Molecular Biophysics & Biochemistry 400a/700a (Advanced Biochemistry)

Computational Aspects of: Electrostatics (I), Basic Forces on Proteins, Macromolecular Simulation (I)

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Classes on 10/13/98 & 10/15/98

Yale University

The Handouts I

- Notes
  - ◊ this class and next (electrostatics I, basic forces, simulation I)
- Presentation Paper
  - ◊ Levitt, M. (1983). Protein folding by restrained energy minimization and molecular dynamics. *J Mol Biol* **170**, 723-64.
  - ◊ Very DENSE! Try to understand why this is innovative and such a virtuoso performance (two key points). Try to see beyond symbols to the ideas. What is overall conclusion?
- No Problem Set Paper

The Handouts II

- Review
  - ◊ Allen, M. P. & Tildesley, D. J. (1987). *Computer Simulation of Liquids.* Claredon Press, Oxford.
    - Not passed out but a good reference
  - ◊ Biosym (1994). *Discover 2.9.5 Manual.* Biosym Inc., San Diego, CA.
  - ◊ McCammon, J. A. & Harvey, S. C. (1987). *Dynamics of Proteins and Nucleic Acids.* Cambridge UP.
  - ◊ Chapter 6 of my thesis, a short on-line description of Monte-Carlo methods.
    - http://bioinfo.mbb.yale.edu/Geometry/mbg-phd
- For Fun
  - ◊ Karplus, M. & McCammon, J. A. (1986). The dynamics of proteins. *Sci. Am.* **254**, 42-51.
    - Not passed out but a good reference

Feedback
on first three computational lectures

- Which lecture did you like better
  ('P' for Packing,
  'S' for Structure Prediction,
  'E' for Electrostatics)?
- Was the structure prediction lecture at right level
  ('1' for too basic, '2' for just right, '3' for too complex)?
- Was the packing lecture at right level
  ('1' for too basic, '2' for just right, '3' for too complex)?
- Was the electrostatics lecture at right level
  ('1' for too basic, '2' for just right, '3' for too complex)?
- Sample responses: 'P, 3, 2,1' or 'E-2-2-2'

Overview: Electrostatics + Basic Forces

- Electrostatics
  - ◊ Polarization
  - ◊ Multipoles, dipoles
  - ◊ VDW Forces
  - ◊ Electrostatic Interactions
- Basic Forces
  - ◊ Electrical non-bonded interactions
  - ◊ bonded, fundamentally QM but treat as springs
  - ◊ Sum up the energy

- Simple Systems First

Overview:
Methods for the Generation and Analysis of Macromolecular Simulations

1 Simulation Methods
- ◊ Potential Functions
- ◊ Minimization
- ◊ Molecular Dynamics
- ◊ Monte Carlo
- ◊ Simulated Annealing

2 Types of Analysis
- ◊ liquids: RDFs, Diffusion constants
- ◊ proteins: RMS, Volumes, Surfaces

- Established Techniques (chemistry, biology, physics)
- Focus on simple systems first (liquids). Then explain how extended to proteins.

Electric potential, a quick review

- E = electric field = direction that a positive test charge would move
- Force/q = E
- Potential = W/q = work per unit charge = Fx/q = Ex
  - ◊ E = - grad ϕ ; E = ($d\phi/dx$, $d\phi/dy$, $d\phi/dz$)

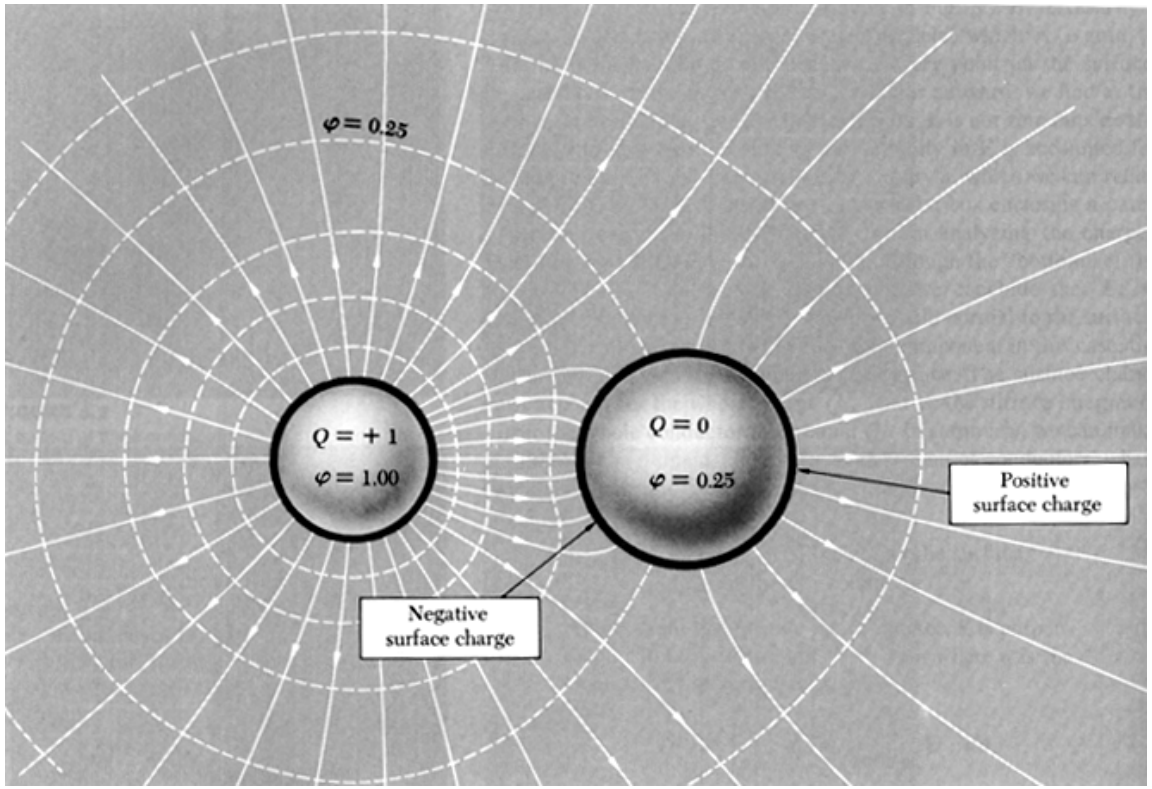


Illustration Credit: Purcell

Maxwell's Equations

- 1st Pair (curl's)
  - ◊ A changing electric field gives rise to magnetic field that circles around it & vice-versa. Electric Current also gives rise to magnetic field.
    [no discuss here]
- 2nd Pair (div's)
  - ◊ Relationship of a field to sources
  - ◊ no magnetic monopoles and magnetostatics: div B = 0
    [no discuss here]
- All of Electrostatics in Gauss's Law!!

$$\text{curl } \mathbf{E} = -\frac{1}{c}\frac{\partial \mathbf{B}}{\partial t}$$

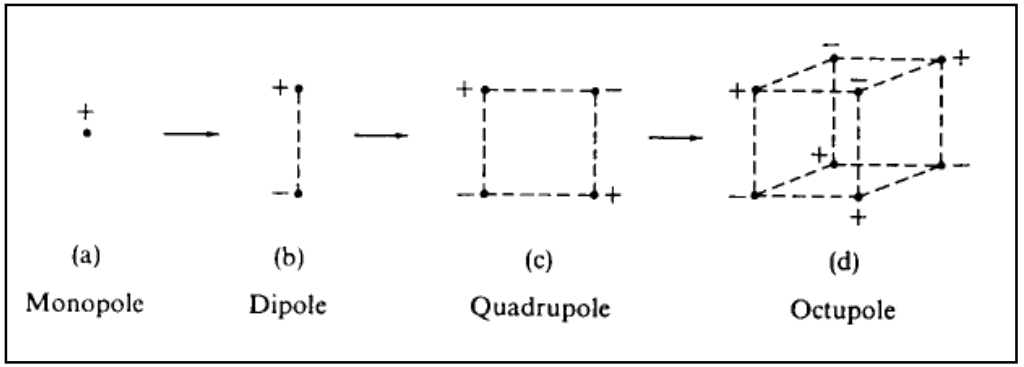
$$\text{curl } \mathbf{B} = \frac{1}{c}\frac{\partial \mathbf{E}}{\partial t} + \frac{4\pi}{c}\mathbf{J}$$

$$\text{div } \mathbf{E} = 4\pi\rho$$

$$\text{div } \mathbf{B} = 0$$

cgs (not mks) units above

Multipole Expansion



- Routinely done when an atom's charge distribution is replaced by a point charge or a point charge and a dipole
  - ◊ Ignore above dipole here
  - ◊ Harmonic expansion of pot.
- Only applicable far from the charge distribution
  - ◊ Helix Dipole not meaningful close-by
- Terms drop off faster with distance

$$\Phi(\mathbf{x}) = \frac{q}{r} + \frac{\mathbf{p} \bullet \mathbf{x}}{r^3} + \frac{1}{2}\sum_{i,j} Q_{ij}\frac{x_i x_j}{r^5} + \cdots$$

$$\Phi(\mathbf{x}) = \frac{K_1 q}{r} + \frac{K_2 q}{r^2} + \frac{K_3 q}{r^3} + \cdots$$

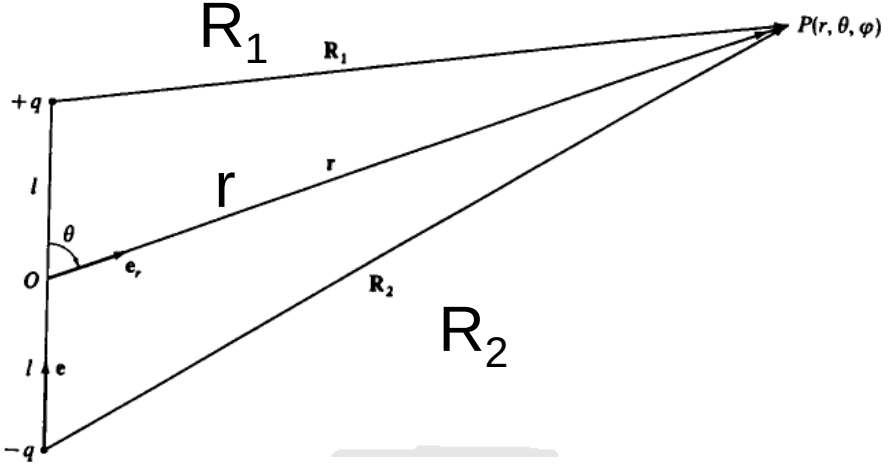
Replace continuous charge distribution with point moments: charge (monopole) + dipole + quadrupole + octupole + ...

Gauss' Law: Electrostatics

- div **E** = $4\pi\rho$
- Coulomb's Law
  - ◊ $\int$ div **E** dV = $\int 4\pi\rho$ dV
  - ◊ $\int$ **E** • d**A** = $\int 4\pi\rho$ dV [Divergence thm.]
  - ◊ Assume spherically symmetrical charge distribution
  - ◊ E $(4\pi r^2) = 4\pi$ Q ==> E = Q/r^2
  - ◊ U = - Q/r [assuming a zero at inf.]
- Equations for the Potential Based on the Charge in a Region plus Boundary Conditions
  - ◊ div grad U = $4\pi\rho$
  - ◊ $\nabla^2 U = 4\pi\rho$ [poisson's equation]
  - ◊ $\nabla^2 U = 0$ [Laplace's equation]

Dipole Derivation

- $\phi(r, \theta) = -q/R_1 + q/R_2$
  - ◊ $\phi(r, \theta) = q(R_1 - R_2)/ R_1R_2$
- If r is very much larger than L
  - ◊ Vectors essentially parallel, like single-slit
  - ◊ $R_1R_2 = r^2$
  - ◊ $R_2-R_1 = 2L \cos \theta$
  - ◊ $q(R_2-R_1) = 2Lq\cos\theta = p \cos \theta$
    $= \mathbf{p}\bullet\mathbf{r}/|r|$
  - ◊ **p** = dipole moment vector
    = [charge][separation]
    in direction from neg. to positive charge
- $\phi(r, \theta) = p \cos \theta / r^2$
  - ◊ E = grad $\phi(r, \theta) \sim 1/r^3$ with a complex angular dependence
- Monopole is 1/r, which dominates over dipole ($1/r^2$), dipole dominates quadrupole



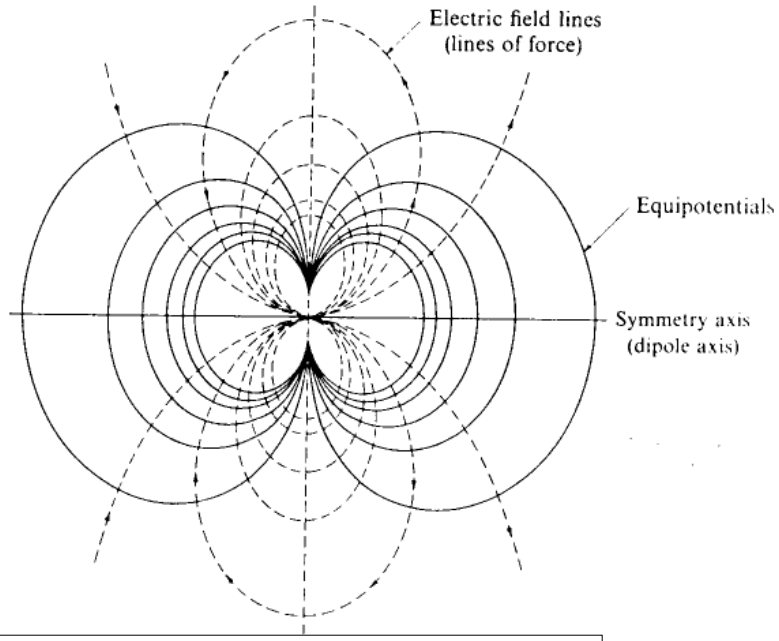
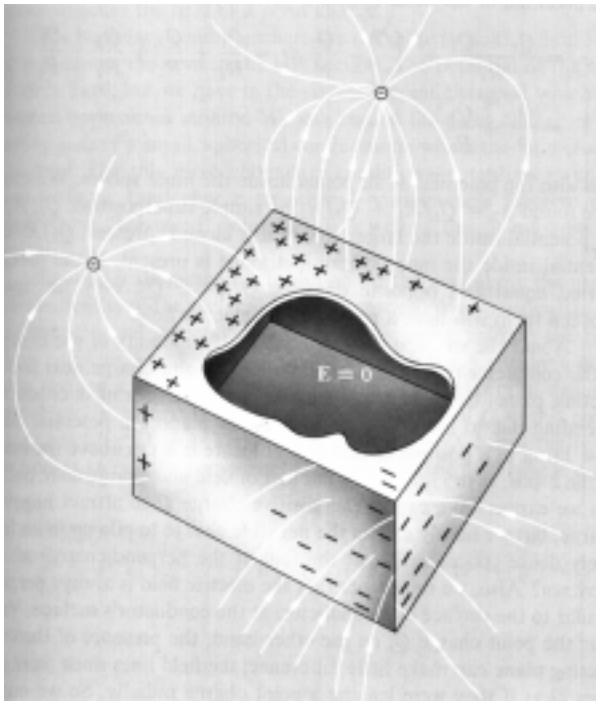
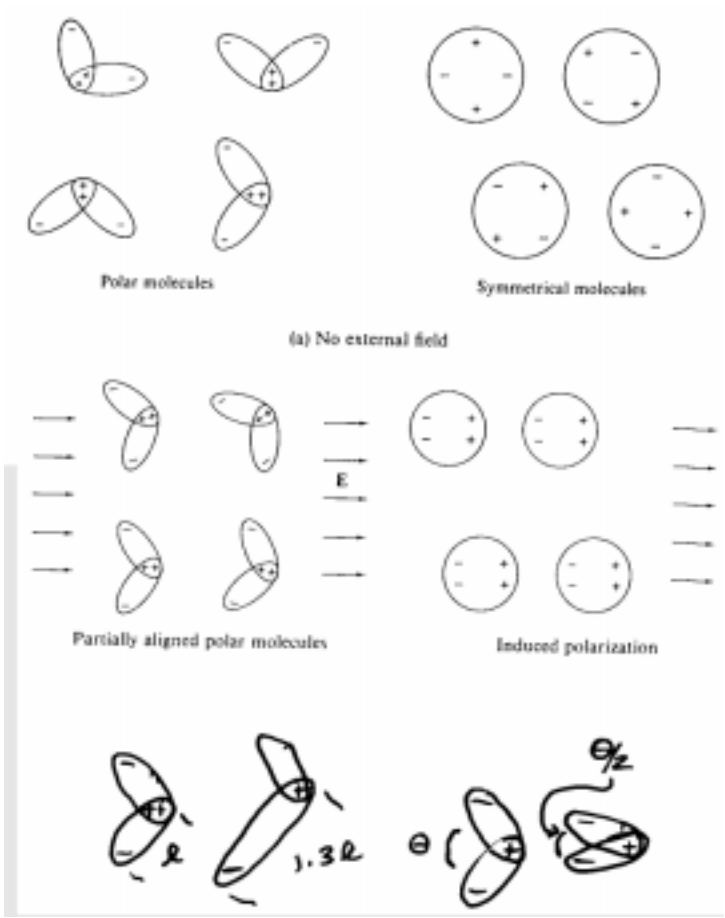


Illustration Credit: Marion & Heald

Polariz-ation





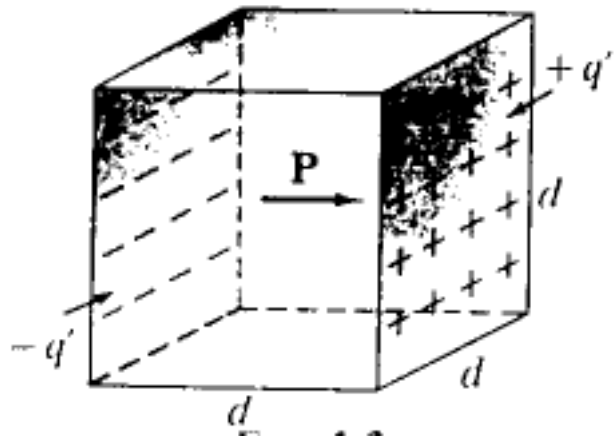
- Charge shifts to resist field
  - ◊ Accomplished perfectly in conductor -- surface charge, no field inside
  - ◊ Insulators partially accommodate via induced dipoles
- Induced dipole
  - ◊ charge/ion movement (slowest)
  - ◊ dipole reorient
  - ◊ molecular distort (bond length and angle)
  - ◊ electronic (fastest)

Illustration Credit: Purcell, Marion & Heald

Dielectric const.

