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

\[ PEF(R) = \sum_{\text{bonds}} K_b (b(R) - b^*)^2 + \sum_{\text{angles}} K_\theta \theta^2 + \sum_{\text{dihedrals}} K_{\phi} \phi + \sum_{\text{non-bonded}} \left[ \frac{A_{ij}}{r_{ij}(R)}^2 - \frac{B_{ij}}{r_{ij}(R)^6} + \frac{q_i q_j}{\varepsilon_{ij} r_{ij}(R)} \right] \]

Forcefields: AMBER, CHARMM, CVF, ECEPP, GROMOS

Non-Bonded Interactions

Bond length

\[ E = \sum_{\text{bonds}} k_r (r - r_o)^2 \]
Non-bonded terms

\[ \sum_{i \neq j} \frac{q_i q_j}{r_{ij}} \]

Electrostatic term

\[ -\frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} \]

 kissing regime

van der Waals attraction regime

Optimized energy

Non-bonded terms (parameters)

Energy Minimization

Model system

Initial conditions

Boundary conditions

Integration algorithm

Constraints

Ensemble

Results

Molecular Dynamics

\[ F_i = m_i a_i \]

\[ a_i = d^2 r_i / dt^2 \]

\[ v_i = dr_i / dt \]

\[ -dE / dr_i = F_i \]

\[ -dE / dr_i = m_i d^2 r_i / dt^2 \]
Periodic Boundary Conditions

MD cycle and integration algorithm

1. Solve for $v_i$ at $t$ using: $rac{dF_i}{dt} = F_i = m_i \cdot a_i(t)$
2. Update $v_i$ at $t + \Delta t$ using: $v_i(t + \Delta t) = v_i(t - \Delta t) + a_i(t) \Delta t$
3. Update $r_i$ at $t + \Delta t$ using: $r_i(t + \Delta t) = r_i(t) + v_i(t + \Delta t) \Delta t$

Calculate potential energy
Calculate force at each atom
Calculate acceleration of each atom
Calculate velocity of each atom
Calculate new atomic coordinates

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 $10^{-5} - 10$

Temperature in molecular dynamics

$$U_{kin} = \frac{1}{2} \sum m_i v_i^2 = \frac{3}{2} N k T$$

$N$ – number of atoms
$k$ – Boltzmann constant
$T$ – absolute temperature

MD Ensemble

Microcanonical $(N,V,E)$
Canonical $(N,V,T)$
Isothermal-isobaric $(N,P,T)$

MD of proteins: Solvent model

Adopted from V. Daggett (1999)

MD simulation of ubiquitin (400 ps)
MD of proteins: radial distribution functions

Water O-O rdf

Protein-water rdf

Adopted from V Daggett (1999)

MD of proteins: mobile regions

Snapshots of V$_{d}$ domain simulation at 300 and 340 K

Adopted from W.J.VanGunsteren (2001)

MD of proteins: long runs

1 microsecond simulation of villin

Adopted from I.D.Kuntz and P.Kollman (2003)

MD: Reversible folding of peptides

Adopted from W.J.VanGunsteren (2001)