CPU by DNA?

SIGHTINGS

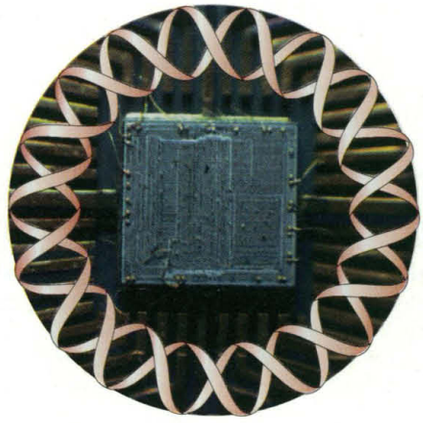
The logic of the genetic code, as manifested in the pairing of only four bases of DNA, is an amazingly simple property that can be exploited in many complex ways. Because of this, DNA has been showing up in experiments far afield from the molecular biology community. A recent report by Braun *et al.* (*1*) highlighted the promising migration of DNA into electronics.

First some background. Researchers in academia and industry are very much interested in miniaturizing electronic circuits as much as possible. For computers in particular, the concept is obvious and profound: the more circuits in a given area, the more processing power a computer has. Current technology for computer chip manufacturing relies on the use of ultraviolet light to create patterns that define the components of integrated circuitry. Because of diffraction, the wavelength of light puts an effective limit on the width of a wire in an integrated circuit. There is ongoing research into the use of other etching modalities, such as x-rays, that can create microscopic wires of smaller sizes.

Enter DNA. How can DNA be used to create small wires? A group at the Weizmann Institute in Israel has applied the unique physical characteristics of DNA and DNA base pairing to the problem (*1*). Only a few steps were involved in generating a system in which DNA was used as an atomic scaffold upon which to build silver wires. The wires connected two gold electrodes that could support an electric current.

First, the researchers constructed two different "anchoring" oligonucleotides (or oligos), each 12 base pairs long and coupled to a disulfide group at their ends. When added to two electrodes (the negative and positive poles), the oligos bound essentially irreversibly via the sulfur group. The oligo-treated electrodes were then placed 12 to 16 mm apart and bathed in a solution containing a derivative of phage lambda DNA. This linear 16-mm-long piece of double-stranded DNA contained termini that could base pair (after denaturation) by standard Watson-Crick pairing with the single-stranded anchoring oligos. Once captured by both anchoring oligos, the DNA molecule acted like a bridge to link the two electrodes.

Next, they needed to turn the DNA strand into a conductor, because DNA by itself does not conduct current. They first treated the mix with ionized silver in a way in which the endogenous sodium on the DNA backbone was replaced with silver molecules. Then, they added a reducing agent to the mix. This caused the silver to precipitate along the DNA molecule, effectively turning



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the DNA bridge into a wire 100 nm in diameter. Conductance tests were performed to prove that the newly minted wire would indeed conduct electricity. The specificity of the silver precipitation process was shown by examining control samples that did not contain DNA—they exhibited no current flow between the electrodes.

The application of DNA-based technology to the formation of electronic circuits is intriguing. Theoretically, a solution containing a mixture of oligonucleotide scaffolds can be mixed with a solid support spatially coated with target oligonucleotides. Hybridization and "development" could produce complex circuitry in one parallel processing step. Although the DNA wires are significantly wider than the 3- to 20-nm wires produced by state-of-the-art laser techniques (*2*), there is the hope that DNA can be a substrate for targeted wiring of future circuitry. Challenges ahead concern how to deposit the oligos on a surface in atomic grids, fabricating atomic grids, and controlling the hybridization of multiple oligonucleotides.

–Robert Sikorski and Richard Peters

References

1. E. Braun, Y. Eichen, U. Silvan, G. Ben-Yoseph. *Nature* **391**, 775 (1998).
2. A. M. Morales and C. M. Lieber, *Science* **279**, 208 (1998).

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Pinpoint Assays

SIGHTINGS

Laboratories, especially those focused on drug discovery, have great interest in finding new ways to perform enzymatic assays. In general, speed, cost, or throughput usually limits any assay's utility in a production system. To increase speed, the assay should be completed in extremely short times and have little set-up time. To decrease cost, the assay should be extremely sensitive so as to use as few reagents as possible. To increase throughput, the assay should lend itself to robust automation with robotic or flow-based systems.

Many enzymes perform cleavage or joining reactions. Methods used to follow the activity of cleaving enzymes (such as proteases or deoxyribonucleases) consist of monitoring the increased concentrations of the cleavage products. For measuring enzymes that catalyze joining reactions (kinases or ligases), the rate of disappearance of the substrate or appearance of the product is followed. Techniques to rapidly measure molecular fragmentation and molecular assembly, in general, would have broad utility in many biochemical reactions.

Two recent publications by the group of Eigen and co-workers (*1*, *2*) described an elegant approach to both types of biochemical reactions. They call their technique dual-color fluorescence cross-correlation spectroscopy, or simply FCS. At the heart of FCS are highly sensitive fluorescence detectors that can detect single photons.

The FCS methodology was tested in a mock system used to measure the activity of a DNA restriction endonuclease (a cleavage reaction). Two different fluors (Cy5 and rhodamine green), which excite and emit at different wavelengths, were attached to the ends of a double-stranded oligonucleotide that contained a recognition site for the enzyme Eco RI. To measure, on average, only one DNA molecule at a time, the samples were diluted to very low (nanomolar) concentrations, and fluorescence measurements were made at very small (femtoliter) volumes. The small volume was actually a small sampling window of a solution that was created on-the-fly by focusing two lasers (at 488- and 633-nm wavelength) into the sample such that their paths crossed within the sample volume. This intersection of the two lasers is, therefore, the only part of the sample that is stimulated at both wavelengths simultaneously. The excited photons emitted from the sample were then collected on detectors at the two wavelengths.

Over time, molecules diffuse into the sampling window and are excited. Only those DNA molecules with both fluors attached will emit at the two measured wavelengths. This fact is the key to the experiment, and it allows sensitive measurements of the cleavage of the DNA molecule. Over time, the number of bifluorescent DNA strands entering the sampling window will decrease as the linkage between the fluors is cleaved. Eventually, none of the fluors will be linked in the same molecule.

By using multiple samplings over time and

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