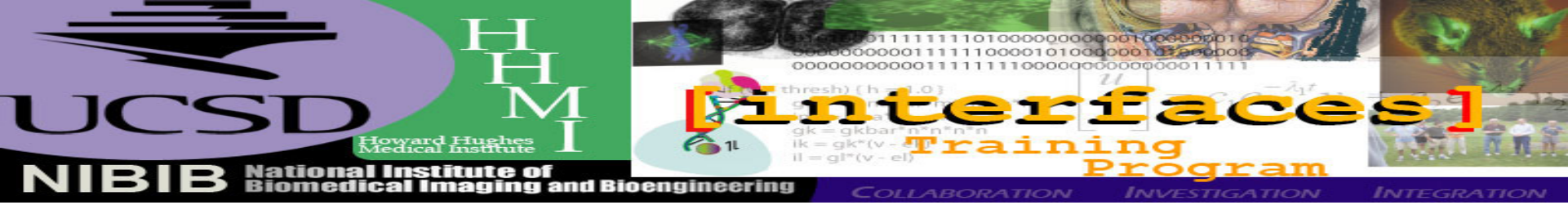


Continuum Diffusion Rate of Enzymes by Solving the Smoluchowski Equation

CHEM 276 & BENG 275

May. 1st, 2007

http://mccammon.ucsd.edu/smol/doc/tutorials/chem276_smol.pdf

Objectives

- Basic theories of Poisson-Boltzmann and Smoluchowski Equations.
- Experiment 1: the born ion
- Experiment 2: 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. Today we try to finish Exp. 1, if you have interest, you can continue Exp. 2.
3. 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

4. All the tutorial materiers can be downloaded from here:

Tutorial directory guide

- NOTE:

tar vczf smol.tar.gz
cd $HOME/smol
source ./tcshrc

- Data structures

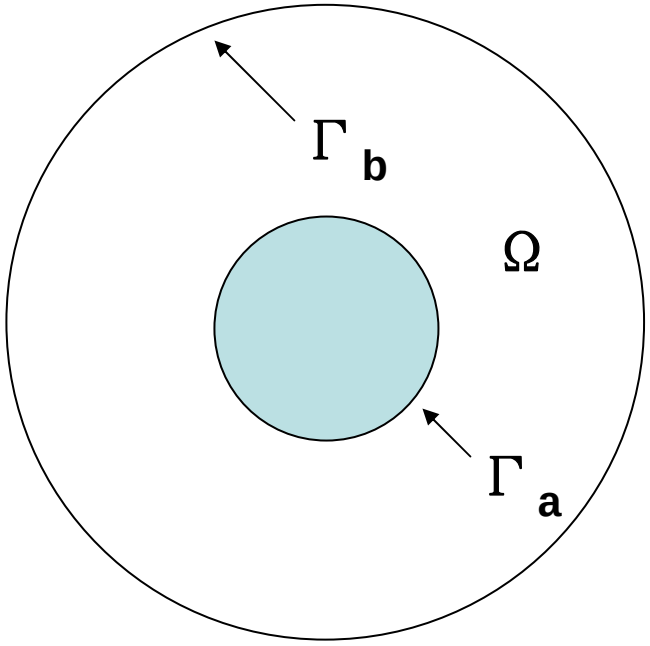
./bin /* all the executable binary files */
./tcshrc /* set some necessary environments */
./mesh /* all the mesh files we will use for this tutorial */
./pqr /* all the PQR files for this tutorial */
./potential /*all the potential scripts for APBS runs. */
./run /* You can do your work under this directory. */
./tools /* Here are some visualization scripts. */

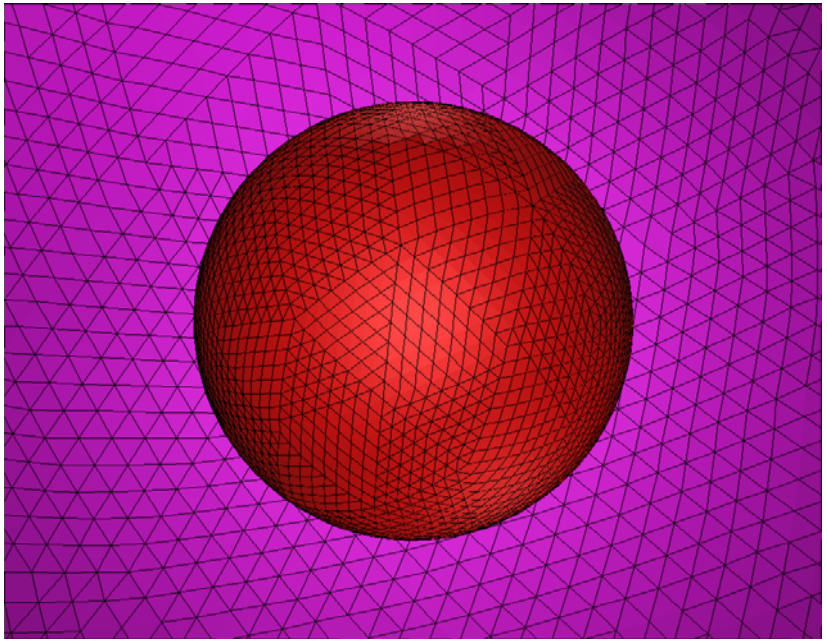
Exp. 1: Mesh preparation

Mesh preparation: Netgen 4.4 (http://www.hpfem.jku.at/netgen/)

Netgen is an excellent mesh generator, especially for the spherical shaped objects.

The finite problem domain is the spherical test case.





Exp. 1: Simple mesh generation

Our first task is to generate the analytical test for the SMOL diffusion.

software: Netgen (http://www.hpfem.jku.at/netgen/)

software tutorial: (http://www.hpfem.jku.at/netgen/ng4.pdf)

source $HOME/smol/tcshrc

cd $HOME/smol/mesh/born

ng

Start from “file”, then “Load Geometry”, then “Generate Mesh”.
Note: The node and element numbers are shown below the software screen

Then you can refine the mesh by choosing “Refinement”. (For example, I have stored a case with 409,886 vertices.)

