Smoldyn: cell biology simulation with spatial detail

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Abstract

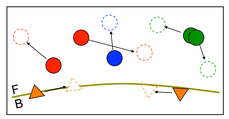
Smoldyn is a simulator for modeling molecular diffusion, chemical reactions, and molecule-membrane interactions with nanometer scale resolution. It represents molecules as individual spherical particles in 1, 2, or 3-dimensional continuous space. Smoldyn is very accurate, easy to install, and easy to use. It is widely used for simulating cell systems and biophysical problems.

New features include: (1) rule-based modeling for simulating protein modification and complexation, which Smoldyn simulates using either the formal BioNetGen language, or a new informal wildcard method, (2) improved excluded volume algorithms for simulating macromolecular crowding, (3) better support for particle tracking, and (4) hybrid simulation capabilities for faster runtimes.

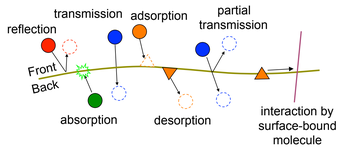
Smoldyn is open source and available for free at http://www.smoldyn.org.

Core Smoldyn

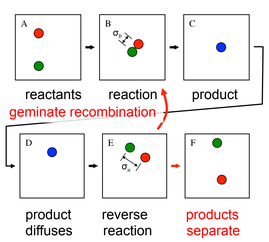
Diffusion. Simulated with Gaussian-distributed random displacements on each coordinate. Can also simulate drift, anisotropic diffusion, and diffusion on surfaces.

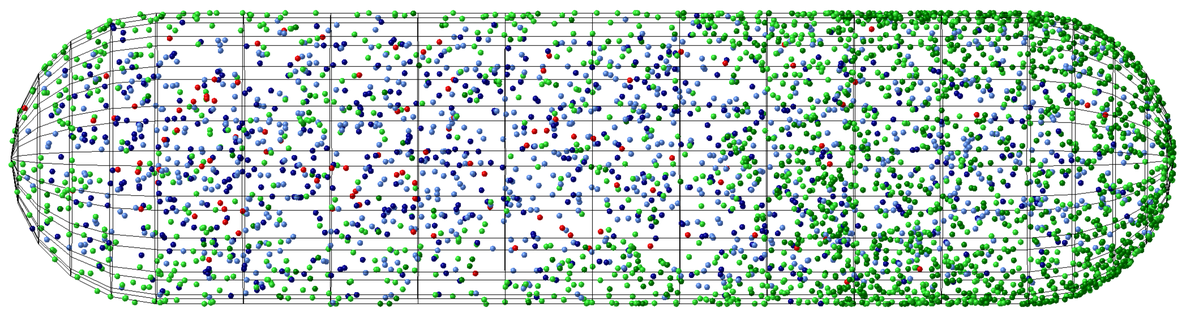


Surface interactions. Molecules can reflect, adsorb, desorb, or transmit through surfaces with user-definable rate coefficients.



Chemical reactions. Two molecules react when they end up within a *binding radius* of each other at the end of a time step. When a molecule dissociates to two products, those products are separated by an *unbinding radius* to control the probability of geminate recombination.

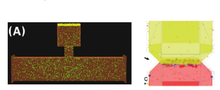




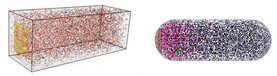
Smoldyn simulation of *E. coli* Min system. The *E. coli* MinC, MinD, and MinE proteins oscillate between the cell poles with a ~20 second period, which promotes cell division at the cell center. It is an intriguing system that has been modeled extensively. Here, the figure illustrates a type of simulation that is well suited to simulation with Smoldyn. Proteins are: cytosolic MinD-ATP in dark blue, membrane-bound MinD-ATP in dark green, MinD-ADP in light blue, MinE in red, and MinD-MinE in light green.

Typical uses

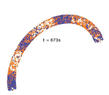
Cell systems



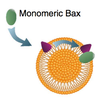
neural dendritic spines



E. coli chemotaxis

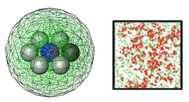


E. coli Min system

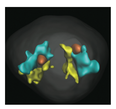


apoptosis

T lymphocyte motility



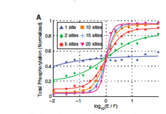
yeast cell signaling



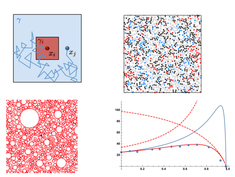
nucleolar tethering

Khan et al. *J Comput. Neurosci.* 31:581, 2011; Singh et al. *PLoS Comp. Biol.* 7:e1002106, 2011; Jilkine et al. *PLoS Comp. Biol.* 7:e1002271, 2011; Lipkow, *PLoS Comp. Biol.* 2:e39, 2006; Lipkow et al., *J. Bact.* 187:45, 2005; Hoffmann and Schwartz *Soft Matter* 10:2388, 2014; Andrews et al., *PloS Comp. Biol.* 6:e1000705, 2010; Subburaj et al., *Nature Comm.* 6:8042, 2015; Liu, Welf, and Haugh, *J. R. Soc. Interface* 12:20141412, 2015; Strongin, Groudine, and Politz, *Nucleus* 5:474-481, 2014.

