

Molecular Biophysics –
Part 3 –
Lecture 4
Relating Molecular Dynamics to
Macroscopic Quantities

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 - Wednesday April 13, 10 AM – noon
 - Or by appointment

Review of Lecture 1:

- Dynamic programming algorithms guarantee the global minimum solution.

Review of Lecture 2:

- Molecular mechanics forcefields approximate the energetics of a molecule using classical mechanics.
- Geometry optimizers
 - Steepest Descent (local minima)
 - Conjugate Gradient (local minima)
 - Simulated annealing (not limited to local minima)
- Molecular dynamics simulates the motion of a molecule as a function of time.

Review of Lecture 3:

- Ergodic Hypothesis
 - Connects the trajectory of MD to an ensemble of structures.
- Free Energy Perturbation

Outline for Lecture 4:

- Review free energy perturbation.
- How to predict conformational free energies.
- Predicting other thermodynamic quantities.
- Implicit solvent models.

Practical Scheme:

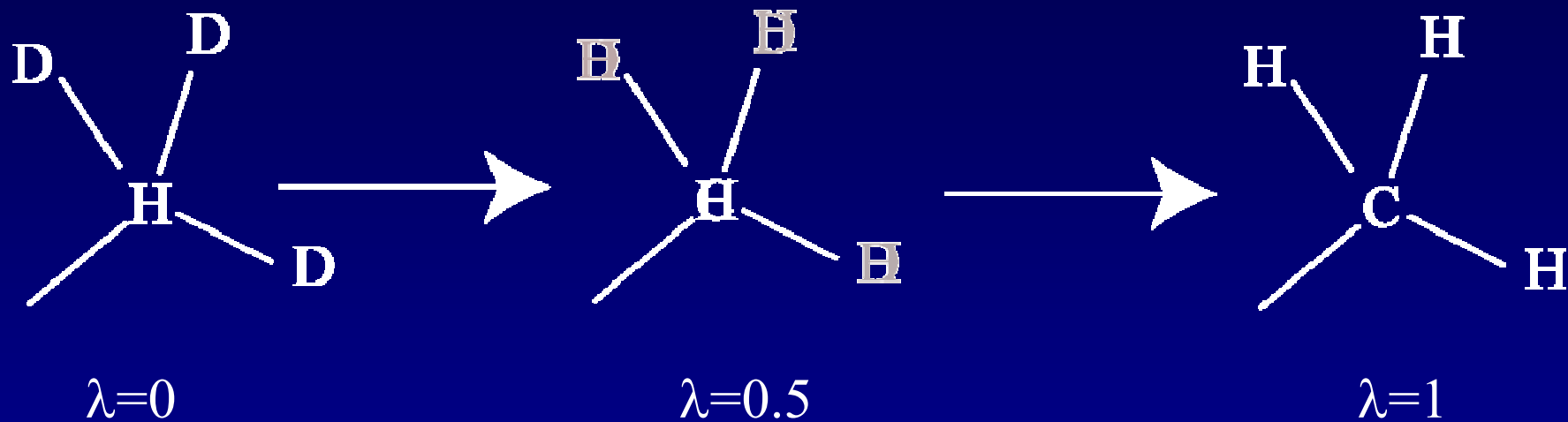
$$\Delta A = -kt \ln \langle e^{V_{BA}/kt} \rangle_A$$

- Errors are smaller if the perturbation term, V_{BA} is smaller.

$$\begin{aligned} V(\lambda) &= (1-\lambda)V_A + \lambda V_B \\ \Delta A &= -kt \int_0^1 \frac{\partial \ln \langle e^{-V(\lambda)} \rangle_\lambda}{\partial \lambda} \partial \lambda \\ &= -kt \int_0^1 \frac{\partial \ln \langle 1 + \frac{-V(\lambda)}{kt} \rangle_\lambda}{\partial \lambda} \partial \lambda \\ &= -kt \int_0^1 \frac{\partial \langle \frac{-V(\lambda)}{kt} \rangle_\lambda}{\partial \lambda} \partial \lambda \\ &= \int_0^1 \frac{\partial \langle -V(\lambda) \rangle_\lambda}{\partial \lambda} \partial \lambda \end{aligned}$$

- Calculation can be divided into a number of calculations from $\lambda = 0$ to $\lambda = 1$.

