BINF 731

Protein Structure Analysis

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2020

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

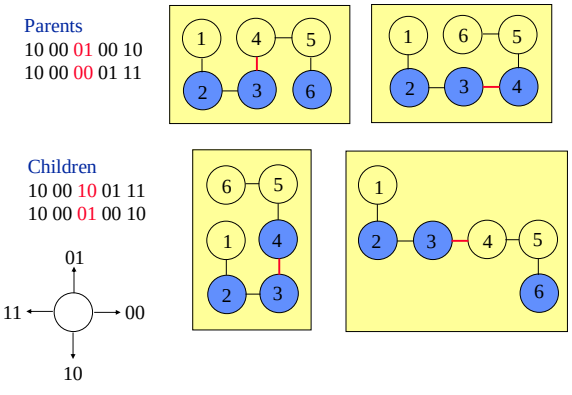
Simplified models
- simplified alphabet (HP)
- simplified representation (lattice)

Build-up techniques

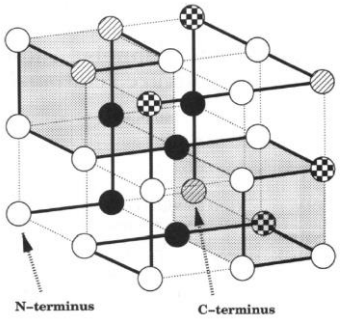
Deterministic methods
- quantum mechanics
- diffusion equations
- DFT

Stochastic searches
- Monte Carlo
- genetic algorithms

Genetic Algorithms Applications



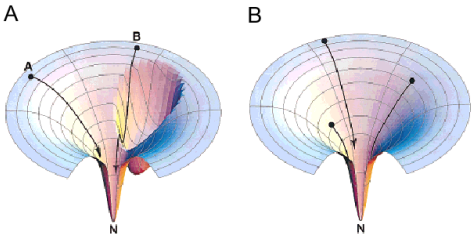
Protein folding funnels



27 unit cubic lattice model

P. Leopold et al., 1992

HP Lattice Models



HP model

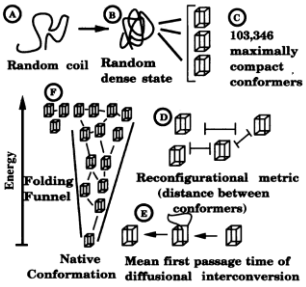
HH	$\varepsilon < 0$
HP	$\varepsilon = 0$
PP	$\varepsilon = 0$

HP+ model

HH	$\varepsilon < 0$
HP	$\varepsilon = 0$
PP	$\varepsilon = 0$
NNC	$\varepsilon > 0$

Chan & Dill, 1998

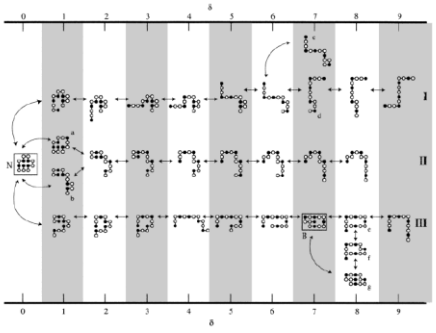
Protein folding funnels



The denatured coil (A) collapses to a random dense structure (B), approximated by a set of maximally compact conformers (C). A reconfigurational distance is defined between compact states (D) and is used to sort pairs of cubes for calculation of the mean first passage time for interconversion (E). The kinetic structure of conformation space (F) shows a folding funnel leading to a unique, locally stable, kinetically accessible state.

