Already, this strategy has produced three peptides that have moved into clinical trials. None are being injected systemically, however, because the researchers consider that route of administration too risky right now. Micrologix Biotech Inc. in Vancouver is currently conducting a late-stage clinical trial of one of these peptides, aimed at seeing whether it will prevent the catheter-related infections caused by many microbes, including the bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*, a gram-positive superbug that now resists most common current antibiotics. Company researchers are also testing whether the peptide will cure severe acne and prevent acute *S. aureus* infections.

Zasloff's team at Magainin is taking another tack: trying to get the body to produce more of its own defensive peptides, which presumably won't damage the cells of their native host. The team began by looking for potential triggers in disease-causing bacteria such as *Staphylococcus* and *Pseudomonas*. Those pathogens did not boost β-defensin gene expression. But much to Zasloff's surprise, beneficial organisms, such as bakers' yeast and *Lactobacillus*, found in yogurt, did. The team then purified the active component from bakers' yeast, which turned out to be the amino acid isoleucine. The amino acid may work by binding to a Toll-like receptor in people, the researchers reported in the *Proceedings of the National Academy of Sciences* in November.

Although isoleucine is a necessary building block of the body's proteins, humans cannot make the amino acid on their own and must get it in their diets. Zasloff suggests that isoleucine is a good signal of an invading pathogen, because the microbes do make the amino acid and would drive isoleucine levels up during infection—either by secreting it or by breaking down host tissue. If so, then something as simple as an amino acid supplement might boost immunity. But it remains to be seen whether such a strategy will be successful in designing actual therapies.

Even if the peptides now being tested don't pan out, there are plenty of other candidates waiting in the wings. "It is becoming clear that the hard-wiring of an animal, even the mammal, can be fine-tuned to very carefully distinguish between different classes of microbe," Zasloff says. **–TRISHA GURA**

Trisha Gura is a science writer in Cleveland, Ohio.

MEETING BIOPHYSICAL SOCIETY

Crossover Research Yields Scents and Sensitivity

BOSTON, MASSACHUSETTS—Over 5000 scientists gathered here last month for the 45th annual meeting of the Biophysical Society.* The meeting brought together physicists, chemists, biologists, and others to discuss how physics can be used to address fundamental biological problems in new ways.

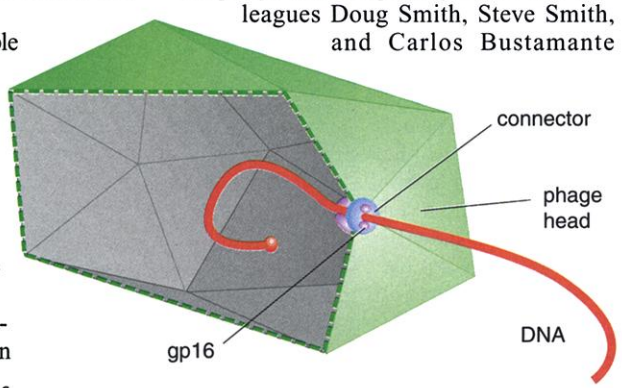
Watching a Virus Get Stuffed

For decades, scientists have used viruses that infect bacteria, known as phages, as models for viruses that infect humans. Yet despite intense scrutiny, how phages manufacture more phages remains mysterious. Now, for the first time, biophysicists from the University of California (UC), Berkeley, have caught a phage in a key act of self-assembly. Using microscopic beads and laser light, they watched the virus stuffing its genome into a protein shell, and they played tug-of-war with its DNA. The results reveal that the microscopic winch responsible for DNA packaging is the most powerful molecular motor ever measured.

"They've done a remarkable job," says Dwight Anderson, a phage biologist at the University of Minnesota, Minneapolis. "For a long time, we've been using an integrated biochemical and genetic approach [to understand packaging], but what we really needed is the biophysics."

The DNA packaging machinery of the phage, known as phi29, has been studied extensively. To stuff DNA into the virus's five-sided head, a phage protein called gp16 brings the DNA to a protein-RNA complex at the base of the head. The gp16 burns up adenosine triphosphate (ATP) fuel and, together with the protein connector, pulls the DNA into the head. Enlarged 600,000 times, the whole process would resemble stuffing a strand of spaghetti into a matchbox. But although its biochemistry is well known, the mechanical details of how the virus pulls the DNA into the head and organizes it in just a few minutes are sketchy.

