**Introduction to Bioinformatics**

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### 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

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### Molecular structure representation

- Elementary particles
- Atoms
- Groups of atoms

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### Potential Energy Function

\[
\text{PEF}(R) = \sum_{\text{bonds}} K_b (b(R) - b_0)^2 + \sum_{\text{angles}} K_\theta (\theta(R) - \theta_0)^2 + \\
\sum_{\text{dihedrals}} K_{\psi} \{1 + \cos[n\phi(R) - \gamma]\} + \\
\sum_{\text{nonbonded atom pairs } ij} \left[ \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{10}} + \frac{q_i q_j}{\varepsilon_{ij} r_{ij}(R)} \right] \quad (1)
\]

**Forcefields:** AMBER, CHARMM, CVF, ECEPP, GROMOS

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### Non-Bonded Interactions

- Torsion
- Bond stretching
- Angle bending

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### Bond length

\[
E = \sum_{\text{bonds}} k_b (r - r_0)^2
\]
**Bond length**

**Bond angle**

\[ E = \sum k_\theta (\theta - \theta_0)^2 \]

**Bond angle**

**Bond length and angle (parameters)**

**Torsion angle**

**Torsional angle (parameters)**

\[ E = \sum A (1 + \cos(n \tau - \phi)) \]
Non-bonded terms

\[
\sum_{i>j} \left( -\frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} \right)
\]

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

\[
\text{PEF}(R) = \sum_{\text{bonds}}^b \left( b(R)-b_0 \right)^2 + \sum_{\text{angles}} \left( \theta_0(R)-\theta_0 \right)^2 + \\
\sum_{\text{dihedrals}}^{2} \left( 1 + \cos[\eta(R) - \gamma] \right) + \\
\sum_{\text{non-bonded}} A_{ij} \left( \frac{1}{r_{ij}^6} - \frac{1}{r_{ij}^{12}} \right) + B_{ij} \frac{q_i q_j}{\varepsilon_i \varepsilon_j r_{ij}(R)}
\]

Forcefields: AMBER, CHARMM, CVF, ECEPP, GROMOS

Energy Minimization

\[ f(x) \]

Global maximum

Global minimum

Local maxima

Local minima
Molecular Dynamics

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

Molecular Dynamics

\[ F_i = m_i \ a_i \]

\[ a_i = \frac{d v_i}{dt} \]

\[ v_i = \frac{d r_i}{dt} \]

\[- \frac{d E}{d r_i} = F_i \]

\[- \frac{d E}{d r_i} = m_i \ \frac{d^2 r_i}{dt^2} \]

Periodic Boundary Conditions

- MD cycle and integration algorithm

  1. Solve for \( a_i \) at \( t \) using:
     \[ \frac{d F_i}{d r_i} = F_i = m_i \ \frac{a_i(0)}{2} \]
  2. Update \( v_i \) at \( t + \Delta t / 2 \) using:
     \[ v_i(t + \Delta t / 2) = v_i(t - \Delta t / 2) + a_i(t) \ \Delta t \]
  3. Update \( r_i \) at \( t + \Delta t \) using:
     \[ r_i(t + \Delta t) = r_i(t) + v_i(t) \ \Delta t + F_i(t) \ \Delta t \]

Time scales

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

Temperature in molecular dynamics

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

- \( N \) – number of atoms
- \( k \) – Boltzmann constant
- \( T \) – absolute temperature
MD of proteins: Solvent model

MD simulation of ubiquitin (400 ps)
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)