# Exploiting the Nanotechnology of Life

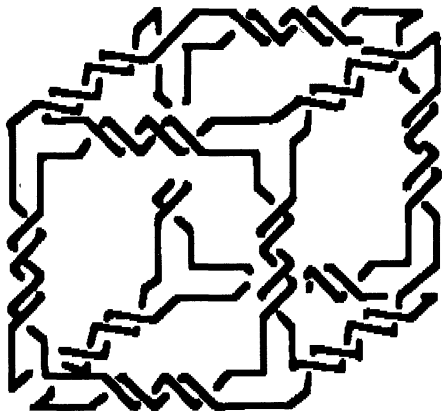
*A group of nanoengineers is raiding the living world, bent on appropriating its tiny protein machines*

IMAGINE BUILDING A COMPUTER THAT RECognizes complex images, converses in spoken English, and even inexpensively manufactures and programs new copies of itself. A pipe dream? Perhaps not, if you consider that a fully functional prototype for such a remarkable contraption is sloshing around inside your skull. Of course, brains have an unfair advantage: They're built out of proteins, nanometer-scale molecules so versatile that they serve living organisms as ultrafast switches, chemical reaction chambers, pattern recognizers, batteries, data libraries, assembly workers, and much more. Too bad we can't build things out of these marvelous molecular devices. Or can we?

Hundreds of scientists, operating at the frontiers of nanotechnology and biology, are betting we can. They're not quite ready to build a brain, but already these researchers are smudging the line between the manmade and the natural, putting biomolecules to new uses in the hope of setting the stage for better computers, medical diagnostic tools, and chemical sensors, among other things. Their simple credo: Why reinvent the wheel? Nature, after all, has spent billions of years perfecting a dazzling orchestra of hardworking biomolecules for sustaining life. "Biomolecular systems have such fantastic properties in and of themselves, and they literally grow in trees," says Stanford chemist Steven Boxer. "We've decided that since we can't beat them, we should join them."

Not that biomolecules are easy to harness. They are so small, so complex, and in many cases so prone to malfunctioning outside their ordinary venues that working with them can be a study in frustration. "We have so many different problems to face in fabricating organized [biomolecular] structures," sighs Tokyo Institute of Technology researcher Masuo Aizawa, a leading figure in Japan's bionanotechnology program. Undaunted, bionanotechnologists around the world are attacking the obstacles with a melange of tools and techniques culled from several disciplines. Genetic engineering makes it possible to tailor a protein's makeup, and hence its function. Organic chemistry provides new materials for anchoring and preserving the altered proteins. And electrical engineering offers ways to detect signals from the internal workings of the proteins. When it all comes together, the result is the conversion of a small assembly of biomolecules, or even an individual biomolecule, into a custom-designed machine.

Take the efforts of Stephen Mann at the University of Bath, who with his colleagues is turning proteins into nanoscale chemical-processing plants. The group has been focusing on ferritin, a protein found in the livers of humans and a wide range of other organisms that forms 8-nanometer-wide cages with a strong affinity for iron oxide. When free iron in our bodies picks up oxygen and forms rust, it does so inside the ferritin structures, which keep the toxic compound safely caged. "We had been studying the structure and properties of the native protein," recalls Mann, "when it occurred to us that we might be able to use the protein as a reaction vessel for controlling the particle size of other materials."



SOURCE: NADRIAN SEEMAN

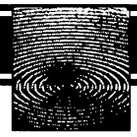
**Not your average double helix.** *DNA is wrought into a cubic scaffolding.*

Mann and his team have found that the protein can cage several other compounds besides iron oxide, including manganese oxide and iron sulfide. The next step is to alter the chemical affinities of the protein itself to get it to trap still other compounds. "We've identified the two key sites in the protein involved in the specific mineralization product," says Mann. "In principle, we should be able to engineer the protein to fit the mineralization product we want inside it." That possibility might appeal to semiconductor researchers, who are now striving to form minute structures with unique quantum-mechanical properties (see page 1306). What's more, caged particles would enjoy an unrestricted ride through the human body, where they might be useful for diagnosing or treating disease.

Other researchers picture biomolecules in more active roles. They hope to capitalize on biomolecules' extraordinary sensitivity to their environment in order to make improved biosensors. Conventional versions of these sensors, widely used in medical diagnosis, typically rely on detecting chemical changes triggered by enzymes that have locked onto a target molecule. But in the new, more sensitive biosensors researchers have in mind, the signal flows directly from the internal workings of individual biomolecules.