Glycine to Alanine:



$$V(\lambda) = (1-\lambda)V_A + \lambda V_B$$

Solving the Integral:

- Use a Gaussian Quadrature to solve the integral:

$$V(\lambda) = (1-\lambda)V_A + \lambda V_B$$

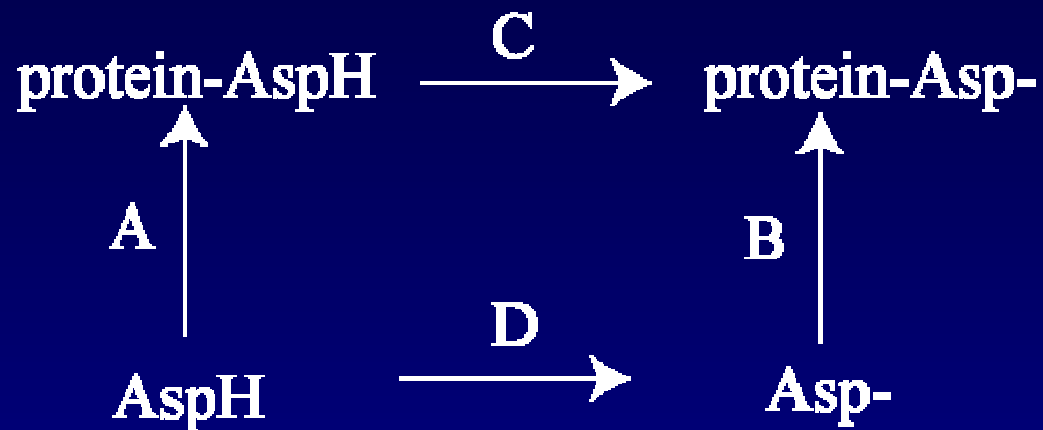
$$\Delta A = \int_0^1 \frac{\partial \langle -V(\lambda) \rangle_\lambda}{\partial \lambda} d\lambda = \sum_{i=1}^n w_i \frac{\partial \langle -V(\lambda) \rangle_{\lambda_i}}{\partial \lambda}$$

- Press *et al.* *Numerical Recipes in {C, Fortran, C++}*. Cambridge University Press.

n	λ_i	w_i
5	.04691	.11846
	.23076	.23931
	.5	.28444
	.76923	.23931
	.95308	.11846
9	.01592	.04064
	.08198	.09032
	.19331	.13031
	.33787	.15617
	.5	.16512
	.66213	.15617
	.80669	.13031
	.91802	.09032
	.98408	.04064

Application: Predicting pKa shifts:

- Simonson, Carlsson, Case. 2004. *JACS* 126:4167.



$$\Delta G = -RT \ln K_a$$

$$\text{p}K_a = -\log_{10} K_a = [1/(2.303kt)]\Delta G$$

$$\text{We want: } \Delta\Delta G = \Delta G_B - \Delta G_A$$

$$\text{Know: } -\Delta G_A + \Delta G_D + \Delta G_B - \Delta G_C = 0$$

$$\text{rearrange: } \Delta\Delta G = \Delta G_B - \Delta G_A = \Delta G_C - \Delta G_D$$

$$\text{p}K_a (\text{C}) = \text{p}K_a (\text{D}) + [1/(2.303kt)]\Delta\Delta G$$