- Macro manifestation of polarization
- Values
  (measured in debye)
  - ◊ Air, 1
  - ◊ Water, 80
  - ◊ Paraffin Wax, 2
  - ◊ Methanol, 33
  - ◊ Non-polar protein, 2
  - ◊ Polar protein, 4
- High-frequency
  - ◊ water re-orient, 1ps
  - ◊ bond, angle stretch
  - ◊ electronic, related to index of refraction

$$q'd = Pd^3$$



- $P = \alpha E$
  P = dipole moment per unit volume
- $\alpha =$ electric susceptability
- $\alpha = (\varepsilon - 1)/4\pi$
- $\varepsilon =$ dielectric const.
- Effective Field Inside Reduced by Polarization

Polarity vs. Polarizability

From Sharp (1999): “Application of a classical electrostatic view to macromolecular electrostatics involves a number of useful concepts that describe the physical behavior. It should first be recognized that the potential at a particular charged atom *i* includes three physically distinct contributions. **The first is the direct or Coulombic potential of j at i. The second is the potential at i from the polarization (from molecule, water and ionic) induced by j. This is often referred to as the screening potential, since it opposes the direct, Coulombic potential. The third arises from the polarization induced by i itself. This is often referred to as the reaction or self potential,** and if solvent is involved, as the solvation potential. When using models which apply the concept of a dielectric constant (a measure of polarizability) to a macromolecule, **it is important to distinguish between polarity and polarizability.** Briefly, polarity may be thought of as describing the density of charged and dipolar groups in a particular region. Polarizability, by contrast, refers to the *potential* for reorganizing charges, orienting dipoles and inducing dipoles. Thus polarizability depends both on the polarity and the freedom of dipoles to reorganize in response to an applied electric field. When a protein is folding, or undergoing a large conformational rearrangement, the peptide groups may be quite free to reorient. In the folded protein these may become spatially organized so as to stabilize another charge or dipole, creating a region with high polarity, but with low polarizability, since there is much less ability to reorient the dipolar groups in response to a new charge or dipole without significant disruption of the structure. Thus, while there is still some discussion about the value and applicability of a protein dielectric constant, it is generally agreed that the interior of a macromolecule is a low polarizable environment compared to solvent. This difference in polarizability has a significant effect on the potential distribution.”

VDW Forces: Start by Deriving Dipole-Dipole Energy

Simplify. Focus on Formula for Parallel Dipoles

$$V(R) = -q p_1 \left(\frac{1}{(R-L)^2} - \frac{1}{(R+L)^2} \right)$$

$$= +q p_1 \left(\frac{4RL}{(R+L)^2 (R-L)^2} \right)$$

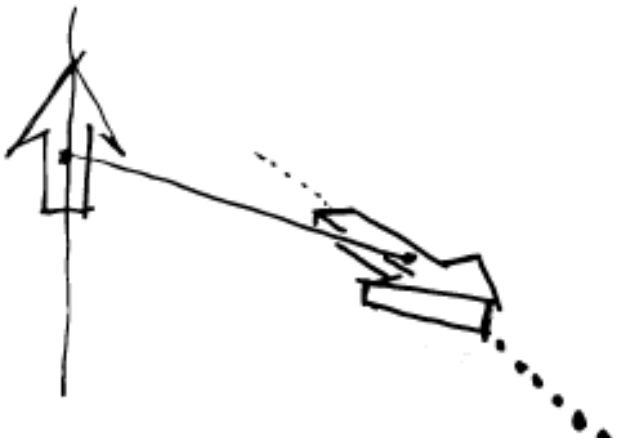
IF $R \gg L$

$$V(R) \doteq +2 \frac{p_1 p_2}{R^3}$$

PARALLEL DIPOLES

IN GENERAL, $V = C \frac{p_1 p_2}{R^3} f$

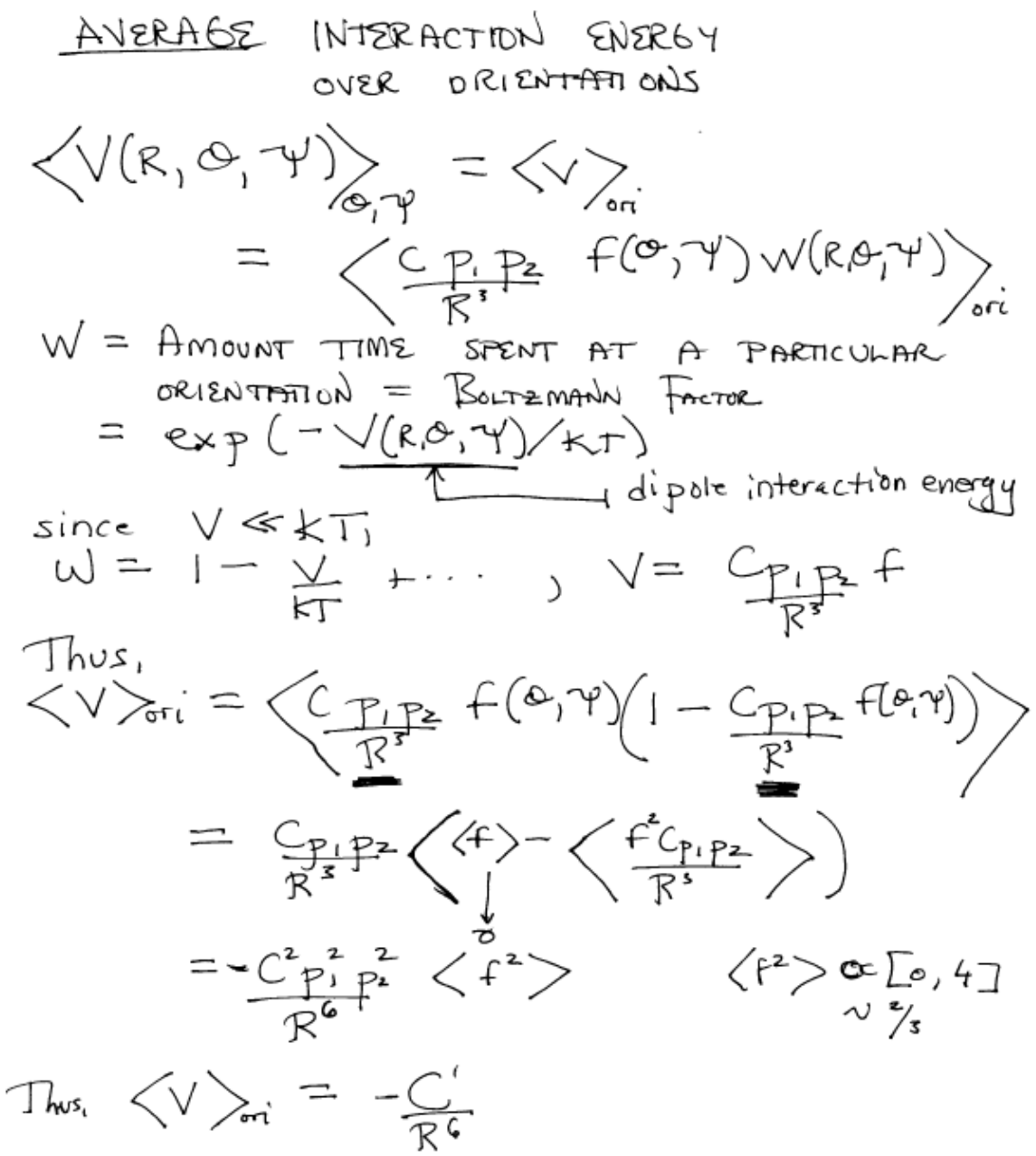
WHERE f IS A FUNCTION OF ORIENTATION ANGLES Θ & Ψ — $f(\Theta, \Psi)$



Interaction energy of a pair of dipoles is a complex function of two angles (Θ, Ψ)

Average Dipole-Dipole Interaction Energy

- Multiplication of dipole-dipole energy ($1/r^3$) and Boltz. Factor (~dipole-dipole energy) gives ($1/r^6$)



Dipole-induced dipole Energy

- Multiplication of dipole-dipole energy ($1/r^3$) and amount of induced dipole ($1/r^3$) gives ($1/r^6$)

INDUCED DIPOLE ($\Rightarrow$, p_2^*) is always parallel to permanent dipole ($\rightarrow$, p_1)

$$\vec{p}_2^{\,*} = \alpha \vec{E}$$

$$\vec{E}_{dipole} = \frac{\nabla\, p_1 \cdot \hat{r}}{R^2} = -\frac{2p_1}{R^3}$$

Using parallel dipole formula above,

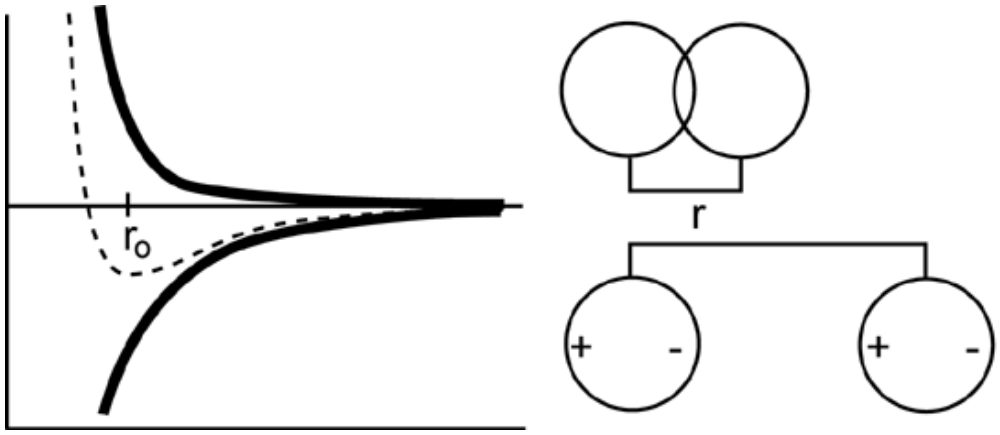
$$V(R) = \frac{2 p_1 p_2^*}{R^3} = -\frac{4 p_1^2 \alpha}{R^6} = -\frac{C}{R^6}$$

VDW Foces:
Induced dipole-induced dipole

- Too complex to derive induced-dipole-induced dipole formula, but it has essential ingredients of dipole-dipole and dipole-induced dipole calculation, giving an **attractive** $1/r^6$ dependence.
  - ◊ London Forces
- Thus, total dipole cohesive force for molecular system is the sum of three $1/r^6$ terms.
- Repulsive forces result from electron overlap.
  - ◊ Usually modeled as A/r^{12} term. Also one can use exp(-Cr).
- VDW forces: $V(r) = A/r^{12} - B/r^6 = 4\varepsilon((R/r)^{12} - (R/r)^6)$
  - ◊ ε ~ .2 kcal/mole, R ~ 3.5 A, V ~ .1 kcal/mole [favorable]

Packing ~ VDW force

- Longer-range isotropic attractive tail provides general cohesion
- Shorter-ranged repulsion determines detailed geometry of interaction
- Billiard Ball model, WCA Theory



Electron Overlap Replusion $U = \varepsilon \left(\frac{r_0}{r}\right)^{12}$

Dispersion Attraction $U = -4\varepsilon \left(\frac{r_0}{r}\right)^{6}$

Close-packing is Default

- No tight packing when highly directional interactions (such as H-bonds) need to be satisfied
- Packing spheres (.74), hexagonal
- Water (~.35), “Open” tetrahedral, H-bonds

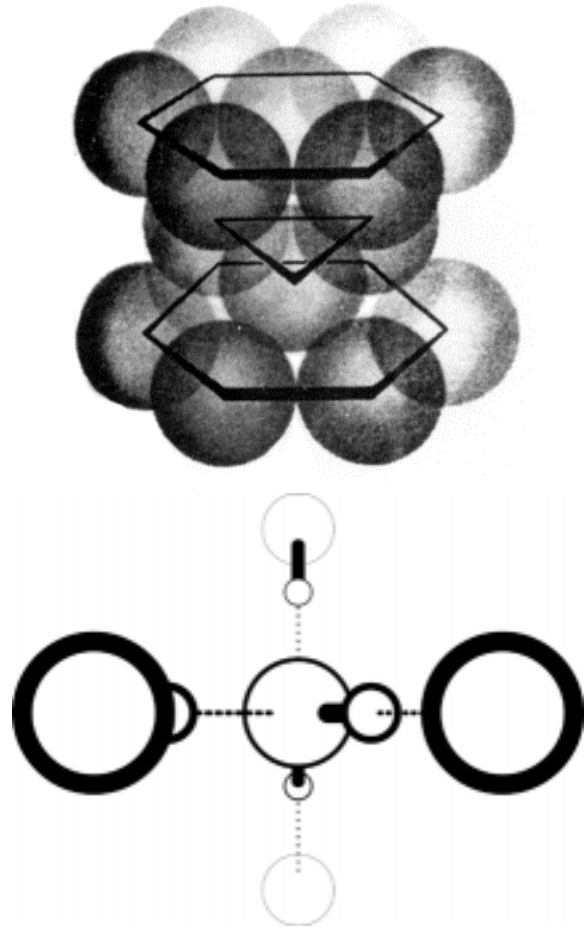
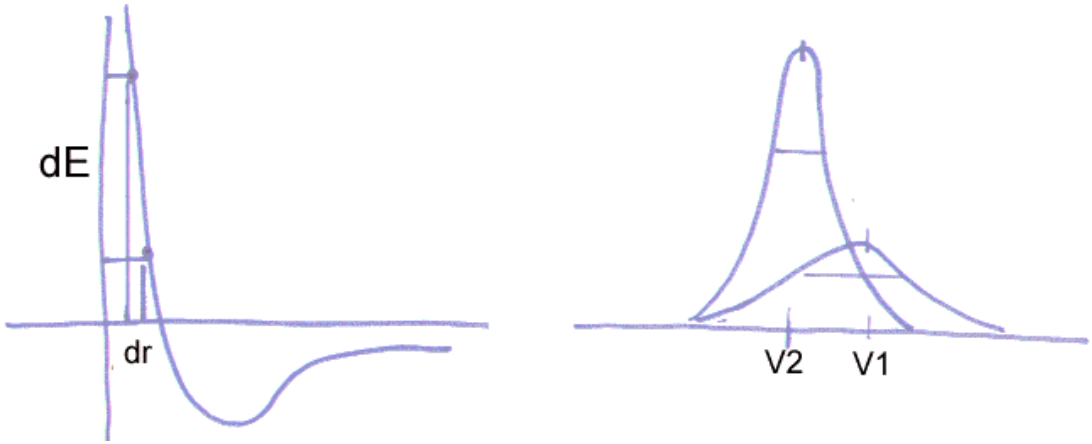


Illustration Credit: Atkins

Small Packing Changes Significant



- Exponential dependence
- Bounded within a range of 0.5 (.8 and .3)
- Many observations in standard volumes gives small error about the mean (SD/sqrt(N))

atom	ε (kJ/ mole)	σ (Å)	**charge** (electrons)
carbonyl carbon	0.5023	3.7418	0.550
α-carbon (incorporating 1 hydrogen)	0.2034	4.2140	0.100
β-carbon (incorporating 3 hydrogens)	0.7581	3.8576	0.000
amide nitrogen	0.9979	2.8509	-0.350
amide hydrogen	0.2085	1.4254	0.250
carbonyl oxygen	0.6660	2.8509	-0.550
water oxygen in interactions with the helix	0.6660	2.8509	-0.834
water hydrogen in interactions with the helix	0.2085	1.4254	0.417
water O in interactions with other waters	0.6367	3.1506	-0.834
water H in interactions with other waters	0.0000	0.0000	0.417

Different Sets of Radii

Despite sensitivity of VDW radius and r_0 parameter there is considerable disagreement!

