

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

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.”

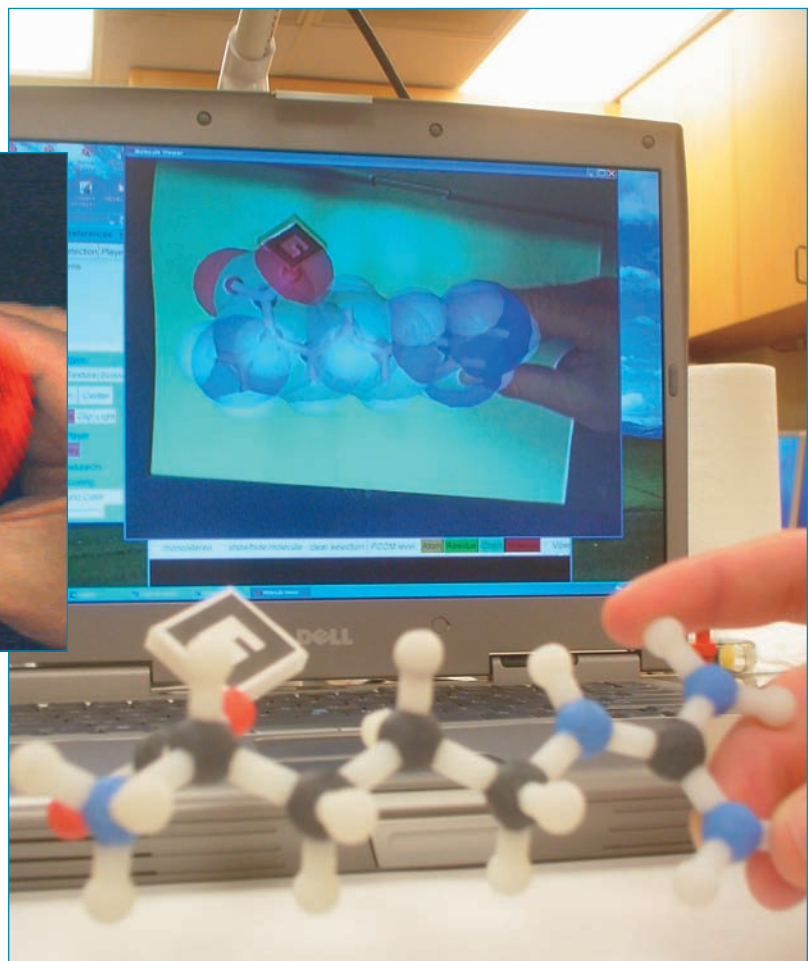
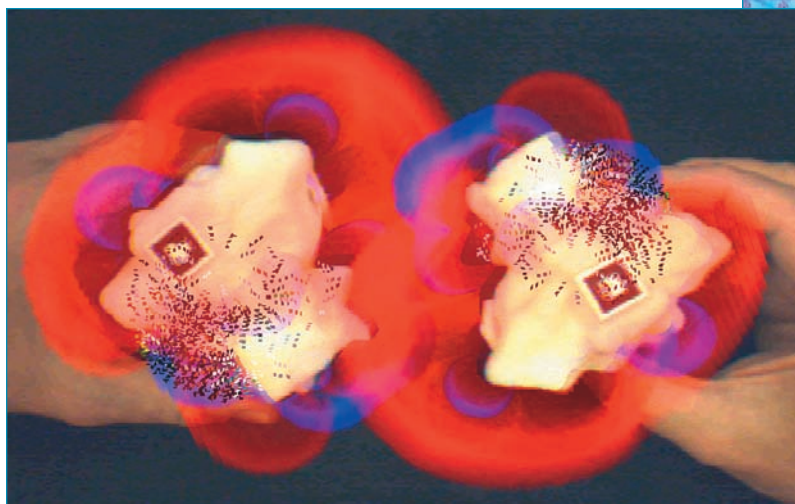
Physical models with augmented reality have an advantage over pure computer models because they’re more easily manipulated, Olson says. “It’s easy to tie a knot in a string with your hands. It’s much harder on the screen.”

