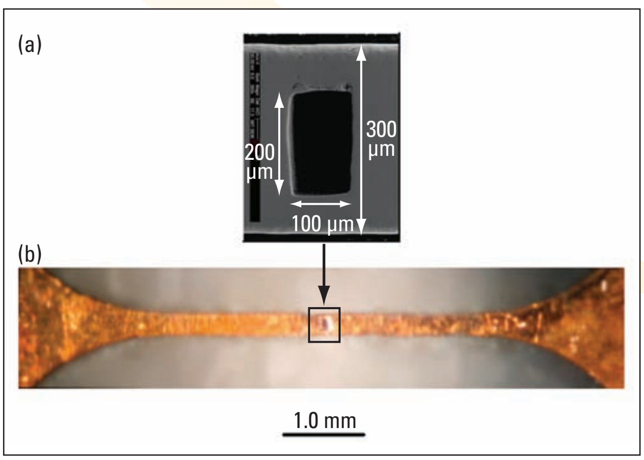
NMR probe gets new geometry

A microslot-based geometry for a miniaturized NMR probe opens up the possibility of analyzing nanomole to picomole quantities.

NMR is an information-rich technique. It tells you the 3D structure of molecules, as well as the temperature, pH, and other physical and chemical parameters of the environment. But its downside is that it's not very sensitive. You need relatively large volumes of samples at pretty high concentrations—just obtaining sufficient amounts of protein for an NMR experiment involves backbreaking, tedious work by a hapless graduate student. So Yael Maguire, Shuguang Zhang, and colleagues at the Massachusetts Institute of Technology designed a new miniaturized NMR probe that needs ~3500× less sample than conventional probes do (*Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 9198–9203).

Previous designs of miniaturized NMR probes were based on coils, and the sample was placed inside the coils. Maguire and colleagues took a different route. They cut out a rectangular microscale slot in a copper wire to produce a probe; the probe's size could range from centimeters to nanometers. The sample was laid on top of the slot. When the ensemble was dropped into an NMR magnet, the investigators found that the performance of their probe was similar to that of conventional ones.



(a) The rectangular slot is etched by a laser into a copper wire. (b) Probe after polishing. (Adapted with permission. Copyright 2007 National Academy of Sciences, U.S.A.)

Because of its different geometry, the prove developed by Maguire and colleagues "allows studies of biological molecules in much smaller volumes and at much lower concentrations than had previously been possible," says Arnold Schwartz, Varian's former director of NMR R&D. "The standard coil geometry used for NMR probes is such that it doesn't scale down very well to very small sample volumes. This is quite a novel geometry for the probe, and it appears to scale down to much smaller volumes than the historical coiled configurations."

Maguire says the inspiration came from wireless technology. "If you look at a cell phone or a laptop that has Wi-Fi connectivity, the antennae operate at around triple the frequency for NMR work. They don't have coils. They are actually just strips of copper. They're designed to enable long-range wireless communication, are inexpensive to make, and simple to fabricate. We wanted to use the same principles for an NMR probe," he says.

Maguire came across literature from the 1970s, when researchers were struggling to make chips for wireless communication. They had found that a little slot in a wire radiated an electromagnetic field that inhibited communication. But if something produces an electromagnetic field, it can also detect one, and Maguire recognized the wire's potential as a detector. He says, "I studied it some more and realized it was a very good geometry for looking at an NMR system. It's scalable and simple to fabricate. I didn't have to go for silicon manufacturing or anything like that. I could send it to the same companies that make circuit boards for electronics and, with a little bit of postprocessing, turn it into a very sensitive microdetector for NMR."

The flat, simple nature of the probe lends itself well to parallelization for simultaneous, multianalyte studies. Furthermore, "because it's planar, you can certainly integrate this [probe] with lots of different fluidic networks," says Jonathan Sweedler at the University of Illinois at Urbana–Champaign. He says the probe can be readily interfaced with most microfluidic device configurations, an advantage that microcoil-based probes don't have.

Indeed, Maguire and colleagues want to integrate microfluidics. "The challenge isn't making the probes. The challenge is how to move small amounts of sample," says Maguire. "The smallest amount of sample I looked at was ~30 nL, and that was starting to be a real challenge because I was doing everything by hand."

The investigators now have several directions in which to go. They want to combine NMR, via their new probe, with orthogonal technologies such as GC/MS or HPLC. They are interested in studying protein folding and protein–ligand interactions. Because the sample lies next to the probe, they also want to analyze cells by NMR, an experiment not possible with conventional probes. But Maguire says the applications for the new probe aren't restricted to biological ones. "There is a lot of small-molecule combinatorial chemistry that goes on," he says. "Being able to look at many samples at once using NMR could be a really interesting thing to do."

—Rajendrani Mukhopadhyay