Finally, from “file”->”Export Mesh”, save the mesh as “born.mesh”

Exp. 1: Simple mesh generation

cp born.mesh mesh.neu

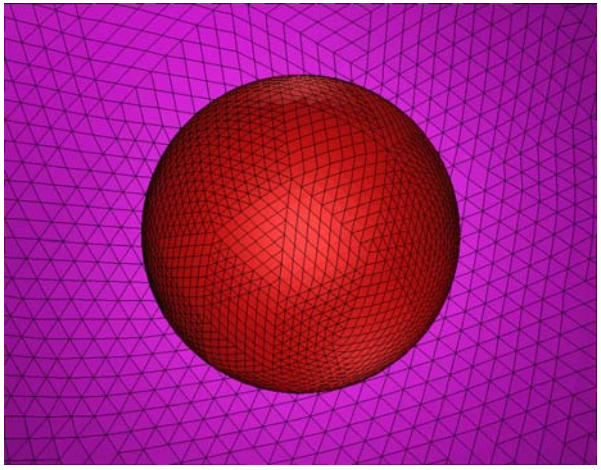
neu2m >& born.m

born.m is exactly the input file we will use for this tutoring.

To visualize your mesh, you can type

mcsf2off --boundary born.m

geomview born.off (OR mcsg born.off)



Exp. 1: analytical solution

For a spherically symmetric system with a Coulombic form of the PMF, W(r) = q/(4 π ε r), the SSSE can be written as

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 Jp) = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 D(\frac{\partial p}{\partial r} - \beta p \frac{qq_l}{4\pi\varepsilon r^2})) = 0$$

Suppose $Q = \frac{\beta q q_l}{4\pi\varepsilon}$, $p(r_1) = 0; p(r_2) = p_{bulk}$

Then, $k_{on} = \frac{4\pi Q D r_1^2}{e^{-\frac{Q}{r_2}} - e^{-\frac{Q}{r_1}}}$ If Q = 0, $k_{on} = \frac{4\pi D r_1^2}{\frac{1}{r_1} - \frac{1}{r_2}}$

SMOL sample input files

- NOTE:
- # model parameters
- charge 0.0 /* ligand charge */
- conc 1.0 /* initial ligand concentration at the outer boundary */
- diff 78000.0 /* diffusion coeficient */
- temp 300.0 /* temperature, unit: Kelvin */
- # potential gradient methods
- METHtype FEM /* you can choose BEM or FEM */
- # mapping method
- map DIRECT /* you can choose NONE/DIRECT/FEM */
- # steady-state or time-dependent
- tmkey SSSE /* you can choose SSSE or TDSE */
- # input paths
- mol ../../pqr/ion_yuhui.pqr
- mesh ../../mesh/sphere_4.m
- mgrid ../../potential/pot-0.dx /* for APBS input */
- dPMF ../../force/evosphere_4.dat /* for BEM 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/smol/run/born

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/smol/run/born

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

vi rate.*.dat

Exp. 1: Visualization of your calculation

OpenDX is applied to show concentration distribution at steady state.

Please select some tutorials from the below list if you want to know more about OpenDX:

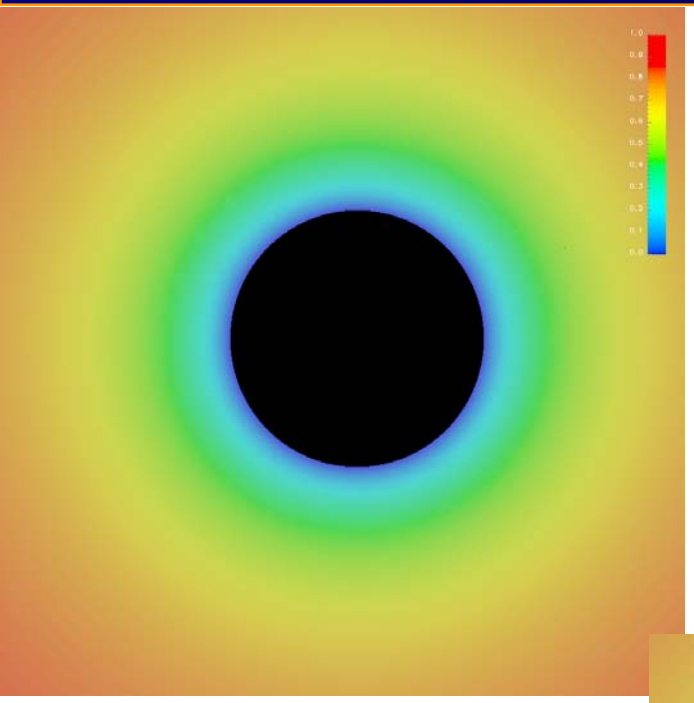
http://ivc.tamu.edu/docs/opendx.pdf

```
source $HOME/smol/tcshrc

cd $HOME/smol/run/born/anal.*.*

dx -edit ../../../tools/visualization/conc.net
```

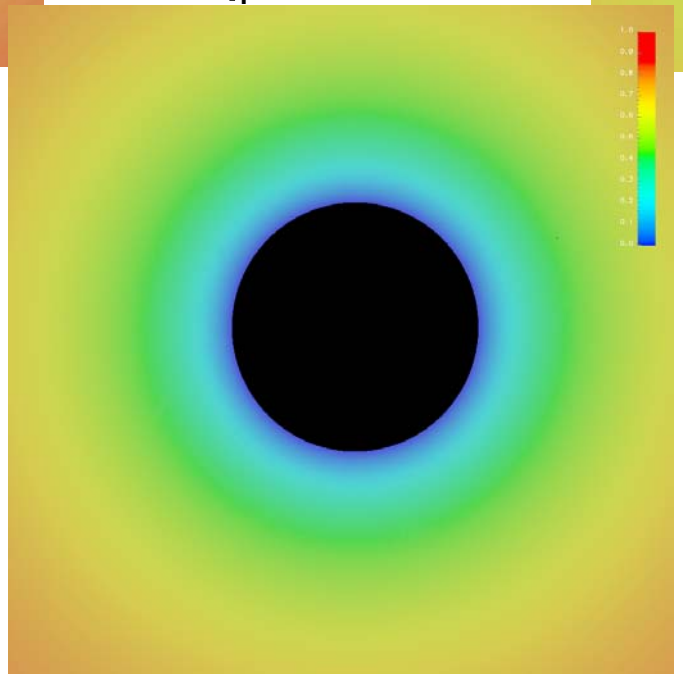
Please let your tutor know if you don’t know how to use OpenDX and really want to learn.

