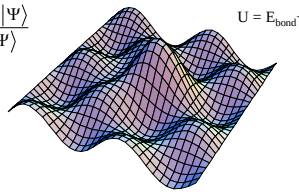
Molecular Simulation III

Quantum Chemistry

$$E = \frac{\langle \Psi | H | \Psi \rangle}{\langle \Psi | \Psi \rangle}$$

Classical Mechanics

$$U = E_{bond} + E_{angle} + E_{torsion} + E_{non\text{-}bond}$$



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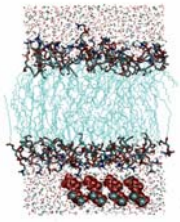
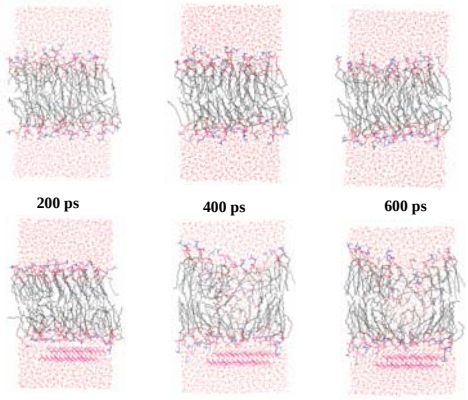
Molecular Dynamics

Crystal-Phospholipid Bilayer Interactions

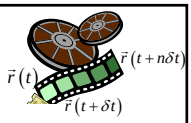
- Pseudogout (human inflamatory disease) caused by presence of *in vivo* crystals of calcium pyrophosphate dihydrate (CPPD).
- Molecular aspect of *in vivo* crystal induced inflammation is unknown
- Rupture of the lysosome phospholipid membrane is a commonly accepted mechanism of inflammation.
- Important to elucidate the nature of crystal-phospholipid bilayer interactions
- The knowledge will aid in developing inhibitors to diminish the adhesion of CPPD to membranes



Solvated DMPC Bilayer in Absence and Presence of CPPD Crystal



MD Review



- Molecular dynamics is a numerical integration of the classical equations of motion

$$\vec{F} = m\vec{a} = m\frac{d^2\vec{x}}{dt^2}$$

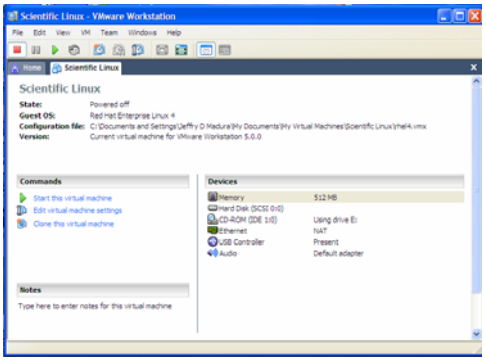
- assuming conservative forces….

$$\vec{F} = -\nabla\vec{U}$$

- …the integrated equations of motion become

$$\vec{r}(t+\delta t) = \vec{r}(t) - \vec{r}(t-\delta t) + \frac{1}{m}\vec{F}(t)\delta t^2$$

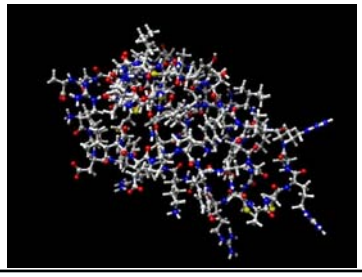
VMWARE



VMWARE

Molecular Dynamics of BPTI

- BPTI: Bovine Pancreatic Trypsin Inhibitor
  - Small protein of 58 amino acid residues
  - Protein used in first MD simulations