P. Leopold et al., 1992

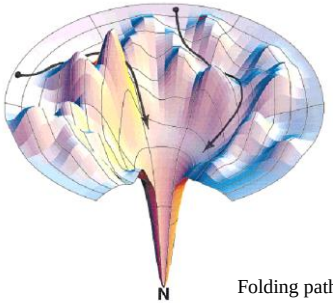
HP Lattice Models



Folding pathways

Chan & Dill, 1998

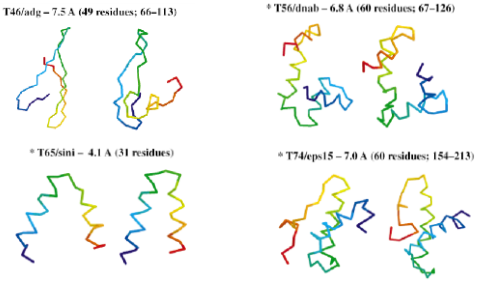
HP Lattice Models



Folding pathways

Chan & Dill, 1998

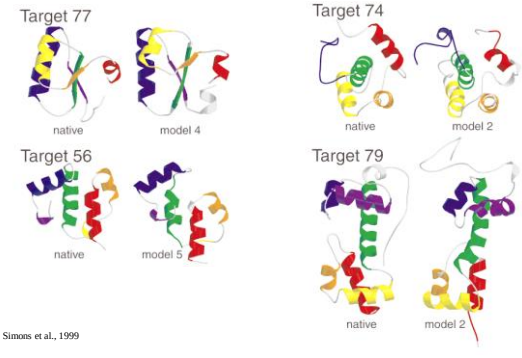
Hierarchical *ab initio* prediction



Lattice models
Knowledge-based scoring functions

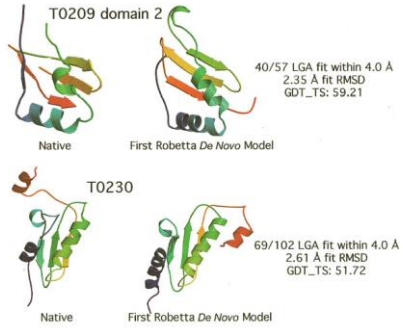
Samudrala et al., 1999

Ab initio prediction using Rosetta



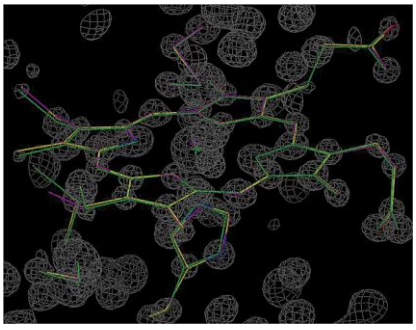
Simons et al., 1999

Ab initio prediction using Robetta



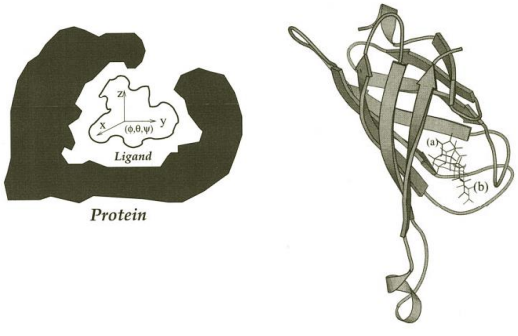
Chivian et al., 2005

Quantum Chemistry Refinement of Protein Structures



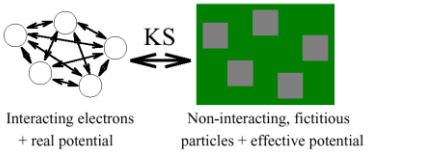
Ryde et al., 2003

Quantum Chemistry Refinement of Protein-Ligand Structures

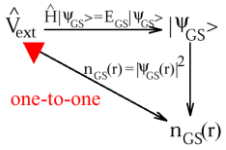


Xiang et al., 2004

Density Functional Theory

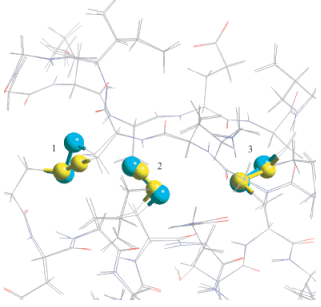


HK theorem: Each local one-particle potential corresponds to exactly one ground state density.



