BIOMEDICAL / **DIAGNOSTICS**

NEWS

Nanotransistor Boosts Sensitivity of Gene Sequencer

New approach could hasten cheap DNA sequencing

By NEIL SAVAGE / DECEMBER 2011

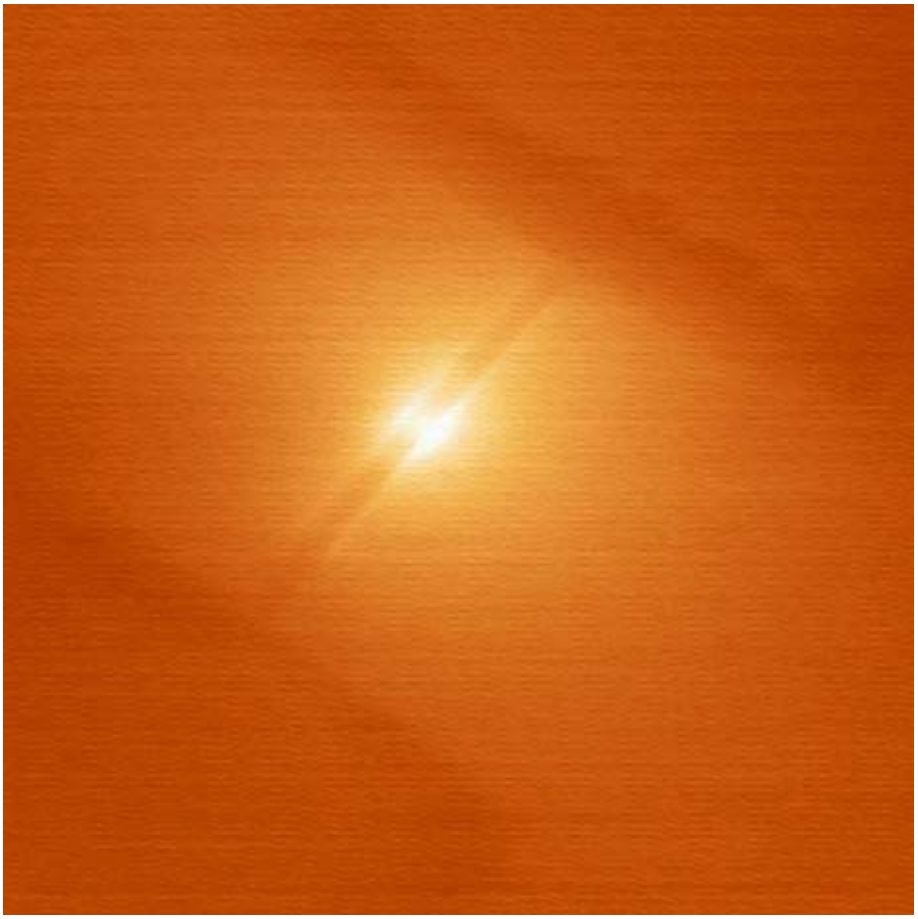

Image: Ping Xie and Charles M. Lieber/Harvard University

20 December 2011—Researchers dream of being able to sequence anybody's genome for less than US $1000, ushering in a new age of personalized medicine where treatments can be tailored to a patient's particular genetic makeup. One of the candidate technologies to achieve that dream is "nanopore sequencing," and researchers at Harvard say they've taken a big step toward making the technology work.

In nanopore sequencing, an electric field pulls ions in the water and strands of DNA through a minuscule protein hole or a hole in a solid-state membrane. Because the pore is not much wider than the DNA strand, when a strand passes through the amount of ionic current is altered. Each of the four nucleic acids in DNA—G, T, C, and A—whose sequence spells out the code for a living thing—can be identified by its distinct effect on the current.

But the current in question is very small, measured in picoamps. And the DNA passes through the pore at such a rapid clip that electronics have a difficult time distinguishing such a small signal in so short a time. One approach has been to try to slow the speed at which the DNA passes, but that's an imperfect solution.

The Harvard team, part of chemistry professor Charles Lieber's laboratory, took a different path—boosting the signal. Their device, described in the online version of *Nature Nanotechnology* this month, consists of a chip that holds a field-effect transistor built from silicon nanowire and placed on a membrane made of silicon nitride. The pore is a small hole through both the nanowire and the membrane. As is typical in nanopore chips, a small chamber on each side of the membrane holds a solution of potassium chloride in which the DNA strand floats. But in most systems, the concentration of solution is the same on both sides of the membrane. In Harvard's chip, the solution on the transistor side is just 1 percent the concentration of the solution on the other side.