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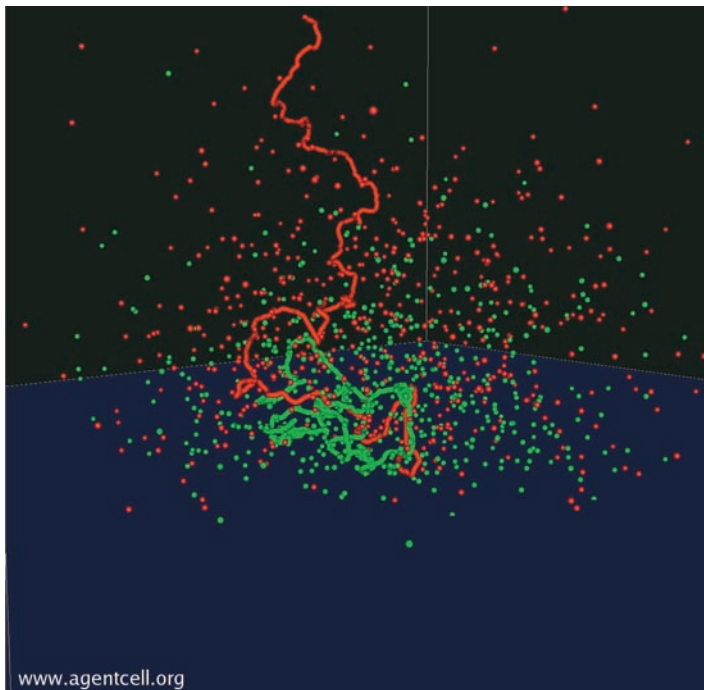
person moves two physical molecules toward one another, the screen might show how the electrostatic fields and electrical potentials change.

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

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*.

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 (tum-

bling). 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.

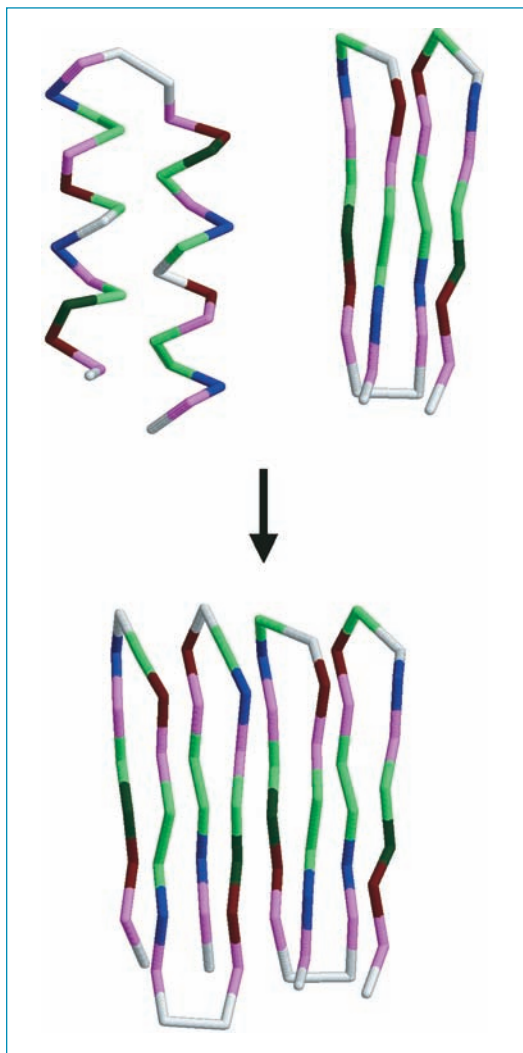
Computer simulations can test competing theoretical models and guide future lab experiments. In the lab, it takes months to grow cells with a mutated protein. In the computer, it takes just a quick and elegant change of the code.

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

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Tom Schmitz, 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. >



A model of prion disease propagation. The correct (helical) form of a protein misfolds to a beta-structure in the presence of the stiff misfolded beta-structure form.
Courtesy of Edyta Malolepsza.

Simulating Faulty Folding: A Theoretical Model of Prion Propagation

Inside a live cell, strings of amino acids instantaneously fold into proteins with very specific shapes. Typically, no harm is done if a protein somehow folds into an unconventional configuration. But, very rarely, a misfolded protein will induce others to unfurl and misfold as well, with disastrous consequences: the nonconformistsglom together, causing diseases such as bovine spongiform encephalopathy (BSE or mad cow), Creutzfeldt-Jakob, and Alzheimer's.

Using computer simulations, a group of theoretical chemists at Warsaw University—Malolepsza, Boniecki, Kolinski and Piela—managed to get a glimpse of how such misfolded proteins—called prions—propagate. Recently, they designed a protein that, in computer simulations, induces other proteins to misfold. The work was published in *Proceedings of the National Academy of Sciences* in May.

