Introduction to Molecular Dynamics

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Molecular Dynamics

- Science of simulating the motions of a system of particles
- Can be applied to many systems
  - Atoms, small molecules,
  - Biological macromolecules – proteins, DNA, RNA, …
  - Systems may go as large as a galaxy
- Essential elements
  - Interaction potential → forces on particles
  - Equations of motion

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Why Molecular Dynamics

- Anfinsen's Hypothesis
  - All the information necessary to determine the structure of a protein is in the primary sequence.
  - The native conformation of a protein is the conformation with the lowest global free energy.
- Levinthal's Paradox
  - The number of possible conformations is far too large for a protein to visit them all in the time available for folding.

3 states for each of 50 a.a. x 2 dihedrals = 3^{100} conformations

10^{13} conformations/sec x 3E7 sec/year = 3E20 conformations per year

Approximately 1.7E27 years to try all the conformations

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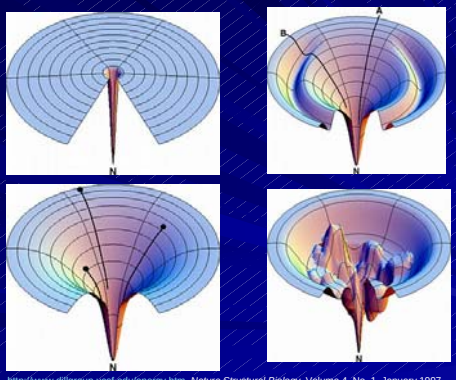
Free Energy Landscape Funnel Shaped?



http://www.dillgroup.ucsf.edu/energy.htm, *Nature Structural Biology*, Volume 4, No. 1, January 1997

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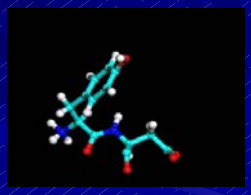
Molecular Dynamics

- Simulates the behavior of molecules by integrating Newton's laws of motion
- A trajectory is obtained by solving the following equation for each time step



$$\frac{d^2 x_i}{dt^2} = \frac{F_{x_i}}{m_i}$$

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Molecular Mechanics Energy Function

$$E = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_q (q - q_{eq})^2 + \sum_{torsions} \frac{V_n}{2}[1 + \cos(nw - g)] + \sum_{i<j} \left\{ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q q_i q_j}{e R_{ij}} \right\}$$

Molecular Dynamics

$$\frac{d^2 x_i}{dt^2} = \frac{F_{x_i}}{m_i}$$

$$x(t + \Delta t) = x(t) + x'(t) \times \Delta t + x''(t) \times \frac{\Delta t^2}{2} + \ldots$$

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Integration Methods

- Finite Difference Methods
  - Verlet Algorithm[1]
  - Leap-frog Algorithm[2]
  - Velocity Verlet Method[3]
- Predictor – Corrector Integration Methods
  - Gear predictor – corrector method[4]

[1] Verlet, Physical Review 159:98-103, 1967

[2] Hockney, Methods in Computational Physics, 9:136-211, 1970

[3] Swope et. al., Journal of Chemical Physics, 76:637-649, 1982

[4] Gear, Numerical Initial Value Problems in Ordinary Differential Equations, Englewood Cliffs, NJ, Prentice Hall, 1971

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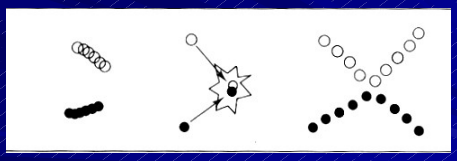
Choosing a time step

- Too small → incomplete sampling
- Too large → instabilities
- Typical Time Steps: 1 – 2 fs (10^{-15} s)



Leach, Molecular Modelling,2nd Edition, 2001

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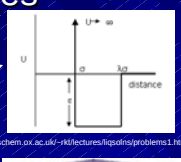
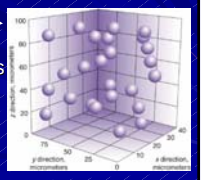
Simulation Types

- Simple Models
  - Hard-sphere model
  - Square-well potential
- Continuous Potentials
  - Lattice / Off lattice simulations
  - United-Atom / All-Atom simulations
  - Implicit / Explicit solvent simulations
- Enhanced Sampling Techniques
  - Replica Exchange Method
  - Locally Enhanced Sampling etc…



http://physchem.ox.ac.uk/~rkt/lectures/liqsolns/problems1.html



http://www.llnl.gov/str/December01/Clague.html

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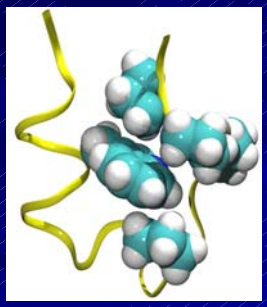
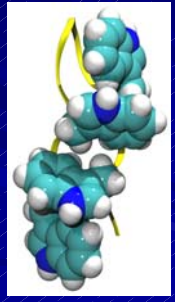
Applications and Selected Results

Trp-Cage



Trpzip



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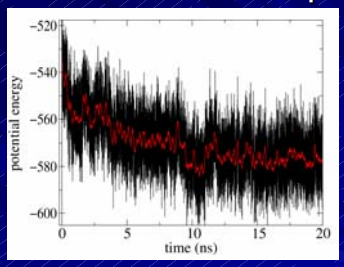
Structure Prediction – Trp-Cage



- Linear initial structure
- Potential energy reaches plateau
- Structure with lowest potential energy selected as “best”

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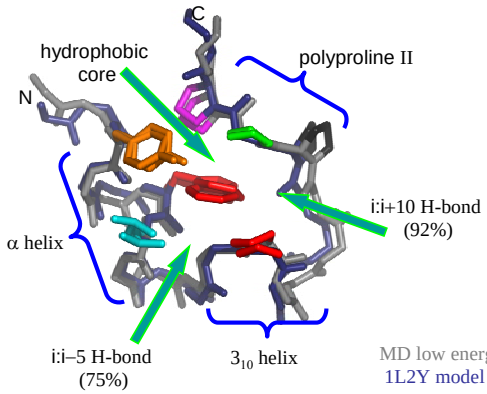

MD low energy 1L2Y model 1

Simmerling, Strockbine and Roitberg., J. Am. Chem. Soc., **124**, 2002

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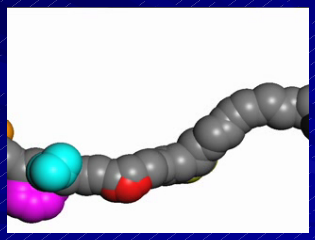
Folding of Trp-Cage



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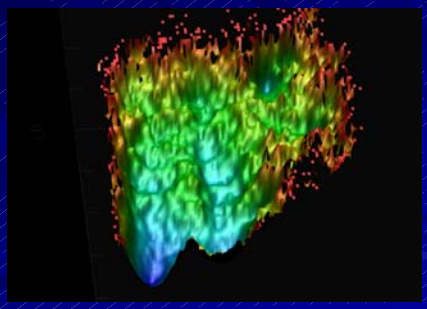
Free Energy Landscape of Trp-Cage



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Conclusions

- Molecular Dynamics can be used in
  - Structure prediction
  - Loop modeling and structure refinement
  - Folding and unfolding kinetics and pathways
  - Thermodynamic properties
  - Drug design
  - Free energy calculations
- Common problems
  - Parameterization
  - Convergence

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