BINF 731

Protein Structure Analysis

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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 recogniion

Knowledge-based methods

Finding patterns in known structures

Deriving rules (usually in the form of PMF)

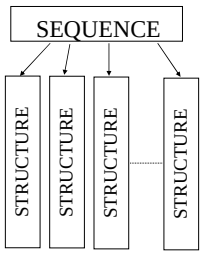
Applying the rules

Fold Recognition

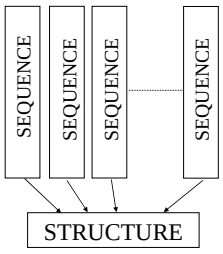
Pattern searching
- sequence patterns
- structure patterns
- residue composition patterns

Threading
- sequence-structure compatibility
- structure-sequence compatibility

Threading



Sequence-structure compatibility (fold recognition)



Structure-sequence compatibility (inverse folding)

Threading

- Only the local environment is taken into account
- Non-local contacts are assumed with generic peptide
- No gaps are allowed in the alignment

Threading Programs

THREADER
(http://insulin.brunel.ac.uk/threader/threader.html)

NCBI Threading
(http://www.ncbi.nlm.nih.gov/Structure/RESEARCH/threading.shtml)

Homology Modeling

- **Identification of structurally conserved regions (using multiple alignment)**
- **Backbone construction (based on SCR)**
- **Loop construction (KB or conformational search)**
- **Side-chain restoration (KB, rotamer, or MM)**
- **Structure verification and evaluation**
- **Structure refinement (energy minimization)**

Homology Modeling Programs

Modeller
(http://guitar.rockefeller.edu/modeller)

Swiss-Model
(http://www.expasy.ch/swissmod)

Whatif
(http://www.cmbi.kun.nl/whatif)

Swiss-Model

- Method:
  Knowledge-based approach.
- Requirements:
  At least one known 3D-structure of a related protein.
  Good quality sequence alignements.
- Procedures:
  Superposition of related 3D-structures.
  Generation of a multiple a alignement.
  Generation of a framework for the new sequence.
  Rebuild lacking loops.
  Complete and correct backbone.
  Correct and rebuild side chains.
  Verify model structure quality and check packing.
  Refine structure by energy minimisation and molecular dynamics.

Methods and Programs used by Swiss-Model

- **Sequence Alignment**
  BLAST (Altschul S.F., *J. Mol. Biol.* **215**:403, 1990)
  SIM (Huang, X., Miller, M. *Adv. Appl. Math.***12**:337, 1991)
  ProModII (Peitsch, M.C. *Unpublished*, Server-specific tool)
- **Knowledge Based Protein Modelling**
  ProMod (Peitsch M.C. *Biochem Soc Trans* **24**:274, 1996)
- **Energy Minimisation**
  Gromos96 (van Gunsteren W.F. *http://igc.ethz.ch/gromos/*)
- **Model evaluation**
  Swiss-PdbViewer
  (*http://www.expasy.ch/spdbv/mainpage.html*)

Swiss-Model Request Types

- First Approach mode.
- Optimise mode.
- Combine mode.
- GPCR mode.

Model Confidence Factors

The Model B-factors are determined as follows:

- The number of template structures used for model building.
- The deviation of the model from the template structures.
- The Distance trap value used for framework building.

The Model B-factor is computed as:

85.0 * (1/ # selected template str.) * (Distance trap / 2.5)
and
99.9 for all atoms added during loop and side-chain building