Atom Type & Symbol		Bondi 1968	Lee & Richards 1971	Shrake & Rupley 1973	Richards 1974	Chothia 1975	Rich-mond & Richards 1978	Gelin & Karplus 1979	Dunfield et al. 1979	ENCAD derived 1995	CHARMM derived 1995	Tsai et al. 1998
$-CH_3$	Aliphatic, methyl	2.00	1.80	2.00	2.00	1.87	1.90	1.95	2.13	1.82	1.88	1.88
$-CH_2-$	Aliphatic, methyl	2.00	1.80	2.00	2.00	1.87	1.90	1.90	2.23	1.82	1.88	1.88
>CH-	Aliphatic, CH	-	1.70	2.00	2.00	1.87	1.90	1.85	2.38	1.82	1.88	1.88
=CH	Aromatic, CH	-	1.80	1.85	*	1.76	1.70	1.90	2.10	1.74	1.80	1.76
>C=	Trigonal, aromatic	1.74	1.80	*	1.70	1.76	1.70	1.80	1.85	1.74	1.80	1.61
$-NH_3+$	Amino, protonated	-	1.80	1.50	2.00	1.50	0.70	1.75		1.68	1.40	1.64
$-NH_2$	Amino or amide	1.75	1.80	1.50	-	1.65	1.70	1.70		1.68	1.40	1.64
>NH	Peptide, NH or N	1.65	1.52	1.40	1.70	1.65	1.70	1.65	1.75	1.68	1.40	1.64
=O	Carbonyl Oxygen	1.50	1.80	1.40	1.40	1.40	1.40	1.60	1.56	1.34	1.38	1.42
-OH	Alcoholic hydroxyl	-	1.80	1.40	1.60	1.40	1.40	1.70		1.54	1.53	1.46
-OM	Carboxyl Oxygen	-	1.80	1.89	1.50	1.40	1.40	1.60	1.62	1.34	1.41	1.42
-SH	Sulfhydryl	-	1.80	1.85	-	1.85	1.80	1.90		1.82	1.56	1.77
-S-	Thioether or –S-S-	1.80	-	-	1.80	1.85	1.80	1.90	2.08	1.82	1.56	1.77

Molecular Mechanics: Simple electrostatics

atom	ε (kJ/ mole)	σ (Å)	charge (electrons)
carbonyl carbon	0.5023	3.7418	0.550
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- U = kqQ/r
- Molecular mechanics uses partial unpaired charges with monopole
  - ◊ usually no dipole
  - ◊ e.g. water has apx. -.8 on O and +.4 on Hs
  - ◊ However, normally only use monopoles for unpaired charges (on charged atoms, asp O)
- Longest-range force
  - ◊ Truncation? Smoothing

	(S)tructure Pred.	(P)acking	(E)lectrostatics
Preferred Lecture			
counts			

	(1) too simple	(2) just right	(3) too complex
Level of Prediction			
counts			

	(1) too simple	(2) just right	(3) too complex
Level of Packing			
counts			

	(1) too simple	(2) just right	(3) too complex
Level of Electrostatics			
counts			

Feedback

H-bonds subsumed by electrostatic interactions

- Naturally arise from partial charges
  - ◊ normally arise from partial charge
- Linear geometry
- Were explicit springs in older models

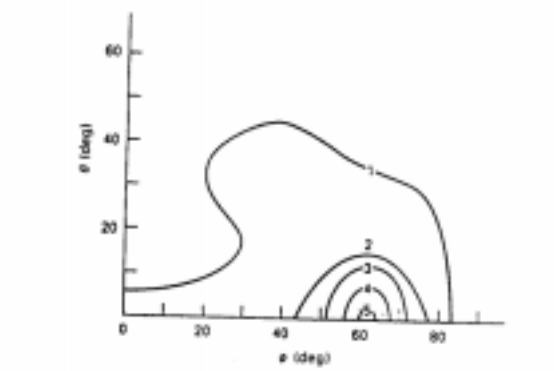


FIGURE 4.4
The geometries of C=O ··· H—N hydrogen bonds observed in crystal structures of small molecules. The definitions of the angles ϕ and θ are illustrated at the *top*, and the relative frequencies of their observed values in intermolecular hydrogen bonds (R. Taylor et al., *J. Amer. Chem. Soc.* 105:5761–5766, 1983) are given by the contours. The angle ϕ measures departures from linearity of the C=O bond and the H atom; the most frequently observed values are in the region of 50°–60°. The angle θ measures the extent to which the H atom lies out of the plane defined by the R, C, and O atoms; the most commonly observed values are in the region of 0°–7°. The lone-pair electrons of the oxygen atom are believed to project at angles of $\phi = 60°$, $\theta = 0°$. The spherical polar coordinate system used here gives a bias toward small values of θ that could be corrected by plotting $\sin\theta$.

Illustration Credit: Taylor & Kennard (1984)

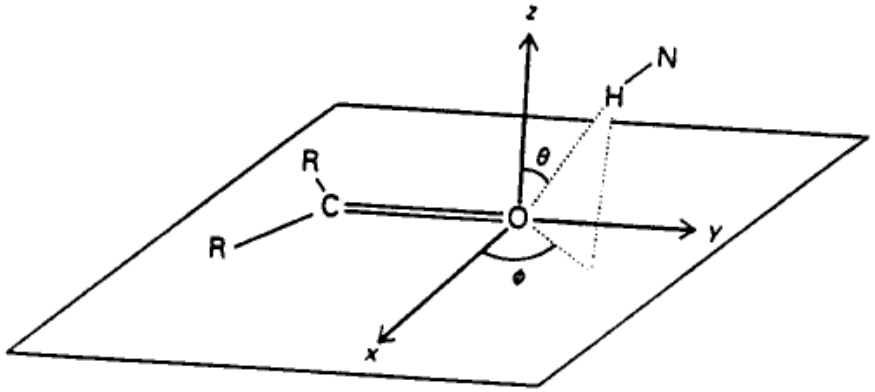


Table 4.7 Lengths of H—N ··· O=C *hydrogen bonds*[a]

Donor	Mean H ··· O Distance for Different Acceptors (Å)		
	Carboxyl[b]	Carboxylate[c]	Amide
>N—H[d]	2.002 ± 0.012	1.928 ± 0.012	1.934 ± 0.005
>N⁺—H[e]	1.983 ± 0.055	1.869 ± 0.028	1.858 ± 0.043
NH_4^+	1.916 ± 0.041	1.886 ± 0.018	1.988 ± 0.075
$R—NH_3^+$	1.936 ± 0.014	1.841 ± 0.008	1.891 ± 0.034
$R_2—NH_2^+$	1.887 ± 0.047	1.796 ± 0.014	1.793 ± 0.070
$R_3—NH^+$		1.722 ± 0.025	1.845 ± 0.014

[a] The N—H distance is generally 1.03 Å; adding this value to the tabulated distances gives the distance between the N and O atoms.

[b] C=O oxygen atom of unionized carboxylic acids and esters.

[c] Oxygen atom of carboxyl anions ($—CO_2^-$).

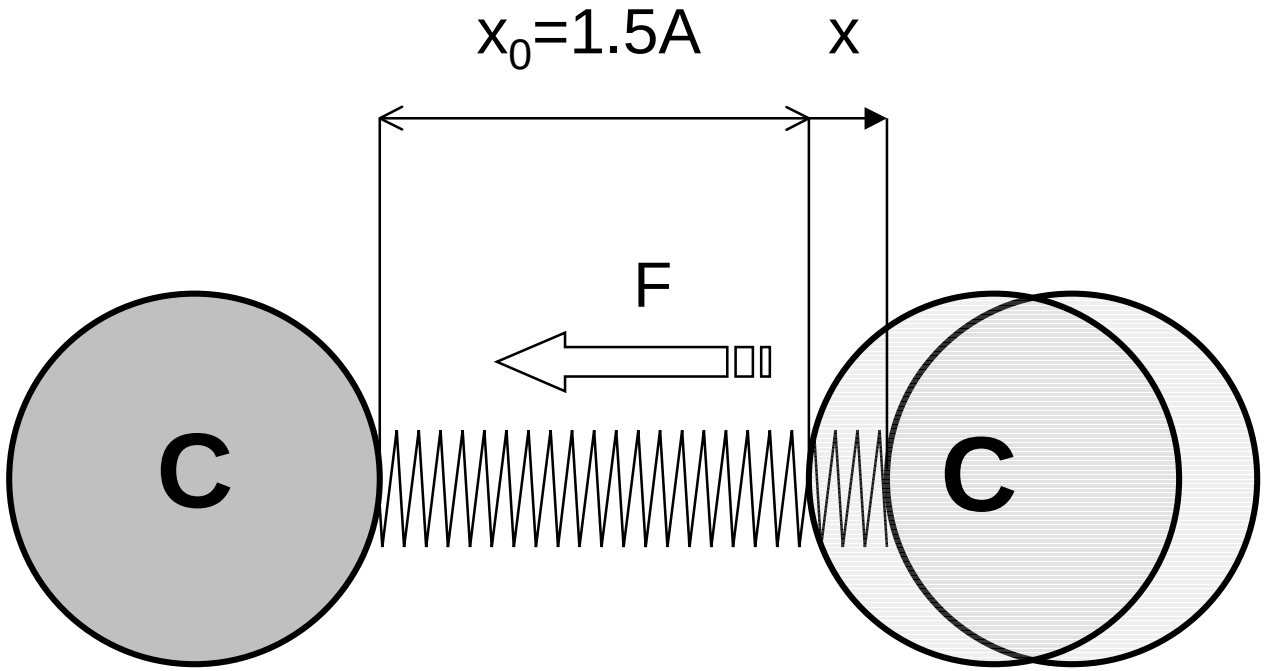
[d] Uncharged donor.

[e] Charged donor with trigonal geometry.

From R. Taylor and O. Kennard, *Acc. Chem. Res.* 17:320–326 (1984).

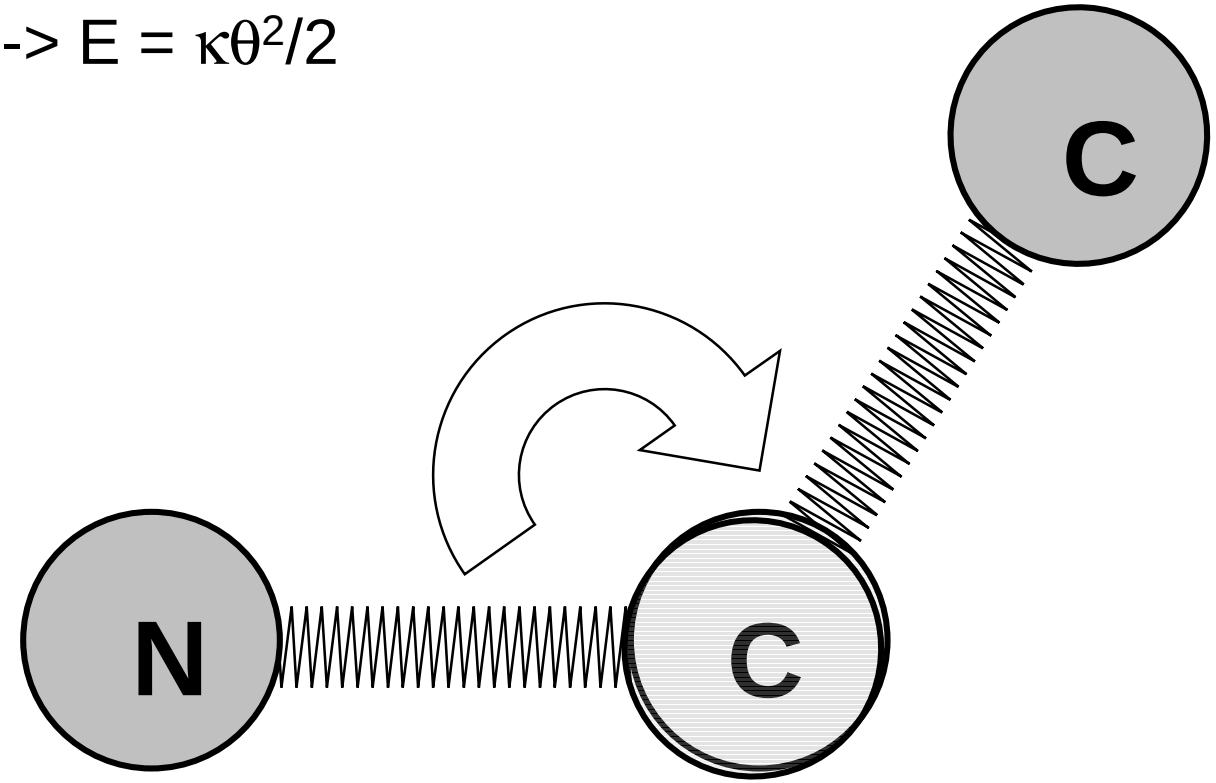
Bond Length Springs

- $F = -kx \rightarrow E = kx^2/2$
- Freq from IR spectroscopy
  - ◊ -> w= sqrt(k/m), m = mass => spring const. k
  - ◊ k ~ 500 kcal/mole*A^2 (stiff!), w corresponds to a period of 10 fs
- Bond length have 2-centers



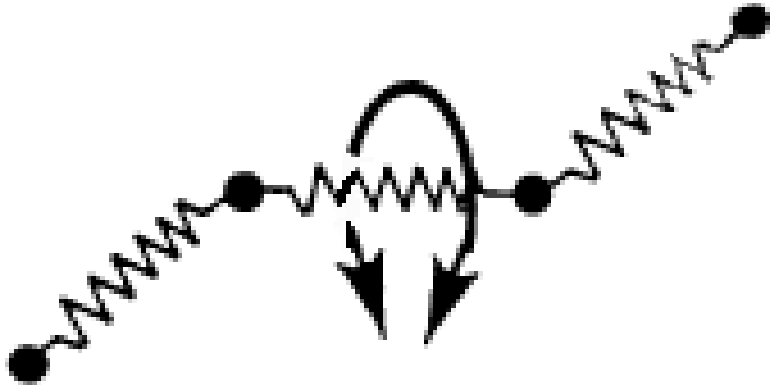
Bond angle, More Springs

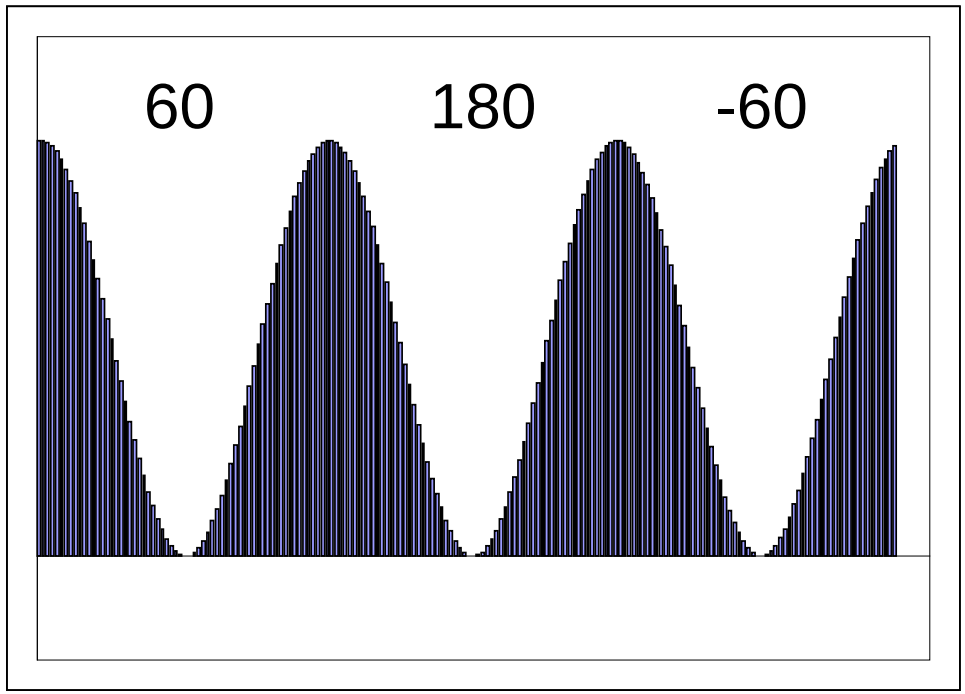
- torque = $\tau = \kappa\theta$ -> $E = \kappa\theta^2/2$
- 3-centers



