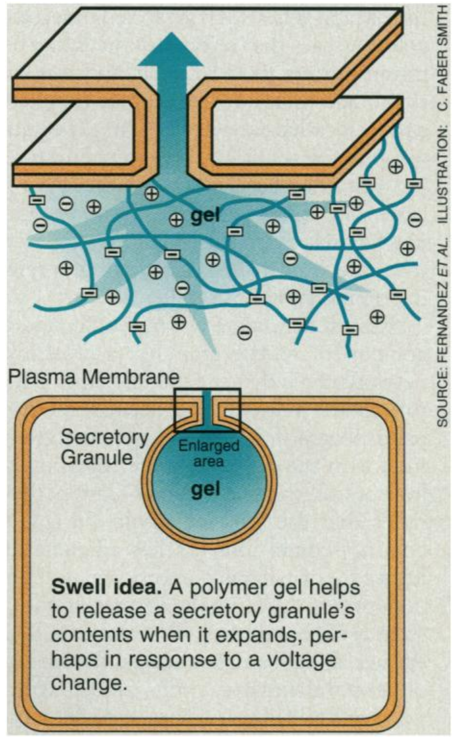
BIOPHYSICS

Unexpected Intelligence Turns Up in a Cellular Gel



Swell idea. A polymer gel helps to release a secretory granule's contents when it expands, perhaps in response to a voltage change.

Even with all the tools of modern science—from the polymerase chain reaction (PCR) to computer simulations—scientists can rarely match nature's inventive powers. Human solar-powered devices pale next to the efficiency of photosynthesis at capturing energy from the sun. Mechanical hands find it difficult to perform tasks—such as picking up an egg without breaking it—that human hands do with complete facility. Many of the best cancer drugs come not from laboratory reaction vessels but from forests and oceans.

Now comes another lesson in humility for the scientific community. Just as researchers begin to manipulate synthetic materials called smart polymer gels—water-filled matrices of long molecules that swell or shrink in response to stimuli (see box)—they find that nature has beaten them to the punch yet again. Hidden in the secretory mechanism of many cells are natural polymer matrices that can change shape when exposed to certain ions. And a report in this issue of *Science* shows that certain of these natural gels are even more responsive than was originally thought: They show dramatic, and unexpected, responses to changes in electrical voltage.

The voltage changes cause the matrix to condense or swell in milliseconds, fast enough to put the best synthetic gels to shame. If confirmed, these findings, reported on page 963 by Chaya Nanavati, now a postdoc at Duke University Medical Center, and her former advisor, Julio Fernandez of the Mayo Clinic in Rochester, Minnesota, may give new insight into the workings of secretion in cells. And they could also teach some new tricks to researchers trying to apply smart gels in drug delivery, micromachines, sensors, and a variety of other settings. "We're going to start learning a lot from these natural systems," predicts Pedro Verduggo of the University of Washington's Center for Bioengineering.

Cutting-edge technology was the last thing on Nanavati and Fernandez's minds when they began their work. Their original goal was to measure the electrical conductance of

Polymer Gels Get Smarter

Nature may have invented the prototypical smart polymer gel (see main story), but chemists, materials scientists, and physicists are struggling to catch up. They are trying their own hand at designing these novel substances and endowing them with a kind of intelligence—the ability to respond to stimuli. Now stirring in labs around the world are sentient gels that swell or shrink, absorbing or expelling water, in response to changes in light, pH, temperature, and electric fields.

Researchers are confident enough in their creations to forecast a range of new gel-based technologies, including muscles for robots and controlled-release systems for drugs. The hopes for the gels are especially high in Japan, where "they're recognized as one of the most promising materials for the 21st century," says physicist Toyoichi Tanaka of the Massachusetts Institute of Technology, a leader in the rapidly growing field and editor of a new journal, *Polymer Networks and Gels*, devoted to the topic.

