

Protein Structure Analysis

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2009

- *Ab initio* methods
- Energy-based methods
- Knowledge-based methods

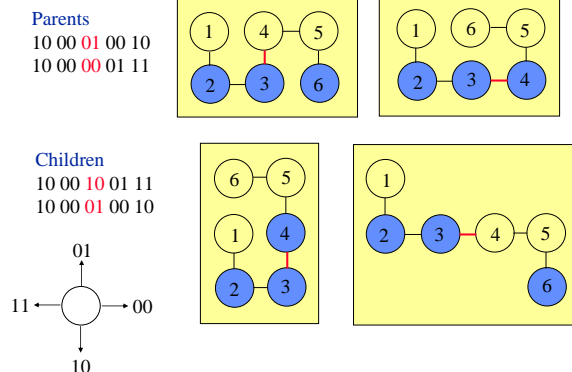
Protein Modeling Methods

- **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

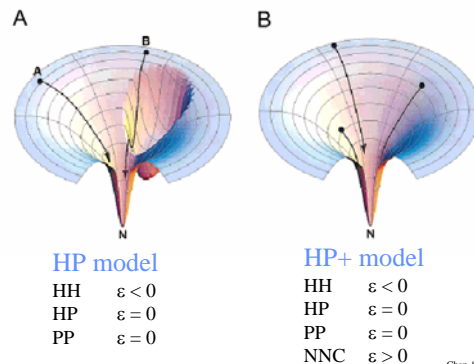
Ab initio Methods

- Simplified models
 - simplified alphabet (HP)
 - simplified representation (lattice)
- Build-up techniques
- Deterministic methods
 - quantum mechanics
 - diffusion equations
 - DFT
- Stochastic searches
 - Monte Carlo
 - genetic algorithms