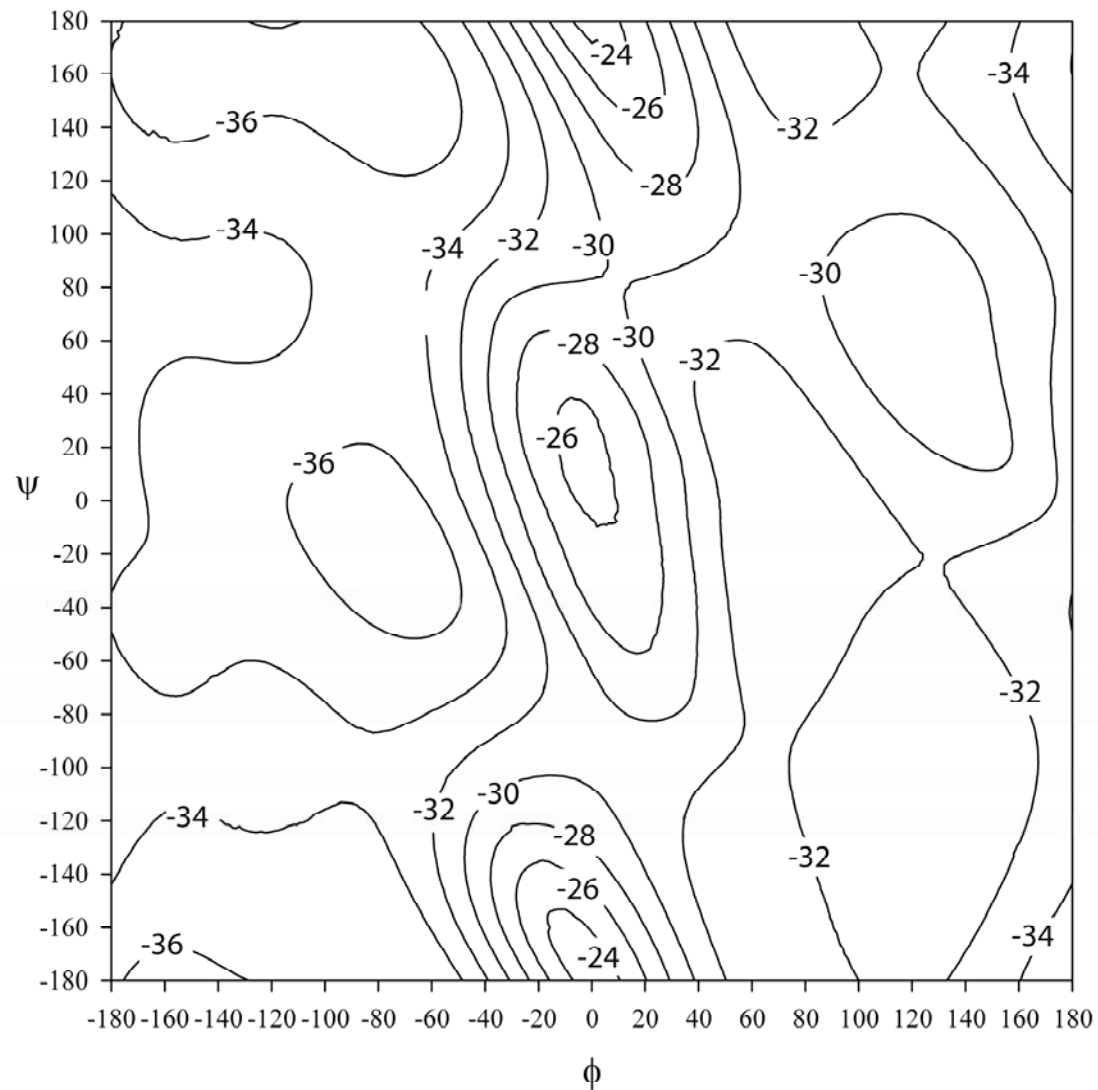
Free Energies of Conformation Changes:

- Change from configuration 1 to configuration 2.
- $A = -kT \ln K$
- $A = -kT \ln P_2/P_1$

where P_2 is the probability of being in configuration 2 and P_1 is the probability of being in state 1.

This method works when the energy barrier is very low, $\sim kT$ (~ 1 kcal/mol).