Exp. 1: Sample output figures

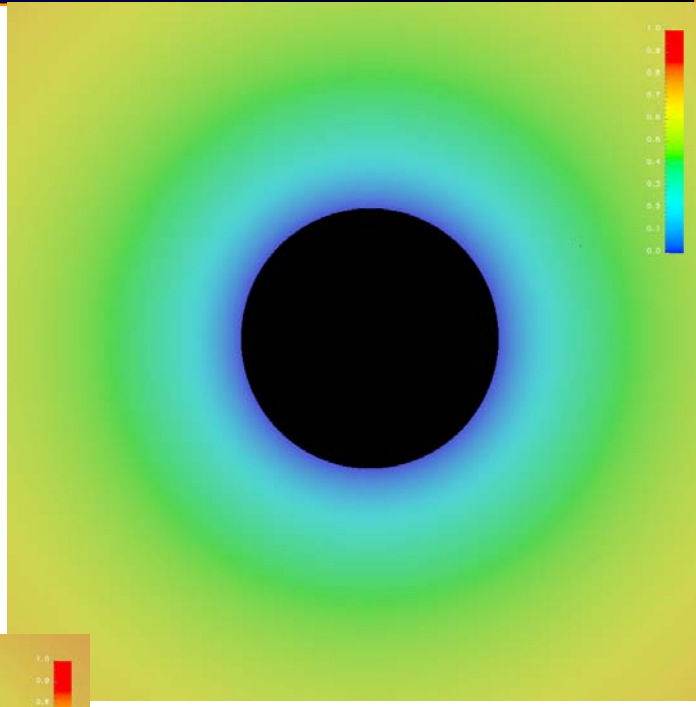
q_l is the charge of the ligand.



$q_l = -1.0e$

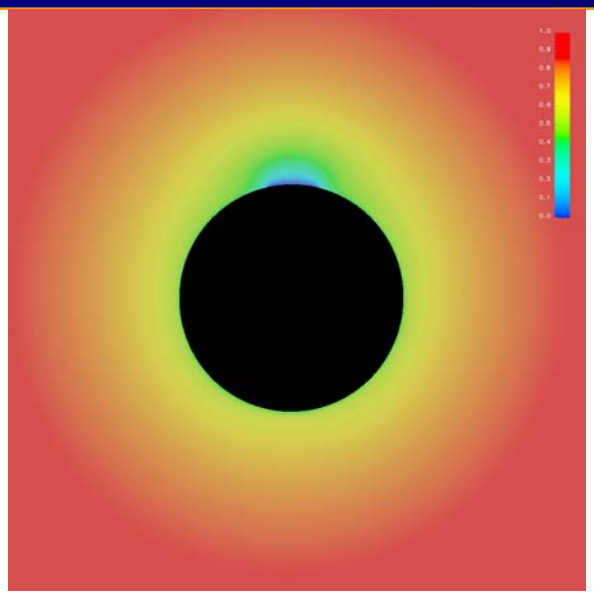


$q_l = 0.0e$

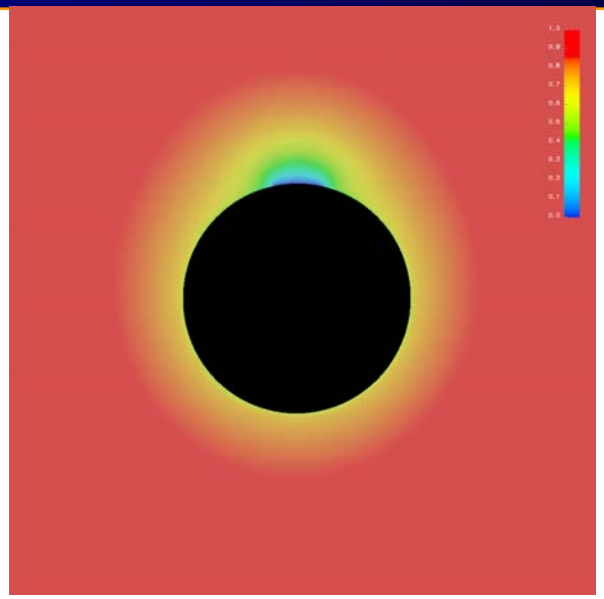


$q_l = 1.0e$

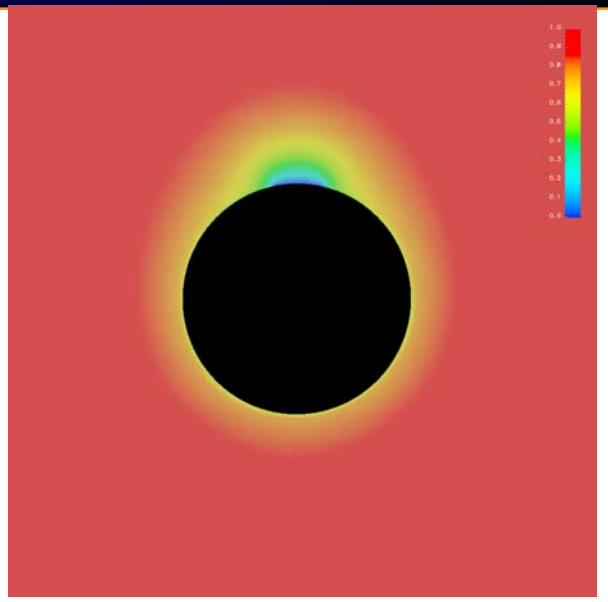
Exp. 1: Sample output I ($qq_l = 1.0$)



