Brownian Dynamics Simulations

SDA

- We will be using SDA - Simulation of the Diffusional Association (of Proteins)

- As we saw from the Ermak-McCammon result, we can simulate any system where we can define an interaction potential U(r) between the two particles

- This potential could be due to anything, but since electrostatic forces are the longest range forces (~1/r), we usually use this to calculate interaction rates

Requirements

- We need several things to perform these simulations
  - protein structures
  - interaction sites (hopefully a co-crystal)
  - electrostatic potentials for each protein
  - partial charges or *effective charges* for each protein
  - translational and rotational diffusion constants for each protein (or mutual diffusion constants)

Interaction Sites

- In order to determine the kinetics of two proteins binding, we need to know where they bind

- The easiest place to start is with a crystal structure of the two proteins bound. Having this, we can determine potential salt bridges or hydrogen bonds that could be formed, and we will monitor these through the course of the simulation

Reaction Criteria
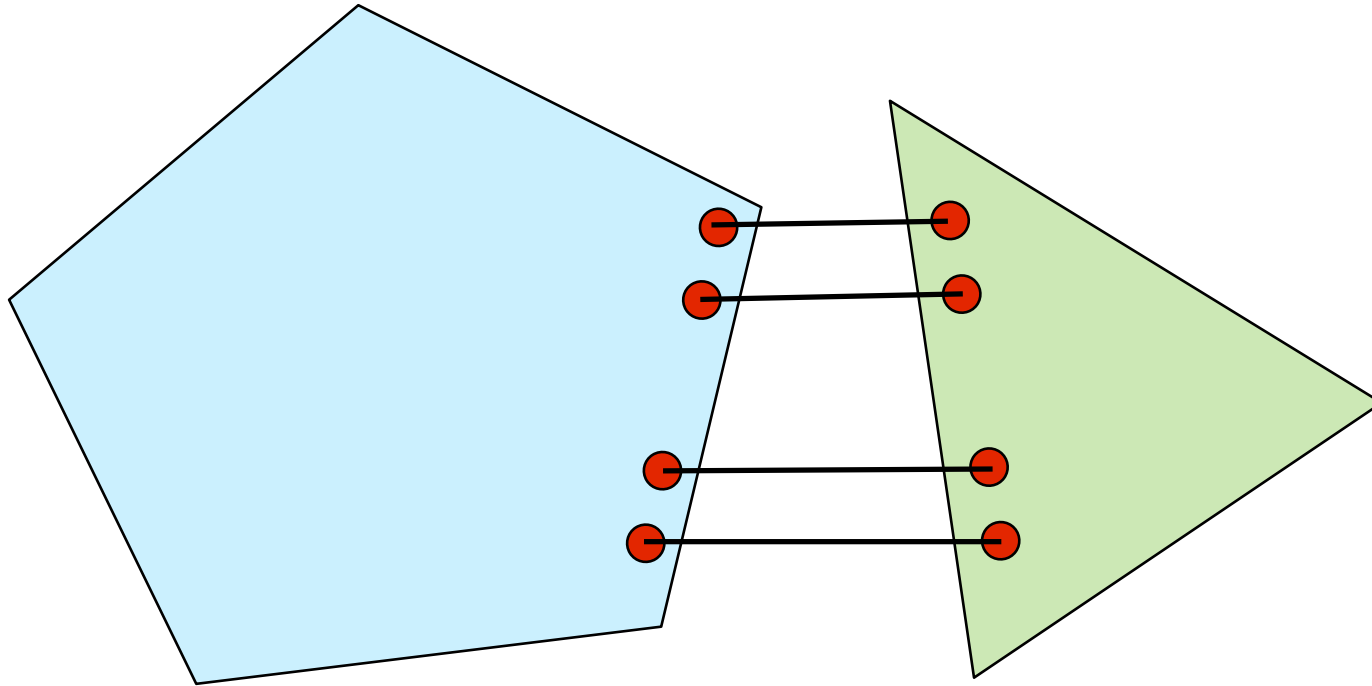
- We will monitor all possible reaction points and determine that a complex is formed if a certain number of bonds are within fixed distance (say 3 bonds within 7 A)

Electrostatic Potentials

- We need to determine the electrostatic potentials for the proteins

- We will use APBS, but since we want primarily long range interaction forces, we will use a relatively coarse grid (1 A spacing) - *N.B. this would not work well for energies*

- We also want the grids to be fairly large (149 A on a side) to capture the long range interactions

Effective Charges

- We could capture the electrostatic forces my multiplying the charges of one protein by the value of the electrostatic potential of the other protein ($F = q\Phi$)

- If we do this for every charge, we would get an accurate result, but we can speed this up by finding a set of effective charges

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Effective Charges

B. Potential Fitting. We define the effective charge distribution ρ^{eff} for a molecule as the point charge distribution $\rho^{eff} = \sum_{j=1}^{n} q_j^{eff} \cdot \delta(\mathbf{r} - \mathbf{r}_j)$ in uniform solvent giving the same potential $\Phi^{(0)}$ outside the molecule (to within the fitting accuracy) as the partial atomic charges in the inhomogeneous dielectric system consisting of the molecule immersed in solvent.

