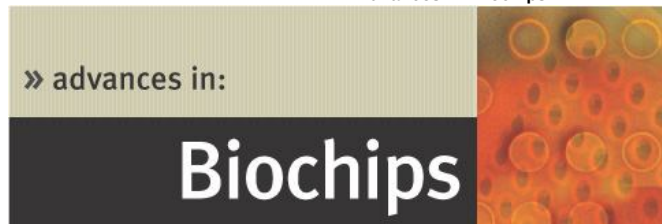


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Advances in: Biochips



Data Delivery for DNA Microarrays As their technology has advanced, DNA microarrays have started to find fresh applications in biomedicine. To facilitate those uses, vendors have had to develop new approaches to storing and analyzing the data that microarrays produce.
by Peter Gwynne and Gary Heebner

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Inclusion of companies in this article does not indicate endorsement by either AAAS or Science, nor is it meant to imply that their products or services are superior to those of other companies.

During the past half decade, DNA microarrays have undergone a transformation from laboratory curiosities to devices that permit scientists to probe entire genomes at an exquisitely detailed level. They have also begun to move from studies of gene expression profiling into broader areas of biomedicine. "Microarrays are now actively used in clinical trials and are needed for drug development because they permit you to assess quickly how a particular drug is working; you can see early what kinds of genes are responding," explains Irene Gabashvili, technical lead for computational biosciences at **Hewlett-Packard (HP)**. "They are also used in diagnostics."

This expansion of applications stems in large measure from developments in DNA microarray technology. "There have been improvements in the robustness of the systems," says Jordan Stockton, marketing manager for informatics at **Agilent Technologies**. "Users have gone from spotted complementary DNAs [cDNAs] to direct synthesis on slides or arrays. The content of arrays has improved dramatically as sequences have become available."

Walter Koch, head of research for **Roche Molecular Diagnostics**, adds to that list. "There have been substantial improvements over the past five years in microarray manufacturing technologies that allow the reproducible, larger scale manufacture of higher-density microarrays with smaller feature size," he says. "Concomitantly, advances in laser scanning technology have resulted in smaller pixel resolution to take advantage of the ever-smaller feature sizes." Gabashvili, meanwhile, sees a continuing process of improvement. "We have better quality control. We have cheap fabrication technologies," she says. "And the main improvements are yet to come, via nanotechnology research at **MIT**, **HP**, and other technology innovators."

Herbert Auer, director of the functional genomics core at **Columbus Children's Research Institute** and chair of the **ABRF Microarray Research Group (MARG)**, an organization that undertakes regular surveys of microarray users, has his own take on advances in the technology. "What's happening now is almost not comparable with what happened five years ago," he says. "Now, scientists can examine all the transcripts of an organism rather than a few thousand. Another thing that has definitely changed is the reproducibility of commercially available microarrays. And the equipment used for home-made microarrays has become better. The probes that I use are much more specific now. Five years ago, pretty much everybody used cDNAs; now they use oligonucleotides for more specificity."

Massive Amounts of Genetic Information

Stephen Fodor and his colleagues invented the microarray in the late 1980s. Fodor, founder, chairman and CEO of **Affymetrix**, the first company to commercialize microarrays, summarizes the impact of the recent advances. "The framework for growth of the field is there," he says. "Today, scientists have the ability to look at massive amounts of genetic information simultaneously in a single experiment."

Those huge amounts of data create an obvious challenge: They have no value until scientists can analyze and make sense of them. "The biggest problem is still as it was through the years: bioinformatics and data analysis," Auer says. Dealing with that problem demands a combination of sophisticated hardware and software, as well as tools such as microarray readers and scientific software that are user-friendly for bench scientists.

Users of microarrays face other issues. "The number two challenge, according to surveys by MARG, is funding of operations," Auer says. "Microarray technology is still relatively expensive — a few hundred dollars per experiment." Siamak Baharloo, marketing manager with the bioinformatics and e-business group at **Invitrogen**, pinpoints another problem. "The challenge is a lack of standards in platforms, protocols, and analysis," he explains. "You can follow the exact same protocol, but if you change a single reagent or the platform, you get entirely different data. Two labs down the same corridor can get entirely different results by using different platforms."

Two Types of Labels

Sample processing for microarrays involves labeling, detection, and data interpretation. Scientists can tag the DNA attached to a microarray with some type of label and then detect it with laser scanners or other devices specifically designed for use with microarrays. Scientists have a choice of two types of label. Radioactive labels, imaged with a phosphorimager or autoradiography film, make up in effectiveness what they may lack in glamour. Companies such as **MP Biomedicals** and **PerkinElmer Life and Analytical Sciences** offer the most common radiolabels for this procedure. Radiolabels most often find use with nylon membrane macroarrays, such as those offered by **BD Biosciences Clontech** and **Millipore**.

Scientists tend to prefer fluorescent labels, which offer less risk of radiation exposure, easier disposal, and greater sensitivity when compared with radioactive labels. To identify multiple samples, a researcher can multiplex experiments on a single microarray, using several different compounds that each emit a different wavelength. Companies that produce fluorescent labels include **GE Healthcare**, **Invitrogen**, and **Sigma-Aldrich**.

Fluorescent imaging systems for microarrays perform several basic operations. They excite the fluorescent labels attached to the samples, collect emitted light, and generate digital images of the fluorescent signal. To collect the fluorescent images, scientists can opt for scanning or imaging. Scanning involves laser excitation with a photomultiplier tube detector while imaging uses filtered white light excitation with a charge coupled device detector. **Affymetrix**, **Hitachi Genetic Systems/MiraiBio**, **Molecular Devices**, and other companies offer **DNA microarray readers** based on these detection systems.

