Protein Structure Analysis

Iosif Vaisman

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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

Ab initio Methods

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

Build-up techniques
  • 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

HP model
HH $\epsilon < 0$
HP $\epsilon = 0$
PP $\epsilon = 0$

HP+ model
HH $\epsilon < 0$
HP $\epsilon = 0$
PP $\epsilon = 0$
NNC $\epsilon > 0$

Chan & Dill, 1998
**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

Density Functional Theory

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

Adopted from Wilfried Aulbur, OSU Density Functional Theory

DFT optimization of NMR structure (1PNH)

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Potential Energy Functions

Potential Energy Function

\[
P_E(R) = \sum_{\text{bonds}} K_b (b(R) - b_0)^2 + \sum_{\text{angles}} K_\theta (\theta(R) - \theta_0)^2 + \sum_{\text{dihedrals}} K_i (1 + \cos[n\psi_i(R) - \gamma]) + \sum_{\text{non-bonded}} \left[ \frac{A_{ij}}{r_{ij}(R)^{12}} - \frac{B_{ij}}{r_{ij}(R)^{6}} + \frac{q_i q_j}{r_{ij}(R)^{\epsilon_i \epsilon_j}} \right]
\]

(1)

Forcefields: AMBER, CHARMM, CVF, ECEPP, GROMOS
Non-Bonded Interactions

- Bond length
- Bond angle
- Bond length and angle (parameters)

\[ E = \sum_{bonds} \kappa_b (r - r_0)^2 \]

Optimum

\[ E = \sum_{angles} \kappa_\theta (\theta - \theta_0)^2 \]
Torsional angle

\[ E = \sum_{\text{tions}} A [1 + \cos(nt - \phi)] \]

Non-bonded terms

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

Electrostatic interactions

Potential Energy Function

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

Boas & Harbury, 2007

Electrostatic potential calculated using PME
Energy Minimization

In the range $f(x) > f(x_j)$ for all $|x_j| < \delta$