THURSDAY
9 MARCH 2006

6.581/20.482 LECTURE 9: ELECTROSTATIC CONTRIBUTIONS TO BINDING AND DESIGN

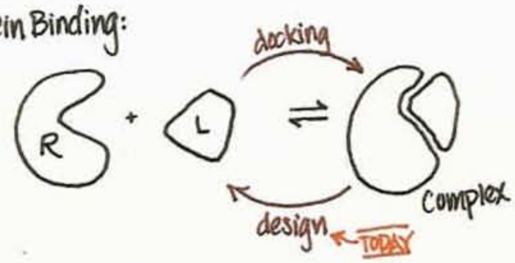
NOTE: Prof. White will finish his previous lecture in the next lecture.

REVIEW:

Molecular Models: $U(\vec{X}^{3N}) = \underset{O(N)}{U_{COVALENT}} + \underset{O(N^2)}{U_{NON\text{-}COVALENT}}$

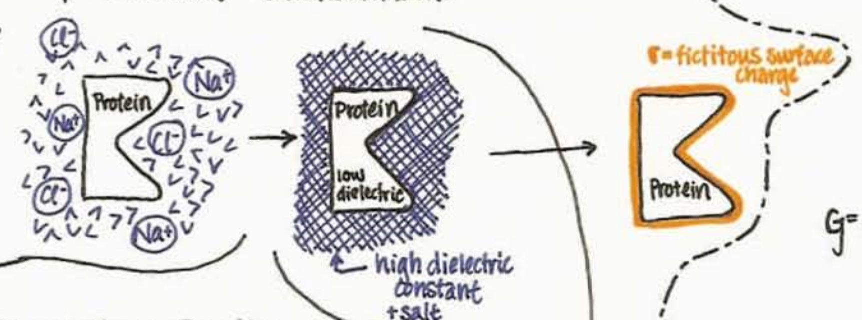
Protein Folding:

Protein Binding:



Simulation & Energy Evaluation:

- Integrating Eqns of Motion { - movie - response to force - statistical mechanical ensemble
- Computing long-range electrostatic energies
  - explicit treatment — numerical approximation to arbitrary accuracy
  - implicit methods — continuum ideas



Poisson-Boltzman Equation

$$\vec{\nabla}\cdot[\varepsilon(\vec{r})\vec{\nabla}\Psi(\vec{r})] - \kappa' \sinh(\Psi(\vec{r})) = -4\pi\rho(\vec{r})$$

non-linear; κ': ionic strength, $\kappa = 0$ for no salt; $\sinh$ term $\rightarrow -\kappa'\Psi(\vec{r})$ (linearized)

Linearized Poisson-Boltzman Eqn:

$$\vec{\nabla}\cdot[\varepsilon(\vec{r})\vec{\nabla}\Psi(\vec{r})] - \kappa'\Psi(\vec{r}) = -4\pi\rho(\vec{r})$$

Explicit Solvent	Continuum Solvent
⊕ physically more accurate	⊕ mean field properties represented well in single frame
⊕ cheaper to compute a single energy	⊕ cheaper to compute free energies
⊖ thermodynamic properties are not expressed in a single frame	⊖ less accurate physically

SOLVED BY:
- Finite Difference
- Finite Element
- Boundary Element*

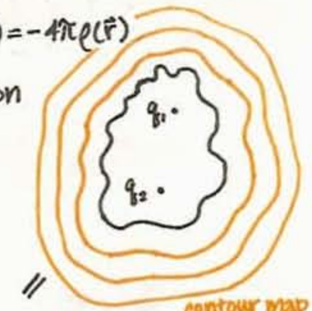
Linearized PB Eqn:

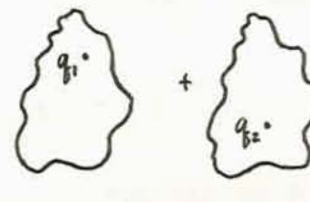
$$\vec{\nabla}\cdot[\varepsilon(\vec{r})\vec{\nabla}\Psi(\vec{r})] - \kappa'(\vec{r})\Psi(\vec{r}) = -4\pi\rho(\vec{r})$$

linear $\Leftrightarrow$ superposition

$f(x+y) = f(x) + f(y)$

$f(ax) = a \cdot f(x)$





$$\vec{\nabla}\cdot\varepsilon(\vec{r})\vec{\nabla}\Psi_1(\vec{r}) - \kappa'(\vec{r})\Psi_1(\vec{r}) = -4\pi\rho_1(\vec{r})$$

$$+\ \vec{\nabla}\cdot\varepsilon(\vec{r})\vec{\nabla}\Psi_2(\vec{r}) - \kappa'(\vec{r})\Psi_2(\vec{r}) = -4\pi\rho_2(\vec{r})$$

$$\vec{\nabla}\cdot\varepsilon(\vec{r})\vec{\nabla}[\Psi_1(\vec{r})+\Psi_2(\vec{r})] - \kappa'(\vec{r})[\Psi_1(\vec{r})+\Psi_2(\vec{r})] = -4\pi[\rho_1(\vec{r})+\rho_2(\vec{r})]$$