Dynamics Output

```
AVER DYN: Step     Time      TOTEner        TOTKe       ENERgy
   TEMPerature
AVER PROP:         GRMS      HFCTote        HFCKe       EHFCor
   VIRKe
AVER INTERN:      BONDs       ANGLes       UREY-b    DIHEdrals
   IMPRopers
AVER CROSS:       CMAPs
AVER EXTERN:    VDWaals         ELEC       HBONds          ASP
   USER
AVER PRESS:        VIRE         VIRI       PRESSE       PRESSI
   VOLUme
 ----------   ---------    ---------    ---------    ---------    -----
   ----
AVER>      100  9.60000   3554.94730    743.24070   2811.70660
   334.83951
AVER PROP>     19.53054   3563.73928    769.68781      8.79198
   865.43486
AVER INTERN>  169.89684    515.51136     54.58767    364.90914
   41.59984
AVER CROSS>  3176.17447
AVER EXTERN>  -77.20274  -1433.76999      0.00000      0.00000
   0.00000
AVER PRESS>     0.00000   -576.95658      0.00000      0.00000
   0.00000
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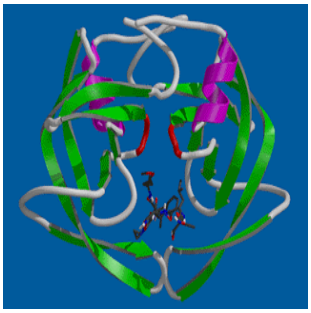
Docking

Ligand-Receptor Docking



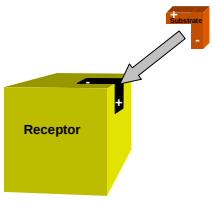
- Deals with **identification of suitable ("best") ligands** for specific receptors in proteins.
- **Ligands** can act either as **activators** or as **inhibitors** of the biological function of the protein in the cell.
- **Artificial ligands** (i.e. drugs) can be used to up-regulate or down-regulate the activity of proteins that are associated with specific diseases.
- To the left, **HIV-1 Protease** complexed with an efficient **inhibitor**, TL-3-093.

Docking

- Three-dimensional molecular structure is one of the foundations of **structure-based drug design**.
- Often, data are available for the shape of a **protein** and a **drug** separately, but not for the two together.
- **Docking** is the process by which two molecules fit together in 3D space.

Docking

- Two general classes
  - "Unbiased"
    - Autodock
  - "Direct"
    - DOCK
    - LUDI
- Goals
  - Robust and accurate
  - Computationally feasible



Ligand-Receptor Docking Approach: Challenges

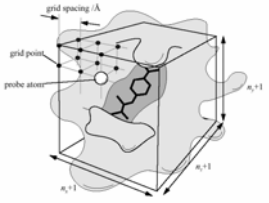
- Must screen **millions** of possible compounds that fit a particular receptor.
- Must **specifically select** those ligands that show a **high affinity**.
- The **set of ligands** selected can then be **screened further** by more involved computational techniques, such as free-energy perturbation theory (ΔG_{bind})
- We would like an **automated, standard protocol** to find the best Ligand-Receptor fit.

Docking

- Terms to consider in docking
  - Shape complementarity
  - Interaction specificity
  - Solvation/desolvation
  - Hydrophobic
  - Hydrogen bonding
- Terms considered in MOE-Dock (Autodock)
  - Van der Waals
  - Hydrogen bonding
  - electrostatics

