

Protein Structure Analysis

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2004

Molecular structure representation

Elementary particles

Atoms

Groups of atoms

Protein Modeling Methods

- **Ab initio methods:**
solution of a protein folding problem
search in conformational space
- **Energy-based methods:**
energy minimization
molecular simulation
- **Knowledge-based methods:**
homology modeling
fold recognition

Potential Energy Function

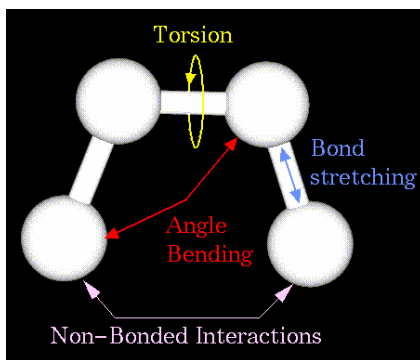
$$PEF(R) = \sum_{\text{bonds}} K_b \{b(R) - b_{eq}\}^2 + \sum_{\text{angles}} K_\theta \{\theta(R) - \theta_{eq}\}^2 +$$

$$\sum_{\text{dihedrals}} \frac{K_\phi}{2} \{1 + \cos[n\phi(R) - \gamma]\} +$$

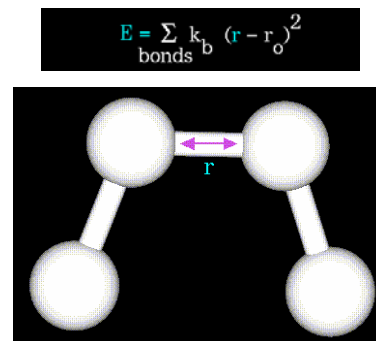
$$\sum_{\text{non-bonded atom pairs } ij} \left[\frac{A_{ij}}{r_{ij}(R)^{12}} - \frac{B_{ij}}{r_{ij}(R)^6} + \frac{q_i q_j}{\epsilon_r \epsilon_0 r_{ij}(R)} \right] \quad (1)$$

Forcefields: [AMBER](#), [CHARMM](#), [CVF](#), [ECEPP](#), [GROMOS](#)

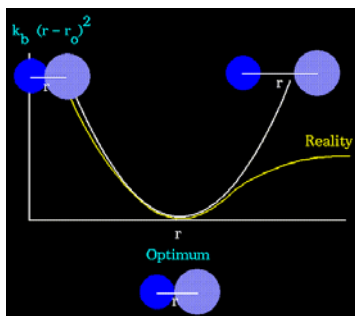
Non-Bonded Interactions



Bond length

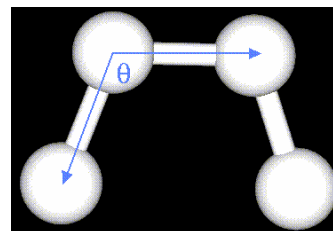


Bond length

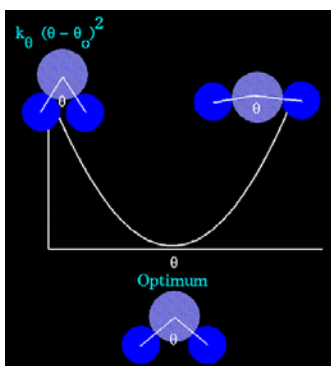


Bond angle

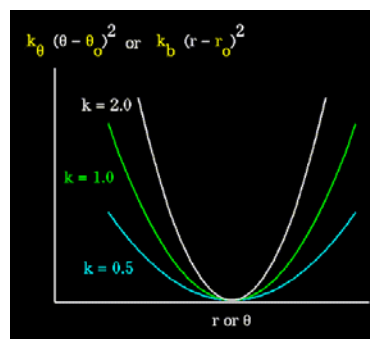
$$E = \sum_{\text{angles}} k_{\theta} (\theta - \theta_o)^2$$



Bond angle

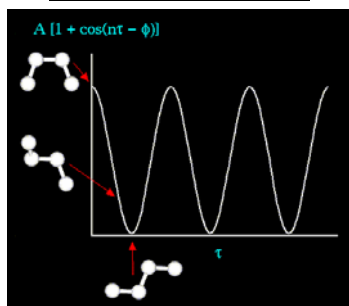


Bond length and angle (parameters)

