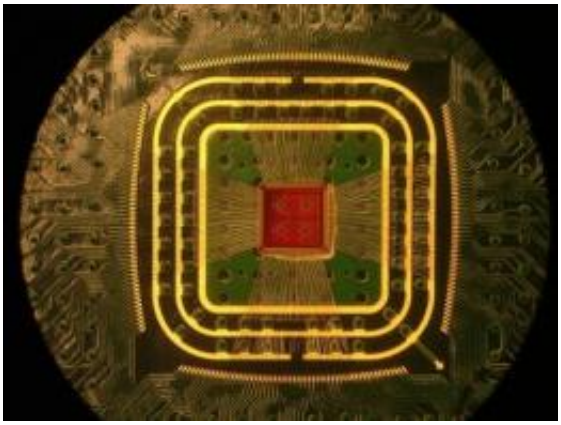
Researchers increase speed of single-molecule measurements

March 18 2012



This is a photograph of the Columbia Engineering team's custom multichannel CMOS preamplifier chip, attached to a circuit board with thin gold wirebonds. Credit: Columbia Engineering

As nanotechnology becomes ever more ubiquitous, researchers are using it to make medical diagnostics smaller, faster, and cheaper, in order to better diagnose diseases, learn more about inherited traits, and more. But as sensors get smaller, measuring them becomes more difficult—there is always a tradeoff between how long any measurement takes to make and how precise it is. And when a signal is very weak, the tradeoff is especially big.

A team of researchers at Columbia Engineering, led by Electrical Engineering Professor Ken Shepard, together with colleagues at the

University of Pennsylvania, has figured out a way to measure nanopores—tiny holes in a thin membrane that can detect single biological molecules such as DNA and proteins—with less error than can be achieved with commercial instruments. They have miniaturized the measurement by designing a custom integrated circuit using commercial semiconductor technology, building the nanopore measurement around the new amplifier chip. Their research will be published in the Advance Online Publication on Nature Methods's website on 18 March.

Nanopores are exciting scientists because they may lead to extremely low-cost and fast DNA sequencing. But the signals from nanopores are very weak, so it is critically important to measure them as cleanly as possible.

"We put a tiny amplifier chip directly into the liquid chamber next to the nanopore, and the signals are so clean that we can see single molecules passing through the pore in only one microsecond," says Jacob Rosenstein, a Ph.D. candidate in electrical engineering at Columbia Engineering and lead author of the paper. "Previously, scientists could only see molecules that stay in the pore for more than 10 microseconds."

Many single-molecule measurements are currently made using optical techniques, which use fluorescent molecules that emit photons at a particular wavelength. But, while fluorescence is very powerful, its major limitation is that each molecule usually produces only a few thousand photons per second. "This means you can't see anything that happens faster than a few milliseconds, because any image you could take would be too dim," explains Shepard, who is Rosenstein's advisor. "On the other hand, if you can use techniques that measure electrons or ions, you can get billions of signals per second. The problem is that for electronic measurements there is no equivalent to a fluorescent wavelength filter, so even though the signal comes through, it is often buried in background noise."

Shepard's group has been interested in single-molecule measurements for several years looking at a variety of novel transduction platforms. They began working with nanopore sensors after Marija Drndic, a professor of physics at the University of Pennsylvania, gave a seminar at Columbia Engineering in 2009. "We saw that nearly everybody else measures nanopores using classical electrophysiology amplifiers, which are mostly optimized for slower measurements," notes Shepard. "So we designed our own integrated circuit instead."

Rosenstein designed the new electronics and did much of the lab work. Drndic's group at the University of Pennsylvania fabricated the nanopores that the team then measured in their new system.

"While most groups are trying to slow down DNA, our approach is to build faster electronics," says Drndic. "We combined the most sensitive electronics with the most sensitive solid-state nanopores."

"It's very exciting to be able to make purely electronic measurements of single molecules," says Rosenstein. "The setup for nanopore measurements is very simple and portable. It doesn't require a complicated microscope or high powered instruments; it just requires attention to detail. You can easily imagine nanopore technology having a major impact on DNA sequencing and other medical applications within the next few years."

Shepard's group is continuing to improve these techniques. "With a next-generation design," he says, "we may be able to get a further 10X improvement, and measure things that last only 100 nanoseconds. Our lab is also working with other electronic single-molecule techniques based on carbon nanotube transistors, which can leverage similar electronic circuits. This is an exciting time!"

Provided by Columbia University