MEETING BRIEFS

Innovation in San Francisco

In San Francisco 2 weeks ago, AAAS and *Science* sponsored a new meeting, Science Innovation '92. The unusual gathering focused not on research results but on new techniques and instruments, particularly for biomedical science. As seen in the stories below, some of the most eye-catching innovations emerged at the intersection of physics and biology.

Electrifying the Petri Dish

The classic Petri dish, the workhorse of biologists for generations, has finally entered the age of electronics. At the AAAS Science Innovation '92 meeting biophysicist Ivar Giaever of Rensselaer Polytechnic Institute (RPI) described a device in which tiny gold electrodes attached to a Petri dish allow researchers to monitor subtle changes in cell motility and shape.

"It's really a unique way of looking at cells. Whatever the cell does, the electrical measurements mirror," says Giaever, who won a Nobel Prize in 1973 for his superconductor studies. Giaever hopes to commercialize his charged-up Petri dish; he thinks it could find a home wherever investigators are interested in tracing the movements of cultured cells. That includes studies of cancer and toxins, both of which can disrupt the normal patterns of cell attachment and spreading.

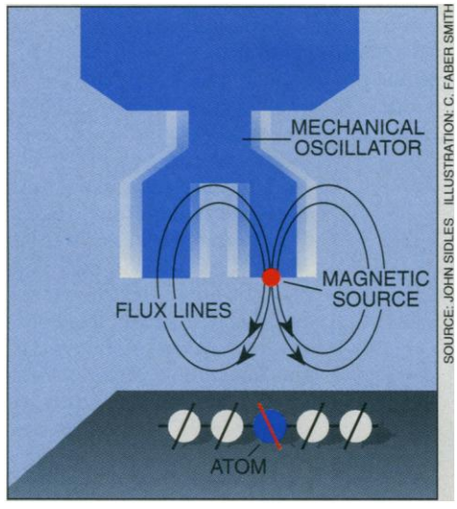
Ordinarily, cells placed in a culture medium anchor themselves to the bottom. Within hours, they lose their typical rounded shape and flatten out, extending footlike processes. To study this behavior, biologists can halt the process at any point—for example, by killing the cells with formalin. Then they can look at the cells under a microscope in search of any abnormalities. But there's no good way to examine the process in real time, says Giaever. One consequence, says Giaever's RPI colleague Charles Keese, is that "most of the current [toxicity] assays look at cell death as the endpoint." Giaever thinks the new tool may refine these and other tests by opening a window on the behavior of living cells.

In this electronics-era Petri dish, the tissue culture medium acts as an electrolyte solution, carrying a current of 1 microamp between flat electrodes on the bottom of the dish. Repeated tests, says Giaever, have shown that this small amount of electricity doesn't change the cells' behavior. But the cells do affect the electrodes, changing their impedance, a ratio of the voltage to current. Surprisingly, the number of cells anchored to an electrode is not the only parameter. Just as protrusions on a car can change its aerodynamics, small changes in cell shape or position can alter the flow of current from the electrode into the medium, thus affecting the impedance. And by monitoring those changes, researchers can electronically observe the cells as they attach, spread, move, and even divide.

In a recent paper in the *Proceedings of the National Academy of Sciences*, for example, Giaever and Keese report that fluctuations in impedance could be used to detect cell motion as small as one nanometer. The RPI duo has also teamed up with a group at John Hopkins University in a study of the motility of metastasizing cancer cells. If the new Petri dish continues to pan out, cell biologists the world over may be reaching for another extension cord.

Tuning in to Single Molecules

John Sidles is living proof of the benefits of interdisciplinary research. The associate professor of orthopedics at the University of Washington in Seattle felt frustrated that not knowing the three-dimensional structure of key proteins—a receptor for a virus, say, or a vital protein altered by a genetic defect—could stymie researchers seeking to cure the diseases he sees every day in the clinic. How, he asked, could existing methods for finding molecular structures be improved on?



Molecular microscope. A minute oscillator resonates with the nuclear spins of atoms.

Sidles may be on a medical school faculty, but he has a physics doctorate. Reaching into his past, he brought forth a brainchild, a scheme for uniting two past imaging breakthroughs: magnetic resonance imaging (MRI) and the atomic force microscope (AFM). What Sidles envisioned was a single-molecule MRI machine—a notion he described at a poster session of the meeting.

Standard structure-determination methods require macroscopic quantities of the substance to be analyzed, often in the form of a pure crystal. That's often hard to come by. But if MRI could be applied on an extremely fine scale, Sidles thought, it might be possible to image individual molecules in their normal environment—you could peruse the key AIDS receptor CD4 as it sits on a cell surface, for example.

That's a radical idea, though, because traditional MRI works by establishing a resonance between a field generated by radio frequencies and the magnetic "spins" of different nuclei in large specimens—say, the human body. The signals emitted by hordes of resonating nuclei can provide a map of their distribution, creating ghostly pictures of living anatomy, for example. But how could you listen in to the resonance of an individual nucleus?

Sidles wondered whether a modified AFM could do the trick. A standard AFM traces the surface of atoms and molecules with a sharp tip attached to an exquisitely precise microcantilever, rather like a phonograph needle playing an atomic-scale record. Sidles' strategy for molecular MRI entails replacing the tip with a mechanical oscillator that hovers above the surface, throwing out a magnetic field. As the vibrating tip passes over each nucleus, the nuclear spin should couple with the magnetic field and exert a force on the oscillator, he thought. That should change the tip's vibration by an amount that reveals the nucleus's resonance frequency. And since a magnetic field penetrates the surface, a scan could provide a three-dimensional plot of the types and positions of the nuclei in a single molecule—the makings of a structural image.

Sidles' theoretical analyses, which he has published in the 24 February *Physical Review Letters* and in this month's *Review of Scientific Instruments*, are already being put to the test by experimentalists, including AFM expert Dan Rugar and his colleagues at IBM's Almaden Research Center in San Jose. "There are a lot of technical challenges to be overcome," says Rugar, pointing out that he and his colleagues are trying to measure forces nearly a billion times smaller than is normally done with an AFM. But the IBM team's early results, though still unpublished and far from being of use for imaging, have encouraged them to continue working on the project.

What's more, Sidles' notion seems to have re-awakened the field of magnetic resonance imaging. "It's very rare in [MRI] now to have new ideas," explains Eric McFarland, a nuclear engineer at the University of California, Santa Barbara. "[Sidles' idea] raised my eyebrows and stimulated my thinking." And that was precisely what Sidles hoped for when he stepped out of his clinic full of needy humans and back into the world of physics.

–John Travis