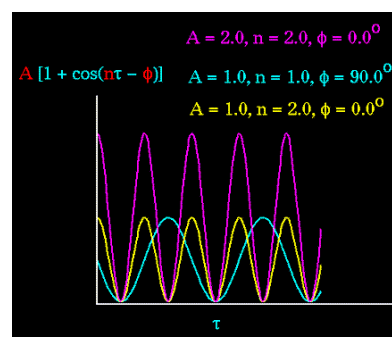


Torsional angle

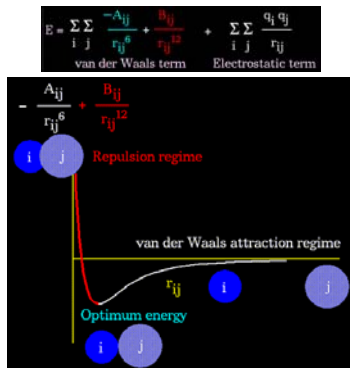
$$E = \sum_{\text{torsions}} A [1 + \cos(n\tau - \phi)]$$



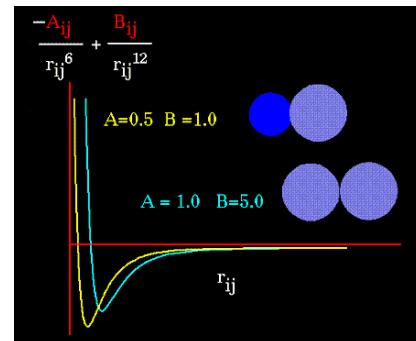
Torsional angle (parameters)



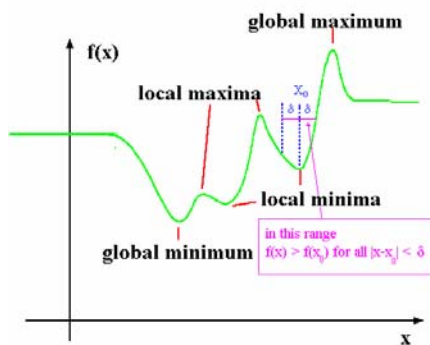
Non-bonded terms



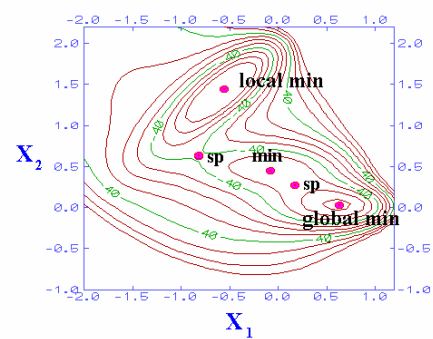
Non-bonded terms (parameters)



Energy Minimazation



Energy Minimazation



Molecular Dynamics

- Model system
- Initial conditions
- Boundary conditions
- Integration algorithm
- Constraints
- Ensemble
- Results

Molecular Dynamics

$$F_i = m_i a_i$$

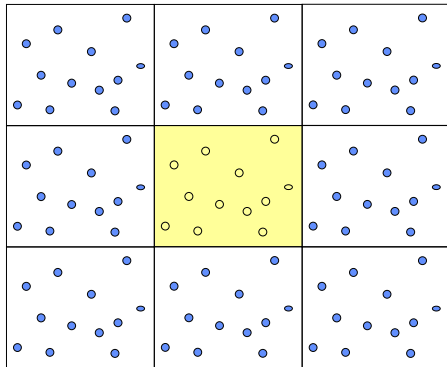
$$a_i = dv_i / dt$$

$$v_i = dr_i / dt$$

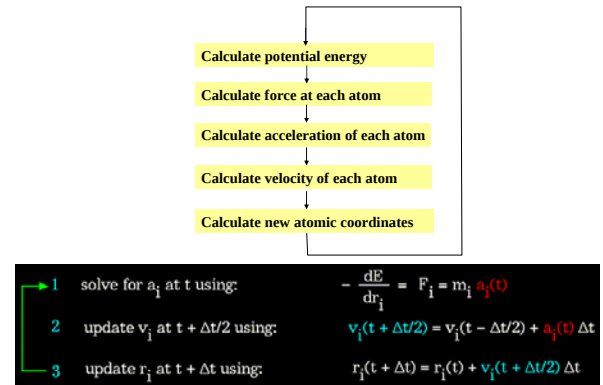
$$-dE / dr_i = F_i$$

$$-dE / dr_i = m_i d^2 r_i / dt^2$$

Periodic Boundary Conditions



MD cycle and integration algorithm



Time scales

Motion	Characteristic time (sec)
Relative vibration of bonded atoms	10^{-14}
Rotation of side chains at protein surface	$10^{-11} - 10^{-10}$
Torsional libration of buried groups	$10^{-11} - 10^{-9}$
Relative motion of different globular regions	$10^{-11} - 10^{-7}$
Rotation of medium-sized side chains in protein interior	$10^{-4} - 1$
Local denaturation	$10^{-5} - 10$

