MEETING BRIEFS

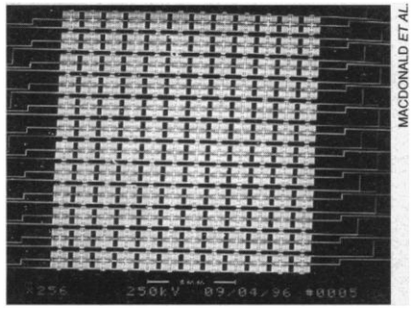
Atomic Landscapes Beckon Chip Makers and Chemists

Researchers convened last month at the annual American Vacuum Society meeting in Philadelphia, Pennsylvania, and the Welch Foundation 40th Conference on Chemical Research in Houston, Texas. Talks covered topics ranging from atomic imaging arrays to glimpses of conformational changes in individual molecules.

Scanning scopes go parallel

Less is indeed more. Or at least it is in the world of computers, where crafting ever smaller transistors allows more of the data crunchers to be crammed on a chip. That quest has some researchers trying to turn their most powerful microscopes—instruments that let them see individual atoms—into tools that could build atom-scale electronic devices. So far, these microscopes, which work by scanning an ultrasharp tip across a surface, are too slow to be taken seriously as chip makers. But researchers are working to build huge arrays of tips that could make the work go faster, by etching thousands of tiny features in parallel. Now that effort is itself picking up speed.

At the American Vacuum Society meeting two weeks ago, a team of researchers led by Cornell University electrical engineer Noel MacDonald reported that they have constructed an array of 144 scanning probe tips. Their array is the largest built to date, although they have yet to design and lay down the intricate electronic connections needed to get this multitude of tips functioning as a single machine. And at the Welch Foundation Conference last week, a second team, led by Calvin Quate and Stephen Minne at Stanford University, reported building an array of 50 probe tips. Though their array is smaller, they've succeeded in getting at least a few of the probes to work in parallel.



Future chip makers? An array of 144 scanning probe microscope tips.

The new results are "very impressive," says Dan Rugar, a scanning probe specialist at the IBM research center in Almaden, California. Rugar is among the many scientists who are intrigued by the possibility of using atomic imaging tips not just for etching transistors but for writing and reading ultrasmall bits of digital data on super-dense recording media—the equivalent of CD-ROMs and computer memory chips. Legions of tips operating in parallel could greatly boost the reading and writing speeds of such devices. But Rugar notes that "[the teams] still have a long way to go" before the arrays will be ready for duty in chip factories and disk drives.

To construct their arrays, both teams built variations of the common atomic force microscope (AFM). In conventional AFMs, the atomic imaging tip sits on the end of a long cantilevered arm that moves up and down as it scans a surface's bumpy atomic contours. A laser beam reflected off the arm detects the movement and shuttles the information back to a computer, which recreates an image of the surface in vivid, atomic detail. To ensure that the tip stays in contact with the surface it's scanning, the data from the laser also are fed back to tiny actuators on a stage that holds the surface in place. Made from so-called piezoelectric thin films, which expand and contract slightly in response to an electric current, the actuators push the sample up and down to meet the probe tip.

One big challenge for the array builders was figuring out ways to move—and monitor—each tip in their array independently. That meant incorporating separate sensors and actuators into each cantilevered arm. Quate's and his colleagues' answer was to create an arm that looks something like a dowsing stick with the probe tip sitting where the two ends meet. An electric current looping through the arm's twin segments allows the system to sense motion. As long as the segments remain straight, the amount of resistance to the current is steady; but when the scanning tip encounters a protruding atom, the segments bend slightly, increasing the resistance. Meanwhile, piezoelectric films at the base of the arm expand and contract to keep it from touching the surface.

MacDonald and his colleagues Scott Miller and Kimberly Turner chose a different shape for the arms in their larger array: more like microscopic teeter-totters, with the scanning tip parked at one end of the moving beam. This configuration allows the researchers to build sensors and actuators out of silicon and metals alone, bypassing often-fragile piezoelectric films. This approach, MacDonald believes, will allow the team to easily build ever larger arrays. The Cornell group has shown that they can scan a sample surface with a single teeter-totter tip. But they have yet to wire up the electronic controls that would allow the tips to move in concert.