Edyta Malolepsza, a graduate student

to what develops in prion disease.

Malolepsza cannot yet explain why one of the proteins could propagate misfolding while the related sequences could not. Figuring this out may yield clues about how to inhibit or reverse prion disease.

“Only one among the studied sequences exhibits the ability to induce prion disease,” says Malolepsza. And just a few amino acids—sometimes only one—made the difference between the protein that acted like a prion and the

Just a few amino acids made the difference between the protein that acted like a prion and the 13 others that didn't.

involved in the work, says she hopes it will help advance our understanding of prion disease. “This is a small model with a protein designed by us, not by nature,” she says. “But because we used a very realistic force field, a real protein could behave similarly.”

Malolepsza's work involved two primary steps: designing protein sequences that might have a propensity to misfold, and simulating what happens when they interact. For the design process, she used trial and error to identify a set of 32-amino-acid chains that met specific criteria: they would naturally fold into a bundle of two alpha-helices, but, at only a slightly higher energy level, could also form a beta-sheet.

After selecting 14 appropriate sequences, Malolepsza began her simulations. Alone, each peptide folded to the native alpha-helical shape at a variety of temperature ranges. However, when allowed to interact with a frozen beta-sheet version of itself, one of the sequences (regardless of its starting conformation) unfolded and then refolded to a beta-sheet shape. It then formed a dimer with the pre-existing beta-sheet. In addition, allowing one frozen beta-sheet molecule to interact with two alpha-helices produced a beta-trimer—a larger aggregate similar

to what develops in prion disease. “Maybe a mutation occurs that allows propagation of the amyloid aggregations seen in prion disease,” says Malolepsza.

Malolepsza is hoping to simulate actual prion proteins soon. It's a more complex task because prions are bigger—the fragment needed for simulations contains about 100 amino acids. “We need a faster simulating program,” she says. “I hope that we will eventually have another paper with a more complete answer as to how prions work.”

An Unfolding Story

To fit an organism's DNA into a single cell, it has to be tightly compacted, first wound around proteins to form chromatin fibers, then further coiled into chromosomes. Computer simulations by scientists at New York University (NYU) have now provided a better understanding of how this folding occurs. The results appeared in the June 7 issue of the *Proceedings of the National Academy of Sciences*.

“It's very important to understand how chromatin folds and unfolds,” says Tamar Schlick, PhD, professor of chemistry, mathematics, and computer science at New York University and senior author on the paper. Chromatin folding is directly involved in gene

PLoS Computational Biology Launched

In June, the Public Library of Science (PLOS) teamed up with the International Society for Computational Biology to publish the first issue of *PLoS Computational Biology*.

Editors hope that bringing the best work together in one place will boost perceptions of the field's importance.

"There's no journal that's devoted to our understanding of living systems using computational biology," says Philip Bourne, PhD, professor of pharmacology at the University of California, San Diego, and editor-in-chief of the new journal. Such papers get peppered all over *PNAS*, the *Journal of Molecular Biology*, *Science*, *Nature*, and *Cell*, he says. "That doesn't help solidify the value of computation to biology."

By focusing on biological applications, the new journal shouldn't infringe on the territory already covered by *Bioinformatics* and *The Journal of Computational Biology*, which are oriented more toward methods and algorithm development. "The future of the field is really with people who develop and then apply methods either in *in silico* labs or in conjunction with wet labs," Bourne says.

Rather than focusing on computational molecular biology, the journal is trying to broaden the perspective. "We're getting very diverse papers with a computational thread," Bourne says. "That includes papers on such topics as computational neurobiology, population genetics, and computational ecology."

Bourne understands that when people have produced an incredible piece of work, they might still try for *Science* or *Nature*. "But," he says, "over time we are trying very hard to make *PLoS Computational Biology* the place where they send their best quality work."