The molecular electrostatic potential of the molecule $\Phi^{(0)}(\mathbf{r})$ may be calculated by numerically solving the finite-difference Poisson−Boltzmann equation taking account of the partial charges on all the atoms, the inhomogeneous dielectric, and a surrounding ionic solution. Effective point charges may be derived to describe the electrostatic interactions of a macromolecule by fitting them to reproduce its molecular electrostatic potential. This can be done in the same way as partial atomic charges are derived from electron densities.[18] n effective charges q_j^{eff} at positions $\mathbf{r}_j$ are obtained by minimizing a fitting functional:

$$J = \int d^3\mathbf{r} \, |\Phi^{(0)}(\mathbf{r}) - \sum q_j^{eff} \cdot F_j(\mathbf{r})|^2 \qquad (8)$$

$$F_j(\mathbf{r}) = \frac{e^{-k_s|\mathbf{r} - \mathbf{r}_j|}}{\epsilon_s \cdot |\mathbf{r} - \mathbf{r}_j|}$$

Integration is carried out over the region of space relevant to intermolecular interactions. The solution is given by a linear system of equations

$$\mathbf{A}\mathbf{q}^{eff} = \mathbf{b} \qquad (9)$$

where $\mathbf{A}$ is a matrix with elements a_{ij},

$$a_{ij} = \int d^3\mathbf{r} \, F_i(\mathbf{r}) \cdot F_j(\mathbf{r})$$

$$\mathbf{q}^{eff} = (q_1^{eff}, q_2^{eff}, ..., q_n^{eff})$$

and

$$\mathbf{b} = (b_1, b_2, ..., b_n), b_i = \int d^3\mathbf{r} \, F_i(\mathbf{r}) \cdot \Phi^{(0)}(\mathbf{r})$$

The fitting accuracy can be measured by

$$\chi = 1 - \int d^3\mathbf{r} \, |\Phi^{(0)}(\mathbf{r}) - \sum q_j^{eff} \cdot F_j(\mathbf{r})|^2 / \int d^3\mathbf{r} \, |\Phi^{(0)}(\mathbf{r})|^2 \qquad (10)$$

It has a maximum value of 1 (100%) when the potential is fitted by itself and is 0 when the fitting potential is zero everywhere.

Effective Charges

The contributions of the individual effective charges to the potential are not orthogonal, but orthogonal (or generalized) contributions can be constructed from linear combinations of effective charges. These linear combinations may be obtained by diagonalization of the matrix $\mathbf{A}$. We use the orthogonal matrix $\mathbf{X}$ ($\mathbf{X}^{-1} = \mathbf{X}^{T}$)[19] with elements x_{ij}, so that $\mathbf{X}^{-1}\mathbf{A}\mathbf{X} = \text{diag}(\lambda_1, \lambda_2, ..., \lambda_n)$. Then the generalized charges $\tilde{q}_i$ (which are linear combinations of the charges on specific sites) with $\tilde{q}_i = \sum_j x_{ji} \cdot q_j^{\text{eff}}$ form an orthogonal set of vectors, and the fitting problem is just

$$\lambda_i \cdot \tilde{q}_i = \tilde{b}_i \tag{11}$$

where $\tilde{b}_i = \sum_k x_{ki} \cdot b_k$. The functional J has a simple form:

$$J = J_0 + \sum_i \lambda_i \cdot (\tilde{q}_i - \tilde{b}_i/\lambda_i)^2 \tag{12}$$

with $J_0 = \int d^3\mathbf{r}\, |\Phi^{(0)}(\mathbf{r})|^2 - \sum_i \tilde{b}_i^2/\lambda_i$ as a minimum value. This representation is useful to distinguish the generalized charges that are more important for the representation of the electrostatic potential from the relatively unimportant generalized charges.

The smaller the eigenvalue, the less important the value of the corresponding generalized charge is. However, when effective charges are constructed by inverse transformation from the generalized charges, it is apparent that all of the generalized charges $\tilde{q}_i$ can make comparable contributions to the values of the effective charges q_j^{eff}. Thus, very small changes in the electrostatic potential to be fit can result in sizable changes in some effective charges. This situation is analogous to the case of partial atomic charge determination[12,13] for small molecules when the charges on some atoms appear to make only small contributions to the molecular potential.

If the fitting is carried out in a spherical shell region at a large distance from the center of the molecule, effective charges are obtained that are equivalent to a one-center multipole expansion of the atomic charges *and* their image polarization charges resulting from the dielectric discontinuity.