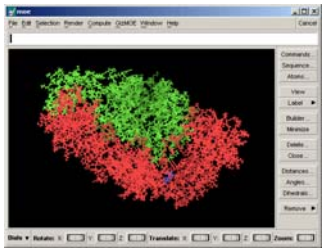
Docking

- Energy evaluation
  - Based on a Grid approach
- Search engine
  - Simulated Annealing (SA)
    - Autodock
    - MOE-Dock
  - Genetic Algorithms (GA)
    - Autodock 3.0



MOE-Dock Application

- We will look at a docking example of a TIBO-like inhibitor to HIV-1 Reverse Transcriptase (HIV-RT).
- Crystal structure to be used: HIV-RT with TIBO-R86183.



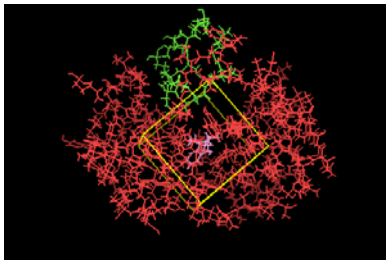
MOE-Dock Application

- Setting up the calculation.
  - *Prepare the protein*. Color the ligand, receptor, and metal ions distinctly. Add H atoms to the X-ray structure if none are given MOE | Edit | Add Hydrogens
  - *Select ForceField.* MOE | Window | Potential Control
  - *Minimize*. MOE | Compute | Energy Min.

Here you can turn on solvation model; Place partial charges on atoms

MOE-Dock Application

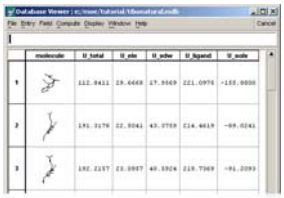
- MOE | Compute | Simulations | Dock



The docking box appears around the ligand.
Graphic shows HIV-RT (red) and its ligand TIBO-R86183.

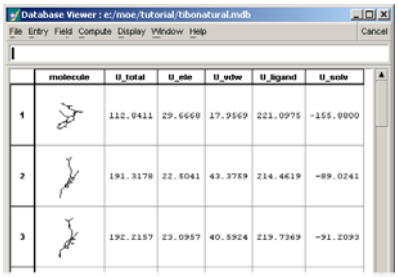
MOE-Dock Application
Docking Results

- Examine the docked structures compared to the crystal structure of the ligand and its receptor.
- In this database, columns contain the total energy of the complex, the electrostatic (U_ele) and van der Waals energies (U_vdw) between the protein and the ligand, and the energy of the (flexible) ligand (U_ligand).



MOE-Dock Application

- **To find the best (lowest energy) docked structure**, you will sort the database in ascending order with respect to the total energy (U_total)

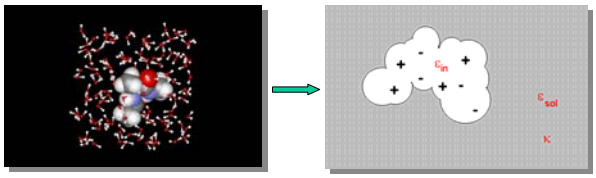


Poisson – Boltzmann Electrostatics

Application Areas of Electrostatics

- Electrostatic Energies
- Electrostatic Forces
- Electrostatic Binding Free Energy
- Electrostatic Solvation Free Energy
- pKa Shifts
- Protein Stability
- Conformational pH Dependence
- Redox
- Electrostatic Steering in Enzyme/Substrate Encounters
- Electrostatic Forces Coupled to Molecular Mechanics/Dynamics

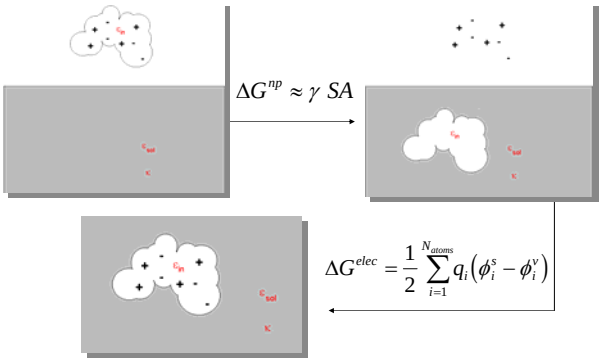
Explicit vs. Continuum Solvent Model



Based on a suggestion by Born, the explicit solvent model may be very crudely approximated by a structureless continuum. In this continuum picture the solvent is represented by a dielectric constant, ε_{sol}, and the effect of ions by, κ. The solute is a set of embedded charges inside a cavity with a dielectric constant of, ε_{in}.

Continuum Solvent Model

$$\Delta G^{solv} = \Delta G^{np} + \Delta G^{elec}$$



Poisson-Boltzmann Model of Molecular Electrostatics

permittivity

"masking" function

$$-\nabla\cdot(\varepsilon\nabla\phi) = 4\pi\rho^f - \kappa^2\phi\lambda$$

electrostatic potential

inverse Debye length

"fixed" charge density

