

Chapter 55

Resolving Sample Traces in Complex Mixtures with Microarray Analyses

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ABSTRACT

High throughput technologies have facilitated the study of thousands of factors simultaneously. A well-known method that has been utilized throughout recent years is microarray technology. Since their advent, microarrays have been used to discover differences between samples, such as those on the level of gene expression or polymorphism detection. This technique has found applications in many areas of life sciences, including forensics. Despite its usefulness, the microarray method is not flawless. Microarray experimentation contains a lot of bias, which makes the use of sophisticated statistical techniques necessary in order to overcome these problems. One basic assumption made from the very first microarray experiments, concerning expression studies, was that samples are homogeneous. This assumption was based on the fact that the biggest part/percentage of a biological sample consists of cells of the same type. For example, tumor biopsies, although considered to be homogeneous, are infiltrated with many other cell types such as macrophages, surrounding fibroblasts and even normal, healthy tissue surrounding tumor cells. As a consequence, forensic samples may consist of tissue mixtures that need to be distinguished.

This chapter reviews the microarray technology and deal with the majority of aspects regarding microarrays. It focuses on today's knowledge of separation techniques and methodologies of complex signal, i.e. samples. Overall, the chapter reviews the current knowledge on the topic of microarrays and presents the analyses and techniques used, which facilitate such approaches. It starts with the theoretical framework on microarray technology; second, the chapter gives a brief review on statistical methods used for microarray analyses, and finally, it contains a detailed review of the methods used for discriminating traces of nucleic acids within a complex mixture of samples.

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INTRODUCTION

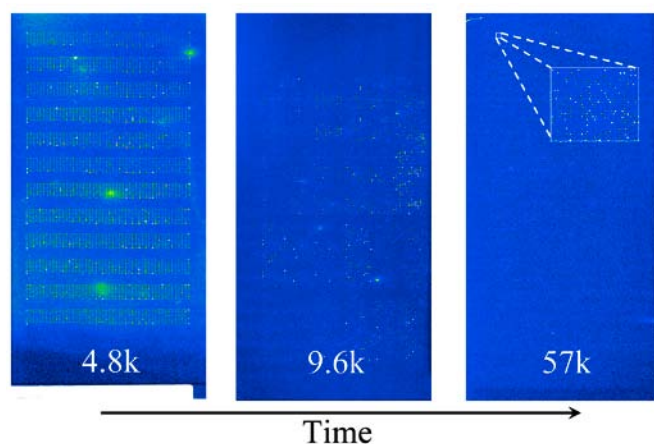
High throughput technologies have facilitated the study of thousands of factors simultaneously. A well-known method that has been utilized throughout the recent years is microarray technology. Microarrays are based, mainly, on the well known trait of nucleic acid sequences to hybridize with their complement chains. One of the best known techniques in science is hybridization which is based on the ‘simple’ property of nucleic acids (i.e. DNA and RNA) to bind to their complementary sequence. In the 1970s *Edward Southern* invented the technique, known as *Southern Blotting* (Southern, 1975, 1992) for DNA hybridization. *Northern Blotting* is the equivalent technique used for RNA hybridization. Microarrays could be regarded as the successor or the continuation of the *Southern* and *Northern* techniques. Microarrays, as the name implies, consist of arrayed series of genes ranging from a few hundreds to the complete transcriptome. The first arrayed DNA sequences were reported back in 1987 (Kulesh, Clive, Zarlenga, & Greene, 1987), spotted on filter paper. In the mid 90’s, the first dense, small scale spotting was reported by *Schena, Brown and Botstein et al.* (1995) at Stanford University (Schena, Sha-

lon, Davis, & Brown, 1995). Although invented elsewhere, Stanford has been regarded as the main developer of microarray technology. Since then, microarrays have evolved both in the number of spotted genes or oligonucleotides (Figure 1) they contain and in the methods of its analysis. In other words, we can say that microarray technology exploits the property of DNA to hybridize to its complementary sequence but *a contrario* to the classical techniques; it allows the hybridization of thousands to tens of thousands of genes simultaneously.

Since their advent, microarrays have been used to discover differences between biological samples. For example, on the level of gene expression, a sample is compared to a reference, in order to discover differences in the gene expression profile. Similarly, microarrays have been used for the detection of polymorphisms. During the past few years, microarray technologies have attracted a major deal of interest from the scientific community due to their potential in screening thousands of factors simultaneously.

Microarrays consist of glass slides or membranes printed with oligonucleotides or cDNA fragments. Later on this chapter we will describe the dynamics of microarray hybridization, since

Figure 1. The evolution of printed chips. The first chips used had a few hundred spots i.e. genes. With time chip densities have increased dramatically, reaching today over 2Mspots on a single slide



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