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Full Atomic Detail

Effective Charges

Match Potential

10
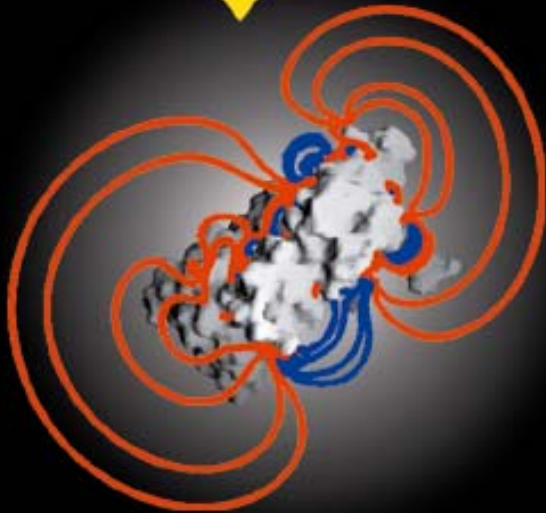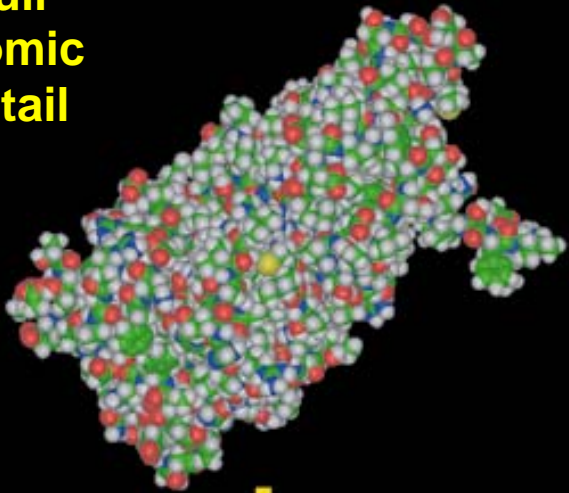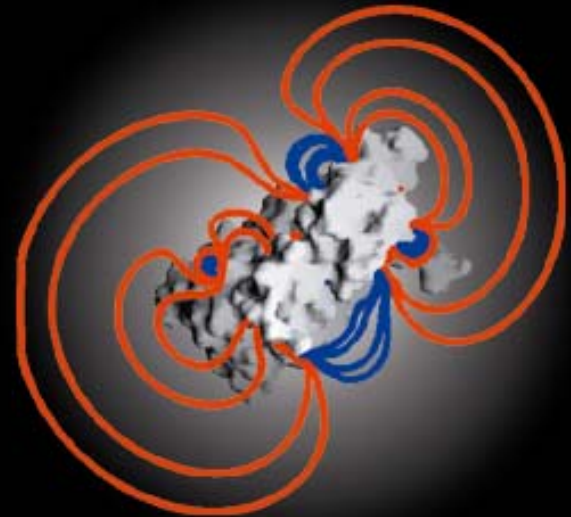
Diffusion Constants

- We use the Stokes-Einstein relation to get the diffusion constants for our proteins
- Recall from the Diffusion lecture that

$$D = \frac{kT}{\gamma}$$

Translation: $\quad D = \dfrac{kT}{6\pi\eta r}$

Rotation: $\quad D = \dfrac{kT}{8\pi\eta r^3}$

Finally ... a BD Simulation

```
- use binary grid here    -------dseed
294.d0
-----------------------------nrun,nprint
1000000,100000,0,4,4.0,0
-----------------------------probes, thres
2.0, 1.  1.10, 8.0
-----------------------------pdb1f,pdb2f
barnase.pdb
barstar.pdb
-----------------------------po1f,po2f
barnase.50mM.grd
barstar.50mM.grd
-----------------------------qef1f,qef2f
barnase.echa_R
barstar.echa_R
-----------------------------rxna1f,rxna2f
barnase.rxn
barstar.rxn
-----------------------------ic1fix,xc1, ic2fix,xc2
```

Finally ... a BD Simulation

```
...
-----------------------------ic1fix,xc1, ic2fix,xc2
0,   0.000 0.000 0.000
0,   0.000 0.000 0.000
-----------------------------icomm, iforce, dind, aiostr
 3   1, 5.0,  0.
-----------------------------dm,dr,drI,irot2f
0.028  ,   4.018e-5,   4.018e-5,1
-----------------------------b,c
75., 200.
-----------------------------rboost,novers
1.0,  150, 5.
-----------------------------dt1,swd1,dt2,swd2,rswd
10.0,   20.,    100.,   140.,   140.
-----------------------------win0,dwin,nwin:
3.00,  0.25, 45, 0, 2
```