RESEARCH NEWS AND VIEWS

Cheap DNA arrays—it's not all smoke and mirrors

Alan P. Blanchard and Stephen H. Friend

Recently, moviegoers in Los Angeles were able to see the latest Star Wars film in a theater equipped with a digital projector. How many in the audience would have imagined that the same technology that brought them images of intergalactic mayhem was also helping to bring down the cost of basic biological research? In this issue, a group of electrical engineers and molecular biologists from the University of Wisconsin present the latest example of how advances in electronics are driving biology forward[1]. The biology comes from synthetic DNA arrays[2,3], which are changing the way many biologists are doing business, and the electronics come from the lucrative field of projecting TV images onto larger and larger walls with increasing resolution.

Sussman and colleagues started with a method of making DNA arrays pioneered by Fodor and coworkers [4], which is based on photolithography, a technique borrowed from the semiconductor industry. This technique works by shining light through a photolithography mask, much like a photographic negative, onto a light-sensitive surface, which reproduces the mask pattern on the surface. The reagents for manufacturing DNA arrays by photolithography are modifications of the usual phosphoramidite reagents in that the dimethoxy trityl (DMT) group that protects the 5′ hydroxyl is replaced by a photolabile protecting group. The synthesis proceeds by photolithographically deprotecting all the areas that are to receive a common nucleoside, coupling that nucleoside by exposing the entire array to the appropriate phosphoramidite, then after the oxidation and washing steps, the procedure must be repeated for the next nucleoside. To make an array of N-mers, 4N cycles of deprotection and coupling are required, one for each of the four bases times N base positions. Thus the procedure requires 4N masks, and therein lies the rub: the masks are not cheap, require days to weeks to make, and are specific to the particular pattern of oligonucleotides that make up the array.

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Enter the technology of television, for what is television other than a cheap, versatile technology for producing detailed patterns of light? Could one not project the image from a television onto the array surface to define the deprotected areas? Television may be bright enough to entertain the masses but it is too dim, and its glow the wrong color, to drive the photochemistry involved in DNA synthesis. The general problem of dimness also plagues manufacturers of projection TV.

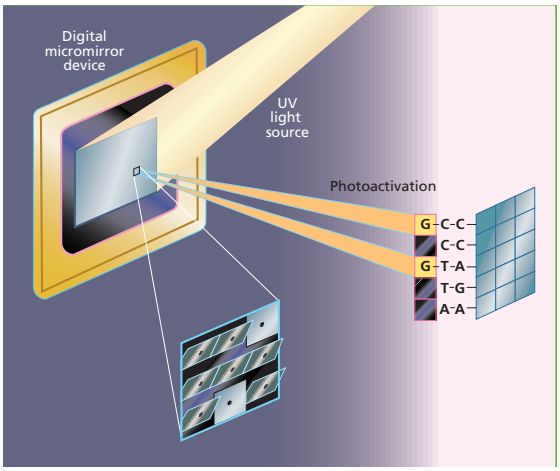

Figure 1. Light from an arc lamp, directed by digitally controlled micromirrors, cleaves photolabile preotecting groups off of the ends of DNA molecules. The illuminated areas will then couple to the next base to be added, and dark areas will remain inert.

The present advance in electronics that addresses these problems comes from Texas Instruments (Dallas, TX), which, after a gestation of more than two decades, has started marketing a projection TV based on an array of up to a million digitally controlled micromirrors. Each mirror corresponds to a pixel of the image, which is bright if the mirror is angled to reflect light from a lamp onto a screen, and dark otherwise. This technology solves the problems of dimness and wavelength, the image is as bright and has the same color as the lamp. Since the image is controlled electronically, changing the pattern of sequences on the array becomes as easy as flipping channels.

The University of Wisconsin group has combined a commercial DNA synthesizer with a digital micromirror system to create a prototype DNA array synthesizer capable of making arrays with tens of thousands of 16 μm features. Arrays made this way have passed several tests, such as demonstrating the ability to detect single-, double-, and triple-base pair mismatches in two genes in *Arabidopsis*. These initial successes bode well for eventually developing a robust, flexible platform for making arrays using extensions of this technology.

Among the remaining thorny issues that could hamper application of technologies that use spatial addressing at the deprotection step, are the requirement for a large number of synthesis steps and the efficiency of the synthesis process. Because each nucleotide must be added separately at each position, 100 cycles are needed to make 25-mers. This is a potential drawback, because of not only the time required to perform the synthesis but also the high cost of the prerequisite phosphoramidites and other reagents[1]. In addition, the efficiency of the photolithography synthesis process is only 95%, which limits the size and quality of oligonucleotide array that can be generated[1]. For example, on average, only 28% of 25-mers will be synthesized as desired. Although this could permit the identification of mismatches, it is unlikely to be applied to monitor heterozygous polymorphisms necessary for exploiting single-nucleotide polymorphisms (SNPs)[5] in health management or in pharmacogenomics.

Despite the issues raised regarding some of the details of this technology, efforts in the next few years are likely to produce methods that will dramatically improve the costs and efficiencies of making DNA microarrays. It is impossible to predict whether in the end these solutions will come from extensions of this maskless photodeprotection technology, from use of ink jet technology for in situ synthesis of DNA[6], or from novel methods to deposit presynthesized DNA. But it is clear that for the scientists wanting to do array experiments, unlike the moviegoers of Los Angeles, the price of admission will soon be falling.

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