RESEARCH SCIENCE

Cell Modeling Tool Makes Complex Calculations User-Friendly

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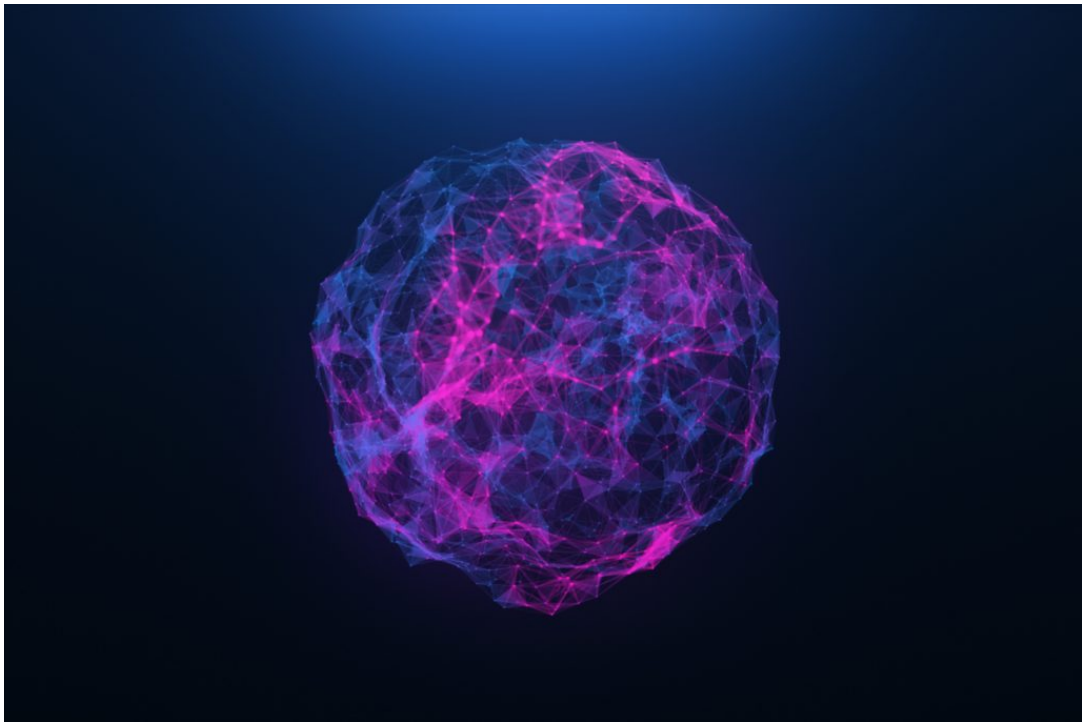
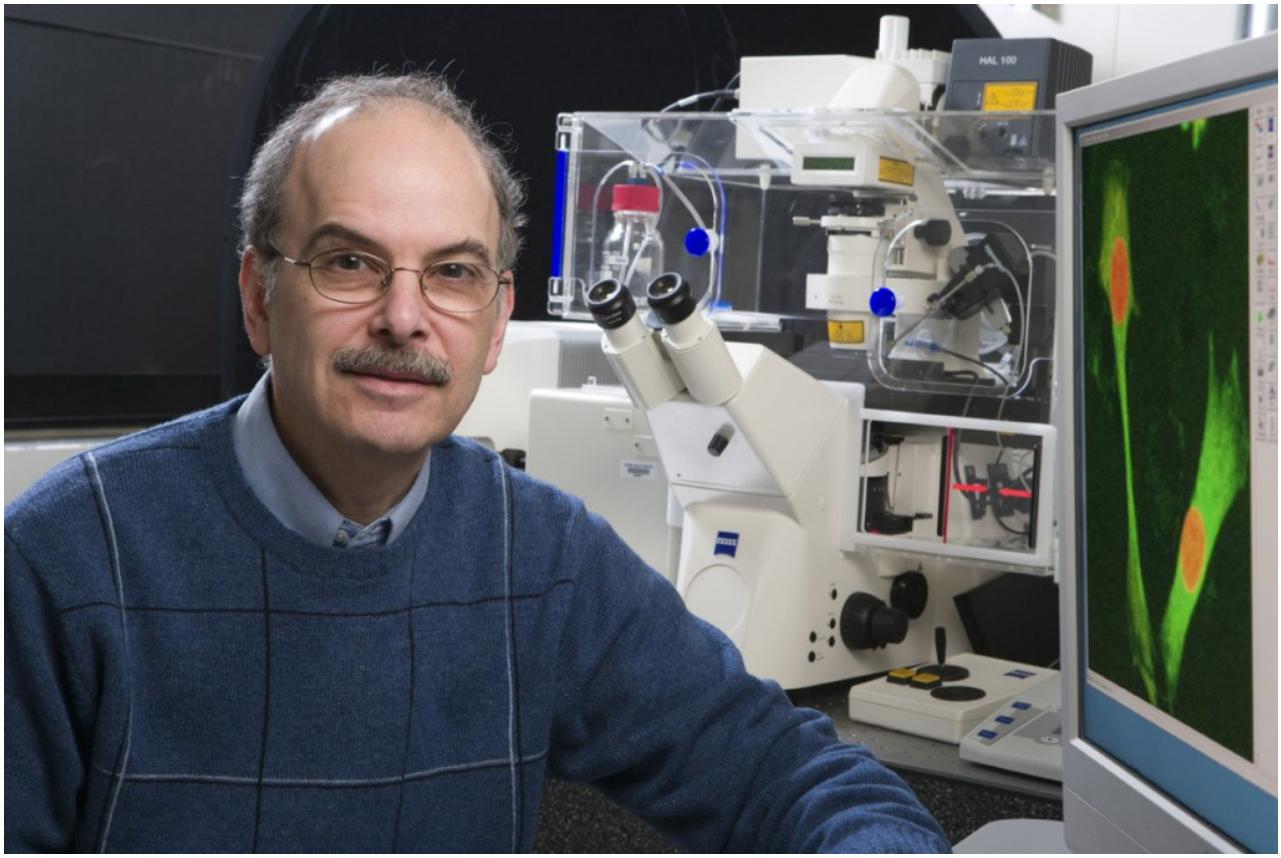


