1 Introduction

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The word biochip was first published in the biotechnological media in 1995. We got the impression that computers were ready for applications in molecular biology. The mysterious “biochip” was on the tip of every molecular-biology tongue, but none of these nonusers of biochips had any understanding of what the whole thing was all about. There were no related publications, manuals, or product descriptions that one could consult.

“The basis of the biochip must be that DNA is bonded onto tiny circuit boards by using an electrical charge. By using hybridization processes the biochip can be harnessed to analyze the amino acid sequences of the attached nuclei.”

That was our naïve perception of these new biochips. Indeed we had expected something much more complicated. Our research, notwithstanding the alleged first “microarray paper” of Shena in 1995, always returned us to Affymetrix. The visual representation we received was always a small window with thousands of dots on a dark web. That’s what a biochip looks like! The questions about the meaning and purpose of the biochips were easily answered: high-throughput screening and cost savings! That was naive as well!! High-throughput screening (HTS) is possible because the analysis of hybridization with a specific sequence is easily automated by arranging a large quantity of various nucleic acid sequences in an extremely small space. The time savings results from the automation, which allows as many of these biochips as the researcher wants to be hybridized and analyzed. Nonetheless, even a fully automatic pipetting and hybridization system has mandatory minimum incubation times, though these can also be realized with microtiter plates. Moreover, the loading of biochips as well as the subsequent quality control and the concluding analysis take a lot of time. The cost of the biochips and the necessary investment is difficult for a layperson to grasp. The first biochips cost more than 1 million US dollars each. This understandably slowed the commercial spread of the chips. Every user must therefore, after the adoption of the biochip, ask himself or herself this fundamental question:

What additional work do I want to introduce to and/or optimize with this technology?

Now in the year 2004 after many “Oh, yeses” and “Oh God, oh God’s,” the leading commercial users and suppliers have created and are still in the midst of lightning-fast and interesting development of the biochip market. The growing number of microarray publications since 1995 (Fig. 1-1) confirms this. The range of biochip products offered
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Fig. 1-1: Relative share of publication of individual microarray experiments during the time period 1995–2002. A predominant number of publications addressed the field of expression analysis, followed by genotyping. Protein microarrays still have a secondary role in publications as this field is still being developed (taken from Schena, 2003).

as well as the necessary equipment is now so substantial that there is no lack of specialization within this relatively new technology. The fundamental question after the adoption of the biochip remains. But a second question must inevitably be added:

Which biosystem do I procure?

This book answers these two questions. We will illustrate a comprehensive overview of the range of applications of biochip technology as well as the necessary instrumentation in separate and self-contained chapters. Furthermore we will demonstrate proven and tested methods for respective biochip applications. Before we delve any deeper into the biochip world we feel it necessary to mention a few common concepts as well as the history behind the development of the biochip.

1.1 Terminology

Why was the biochip named a biochip? In the mid-nineties we found ourselves in a rapid-development stage of computer technology. A similar growth potential was forecast for the highly technological biotechnology field. It was only a matter of time before the terms bio and chip were combined. After the biochip saw the light of the micro-world, a proverbial boom of chips exploded onto the scene: DNA, protein, peptide, proteome, SMD chips, etc. Microarray technology was coined as the generic term for this technology. What does that mean? Micro, it’s clear, is something small! But what does array mean? The dictionary displays a number of options, but the most appropriate is the following: array = an impressively large assembly. A large number of molecules are assembled or exposed on a very small space. What do we mean by “a large number”? Today’s microarrays may have more than 200,000 (!) points or spots spaced on a square centimeter, or they may have only a few hundred positioned on the same square centimeter. This depends largely on the bound molecules, the spotting technology used, and the problems that need to be solved. But if the format is smaller than with the well-known microtiter plates, pretty much everybody now uses the terms biochip and microarray.