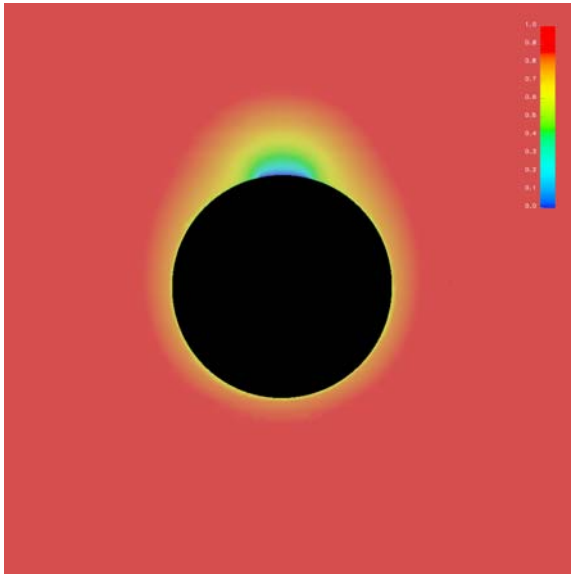
0.000M



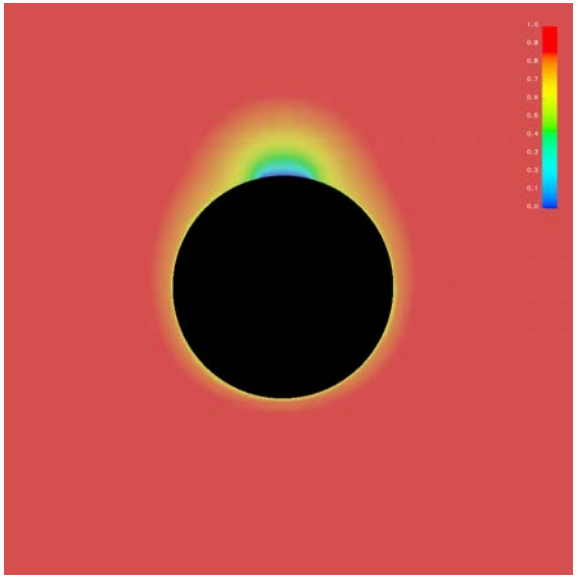
0.075M



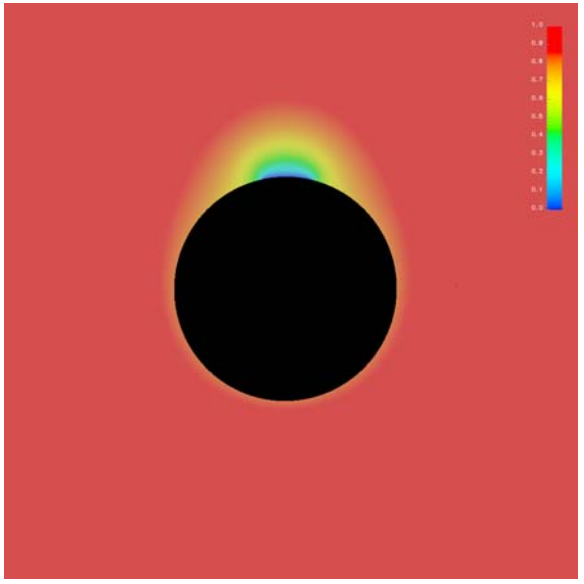
0.150M



0.300M

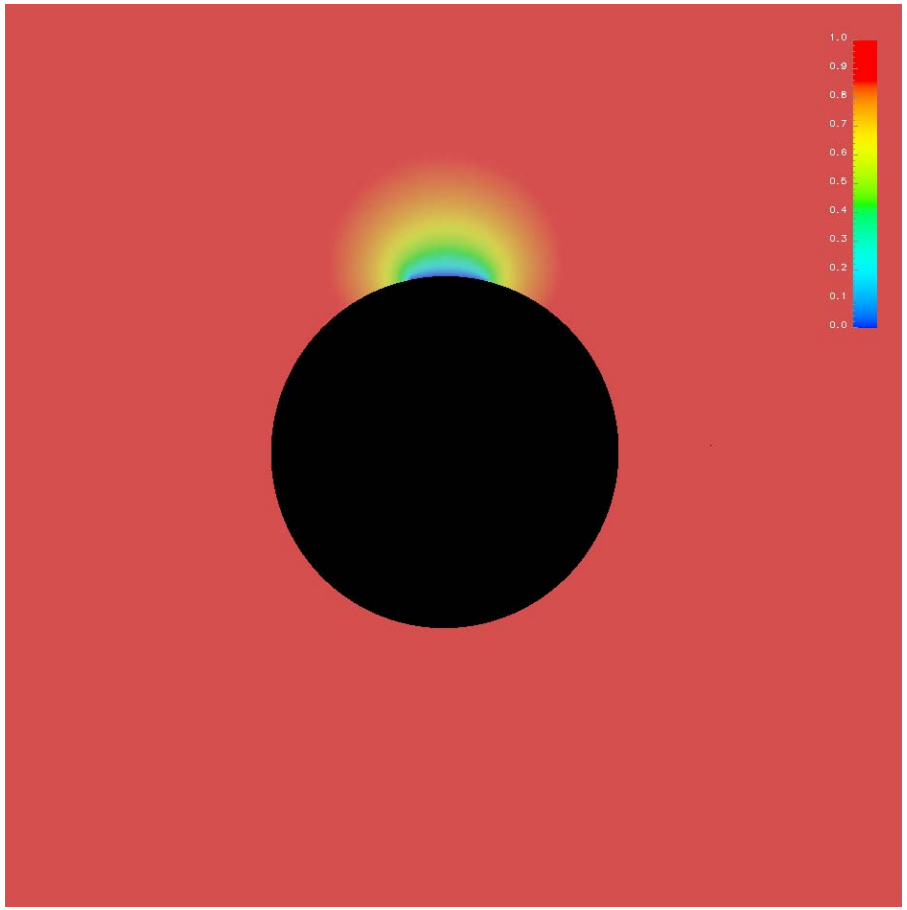


0.450M

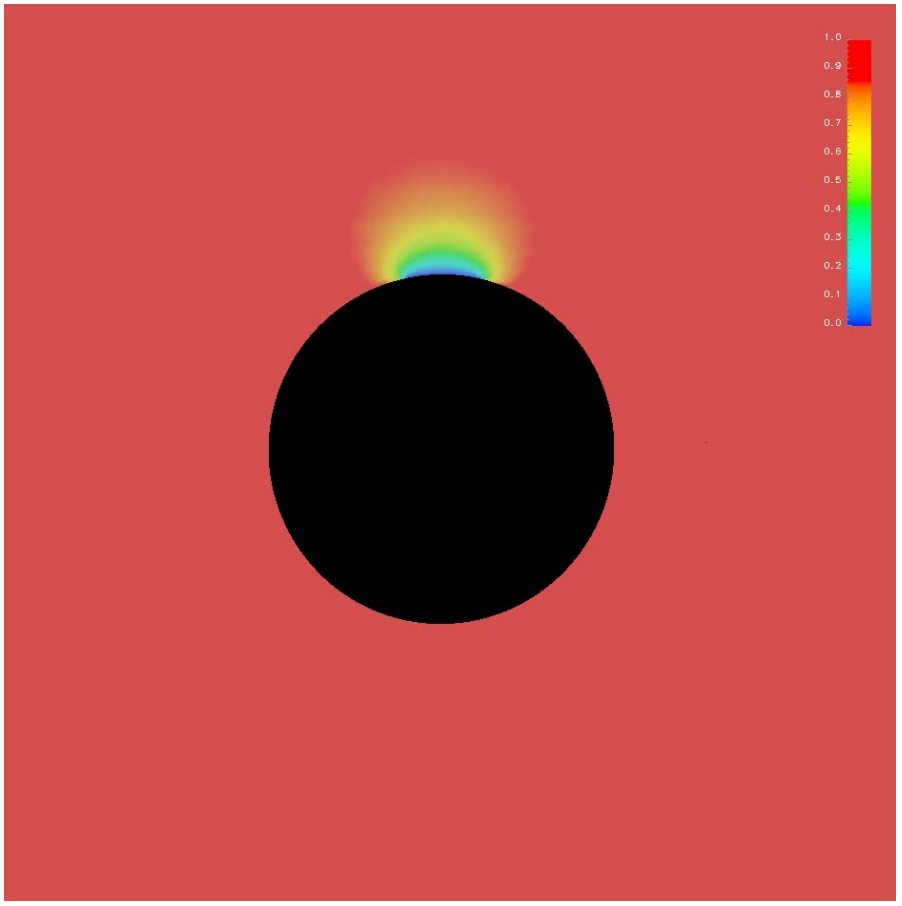


0.670M