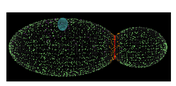
Biophysics studies



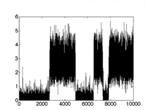
multi-site phosphorylation



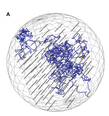
macromolecular crowding



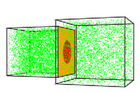
cell division diffusion barriers



bistability



transcription factor dynamics

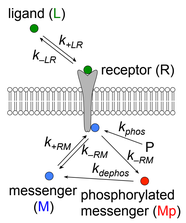


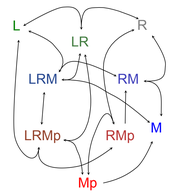
electropulse induced fusion

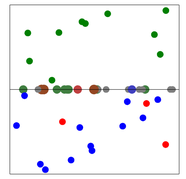
Dushek et al. *Biophys. J.* 100:1189, 2011; Marquez-Lago et al. *IET Syst. Biol.* 6:134, 2012; Zavala and Marquez-Lago, *PLoS Comp. Biol.* 10:e1003725, 2014; Andrews *et al.*, In D. Gilbert, M. Heiner, K. Takahashi, and A.M. Uhrmacher, eds. *Multiscale Spatial Computational Systems Biology* 170-187, 2015; Meinecke, L. and M. Eriksson, *ArXiv* 2016; Meinecke, L., *ArXiv* 2016; Endres, *PLoS ONE* 10:e0121681, 2015; Schmidt, Sewitz, Andrews, and Lipkow, *PLoS ONE* 9:e108575, 2014; Gerisch *et al.*, *J. Cell Science* 127:4507-4517, 2013.

Rule-based modeling

Problem. Proteins that can be post-translationally modified (e.g. phosphorylated) and/or form multimeric complexes can produce a large number of variations. This leads to a lot of chemical species and reactions.







Network expansion with BioNetGen. Modelers can define reaction "rules" in the BioNetGen language, which Smoldyn expands with BioNetGen. It estimates diffusion coefficients and surface interactions for resulting species and reactions.

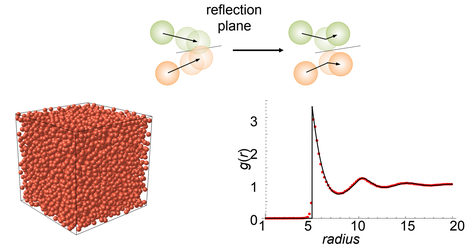
```
L(l2r) + R(r2l) <-> L(l2r!1).R(r2l!1) krlon,krloff
R(r2m) + M(m2r) <-> R(r2m!1).M(m2r!1) krmon,krmoff
R(r2l!+,r2m!1).M(m2r!1,psite~u) -> R(r2l!+,r2m!1).M(m2r!1,psite~p) kphos
M(psite~p) -> M(psite~u) kunphos
```

Network expansion with wildcards. Modelers can also define reaction "rules" using a new wildcard method. Wildcards specify species groups much like operating system wildcards specify groups of files. This is generally simpler than BioNetGen, but inferior for large networks.

```
L(fsoln) + R*(up) <-> LR*(up)     KLRON KLROFF
*R(up) + M*(bsoln) <-> *RM*(up)   KRMON KRMOFF
LRM(up) -> LRMp(up)         KPHOS
Mp(soln) -> M(soln)         KUNPHOS
```

Excluded volume

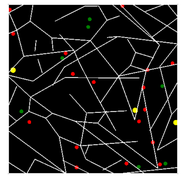
New algorithm. Reflect molecules off of each other using their straight-line trajectories. Result is fast and accurate.



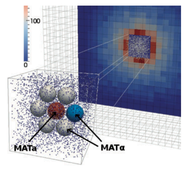
Simulated 6112 molecules with 5 nm diameters (0.1 ns time steps). Radial distribution function agreed well with theory.

Particle tracking, hybrid

Particle tracking. Molecules have serial numbers, which can be preserved during binding and unbinding reactions, allowing molecule tracking. Smoldyn can output data and log reactions for molecules with specific serial numbers.



Hybrid simulation. Simulations can combine particle-based methods with the lattice-based spatial Gillespie method, which is less accurate but more efficient. Representations can be adjacent or overlapping.



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2. Andrews, "Accurate particle-based simulation of adsorption, desorption, and partial transmission" *Phys. Biol.* 6:046015, 2009.
3. Andrews, Addy, Brent, and Arkin, "Detailed simulations of cell biology with Smoldyn 2.1" *PLoS Comp. Biol.* 6:e1000705, 2010.
4. Andrews, "Spatial and stochastic cellular modeling with the Smoldyn simulator" *Meth. Mol. Biol.* 804:519-542, 2012.
5. Robinson, Andrews, and Erban, "Multiscale reaction-diffusion simulations with Smoldyn" *Bioinf.* 31:2406-2408, 2015.
6. Andrews, "Smoldyn: particle-based simulation with rule-based modeling, improved molecular interaction, and a library interface" *Bioinf.* submitted, 2016.
7. Andrews, "Rule-based modeling in Smoldyn using wildcards" in preparation, 2016.