Torsion angle

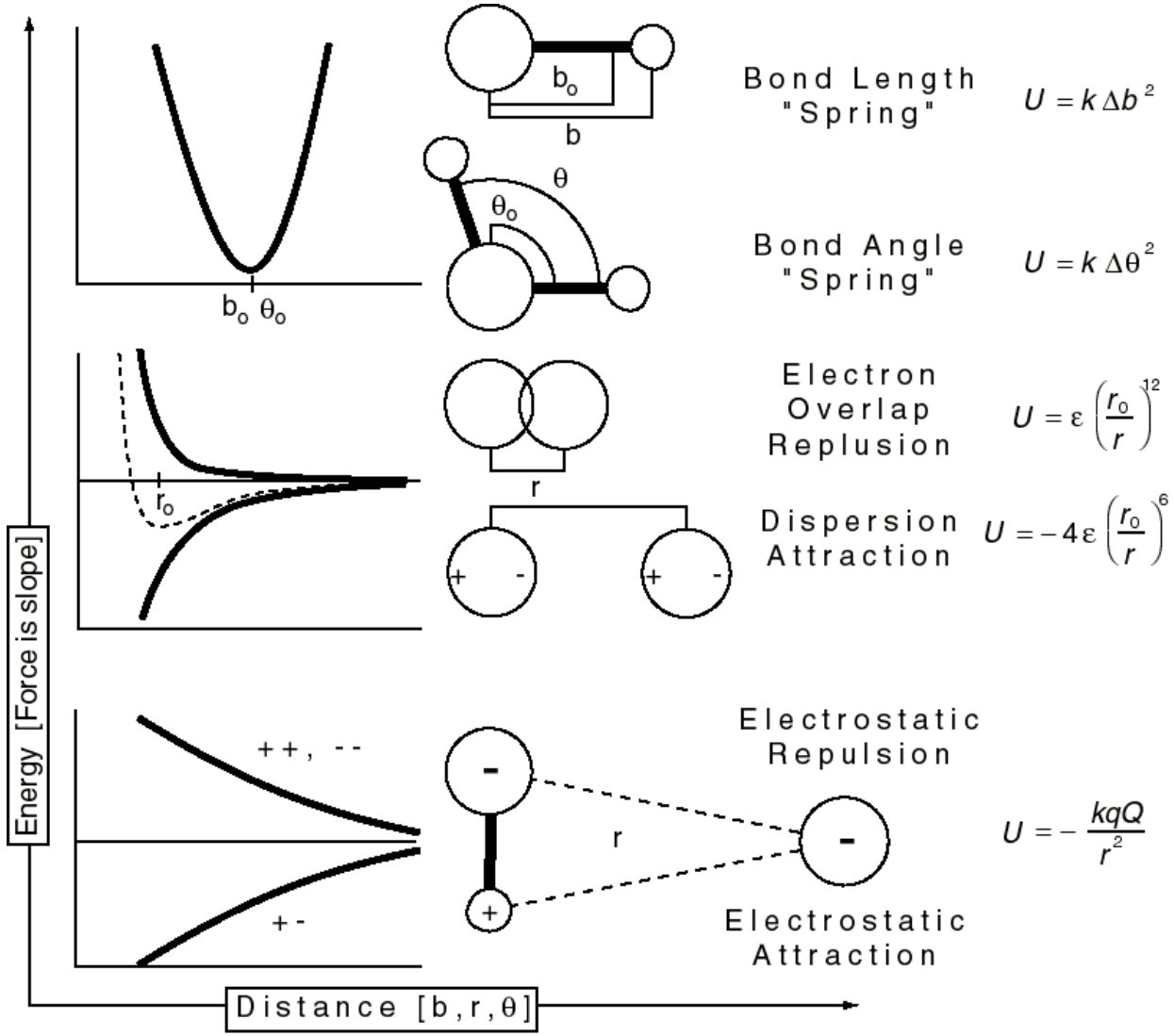
- 4-centers
- U(A)=K(1-cos(nA+d))
  - ◊ cos x = 1 + $x^2/2$ + ... , so minima are quite spring like, but one can hoop between barriers
- K ~ 2 kcal/mole





Potential Functions

- Putting it all together
- Springs + Electrical Forces



Sum up to get total energy

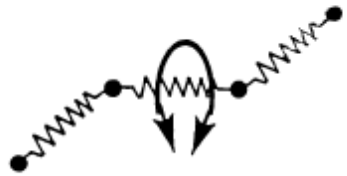
- Each atom is a point mass (m and **x**)
- Sometimes special pseudo-forces: torsions and improper torsions, H-bonds, symmetry.

$$E_{empirical} =$$

$$\sum_{bonds} k_o(b - b_o)^2$$

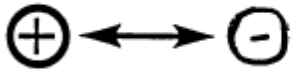
$$+ \sum_{angles} k_\Phi(\Phi - \Phi_o)^2$$

$$+ \sum_{dihedrals} k_\Psi \cos(n\Psi + \delta)$$

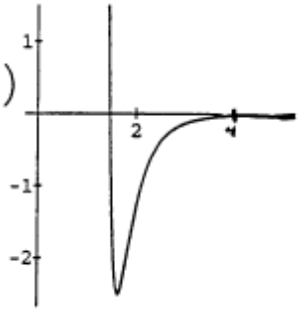


$$+ \sum_{chiral,planar\ centers} k_\omega(\omega - \omega_o)^2$$

$$+ \sum_{non-bonded} (Qr^{-1} + Ar^{-12} - Br^{-6})$$



$$+ \sum_{symmetry\ non-bonded} (Qr^{-1} + Ar^{-12} - Br^{-6})$$



Energy Scale of Interactions

THE SCALE OF INTERACTIONS

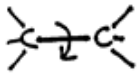
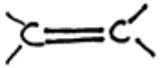
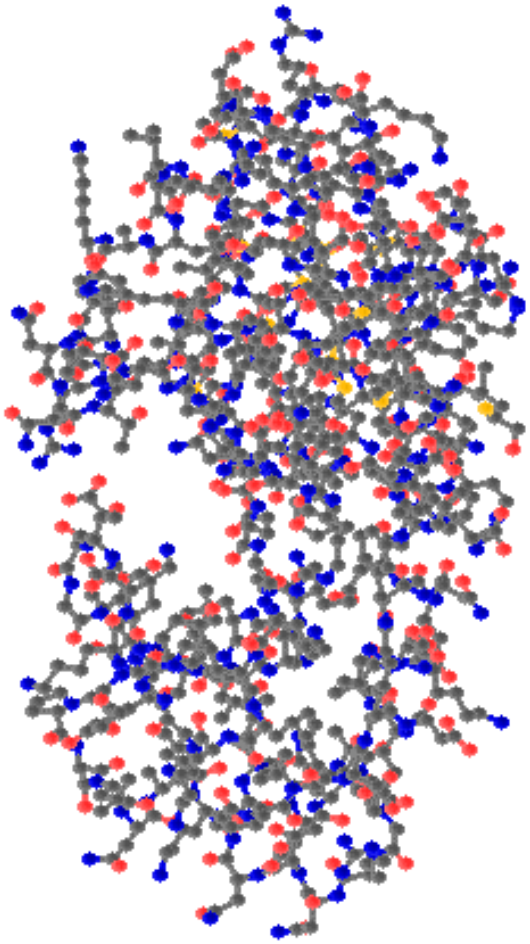
Interaction	Energy (kcal/mole)	
van der Waals in water	−0.1	
van der Waals in vacuo	−0.3	
Hydrogen bond in water	−1.0	
Hydrogen bond in vacuo	−5.0	
Torsion barrier about single bond	+3.0	
Torsion barrier about double bond	+20	
Barrier to breaking a bond	+100	C—C
Energy to change a bond angle by 10°	+2	
Energy to stretch a bond length by 0.1 Å	+2.5	C—C →
Thermal energy at 300°K	0.6	kT

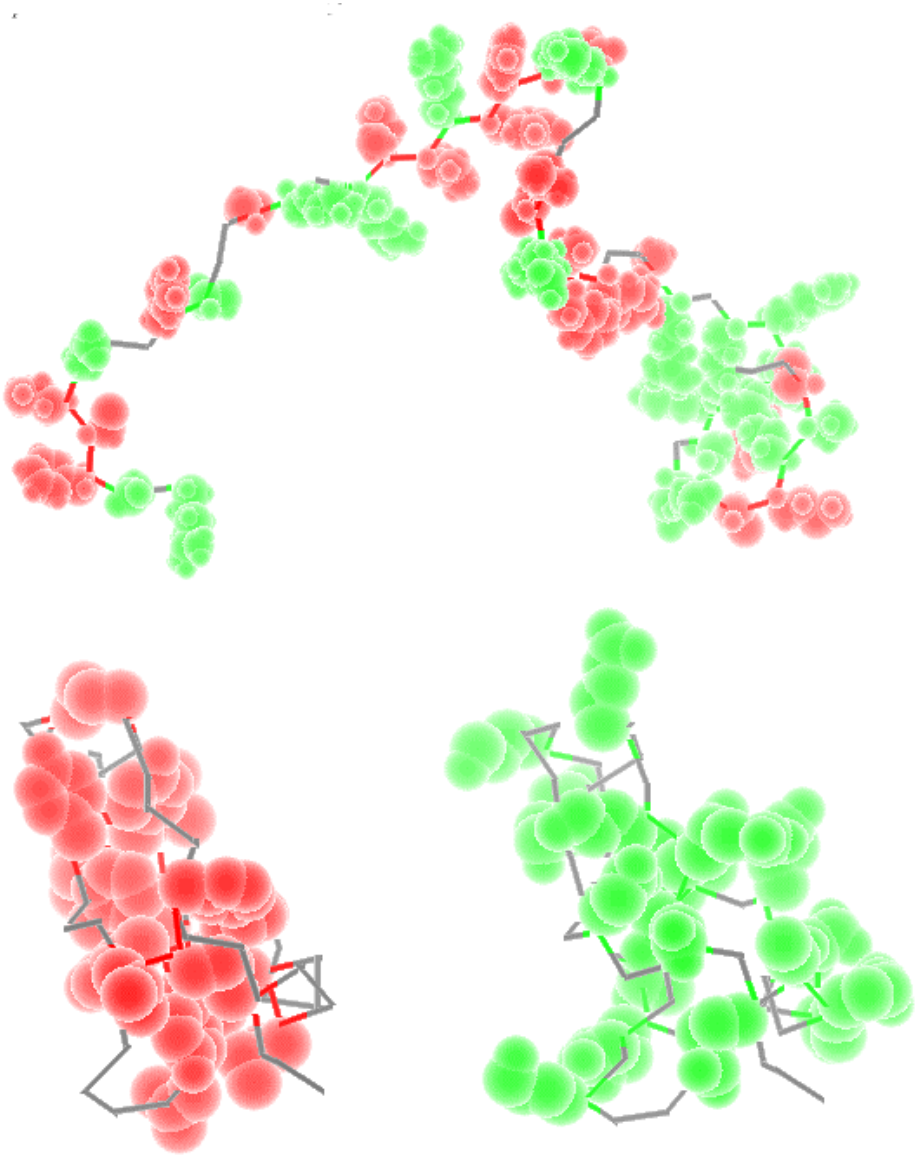
Illustration Credit: M Levitt

Elaboration on the Basic Protein Model

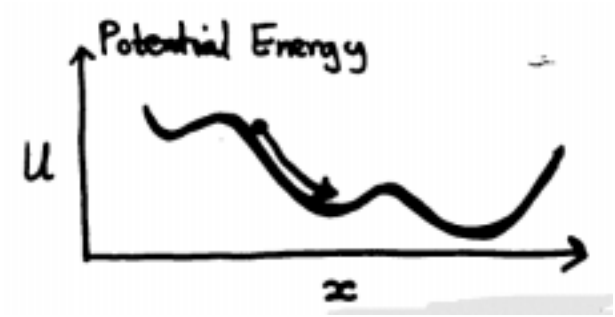
- Geometry
  - ◊ Start with X, Y, Z's (coordinates)
  - ◊ Derive Distance, Surface Area, Volume, Axes, Angle, &c
- Energetics
  - ◊ Add Q's and k's (Charges for electrical forces, Force Constants for springs)
  - ◊ Derive Potential Function U(x)
- Dynamics
  - ◊ Add m's and t (mass and time)
  - ◊ Derive Dynamics (v=dx/dt, F = m dv/dt)



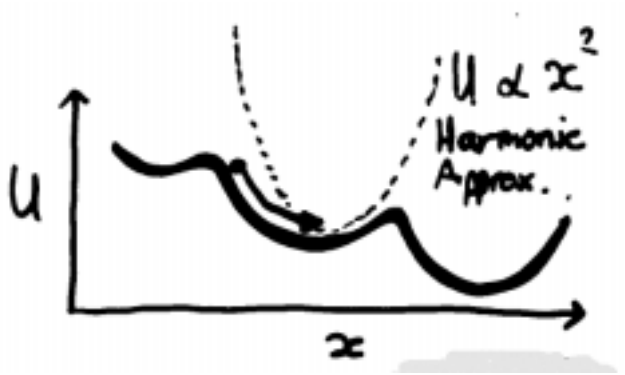
Goal: Model Proteins and Nucleic Acids as Real Physical Molecules



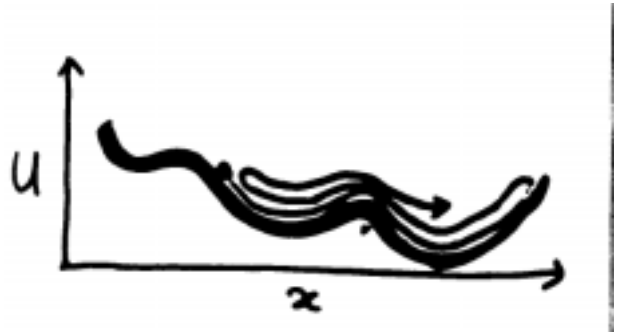
Ways to Move Protein on its Energy Surface



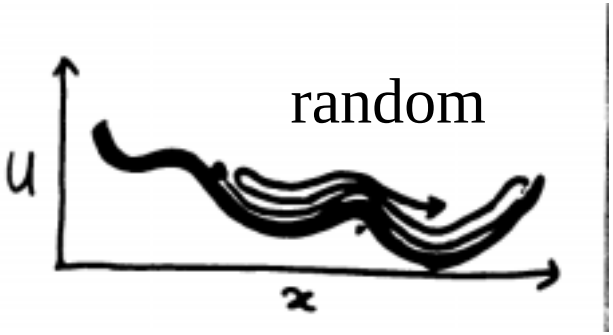
Minimization



Normal Mode Analysis (later?)



