BINF 731

Protein Structure Analysis

Iosif Vaisman

2012

Protein Modeling Methods

- ***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 recogniion

Ab initio Methods

Simplified models
- simplified alphabet (HP)
- simplified representation (lattice)

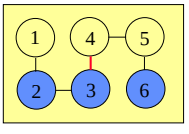
Build-up techniques

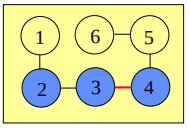
Deterministic methods
- quantum mechanics
- diffusion equations
- DFT

Stochastic searches
- Monte Carlo
- genetic algorithms

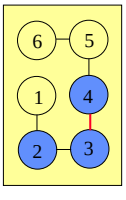
Genetic Algorithms Applications

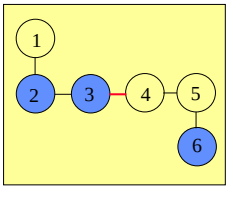
Parents
10 00 01 00 10
10 00 00 01 11

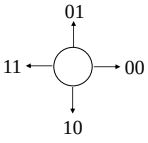




Children
10 00 10 01 11
10 00 01 00 10

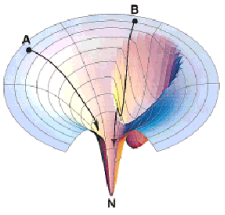






HP Lattice Models

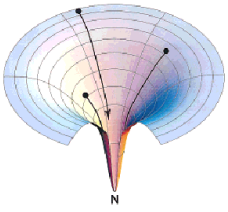
A



HP model

HH	ε < 0
HP	ε = 0
PP	ε = 0

B

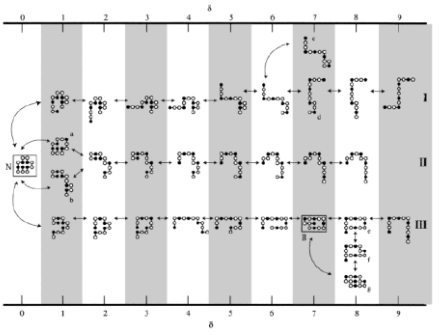


HP+ model

HH	ε < 0
HP	ε = 0
PP	ε = 0
NNC	ε > 0

Chan & Dill, 1998

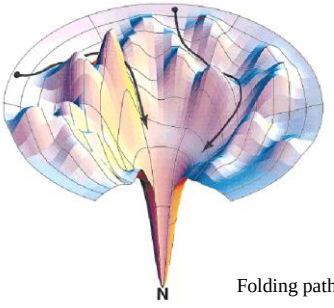
HP Lattice Models



Folding pathways

Chan & Dill, 1998

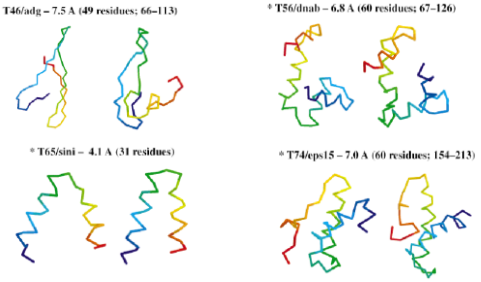
HP Lattice Models



Folding pathways

Chan & Dill, 1998

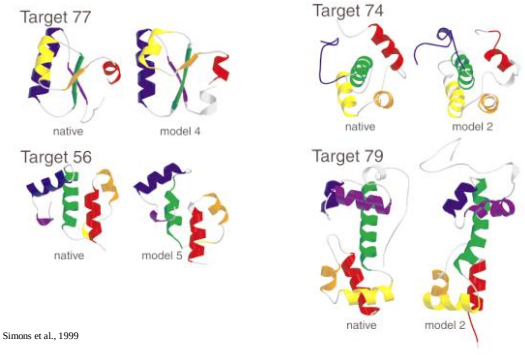
Hierarchical *ab initio* prediction



Lattice models
Knowledge-based scoring functions

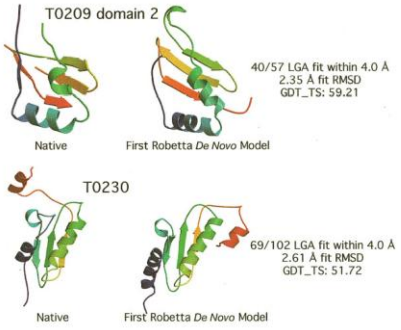
Samudrala et al., 1999

