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Better Pictures of Proteins

An ultrasensitive NMR probe could improve the diagnosis of diseases such as Alzheimer's.

By Katherine Bourzac

MIT researchers have significantly increased the sensitivity of nuclear magnetic resonance (NMR) spectroscopy, an analytical technique that can give detailed pictures of the structures of complex molecules like proteins. Improved NMR could help drug companies quickly screen libraries of potential therapies. It might also be used one day to test patients for the presence of abnormal proteins, such as those that build up in the brain as a result of Alzheimer's and Huntington's disease.

Until now, the use of NMR has been limited because the technique is costly and time intensive, and it requires researchers to gather relatively large samples of the molecule they'd like to study. The MIT method, which relies on a new kind of magnetic probe, could cut down the time it takes to perform these tests by a factor of 100, estimates Arnold Schwartz, former director of research and development at Varian (http://www.varianinc.com/cgi-bin/nav?index&cid=JNQLOQHNFI) , a manufacturer of NMR machines based in Palo Alto, CA. "This is a very novel approach compared to those taken over the past 30 years," says Schwartz.

NMR spectroscopy gives researchers information on the chemical composition and three-dimensional structure of molecules. "NMR allows you to make measurements between atoms and figure out a molecule's structure," says Yael Maguire (http://www.thingmagic.com/html/about/yaelmaguire.htm) , who developed the new NMR probe for his thesis work at MIT's Media Lab and presented the work this week at the European Symposium of the Protein Society (http://www.proteinsociety.org/) in Zurich, Switzerland.

A tool for determining the chemical structure of proteins has great potential clinical relevance, says Shuguang Zhang (http://web.mit.edu/lms/www/) , associate director of MIT's Center for Biomedical Engineering. The activity of protein drugs, for example, depends on the proteins' shapes. And the accumulation of misshapen proteins in the brain is believed to be at the root of neurodegenerative diseases like Alzheimer's. X-

ray crystallography can provide structural information similar to what's provided by NMR spectrometry, but it can take years of effort to get a protein to crystallize, says Maguire, and not all proteins will crystallize.

Because the radio-frequency signals that NMR spectroscopy relies on are very weak, large samples are needed to perform experiments. The instruments also require large, powerful magnets, which contribute to their size and expense. Hence, biochemists have had limited access to the machines. Maguire and his collaborators, who include Zhang and Neil Gershenfeld (http://web.media.mit.edu/~neilg/) of MIT's Center for Bits and Atoms, want to make NMR more widely available. "We dream of making it a tabletop machine in every lab and hospital," says Maguire.

Traditional NMR uses coils to detect the radio-frequency signals produced by some atoms, including hydrogen and carbon, when they are exposed to a magnetic field. But the complex shape of the coils makes them difficult to further miniaturize. In contrast, the MIT researchers fabricated a highly sensitive NMR probe out of a flat strip of copper similar to the antennas in laptops and cell phones. "It's simple to fabricate," says Maguire. "The same companies that make antennas can make these." A quick cut with a laser creates a small hole out of which a magnetic field can flow.

So far, the MIT researchers have used the probe to confirm known structures. In tests on a protein called ribonuclease, they were able to use 3,000 times less of the compound than is normally required to perform NMR spectroscopy; in tests on sucrose, they used 10,000 times less.

Zhang expects the more sensitive NMR system to be adopted first by structural biologists, then by the medical community. "As more and more people in other fields, including medical science and clinics, become more aware of NMR's power and sensitivity for diagnosis of protein-conformational diseases, they will inevitably use it," he says.

Maguire now hopes to integrate smaller magnets with the spectrometers so that they can truly fit on tabletops. He also hopes to integrate multiple NMR probes with microfluidic chips for future clinical tests that look for multiple biomarkers (like misfolded proteins) in a patient's blood or spinal fluid.
