Continuum Diffusion Rate of Enzymes by Solving the Smoluchowski Equation

Lab Tutorial

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http://mccammon.ucsd.edu/smol/doc/tutorials/nbcr080609_lab.pdf

Objectives

- Basic theories of Poisson-Boltzmann and Smoluchowski Equations.
- Experiment: mouse AChE enzyme
- Assignments

Lecture Review

- Before you start this tutorial, please try to answer the below questions:

  1. What's the Poisson-Boltzmann equation (PBE)? What does it describe? Why do we need to solve it and what's the output?

  2. What's the Smoluchowski diffusion equation? What's the relationship with the PBE? What's the problem domain? Is it the same with the PBE?

Poisson-Boltzmann equation

$$-\nabla \cdot \varepsilon(x)\nabla U(x) \quad + \quad \bar{\kappa}^2(x)\sinh U(x) \quad = \frac{4\pi e_c^2}{kT}\sum_i z_i \delta(x - x_i)$$

Linearized Poisson-Boltzmann equation also useful:

$$-\nabla \cdot \varepsilon(x)\nabla U(x) + \bar{\kappa}^2(x)U(x) = \frac{4\pi e_c^2}{kT}\sum_i z_i \delta(x - x_i)$$

$$U(x)\big|_{x\in\partial\Omega} = g(x)\big|_{x\in\partial\Omega}$$

Additional notation for charge distribution term:

$$f(x) = \frac{4\pi e_c^2}{kT}\sum_i z_i \delta\left(x - x_i\right)$$

Smoluchowski Equation

Describes the over-damped diffusion dynamics of non-interacting particles in a potential field.

$$\frac{\partial p(\vec{r},t\,|\,\vec{r}_0,t_0)}{\partial t} = -\nabla \cdot D\left[\nabla - \beta\vec{F}(\vec{r})\right]p(\vec{r},t\,|\,\vec{r}_0,t_0)$$

Or for $\vec{F}(\vec{r}) = -\nabla U(\vec{r})$

$$\frac{\partial p(\vec{r},t\,|\,\vec{r}_0,t_0)}{\partial t} = -\nabla \cdot Jp(\vec{r},t\,|\,\vec{r}_0,t_0)$$

$$= -\nabla \cdot De^{-\beta U(\vec{r})}\nabla e^{\beta U(\vec{r})}p(\vec{r},t\,|\,\vec{r}_0,t_0)$$

Steady-state Formation

$$\frac{\partial p(\vec{r},t)}{\partial t} = 0$$

$$\Rightarrow \quad \nabla \cdot D e^{-\beta U(\vec{r})} \nabla e^{\beta U(\vec{r})} p(\vec{r},t \mid \vec{r}_0,t_0) = 0$$

Suppose

$$D'(\vec{r}) = D e^{-\beta U(\vec{r})} \quad \text{and} \quad p'(\vec{r},t) = e^{\beta U(\vec{r})} p(\vec{r},t \mid \vec{r}_0,t_0)$$

Finally, we have

$$-\nabla \cdot D'(\vec{r}) \nabla p'(\vec{r},t) = 0$$

$$\longrightarrow p(\vec{r},t \mid \vec{r}_0,t_0) = e^{-\beta U(\vec{r})} p'(\vec{r},t)$$

Modeling procedure

1. According the above couple of slides, we have to solve PBE using APBS first and then read the output potential into the Smoluchowski equation to solve the diffusion equation.
2. Ask your tutor for help to accomplish this tutorial. For further questions about the diffusion solver, please go to SMOL homepage:

   http://mccammon.ucsd.edu/smol

Tutorial directory guide

- NOTE:

cd $HOME/public/smol2009

source bashrc

- Data structures

./bin /* all the executable binary files */

./mesh /* all the mesh files we will use for this tutorial */

./pqr /* all the PQR files for this tutorial */

./potential /*all the potential scripts for APBS runs. */

./run /* You can do your work under this directory. */

./fetk /* FEtK source code. */

./smol.0.0.2 /* SMOL source code */

SMOL sample input files

- NOTE:
- # model parameters
- Diff_coef 78000.0 /* diffusion coeficient */
- sub_charge 0.0 /* ligand charge */
- Sub_conc 1.0 /* initial ligand concentration at the outer boundary */
- temp 300.0 /* temperature, unit: Kelvin */
- # mapping method
- map DIRECT /* you can choose NONE/DIRECT/FEM */
- # steady-state or time-dependent
- tmkey SSSE /* you can choose SSSE or TDSE */
- #output options
- Diff_Mesh NO /* YES=output meshes of diffusion domain;NO= no output */
- Entropy NO /* YES=output entropy density;NO=no output */
- Gibbs NO /* YES=output Gibbs free energy density; NO=no output */
- # input paths
- mol ../../pqr/ion_yuhui.pqr
- mesh ../../mesh/sphere_4.m
- mgrid ../../potential/pot-0.dx /* for APBS input */
- active ../../active.dat /* user defined active site input */
- end 0