Molecular Dynamics (MD)

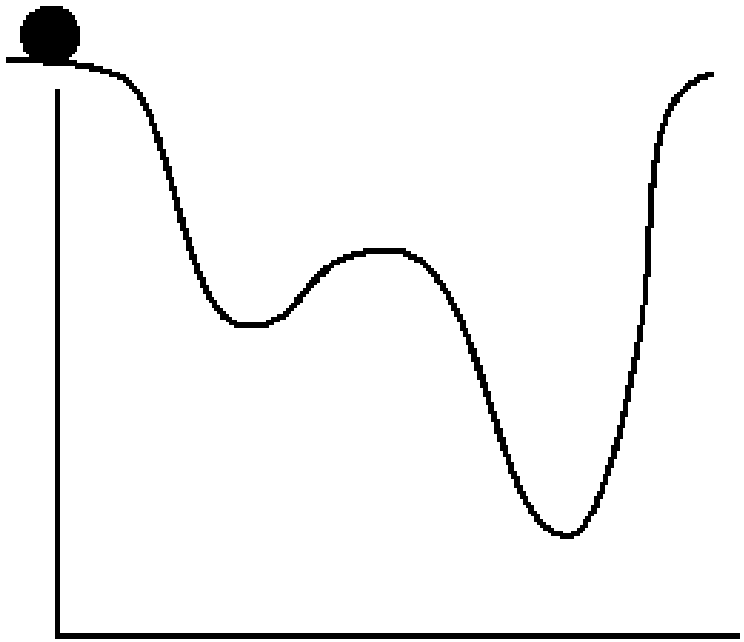


Monte Carlo (MC)

Illustration Credit: M Levitt

Steepest Descent Minimization

- Particles on an “energy landscape.” Search for minimum energy configuration
  - ◊ Get stuck in local minima
- Steepest descent minimization
  - ◊ Follow gradient of energy straight downhill
  - ◊ i.e. Follow the force:
    step ~ **F** = -∇ U
    so
    x(t) = **x**(t-1) + a **F**/|**F**|



Multi-dimensional Minimization

- In many dimensions, minimize along lines one at a time
- Ex: $U = x^2+5y^2$, $F = (2x,10y)$

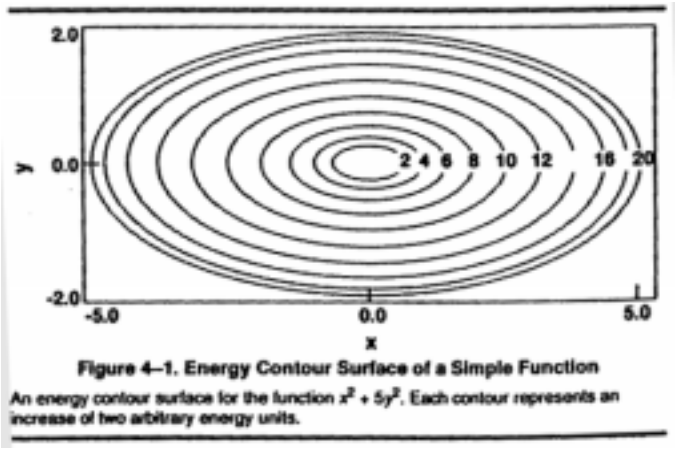


Figure 4–1. Energy Contour Surface of a Simple Function

An energy contour surface for the function $x^2 + 5y^2$. Each contour represents an increase of two arbitrary energy units.

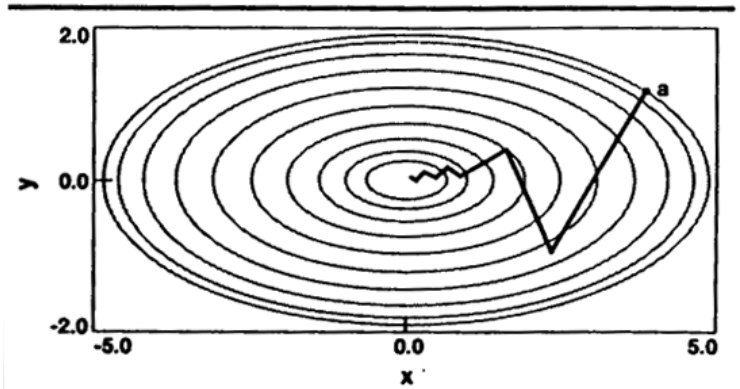


Figure 4–5. Minimization Path following a Steepest-Descents Path without Line Searches

The searching starts from point a and converges on the minimum in about 12 iterations. Although the number of iterations is slightly larger than in Figure 4–4, the total minimization is five times faster since, on average, each iteration used only 1.3 function evaluations. Note that, in most applications in molecular mechanics, the function evaluation is the most time-consuming portion of the calculation.

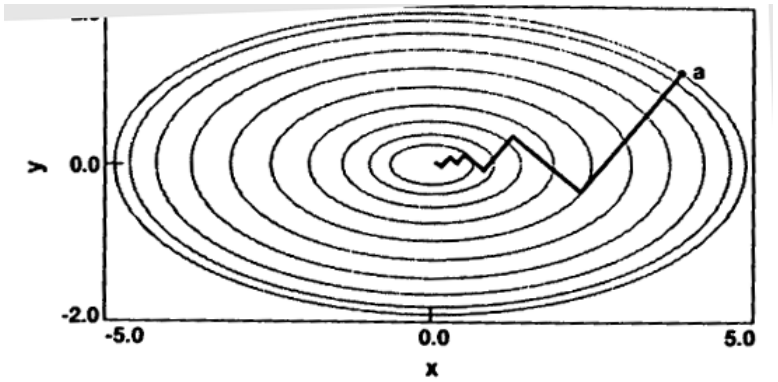


Figure 4–4. Minimization Path following a Steepest-Descents Path

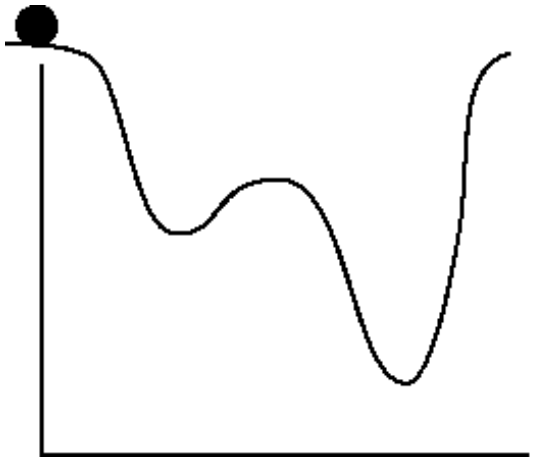
When complete line searches starting from point a are used, the minimum is reached in about 12 iterations. Here, where a rigorous line search is carried out, approximately 8 function evaluations are needed for each line search using a quadratic interpolation scheme. Note how steepest descents consistently overshoots the best path to the minimum, resulting in an inefficient, oscillating trajectory.

Illustration Credit: Biosym, discover manual

Other Minimization Methods

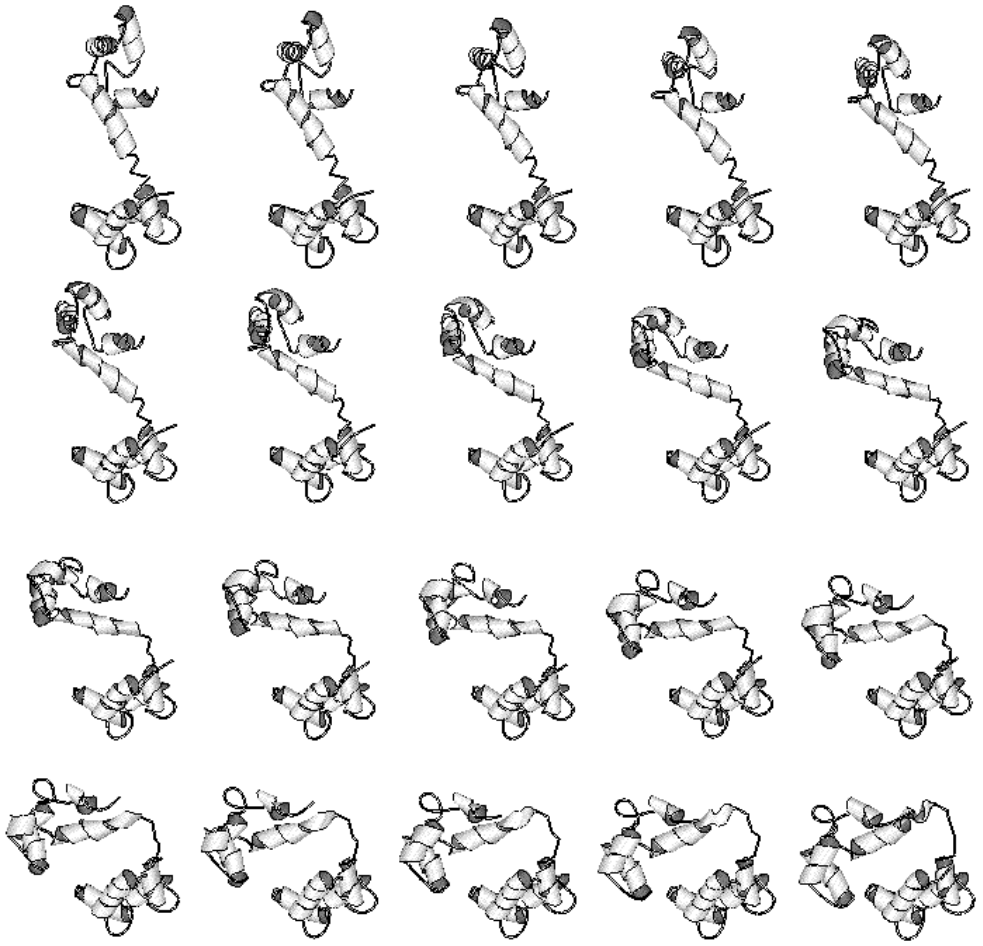
- Simplex, grid search
  - ◊ no derivatives
- Conjugate gradient
  step ~ F(t) **-** b**F**(t-1)
  - ◊ partial 2nd derivative
- Newton-Raphson
  - ◊ using 2nd derivative, find minimum assuming it is parabolic
  - ◊ V = ax2 + bx + c
  - ◊ V' =2ax + b & V'' =2a
  - ◊ V' =0 -> x* = -b/2a

- Problem is that get stuck in local minima
- Steepest descent, least clever but robust, slow at end
- Newton-Raphson faster but 2nd deriv. can be fooled by harmonic assumption
- Recipe: steepest descent 1st, then Newton-raph. (or conj. grad.)



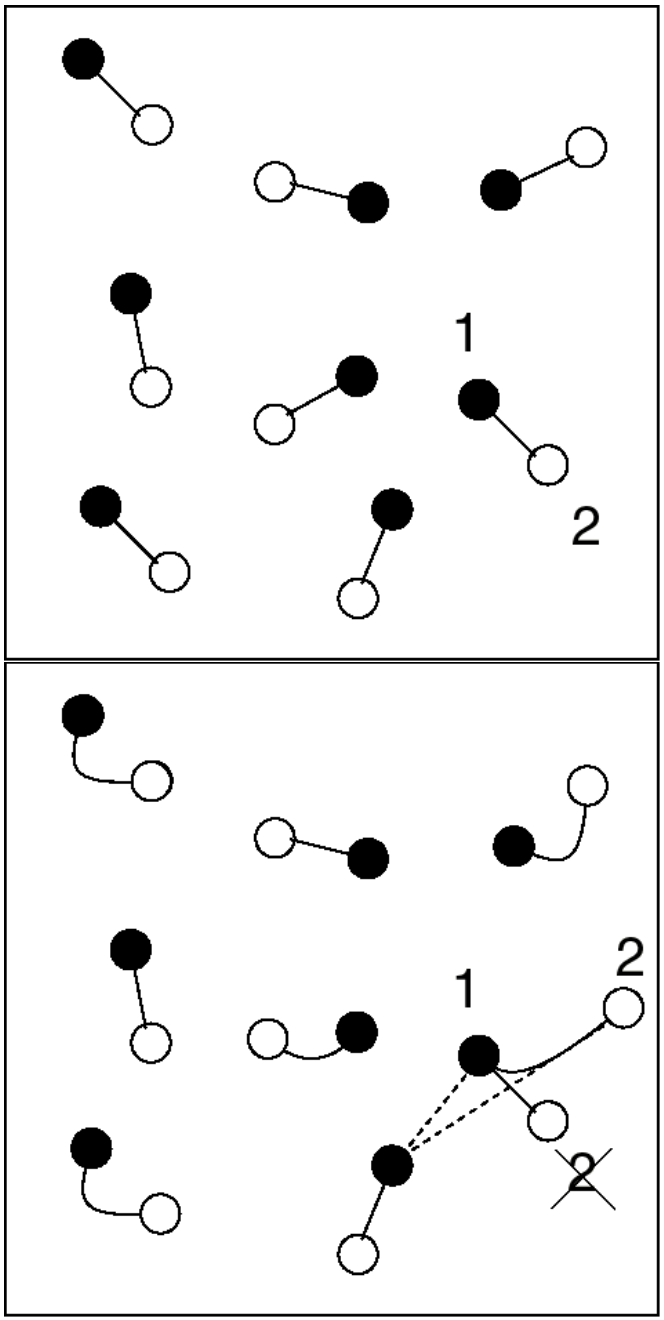
Adiabatic mapping

- Interpolate then minimize
  - ◊ Gives apx. energy (H) landscape through a barrier
  - ◊ can sort of estimate transition rate
    rate = (kT/h) exp (-dG/kT)
  - ◊ Used for ring flips, hinge motions



Molecular Dynamics

- Give each atoms a velocity.
  - ◊ If no forces, new position of atom (at t + dt) would be determined only by velocity
    x(t+dt) = **x**(t) + **v** dt
- Forces change the velocity, complicating things immensely
  - ◊ **F** = d**p**/**dt** = m d**v**/dt



Molecular Dynamics (cont)

- On computer make very small steps so force is nearly constant and velocity change can be calculated (uniform a)

$$\Delta \mathbf{v} = \frac{\mathbf{F}}{m} \Delta t$$

[Avg. **v** over Δt] = (**v** + Δ**v**/2)

- Trivial to update positions:

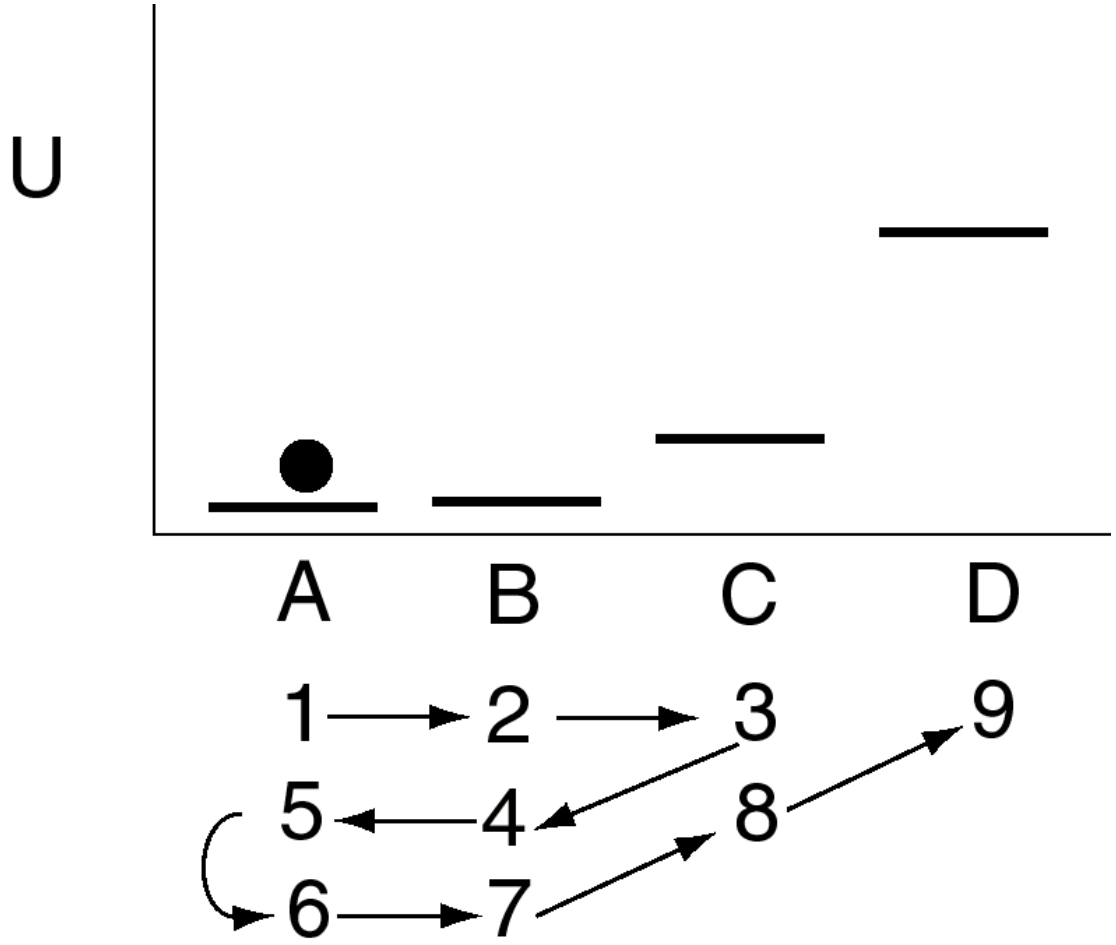
$$\mathbf{x}(t + \Delta t) = \mathbf{x}(t) + (\mathbf{v} + \frac{\Delta \mathbf{v}}{2}) \Delta t$$

$$= \mathbf{x}(t) + \mathbf{v} \Delta t + \frac{\mathbf{F}}{2m} \Delta t^2$$

- Step must be very small
  - ◊ Δt ~ 1fs (atom moves 1/500 of its diameter)
  - ◊ This is why you need fast computers
- Actual integration schemes slightly more complicated
  - ◊ Verlet (explicit half-step)
  - ◊ Beeman, Gear (higher order terms than acceleration)