Adopted fromWilfried Aulbur, OSU

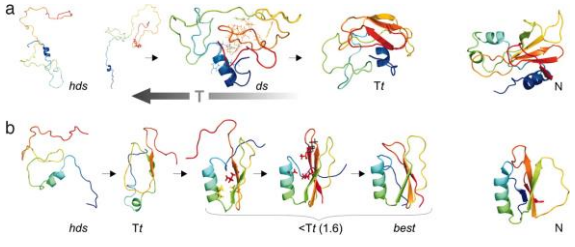
Density Functional Theory



DFT optimization of NMR structure (1PNH)

Andreoni et al., 1999

Folding simulations of high resolution reduced lattice model using Monte Carlo dynamics



S.Kmiecik and A.Kolinski, 2007

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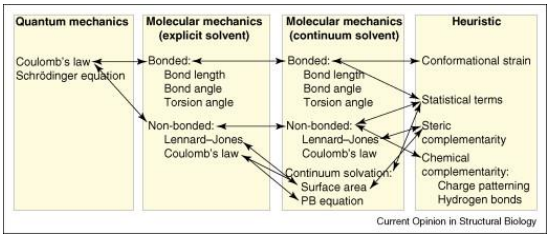
Potential Energy Functions



Boas & Harbury, 2007

Potential Energy Function

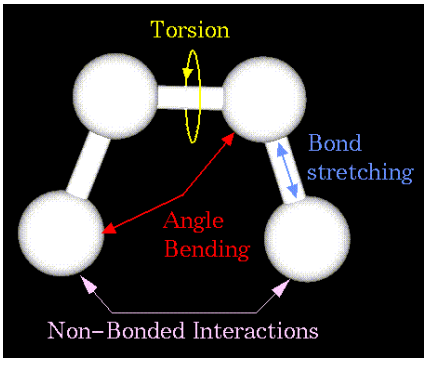
$$PEF(R) = \sum_{bonds} K_b\{b(R)-b_{eq}\}^2 + \sum_{angles} K_\theta\{\theta(R)-\theta_{eq}\}^2 +$$

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

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

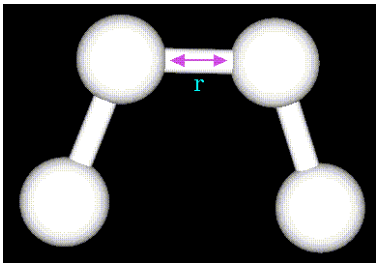
Forcefields: AMBER, CHARMM, CVF, ECEPP, GROMOS

Non-Bonded Interactions

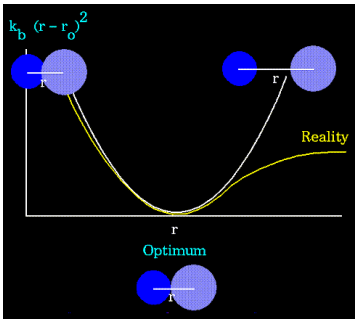


Bond length

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

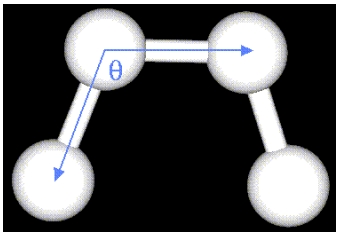


Bond length

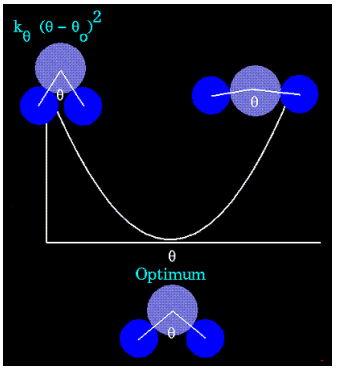


Bond angle

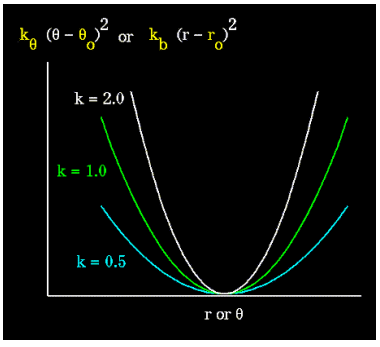
$$E = \sum_{\text{angles}} k_\theta \, (\theta - \theta_o)^2$$