$$\kappa^2 = \frac{8\pi e^2 N_A I}{1000\varepsilon k_B T}$$

Solving the FDPB Equation

- In practice, one knows the
  - charge density (ρ) from the fixed charges in the receptor and substrate.
  - the permittivity (dielectric constant).
  - Kappa (κ), which is related to the ionic strength.
- Make a guess at the potential.
- Solve the equation for a new potential.
- Continue to solve until the change in potential is small.

Poisson-Boltzmann Electrostatic Forces

$$\vec{f} = F^{Coul} + F^{RF} + F^{DBF} + F^{IBF}$$

F^{Coul} is the Coulombic force which is the interaction of all the solute atoms with each other and is referred to as the "qE" force.

F^{RF} is the reaction field force, $F^{RF} = qE^{RF}$ where E^{RF} is the solvent reaction field acting at an atom.

F^{DBF} is the dielectric boundary force. This is due to the tendency of high dielectric medium to reduce the field energy by moving into regions of low-dielectric constant.

F^{IBF} is the ionic boundary force and is generally small in comparison with the other forces in the system. This force results from the tendency of mobile ions to reduce the field energy by moving into regions of zero ionic strength (i. e. the molecular interior).

Langevin Dynamics

mass

position

Random flucuations due to interactions with the solvent

$$m\frac{d^2x(t)}{dt} = \vec{F}(x) - m\gamma\frac{dx(t)}{dt} + \vec{R}(t)$$

Force which depends upon the position of the particle relative to the other particles

Force due to the motion through the solvent

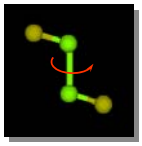
$$\gamma = \frac{k_B T}{mD}$$

diffusion constant

Dichloroethane

Summary of simulation parameters

$\varepsilon_i = 1$
$\varepsilon_s = 80$
$\gamma = 6.5\ ps^{-1}$
dt = 0.001 ps
T = 1000 K
grid spacing = 0.5 to 1.2 A



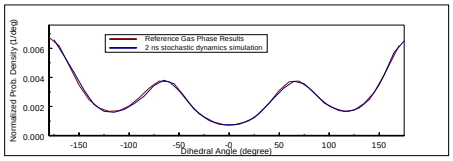
Atom Type	Charge (e)	Radius (Å)
Cl	-0.25	1.82
CH_2	0.25	1.99

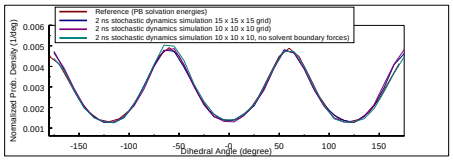
Trans conformer dominates in the gas phase

Increased gauche conformer in liquid phase

Dichloroethane

Summary of simulation results

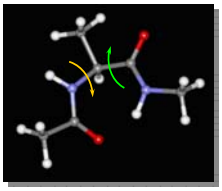




Alanine "dipeptide"

Summary of simulation parameters

$\varepsilon_i = 1$
$\varepsilon_s = 80$
$\gamma = 6.5\ ps^{-1}$
dt = 0.001 ps
T = 1000 K
grid spacing = 0.7 to 1.7 A



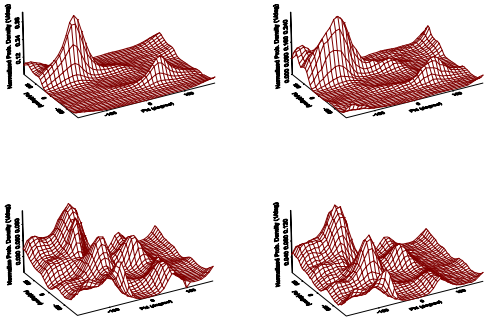
Conclusions

Good equilibration
Good agreement with other computational models
Weak sensititvity to grid spacing
No heating from numerical forces

Alanine "dipeptide"

in vacuo

Aqueous

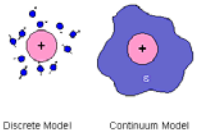


Reference

2 ns stochastic dynamics

Thermodynamic Treatment of Ion-Solvent Interactions:
The Born Model

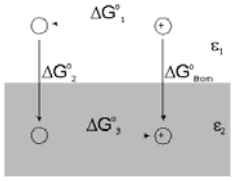
- **Ion-Solvent interaction**: Consists of solvent dipoles interacting with the electric field of the ion.