At this point, neither team has tried to use their arrays to carve circuit features on a chip, or write bits of data on a surface. But Quate impressed his audience at the Welch conference with images showing four side-by-side tips imaging different portions of a surface in parallel. And he says that's just the beginning. By next year's Welch conference, Quate predicts that "we'll be writing 1-cm-by-1-mm areas and we'll be doing it very fast." For devotees of the very small, those are big numbers.

Lone shape shifters spotted

Shape shifting isn't just for science fiction. It's part of the everyday repertoire of proteins and other molecules, which change their shape, or conformation, as they interact with each other. Until recently, researchers only could track these changes indirectly, with imaging techniques such as nuclear magnetic resonance spectroscopy that have to sample millions of copies of a molecule before yielding a composite portrait. But at the annual AVS meeting, a group of IBM researchers reported that it has taken snapshots of individual molecules as they change shape—a first for investigators of the submicroscopic world.

The feat offers researchers a new way to investigate how the properties of individual molecules change as they alter their shapes, says Paul West, a physical chemist at Topometrix, a company that makes atomic imagers in Santa Clara, California. That could provide scientists with a new strategy for improving the performance of a host of electronic devices, including light-emitting diodes (LEDs), says IBM physicist Thomas Jung, who reported the study at the meeting. Researchers developing LEDs made from organic materials have long sought molecules that could channel more electric charge, and hence generate brighter light. Watching the gymnastics of candidate molecules might help researchers choose organics with the most promising electronic properties.

For their studies of shape shifting, Jung and his IBM colleagues Reto Schlittler and James Gimzewski turned to the porphyrins, a class of organic molecules that adhere readily to metal surfaces. The porphyrins the researchers studied look something like 4-poster beds, with a flat, square-shaped group in the middle (the mattress) surrounded by bulky

hydrocarbon groups at each corner (the legs). Earlier this year, the researchers succeeded in moving around individual porphyrins deposited on a metal sample with the ultrafine probe of a scanning-tunneling microscope, a device that can read a surface's atomic contours. (*Science* 12 January, p. 181).

In the study reported at the conference, the researchers discovered that the 4-poster porphyrins adopted different conformations on different metallic surfaces, as the legs of the molecules bent to adapt to the spacing of the atomic rows on the metal surfaces as well as the amount of electrical attraction between the mattress and the various surfaces. On copper, for example, the legs were oriented roughly in squares, while on silver they were positioned in long rectangles. On gold, the porphyrins adopted two different shapes, and the researchers were able to take before-and-after snapshots of the transition.

When they briefly heated a sample of gold coated with porphyrins, the individual porphyrin molecules adopted a rectangular shape. But after heating the sample for another 20 min, the same porphyrins stretched into longer rectangles. The researchers believe that the extra heat allowed the porphyrin molecules to wiggle into a more energetically stable binding position, in which the long axis of the rectangular porphyrins straddled the rows of gold atoms.

The next step is to see whether researchers can understand how precise conformational changes influence properties such as the ability of the molecules to conduct electrical charges. If they succeed, techniques for mastering shape shifting could trigger some technological shifts as well.

–Robert F. Service

APOPTOSIS

Life-Death Balance Within the Cell

When it was first identified more than two decades ago, tumor necrosis factor (TNF) seemed like a promising cancer killer. Indeed, this signaling molecule, which is made by cells of the immune system, was named for its ability to shrink tumors. But researchers soon learned—much to their disappointment—that TNF doesn't kill most types of cancer cells. Now, three research teams, in separate reports in this issue, have unmasked the reason for its fickleness.

As many researchers have suspected, TNF undermines its own killing powers. Even though it triggers a biochemical pathway that leads to the programmed form of cell suicide known as apoptosis, it also activates a key molecule that can block this very pathway, and so sets up a delicate life-death balance within the cell. And these findings have again raised hopes for potential therapies, for the researchers also show that disrupting the protective mechanism makes cells much more vulnerable to killing, not only by TNF but also by radiation and a chemotherapy drug. "The data are crying out for clinical trials," says cell-death researcher Vishva Dixit, of the University of Michigan.

