MICROSCOPY

An Attractive New Way to Pin an ID on Atoms

It's not simple to get a good look at a complex molecule. Scientists use x-ray crystallography to see the atomic makeup and three-dimensional structure of molecules such as proteins, yet the technique is arduous, sometimes requiring months to resolve the structure of a large protein. Finding a better way has been the dream of a small group of microscopists for some time—and now they've come one step closer to it.

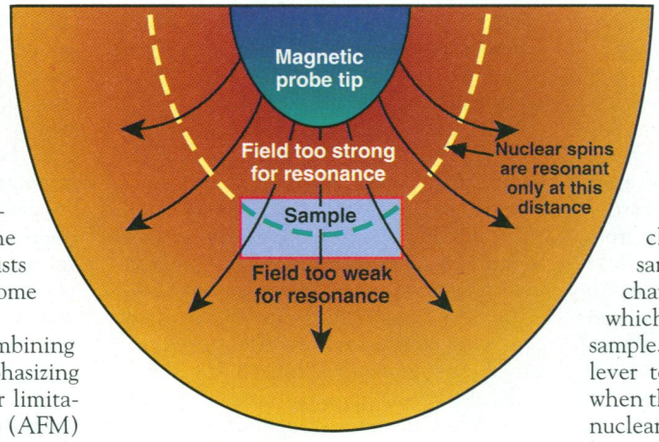
The basis of their dream is combining two powerful techniques—emphasizing their strengths while avoiding their limitations. The atomic force microscope (AFM) has been hailed for its ability to see single atoms. Yet the AFM can't provide that atom's chemical identity, nor can it probe beneath the surface of a sample. Nuclear magnetic resonance (NMR) imaging, on the other hand, can identify chemistry, but doesn't zero in on atoms as well as the AFM.

On page 1560 of this issue of *Science*, physicist Dan Rugar and his colleagues at the IBM Almaden Research Center in San José, California and Freie Universität in Berlin report that they have combined the ability of the AFM to home in on atoms with the power of NMR imaging to pin an elemental ID on those atoms. What is more, the new combined technique—dubbed magnetic resonance force microscopy (MRFM)—can do this both at and below the surface of a sample.

The new technique isn't yet by any means as precise as AFM alone. The current sensitivity only allowed the scientists to pin atomic ID tags on a collection of 10 trillion hydrogen atoms in a sample of ammonium nitrate. But even that is 100 times better than standard NMR detectors. And other researchers are hailing the result.

"It's really a fantastic experiment," says John Sidles, an associate professor of orthopedics at the University of Washington, who originally hatched the idea of combining NMR and AFM scanners (*Science*, 7 August 1992). "If the technique eventually can be used to image individual molecules, it will be extremely useful," adds Marc Desrosiers, a research chemist at the National Institute of Standards and Technology in Gaithersburg, Maryland.

Standard AFM produces a surface view of atomic landscapes with a probe on the end of a sensitive cantilever arm. Repulsive forces between the probe and an atom produce movements in the cantilever to reveal an atom-by-atom relief map. Rugar's group wanted to get that kind of precision, but they wanted a chemical ID as well.



Inside insight. Unlike other atomic imaging techniques, magnetic resonance force microscopy can peer at the interior of a sample.

SOURCE: DAN RUGAR AND JOHN SIDLES ILLUSTRATION: E. CARROLL

NMR can identify certain atoms based on the unique behavior of their nuclei. Researchers have long known that the nuclei of certain isotopes act like tiny bar magnets, with north and south poles. When placed in an external magnetic field, these "nuclear magnets" start to align with the field. But energy from an atom's temperature knocks them out of alignment. The nuclear bar magnets rotate in circles, much as a top travels across a flat surface while it spins. The rate at which these magnets rotate is different for different isotopes. In hydrogen nuclei, for example, it rotates four times faster than it does in carbon-13. Researchers can use these unique rotational signatures to identify particular atoms.

To make use of those rotational signatures, Rugar's group started with an exquisitely sensitive cantilever that, as in an AFM, translates a force into movements of the cantilever that can be spotted optically. In this setup, however, the forces used are magnetic, not the repulsive force between an atom and a standard AFM probe.

On one side of the vertically aligned cantilever, Rugar's team placed a tiny sample of hydrogen-rich ammonium nitrate molecules. To the side, they positioned a tiny iron magnet and, above, another magnetic field generator, called a radiofrequency (rf) coil (see diagram on p. 1561). Then the nuclear bar magnets in the sample began to align with the external magnetic field. Their north poles were attracted to the south pole in the iron particle, pulling the two closer together and causing the cantilever to bend.

The team then turned to the rf field—which changes its direction, or oscillates, very quickly. The frequency of the rf field can be tuned to oscillate at different rates. When tuned to match the rotation frequency of particular nuclear magnets, the rf field nudges the magnets again and again as they circle, pushing them farther and farther over until the poles eventually reverse.

By reversing the poles of the nuclear magnets, the force between the sample and the iron particle was changed from attractive to repulsive, which pushed the cantilever away from the sample. Continued reversals cause the cantilever to vibrate. Since this only happens when the rf field and the rotation rate of the nuclear magnets match, the cantilever vibration is a signal that a certain isotope is present in the sample.

Getting a peek at the interior of a sample is a byproduct of this approach. The magnetic field emanating from the iron next to the cantilever weakens over distance, Rugar says. "This means that different parts of the sample experience a different [magnetic] field," he explains. "The part of the sample closer to the iron particle sees a stronger magnetic field than that farther away." And only a narrow slice of atoms at a precise distance from the iron particle experiences the precise magnetic field strength needed to produce the NMR effect. To map the distribution of a single element within a sample therefore only requires moving the iron particle slightly in relation to the sample.

Of course, drastic improvements in resolution and sensitivity will be needed if the device is ever to focus on single atoms and help map the atomic makeup and structure of proteins and other biological molecules. The group will have to miniaturize the iron particle much further and move it closer to the sample, Rugar says, to increase the magnetic sensitivity. They will also have to operate the apparatus at lower temperatures to dampen the cantilever's natural vibrations, allowing smaller forces to be observed. "I think it's a lofty goal," says California Institute of Technology physics professor Michael Roukes. "But it looks promising to me."

Rugar agrees that "it's going to be hard," but notes that the physics behind the idea seem sound. "The key is that nobody has seen a showstopper in terms of physics," he says. And therefore, the scientists say, the show will go on.

–Robert F. Service