Bond angle

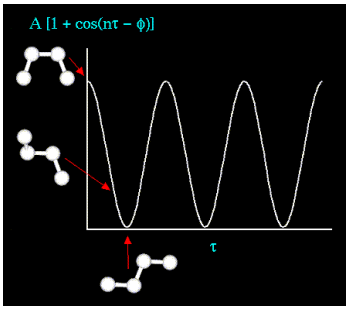


Bond length and angle (parameters)

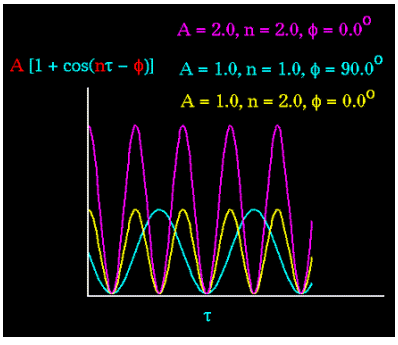


Torsional angle

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



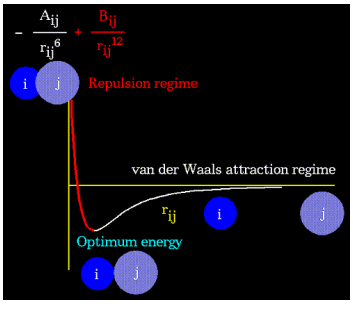
Torsional angle (parameters)



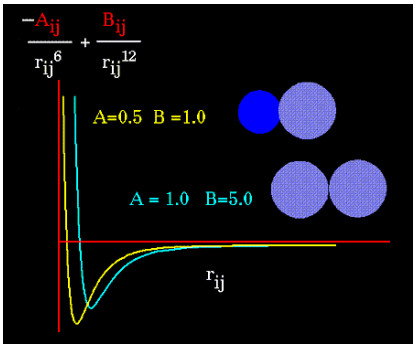
Non-bonded terms

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

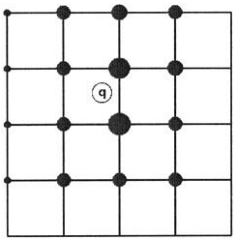
van der Waals term Electrostatic term



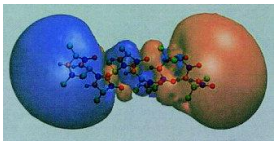
Non-bonded terms (parameters)



Electrostatic interactions



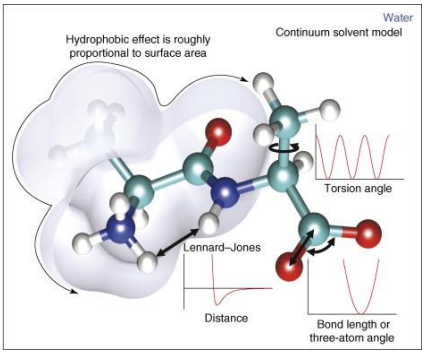
particle-mesh Ewald (PME) summation



electrostatic potential calculated using PME

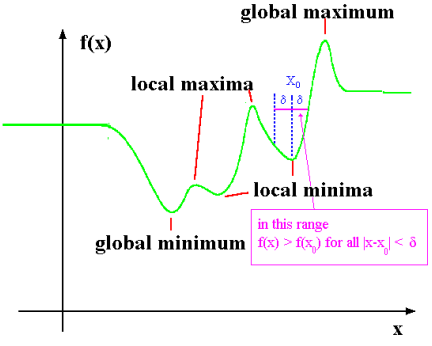
Adopted from J.C.Phillips et al. (2005)

Potential Energy Function



Boas & Harbury, 2007

Energy Minimazation



Energy Minimazation