Phase Space Walk

- Trajectories of all the particles traverses space of all possible configuration and velocity states (phase space)
- Ergodic Assumption:
  Eventually, trajectory visits every state in phase space
- Boltzmann weighting:
  Throughout, trajectory samples states fairly in terms of system's energy levels
  - ◊ More time in low-U than high-U states
  - ◊ Probability of being in a state ~ exp(-U/kT)
- Consequently, statistics (average properties) over trajectory are thermodynamically correct



Example Phase Space Walk

$$\langle X \rangle = 3X_A + 3X_B + 2X_A + 1X_D$$

$$\langle U \rangle = 6U_{AB} + 2U_A + 1U_D$$

Monte Carlo

- Other ways than MD to sample states fairly and compute correctly weighted averages? Yes, using Monte Carlo calculations.
- Basic Idea:
  Move through states randomly, accepting or rejecting them so one gets a correct "Boltzmann weighting"

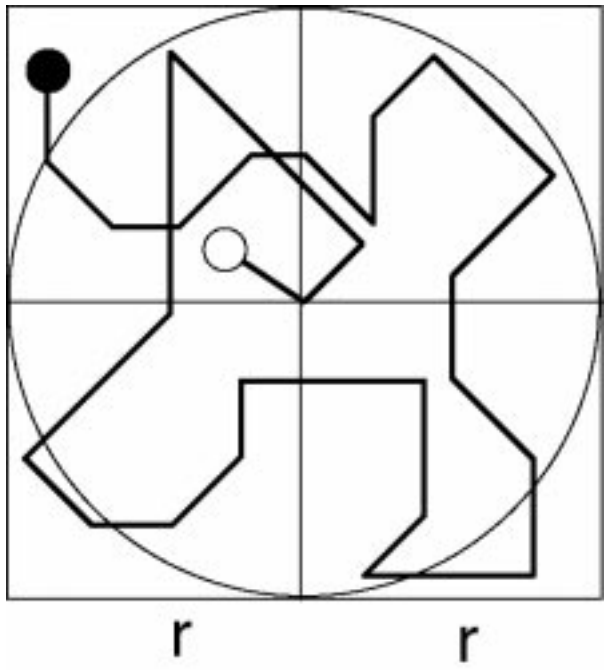
- Formalism:
  - ◊ System described by a probability distribution ρ(n) for it to be in each state n
  - ◊ Random ("Markov") process π operates on the system and changes distribution amongst states to πρ(n)
  - ◊ At equilbrium original distribution and new distribution have to be same as Boltzmann distribution

$$\pi\rho(n) = \rho(n) = \frac{1}{Z}\exp\left(\frac{-U(n)}{kT}\right)$$

Monte Carlo (cont)

- Metropolis Rule (for specifying π)
  1. Make a random move to a particle and calculate the energy change dU
  2. dU < 0 –> accept the move
  3. Otherwise, compute a random number R between 0 and 1:
     R < ~ exp(-U/kT) –>
     accept the move
     otherwise –>
     reject the move

- "Fun" example of MC Integration
  - ◊ Particle in empty box of side 2r (energy of all states same)
  - ◊ π = 6 x [Fraction of times particles is within r of center]



MC vs/+ MD

- MD usually used for proteins. Difficult to make moves with complicated chain.
- MC often used for liquids. Can be made into a very efficient sampler.
- Hybrid approaches (Brownian dynamics)
- Simulated Annealing. Heat simulation up to high T then gradually cool and minimize to find global minimum.

Moving Molecules Rigidly

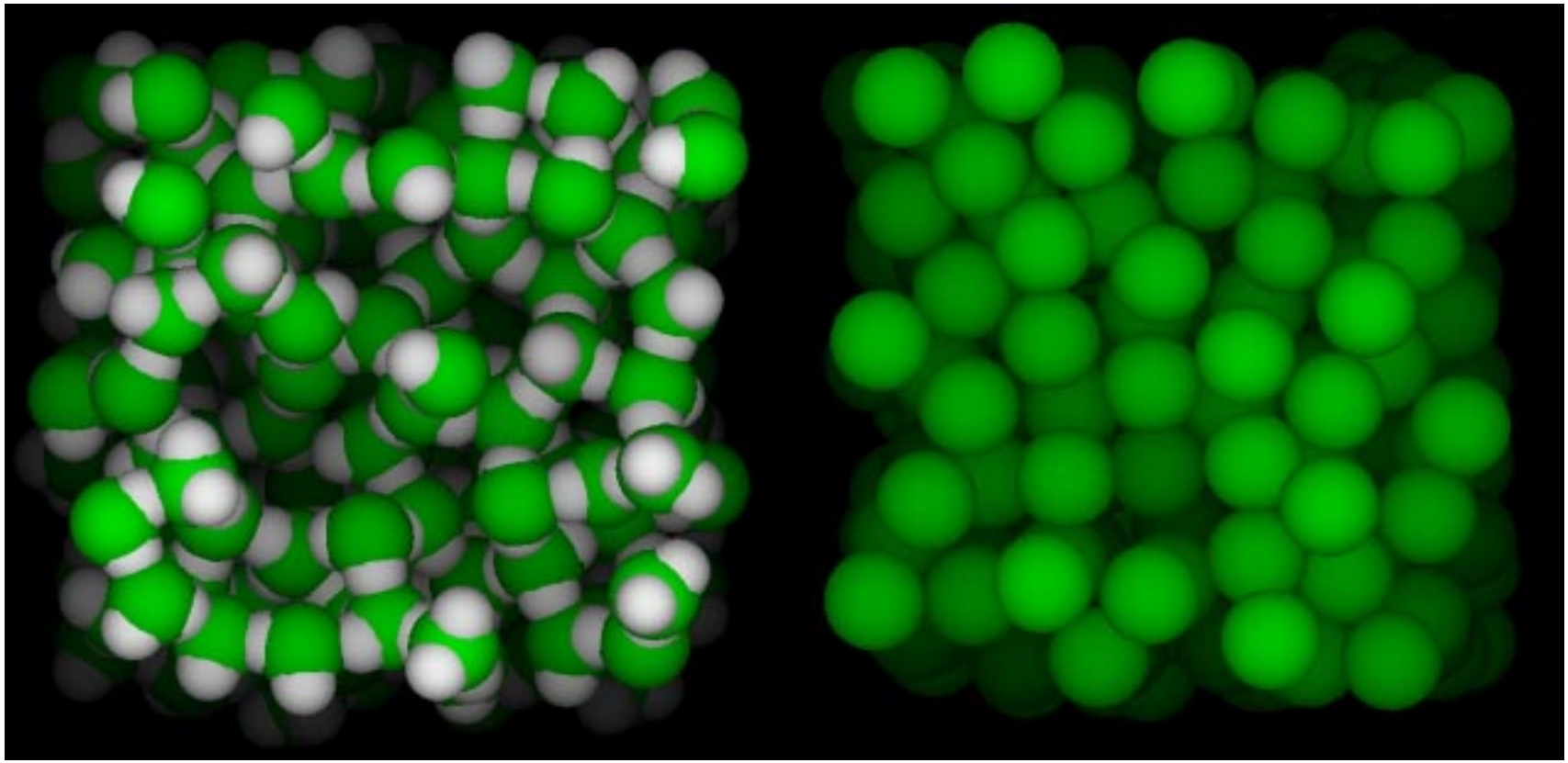
- $\mathbf{X_i}(t+1) = (x_i(t),y_i(t),z_i(t))$ = coordinates of ith atom in the molecule at timestep t
- Rigid-body Translation of all i atoms
  - ◊ For each atom atom i do $\mathbf{x}_i(t+1) = \mathbf{x}_i(t) + \mathbf{v}$

- Rigid-body Rotation of all i atoms
  - ◊ For each atom atom i do $\mathbf{x}_i(t+1) = \mathbf{R}(\phi,\theta,\psi)\ \mathbf{x}_i(t)$
  - ◊ Effectively do a rotation around each axis (x, y, z) by angles ϕ,θ,ψ (see below)
  - ◊ Many conventions for doing this
    - **BELOW IS ONLY FOR MOTIVATION**
    - Consult Allen & Tildesley (1987) or Goldstein for the formulation of the rotation matrix using the usual conventions
  - ◊ How does one do a random rotation? Trickier than it seems

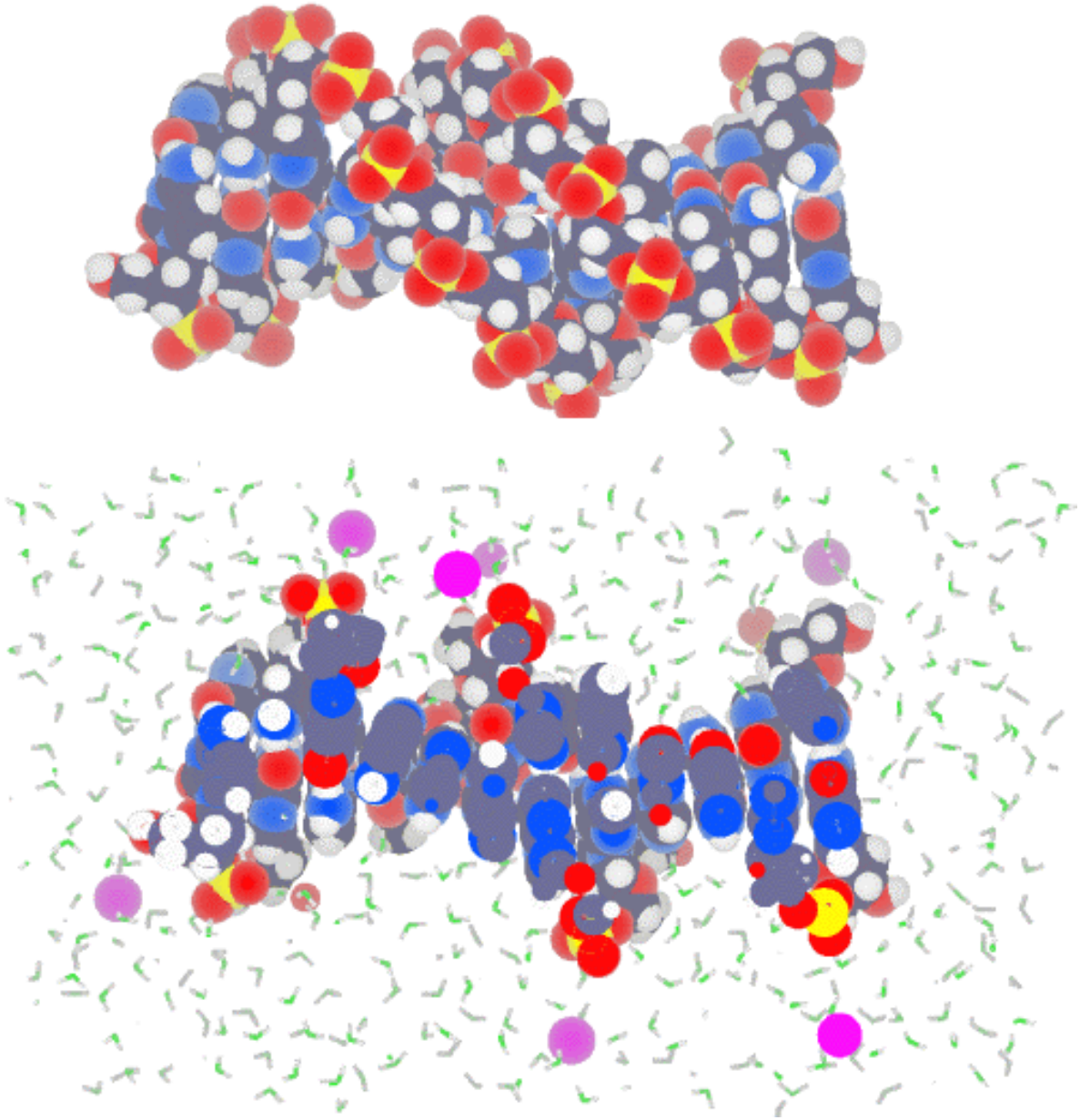
$$\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

$$\begin{pmatrix} x' \\ y' \\ z' \end{pmatrix} = \underbrace{\begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}}_{\text{Finally, rotate by } \theta \text{ around z axis}} \underbrace{\begin{pmatrix} \cos\phi & 0 & -\sin\phi \\ 0 & 1 & 0 \\ \sin\phi & 0 & \cos\phi \end{pmatrix}}_{\text{Second, rotate by } \phi \text{ around y axis}} \underbrace{\begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos\psi & -\sin\psi \\ 0 & \sin\psi & \cos\psi \end{pmatrix}}_{\text{First, rotate by } \psi \text{ around x axis}} \begin{pmatrix} x \\ y \\ z \end{pmatrix}$$

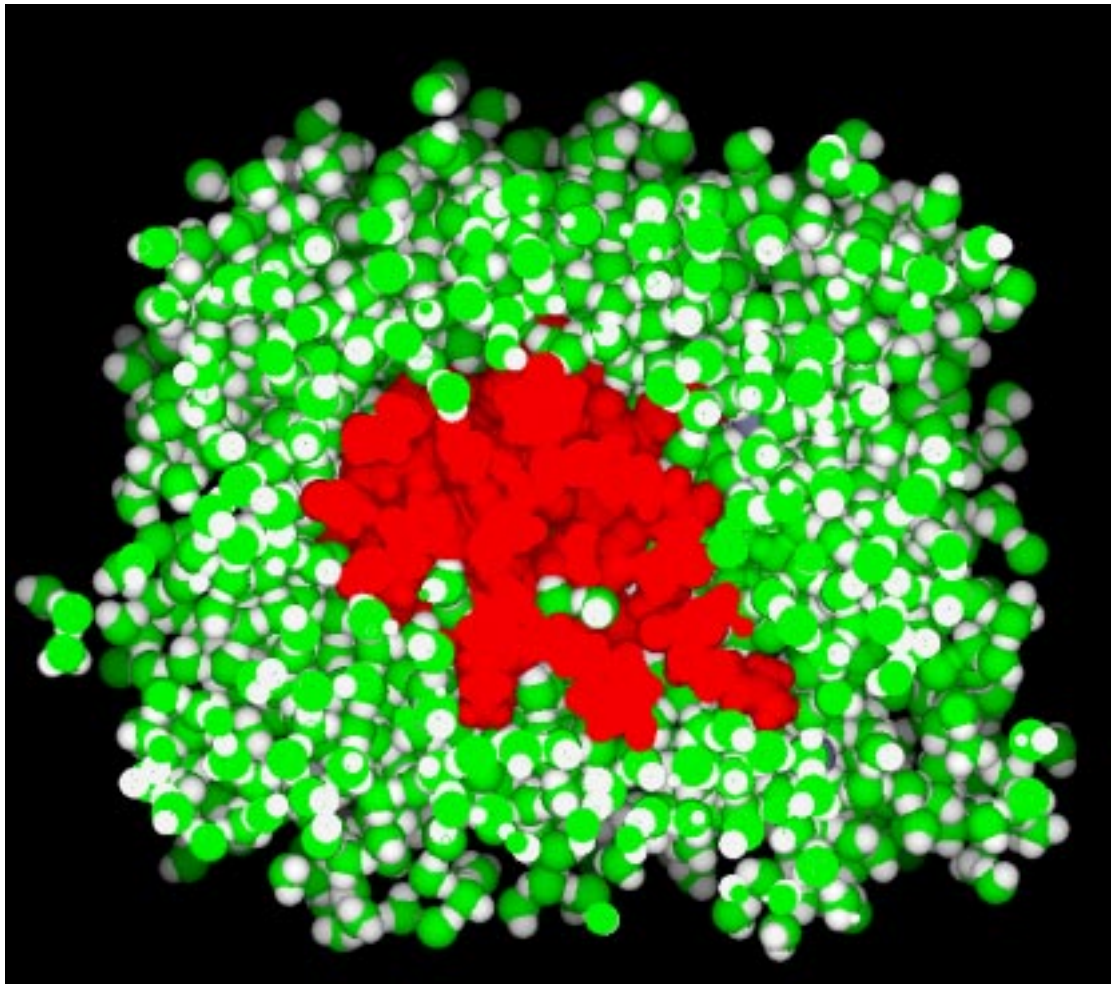
Typical Systems: Water v. Argon



Typical Systems: DNA + Water



Typical Systems: Protein + Water



Practical Aspects: simulation cycle I

- Divide atoms into types (e.g. alpha carbon except for Gly, carbonyl oxygen)
- Initially
  - ◊ Associate each atom with a mass and a point charge
  - ◊ Give each atom an initial velocity
- Calculate Potential
- Calculating non-bonded interactions take up all the time
  - ◊ Electrostatics hardest since longest ranged
  - ◊ Neighbor lists

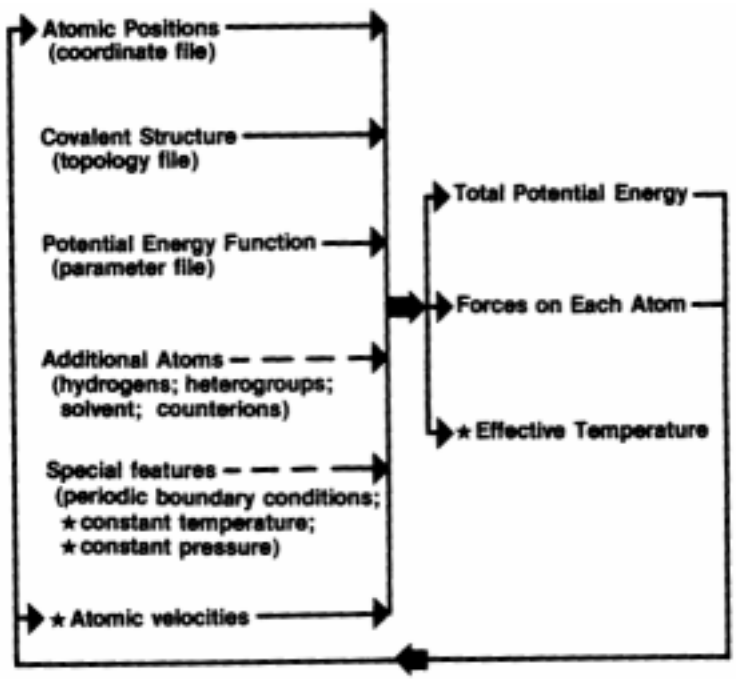


Fig. 4.1. Schematic flow chart of algorithms for energy minimization and molecular dynamics. Features which apply only to molecular dynamics are indicated by asterisks. Dashed lines indicate optional input. Each cycle of energy minimization represents a step in conformation space, while each cycle of molecular dynamics represents a step in time.

