Smoldyn: a Simulator for Cellular Systems Biology

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Abstract

What is Smoldyn?
Smoldyn is a program that performs detailed simulations of cell biology. Proteins and other molecules of interest are represented by point-like particles which diffuse within a continuous (non-lattice) space. Smoldyn accurately simulates diffusion, chemical reactions, conformational spread, realistic membrane geometries, and molecule-membrane interactions. It is typically most useful on scales from nanometers to microns and sub-microsecond to several seconds. Smoldyn is designed for both the research and teaching communities.

The Program
Smoldyn is easy to use, freely available, and open source. It is written in C and was compiled on OS X using gcc. OpenGL is used for graphics, libtiff for saving tiff format images, and the Mersenne Twister for random number generation. Smoldyn also runs natively on Linux was cross-compiled for Windows from OS X using the mingw compiler.

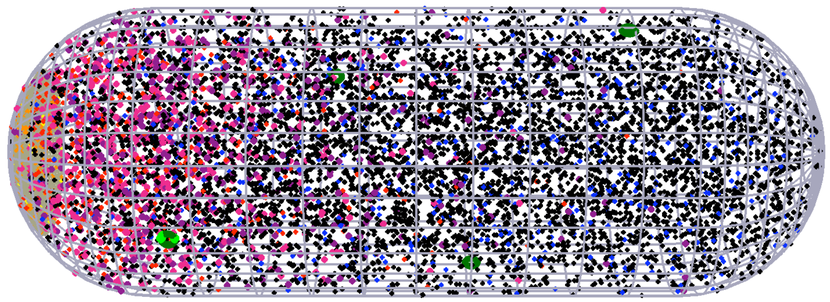
Objectives

A general-purpose biochemical simulator, which accounts for *spatial structure*, *stochastic effects*, and as many *fundamental biochemical processes* as practical. It can be used to explore hypotheses of how cells work.

Representative applications:
- intracellular signal transduction
- bacterial cell division
- effects of macromolecular crowding on diffusion and/or reaction rates
- dynamics within neural synapses
- simulated fluorescence microscopy (*e.g.* fluorescence recovery after photobleaching)

This simulator needs to be:
- easy enough for quick "back of the envolope" models
- accurate enough for rigorous computational modeling
- efficient enough that a single processor is adequate
- extensible enough for large multi-node clusters

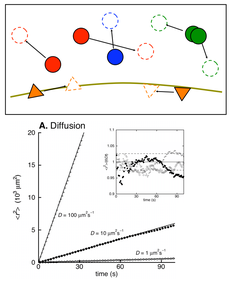
Accuracy:
- well-defined underlying mathematical model
- results approach model as time step size is reduced to 0

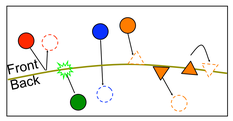


Smoldyn model of the chemotaxis system within the 2 μm long bacterium *Escherichia coli*. This signaling system senses attractants using receptors that are clustered at the left cell pole (tan), amplifies the signal with CheA proteins (yellow and orange), transmits it across the cell with CheY proteins (unphosphorylated are black, phosphorylated are red), and uses the signal to control flagellar motors (motor proteins are dark green for inactive and bright green for active). CheY proteins are reset with CheZ proteins (blue and magenta). See "Example: protein gradients."

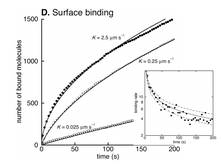
Algorithms

Diffusion. Each molecule moves with a Gaussian-distributed displacement at each time step, independent of surfaces or other molecules. Surface-bound molecules are then moved back to the surface along the local normal vector.

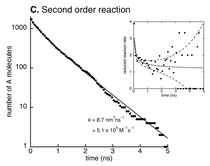




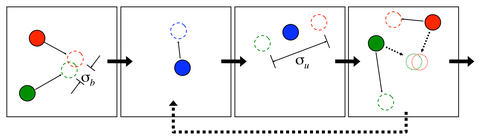
Surface interactions. An interaction is performed for each molecule that diffused across a surface. Depending on the molecular species, surface properties, and the face contacted, options include: reflect, absorb, transmit, or adsorb. Surface-bound molecules can desorb or change state.



Chemical reactions. A bimolecular reaction occurs when two reactants diffuse to within a *binding radius*, σ_b, of each other.

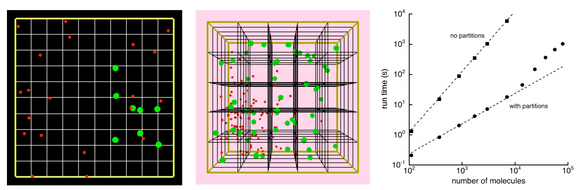


If the reaction is reversible, there is a fixed probability of dissociation during subsequent time steps. These products are initially separated by an *unbinding radius*, σ_u. These new products may diffuse away from each other, or rebind in a *geminate recombination*.



Performance

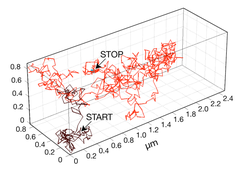
Scaling. Every algorithm in Smoldyn is linear with respect to system size. This is achieved by spatially partitioning the system volume so that chemical reactions need to be checked only for molecules that are known to be close to each other, and surface interactions are checked only for molecules known to be near surface panels.



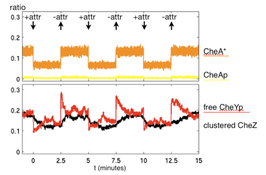
partitioning in 2-D | partitioning in 3-D | benefit of partitioning

Overall. Smoldyn is generally convenient with systems with up to 10,000 molecules. Larger systems exhaust the cache memory (on a MacBook Pro), so run slower. We are working on parallelizing Smoldyn.

Example: bacterial signalling



diffusion trace of a single CheY molecule

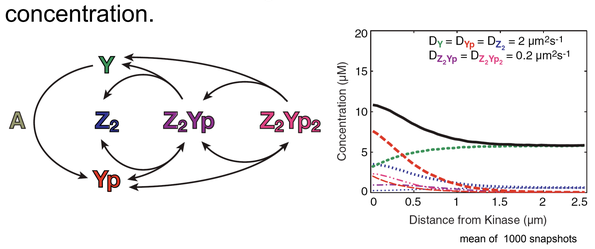


total molecule numbers in the cell

To relay signals from the polar chemoreceptors to the lateral flagellar motors, signalling molecules are phosphorylated in a regulated cascade and diffuse through the cell. Smoldyn helped us to visualise the stochasticity of this process and to assess the effects of spatial distribution and dynamics.

Example: protein gradients

Because proteins diffuse across a cell in several seconds, it is often believed that concentration gradients cannot be stable. However, if two forms of a protein have different diffusion coefficients, and conversion between these forms occurs in different parts of the cell, then stable gradients will exist. For example (see large figure), the *E. coli* CheY protein is only phosphorylated near one of the cell poles, but can be dephosphorylated elsewhere. Because the phosphorylated form binds to the CheZ protein, it is probable that its intracellular diffusion coefficient differs from that of unphosphorylated CheY. This will cause a gradient in the overall CheY concentration.



Conclusions

Smoldyn is a new tool for simulating cell biology at a high level of detail. It is accurate, easy to use, and computationally efficient. Smoldyn is especially useful for simulating diffusion and reactions in complex systems. It is written in C on OS X and runs on Macs, Linux, and Windows. For more information, please visit:

http://www.smoldyn.org

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