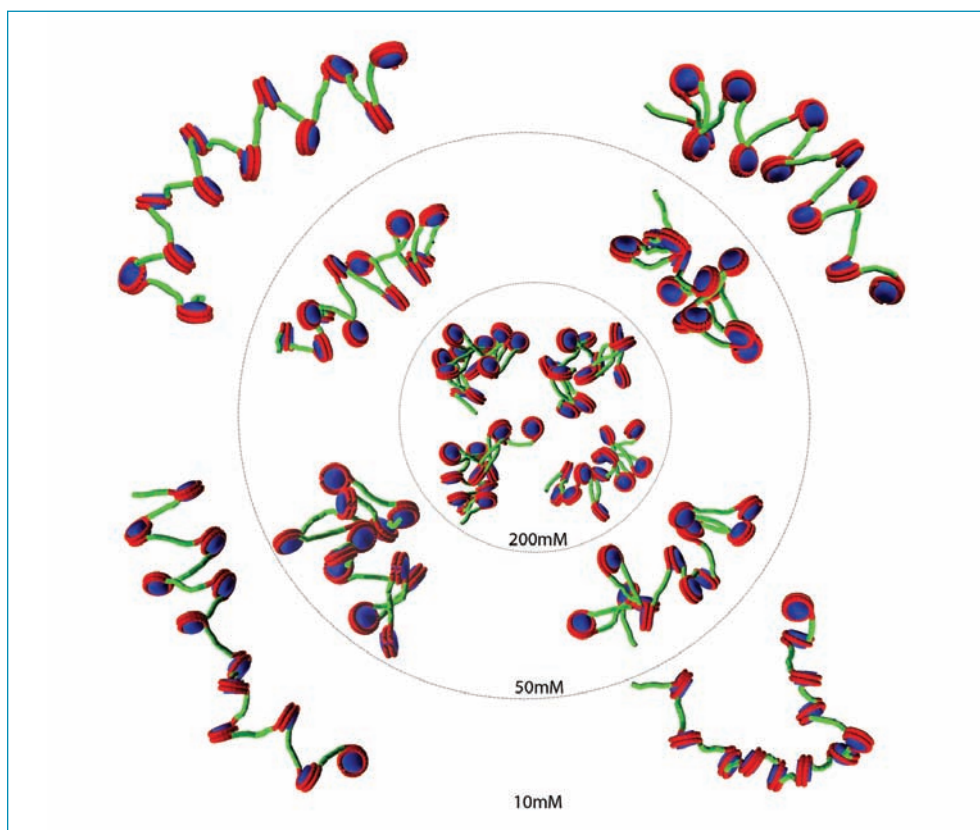
expression and silencing: chromatin—a complex of DNA and specialized proteins—must unwind so that the cellular machinery can access the DNA and begin copying or transcribing the genetic information into proteins.

A stretched-out chromatin fiber looks like "beads on a string." The DNA is wound around repeating 8-protein complexes at approximately regular intervals; each DNA/protein "bead" is called a nucleosome. Scientists already knew that chromatin unfolds in low-salt solutions and folds in high-salt solutions, such as found in cells. But they couldn't distinguish between four possible folding structures (perpendicular and parallel zig-zag, and perpendicular and parallel solenoid), until now.

The scientists at NYU modeled the folding of a 12-nucleosome fragment of chromatin using what they believe is the highest-resolution simulation of

chromatin folding to date. Chromatin is too large and complex to model atom-by-atom with today's computing power. But modeling at the level of macromolecules (proteins and DNA) is too crude to give a realistic picture. So, NYU scientists compromised: Using structural experimental information about each nucleosome and the electrostatic forces associated with each atom, they built a realistic mechanical model containing essential features of the system while approximating others. They modeled the key positive and negative charges found on the amino acids and nucleotides, without explicitly modeling every atom. Chromatin folds according to the attraction and repulsion of these charged particles with each other and with the salt solution.

"This allows us to do long-time simulations of the complex system using what is a very realistic model of



A 12-nucleosome array adopts extended beads-on-a-string conformations in a low salt solution (outer ring), while it compacts at midlevel salt concentrations (middle ring) and folds into irregular zig-zag structures at high salt concentrations (inner ring). Courtesy of Tamar Schlick.

what the nucleosome core would look like.” Schlick says.

Regardless of which of the four folding models they started their simulation with, they found that their virtual chromatin always folded into an irregular zig-zag conformation after enough computational steps. They also pinpointed the key electrostatic attractions and repulsions that drive chromatin folding and unfolding.

“This is not the first attempt to model the chromatin fiber, but this one makes the fewest artificial assumptions,” says Sergei Grigoryev, PhD, assistant professor of biochemistry and molecular biology at Penn State University College of Medicine.

Their findings agree with the experimental data he has collected on chromatin folding using electron microscopy.