Exp. 1: Sample output II ($qq_l = 0.0$)



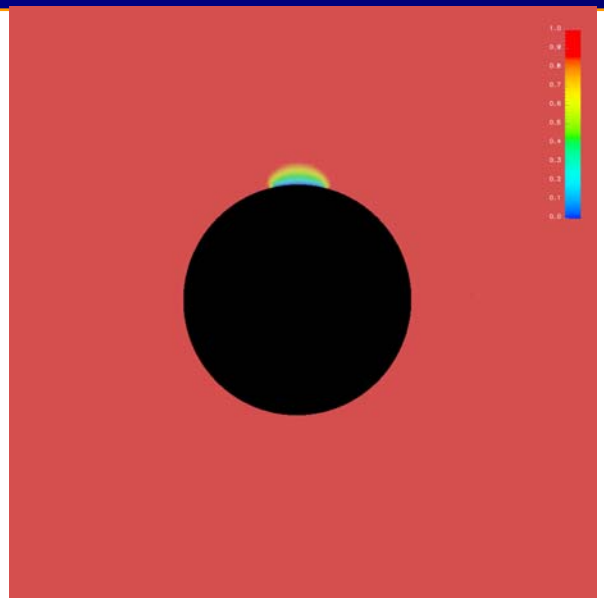
0.000M



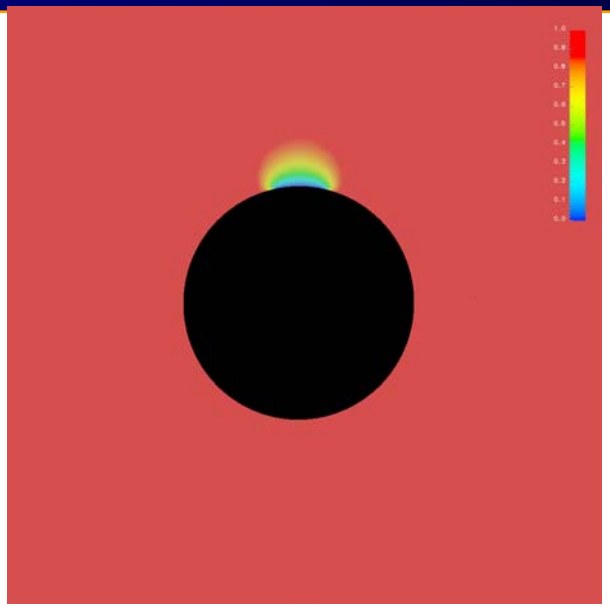
0.600M

Certainly, there is no difference at any ionic strength.

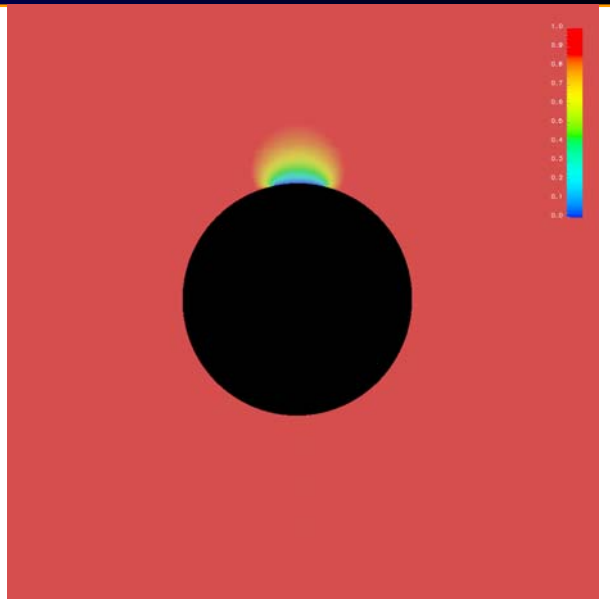
Exp. 1: Sample output III ($qq_l = -1.0$)



