Identification these mutations require determining the exact sequence for thousand of SNPs distributed throughout the genome. Using microarray, it is possible to scan the whole genome and look for genetic similarities among a group of people who share the same disease. Using microarray to genotype 10, 000 to 100, 000 SNPs, it is possible to identify the gene or group of genes that contribute to disease. For example, if a large group of people with a given diagnosis have several SNPs in common, but not healthy people, then mutations may be looked for within those SNPs. A genotyping microarray may look for up to 100, 000 SNPs or more [21].

3. 4 Fabrication

DNA “ spotting” may be accomplished by depositing PCR amplified ESTs (500-5000 base pairs), or by in suit synthesis of oligodeoxynucleotide sequences (20-50 base pairs) on the substrate. There are variety of spotting techniques that include mechanical and ink-jet style application.

The GeneChip brand arrays provide high levels of reproducibility, sensitivity, and specification. The following process steps are used for fabrication of the GeneChip:

1) GeneChip probe array are manufactured through a combination of photolithography (Fig 1. 2) and combinatorial chemistry. With a calculated minimum number of synthesis steps, GeneChip technology produce array with hundreds of thousands of different probes packed at an extremely high density. Small sample volumes are required for study. Manufacture is scalable because the length of the probe, not their number, determines the number of synthesis steps required.

2) Manufacturing begins with a 5-in square quartz wafer. Initially the quartz is washed to ensure uniform hydroxylation across its surface. Because quarts is naturally hydroxylated, it provides an excellent substrate for the attachment of chemical, such as linker molecules, that are later used to position the probes on the arrays.

Fig 1. 2 Photolithographic technique are used to locate and add nucleotides for fabrication of array of probe (Image courtesy of Affymetrix)

3) The wafer is placed in a bath of silane, which reacts with hydroxyl groups of quartz, and forms a matrix of covalently linked molecules. This distance between these silane determines the probes' packing density, allowing array to hold over 500, 000 probe location, or features, within a mere 1. 28cm2. Each of these features harbors millions of identical DNA molecules. The silane film provides a uniform hydroxyl density to initiate probe assembly. Linker molecules, attached to the silane matrix, provide a surface that may be spatially activated by light (Fig 1. 3).

4) Probe synthesis occurs in parallel, resulting in the addition of an A, C, T or G nucleotide to multiple growing chains simulataneously. To define which oligonucleotide chains will receive a nucleotide in each step, photolithographic masks, carrying 18 to 20 Î¼m2 windows that corresponds to the dimensions of individual features, are placed over the coated wafer. The windows are distributed over the mask based on the desired sequence each. When the UV light is shone over the mask in the first step of synthesis, the exposed linkers become deprotected and are available for nucleotide coupling. critical to this step is the precise alignment of the mask with the wafer before each synthesis step. To ensure that this critical step is accurately completed, chrome marks on the wafer and on the mask are perfectly aligned.

5) Once the desired features have been activated, a solution containing a single type of deoxynucleotide with a removable protection group is flushed over the wafer’s surface. The nucleotide attaches to the activated linkers, initiating the synthesis process.

6) Although the process is highly efficient, some activated molecules fail to attach the new nucleotide. To prevent these “ outliers” from becoming probes with missing nucleotides, a capping step is used to truncate them. In additional, the side chains of the nucleotides are protected to prevent the formation of branched oligonucleotides.

Fig 1. 3 GeneChip fabrication steps (Image courtesy Affmetrix).

7) In the next synthesis step, another mask is placed over the wafer to allow the next round of deprotection and coupling. The process is repeated until the probes reach their full length, usually 25 nucleotides.

8) Although each position in the sequence of an oligonucleotide can be occupied by one of four nucleotides, resulting in an apparent need for 24Ã-4, or 100, different masks per wafer, the synthesis process can be designed to significantly reduce this requirement. Algorithms that help minimize mask usage calculate how to best coordinate probe growth by adjusting synthesis rates of individual probes and identifying situations when the same mask can be multiple times.

9) Once the synthesis is completed, the wafer are deprotected and diced, and the resulting individual arrays are picked and packed in flowcell cartridges. Depending on the number of probe features per array, a single wafer can yield between 49 and 400 arrays.

10) The manufacturing process ends with a comprehensive series of quality control tests. Additional, a sampling of array from every wafer is used to test the batch by running control hybridizations. A quantitative test of hybridization is also performed using standardized control probes [22].