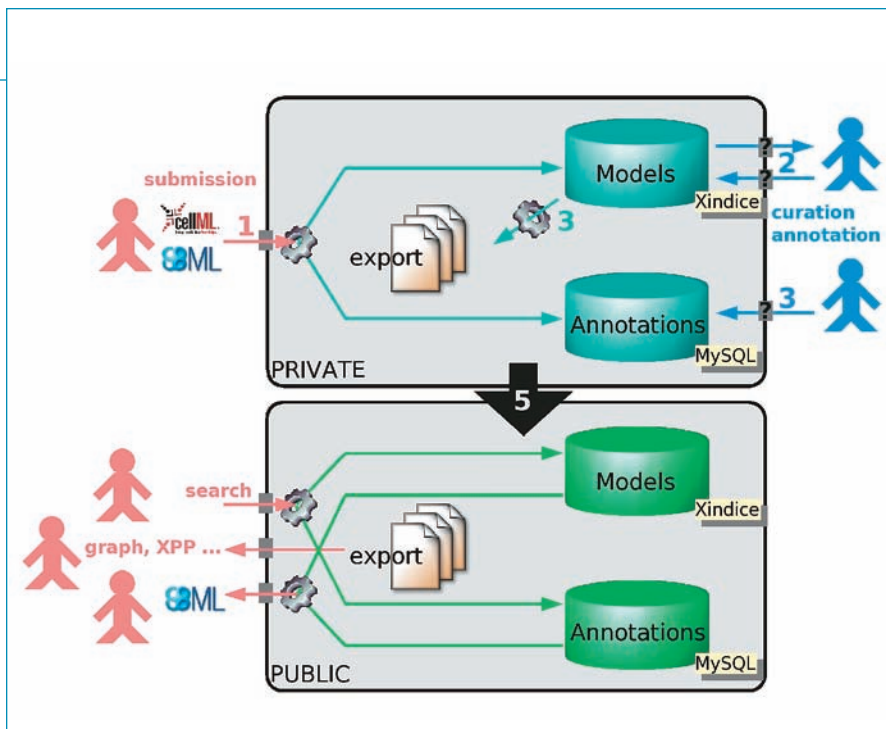
“I really admire their paper,” he says. “For the first time it produced a nucleosome array model that really matches biological observations.”

Reliable Models Now Available

As systems biologists develop models that attempt to simulate life, they need a good way to make them accessible to others as well as a good way to access other people’s models—and to know they can be trusted to work. An international collaboration known as BioModels intends to provide just that; in April they released an initial set of fully annotated models for public use.

“We are storing quantitative, peer-reviewed models so that people can use them,” says Nicolas Le Novère, PhD, a computational neurobiologist with the European Bioinformatics Institute (EBI) in the United Kingdom. “We want it to be a kind of golden resource.” BioModels is the result of a collaboration led by EBI and the SBML Team, an international group that develops open-source standards to describe biological systems.

The project staff only accepts models that have been published in peer-reviewed literature. Curators then check to make sure that, when down-



A graphical depiction of the private BioModels submission (1), checking (2), and annotation (3) steps (above) and the public access steps (below). Courtesy of Nicolas Le Novère.

loaded and run in the appropriate simulation software, the model will do what it’s supposed to do. Next, annotators add model descriptions and cross-links to related models and papers. At that point, the model is released for public use.

The systems biology community is wagering that this collection of models will prove extremely valuable. According to an editorial in *Nature*, “It is hoped that BioModels will form the basis of a universally accepted repository that can do for systems biology what GenBank and the Protein Data Bank have done for genetics and structural biology.” *Nature* 435, 1 (5 May 2005)

The majority of early submissions to the database deal with signaling pathways or metabolic networks, but they are quantitative and dynamic models—not just pathways. “You can import these models into a simulator, click ‘run,’ and see things happen, see

values updated,” says Le Novère.

Formalized, realistic models of subcellular parts or even muscles can also be stored in BioModels. And although models of that type haven’t arrived yet, Le Novère says the project already has a backlog of submissions. “We have so many good models arriving that we have to prioritize.”

BioModels’ initial users are primarily the people who’ve created the models, says Le Novère, but he anticipates that will soon change. The site should prove extremely valuable to experimental biologists who want to have an idea of how a system works before designing an experiment. And

pharmaceutical companies could turn to it as well, in order to test the likely effect of enhancing or inhibiting a molecule or doing things that affect several parts of a network at the same time.

For more information, visit <http://www.ebi.ac.uk/biomodels/> □

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