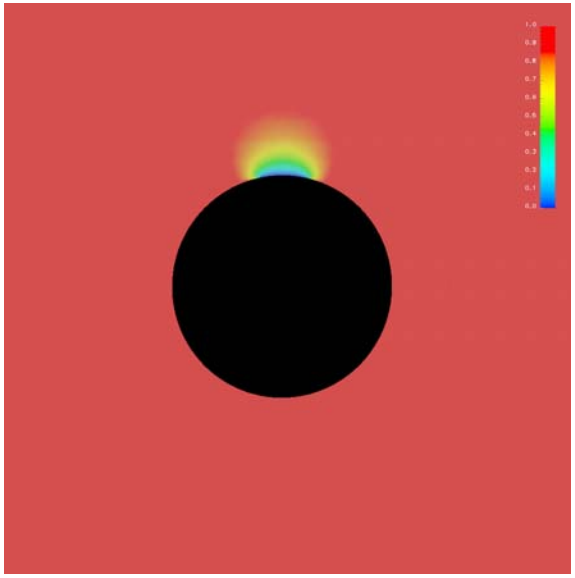
0.000M



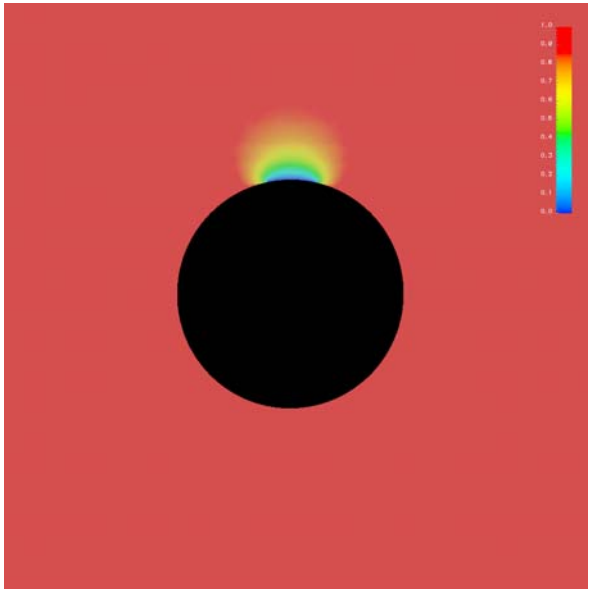
0.075M



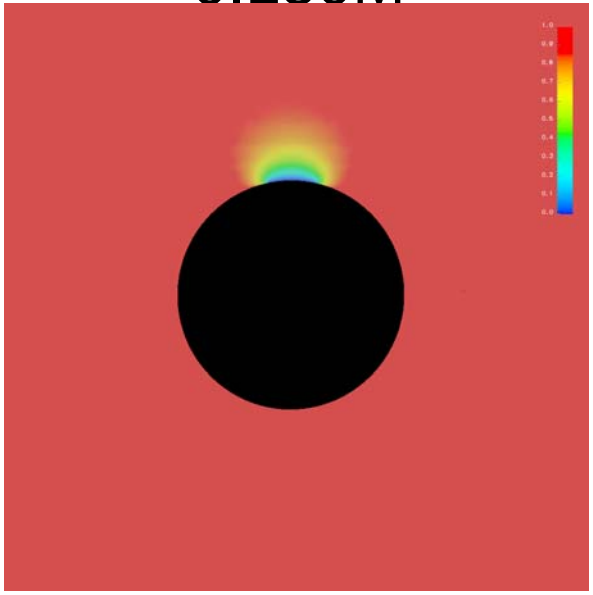
0.150M



0.300M



0.450M



0.600M

Note

Your output should be different from the above three figures, for the whole molecular surface is active. However, part of the molecular surface has been assigned as the reactive boundary. Can you find which part of the molecule is reactive?

To learn how to assign the reactive boundary, please go through the next example: mouse acetylcholinesterase.

Exp. 2: mesh and pqr file

- The mAChE mesh file was generated by Mol-LIBIE invented by Chandrajit's group.

- PQR file can be generated from PDB by Nathan's PDB2PQR server:

http://pdb2pqr.sourceforge.net/

- Assign the reactive boundary

Make sure to set the coordinate of carbonyl carbon of S203 at (0, 0, 0), and align the active site gorge with the y axis.

source $HOME/smol/tcshrc

cd $HOME/smol/mesh/mache

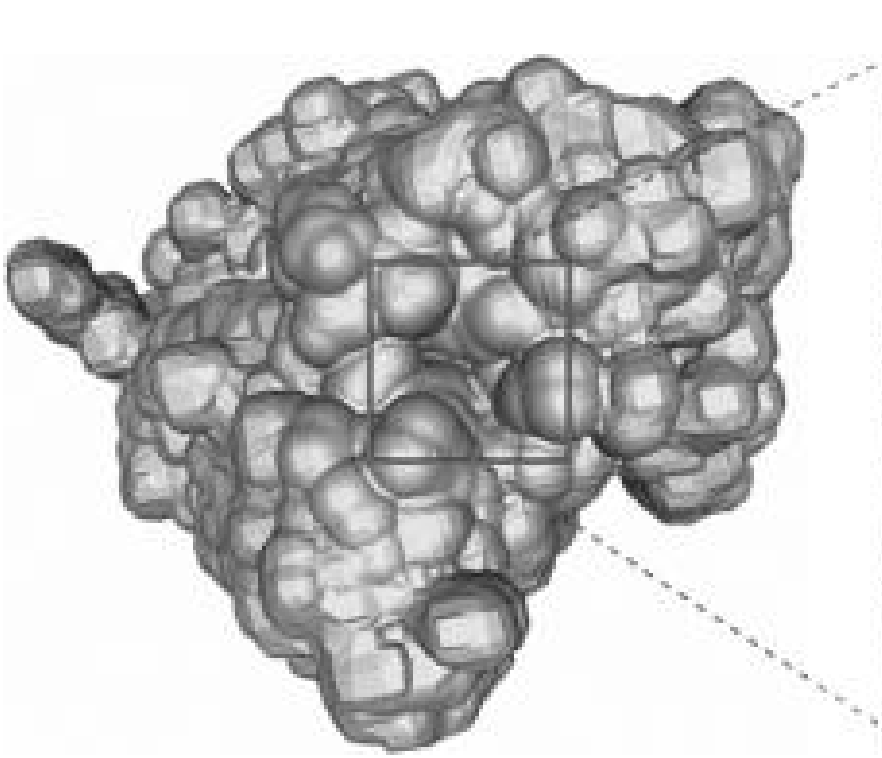
./assignBoundary.csh >& ./assignBoundary.log &