Researchers at UConn Health have just released a new version of the Virtual Cell that allows biologists without strong math or computer programming skills to more easily build models and simulate how a cell functions. (Getty Images)

Programming a molecular biology experiment can be similar to playing Sudoku; both are simple if you're working with only a few molecules or a small grid, but they explode in complexity as they grow. Now, in a paper published on Oct. 3 in the *Biophysical Journal,* researchers at UConn Health's Virtual Cell Project (vcell.org) have made it far easier for cell biologists to build complex biological models.



UConn Health biophysicist Leslie Loew, director of the Center for Cell Analysis and Modeling. (Lanny Nagler for UConn Health, File Photo)

The Virtual Cell, or VCell as it's known, is a software platform that offers the most comprehensive set of modeling and simulation capabilities for cell biology in the world. It allows biologists without strong math or computer programming skills to build models and simulate how a cell functions. VCell first came online almost 20 years ago, in 1998, and the UConn Health team headed by UConn Health biophysicist Leslie Loew has developed and maintained it since. Using VCell, a biologist can predict what happens when a certain drug encounters a filtration cell in the kidney, for example, or how a hemoglobin molecule in a red blood cell deals with a spike in carbon dioxide.

But until now, a biologist still needed strong programming skills to do detailed cell models at the molecular level, and even more than that, patience. Each molecule involved in a model has a certain number of states, or things it can do and places it can be. Each possible combination of molecules and their states had to be coded out by hand. And as the number of moving parts increases, the number of lines of computer code do, too. If you increase the size of a Sudoku grid to nine by nine, you suddenly have 6.7 sextillion possible scenarios ... and you get an idea of the nightmare molecular biologists faced when they tried to code even a slightly complex biological system. The common name for this problem is a "combinatorial explosion," and the

solution to it, called “rule-based modeling,” was developed 12 years ago by VCell team member Michael Blinov and colleagues James Faeder and William Hlavacek, who all worked during that time at Los Alamos National Laboratory.

However, every modeler using rule-based modeling faced a complication. The program detailing interactions among molecules had to be written out in text. In this age of iPhones and computers you can navigate with swipe and click, everyone expects a computer to have a gorgeous graphic interface. Until now, using rule-based modeling wasn’t like that. It looked more like the text command boxes you can call up if you need to navigate the guts of your machine quickly. But it gets tiresome fast, and catching mistakes in thousands of lines of repetitive, almost-but-not-quite-identical code can be maddening. Cell biology models quickly get so unwieldy that only an experienced modeler or programmer can handle them. This sharply limited who could use such modeling.

“Before, only programmers or experienced modelers could create rule-based models to describe details of molecular interactions,” says Loew. “We wanted to make rule-based modeling available to the cell biologists who really need it.”

Loew and the VCell team of Michael Blinov, Ion Moraru, James Schaff, and Dan Vasilescu decided to make things easier. In their new paper, they describe a user interface for VCell that uses colored shapes to represent molecules. The shapes look a bit like colored bricks. Bubbles show binding sites, and lines show links between molecules. The links can also be different colors and shapes to represent different interactions. A simple model describing hemoglobin resembles a map or wiring diagram.

Instead of writing thousands of lines of code, biologists using VCell can now just define their molecules and explain to VCell how they can interact with each other. The biologist doesn’t have to worry about the combinatorial explosion. The computer – all 60 teraflops, 3,000 processors, and 2 petabytes of storage hosted at UConn Health’s Cell and Genome building – handles it.

Loew and Blinov believe the new version of VCell will dramatically expand the number of people who can use rule-based modeling. This is because it allows scientists to use the comprehensive set of simulation methods available in VCell with rule-based models in a single, unified, user-friendly software environment.

Now, a trained biologist should be able to take a day to go through the tutorials on the site and learn enough to figure out how to model a new problem on VCell. Previously, there were about 5,800 active users of VCell globally (you can log in from anywhere that has an internet connection). Those modelers had created 76,600 models and run about 479,000 different simulations on them. These simulations test everything from whether a certain mutation causes cancer to how a new drug might interact with the heart. And with the newly released version of VCell, the number of active users should increase.

So far, VCell hasn't helped with a Sudoku game. But someone might just write a model for that.

VCell has been supported through the years by various grants from the National Institutes of Health (NIH) and the National Science Foundation (NSF), and is currently supported by a "Biomedical Technology Research Resource" grant from the National Institute of General Medical Science at NIH.

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