- **Two cases to consider for the solvent**:
  - A structure-less **continuum** of dielectric ε ("The Born Model")
  - **Discrete molecules** with dipoles, polarizability, etc.



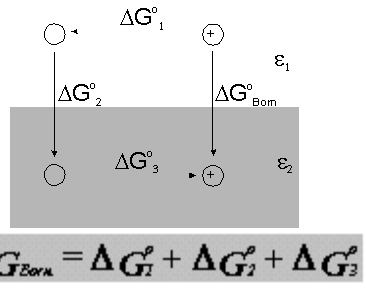
The Born Model

- Consider: Continuum model of ion solvation.

If medium 1 is a vacuum, ΔG_{born}. is just the free energy of solvation.



We will calculate the free energy of **transfer of an ion from medium 1 (ε_1) to medium 2 (ε_2).** This will be called ΔG_{born}.

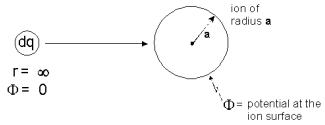


The path for ΔG_{born} refers to:

First **discharging** the ion in medium 1 (ΔG^o_1)
Transferring the ion from medium 1 to medium 2 (G^o_2)
Recharging the ion in solvent 2 (ΔG^o_3)

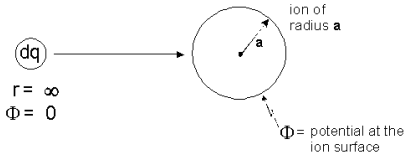
The Charging Process

- Energies of charging/discharging:
  - computed by a model where *infinitesimal pieces of charge* are brought from infinity,
  - and placed on the surface of the ion until the final charge is obtained



The charging process

The Charging Process



The charging process

What is the energy of bringing a charge dq from infinity and placing it on the surface of a sphere with radius a?

$$dG = \Phi dq$$

The Charging Process

- Knowing the potential (Φ) of a point charge, we have,

$$dG_{charging} = \Phi dq = \frac{q}{4\pi \varepsilon_o \varepsilon a} dq$$

Integrating this from 0 to the final charge on the ion, Ze (where Z is the valence)…..(Next Slide)

The Charging Process

$$\Delta G_{charging} = \frac{Z^2 e^2}{8\pi \varepsilon_o \varepsilon a}$$

Therefore, For ΔG^o_1 , ΔG^o_2, and ΔG^o_{born} we have…(Next Slide)

$$\Delta G_{discharging} = -\Delta G_{charging}$$

The Charging Process

$$\Delta G_1^o = -\frac{Z^2 e^2}{8\pi \varepsilon_o \varepsilon_1 a}$$

$$\Delta G_2^o = +\frac{Z^2 e^2}{8\pi \varepsilon_o \varepsilon_2 a}$$

$$\Delta G_{Born}^o = \frac{Z^2 e^2}{8\pi \varepsilon_o a}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right) + \Delta G_2^o$$

If $\varepsilon_2 < \varepsilon_1$, then $\Delta G^o > 0$

It takes work to move an ion from water to a less polar solvent (such as vacuum or hydrocarbon)

Free Energy of Solvation

- Consider: Transferring an ion from a vacuum to a medium of ε.
  - Assume $\mathbf{\Delta G^o}_2 = 0$. (No interaction between solvent and discharged ion).

$$\Delta G_{solvation}^o = \frac{Z^2 e^2}{8\pi \varepsilon_o a}\left(\frac{1}{\varepsilon} - 1\right)$$

Two points to note:
1. $\Delta G < 0$ if $\varepsilon > 1$
2. ΔG increases as ionic Radius increases. Why? The field and the potential At the ion surface becomes Less.

Generalized Born

- Widely used to represent the electrostatic contribution to the free energy of solvation