Free Energy:

$$G = \frac{1}{2}\int \rho(\vec{r})\Psi(\vec{r})\,d\vec{r} = \frac{1}{2}\sum_{i=1}^{N} q_i\Psi_i$$

$$= \frac{1}{2}[q_1\ q_2\ \cdots\ q_N]\cdot\begin{bmatrix}\Psi_1\\ \Psi_2\\ \vdots\\ \Psi_N\end{bmatrix}$$

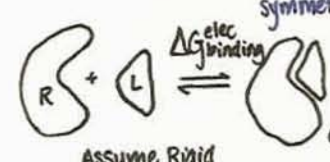
$\Psi_i = \Psi_i$ due to q_1 + Ψ_i due to q_2 + … + Ψ_i due to q_N

$$\begin{bmatrix}M'_{11} & M'_{12} & \cdots & M'_{1N}\\ M'_{21} & M'_{22} & \cdots & M'_{2N}\\ \vdots & \vdots & \ddots & \vdots\\ M'_{N1} & M'_{N2} & \cdots & M'_{NN}\end{bmatrix}\begin{bmatrix}q_1\\ q_2\\ \vdots\\ q_N\end{bmatrix}$$

$$G = \frac{1}{2}\vec{q}^T M'\vec{q} = \vec{q}^T M\vec{q} \quad \text{where } M = \frac{1}{2}M'$$

$$\Rightarrow \boxed{G = \vec{q}^T M\vec{q}}$$

symmetric due to reciprocity



Assume Rigid binding

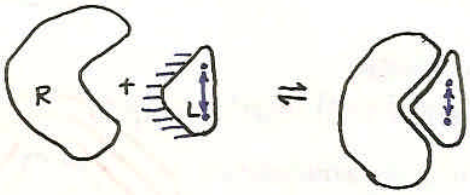
$$\Delta G^{elec}_{binding} = G_{bound} - G_{unbound} = \vec{q}^T M^{bound}\vec{q} - \vec{q}^T M^{unbound}\vec{q} = \vec{q}^T(\Delta M)\vec{q}$$

$$= \begin{bmatrix}\vec{q}_L\\ \vec{q}_R\end{bmatrix}^T\begin{bmatrix}L & C\\ C^T & R\end{bmatrix}\begin{bmatrix}\vec{q}_L\\ \vec{q}_R\end{bmatrix}$$

L: ligand-ligand interactions; C: ligand-receptor interactions; R: receptor-receptor interactions

$$\Rightarrow \Delta G^{elec}_{binding} = \begin{bmatrix}\vec{q}_L\\ \vec{q}_R\end{bmatrix}^T\begin{bmatrix}L\vec{q}_L + C\vec{q}_R\\ C^T\vec{q}_L + R\vec{q}_R\end{bmatrix} = \vec{q}_L^T L\vec{q}_L + \vec{q}_L^T C\vec{q}_R + \vec{q}_R^T C^T\vec{q}_L + \vec{q}_R^T R\vec{q}_R$$

$$= \vec{q}_L^T L\vec{q}_L + 2\vec{q}_L^T C\vec{q}_R + \vec{q}_R^T R\vec{q}_R$$



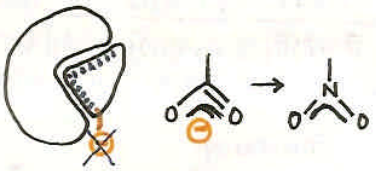
$$\Delta G^{elec}_{binding} = \underbrace{\vec{q}_L^T L \vec{q}_L}_{\text{ligand desolvation}} + \underbrace{2\vec{q}_L^T C \vec{q}_R}_{\text{interactions recovered}} + \underbrace{\vec{q}_R^T R \vec{q}_R}_{\text{receptor desolvation}}$$

$$\vec{\nabla}_{\vec{q}_L}\left(\Delta G^{elec}_{binding}\right) = 2L\vec{q}_L + 2C\vec{q}_R = \vec{0}$$

$$\Rightarrow L\vec{q}_L = -C\vec{q}_R$$

$$\Rightarrow \boxed{\vec{q}_L^{opt} = -L^{-1}C\vec{q}_R}$$

JPhys B 105: 880-888 (2001).
chorismate mutase



JACS 125: 5598-9 (2003).
10-fold improvement in binding