Instead of measuring a change in current caused by a passing bit of DNA, the chip measures the conductance of the nanowire transistor near the nanopore, which is proportional to the current and voltage. The lower concentration of ions

on the transistor side of the membrane produces a localized distribution of voltage around the pore opening, which controls a large current passing through the nearby transistor and thus magnifies the signal. Ping Xie, a postdoctoral researcher in Lieber's lab, says other nanopore systems have to measure a current signal from tens of picoamps to a few nanoamps. "Now we can measure tens of nanoamps to hundreds of nanoamps," he says.

Where other nanopore systems operate at a rate of 10 to 100 kilohertz—not fast enough for DNA moving through the pore at roughly 1 million chemical units, or bases, per second—Xie says the Harvard version should in principle operate at a few gigahertz, far faster than the DNA moves, although they didn't have the equipment to measure that.

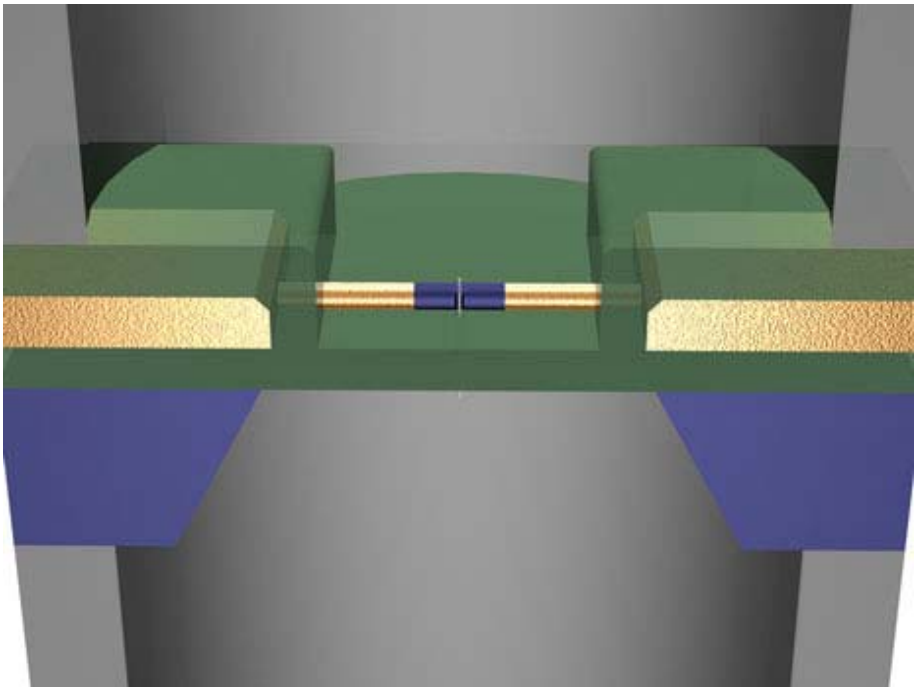

Image: Ping Xie and Charles M. Lieber/Harvard University

DNA SLIPSTREAM: Ionic current pushes DNA through a nanometer-scale pore and past a nanowire transistor [blue center]. The transistor amplifies the change in current allowing the DNA's sequence to be read.

An individual genome is a sequence of about 3 billion nucleic acids, so even at high speeds, sequencing with a single nanopore would take too long. Practical sequencers would have to consist of multiple nanopores. However, in previous nanopore sequencer designs, electrical cross talk would occur between adjacent nanopores unless each one was secluded in its own chamber of solution. The Harvard version relies on the highly localized voltage, which is concentrated within just 30 to 50 nanometers of the opening, preventing cross talk with other nanopores as long as they are at least a few micrometers apart. Xie says the design should allow many nanopores to be grouped together on a single chip with shared solution chambers.

Joshua Edel, a senior lecturer in micro- and nanotechnology at Imperial College London, says the scheme could work. Because it measures conductance, "ultimately this has the potential to achieve much higher resolution in order to distinguish different DNA bases when compared [with] the ionic current approach," Edel says.

"I think this is an exciting and promising approach and a great direction to go into," says Marija Drndic, associate professor of physics at the University of Pennsylvania. Both her group and Lieber's are separately exploring the replacement of silicon nanowires in nanopore sequencers with graphene nanowires, which should have even higher conductance and therefore produce an even stronger signal.

About the Author

Neil Savage writes about strange semiconductors and amazing optoelectronics from Lowell, Mass. In October 2011 he reported on a laser-powered mechanical memory chip.