MD Ensemble

Microcanonical (N,V,E)

Canonical (N,V,T)

Isothermal-isobaric (N,P,T)

Temperature in molecular dynamics

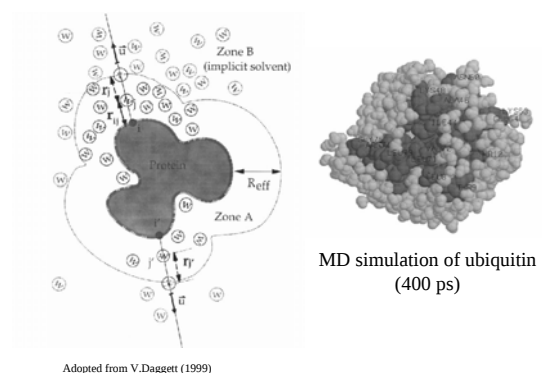
$$U_{kin} = \sum \frac{1}{2} m_i v_i^2 = \frac{3}{2} NkT$$

N – number of atoms

k – Boltzmann constant

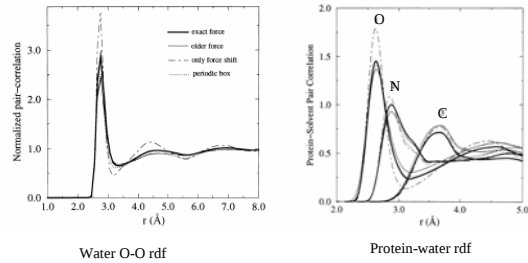
T – absolute temperature

MD of proteins: Solvent model



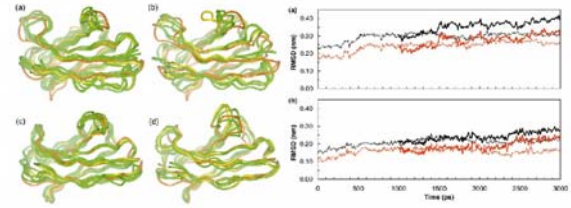
Adopted from V.Daggett (1999)

MD of proteins: radial distribution functions



Adopted from V.Daggett (1999)

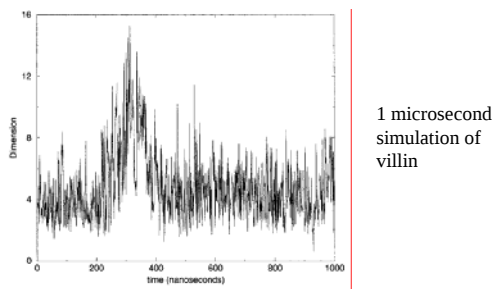
MD of proteins: mobile regions



Snapshots of V_H domain simulation
at 300 and 340 K

Adopted from W.F.VanGunsteren (2001)

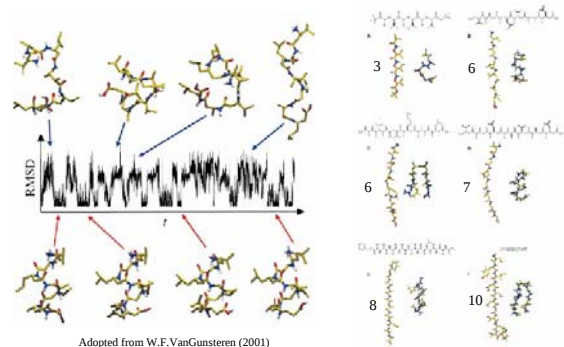
MD of proteins: long runs



1 microsecond
simulation of
villin

Adopted from I.D.Kuntz and P.Kollman (2001)

MD: Reversible folding of peptides



Adopted from W.F.VanGunsteren (2001)