Alanine Dipeptide:

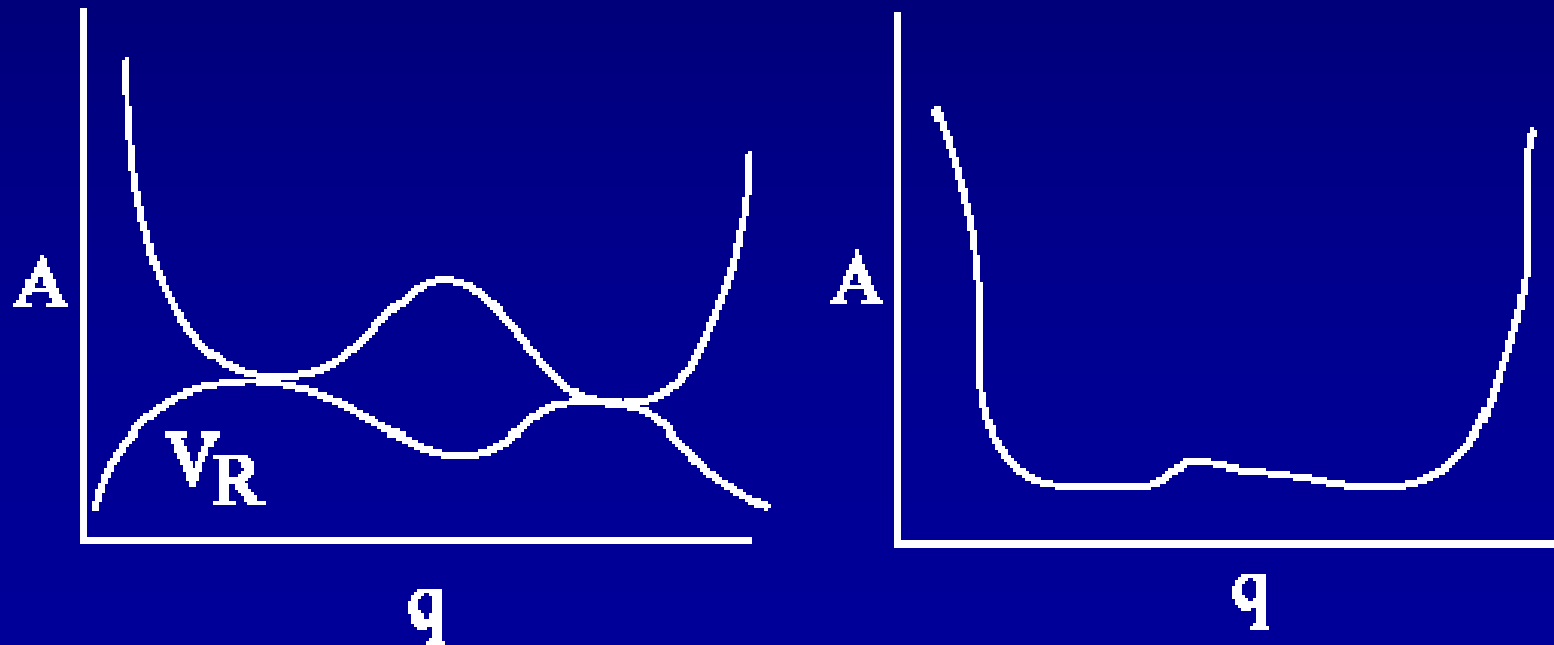


(Free Energies):

- $K = e^{-\Delta A/RT}$
- At 37 °C (310.15 K):
 - $2 = e^{(0.43 \text{ kcal/mol})/RT}$
 - $10 = e^{(1.42 \text{ kcal/mol})/RT}$
 - $100 = ??$