The first clues to TNF's dual nature came several years ago when a number of groups observed that cells treated with drugs that block protein synthesis are more easily killed by TNF. "Clearly genes were being turned on that could protect against cell death," says David Goeddel, who studies TNF at Tularik, Inc., in South San Francisco. Researchers suspected those genes may be getting switched on by a protein called nuclear factor kappa B (NF-κB), which is activated by TNF and, in turn, turns on genes involved in the body's response to inflammation, infection, and stress.

That idea gained support last year when David Baltimore's group at the Massachusetts Institute of Technology reported that knockout mice missing NF-κB die before birth, apparently of a massive die-off of liver cells. That implied that NF-κB protects embryonic liver cells from committing suicide, but, says Baltimore, "we couldn't generalize it" to other cell types, since other parts of the embryos seemed fine.

Then Gail Sonenshein's group at Boston University Medical School reported earlier this year that inhibiting NF-κB causes the B cells of the immune system to die of apoptosis. But her findings weren't generalizable either, because B-lymphocytes are a special case: NF-κB is always active in these cells, whereas in most other cell types it is bound up in the cytoplasm by an inhibitor molecule called IκB, which must be destroyed for NF-κB to be activated.

The new papers, from Baltimore's group (p. 782), Inder Verma's team at the Salk Institute in San Diego (p. 787), and Albert Baldwin's group at the University of North Carolina (p. 784), broaden the earlier findings and link them to the TNF puzzle. Baltimore's group treated cells taken from NF-κB knockout mice with TNF, and compared their response to that of cells from normal mice. The normal cells were fine, but those lacking NF-κB died. Baldwin's and Verma's groups took a different approach: They introduced into a variety of cultured tumor and nontumor cells a mutant form of IκB that acts as a "super-repressor," keeping NF-κB irreversibly shackled in the cell's cytoplasm. With NF-κB out of the picture, TNF could kill all the cell types. Goeddel and Michael Karin, of the University of California, San Diego, have similar results in press. As Sonenshein puts it, "there appears to be quite a general role for NF-κB in [preventing] apoptosis."

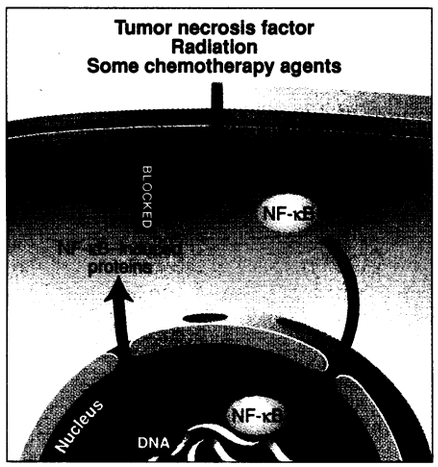


ILLUSTRATION: K. SUTLIFF

Suicide prevention. NF-κB turns on protective proteins that can help cells resist death.

Baldwin's group has already begun to explore the implications of that role for cancer therapies, many of which work by triggering cell suicide. Noting that radiation also activates NF-κB, Baldwin says, "I started thinking, can we make tumor cells respond better to radiation by blocking their NF-κB activation?" The answer turned out to be yes; Baldwin's team found that a human tumor cell line in which NF-κB was bound up by the IκB super-repressor was much more readily killed by radiation, and by the chemotherapy drug daunorubicin, than were normal cells.

Even cancers that at first respond well to radiation or drugs often develop resistance by turning off their suicide response, and Sonenshein thinks drugs that inhibit NF-κB, several of which are already in clinical trials for AIDS, may help turn it back on. At least some tumor cells show changes in NF-κB that could contribute to their resistance to death: Sonenshein has unpublished results that human breast cancer cells have NF-κB continuously turned on, while normal breast cells do not. If turning off NF-κB could reboot the suicide pathway in tumor cells, says molecular oncologist David E. Fisher of Harvard Medical School, that would be a boon. But he cautions that suicide may be turned off in cancer cells in a variety of ways, and not all of them may respond to NF-κB inactivation.

Fisher adds another caution: An anti-NF-κB approach would have to be tumor specific, or it might wreak havoc by increasing the killing of normal as well as cancer cells. Nevertheless, this view of cells' life-and-death balance might eventually provide a boost to cancer treatments or even help tumor necrosis factor finally live up to its name.

–Marcia Barinaga