Ab initio prediction using Rosetta



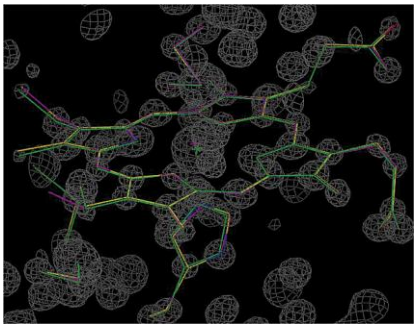
Simons et al., 1999

Ab initio prediction using Robetta



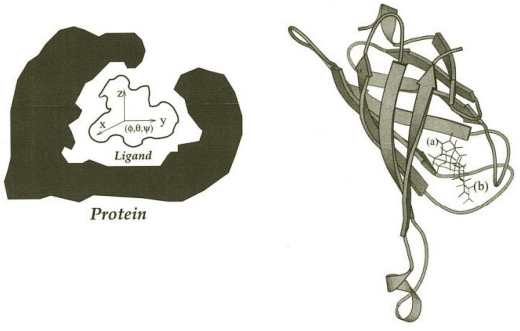
Chivian et al., 2005

Quantum Chemistry Refinement of Protein Structures



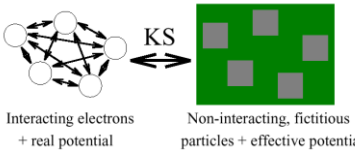
Ryde et al., 2003

Quantum Chemistry Refinement of Protein-Ligand Structures

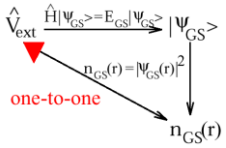


Xiang et al., 2004

Density Functional Theory

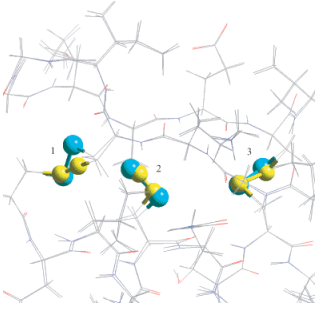


HK theorem: Each local one-particle potential corresponds to exactly one ground state density.



Adopted fromWilfried Aulbur, OSU

Density Functional Theory



DFT optimization of NMR structure (1PNH)

Andreoni et al., 1999

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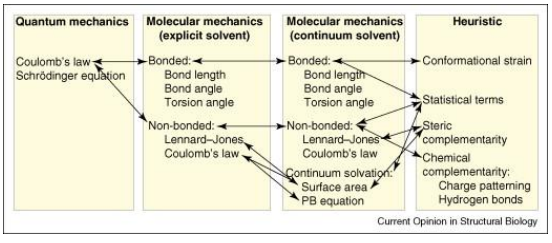
Potential Energy Functions



Boas & Harbury, 2007

Potential Energy Function

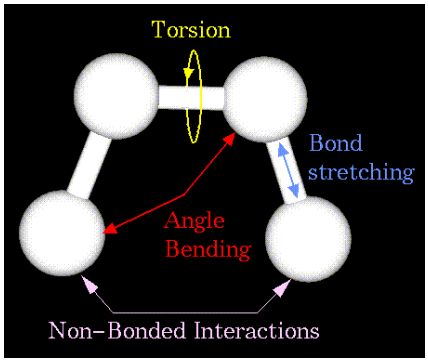
$$PEF(R) = \sum_{bonds} K_b\{b(R)-b_{eq}\}^2 + \sum_{angles} K_\theta\{\theta(R)-\theta_{eq}\}^2 +$$

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

$$\sum_{\substack{non\text{-}bonded\\ atom\ pairs\ i,j}} \left[\frac{A_{ij}}{r_{ij}(R)^{12}} - \frac{B_{ij}}{r_{ij}(R)^{6}} + \frac{q_i q_j}{\varepsilon_r \varepsilon_0 r_{ij}(R)} \right] \quad (1)$$

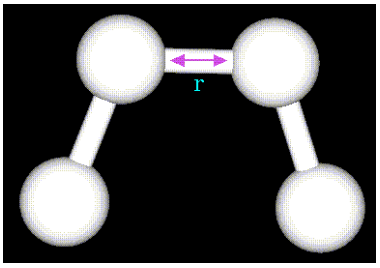
Forcefields: AMBER, CHARMM, CVF, ECEPP, GROMOS