Opportunities for Career Advancement

If you want to advance your career in research on microarrays — or any other field — you can visit [ScienceCareers.org](http://www.sciencereaders.org), the American Association for the Advancement of Science's site that brings together recruiters and job seekers. There you will find a wide selection of job opportunities in research, along with information to help you to further your career in science.

<http://www.sciencereaders.org>

Affymetrix has developed the GeneChip Scanner 3000 7G, related to the company's GeneChip Scanner 3000 series, for use with next-generation higher density arrays. It scans 5 μ m features, enabling an increase in genomic content of 500 percent over the previous arrays. The scanner supports the latest high density, high information content microarrays for tiling, and up to 500,000 SNP genotyping research. Combined with Affymetrix's GeneChip AutoLoader, the 3000 7G provides sample tracking, temperature control, and walk-away freedom from scanning.

The scanner processes vast amounts of information. "At a 5 micron feature size, our standard 1-cm. square chip contains about 6.5 million probes," Fodor says. "That's a lot of data, and the 7G is capable of reading it."

Interpreting the Results

Having scanned the array, scientists need to interpret the results. Storing and analyzing information from microarrays that contain thousands of samples or spots offer a serious challenge. "Data analysis represents a bottleneck today," says Scott Cole, marketing manager for Agilent. Scientists typically spend many hours at their desks, working with computers and specialized software to store and manage sequence data, design microarray formats, and analyze the data gathered from those studies.

The situation is improving, however. "A few years ago, scientists didn't know what questions to ask," Cole's colleague Stockton explains. "Now we have tools to guide them." Several companies, including **Agilent**, **Invitrogen**, **Premier BioSoft**, **Spotfire**, and **TeleChem International**, offer software and other products for microarray design and analysis.

Through its InforMax subsidiary, **Invitrogen** offers **Vector NTI Advance** and **Vector Xpression** software packages for microarray data analysis. And in June, the company released **iPath**, a bioinformatics system that consists of 225 high-level, annotated, validated maps of human cell signaling and metabolic pathways compiled by **GeneGo, Inc.** "iPath has very useful and rich bioinformatics content," Baharloo explains. "Customers can search the signaling and metabolic pathways by the name of the pathway. They'll land at a very user-friendly graphical interface with proteins and other objects in the pathway indicated by symbols. The software also indicates bindings, translocations, phosphorylations, and other reactions symbolically."

In practice, users can seek pathways by querying the software with a keyword, a gene's name or ID, or IDs from specific arrays. "We have associated the IDs with the genes, and then associated them with the pathways the genes are involved with," Baharloo explains. "It deconvolutes the various pathways." To update pathways, a group at **GeneGo** combs through the peer-reviewed literature. "we'll update significant changes instantly and minor ones shortly," Baharloo says. **Affymetrix**, meanwhile, recently launched a **GeneChip Compatible Software Partners Program** that provides users of microarrays with a broad spectrum of integrated solutions for biomedical research and development.

Software and Hardware

Agilent's Silicon Genetics unit specializes in software for expression data analysis and management. Its **GeneSpring** software product is a powerful visualization and analysis solution, designed for use with genomic expression data from virtually any source, that can display and analyze large datasets on a typical desktop computer. "GeneSpring is

the center of our code base. we're aiming to add new applications and uses for any high throughput technologies," Stockton says. "Data generated from many different types of microarray applications tend to be useful in the same experiment," Cole adds. "So it's becoming important to leverage many pieces of microarray data. we're working on tools to do that in the GeneSpring platform."

Microarray applications are clearly pressing the limits of conventional computing power. Hardware companies such as **Apple**, HP, and **IBM** are working on ways to obtain more power from existing computers, to develop more powerful computers, and to devise more capable software. "We are doing our own research and supporting research at academic institutions," HP's Gabashvili says. "For real-time results you need good middleware, which we are designing. Ours is unique in that our customers can decide just what they want."

The firm also takes a highly customized approach to bioinformatics, aiming to determine the optimum high performance architectures for its customers' needs. "Every bioinformatics company says that it offers customized software," Gabashvili says. "But we are supporting the IEEE standardization initiative for bioinformatics — in particular in microarrays — to increase productivity in the field."

HP also encourages a move of microarraying into the diagnostic arena. "One of our collaborators, Harvard Partners Centers for Genetics and Genomics, is using microarrays to diagnose certain diseases such as deafness, particularly in babies," Gabashvili says. "And another partner, at the Biomedical Engineering department of the Georgia Institute of Technology and Emory University, is integrating the microarray technology with bionanotechnology in cancer research for uses such as early detection, diagnosis, prognosis, and therapeutics."

Diagnostic Applications in View

Roche Molecular Systems has taken that movement a stage further. The **U.S. Food and Drug Administration** has cleared its first microarray based test, the AmpliChip CYP450 Test, powered by Affymetrix microarray technology, for diagnostic use in the United States. "The test detects variations in the CYP2D6 and CYP2C19 genes, which play a primary role in the metabolism of many widely prescribed drugs," Koch explains. "The test also provides a predicted phenotype — that is, poor, intermediate, extensive, or ultrarapid metabolizer."

That represents just a start. "We are continuing to develop other innovative clinical diagnostic AmpliChip tests based on the Affymetrix high-density oligonucleotide microarray platform," Koch says. "Several other companies are also working on developing microarrays for diagnostic use, so one might say a trend is beginning."

Microarrays have proven their utility for research in several areas, including expression profiling, SNP analysis, and tumor sub-typing. The data from these devices just keeps on coming as microarrays gain popularity with researchers worldwide. And as progress continues in developing standards and more application-specific arrays come to market, these new tools will become increasingly useful in revealing more and more scientific data from less and less sample.



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