3. 5 Microarray Data Analysis

Data filtration is performed by selecting threshold pixel intensity; and 2-, 5-, or 10- fold difference between the samples. Different genes with an identical profile may represent a coordinate response to a stimulus. Genes with

opposite profiles may represent repression. To compare expression profiles it is necessary to define a set of metrics, or operations that return a value that is proportional in some way to the similarities or difference between two expression profiles. The most commonly used metrics are Euclidean distance and Pearson coefficient of correlation [23].

3. 5. 1 Euclidean Distance

Two or more profile of each of two genes are compared as a mathematical matrix operation of n-dimensional space, where n is the number of expression patterns available. The Euclidean distance is the square root of the summation of the difference between all pairs of corresponding values. For two genes the distance is as follows:

Where

d is the distance,

e1 is the expression pattern of gene1,

e2 is the expression pattern of gene 2, and

i is the element of the expression profile:

Gene1 (e11, e12, …., e1n) and gene1 (e21, e22, …., e2n).

3. 5. 2 Pearson Correlation Coefficient

The Pearson correlation coefficient (r) gives a value of from -1 to 1, and closer to 1 (negative and positive correlation, respectively). The closer two profiles have the same expression, the closer the value will be to 1:

Where and Sen are the mean and typical deviation of all of the point of the nth profile, respectively.

4. Protein Microarray and Fabrication

4. 1 Introduction

Protein microarrays are becoming an important tool in proteomics, drug discovery programs, and diagnostics [24]. The amount of information obtained from small quantities of biological samples is significantly increased in the microarray format. This feature is extremely valuable in protein profiling, where samples are often limited in supply and unlike DNA, cannot be amplified [25]. Protein microarrays are more challenging to prepare than are DNA chips [26] because several technical hurdles hamper their application. The surfaces typically used with DNA are not easily adaptable to proteins, owing to the biophysical differences between the two classes of bioanalytes [27]. Arrayed protein must be immobilized in a native conformation to maintain their biological function. Unfortunately, proteins tend to unfold when immobilized onto a support so as to allow internal hydrophobic side chains to from hydrophobic bonds with the solid surface [28]. Surface chemistry, capture agents, and detection methods take on special significance in developing microarrays. Microarrays consist of microscopic target spots, planer substrates, rows and columns of elements, and probe molecules in solution. Each protein assessed by a microarray should be the same as the partial concentration of each protein in the biological extract [29]. The past ten years have witnessed a fascinating growth in the field of large-scale and high-throughput biology, resulting in a new era of technology development and the collection and analysis of

information. The challenges ahead are to elucidate the function of every encoded gene and protein in an organism and to understand the basic cellular events mediating complex processes and those causing diseases [30-33]. Protein are more challenging to prepare for the microarray format than DNA, and protein functionality is often dependent on the state of proteins, such as post-translational modification, partnership with other proteins, protein subcellular localization, and reversible covalent modification (e. g. phosphorylation). Nonetheless, in recent years there have been considerable achievements in preparing microarray containing over 100 proteins and even an entire proteome [34-36]. Randox Laboratories Ltd. Launched Evidence, the first protein Biochip Array Technology analyzer in 2003. In protein Biochip Array Technology, the biochip replaces the ELISA (Enzyme-linked immunosorbent assay) plate or cuvette as the reaction platform. The biochip is used to simultaneously analyze a panel of related tests in a single sample, producing a patient profile. The patient profile can be used in disease screening, diagnosis, monitoring disease progression or monitoring treatment (wiki Biochip). Protein expression profiling, protein-protein binding, drug interaction, protein folding, substrate specificity, enzymatic activity, and the interaction between protein and nucleic acids are among the application of protein microarrays.

Abundance-based microarray, including capture microarray and reverse-phase protein blots, measure the abundance of specific biomolecules using well defined and high specific analyte-specific reagents (ASRs). Different classes of molecules can act as capture molecules in microarray assays,

including antigen-antibody, protein -protein, aptamer-ligand, enzyme-substrate, and receptor-ligand [37].

4. 2 Spotting

In situ synthesis of protein microarrays as done for DNA microarrays is impractical. Other forms of delivery-based technology must be incorporated. One-drop-at-a-time (microspotting) techniques including use of pins, quills or hollow needles that repeatedly touch the substrate surface depositing one spot after the next in an array format; shooting microdroplets from a ejector similar to ink-jet printing; and depositing charged submicron-sized droplets by electrospray deposition (ESD). Alternatively, parallel techniques such as microcontact printing (Î¼CP), digital ESD, and photolithographic controlled protein adsorption can be used. Currently, micospotting by robotic techniques has greater use in the research setting, whereas parallel techniques offer cost saving for mass production for commercial use [38].