In parallel with the development of microarrays and with of the realization of the Human Genome Project (HUGO), many new terms were coined in the world of
Table 1-1: List of common **omics** terms. A complete description of these and other *omes* as well as *omics* terms can be accessed on the Internet at www.genomicglossaries.com.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Biomics</td>
<td>All-embracing term for the biological <em>omics</em> family</td>
</tr>
<tr>
<td>Cellomics</td>
<td>The study of cell functions by the use of incubation with biocatalysts</td>
</tr>
<tr>
<td>Degradomics</td>
<td>The study of protease activity</td>
</tr>
<tr>
<td>Genomics</td>
<td>The study of genomes, which includes genome mapping, gene sequencing and gene function</td>
</tr>
<tr>
<td>Peptidomics</td>
<td>The study of peptides</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>The study of the effect of drugs on genes</td>
</tr>
<tr>
<td>Pharmacoproteomics</td>
<td>The study of the effect of drugs on proteomes</td>
</tr>
<tr>
<td>Proteogenomics</td>
<td>The study of genomics and proteomics</td>
</tr>
<tr>
<td>Proteomics</td>
<td>The study of cell proteins</td>
</tr>
<tr>
<td>Transcriptomics</td>
<td>The study of the mRNA expression</td>
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The nineties were the decade of *omes* and *omics*. It started with *genome* and *genomics* for the analysis of gene regulation, then *proteomes* and *proteomics* (analysis of cell proteins) and many other *omes* and *omics* followed. Table 1-1 is a listing of common *omes* and *omics* terms. A complete description of these and other *omes* as well as *omics* terms can be accessed on the Internet at www.genomicglossaries.com.

### 1.2 Design and Development of Microarrays

Why is it that microarrays were able to establish themselves in the presence of microtiter plates? (We can’t really say yet that they have taken over.) As with other molecular biological methods, HUGO provided the push. With the sequencing of the human gene information (even though we haven’t even begun to unlock all of this information) we all of a sudden are confronted with huge amounts of data. At the same time SNPs (single-nucleotide polymorphisms) and the knowledge of regulation of gene expressions have contributed to a demand for affordable high-throughput systems that is constantly growing. The demand was for screening methods that made it possible to let a large number of different molecules (nucleic acids or biocatalysts for drug-target screening (Section 6.2)] react with each other in a manageable time frame. These millions and millions of reactions could not be accomplished with the costly microtiter plate methods, as these required additional reagents and verifications in order to analyze the results. So the path to microarrays was necessary and logical. It was now possible
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![DNA Microarray Methodology - Flash Animation](image)

Fig. 1-2: Flash animation of microarray technology. At the Web site (www.bio.davidson.edu/courses/genomics/chip/chip.html) of Bio Davidson you can launch an easy-to-understand Flash animation depicting a complete microarray experiment. The animation starts with the unlocking of yeast cells and continues through the RNA cleaning, cDNA synthesis, spotting, and hybridization, and finally to the spot analysis.

...to reduce the volume per reaction to a few billionths of a liter of solution. The advantage was realized and the boom started in earnest in the mid-nineties. Now we needed robots that could recognize, pipette, and transfer nano- and picoliters reproducibly to a diameter of 100, 10, and \(<1 \mu m\). Measuring instruments had to be developed that could measure and store the reactions. Software systems had to be written that would analyze, describe, and compare the results.

Finally, all the systems that had been developed for microtiter plates had to be adapted for microarrays. The microtiter industry reacted with the development of 384- and 1536-cup microtiter plate systems. These systems also allowed for a reduction in reaction volume and higher throughput. But the microarrays were and still are just too “trendy.” That’s why every high-tech-experienced biotechnologist prefers to work with biochips rather than the “awkward” and “old-fashioned” microtiter plates.

We want to mention at this time that we are defenders of microtiter plates, at least for those users who process fewer than 1000 molecular incubations per day. At that volume one can justify the conversion to microarray technology. And for the low-throughput user one can always say, “Not today, but maybe tomorrow.”

In the following chapters you will get an overview of microarray technology, applications, and experiment design and an overview of manufacturers and distributors...
of various microarray products. A microarray experiment encompasses a huge bandwidth of different biotechnical methods. In order to be able to plan the experiment properly from beginning to end it is necessary, or at least helpful, to have some knowledge of molecular biology, protein chemistry, cell biology, and immunology.

If you have adequate knowledge of laser- and scanner technology combined with profound experience with microarray software, you will have no problem understanding the analysis of a microarray. But even a freshman does not have to fear the mystery of the technology, as any experienced experimenter can easily port his microtiter knowledge to the microarray dimension.

If you want to get a quick overview of microarray technology, surf Bio Davidson’s Web site (www.bio.davidson.edu/courses/genomics/chip/chip.html), double-click the Flash animation, sit back in your armchair, and see how simple it is to prepare, execute, and analyze a complete microarray experiment (Fig. 1-2).

After that, if you are so inclined, read a few chapters of this book and you will have a much easier time seeing the big picture. In addition there are many other books covering microarray technology. A must read is Microarray Analysis by Mark Schena.

**Literature**


Web site of Genomics Glossaries: www.genomicglossaries.com