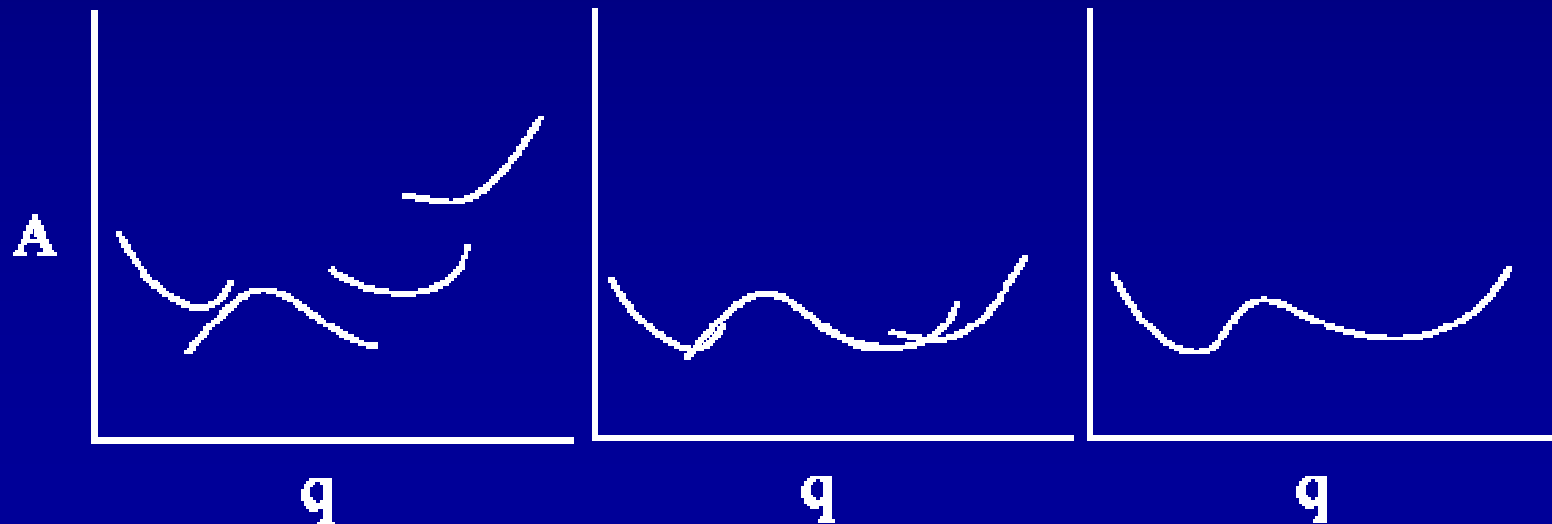
Potential of Mean Force Calculation:

- $A(q) = -kT \ln P(q)$, where q is the reaction coordinate, is the potential of mean force.
- Reduce the barrier height with a restraint potential (called Umbrella Sampling):



Potential of Mean Force:

- $A(q) = -kT \ln P(q)$
- $P(q) = P_R(q)[e^{V_R(q)/kT}/C]$
- $-kT \ln (P(q)) = -kT \ln (P_R(q)[e^{V_R(q)/kT}/C])$
- $A(q) = A_R(q) - V_R(q) + C'$
- WHAM (Weighted Histogram Analysis Method):



Other Thermodynamic Parameters:

Entropy:

$$-T \frac{\partial S}{\partial \lambda} = \frac{1}{kT} \left(\left\langle \frac{\partial V}{\partial \lambda} V \right\rangle_{\lambda} - \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} \langle V \rangle_{\lambda} \right)$$

Enthalpy:

$$E = A + TS$$

$$\frac{\partial E}{\partial \lambda} = \frac{\partial A}{\partial \lambda} + T \frac{\partial S}{\partial \lambda}$$

$$\Delta E = \langle V_B \rangle_B - \langle V_A \rangle_A$$

This is error prone because it requires lots of sampling.

Temperature:

$$T(t) = \frac{1}{3Nk} \sum_{i=1}^N |\mathbf{v}(t)|^2$$

Where N is the number of atoms.

