



Design and Analysis of DNA Microarray Investigations

by Richard M. Simon, Edward L. Korn, Lisa M. McShane, Michael D. Radmacher, George W. Wright, and Yingdong Zhao
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Out damned spot! Out, I say!
—William Shakespeare, *Macbeth*

Or put another way, so many spots, yet so little space. Like the computer chip, the microarray chip represents a relentless striving toward cramming ever-increasing information (be it integrated circuits, DNA sequences, or proteins) onto an ever-

shrinking area. The goals are greater complexity and miniaturization. Although the microarray industry will probably never approach the impact that computers have had, the innovative uses of microarrays in nearly all aspects of biologic, pharmaceutical, and medical research make it a force to be reckoned with both scientifically and economically. The microarray chip, like the computer chip, invokes a daunting, sometimes overwhelming amount of data. Thus, microarray experiments must be properly designed and carried out to reduce costs and limit misleading and statistically insignificant data.

This book by Richard Simon and his colleagues at the National Cancer Institute will help keep costs and lousy data minimal. It covers essentially three major topics: how to design microarray experiments, how to carry out microarray experiments, and how to analyze microarray data. The book is intended for scientists who wish to learn more about the design and analysis of microarray experiments and for computational scientists who want to learn what functional genomics is all about. It is also appropriate for graduate students interested in newer technologies. Its most positive aspect is the emphasis on experimental design, essential to a genomics experiment—a facet that is barely touched on and more often ignored by other books. Careful design helps minimize false positives, and when scanning the results of 30,000 genes per time point and/or dosage, extraneous data can become an issue.

For nonmolecular biologists, the authors admirably describe how benchtop techniques are carried out for different microarray platforms.

One appendix explains some relevant basic cellular biology and another describes some noted examples of how microarray data sets have been applied to medical and biologic research. Mostly the book addresses data analysis (including a third appendix identifying some useful data analysis software tools). These chapters ably cover one of the most rapidly progressing fields in biology, high-throughput computational analysis. Most recently developed microarray analysis methods are described in sufficient detail that the nonmathematician can understand the underlying premise.

The book contains a few weaknesses, omissions, and errors. Unfortunately, one of the potentially most important and useful sections of the book—on experimental designs—is somewhat dogmatic without sufficiently covering other design options or referencing some relevant work in the area. The designs are rigidly divided into reference design (RD), balanced block design (BBD), and loop design (LD), without considering the possibility of mixing different types. For example, BBD is the most efficient for comparing only two classes of samples, whereas RD is most appropriate for comparing a very large number of samples. However, most microarray experiments actually fall between these two extremes, and the most appropriate design often warrants a combination of the three. The authors are particularly and unfairly critical of the LD, describing only one possible instance, in which each sample is tested twice and no “spokes” connecting nonadjacent experimental conditions are used. A simple modification, in which differentially labeled biologic replicates instead of same sample replicates are used, would significantly improve the efficiency of the design. Further, adding more spokes would greatly reduce the effect that a few bad arrays will have on the outcome while maintaining statistical superiority over the reference design in the number of effective measurements. Readers are urged to seek additional references when choosing their design. Lastly, there are a few minor printing mistakes; for example, the legends for Figures 3.3 and 3.4 are switched. Nonetheless, the book is a well-written, fairly comprehensive introduction on how to carry out functional genomics studies and can be recommended to students and researchers in mathematics, computer science, or bioinformatics as well as biology or medicine.

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