Biosensor developer Felix Hong of Wayne State University Medical School, for example, is exploiting a light-sensitive bacterial protein called bacteriorhodopsin. Exposure to light causes bacteriorhodopsin to pump out a proton, resulting in a minute electronic signal that Hong can detect. The pumping action, and hence the signal, depends on the molecule's chemical environment—and the specific chemical sensitivity changes with the frequency of the light. Hong has discovered, for example, that when the molecule is exposed to one frequency, it emits a signal that falls off as the acidity of the medium increases, while a different frequency leaves the molecule sensitive only to the concentration of chloride ions. The result: a prototype dual-function biosensor that, in response to a simple shift in light frequency, can switch between measuring acidity and chloride concentration.

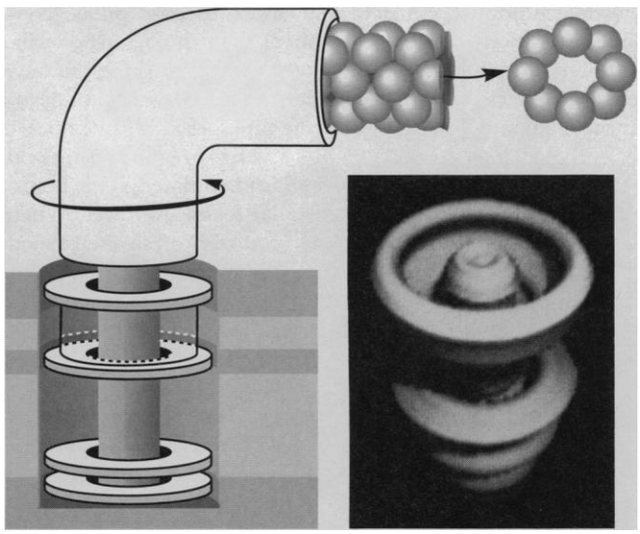
To other researchers, such sensitivity has made certain proteins into tempting candidates for biomolecular switches that might someday give semiconductor technology a run for its money. Stanford's Boxer, for example, is pinning his hopes on another bacterial protein that responds to light, in this case by pumping out an electron. In nature, the electron displaced by this "photosynthetic reaction center" drives chemical reactions that provide energy for the organism's vital processes. Boxer instead gets the reaction center to hand off the electron to other proteins or directly to metal electrodes. Because the light-driven hand-off can be switched off and on with a second beam of light or with an external electric field, the protein could theoretically serve as a transistor-like element in an elec-



tronic or optoelectronic circuit.

Why bother making protein transistors, when researchers are busily shrinking microcircuits made of conventional semiconductors? Boxer sees the promise that researchers might someday find a way to coax biomolecular components to connect themselves up right in the vat. "The real advantage to making things out of biological molecules is that they can self-assemble," says Boxer. "You only have to look in the mirror to see a good example of that."

Boxer warns that he has a way to go before he's churning out self-wiring biotransistors. Right now, he's wrestling with the task of getting the protein to stick to electrodes and other surfaces, a feat he accomplishes by genetically altering the bacteria so that they produce a modified protein equipped with small molecular hooks. "Once you build the interface between biological molecules and electronic components," he explains, "there are a lot of things you can do."



SOURCE: *MOLECULAR CELL BIOLOGY*. ILLUSTRATION: D. DEFRANCESCO (LEFT); SOSINSKY, FRANCIS, STALLMEYER, AND DEROSIER (RIGHT)

**An inspiration for nanoengineers.** *A molecular motor powers the flagellum of a bacterium* (left). *A computer-processed electron micrograph shows the base of the motor* (right), *seen from below.*

Syracuse University chemist Robert Birge is also trying to develop biomolecular computer components, but he doesn't want to wait for an interface. To get around the need for contacts and wires, he has turned to bacteriorhodopsin, the same molecule Hong has fashioned into biosensors. Besides generating an electrical signal when struck by light, bacteriorhodopsin changes its optical properties—a feature Birge has exploited to build a fully optical computer memory. By laying down a thin film of bacteriorhodopsin on a glass disk and then shining a sharply focused laser on tiny spots, Birge is able to "write" information on the film, then "read" it by employing a second laser to determine which spots have been optically altered. Birge's prototype is as fast as the fastest semiconductor memory, and he predicts the commercial version will cost about a tenth as much.

