MICROSCOPY

Good vibrations

A microscopy platform that brings magnetic resonance imaging to the nanometer scale offers a promising new tool for three-dimensional molecular visualization.

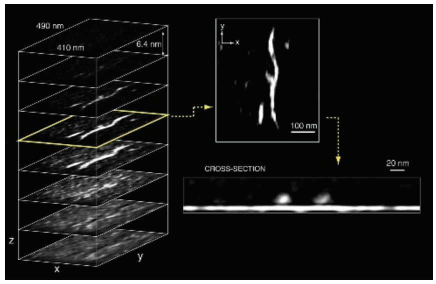
Magnetic resonance imaging (MRI) generates high-resolution three-dimensional images of complex tissues such as the brain without the need for potentially harmful radiation and has become a standard tool for doctors and clinical researchers alike.

However, this method is also appealing to scientists working with far smaller specimens. "It's 3D, non-destructive, and it has chemical selectivity—those are all great reasons for trying to extend this to the molecular scale," explains Dan Rugar, of IBM's Almaden Research Center. It poses an extreme challenge to detect weak signals produced by magnetic resonance in samples of this scale, but recent work from Rugar's team has demonstrated a promising MRI-based platform that attains imaging of biological samples at a resolution that rivals that of scanning electron microscopy (Degen *et al.*, 2009).

Rugar's early work at IBM focused on atomic force microscopy, in which a tiny probe is scanned along the surface of a sample, producing vibrations that yield detailed structural information. When he began applying this method for analyzing magnetic bits on hard drives, it caught the attention of John Sidles at the University of Washington. "He had a vision of trying to come up with a molecular structure microscope based on measuring signals from the magnetic nuclei of atoms," recalls Rugar.

Their collaboration laid the groundwork for a new high-resolution imaging system, magnetic resonance force microscopy (MRFM), which Rugar and Sidles developed in the early 1990s. Like MRI, MRFM uses a magnetic field to induce alignment of the axis of spin among the hydrogen atoms in a sample, which are then subjected to pulses from a secondary magnetic field at an appropriate resonance frequency. In MRFM, however, the sample is positioned at the tip of an extremely thin silicon cantilever; when protons in the sample flip their orientation in reaction to the magnetic pulses, the cantilever produces tiny yet detectible vibrations.

To maximize the signal generated by these protons, the sample must be subjected to a very strong yet focused magnetic field. This



MRFM image reconstruction. MRFM was used to collect two-dimensional image data at multiple *z* layers (left) of individual tobacco mosaic virus particles (upper right), which were assembled into a high-resolution three-dimensional reconstruction (bottom right). Image courtesy of IBM.

is accomplished by a specially designed magnetic tip that establishes a dome-shaped 'resonant slice'. The tip is scanned laterally and at increasing degrees of proximity to the sample, with detectable resonance occurring only in regions that fall within this thin slice; the resulting information can then be reconstructed into three-dimensional images with nanoscale resolution.

An early test of MRFM achieved 90-nm resolution with an inorganic sample (Mamin *et al.*, 2007), but now Rugar and colleagues have surpassed this by a full order of magnitude, successfully imaging individual tobacco mosaic virus particles with a resolution of 4 nanometers. As impressive as this level of detail is, Rugar believes that subnanometer resolution should be achievable. "I can foresee sensitivity improvements by factors of at least ten to a hundred," he says, "mainly by improving the magnetic tips."

Future goals include modifying MRFM to detect other biologically relevant elements and developing preparation methods that will enable the imaging of hydrated organic samples. But above all, Rugar's primary focus is on pushing the resolution as far as it can go. "Can we build a microscope where you can just go in and take a 3D picture of molecules and determine their structures and interactions by direct imaging?" he asks. "That's the vision that drives us."

Michael Eisenstein

RESEARCH PAPERS

Degen, C.L. *et al.* Nanoscale magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **106**, 1313–1317 (2009).

Mamin, H.J. *et al.* Nuclear magnetic resonance imaging with 90-nm resolution. *Nat. Nanotechnol.* **2**, 301–306 (2007).