Chapter XIII
Gene Expression Profiling with the BeadArray™ Platform

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ABSTRACT

This chapter describes the application of the BeadArray™ technology for gene expression profiling. It introduces the BeadArray™ technology, shows possible approaches for data analysis, and demonstrates to the reader how the technology performs in comparison to alternative microarray platforms. With this technique, high quality results can be achieved so that many researchers consider employing it for their projects. It can be expected that the technology will gain much importance in the future. The author hopes that this résumé will introduce researchers to this novel way of performing gene expression experiments, thus giving them a profound base for judging which technology to employ.

INTRODUCTION

Microarrays have emerged as the most popular technology for performing gene expression profiling. They provide researchers with the means to screen all genes of an organism simultaneously thus alleviating the investigation of complex diseases like cancer or diabetes. Closely coupled with the development of the technology are the reliability issues culminating in the publication of contradictory results achieved on different microarray platforms. While in the starting phase of the microarray technology reliability issues arose from the imperfect technique, e.g. distorted spotting needles, thus requiring a compensation by a sophisticated image analysis (Steinfath,M. et al., 2001, Kamberova, G., 2002) a continuous process of improvement using proved industrial methods gives better but far from perfect results. The BeadArray™ technology described in this chapter proves that an industrial production process facilitates reliable experiments of high quality.

The rest of this chapter is organized as follows. We motivate the BeadArray™ technology. Subsequently, we describe viable approaches for analyzing data produced with this technology, introducing

the proprietary software BeadStudio and freely available solutions from the R Bioconductor environment. We introduce our pipeline design for the analysis of bead-summary data. Then we demonstrate the position of the BeadArray™ technology in comparison to other microarray platforms. Finally, we summarize our experiences with the new technique.

THE BEADARRAY™ TECHNOLOGY

 In the first phase of microarray technology probes were spotted by robots at known locations onto a dedicated substrate. Probes were then hybridized with a radioactive or fluorescent labeled target. Thus, the abundance of hybridized material was transformed into a signal which could be read by a scanner. Many error sources influenced the results achieved by this technique: twisted spotting needles, needles transferring different DNA volumes, labelling differences for, e.g. red and green channel, dust on the substrates, systematic local background changes, bad signal-to-noise rates in the scanned image, etc. . A great improvement in quality was achieved by synthesizing oligonucleotides using photolithographic processes known from the semiconductor industry. As a logical consequence the product was called "chip" as a reference to the origin of its manufacturing technique.

An alternative approach claiming to reach similar quality benchmarks as the chips is the BeadArray™ technology. It takes advantage from the ability of beads to be randomly assembled at very high densities. In the literature it has been described that beads of 300nm have been randomly assembled into 500nm wells (Michael et al., 1998). For the BeadArray™ technology at present a size of 3μm is used for the silica beads. The beads are generated by joining oligonucleotides to their surfaces and are pooled in libraries. They are self-assembled into etched substrates.

With the beads randomly distributed over the array the problem of decoding each bead's information content arises. The solution of this problem is described in (Gunderson, K. et al., 2004) and is an essential precondition for the employment of the technique.

The probes consist of a gene-specific 50-mer oligonucleotide and a 23-mer oligonucleotide "address" (see Figure 1). They are immobilized to the beads and decoded by a minimized amount of hybridization steps in the manufacturing process. The number of hybridization stages *s* is given by:

$$s = \log_b n$$

where *n* is the number of different beads and *b* is the number of different states that can be detected after the image analysis, e.g. b=2 if only red and green can be detected or b=4 if red, green, yellow and black can be detected Thus, every chip is unique and is delivered bundled with media containing the information of the bead locations. (Gunderson,K. et al., 2004) claim to have a misclassification rate of the beads of 1.2×10^{-5} in the mean and 1.4×10^{-4} in the worst case in a random sampling of 100 manufactured array matrices. The misclassification problem can be tackled by using a sufficiently high number of replicates of beads. It is guaranteed that – in average – there are more than thirty replicates and – in minimum – there are more than five. In a random sample of twenty chips the author calculated a median number of 42 replicates of beads.

The address oligonucleotides are designed to have low similarity to genetic sequences, minimal complementary sequences versus each other and similar GC content. The probe oligonucleotides, on

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