Illustration Credit: McCammon & Harvey (1987)

Practical Aspects: simulation cycle II

- Update Positions with MD equations, then recalculate potential and continue
- Momentum conservation
- Energy Conserved in NVE ensemble
- Hydrophobic interaction naturally arises from water behavior

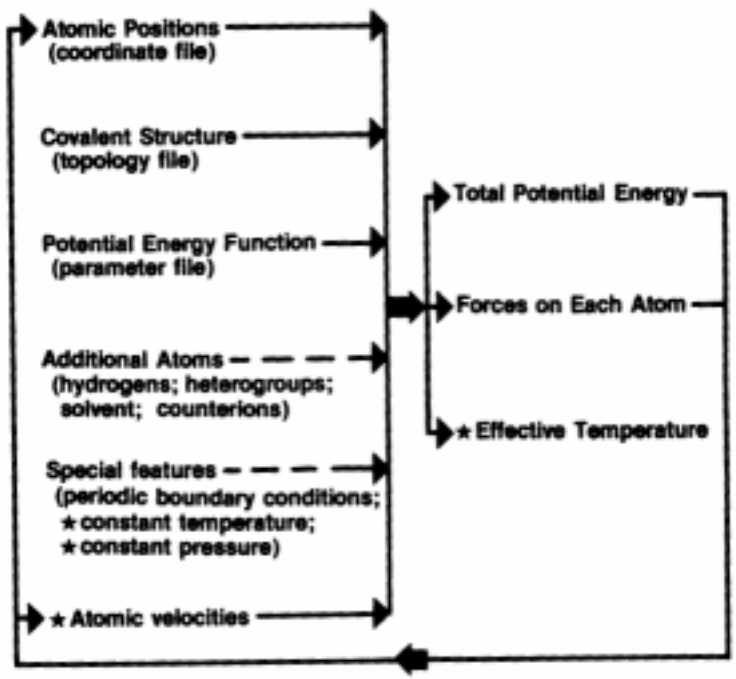


Fig. 4.1. Schematic flow chart of algorithms for energy minimization and molecular dynamics. Features which apply only to molecular dynamics are indicated by asterisks. Dashed lines indicate optional input. Each cycle of energy minimization represents a step in conformation space, while each cycle of molecular dynamics represents a step in time.

Illustration Credit: McCammon & Harvey (1987)

Sample Protein Parameters (toph19.pro)

```
REMARKS TOPH19.PRO ( protein topology )
REMARKS ==============================
REMARKS Charges and atom order modified for neutral GROUPs.
REMARKS Histidine charges set to Del Bene and Cohen sto-3g calculations
REMARKS Amide charges set to match the experimental dipole moment.
REMARKS Default for HIStidines is the doubly protonated state

set echo=false end
!! for use with PARAM19 parameters ( no special hydrogen bonding potential )
!! donor and acceptor terms just for analysis

AUTOGENERATE  ANGLES=TRUE  END
{*===========================*}

{* protein default masses *}
MASS   H      1.00800! hydrogen which can h-bond to neutral atom
MASS   HC     1.00800!    ="=     ="=     ="=    to charged atom
MASS   HA     1.00800! aliphatic hydrogen
MASS   CT    12.01100! aliphatic carbon
MASS   C     12.01100! carbonyl carbon
MASS   CH1E  13.01900! extended atom carbon with one hydrogen
MASS   CH2E  14.02700!    ="=      ="=     ="=   two hydrogens
MASS   CH3E  15.03500!    ="=      ="=     ="=   three hydrogens
MASS   CR1E  13.01900!    ="=      ="=      in an aromatic ring with one H
MASS   N     14.00670! peptide nitrogen with no hydrogens attached
MASS   NR    14.00670! nitrogen in an aromatic ring with no hydrogens
MASS   NP    14.00670! pyrole nitrogen
MASS   NH1   14.00670! peptide nitrogen bound to one hydrogen
MASS   NH2   14.00670!    ="=       ="=      ="= two hydrogens
MASS   NH3   14.00670! nitrogen bound to three hydrogens
MASS   NC2   14.00670! charged guandinium nitrogen bound to two hydrogens
MASS   O     15.99940! carbonyl oxygen
MASS   OC    15.99940! carboxy oxygen
MASS   OH1   15.99940! hydroxy oxygen
MASS   S     32.06000! sulphur
MASS   SH1E  33.06800! extended atom sulfur with one hydrogen

!some empirical rules for the following topologies:
!
```

Sample Protein Parameters (toph19.pro)

```
. RESIdue ALA
 GROUp
  ATOM N    TYPE=NH1   CHARge=-0.35   END
  ATOM H    TYPE=H     CHARge= 0.25   END
  ATOM CA   TYPE=CH1E  CHARge= 0.10   END
 GROUp
  ATOM CB   TYPE=CH3E  CHARge= 0.00   END
 GROUp
  ATOM C    TYPE=C     CHARge= 0.55   END  !#
  ATOM O    TYPE=O     CHARge=-0.55   END  !#

 BOND N    CA
 BOND CA   C
 BOND C    O
 BOND N    H
 BOND CA   CB

 IMPRoper  CA     N    C  CB  !tetrahedral CA

 DONOr H    N
 ACCEptor O C

 IC   N    C    *CA  CB     0.0000    0.00  120.00    0.00   0.0000

END {ALA}

!---------------------------------------------------------------------

RESIdue ARG
 GROUp
  ATOM N     TYPE=NH1   CHARge=-0.35   END
  ATOM H     TYPE=H     CHARge= 0.25   END
  ATOM CA    TYPE=CH1E  CHARge= 0.10   END
 GROUp
  ATOM CB    TYPE=CH2E  CHARge= 0.00   END
  ATOM CG    TYPE=CH2E  CHARge= 0.00   END
 GROUp
  ATOM CD    TYPE=CH2E  CHARge= 0.10   END  !#
  ATOM NE    TYPE=NH1   CHARge=-0.40   END  !#
```

Sample Protein Parameters (param19.pro)

```
remark - parameter file PARAM19 -

bond C    C      450.0  1.38!  B. R. GELIN THESIS AMIDE AND DIPEPTIDES
bond C    CH1E   405.0  1.52!  EXCEPT WHERE NOTED.  CH1E,CH2E,CH3E, AND CT
bond C    CH2E   405.0  1.52!  ALL TREATED THE SAME. UREY BRADLEY TERMS ADDED
bond C    CH3E   405.0  1.52
bond C    CR1E   450.0  1.38
bond C    CT     405.0  1.53
bond C    N      471.0  1.33
bond C    NC2    400.0  1.33!  BOND LENGTH FROM PARMFIX9 FORCE K APPROXIMATE
bond C    NH1    471.0  1.33
bond C    NH2    471.0  1.33
bond C    NP     471.0  1.33
bond C    NR     471.0  1.33
bond C    O      580.0  1.23
bond C    OC     580.0  1.23!  FORCE DECREASE AND LENGTH INCREASE FROM C O
bond C    OH1    450.0  1.38!  FROM PARMFIX9 (NO VALUE IN GELIN THESIS)
bond C    OS     292.0  1.43!  FROM DEP NORMAL MODE FIT
bond CH1E CH1E   225.0  1.53
bond CH1E CH2E   225.0  1.52
bond CH1E CH3E   225.0  1.52
bond CH1E N      422.0  1.45
bond CH1E NH1    422.0  1.45
bond CH1E NH2    422.0  1.45
bond CH1E NH3    422.0  1.45
bond CH1E OH1    400.0  1.42!  FROM PARMFIX9 (NO VALUE IN GELIN THESIS)
bond CH2E CH2E   225.0  1.52
bond CH2E CH3E   225.0  1.54
bond CH2E CR1E   250.0  1.45!  FROM WARSHEL AND KARPLUS 1972 JACS 96:5612
bond CH2E N      422.0  1.45
bond CH2E NH1    422.0  1.45
bond CH2E NH2    422.0  1.45
bond CH2E NH3    422.0  1.45
bond CH2E OH1    400.0  1.42
bond CH2E S      450.0  1.81!  FROM PARMFIX9
bond CH2E SH1E   450.0  1.81
bond CH2E NH1    422.0  1.42
```

Sample Protein Parameters (param19.pro)

```
angle C    C    C       70.0 106.5!  FROM B. R. GELIN THESIS WITH HARMONIC
angle C    C    CH2E    65.0 126.5!  PART OF F TERMS INCORPORATED. ATOMS
angle C    C    CH3E    65.0 126.5!  WITH EXTENDED H COMPENSATED FOR LACK
angle C    C    CR1E    70.0 122.5!  OF H ANGLES.
angle C    C    CT      70.0 126.5
angle C    C    HA      40.0 120.0!  AMIDE PARAMETERS FIT BY LEAST SQUARES
angle C    C    NH1     65.0 109.0!  TO N-METHYL ACETAMIDE VIBRATIONS.
angle C    C    NP      65.0 112.5!  MINIMIZATION OF N-METHYL ACETAMIDE.
angle C    C    NR      65.0 112.5
angle C    C    OH1     65.0 119.0
angle C    C    O       65.0 119.0 ! FOR NETROPSIN
angle CH1E C    N       20.0 117.5
angle CH1E C    NH1     20.0 117.5
angle CH1E C    O       85.0 121.5
angle CH1E C    OC      85.0 117.5
angle CH1E C    OH1     85.0 120.0
angle CH2E C    CR1E    70.0 121.5
angle CH2E C    N       20.0 117.5
angle CH2E C    NH1     20.0 117.5
angle CH2E C    NH2     20.0 117.5
angle CH2E C    NC2     20.0 117.5 ! FOR NETROPSIN
angle CH2E C    NR      60.0 116.0
angle CH2E C    O       85.0 121.6
angle CH2E C    OC      85.0 118.5
angle CH2E C    OH1     85.0 120.0
angle CH3E C    N       20.0 117.5
angle CH3E C    NH1     20.0 117.5
angle CH3E C    O       85.0 121.5
angle CR1E C    CR1E    65.0 120.5
angle CR1E C    NH1     65.0 110.5! USED ONLY IN HIS, NOT IT TRP
angle CR1E C    NP      65.0 122.5
angle CR1E C    NR      65.0 122.5
angle CR1E C    OH1     65.0 119.0
angle CT   C    N       20.0 117.5
angle CT   C    NH1     20.0 117.5
angle CT   C    NH2     20.0 117.5
angle CT   C    O       85.0 121.5
angle CT   C    OC      85.0 118.5
angle CT   C    OH1     85.0 120.0
angle HA   C    NH1     40.0 120.0
angle HA   C    NH2     40.0 120.0
```

Sample Protein Parameters (param19.pro)

```
!angle NR   FE   CM      5.0      180.0
!angle NR   FE   OM      5.0  180.0! JUST A GUESS FROM EXISTING FE CM DATA


dihe CH1E C    N    CH1E 10.0      2     180.0! PRO ISOM. BARRIER 20 KCAL/MOL.
dihe CH2E C    N    CH1E 10.0       2     180.0
dihe CR1E C    C    CR1E 5.0       2     180.0! => TRP OOP. VIB 170CM 1
dihe CR1E C    C    C    2.5       2     180.0! SEE BEHLEN ET AL JCP 75:5685 81
dihe CR1E C    C    NH1  2.5       2     180.0
dihe X    C    CH1E X    0.0       3       0.0! FROM GELIN THESIS AMIDES
dihe X    C    CH2E X    0.0       3       0.0! USING A SINGLE
dihe X    C    CR1E X   10.0       2     180.0! DIHEDRAL PER BOND RATHER
dihe X    C    CT   X    0.0       3       0.0! THAN MULTIPLE TORSIONS
dihe X    C    N    X    8.2       2     180.0! ALKANE TORSION REDUCED TO
dihe X    C    NC2  X    8.2       2     180.0! 1.6 FROM 1.8 TO COINCIDE WITH
dihe X    C    NH1  X    8.2       2     180.0! THE EXPERIMENTAL BARRIER.
dihe X    C    NH2  X    8.2       2     180.0
dihe X    C    OH1  X    1.8       2     180.0
dihe X    C    OS   X    1.8       2     180.0 ! INFERRED FROM C-OH1
dihe X    CH1E CH1E X    1.6       3       0.0
dihe X    CH1E CH2E X    1.6       3       0.0
dihe X    CH1E N    X    0.3       3       0.0! FROM HAGLER ET AL TABULATION OF
dihe X    CH1E NH1  X    0.3       3       0.0! EXP. DATA AND 6 31G CALC.
dihe X    CH1E NH2  X    1.8       3       0.0! PROTONATED SECONDARY AMINE
dihe X    CH1E NH3  X    0.6       3       0.0! 1/PROTON SO 3 FOR THE BOND
dihe X    CH1E OH1  X    0.5       3       0.0! CHANGED TO ROUGHLY MEOH
dihe X    CH2E CH2E X    1.6       3       0.0
dihe X    CH2E N    X    0.3       3       0.0! SEE CH1E COMMENTS
dihe X    CH2E NH1  X    0.3       3       0.0
dihe X    CH2E NH2  X    0.6       3       0.0
dihe X    CH2E NH3  X    0.6       3       0.0
dihe X    CH2E OH1  X    0.5       3       0.0
dihe X    CH2E S    X    1.2       2       0.0
dihe X    CT   CT   X    1.6       3       0.0
dihe X    CT   N    X    0.3       3       0.0! SEE CH1E COMMENTS
dihe X    CT   NC2  X    0.3       3       0.0
dihe X    CT   NH1  X    0.3       3       0.0
dihe X    CT   NH2  X    0.6       3       0.0
dihe X    CT   NH3  X    0.6       3       0.0
dihe X    CT   OH1  X    0.5       3       0.0
dihe X    CT   S    X    1.2       2       0.0
!dihe X    FE   NR   X    0.05      4       0.0
```

Sample Protein Parameters (param19.pro)