Like their natural counterparts, artificial gels consist of a solvent, usually water, held in place by a hydrophilic lattice of long-chain molecules—in many cases synthetic polymers such as polyacrylamide and polymethacrylic acid. The gels' structure reflects a fragile balance between the electrostatic repulsion of adjacent polymer strands and the osmotic pressure exerted by the ions in the solvent liquid; as a result, disrupting a gel's charge distribution by altering its environment can trigger it to swell or shrink a thousand-fold. And scientists are now finding that by adding side chains to the polymer networks or otherwise altering their structure, they can control when and how the materials respond.

A host of researchers, in universities and industrial labs, are now rushing to exploit their newfound mastery over these materials, aiming for everything from biosensors to superabsorbent diapers. And since gels can exert a force when they swell, they even have potential as actuators or artificial muscles for robots or prostheses. Toshio Kurauchi and his colleagues at the Toyota Central Research and Development Labs in Japan, for example, have already made a mechanical hand composed of four smart polymer "fingers" that can pick up and hold a quail egg and an artificial "fish" that swims—slowly—as its tail, an electrically responsive polymer, flaps back and forth.

Current artificial gels are handicapped in such applications, however, because they respond slowly, taking seconds to minutes to react to changes in their environments. Nearer to practical application may be gel-based drug delivery. In the simplest version, a pH-sensitive gel loaded with medicine might efficiently carry the drug to the stomach: It would swell on reaching the stomach's acidic environment, absorbing large quantities of water and slowly releasing its soluble cargo through diffusion. A more sophisticated approach is embodied in the design of a gel-based insulin pump recently patented by researchers at the University of Washington. The pump combines a pH-sensitive gel and an enzyme that converts glucose to lactic acid. When blood glucose levels rise too high, the acid produced by the enzyme causes the gel to swell, forcing a squirt of insulin out of the pump.

Those plans suggest that the field is moving quickly toward a host of practical applications, but Tanaka and others have ideas that are still more ambitious. They envision gels that would react to specific molecules—the basis, perhaps, for intelligent sponges that would mop up specific pollutants, or biomedical devices that react to specific markers of disease. The only limit to smart gels, it seems, is the intelligence of researchers.

–J.T.

the natural gels, which are found in secretory granules, sacs that ferry substances like neurotransmitters, growth factors, and hormones to the cell surface, where they are expelled in a process called exocytosis. "Our expectation was that the result would be very uninteresting, just a number," says Fernandez. As a test case, they chose certain easily studied granules found in mast cells, immune-system cells that play a role in allergic reactions by releasing their cargo of histamine.

Researchers already knew that another component of the granules, a crosslinked network of a polymer called heparin, plays a role in the release. The heparin mesh expands several-fold when a secretory granule fuses with the cell membrane, allowing ions from outside the cell to rush in. Current theory holds that the swelling results because incoming sodium ions are less efficient than histamine or calcium—another granule component—at shielding the negatively charged strands of heparin from one another. When enough sodium enters, the strands repel each other and the matrix swells, absorbing more water and allowing its contents to diffuse out.

Nanavati and Fernandez's work, however, suggests that the ion exchange might not be the only swelling mechanism at work. They isolated mast cell matrices and placed them in a glass pipette to which they could apply varying voltage. At positive voltage, the granule matrices were condensed, opaque, and poorly conducting. But when the voltage was negative, the matrices swelled in milliseconds, becoming transparent and highly conducting. Fernandez speculates that such voltage-stimulated swelling may also occur during exocytosis, triggered by a voltage that may be generated when a granule first opens to the extracellular space.

Others aren't sure the laboratory results say anything about processes in the living cell. "I think it may have a physical significance but not a physiological one," says cell biologist Michael Curran at Baylor College of Medicine. Indeed, the arresting properties of the heparin matrix do make it seem destined for roles on a larger stage. The Mayo Clinic certainly thinks so; it has filed a patent covering several possible uses of the gel.

Because its conductance varies with voltage, for example, the matrix might serve as a biocompatible electrical diode for implantable mechanisms. The patent also suggests that the electrically induced optical properties of these matrices might give them a role in display technology. And because the gel is strong as well as sensitive, exerting a force equivalent to a few hundred pounds per square inch as it swells, it could drive gears in micromachines, says Fernandez. All those possibilities may mean that human technologists will once again be taking their lessons from nature.