Temperature can be regulated by scaling (Berendsen Coupling):

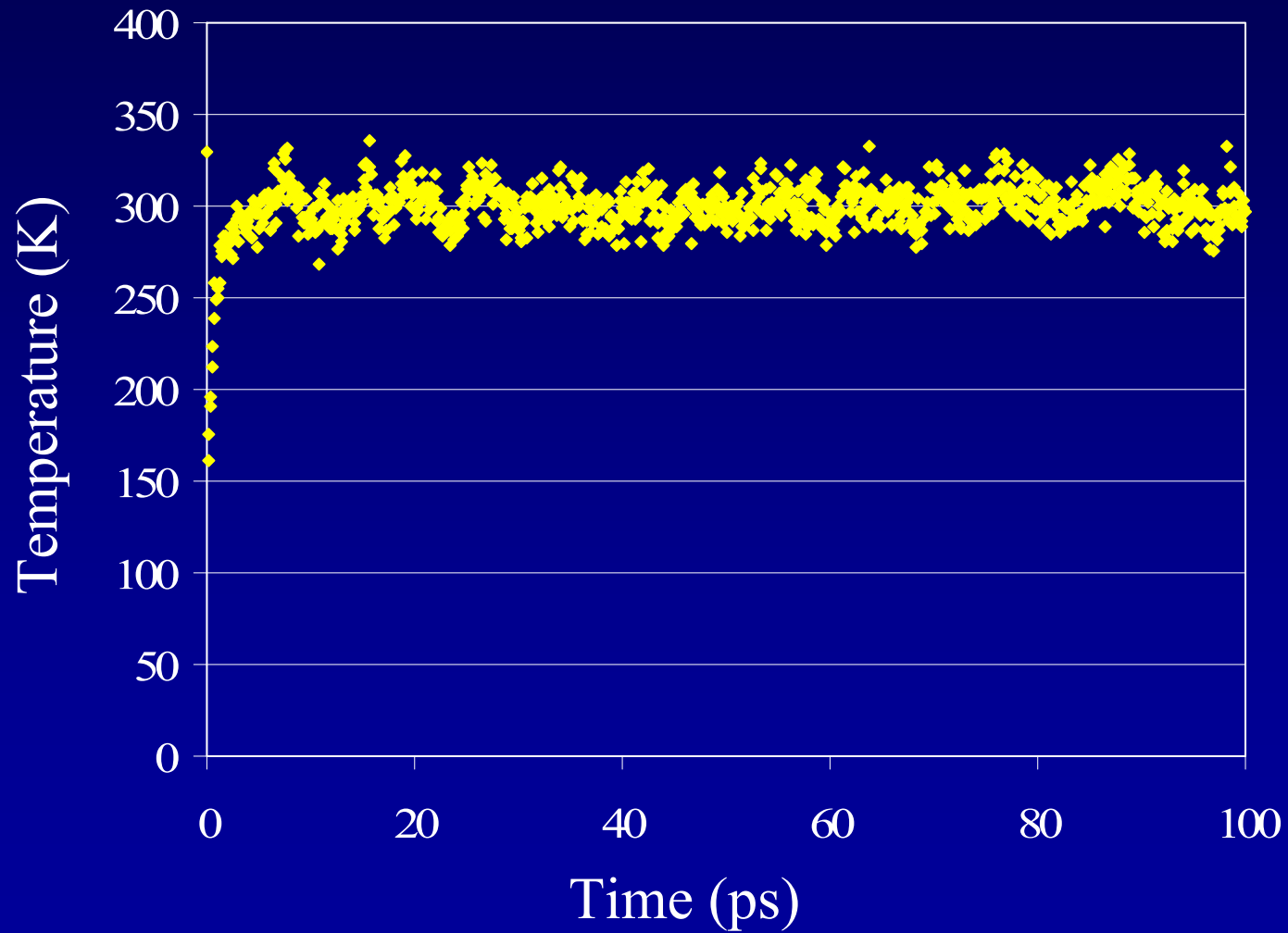
$$\mathbf{F}_i(t) = -\nabla V_i(t) + \frac{\mathbf{p}_i}{\tau} \left[\frac{T_0}{T(t)} - 1 \right]$$

T_0 is the target temperature, \mathbf{p}_i is the momentum of atom i , and τ is a relaxation constant.

