

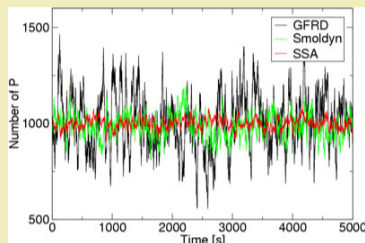


Comparison of mesoscopic methods for biochemical systems

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Motivation

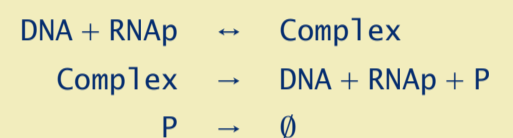
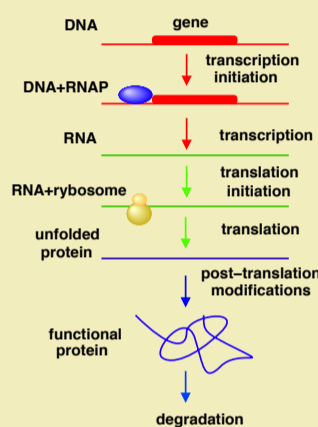
Different mesoscopic methods can predict different fluctuations although averages are the same.



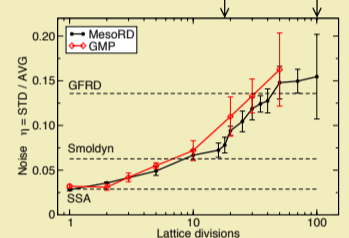
Implementations
SSA[3] – solves CME (no space)
MesoRD[4] – next reaction method
GMP[2] – splitting diffusion and reactions



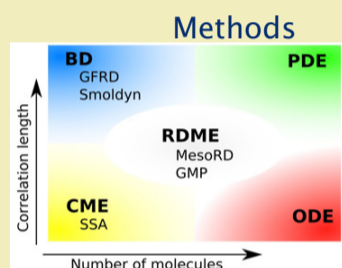
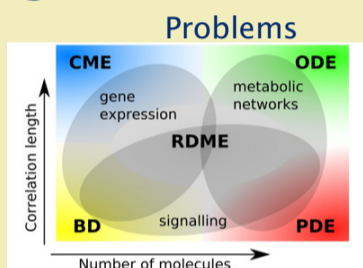
Test case



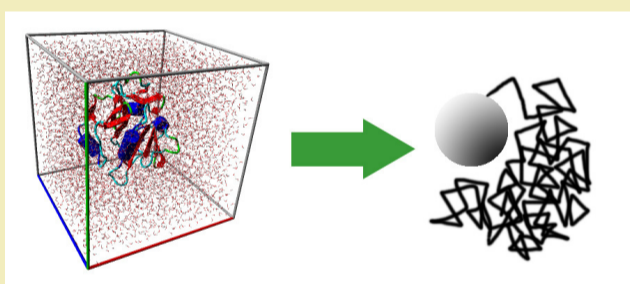
Protein noise vs lattice size



Regimes



Brownian dynamics



N degrees of freedom

reduced to $M \ll N$

GFRD[5]

- event-driven scheme (variable time-step),
- tabulated analytical solutions of Smoluchowski diffusion equation,
- 2 molecules can react per Δt ,
- not a package

Smoldyn[1]

- every collision of reactive species leads to reaction,
- forward reaction rate \rightarrow binding/unbinding radii,
- usable package.

Reaction-Diffusion Master Equation

Variables: number of particles $\{U_{i,j}\}$ of species i in cells j .

$$\frac{d}{dt} P(\{U_{i,j}\}; t) = \sum_{\{U'_{i,j}\}} W(\{U'_{i,j}\} | \{U_{i,j}\}) P(\{U'_{i,j}\}; t) + \text{in-flux from the neighbors to cell } j - \text{out-flux from cell } j$$

Conclusions

GFRD: properly models diffusion-limited reactions.

Smoldyn: not able to reproduce higher moments.

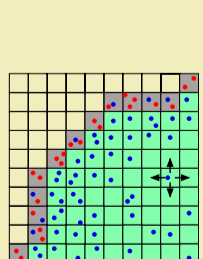
RDME (GMP, MesoRD):

- properly accounts for spacial effects,
- smaller lattice size yields correct higher moments.

References

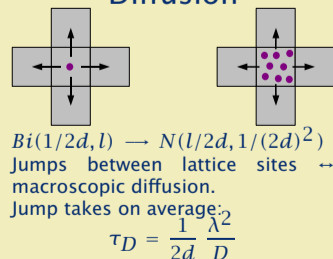
- [1] Steven S. Andrews and Dennis Bray. Stochastic simulation of chemical reactions with spatial resolution and single molecule detail. *Physical Biology*, 1, 2004.
- [2] Jordi Vidal Rodríguez et.al. Spatial stochastic modelling of the phosphoenolpyruvate-dependent phosphotransferase (pts) pathway in escherichia coli. *Bioinformatics*, 2006.
- [3] Daniel T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.*, 81(25), 1977.
- [4] Johan Hattne, David Fange, and Johan Elf. Stochastic reaction-diffusion simulation with mesord. *Bioinformatics*, 21(12), 2005.
- [5] Jeroen S. van Zon and Pieter Rein ten Wolde. Green's-function reaction dynamics: A particle-based approach for simulating biochemical networks in time and space. *J. Chem. Phys.*, 123, 2005.

GMP - Gillespie-MultiParticle method



- Lattice with L^d cells
- No exact position of particles
- Diffusion between cells
- Reactions in well-mixed cells
- Membrane reactions possible

Diffusion



Reactions

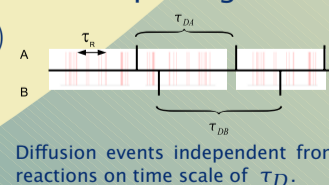
Cells assumed to be well-mixed. Exponential distribution of next reaction events simulated with SSA[3]

$$P(\tau_R, \mu) = a_\mu \exp(-a_0 \tau_R)$$

$$a_\mu = k_\mu \frac{AB}{V N_A}$$

$$a_0 = \sum_{\mu=1}^M a_\mu$$

Splitting



Diffusion events independent from reactions on time scale of τ_D .

Limitations

Choosing proper lattice size:

- Physical limit - 2σ , size of two particles
- Reaction mean free path:

$$\lambda_{RMFP} = \sqrt{\tau_R D_{mutual}}$$