NewsBytes

BY KATHARINE MILLER AND KRISTIN COBB, PhD

Interactive Handheld Molecules

Thirty years ago, molecular biologists routinely constructed protein models out of brass rods ("Kendrew models"). In recent years, researchers put away such tinker toys and turned to computer graphics.

But now scientists at The Scripps Research Institute are combining the two mediums. They "print" three-dimensional models of biological molecules that, when held and manipulated, interact with the computer that printed them. The work was published in the March issue of *Structure*.

"Everyone has a gut feeling that there's something different about holding an object versus looking at it on the screen," says Art Olson, PhD, professor of molecular biology and director of the Molecular Graphics Laboratory at The Scripps Research Institute. "But because these models are essentially computer output, they have a special relationship to the data in the computer that actually made them."

Olson and his colleagues generate handheld molecules with 3D fabricating printers that can make solid objects out of layers of plaster or plastic. Then, as a person turns or twists the object, a digital video camera tracks its movements. The computer displays these manipulations as well as additional information about the molecule in what is known as "augmented reality." For example, as a person moves two physical molecules toward one another, the screen might show how the electrostatic fields and electrical potentials change.

Why bother with physical models at all? "If you can print out a custom interface that's easy to handle and will address whatever problem you're interested in, then why not try to do that?" Olson says. "You have more tools and more cues if you have the analog physical object."

Physical models with augmented reality have an advantage over pure computer models because they're more easily manipulated, Olson says. "It's easy to tie a knot in a string with your hands. It's much harder on the screen."

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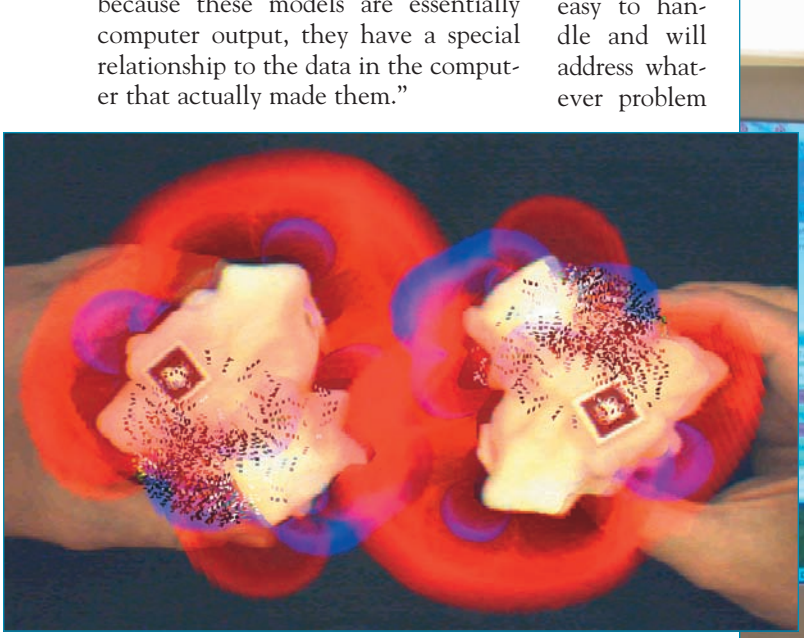
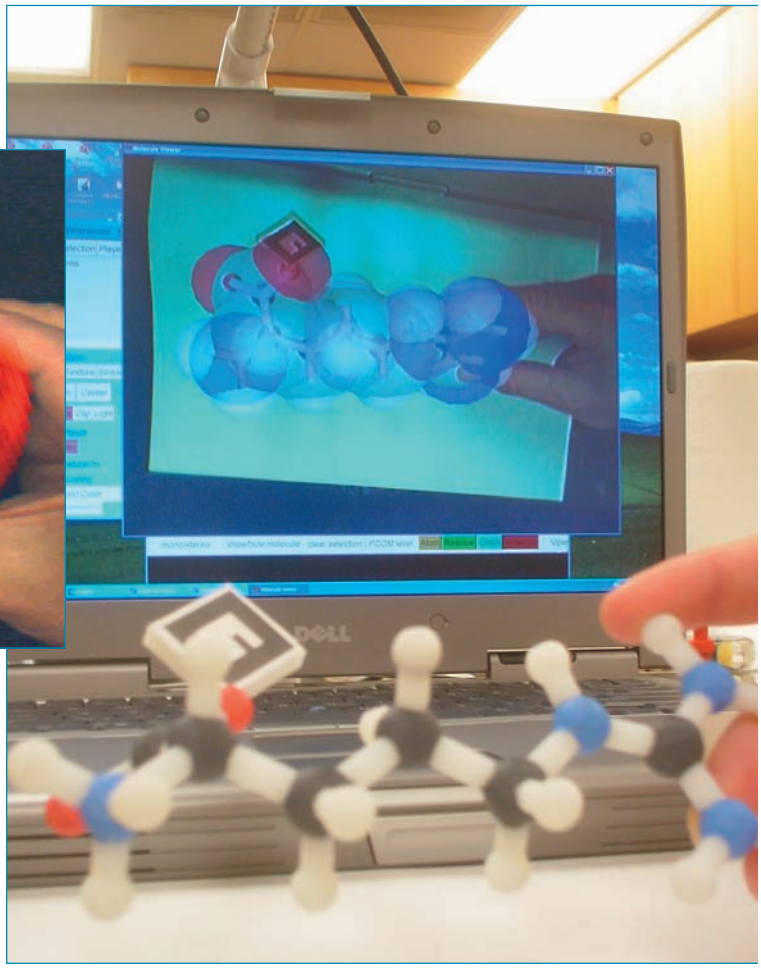
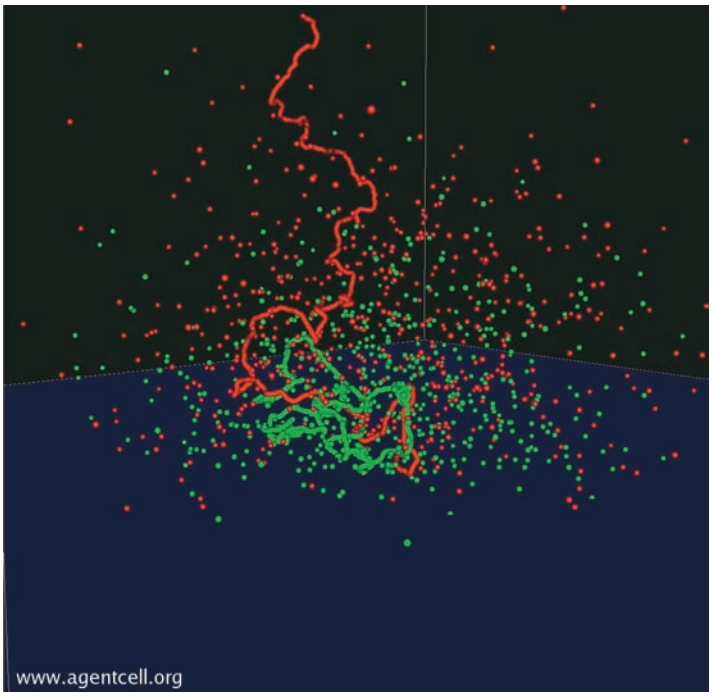
Given a flexible model of a protein, a researcher can pick apart the end terminus and see how it might interact if laid against a different part of itself. "Doing that with a mouse would be relatively difficult."