Temperature Regulation:

- Advantage-
 - Required for NVT or NPT calculations.
 - Equilibration method.
- Disadvantage-
 - Trajectory does not conserve energy.
 - Trajectory is not reversible.
- In Practice-
 - A simulation is started with a small relaxation constant.
 - Once equilibration is finished, the relaxation constant is increased to lessen the effect of the thermostat.

Actual Simulation:



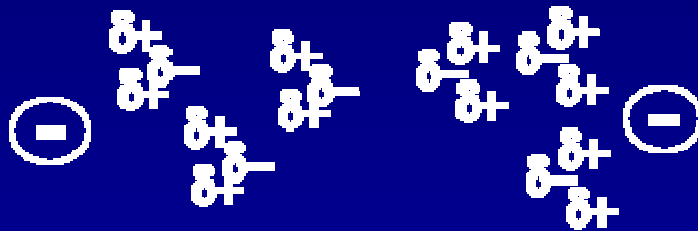
Solvation Effects:

Vacuum:



$$V(\text{electrostatic}) = \frac{q_1 q_2}{\epsilon r} = \frac{q_1 q_2}{r}$$

Aqueous:



$$V(\text{electrostatic}) + V(\text{solvation}) = \frac{q_1 q_2}{\epsilon_{\text{water}} r}$$

$$\left| \frac{q_1 q_2}{\epsilon_{\text{water}} r} \right| < \left| \frac{q_1 q_2}{r} \right|$$

Implicit Solvation:

- Implicit solvation is a method for including the energy of charge polarization, without the need for including explicit water molecules in the simulation.

Generalized Born Solvation:

- Place a conducting sphere of charge q with radius a in polarizing solvent. The charge will distribute on the surface:

$$\rho(r) = \text{charge density} = \frac{q}{4\pi a^2}$$

Inside the sphere :

$$\Phi(r) = \text{electric field} = 0$$

Outside the sphere (equivalent to a point charge at center of sphere) :

$$\Phi(r) = \frac{-q}{\epsilon r^2}$$

where ϵ is the exterior dielectric constant.

$$A = -\frac{1}{2} \int \rho(r)\Phi(r)dr$$

On the surface :

$$A = -\frac{1}{2} \int \left(\frac{q}{4\pi a^2} \right) \left(\frac{-q}{\epsilon r^2} \right) dr = \frac{q^2}{2a \epsilon}$$

Generalized Born Solvation:

- Solvation energy is the energy difference between vacuum $\epsilon = 1$ (Gaussian Units) and in solvent $\epsilon = \epsilon$.

$$A_s = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \frac{q^2}{a}$$

This is the Born equation.

Generalized Born applies this equation to molecules:

$$A_s = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \sum_{k,k'}^{\text{atoms}} q_k q_{k'} \gamma_{kk'}$$

A good function for $\gamma_{kk'}$ is:

$$\gamma_{kk'} = \left(r_{kk'}^2 + \alpha_k \alpha_{k'} e^{-4r^2/\alpha_k \alpha_{k'}} \right)^{-1/2}$$

where α is the effective Born radius that is a function of how buried an atom is in the interior of the molecule.

Note that at long distances:

$$\gamma = 1/r$$

When $k = k'$

$$\gamma = \frac{1}{\alpha}, \text{ so the Born equation applies}$$

Implicit Solvent vs. Explicit:

- Advantages:
 - Faster (fewer atoms).
 - Reduced viscosity allows faster sampling of conformations.
- Disadvantages:
 - Approximation.