To get a handle on the problem, Sander Tans of UC Berkeley literally took hold of the phage while it packaged. He and colleagues Doug Smith, Steve Smith, and Carlos Bustamante strung a phage head and DNA between two small plastic beads, attaching them with a protein glue. Using suction, the researchers held the bead with the phage head on the end of a micropipette. The DNA bead, meanwhile, was caught in a laser trap—a specially focused laser beam that holds the bead stationary. By pulling on the DNA–phage head assembly and measuring the deflection of the laser trap's light, the researchers could measure the force on the bead—and thus on the biological molecules attached to it. After assembling the complex, they added ATP and watched.



Packaging power. The protein motor that stuffs DNA into virus heads is the strongest yet.

ILLUSTRATION: J. MOGLIA

As the motor pulled the DNA into the phage head, the researchers saw the beads moving closer and closer together. The DNA packaging began smoothly, at a constant rate of 100 base pairs per second. But once the head was half full of the DNA, the pressure began to build up and the motor to slow down. Tans and his co-workers used the optical trap to pull against the packaging motor. They could bring the motor to a stop by resisting with a force of 57 piconewtons—the highest "stalling force" ever seen for a molecular motor. From that force and the volume inside a phage head, Tans calculates that the pressure inside a fully stuffed head is 15 megapascals. "That's the pressure inside an oxygen bottle," he says. He conjectures that the high pressure may help the phage inject its DNA when it attaches to the outside of a cell it's going to infect.

A thorough understanding of packaging, Anderson says, could reveal a new target for novel antiviral drugs. Other scientists are also excited by the application of biophysical techniques to the problem. Without them, "we would never learn what a strong engine the virus packaging machinery has," says Roman Tuma of the University of Helsinki in Finland.

* 17 to 21 February 2001, Hynes Convention Center, Boston, Massachusetts.

A Sniff in Time Scents Mines

Natural olfactory systems, such as the one inside the nose of a dog, can distinguish tens of thousands of different smells and can learn new ones. Artificial noses are much less versatile. Most of those developed to date are geared toward detecting a particular class of smell, such as spilled gasoline or rotting food. The reason is that a living nose contains perhaps 1000 different chemical receptors for identifying smells, a number no machine has come close to matching.

Sniffing out danger. Joel White uses an artificial nose to hunt for landmines in a field test.

Drawing on their years of studying the olfactory system of the salamander, neuroscientists are now working around that numbers gap. John Kauer and Joel White of Tufts University School of Medicine in Boston have built a device that, Kauer says, employs "about 20 different attributes" of natural noses. Like many similar machines, the device uses an array of sensors, each of which consists of a fluorescent dye embedded in one of many subtly different polymers. When an odor molecule diffuses into the matrix, it changes the fluorescent properties of the dye. The resulting pattern of fluorescence on the entire array gives a signature of the molecules in the air sample.

Unlike other array-based noses, though, the Tufts Medical School nose "sniffs" air samples by periodically puffing air across its sensors. Monitoring how sensors change over time, Kauer says, enables it to discriminate among more odors with the same number of sensors. Other features drawn from nature include feedback mechanisms to keep the sensors from getting saturated and odor-analyzing algorithms based on olfactory nerve circuits.

The device can detect a panoply of odors, Kauer says, including one that is both faint and grim. With funding from the Defense Advanced Research Projects Agency and the Office of Naval Research, Kauer has investigated whether the artificial nose can be used to detect landmines in the field. Most of the estimated 100 million landmines buried throughout the world contain TNT (trinitrotoluene). Dogs can scent landmines, probably by cueing on the byproduct DNT (dinitrotoluene). But an artificial device wouldn't get fatigued like a four-legged nose and could be operated remotely (*Science*, 3 September 1999, p. 1476).