Above: Computer augmentation of two subunits of the SOD dimer which are tracked and manipulated independently. The electrostatic field is shown with small arrows that point along the local field vectors (they appear as small as dots in this picture), and the potential is shown with volume rendered clouds, with positive in blue and negative in red. At Right: A physical ball and stick model of an amino acid is augmented by computer graphics showing the spacefilling model superimposed. Courtesy of Art Olson, Molecular Graphics Laboratory, The Scripps Research Institute.



Digital E. coli swim randomly in a nutrient-free medium (green cells) or up a gradient of nutrient (red cells). Solid red and green lines indicate average position of each population. Courtesy of Thierry Emonet.

The physical models might also prove valuable as talking devices when structural biologists collaborate with scientists who don't routinely think about structure, Olson says. And adding augmented reality to physical models may prove helpful in explaining complex concepts to students. In early tests, one thing is for sure, says Olson, "The students like it better."

Bacteria with Byte

When a bacterium swims toward food, it follows a chaotic path, alternating between spinning randomly and driving forward, or 'tumbling' and 'running.' Computer scientists at the University of Chicago have now created a virtual colony of *E. coli* bacteria—complete with digital receptors, motors, and signaling pathways—that run and tumble just like real bacteria.

The simulation program, AgentCell, is the first to model a biochemical network at the molecular, single cell, and population levels simultaneously. By doing so, it might provide a framework for modeling other biological systems, including cancer and antibacterial resistance. AgentCell was introduced in the June 1 issue of *Bioinformatics*.

"We used AgentCell's chemotaxis network, but you can use the program for any kind of network you want," says Thierry Emonet, PhD, a research scientist at the University of Chicago and lead author on the paper.

AgentCell uses agent-based simulation, a type of software developed to model social behavior, such as the stock market. An agent is a software object that makes completely autonomous decisions. In AgentCell, each single-celled bacterium decides to run or tumble based on input from the virtual environment and fluctuating intracellular signals. The program models the behavior of thousands of bacteria acting independently. Future versions will allow the bacteria to interact.

The researchers used bacterial chemotaxis as a test-bed for AgentCell because it is one of the best characterized systems in biology. An *E. coli* bacterium swims toward nutrients and away from poisons by alternating the rotation of its flagella: counterclockwise motion causes flagella to bundle into a tight propeller (running); clockwise motion causes the flagella to fly apart (tumbling). Chemical signals in the bacteria control the switch between run and tumble, but the mechanism is noisy: the frequency of switching is highly variable between two genetically identical cells in the same environment.

Using AgentCell, Emonet hopes to better understand how cells make decisions in the face of such variability. Chemotaxis is super-simple decision-making; a more complicated decision for a cell is whether or not to divide, Emonet says. When customized, AgentCell could be used to study how cell division goes awry in cancer.

Computer simulations can test competing theoretical models and guide future lab experiments. In the lab, it takes months to grow cells with a mutated protein. In the computer, it takes just a quick and elegant change of the code.

AgentCell will soon be available as open source code on the website: www.agentcell.org. "We'd love to have people grabbing the code and adding modules, adapting it to their own needs," Emonet says.

"Because of its modular architecture, the system readily integrates pre-existing simulators and algorithms with very little development overhead," says Tom Schmizu, a post-doctoral fellow at Harvard University. For example, you could easily swap in your own favorite model of intracellular signaling or of receptor binding into AgentCell, and then test it against data from the real world. >

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