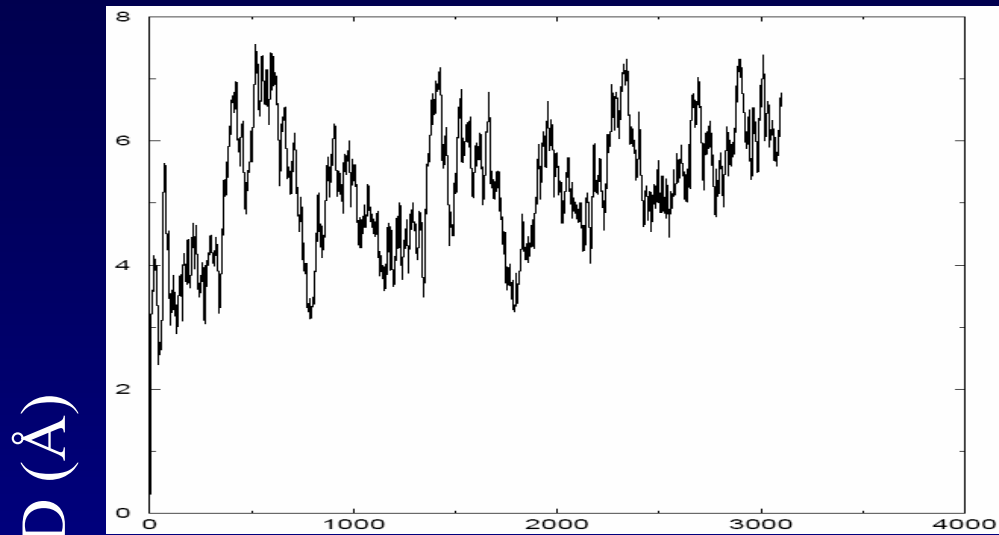
RMSD:

$$\text{RMSD} = \sqrt{\frac{\sum_{i=1}^N (\mathbf{r}_{\text{sim}} - \mathbf{r}_{\text{exp}})^2}{N}}$$

Commonly used method for assessing the quality of a simulation.

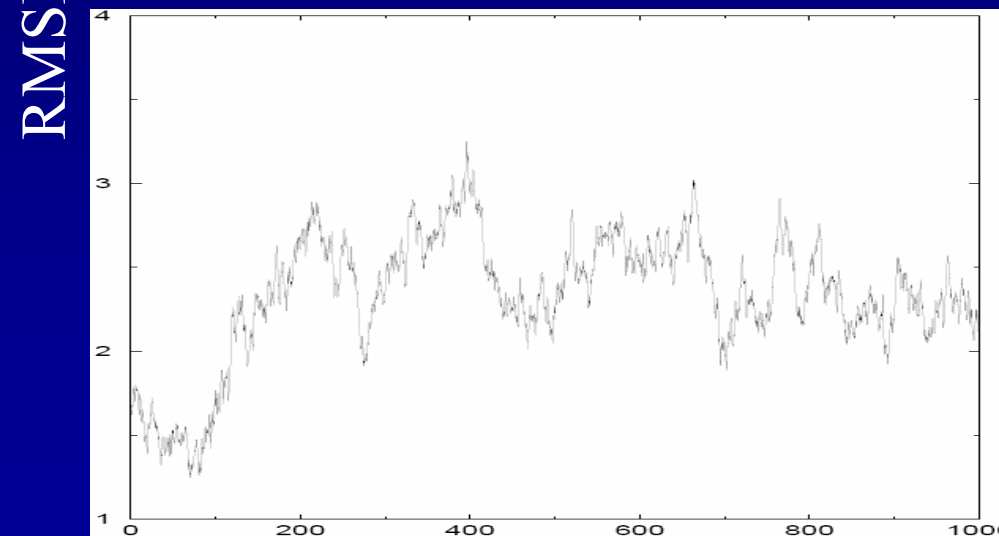
Actual Simulations:

Implicit:



(45 nucleotide RNA kissing hairpin)

Explicit:



Time (ps)

Summary:

- Free energy methods.
 - Free energy perturbation.
 - Umbrella Sampling
- Scaling temperature.
- Generalized Born solvation (implicit solvation).