In such efforts, the idea is to coax proteins to perform the same functions now filled by nonbiological components in conventional computers. But Wayne State University computer scientist and biophysicist Michael Conrad thinks a future biomolecular computer might operate on very different principles. Sure, Conrad says, some biomolecules can process electrical or optical signals, but what proteins are really good at is recognizing and reacting to one another's shape. That's how antibodies and enzymes find their target molecules, he points out.

As a first step toward a full-scale "neuromolecular computer," Conrad proposes putting that shape-detecting ability to work in a computer-in-a-jar that could recognize patterns—a long-standing challenge to computer science. In Conrad's scheme, an unidentified pattern—an image, say—would determine the mixture of proteins released into a reaction vessel. The solid color and long, thin shape of a pencil might release one particular set of proteins, for example, while the varied contours of a telephone would release a very different set. Each of these protein sets would self-assemble into a particular "mosaic." To identify the mosaic—and thus the original image—the device would monitor the activity of a diverse set of enzymes, each of which tended to lock onto a particular mosaic. The enzyme activity would thus reveal the original pattern as a pencil, a telephone, or something else. With that strategy, says Conrad, "We've converted what would ordinarily be a digital signal-processing problem into a problem where we can let physics do all the work."

So far, Conrad's pattern-recognition machine exists only as a simulation on a conventional silicon-based computer, though he has tested some of its principles in the laboratory. "The technology has to improve a bit before we could do this sort of thing," he concedes. "But if researchers can engineer proteins to act as switches, they can certainly engineer them to perform their more natural functions of shape recognition and self-assembly."

As visionary a project as a neuromolecular computer may seem, it's tame compared to Stuart Hameroff's long-term goal: biomolecular "nanorobots" capable of traveling through the human body and making intricate repairs to damaged tissue. Hameroff, a researcher at the University of Arizona, has spent much of the past 20 years studying microtubules—long, thin cylinders of protein molecules that lend structure to neurons and many other cells. Microtubules can grow, shorten, and bend by adding or losing protein units in response to various chemical and other cues. As the twitching and bending of one microtubule influences neighboring ones, a signal can propagate throughout a cell's microtubule network. In this way, asserts Hameroff, microtubules provide a sort of intracellular intelligence that monitors a cell's environment and triggers many of its responses. "Microtubules are nature's computers," he says. "If we could understand their coding and information-processing mechanisms and access them with some sort of genetic input, we could control their behavior."

To that end, Hameroff and colleagues have been modeling information flow through microtubular networks on a computer, and they are now getting ready to test parts of the model. Using a two-tipped scanning tunneling microscope, currently under development at the University of Arizona and elsewhere, they plan to stimulate microtubule networks electrically with one tip and detect how the signal propagates with the other. Once the researchers understand the effects of different signals, Hameroff intends to try "programming" microtubule networks by genetically altering their constituent proteins and exposing the networks to specific signal sequences. His long-term, outside-chance hope: persuading microtubules to self-assemble into structures that could be let loose in the human body to perform useful search-and-destroy missions, rather like custom-made white blood cells. "Either by themselves, or enveloped in a cell-like membrane, assemblies of microtubules could seek out an Alzheimer's neurofibrillary tangle and destroy it with enzymes," he says.

Should Hameroff's nanorobots ever need propulsion, he can talk to University of Utah biologist David Blair, who has been studying the 25-nanometer-wide molecular motor that powers the propeller-like flagellum of many bacteria. Spinning at up to 18,000 revolutions per minute, the motor pushes an average-sized cell at 30,000

nanometers, or about 15 body-lengths, each second—and it's reversible, too. "It's a triumph of engineering," gushes Blair. To tease out the motor's "parts list," Blair has been altering genes coding for proteins in the motor and studying the effect of each change. So far, the only part he's clearly identified is the "fuel injector"—a proton channel that provides the motor's energy source—but he expects to be able to nail down parts corresponding to a rotor, stator, motor mount, and transmission.

Blair notes that transferring the motor intact to a different structure would be difficult, but he doesn't rule it out. He also points out that the motor seems to be constructed of molecular rings that might be useful by themselves as tinker-toy-style connectors or as "junction boxes" in other structures. "Or maybe we can use the motor to make really tiny CD players," he says. "Just kidding."

