

### 6.581/20.482J Problem Set #3

**Due: 5 PM Thursday 3/30/06**

In this problem set, you will design ligand charges to minimize the binding free energy of the ligand-receptor system shown in Figure 1. This is a highly fictitious molecule. (Don't worry about how the ligand gets into the receptor!) You will need to download the MATLAB scripts available on the MIT server. The script `loadComplex.m` contains the charge locations for these problems.

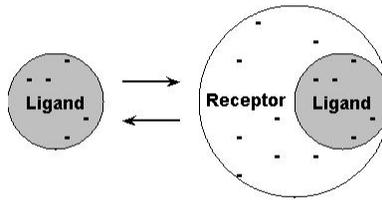


Figure 1: Ligand and receptor combine into a spherical complex

#### 1. Ligand-Receptor Coulombic Interactions.

Please recall that in order to make a binding event more favorable, one wishes to maximize the change in free energy (make it as negative as possible). This change in free energy has three components: the ligand desolvation penalty, the intermolecular interaction, and receptor desolvation penalty:

$$\Delta G = q_L^T L q_L + 2q_L^T C q_R + q_R^T R q_R. \quad (1)$$

The binding energy is the difference between the energy of the bound state (shown in Figure 1) and the energy of the unbound state, where the receptor is assumed to be infinitely far away from the ligand. For this question, you will consider the case of a homogeneous background medium and you will assume that all receptor charges have value 1, and that all ligand charges have the same value  $q$ . As you will discover in the first part, you will only need to consider the Coulombic interaction between the bound ligand and receptor.

- When the background media is homogeneous, the *change* in free energy,  $\Delta G$ , has no terms of the form  $q_L^T L q_L$  or  $q_R^T R q_R$ . Please explain why (hint: consider the bound and unbound cases, which of the three energy terms change?)
- Calculate the intermolecular interaction matrix  $C$  where

$$C_{ij} = \frac{1}{8\pi\epsilon_0 \|\vec{r}_{L_i} - \vec{r}_{R_j}\|}. \quad (2)$$

- Plot the Coulombic energy of the system  $2q_L^T C q_R$  versus  $q$ .
- Now assume the homogeneous background is water, in which case  $\epsilon = 80\epsilon_0$ . How will the calculated  $\Delta G$  change? To make your comparison, please plot the Coulombic energy of the system  $2q_L^T C q_R$  versus  $q$ .

- (e) How will the predicted  $\Delta G$  change if the homogeneous background is a solvent with mobile ions, in which case the matrix elements are given by

$$C_{ij} = \frac{e^{-k\|\vec{r}_{L_i} - \vec{r}_{R_j}\|}}{8\pi\epsilon_0\|\vec{r}_{L_i} - \vec{r}_{R_j}\|}. \quad (3)$$

Use  $k = 3$  and  $\epsilon = 80\epsilon_0$  to calculate the energy. To make your comparisons, please plot energy variation with respect to  $q$  for all 3 media in the same figure.

2. **Ligand-Receptor Electrostatic Optimization.** In this problem you will consider a more physically accurate model in which the background medium is inhomogeneous: molecular interiors have small  $\epsilon$  and the solvent has large  $\epsilon$  and mobile ions. In this model, the desolvation penalty terms return. You will use some provided scripts to compute the  $L$  matrix in equation (1) and carry out the charge optimization problem for the ligand-receptor complex in Figure 1.

- (a) To calculate  $L$ , we must calculate the *change* in reaction potentials at the ligand charge locations between the bound state and the unbound state. For instance, the  $i^{\text{th}}$  column of  $L$  is equal to

$$L_i = \phi_b(e_i) - \phi_u(e_i) \quad (4)$$

where  $e_i$  means that we have set all the ligand charges to zero except the  $i^{\text{th}}$ , which is set to 1, and  $\phi_b(e_i)$  denotes the reaction potential at the charge locations in the bound state due to the single unit charge. Use the provided script `computeReactionPotential.m` to compute the  $L$  matrix.

- (b) Since equation (1) is a quadratic function, its optimal solution can be computed by solving a linear system:

$$Lq_L + Cq_R = 0. \quad (5)$$

Compute the optimal ligand charge magnitudes for the given receptor charges using

$$q_L^{\text{opt}} = -L^{-1}Cq_R. \quad (6)$$

- (c) Theoretically, the matrix  $L$  should be symmetric and positive definite. Is it? Characterize its deviation from these conditions.

3. **Long-range electrostatic interactions II.** In problem set #2, we used an eigendecomposition to look at rank-reduction of long-range electrostatic interactions in a symmetric system. In this problem, we will consider the more general case of two independent, non-symmetric clusters of charge. Details on the SVD decomposition may be found on the course website.

- (a) Generate  $P$ , as described in problem set #2, question 2 using `estatic_svd.m`. Use MATLAB's `svd` function to decompose  $P$  into the matrices  $U$  and  $V$ , and the diagonal matrix  $S$  of the singular values. Check that:

$$P = USV^T \quad (7)$$

and that the columns of both  $U$  and  $V$  are orthonormal (in other words,  $U$  and  $V$  are *unitary*). Look at the entries of  $S$  when the separation distance is small and when the separation distance becomes very large. How does the spectrum of singular values change?

- (b) As in the case of the eigendecomposition, we can eliminate the vectors corresponding to small magnitude singular values in order to create a *rank-reduced* representation of the interaction matrix. In this case, our low-rank approximation to  $Pq$  ( $\hat{P}q$ ) is:

$$Pq \approx \hat{P}q = \hat{U}\hat{S}\hat{V}^T q \quad (8)$$

where  $\hat{U}$  and  $\hat{V}$  denotes the vectors corresponding to the largest  $k$  singular values and  $\hat{S}$  is the  $k$  by  $k$  matrix of those singular values. Calculate  $\hat{P}$  for  $k = \{1, 2, 8\}$ .

- (c) Vary the separation between the molecules and plot the relative errors  $\|Pq - \hat{P}q\|$  as the separation increases.