Microarrays

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INTRODUCTION

Microarray technology was based on the basic property of nucleic acids, which is the selective binding of two complementary chains/sequences. The basic technological idea on the exploitation of this property already existed (Gillespie & Spiegelman, 1965; Southern, 1975), but what gave a huge rash into this technology was the discovery of microarrays. However, this could not have been feasible without the unraveling of the sequence of the human genome. At the same time advances in technological aspects such as the miniaturization of arrays and high-density printing on a solid substrate have allowed the appearance of microarray chips (H. C. Causton & Game, 2003).

In general, a DNA microarray is an array of immobilized nucleic acids of known sequence, known as *probes*, or -according to the *Minimum Information about a Microarray Experiment* initiative (MIAME) terminology- as *references* or *reporters*, which are produced with "*printing*" on a solid surface, typically glass or silicon. The exact locations of the reporters on the microarray chip are known -according to MIAME- as *attributes* or *features*. Microarrays are commonly used in order to measure the amount of mRNA that is located in the biological sample under investigation through a hybridization experiment (Scherer et al., 2009). The solution with the labeled amount of mRNA under investigation that is used for the microarray hybridization is known as *extract for hybridization* (according to MIAME).

The advent of this technology has given the initial idea that questions arising for cellular and molecular events could easily be answered through a comparison between the "control" and the "investigated" samples. However, it appeared that this problem had many more manifolds and it became a very dreadful opponent in revealing its secrets. Microarray technology was initially applied in molecular investigations on the genome level in the end of the 90's (J. DeRisi et al., 1996; J. L. DeRisi, Iyer, & Brown, 1997).

BACKGROUND

DNA microarrays detect patterns of gene expression, therefore they can be used for acquiring such "images" and the induction of conclusions on cell state (Diehn, Alizadeh, & Brown, 2000). cDNA microarrays have been used for a plethora of experiments: virtually any property of a DNA sequence which can be experimentally modified, may be determined as far as its differential expression is concerned, and this can be performed on thousands of sequences simultaneously. In that sense, microarrays have been used in gene mapping studies (Comparative Genomic Hybridization, CGH microarrays), mutational analysis and monitoring changes in gene expression of the genome (Eisen & Brown, 1999).

Research questions that can be answered with DNA microarrays are related mainly to the investigation of gene expression. They can compare the relative abun-

dance of mRNA of a gene under investigation, between two different cells or tissue samples. For example, an experiment could compare cells before and after an experimental intervention, or at successive moments of a specific process, or between stages of differentiation or mRNA expressed in a mutant cell compared to that of wild type. This would be the simplest type of experiment.

In particular, microarrays have been applied for the diagnosis of cancer (Armstrong et al., 2002; Golub et al., 1999). They have been used to investigate the hypothesis that the classification of cancers can be based on their gene expression profiles, eliminating thus the need for histopathological diagnosis (Ramaswamy & Golub, 2002). Microarray analysis has been used to predict "tumor grades" or subtypes of cancers, regardless of prior knowledge of their biology (Kees et al., 2003). It can also provide an opportunity to study the possibility of tumor gene expression correlation with the prediction of disease outcome. The first study that attempted to correlate the disease outcome with gene expression before treatment was that of *Alizadeh* and *Eisen* (2000). In the simplest case, genes that are over-expressed in diseased cells (e.g. Her-2/Neu in breast cancer) can be the drug targets. Furthermore, known drugs with unknown mechanism of action, could be studied with DNA microarrays. Their effects on gene expression profiles could reveal this mechanism and provide evidence for the discovery of new drugs with similar action (Diehn et al., 2000; Diehn et al., 2003; Wick & Hardiman, 2005). Especially in the field of pharmacogenomics *Petricoin* et al (2002) predicted that microarrays will play a significant role in drug design and production in all implicated stages of this process (Petricoin et al., 2002).

In particular, in the medical field, microarray application can be distinguished into three main categories: (a) *class comparison*, which involves the discovery of differences in expression levels between two or more samples, (b) *class prediction*, which relates to the discovery of the class to which a sample belongs (based on its gene expression profile) and (c) *class discovery*, where a global gene expression profile is analyzed in order to discover subsets with common characteristics (Tarca, Romero, & Draghici, 2006). For example, in the field of oncology DNA microarray data can provide information for the stage of the tumour, where accurate and timely diagnosis plays a crucial role. In addition, DNA microarrays cannot only be used for the differential diagnosis of tumors, and the clarification of new types of tumors that are indistinguishable histologically, but also to provide information on disease outcome (H. Causton, Quackenbush, & Brazma, 2003; H. C. Causton & Game, 2003).

MICROARRAY TECHNOLOGIES

Up to date several technologies have been applied for the construction of DNA microarrays. Those technologies can be categorized into three main classes: (a) based on the reporter length (e.g., if printed sequences are of several hundred nucleotides in length or twenty to thirty nucleotides in length), (b) the method of production (e.g., if a microarray slide is printed directly (spotted arrays) on a surface, or *in situ*) and (c) the number or biological samples that can be hybridized simultaneously on one slide (e.g., single color or single channel microarrays examine one sample per hybridization, while two-color or dual channel microarrays examine two samples labeled differently on the same slide). Finally, we can discriminate between two additional types of microarray platforms, in-house fabricated and commercial.

Spotted Microarrays

Spotted microarrays were the first to be created (Schena, Shalon, Davis, & Brown, 1995). They are produced by use of a robotic system known as "printer." In order to be produced several steps are required. The first step is reporter synthesis, the second is reporter printing and finally, array post-printing processing (Scherer et al., 2009; Stekel, 2003). Spotted arrays are further categorized into more classes based on reporter type and type of chemical bonding between solid substrate and nucleic acid sequence (Scherer et al., 2009; Stekel, 2003). In the case of long nucleic acid sequences we speak of cDNA microarrays while in the case of short sequence nucleic acids we speak of oligonucleotide microarrays. On the other hand, there is a method for printing arrays from distance using inkjet technology. Based on this technology, nucleic acid solution is "thrown" on the solid substrate having the same effect as pin-spotted arrays (M.-L. T. Lee, 2004). The final stage of array processing includes the stabilization of the substrate by a process called *fixation*. Fixation

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