4. 3 Microcontact printing (Î¼CP)

In microcontact printing stamps are typically made from a silicon elastomer and used to make a microarray of spots with feature size from 0. 01 to 0. 1Î¼m. Steps for stamping include the following [38]:

1) Activation of the stamp surface to increase hydrophilicity or to introduce grups for inking to target molecules such as antibodies, protein A, or streptavidin.

2) Direct adsorption of protein molecules or their binding to capture molecules over a period of 0. 5-1 hours.

3) Rinsing.

4) Drying in a nitrogen stream for about a minute.

5) Pressing the stamp against a suitable substrate for about a minute to allow transfer of the semidry materials.

Disadvantages include poor control of the amount of materials transferred, small amount of deposited materials, and possible changes in protein function. Microarrays containing up three different proteins were fabricated by Î¼CP technique and tested as a detection system for specific antibodies [39]. Immunoassay were successfully performed using the patterned protein microarrays, and were characterized by fluorescence microscopy and scanning- probe microscopy. The characterization revealed the quality of the protein deposition and indicated a high degree of selectivity for the targeted antigen-antibody interaction.

4. 3 Electrospray Deposition (ESD)

The basic physics underlying the newly emerging technique of electrospray deposition (ESD) as applied to biological macromolecules. Fabrication of protein films and microarrays are considered as the most important applications of this technology. All the major stages in the ESD process (solution electrification, formation of a cloud of charged microdroplets, transformation of microdroplets into ions and charged clusters, deposition, and neutralization) are discussed to reveal the physical processes involved, such as space charge effects, dissipation of energy upon landing and neutralization mechanisms [40]. In electrospray deposition, protein is transferred from the glass capillary positioned 130-350 Î¼m above a

conducting surface. Micro-sized charged droplets move in an electric field created by the difference in electric field potential between the tip and the substrate surface and by the spatial charge of the droplet cloud. The electrostatic repulsion expands the cloud, and microdroplets are deposited as a round spot. The spot density is greater at the center [38].

Two new techniques were recently developed in these laboratories for fabrication of protein microarrays: electrospray deposition of dry proteins and covalent linking of proteins from dry deposits to a dextran-grafted surface. Here we apply these techniques to simultaneously fabricate 1200 identical microarrays. Each microarray, 0. 6 Ã- 0. 6 mm2 in size, consists of 28 different protein antigens and allergens deposited as spots, 30âˆ’40 Î¼m in diameter. Electrospray deposition (ESD) of dry protein and covalent linking of proteins from dry deposits to a dextran-grafted surface has been studied from fabrication of microarrays. Electrospray (ES) deposition has been applied to fabricate protein microarrays for immunochemical assay. Protein antigens were deposited as arrays of dry spots on a surface of aluminized plastic. Deposition was performed from water solutions containing a 10-fold (w/w of dry protein) excess of sucrose. Upon contact with humid air, the spots turn into microdroplets of sucrose/protein solution from which proteins were either adsorbed or covalently linked to clean or modified aluminum surfaces. It was found that covalent binding of antigens via aldehyde groups of oxidized branched dextran followed by reduction of the Schiff bonds gives the highest sensitivity and the lowest background in microarray-based ELISA, as compared to other tested methods of antigen immobilization [41].

Protein microarray with an antibody-based protein array for high-throughput immunoassay, with an ESD method using a quartz mask with holes made by an abrasive jet technique, has been performed. An antibody solution was electrosprayed onto an ITO glass, and then antibodies were deposited and cross-linked with a vapor of glutaraldehyde. The dimeters of the spots were approximately 150 Î¼m. The arrays were then incubated with corresponding target antigenic molecules and washed. The captured antigens were collectively detected by fluorescence and chemiluminescence. The signals were quantitatively visualized with a high-resolution CCD [42].

4. 4 Surface immobilization

In many proteomics applications, one is interested in the facile and covalent immobilization of protein molecules without the use of any special tag or chemical modification. This is most conveniently achieved via chemical reactivity towards the commonly available -NH2 groups on the surface of protein molecules. One of the most efficient leaving groups towards -NH2 is N-hydroxysuccinimide (NHS) attached via an ester bond. We have developed an NHS surface based on the zero background PEG coating. It allows for fast immobilization reactions with the remaining NHS groups easily washed off to expose the zero background PEG coating (Fig 1. 4). In subsequent assays, the PEG functionality ensures that binding of particular molecules to the surface is only through the specific interaction with the immobilized protein molecule and the commonly seen background problem is solved without the need of a blocking step.