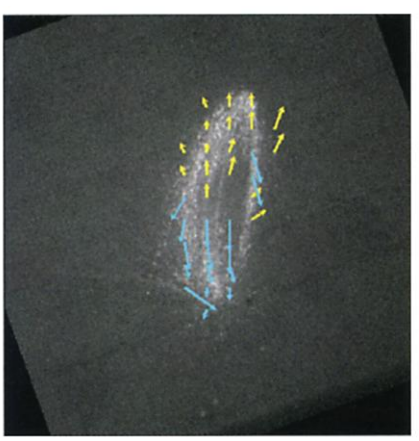
To see how the artificial schnoz would fare, Kauer tested it "nose-to-nose" against dogs in a special chamber. Kauer's nose proved about 10 to 15 times less sensitive than a dog's, which can detect 1 part per billion or less of DNT and related compounds. In a field test, the nose detected rough signatures of landmines but couldn't locate them precisely, Kauer says—probably because varying background odors cloak vapor emitted by landmines.

Locating landmines is a difficult problem, says chemist David Walt of Tufts University, Medford, and whether artificial noses will ever be up to the task remains to be seen. But, he adds, "there have been some incredible advances." Kauer says that those advances could be applied to other, more tractable problems, including monitoring complex environments such as the inside of airplane cabins for toxic fumes.

Old Movies Reveal New Moves

As a cell grows, moves, or divides, it repeatedly has to tear down and rebuild parts of its own structure called the cytoskeleton. Amid the confusion of a living cell, scientists can get only fleeting glimpses of that process of creative destruction. But a twist on an off-the-shelf image-processing technique may help them squeeze new kinds of data out of old cytoskeletal images.

The technique—a computer algorithm called cross-correlation—was developed to detect patterns in signals of many kinds. Zachary Perlman and colleagues at Harvard Medical School in Boston realized it could also be used to study mitotic cell division. During mitosis, protein filaments called microtubules form a network known as the mitotic spindle, which aligns paired chromosomes down the middle of the cell. The microtubules pull the chromosomes to opposite sides of the cell so accurately and efficiently that, when the cell splits in two, each of the resulting cells has a full complement of chromosomes. Scientists know that somehow the microtubules migrate from the center of the cell toward the poles in the process, but many important details of the process remain murky.



Tracking speckles. Image analysis tracks hard-to-follow speckles that mark cytoskeleton movement in dividing cells.

In 1998, cell biologists Ted Salmon and Clare Waterman-Storer of the University of North Carolina, Chapel Hill, discovered a new way to track microtubule movement. Using a standard technique, they assembled microtubules from subunits of the protein tubulin, some of which were labeled with fluorescent tags. Because the researchers used less tagged tubulin than usual, the microtubules wound up speckled with glowing spots. By carefully watching the speckles move in a mitotic spindle, the scientists could track the gyrations of the microtubules in their cellular dance.

Interpreting the motions was another matter. Data were hard to analyze; it could take weeks to convert just a couple of spots to hard numbers. Spindles would drift around the microscope slide. Speckles would move in and out of focus and then fade.

To improve on the method, Perlman and his colleagues Tarun Kapoor and Tim Mitchison set out to find a better way to analyze the images. Using cross-correlation, they took successive images of a moving spindle and rotated them into alignment. By comparing spots on the altered images, they could determine how fast and in which direction the spots were moving. "Cross-correlation is not anything that would shock someone in image processing," Perlman says, but applying it to cell biology has allowed him to extract quantitative data from a previously qualitative experiment.

The technique is useful for more than mitosis, Perlman says. When eukaryotic cells move along a surface, polymerization of other cytoskeletal structures called actin filaments pushes the edge of the cell forward. Perlman has already used cross-correlation to analyze movies of cells with fluorescently labeled actin fibers.

Waterman-Storer, now at the Scripps Research Institute in La Jolla, California, suspects that cross-correlation may have trouble accurately comparing complicated patterns of speckles. But Salmon predicts that the technique will prove to be a powerful way to mine new information from speckle images. "There's a great need to have intelligent computer image-processing technology developed" to analyze such images, he says.

–R. JOHN DAVENPORT

CREDITS: (TOP TO BOTTOM) J. KAUER/TUFTS UNIVERSITY; Z. PERLMAN/HARVARD MEDICAL SCHOOL