- Model is comprised of a system of particles with radii a_i and charges q_i
- The total electrostatic free energy is given by the sum of the Coulomb energy and the Born free energy of solvation in a medium of relative permittivity ε.

$$G_{elec} = \sum_{i=1}^{N}\sum_{j=i+1}^{N}\frac{q_i q_j}{\varepsilon r_{ij}} - \frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{N}\frac{q_i^2}{a_i}$$

Generalized Born

- The previous equation can be re-written into the generalized Born equation

$$\Delta G_{elec} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{N}\sum_{j=1}^{N}\frac{q_i q_j}{f\left(r_{ij}, a_{ij}\right)}$$

- $f(r_{ij},a_{ij})$ depends upon the interparticle distances r_{ij} and the Born radii a_i.

$$f\left(r_{ij}, a_{ij}\right) = \sqrt{r_{ij}^2 + a_{ij}^2 e^{-D}}$$

$$a_{ij} = \sqrt{a_i a_j} \qquad D = \frac{r_{ij}^2}{\left(2a_{ij}\right)^2}$$

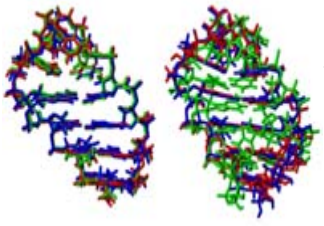
Generalized Born

- Note the following
  - When $i=j$ the equation returns the Born expression
  - When $r_{ij} << a_i$ and a_j the expression is close to the Onsager result (I.e. a dipole)
  - When $r_{ij} >> a_i$ and a_j the result is very close to the sum of the Coulomb and Born expression
- A major advantage to this formulation is that the expression can be differentiate analytically, thereby enabling the solvation term to be included in gradient-based optimization methods

MacroModel GB/SA Solvation Model

- Accounts for solvation effects, especially in complex systems.
- Generalized Born/Surface Area (GB/SA) approach (continuum).
  - increases the speed of the calculation
  - avoids convergence problems, apparent in explicit models, where longer simulations or different solvent starting geometries yield different final energies.
- The GB/SA model can be used to calculate absolute free energies of solvation.

Application of GB/SA Solvation Model



- Hall group applied the GB/SA continuum solvation model to RNA hairpins with much success.
- Simulations of the UUCG tetraloop give average structures within 1.2 Å of the initial NMR model, in agreement with an explicit solvent simulation (Williams, D. J., Hall, K. B. 1999. Biophys J. 76:3192-3205).

Electrostatic Free Energy of Solvation Calculation

- In this calculation one computes the electrostatic energy difference between the molecule in the aqueous phase and in vacuum.
  - This is equivalent to computing the work in moving a charge from a low dielectric to a high dielectric.
  - This work is equivalent to a change in the free energy.
  - MOE-Electrostatics can be used by performing two calculations
    - Compute the electrostatic energy with both dielectric constants set to 1
    - Compute the electrostatic energy with the interior dielectric set to 1 and the exterior dielectric set to 80.