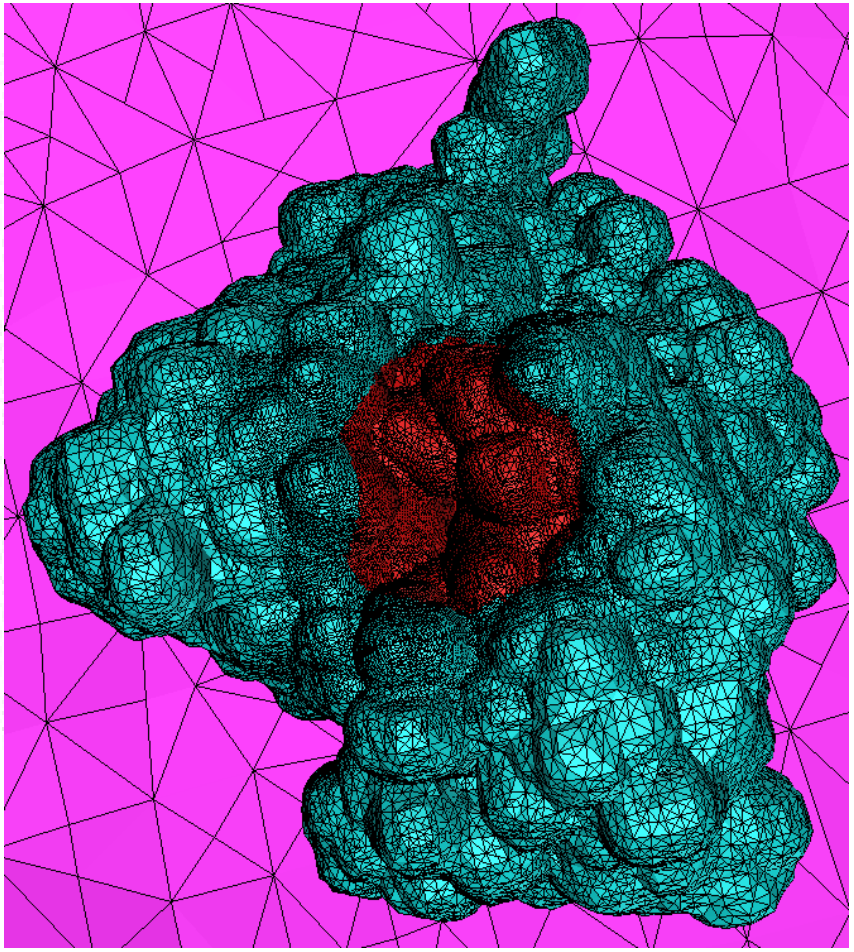
Exp. 2: Visualize your new mesh

To visualize your mesh, you can type

mcsf2off --boundary mol-bc1.m

geomview mol-bc1.off (OR mcsg mol-bc1.off)





Exp. 2: potential calculation

Note:

1.I cannot guarantee the below calculation can successfully be done using APBS, since it might need big memory and large quota of the hard drive. Please ask your tutor for help if you undergo any trouble.

2. You can edit the value of “i” in “calc-all-pot.csh” to execute different calculations.

```
source $HOME/smol/tcshrc

./ calc-all-pot.csh >& calc-all-pot.log &
```

Exp. 2: steady-state diffusion calculation

```
source $HOME/smol/tcshrc

cd $HOME/smol/run/mache

./solve-all.csh >& solve-all.log &
```

Please be patient to wait a couple of minutes to read output…

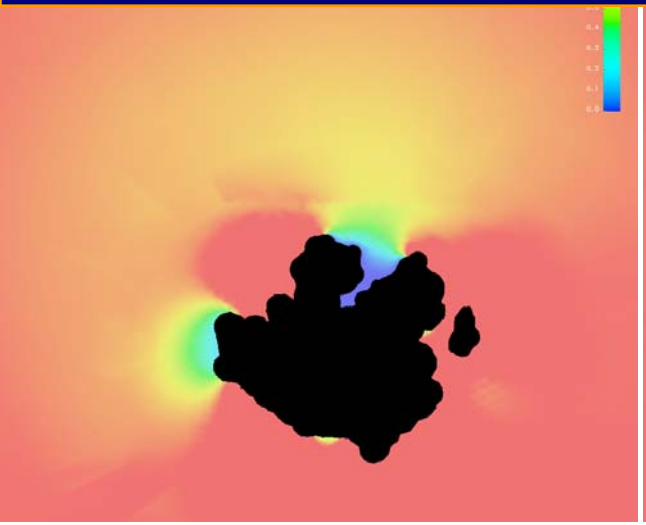
Exp. 2: Visualization of your calculation