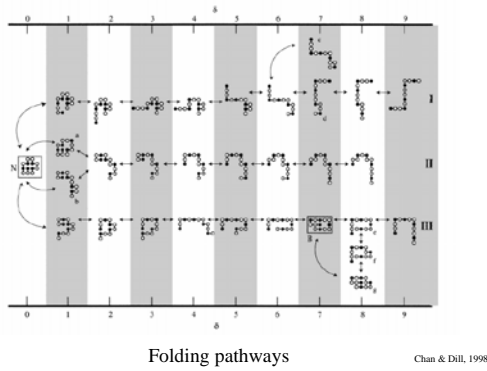
Genetic Algorithms Applications



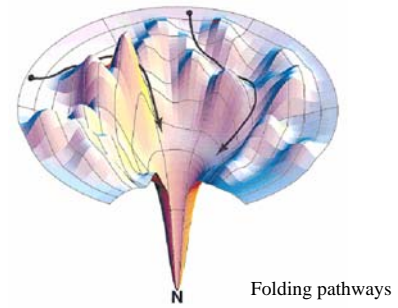
HP Lattice Models



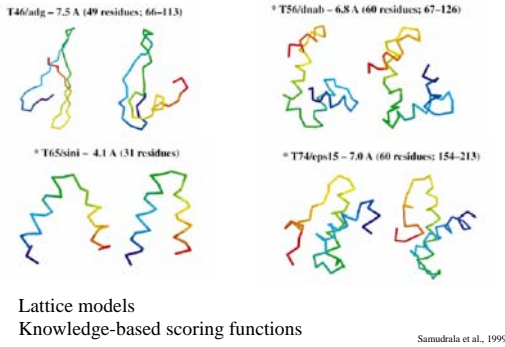
HP Lattice Models



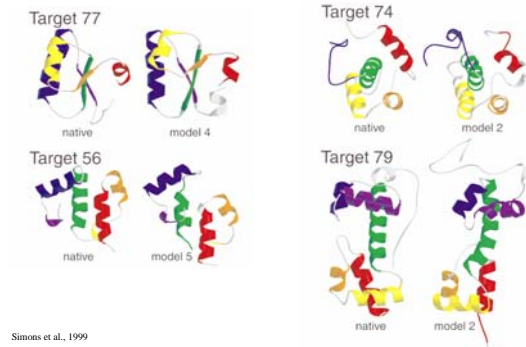
HP Lattice Models



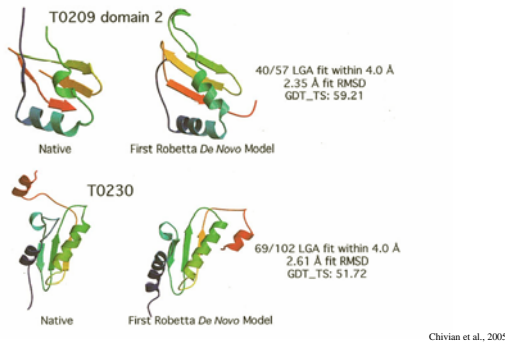
Hierarchical *ab initio* prediction



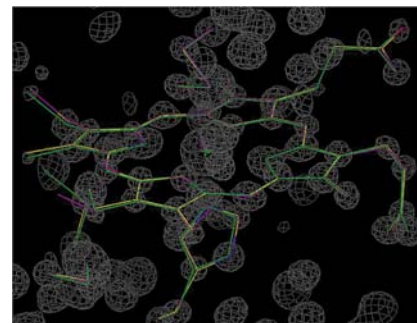
Ab initio prediction using Rosetta



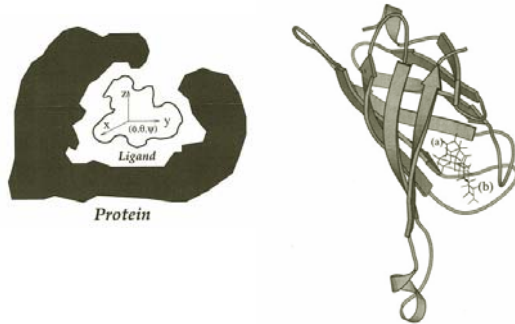
Ab initio prediction using Robetta



Quantum Chemistry Refinement of Protein Structures

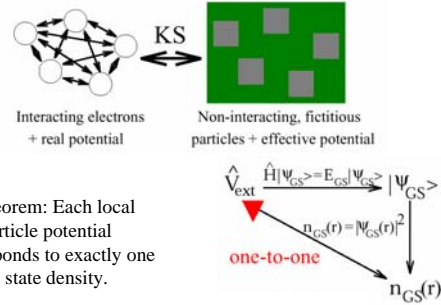


Quantum Chemistry Refinement of Protein-Ligand Structures



Xiang et al., 2004

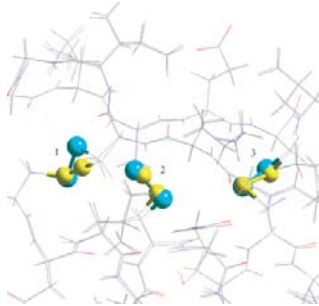
Density Functional Theory



HK theorem: Each local one-particle potential corresponds to exactly one ground state density.

Adapted from Wilfried Andur, OSU

Density Functional Theory



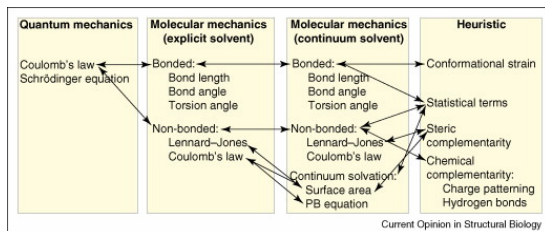
DFT optimization of NMR structure (IPNH)

Andreoni et al., 1999

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Potential Energy Functions



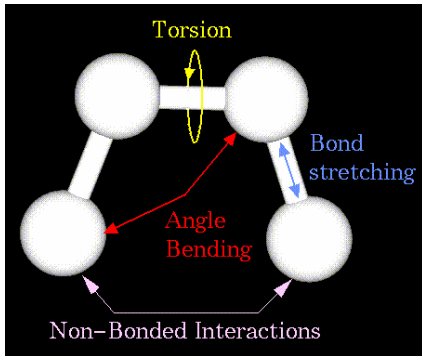
Boas & Harbury, 2007

Potential Energy Function

$$PEF(R) = \sum_{\text{bonds}} K_b \{b(R) - b_{eq}\}^2 + \sum_{\text{angles}} K_\theta \{\theta(R) - \theta_{eq}\}^2 + \sum_{\text{dihedrals}} \frac{K_\psi}{2} \{1 + \cos[n\phi(R) - \gamma]\} + \sum_{\text{non-bonded atom pairs } ij} \left[\frac{A_{ij}}{r_{ij}(R)^{12}} - \frac{B_{ij}}{r_{ij}(R)^6} + \frac{q_i q_j}{\epsilon_r \epsilon_0 r_{ij}(R)} \right] \quad (1)$$

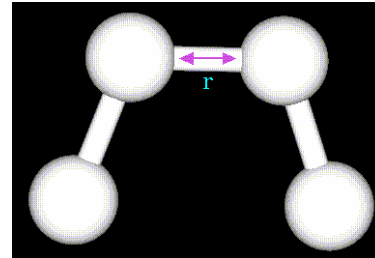
Forcefields: [AMBER](#), [CHARMM](#), [CVF](#), [ECEPP](#), [GROMOS](#)