–John Travis

MEETING BRIEFS

Mathematicians Gather to Play the Numbers Game

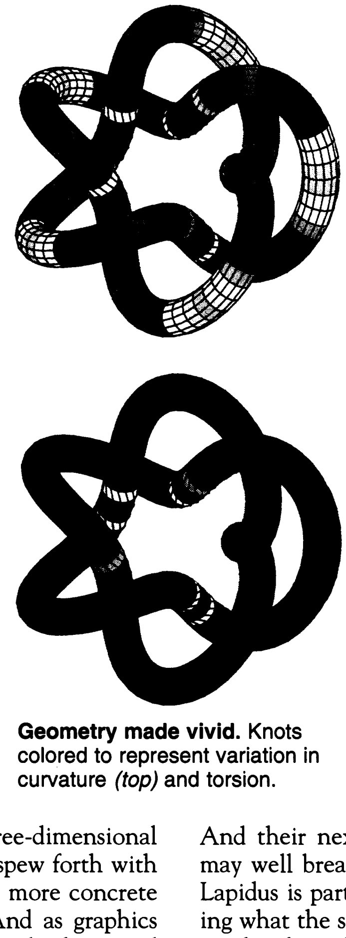
The Riverwalk area in San Antonio was crawling with mathematicians for a week in January, when the American Mathematical Society and the Mathematical Association of America held their joint annual meetings. Among the topics that kept the bars, halls, and lecture rooms abuzz from 11–16 January were the latest results on some venerable problems in the field and the effect of a brand-new technology, computer graphics, on the process of mathematical discovery.

Abstract Expressionism In Math

Mathematicians often talk about the beauty of a theorem or proof, but that beauty is rarely apparent to nonmathematicians. Now, however, computer graphics is helping to change that. Increasing power and decreasing costs have turned even the least artistically talented mathematician into a Rembrandt with a laser printer. But to mathematicians, the resulting images are more than just a vivid way to advertise their work to the public. In some cases, in fact, the computer's capacity for graphics is changing the direction of mathematical research.

Alfred Gray of the University of Maryland, who drew the twin "torus" knots at right using the computer algebra system *Mathematica*, thinks graphics is driving such a change in differential geometry. Loosely defined as the study of curvature, differential geometry has found applications in fields as disparate as Einstein's theory of general relativity and molecular biology, where researchers have become interested in what it has to say about such things as the supercoiling of DNA.

In recent years, though, mathematicians' explorations of the subject have begun to turn increasingly abstract, with algebraic symbols playing a bigger role than geometric shapes. But now that tide is beginning to flow in the other direction, thanks to the accurate, three-dimensional images that computers can spew forth with ease. "People are looking at more concrete things [now]," Gray says. And as graphics technology gets into more hands, that trend is likely to continue. "The revolution is only in its beginning stages," he adds, but already it's aided mathematicians in such things as the discovery, in the mid-1980s, of an entire new class of "minimal" surfaces.



ALFRED GRAY

Geometry made vivid. Knots colored to represent variation in curvature *(top)* and torsion.

Differential geometry is not the only place where pictures help. Michel Lapidus of the University of California, Riverside, is looking to computer graphics to gain extra insight into analytical theories he's been developing over the past several years. Lapidus is interested in the reverberations of mathematical "drums" with fractal boundaries (*Science*, 13 December 1991, p. 1593). The interaction of wave phenomena and fractals is an important aspect of scattering theory for applications such as radar ranging, Lapidus points out, but it also contains many problems of purely mathematical interest.

Recently, Lapidus has begun analyzing the waveforms produced when the fractal drums reverberate. For help, he turned to Robert Renka and John W. Neuberger at the University of North Texas, who wrote programs to produce pictures of standing waves on a fractal shape known as the Koch snowflake. The picture on the next page shows how the "energy" of a waveform is concentrated at a relatively few peaks, Neuberger notes. That image isn't breaking new ground—it confirms what the researchers already knew—but it does give them confidence in their numerical methods. And their next steps in computer artistry may well break new mathematical ground. Lapidus is particularly interested in exploring what the standing wave looks like close to the fractal drum's infinitely crinkled