To install the motor in a larger structure, or to assemble any combination of switches, reaction chambers, and other biomolecular widgets, the well-equipped bionanoengineer will need a scaffolding. And for that purpose, New York University biochemist Nadrian Seeman thinks DNA may be just the thing. Seeman credits his original idea that DNA could be coaxed into a lattice structure to an M.C. Escher print that suggested a scheme for interweaving the DNA strands. Last year, by altering key sequences in the molecule, he got an assembly of DNA branches to fold itself into a cube, and he's confident more complex structures will soon follow. "The next step is to have other molecules associate with the DNA," he says. "Then you could have molecules with electronic properties riding the DNA into place, forming circuits."

The idea of trying to subvert DNA's function, transforming it from genetic material into molecular assembler, may strike some biologists as audacious, even irreverent. But bionanotechnologists are getting used to their colleagues' raised eyebrows. Even one Japanese funding group's stated goal of assembling biomolecular circuits into a working replica of what may be nature's most exquisite mechanism—the human brain—fails to affront as it would have just a few years ago. "When I first heard about that, I thought they were crazy," says Stanford's Boxer. "Now I look at it like people once thought about going to the moon, or building the SSC. It's, well, interesting."

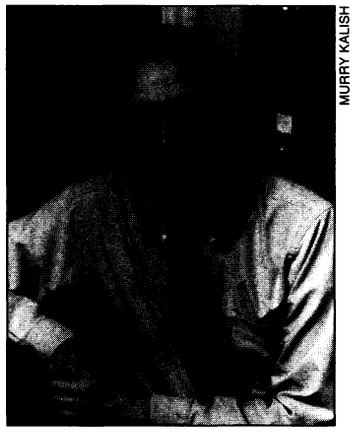
■ DAVID H. FREEDMAN

*David H. Freedman is a free-lance science writer in Brookline, Massachusetts.*

# The Apostle of Nanotechnology

*K. Eric Drexler has made it his mission to tell the world how far molecular-scale technologies could be taken*

K. ERIC DREXLER LIKES TO THINK OF HIMSELF as a technology visionary with a message the world can't afford to ignore. In a matter of decades, he says, the fabric of human culture will be in for a drastic reweaving by protein-sized machines capable of manufacturing, molecule by molecule, anything an engineer might design within the constraints of nature. Over the past 10 years, Drexler's tireless promotion of that vision has turned him into "Mr. Nanotechnology," at least in the public eye.



MURRY KALISH

***Nanotechnology "will bring changes as profound as the industrial revolution, antibiotics, and nuclear weapons all in one."*** —Eric Drexler

To some researchers working in the field, however, he is anathema. "The man is a flake," says Phillip Barth, a microdevice developer at the Hewlett-Packard Company in Palo Alto. Others, such as electrical and microengineer Richard S. Muller of the University of California, Berkeley, fear that Drexler's fantastic descriptions of future technologies will plant unrealistic expectations in the minds of the public, policy makers, and grant committees. And some bench scientists simply think Drexler, who does his "exploratory engineering" research by pushing ideas to their theoretical extremes and running molecular modeling programs through powerful computers, rather than by building working devices, is just plain wrong in his visions of what might be.

But whatever they might think of him, many scientists agree that the bookish, soft-spoken, 36-year-old Drexler has had an impact on their field. An independent theoretician and occasional lecturer at Stanford University, Drexler wields formidable organizational skills and an ability to communicate ideas to nontechnical audiences. By writing an endless stream of books, encyclopedia articles, and technical papers, spawning nanotechnology study groups at universities, giving dozens of lectures around the world, and even speaking to Congress, Drexler has probably done more to raise public consciousness about nanotechnological possibilities than any other scientist. Along the way, he has attracted a nationwide stable of devotees who see the future exactly as he does.

His promotional zeal isn't confined to the popular realm, however. When a dozen or so established researchers who are pushing the envelope in building molecular-scale structures and devices shared their work with another 100 or so scientists, onlookers, and journalists in Palo Alto earlier this month, for example, they did so at Drexler's invitation. And some mainstream researchers give him credit for that kind of effort. Robert Birge, a respected player in molecular electronics at Syracuse University, says Drexler "has gotten a lot of people to think about what might be possible." Birge also praises Drexler for getting people in different areas of molecular science to talk to one another. "If there has been a flaw, it is that he hasn't submitted his ideas to refereed journals where he would get feedback to tone down his ideas."

Toning down is just what Drexler's popular writings seem to invite. Take his first book, *Engines of Creation: The Coming Era of Nanotechnology*, published in 1986, in which hypothetical protein- and organelle-sized machines "bring changes as profound as the industrial revolution, antibiotics, and nuclear weapons all rolled up