source $HOME/smol/tcshrc

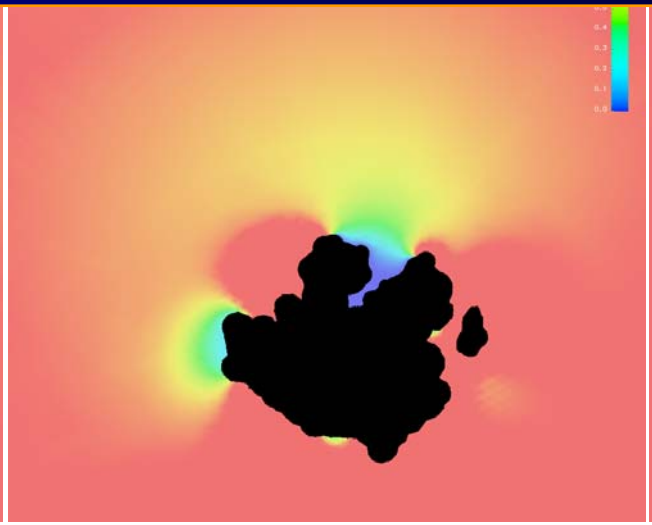
cd $HOME/smol/run/mache/mache.*.*

dx -edit ../../../tools/visualization/conc.net

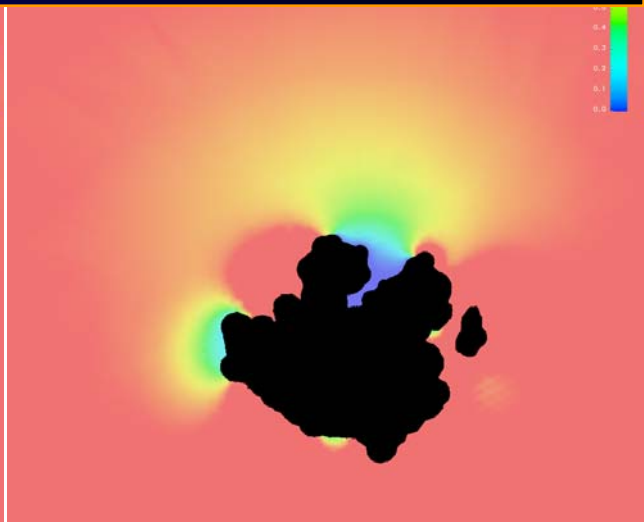
Exp. 2: Sample outputs



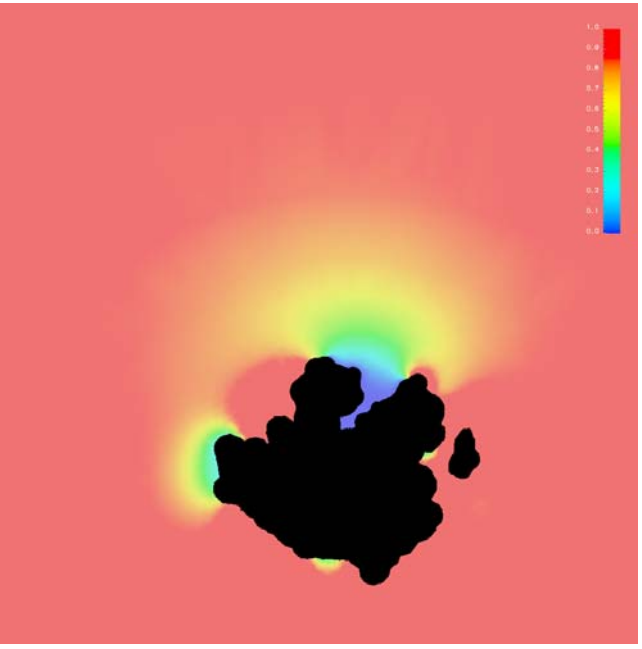
0.025 M



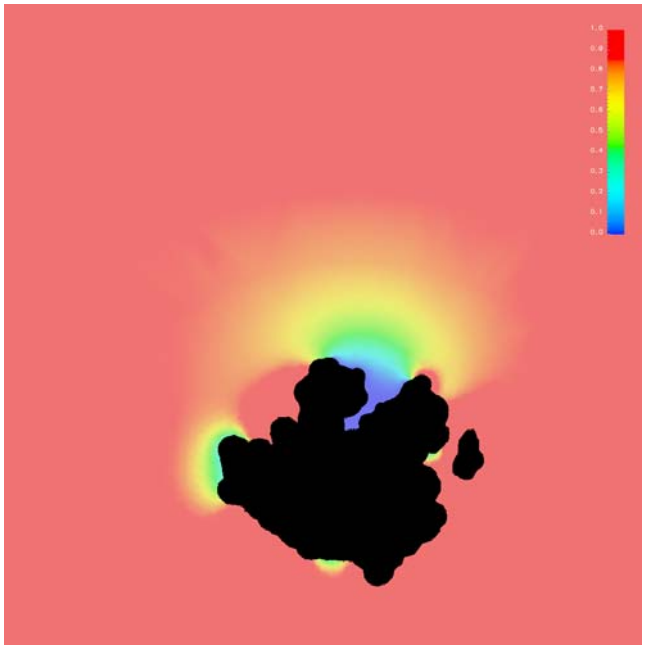
0.050 M



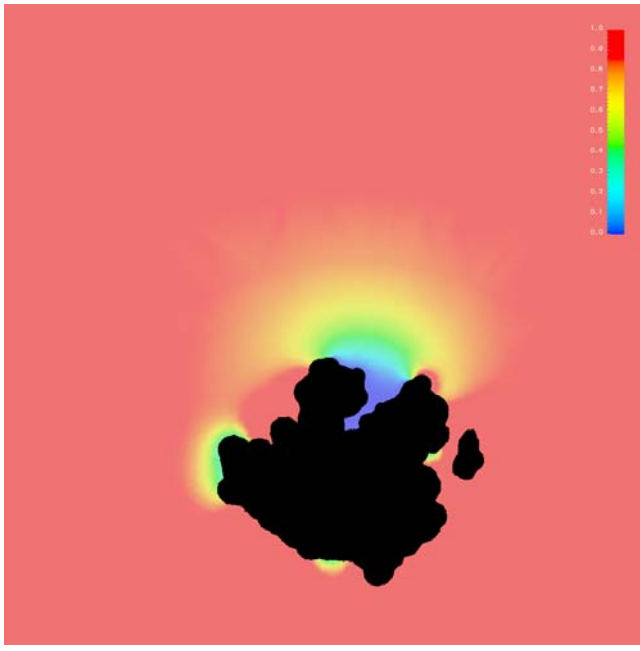
0.100 M



0.225 M



0.450 M



0.670 M

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. *Biophysical Journal*, 92(2007), 3397-3406

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!