Researchers make the leap to whole-cell simulations

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Using data supplied by researchers at the Max Planck Institute, University of Illinois postdoctoral researcher Elijah Roberts and chemistry professor Zaida Luthey-Schulten built a computer model of a bacterial cell that accurately simulates the behavior of living cells. Credit: L. Brian Stauffer

Researchers have built a computer model of the crowded interior of a bacterial cell that – in a test of its response to sugar in its environment – accurately simulates the behavior of living cells.

The new "in silico cells" are the result of a collaboration between experimental scientists at the Max Planck Institute of Biology in Germany and theoretical scientists at the University of Illinois using the newest GPU (graphics processing unit) computing technology.

Their study appears in the journal *PLoS Computational Biology*.

"This is the first time that we're modeling entire cells with the complete contents of the cellular cytoplasm represented," said Illinois postdoctoral researcher and lead author Elijah Roberts. "We're looking at the influence of the whole cellular architecture instead of modeling just a portion of the cell, as people have done previously."

University of Illinois chemistry professor Zaida Luthey-Schulten, who led the research, had done molecular dynamics simulations of individual molecules or groups of molecules involved in information processing, but never of a system as large and complex as the interior of an entire cell.

Then in 2006 she saw a paper by Wolfgang Baumeister and his colleagues at Max Planck that located every one of a bacterium's ribosomes, its protein-building machines, inside the cell.

That image spurred Luthey-Schulten to think about modeling an entire cell, and she asked Baumeister and his colleague Julio Ortiz if they would repeat the study in *Escherichia coli* (*E. coli*), a bacterium that has been the subject of numerous molecular studies.

Once the new ribosome data were available, Roberts looked to other studies that described the size distribution of the rest of the molecules that take up space in the cell. By adding these to the ribosome data, he developed a three-dimensional model that showed the degree of "molecular crowding" in a typical *E. coli* cell.

Luthey-Schulten was amazed at how little "space" remained inside the cell, she said.

"I think, like everybody else, my perception of the cell up until Wolfgang and Julio's 2006 article had always been that it's a pretty big sack of water where a lot of chemical reactions occur," she said.

"But in fact there are a lot of obstacles in the cell, and that is going to affect how individual molecules move around and it's going to affect the reactions that occur."

Other researchers have begun studying the effects of molecular crowding on cellular processes, but never at the scale of an entire cell.

Those studying live cells can – by conducting fluorescence experiments – discover variations in the copy number of a particular protein in a population of cells. But they are less able to observe the microscopic details that give rise to such differences between genetically identical cells. Well-designed computer simulations of whole cells can track every reaction within the cells while also accounting for the influence of molecular crowding and other variations between cells, Luthey-Schulten said.

For example, by running simulations on models of two *E. coli* strains, the researchers were able to see that "bacterial cell architecture does indeed affect the reactions that occur within the cells," Luthey-Schulten said. When sugar was present in its environment, a longer, narrower *E. coli* strain was able to ramp up production of a sugar-transporter protein much more quickly than a bigger strain, the researchers found. That difference had a lot to do with the distribution of molecules in each cell type, Roberts said.

The computer simulation also showed how molecular crowding influences the behavior of a molecule that, when it binds to DNA, shuts down production of the sugar-transporter protein. Even when it wasn't bound to DNA, this repressor remained close to the binding site because other molecules in the cell blocked its escape. These intracellular obstacles reduced its ability to diffuse away.

The new model is only a first step toward an accurate simulation of a

whole working cell, the researchers said. The development of better models will rely on the work of those conducting research on actual cells. Their data provide the framework for improving computer models, Luthey-Schulten said, and offer a real-world test of the in silico cells' ability to recreate the behavior of living cells.

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