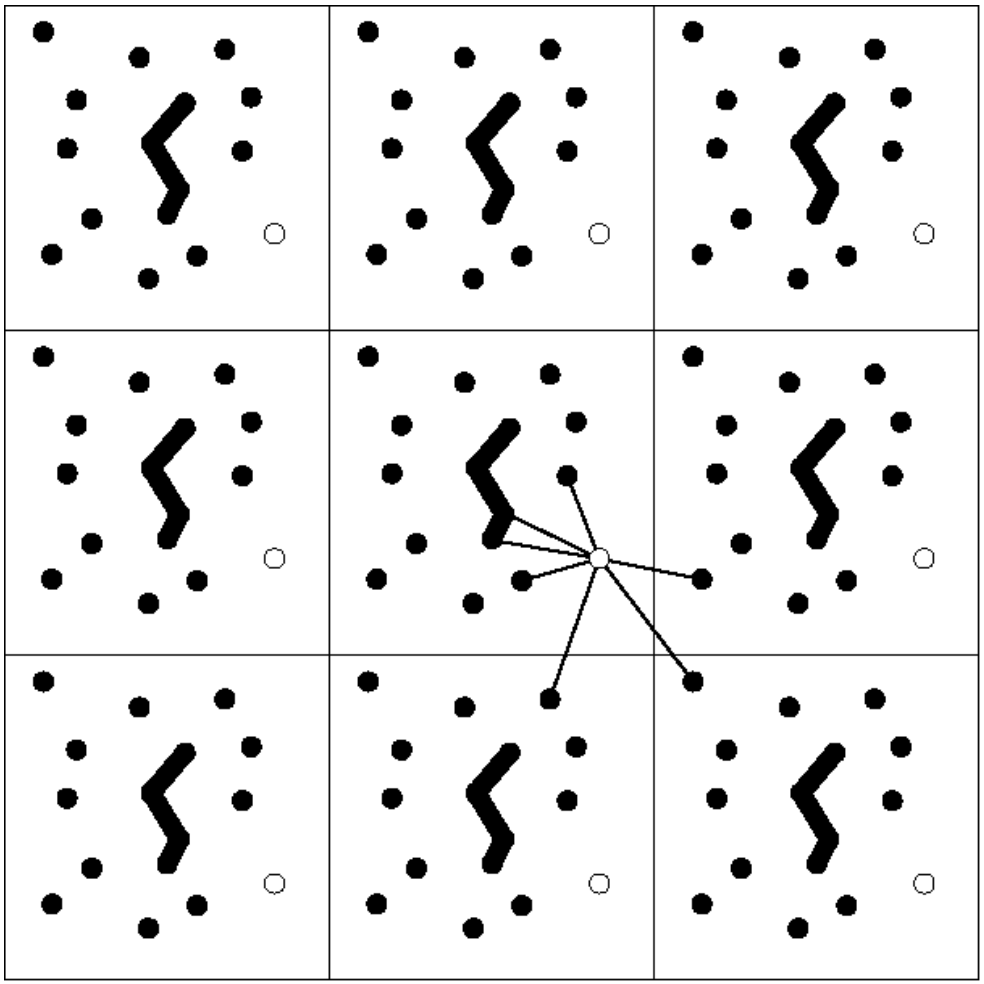
```
{* nonbonding parameter section *}
{* ============================ *}
nbonds
      atom cdie shift eps=1.0  e14fac=0.4   tolerance=0.5
      cutnb=9.0 ctonnb=7.5 ctofnb=8.0
      nbxmod=5 vswitch wmin 1.0
end


 !                eps     sigma       eps(1:4) sigma(1:4)
 !                (kcal/mol) (A)
 !                -------------------------------------
 NONBonded  H       0.0498   1.4254      0.0498   1.4254
 NONBonded  HA      0.0450   2.6157      0.0450   2.6157 !- charged group.
 NONBonded  HC      0.0498   1.0691      0.0498   1.0691 !   Reduced vdw radius
 !
 NONBonded  C       0.1200   3.7418      0.1000   3.3854 ! carbonyl carbon
 NONBonded  CH1E    0.0486   4.2140      0.1000   3.3854 ! \
 NONBonded  CH2E    0.1142   3.9823      0.1000   3.3854 !  extended carbons
 NONBonded  CH3E    0.1811   3.8576      0.1000   3.3854 ! /
!! NONBonded  CM      0.0262   4.4367      0.1000   3.3854
 NONBonded  CR1E    0.1200   3.7418      0.1000   3.3854 !  ring carbons
!! NONBonded  CT      0.0262   4.4367      0.1000   3.3854
 !
 NONBonded  N       0.2384   2.8509      0.2384   2.8509
 NONBonded  NC2     0.2384   2.8509      0.2384   2.8509
 NONBonded  NH1     0.2384   2.8509      0.2384   2.8509
 NONBonded  NH2     0.2384   2.8509      0.2384   2.8509
 NONBonded  NH3     0.2384   2.8509      0.2384   2.8509
 NONBonded  NP      0.2384   2.8509      0.2384   2.8509
 NONBonded  NR      0.2384   2.8509      0.2384   2.8509
 !
 NONBonded  O       0.1591   2.8509      0.1591   2.8509
 NONBonded  OC      0.6469   2.8509      0.6469   2.8509
 NONBonded  OH1     0.1591   2.8509      0.1591   2.8509
!! NONBonded  OM      0.1591   2.8509      0.1591   2.8509
 NONBonded  OS      0.1591   2.8509      0.1591   2.8509
 !
 NONBonded  S       0.0430   3.3676      0.0430   3.3676
 NONBonded  SH1E    0.0430   3.3676      0.0430   3.3676
 !
!! NONBONDED FE        0.0000    1.1582      0.0000 1.1582

set echo=true end
```

Periodic Boundary Conditions

- Make simulation system seem larger than it is
- Ewald Summation for electrostatics (Fourier transform)



Average over simulation

- Deceptive Instantaneous Snapshots (almost anything can happen)
- Simple thermodynamic averages
  - ◊ Average potential energy <U>
  - ◊ T ~ < Kinetic Energy > = ½ m < v^2 >
- Some quantities fixed, some fluctuate in different ensembles
  - ◊ NVE protein MD (“microcanonical”)
  - ◊ NVT liquid MC (“canonical”)
  - ◊ NPT more like the real world

Timescales

Motion	length (Å)	time (fs)
bond vibration	0.1	10
water hindered rotation	0.5	1000
surface sidechain rotation	5	10^5
water diffusive motion	4	10^5
buried sidechain libration	0.5	10^5
hinge bending of chain	3	10^6
buried sidechain rotation	5	10^{13}
allosteric transition	3	10^{13}
local denaturation	7	10^{14}

(From McCammon & Harvey, Eisenberg & Kauzmann)

D & RMS

- Diffusion constant
  - ◊ Measures average rate of increase in variance of position of the particles
  - ◊ Suitable for liquids, not really for proteins

$$D = \frac{\langle \Delta r^2 \rangle}{6\Delta t}$$

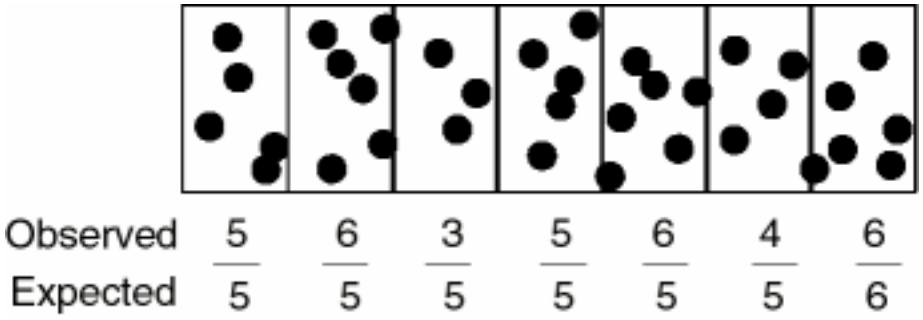
- RMS more suitable to proteins

$$RMS\ (t) = \sqrt{\frac{\sum_{i=1}^{N} d_i(t)}{N}}$$

$$d_i(t) = \mathbf{R}(\mathbf{x}_i(t) - \mathbf{T}) - \mathbf{x}_i(0)$$

  - ◊ di = Difference in position of protein atom at t from the initial position, after structures have been optimally rotated translated to minimize RMS(t)
  - ◊ Solution of optimal rotation has been solved a number of ways (Kabsch, SVD)

Number Density

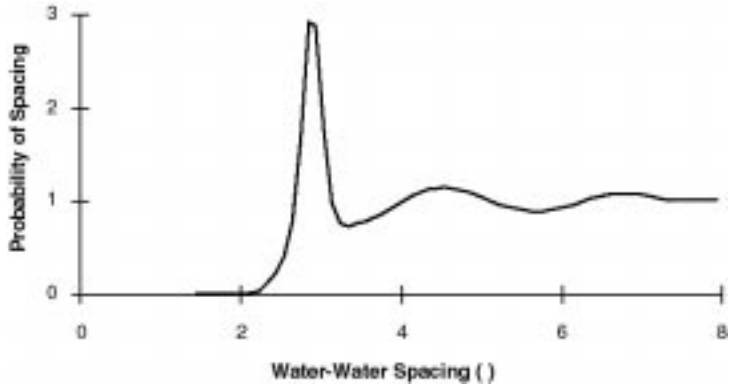


= Number of atoms per unit volume averaged over simulation divided by the number you expect to have in the same volume of an ideal "gas"

Spatially average over all directions gives

1D RDF =

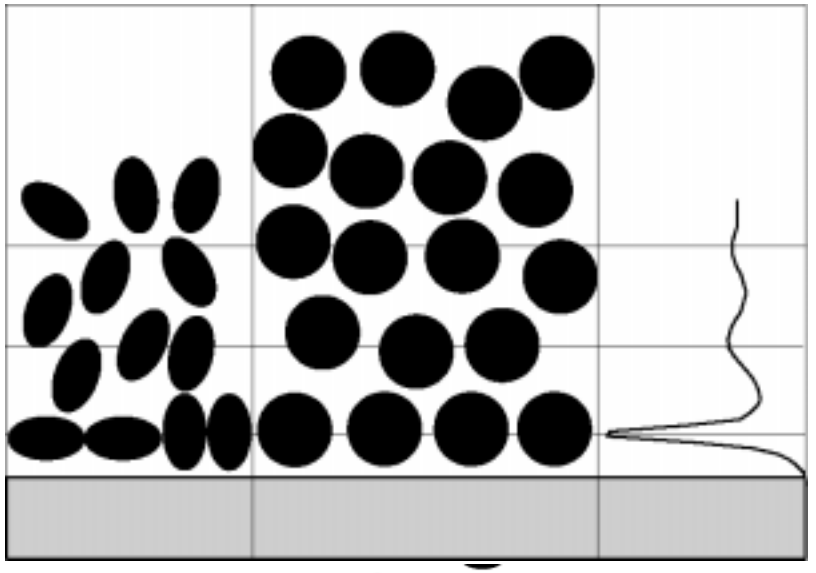
[Avg. Num. Neighbors at r]
[Expected Num. Neighbors at r]

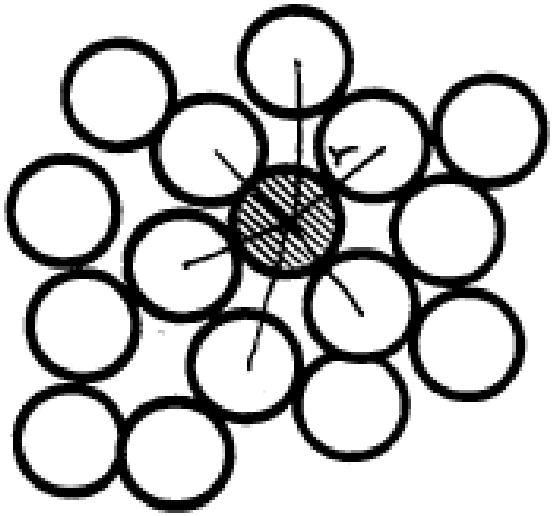


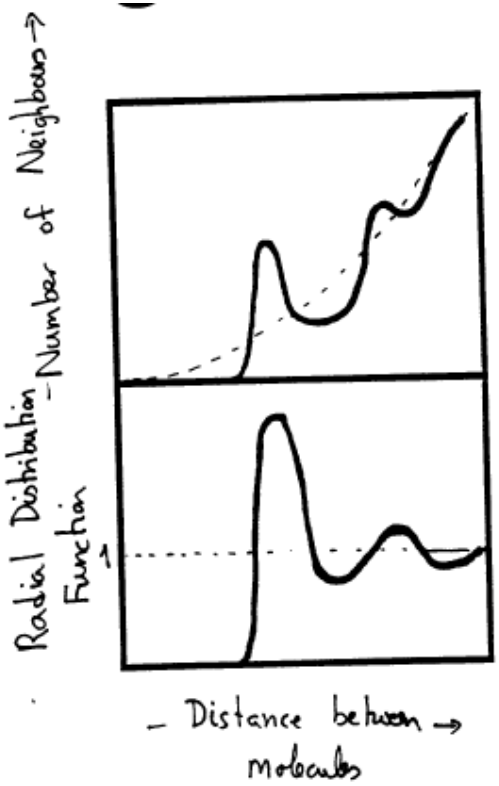
"at r" means contained in a thin shell of thickness dr and radius r

Number Density (cont)

- Advantages: Intuitive, Relates to scattering expts
- D/A: Not applicable to real proteins
  - ◊ 1D RDF not structural
  - ◊ 2D proj. only useful with "toy" systems
- Number densities measure spatial correlations, not packing
  - ◊ Low value does not imply cavities
  - ◊ Complicated by asymmetric molecules
  - ◊ How things pack and fit is property of instantaneous structure - not average







Major Protein Simulation Packages

- AMBER
  - ◊ http://www.amber.ucsf.edu/amber/amber.html
  - ◊ http://www.amber.ucsf.edu/amber/tutorial/index.html
- CHARMM/XPLOR
  - ◊ http://yuri.harvard.edu/charmm/charmm.html
  - ◊ http://atb.csb.yale.edu/xplor
  - ◊ http://uracil.cmc.uab.edu/Tutorials/default.html
- ENCAD
- GROMOS
  - ◊ http://rugmd0.chem.rug.nl/md.html
  - ◊ “Advanced Crash Course on Electrostatics in Simulations” (!) (http://rugmd0.chem.rug.nl/~berends/course.html)

References

- llen, M. P. & Tildesley, D. J. (1987). *Computer Simulation of Liquids.* Claredon Press, Oxford.
- Biosym (1994). *Discover 2.9.5 Manual.* Biosym Inc., San Diego, CA.
- Brooks, B. R., Bruccoleri, R. E., Olafson, B. D., States, D. J., Swaminathan, S. & Karplus, M. (1983). CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations. *J. Comp. Chem.* **4**, 187-217.
- Daggett, V. & Levitt, M. (1993). Realistic Simulations of Native-Protein Dynamics in Solution and Beyond. *Ann. Rev. Biophys. Biomol. Struct.* **22**, 353-380.
- Gelin, B. R. & Karplus, M. (1979). Side-chain torsional potentials: effect of dipeptide, protein, and solvent environment. *Biochemistry* **18**, 1256-1268.
- Goldstein, H. (1980). *Classical Mechanics.* 2nd edition. Addison-Wesley, New York.
- Jackson, J. (1975). *Classical Electrodynamics.* Wiley, New York.
- Karplus, M. & McCammon, J. A. (1986). The dynamics of proteins. *Sci. Am.* **254**, 42-51.
- Karplus, M. & Petsko, G. A. (1990). Molecular dynamics simulations in biology. *Nature* **347**, 631-639.
- Levitt, M. (1982). Protein conformation, dynamics, and folding by computer simulation. *Ann. Rev. Biophys. Bioeng.* **11**, 251-271.
- Levitt, M. (1983a). Molecular dynamics of a native protein. I. Computer simulation of trajectories. *J. Mol. Biol.* **168**, 595.
- Levitt, M. (1983b). Molecular dynamics of a native protein. II. Analysis and Nature of the Motion. *J. Mol. Biol.* **168**, 621-657.
- Levitt, M. (1983c). Protein folding by restrained energy minimization and molecular dynamics. *J Mol Biol* **170**, 723-64.
- Levitt, M., Hirschberg, M., Sharon, R. & Daggett, V. (1995). Potential Energy Function and Parameters for Simulations of the Molecular Dynamics of Proteins and Nucleic Acids in Solution. *Computer Phys. Comm.* **91**, 215-231.

References 2

- Levitt, M. & Sharon, R. (1988). Accurate Simulation of Protein Dynamics in Solution. *Proc. Natl. Acad. Sci. USA* **85**, 7557-7561.
- Marion, J. B. & Heald, M. A. (1980). *Classical Electromagnetic Radiation.* Academic Press, New York.
- McCammon, J. A. & Harvey, S. C. (1987). *Dynamics of Proteins and Nucleic Acids.* Cambridge UP,
- Pettitt, B. M. & Karplus, M. (1985). The Potential of Mean Force Surface for the Alanine Dipeptide in Aqeous Solution: A Theoretical Approach. *Chem. Phys. Lett.* **121**, 194-201.
- Atkins, P. (1990). *Physical Chemistry.* Oxford UP
- Press, W. H., Flannery, B. P., Teukolsky, S. A. & Vetterling, W. T. (1992). *Numerical Recipes in C.* Second. Cambridge University Press, Cambridge.
- Purcell, E. M. (1985). *Electricity and Magnetism.* McGraw-Hill, New York.
- Brünger, A. T. (1993). *X-PLOR 3.1, A System for X-ray Crystallography and NMR.* Yale University Press, New Haven.
- Brünger, A. T., Kuriyan, J. & Karplus, M. (1987). Crystallographic R factor refinement by molecular dynamics. *Science* **235**, 458-60.
- Rice, L. M. & Brunger, A. T. (1996). Torsion angle dynamics: Reduced variable conformational sampling enhances crystallographic structure refinement. *Proteins* **19**, 277-290