Fig 1. 4 NHS activated surfaces for the immobilization of proteins, peptides, & antibodies (Image courtesy: ZeroBkg®)

Peptide and protein microarrays fabricated on NHS/PEG/glass slides (Fig 1. 5) Nanoliter droplets of peptide (21 amino-acids) or protein (fibrinogen) solution containing 10% glycerol are deposited on the glass slide with a robotic arrayer and incubated for 10 minutes. NHS-groups in remaining area are removed by a deactivating buffer for 30 minutes at room temperature. The immobilized peptide or protein on the surface is detected by incubation with the primary antibody specifically against the peptide or fibrinogen, followed by wash and incubation with cy3-conjugated secondary antibody. The glass slides are imaged on a laser scanner. The most important result is the exceptionally low background due to the PEG coating. While the NHS/PEG coated glass slides are ideal for protein, peptide, and antibody arrays, they are also useful as low background surfaces for other microarrays, such as oligonucleotides, carbohydrates, and other small molecules. The non-fouling property of the high density PEG coating becomes critically important when one uses such an array for the study of complex biological samples, such as plasma or serum. In order to detect molecules of low abundance, such as cancer biomarkers, one needs to minimize non-specific adsorption of other abundant biomolecules [43].

Fig 1. 5 Fluorescence images of peptide (left) and protein (Fibrinogen, right) microarrays fabricated on NHS/PEG/glass slides and detected by immunostaining. The diameter of each spot is ~100 Î¼m (Image courtesy: ZeroBkg®).

4. 5 Self-assembling Protein Microarrays

Molecular fabrication of SAMS depends on chemical complementarily and structural compatibility, both of which confer the weak and noncovalent

interaction that bind building blocks together during self-assembly. Water-mediated hydrogen bonds are important for living system. In nature the assembly of peptide and proteins has yielded collagen, keratin, pearl, shell, coral and calcite microlenses, and optical waveguides [44]. The application of self-assembly techniques in the design of biocompatible protein microarray surfaces, immobilizing cells, and lipid layers, and spotting techniques has been reviewed by others [45-46].

4. 6 Detection Strategies

Detection and readout of complex formation in each spot is performed with fluorescence, chemiluminescence, mass spectrometry, radioactivity, or electrochemistry. Label-free methods include mass spectrometry and SPR. Labeled probe methods include use of a chromogen, fluorophor, or a radioactive isotope. Direct strategies use a labeled antibody to directly bind to the target molecule immobilized on the substrate. Amplification strategies based on avidin-biotin binding enhance sensitivity. Indirect strategies use an immobilized antibody for capturing labeled, specific molecules from the sample. Sandwich assay as noted earlier require two distinct antibodies foe detection of a capture molecule. The first antibody is immobilized on the substratum, and serves to capture the molecule of interest. A second labeled antibody then binds to the first complex allowing detection [47].

5. Application of Microarray

Ever since the first 1000 probe DNA microarray was reported over a decade ago [48], great strides have been made in both quantitative and qualitative applications. Today, a standard DNA chip contains up to 6. 5 million spots and can encompass entire eukaryotic genomes. A plethora of alternative

applications are continually reported, albeit at various stages of maturity. What was once seen solely as a transcript profiling technology has now emerged as a reliable format for genotyping, splice variant analysis, exon identification, ChIP-on-chip, comparative genomic hybridization (CGH), resequencing, gene synthesis, RNA/RNAi synthesis and onchip translation [49]. Perhaps the most exciting recent developments from a drug discovery perspective come from the integration of diverse technological innovations into microarray-based solutions, especially for other classes of molecular entity. From small molecules (e. g. metabolites, nucleotides, amino acids, sugars) to oligomeric and polymeric derivatives thereof, microarrays are now allowing us to examine the intra-class (e. g. protein-protein) and inter-class (e. g. protein: small molecule) interactions of these bio-system components on a systems-wide level. Yet, despite the appearance of a diversity of microarray types (e. g. Small Molecule Microarrays (SMMs) [51], Protein-Nucleic acid (PNA) microarrays [52], Glyco-chips [53], peptide chips [54], antibody chips [55], cell and tissue microarrays [56]), each differs in their relative contribution to the Voltaire challenge. Certainly the foremost of such opportunities are thos