Non-Bonded Interactions

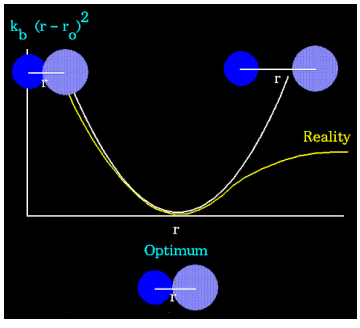


Bond length

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

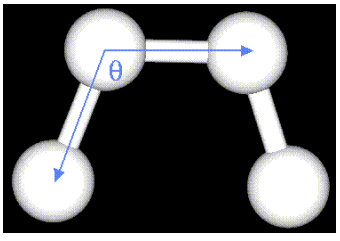


Bond length

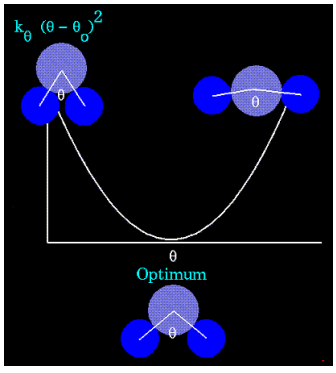


Bond angle

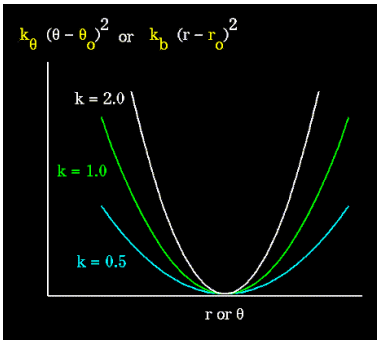
$$E = \sum_{angles} k_\theta (\theta - \theta_o)^2$$



Bond angle

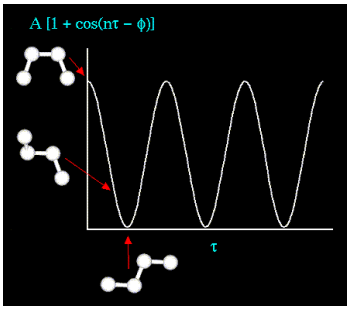


Bond length and angle (parameters)

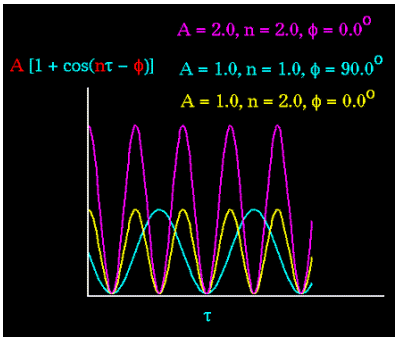


Torsional angle

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



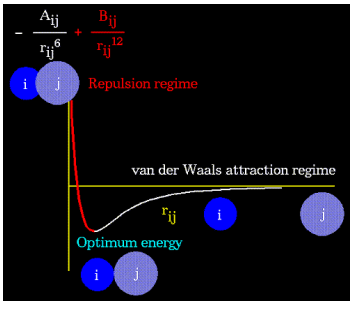
Torsional angle (parameters)



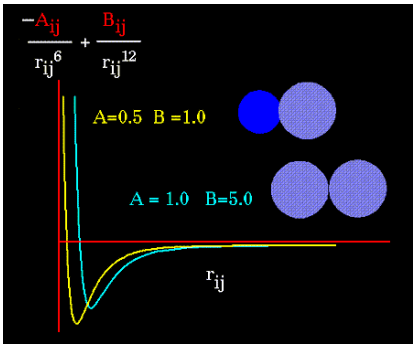
Non-bonded terms

$$E = \sum_i \sum_j \frac{-A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} + \sum_i \sum_j \frac{q_i q_j}{r_{ij}}$$

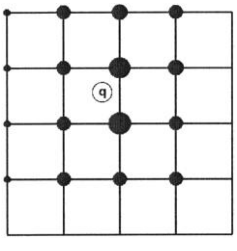
van der Waals term — Electrostatic term



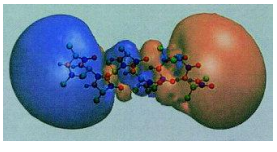
Non-bonded terms (parameters)



Electrostatic interactions



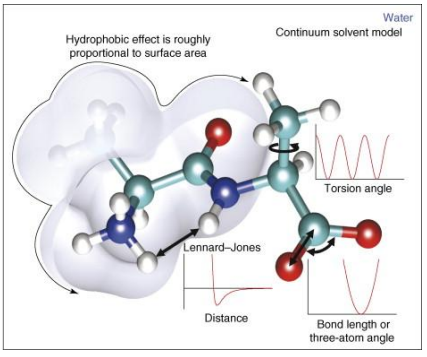
particle-mesh Ewald (PME) summation



electrostatic potential calculated using PME

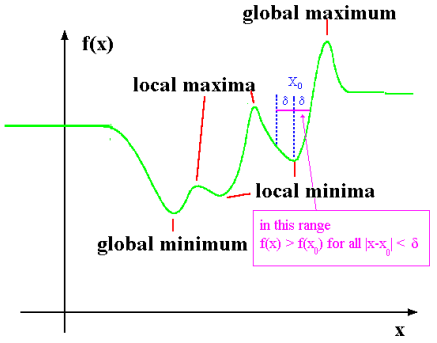
Adopted from J.C.Phillips et al. (2005)

Potential Energy Function



Boas & Harbury, 2007

Energy Minimazation



Energy Minimazation