Manage your input parameters

- NOTE:

${solver}

- the default input file: smol.in

${solver} -ifnam filename

- the default iteration method: CG(lkey=2).

BCG (lkey=4 or 5), BCGSTAB(lkey=6)

${solver} -lkey 2

- default maximal number of iterative steps: 5000

${solver} –lmax 8000

Manage your input parameters (cont.)

- NOTE:
- the default timestep: $5.0*10^{-6}\mu s$

${solver} -dt $5.0*10^{-5}$

- the default number of time steps:500

${solver} –nstep 1000

- the default concentration output frequency: 50

${solver} –cfreq 100

- the default reactive integral output frequency: 1

${solver} –efreq 5

- the default restart file writing frequency: 1000

${solver} –pfreq 5000

Exp. 1: Steady-state Diffusion calculation

cd $HOME/public/smol2009/run/mache

vi solve-all.csh

- Please use any text editor to edit “solve-all.csh” to control your calculations.
- AND check your “smol-template.in”, you can use the potential files you calculated. Make sure that the potential path is correct.
- ./solve-all.csh >& ./solve-all.log &

Exp. 1: Steady-state Diffusion Output

cd $HOME/public/smol2009/run/mache

- In “rate.*.dat” file there are the k_{on} simulation and analytical values.

vi rate.*.dat

Visualization of your calculation

GMV is applied to show concentration distribution at steady state.

Please read through the user guide from the below link if you want to know more about OpenDX:

http://www-xdiv.lanl.gov/XCM/gmv/doc.color.pdf

source $HOME/public/smol2009/tcshrc

cd $HOME/public/smol2009/run/mache/mache.0.001.1.0

linuxMesa outputNUM.gmv

Additional reading materials

1. http://en.wikipedia.org/wiki/Diffusion
2. Berg, H C. *Random Walks in Biology*. Princeton: Princeton Univ. Press, 1993
3. advanced diffusion materials:

http://www.ks.uiuc.edu/Services/Class/PHYS498NSM/

4. Adaptive Multilevel Finite Element Solution of the Poisson-Boltzmann Equation I: Algorithms and Examples. *J. Comput. Chem.*, 21 (2000), pp. 1319-1342.
5. Finite Element Solution of the Steady-State Smoluchowski Equation for Rate Constant Calculations. *Biophysical Journal,* 86 (2004), pp. 2017-2029.
6. Continuum Diffusion Reaction Rate Calculations of Wild-Type and Mutant Mouse Acetylcholinesterase: Adaptive Finite Element Analysis. *Biophysical Journal,* 87 (2004), pp.1558-1566.
7. Tetrameric Mouse Acetylcholinesterase: Continuum Diffusion Rate Calculations by Solving the Steady-State Smoluchowski Equation Using Finite Element Methods. *Biophysical Journal,* 88 (2005), pp. 1659-1665.
8. Finite Element Analysis of the Time-Dependent Smoluchowski Equation for Acetylcholinesterase Reaction Rate Calculations. Biophys. J., 92(2007), pp. 3397-3406
9. Diffusional Channeling in the Sulfate Activating Complex: Combined Continuum Modeling and Coarse-grained Brownian Dynamics Studies. *Biophys. J.,* 95(2008), pp. 4659-4667

Assignments

1. Please modify the keyword “SSSE” in “smol-template.in” to “TDSE”, i.e. to solve time-dependent SMOL equation instead of steady-state SMOL equation, rerun the whole scripts, what will happen?

2. Here are more movies from solving the time-dependent SMOL equation for the mAChE:

http://mccammon.ucsd.edu/smol/doc/demo/

mache_conc.mpg is the ligand concentration distribution dependent on the diffusion time.

log_conc.mpg is the free energy flow dependent on the diffusion time.

Have fun!