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

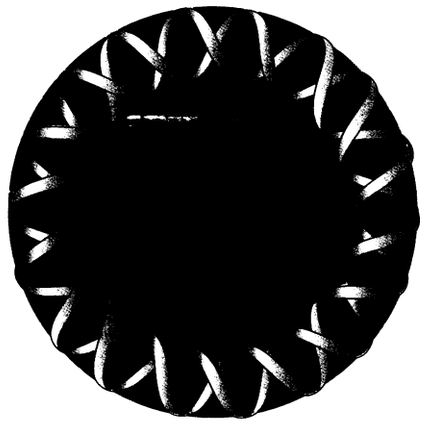

PHOTO: DAN MCCOY/PNI

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

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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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performing computer analysis of the results, the investigators could correlate the existence of both fluors in the same space—that is, attached to the same molecule. To measure a fragmentation reaction, they just looked for loss of the correlated signal. It is easy to see then that the reverse reaction (ligation) could also be recorded as the increase in correlated signal.

In an accompanying paper (2), the group went on to show that the FCS technique could be done fast and in small volumes. Amazingly, they were able to create conditions in which a sample volume as small as 1 fl (the size of the bacterium *Escherichia coli*) could be measured. The entire assay took only 1 s to complete.

Obviously, many uses of FCS in assembly and fragmentation reactions are possible. The only limitations seem to be attachment of the fluor groups and ensuring that they do not interfere with the reaction being measured. With current technology, it should be possible to measure 10^5 samples in a single day. Nonenzymatic assays, such as DNA-DNA or DNA-RNA hybridization would also lend themselves to FCS methodology, potentially paving the way for high-volume genotyping or sequencing applications.

–Robert Sikorski and Richard Peters

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Virtual Meetings

NET TIPS

Every successful scientist today relies on the timely exchange of information. Scientific meetings in particular have traditionally offered a forum to swap ideas, contacts, or stories with one's peers. With the explosion of the Internet, a number of online collaboration tools have been developed that could make many physical meetings all but obsolete in the near future. This brief review looks at one such Web-based collaboration product called NetMeeting from Microsoft. We focus on NetMeeting for two reasons: first, it is free, and second, it has consistently been rated as one of the best collaboration tools available. For instance, NetMeeting was one of the finalists in a review of Web communication applications performed by *PC Computing* magazine (January 1998 issue). Perhaps the major drawback about NetMeeting, however, is that it only runs on PCs that operate with Windows95. So far, there is no Macintosh version.

Application sharing is clearly one of the product's best features. You can use the NetMeeting World Wide Web interface to share the use of an entire application on your PC over the Internet with others, even if they do not have the application installed on their machine. There are two operating modes in NetMeeting: sharing and collaboration. In the sharing mode, you control the application while others watch over the Internet. In the collaboration mode, others can take control of the application over the Internet (or your LAN). You can also draw on a shared whiteboard, send text messages (chat), and transfer files among the group. The shared clipboard function lets you copy information (text or graphics) from a local document and paste its contents as part of a group collaboration. Finally, the latest version of NetMeeting has added a videoconferencing capability, which allows users to communicate with someone running another standards-based videoconferencing product such as Intel's Internet VideoPhone. If you do not have a camera to display images, you can still use the software as an Internet phone.

NetMeeting participants actually "meet" at a remote server somewhere on the Internet. By default, the meeting is automatically hosted on one of Microsoft's remote servers, which they call Internet Locator Servers. You can, however, choose another meeting place as well. A list of third-party servers capable of supporting such meetings is available at http://ils.microsoft.com/.

Although the company claims that the product can be used with modem connections as slow as 14.4 kb/s, it is generally advised that users dial-up with a connection at least as fast as an ISDN line, especially if you will be exchanging audio data. The majority of scientists have fast Internet access provided by their institutions, so this should not be a big issue. At the moment, the product is only available through Microsoft's Web site, where it can be downloaded free of charge (www.microsoft.com/netmeeting/); NetMeeting is not available on floppy disks or CDs. Microsoft has stated that NetMeeting will become an integrated component in the future operating system release, Windows98, along with Internet Explorer 4.0.

Overall, NetMeeting is an early version of a very neatly designed collaboration tool that is worth looking into. Given its early-stage release, it may not be for the faint of heart just yet, but there is little doubt that these types of tools will be applied to science soon.

For more info on NetMeeting check out www.cnet.com/Content/Reviews/JustIn/Items/0,118,33,00.html or www.medsitenavigator.com/tips.

–Richard Peters and Robert Sikorski

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Yeast Sites on the Net

SITE FINDER

A wealth of information useful to the yeast molecular biologist can now be found online. The yeast community has clearly extended their open and sharing culture to the Internet. Here are a few of the many sites on the Web:

Saccharomyces Genome Database
http://genome-www.stanford.edu/Saccharomyces/
This site at Stanford is a major access point for genomic information about this particular yeast. Resources here include the entire yeast sequence, detailed chromosome maps, sequence analysis software, and links to major yeast Web sites.

XREF Database
www.ncbi.nlm.nih.gov/XREFdb/
This online database is designed to find matches between human genes and those found in yeast. You can send your query sequence directly or sign up for an online account that will keep track of your favorite gene as the database is updated.

The Definitive Yeast Transformation Homepage
www.umanitoba.ca/faculties/medicine/human_genetics/gietz/Trafo.html
The title says it all. In fact, this site does a great job collecting protocols and tips for rapid introduction of DNA into yeast.

Gottschling Lab Home Page
www.fhcrc.org/~gottschling/homepage.html
This site has a nice collection of core yeast protocols with links to other yeast lab sites. By visiting a few of these lab home pages, you can find many useful technical tips.

–Robert Sikorski and Richard Peters

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