

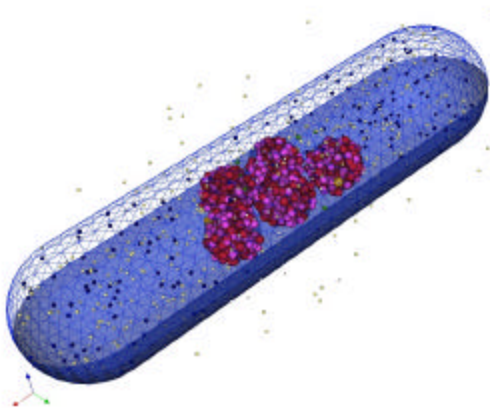
ChemCell: A Particle-based Cell Simulation Tool

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One of the next grand challenges in biology, building on the deluge of genomics and proteomics data, is to understand how individual cells function as a collection of interacting biochemical molecules and molecular machines. From a modeling perspective, microbial organisms are an ideal starting point for building cellular models because their structure is simple and they contain a relatively small number of large biomolecules. For example, *Escherichia Coli* (E. Coli), the best understood of all microbes, is cylindrical in shape, a few cubic microns in size, and has a dozen flagella. Its single strand of DNA has 4,500 genes, most of whose functions are known. The volume of an E. Coli cell contains a few million protein molecules, tens of thousands of ribosomes, similar numbers of tRNA and mRNA molecules, and tens of millions of small organic molecules and ions, with the remaining 70 percent of the cell volume being water. From a high-performance computing standpoint, where simulations of tens of millions or even billions of particles or grid cells are becoming commonplace, a detailed simulation of an E. Coli cell could potentially model all its biomolecules (excluding water).

As part of the Sandia National Laboratories-Oak Ridge National Laboratory Genomics:GTL project, “Carbon Sequestration in *Synechococcus* Sp.: From Molecular Machines to Hierarchical Modeling,” we have developed a cellular simulation tool called ChemCell, which treats proteins, protein complexes, and other organic molecules as particles that diffuse via Brownian motion and react with nearby particles in accord with input chemical rate equations. The 3-D geometry of the cell is represented as a collection of triangulated surfaces (membranes, organelle boundaries, etc.) along which and between which the particles diffuse and react. We have used the code to model portions of the carbon-fixation metabolic pathway in *Synechococcus*, the cyanobacterium that is the focus of our GTL project.



Snapshot of a ChemCell simulation of a *Synechococcus* cell with carboxysome organelles where carbon fixation reactions occur.

ChemCell is designed as a flexible tool that could be used to model signaling and metabolic or regulatory pathways in a variety of prokaryotic or eukaryotic cells. It simulates individual particles and can track spatial and temporal variations in species concentrations from stochastic levels to continuum, limited only by compute power. We wrote it as a modular, extensible code that we hope will be useful to ourselves and others

as a testbed for new algorithmic and modeling ideas, particularly as reaction network data is produced in increasing volumes from high-throughput experiments.

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A prototypical kinase signaling cascade modeled with ChemCell and a nonspatial Gillespie algorithm. The two methods agree when reactions dominate (high diffusivity), but spatial effects become important when diffusion is the rate-limiting process.

