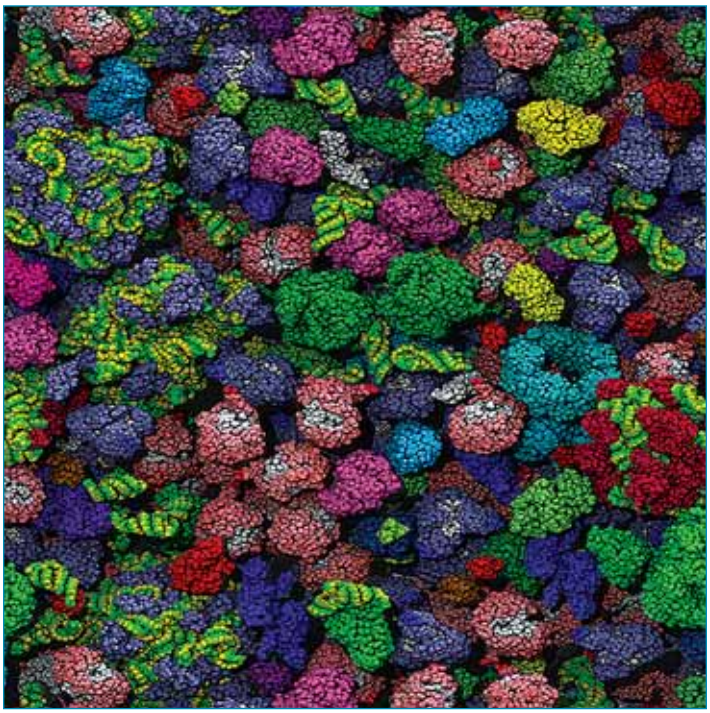
# NewsBytes

## Simulating Crowded Cytoplasm

In biology textbooks, the carefully rendered cross-section of an *E. coli* cell often resembles a well-organized and spacious apartment, with everything in its place and ample room for movement. But a recent computational recreation of the scene looks more like a Friday night dance floor, with molecules bumped up against one another in every direction. In addition to providing a dramatic, qualitative description of the crowded cytoplasm, this first atomically detailed computational model of *E. coli* innards is also a tool for quantitative predictions of molecular conduct within the cell. The model is described in the March 2010 issue of *PLoS Computational Biology*.



***Combining all available known details about the atomic structures and concentrations of 50 of the most common proteins within* E. coli*'s cytoplasm, Elcock and McGuffee created a model of what it might be like inside the crowded cell. They then simulated 20 microseconds of jostling with and without various types of molecular interactions, including crowding (excluded volume effect) and electrostatic and hydrophobic interactions. They then compared the results to experimental observations. Reprinted from McGuffee SR, Elcock AH, 2010 Diffusion, Crowding & Protein Stability in a Dynamic Molecular Model of the Bacterial Cytoplasm.* PLoS Comput Biol *6(3): e1000694. doi:10.1371/journal.pcbi.1000694.***

"This is an attempt to build a virtual lab, in which we can study various biological and biophysical processes as they might occur inside the cell," says **Adrian Elcock, PhD**, coauthor and associate professor of biochemistry at the University of Iowa.

The sea of floating proteins inside every cell is the background against which many cellular reactions take place. Scientists realized years ago that the cytoplasm is generally not an invisible player in those reactions. One of the best-studied examples is macromolecular crowding (also called excluded volume effect). Having large neighbors on every side changes a protein's effective concentration and influences its movement and ability to react. A biological reaction observed in dilute solution can be much faster or slower than the same reaction inside a crowded cell.

To create the model, Elcock and then graduate student **Sean McGuffee, PhD**, started by gathering known structural data for 50 of the most common *E. coli* proteins. They then combined the detailed representations inside a computer model at known cellular concentrations, creating a strikingly dense model of 1008 proteins. The researchers then set that image in motion, running independent Brownian dynamics simulations governed by varying energetic descriptions of intermolecular interactions. The simplest description included only the excluded volume effect: no molecule could take the space of another molecule. The most complex scenario they ran included excluded volume, electrostatic interactions, and favorable short-range hydrophobic interactions. The more complex simulations performed surprisingly well when asked to predict molecular behaviors, such as diffusion and stability, in the *E. coli* cytoplasm.

The model was able to match experimental observations of how quickly green fluorescent protein diffuses in the *E. coli* cytoplasm. And it was able to predict the greater stability of the unfolded state of the protein CRABP, cellular retinoic acid binding protein, over the folded state inside *E. coli*. Although the presence of close neighbors (crowding) generally stabilizes a large folded protein, the specific electrostatic and hydrophobic interactions of unfolded CRABP with other cytoplasmic proteins counteract the crowding effect.

"What this doesn't mean," Elcock emphasizes, "is that crowding effects are unimportant. It means that crowding is only part of the story."

A computational box of 1008 proteins is still a far stretch from the complex *E. coli* cytoplasm, says **Allen Minton, PhD**, a pioneer in the study of crowding effects and researcher of physical biochemistry at the National Institutes of Health. "But there are a lot of questions that only this type of computation can answer," he says. "From a computational point of view, it is a real tour-de-force."

***—By Louisa Dalton***

## Animating Molecular Biology

These days, molecular biologists often gather data over a period of time—observing shifts as they occur inside groups of cells undergoing natural changes. The researchers then face the daunting task of making sense of it all. Now, computational biologists have devised a software program to easily visualize and analyze these mountains of time-series data in animated movie form. While these flicks might never