Non-Bonded Interactions

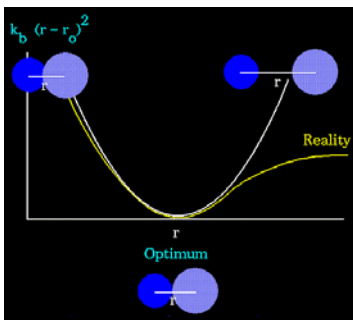


Bond length

$$E = \sum_{\text{bonds}} k_b (r - r_o)^2$$

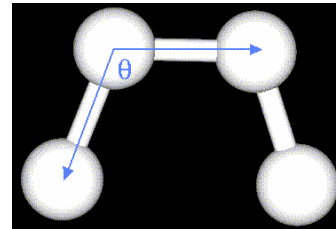


Bond length

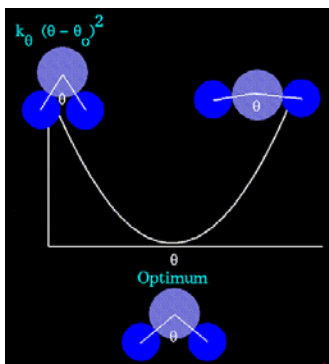


Bond angle

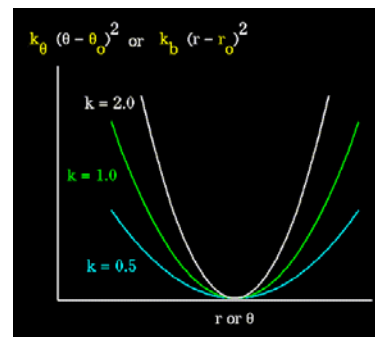
$$E = \sum_{\text{angles}} k_\theta (\theta - \theta_o)^2$$



Bond angle

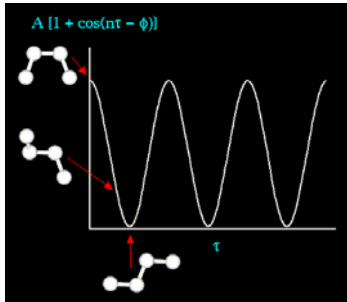


Bond length and angle (parameters)

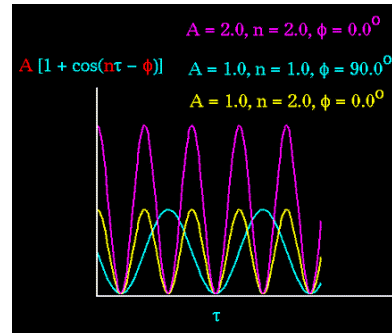


Torsional angle

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



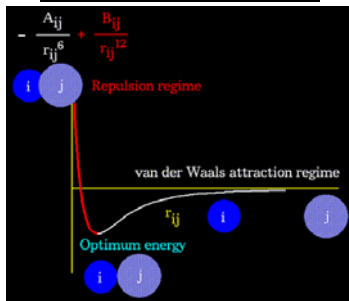
Torsional angle (parameters)



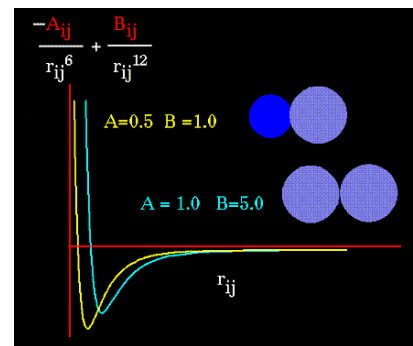
Non-bonded terms

$$E = \sum_{i,j} \sum \frac{-A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} + \sum_{i,j} \sum \frac{q_i q_j}{r_{ij}}$$

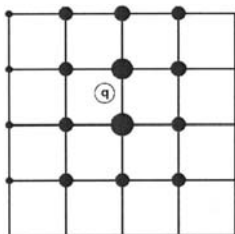
van der Waals term Electrostatic term



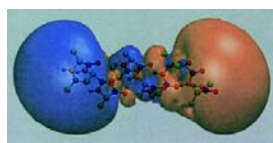
Non-bonded terms (parameters)



Electrostatic interactions



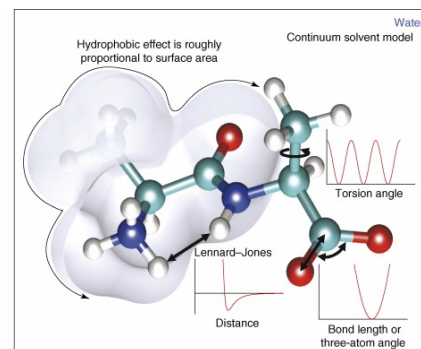
particle-mesh Ewald (PME) summation



electrostatic potential calculated using PME

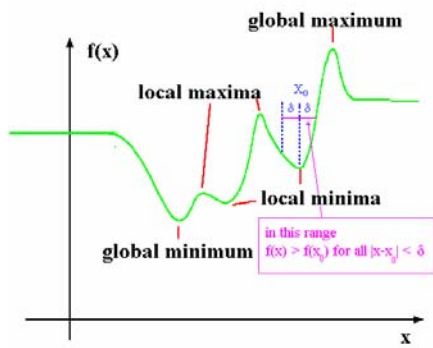
Adopted from J.C.Phillips et al. (2005)

Potential Energy Function



Boas & Harbury, 2007

Energy Minimization



Energy Minimization

