

Protein Structure Analysis

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Knowledge

Knowledge is a pattern that exceeds certain threshold of interestingness.

- Factors that contribute to interestingness:
- coverage
 - confidence
 - statistical significance
 - simplicity
 - unexpectedness
 - actionability

Fold Recognition

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

- Threading
- sequence-structure compatibility
 - structure-sequence compatibility

- **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

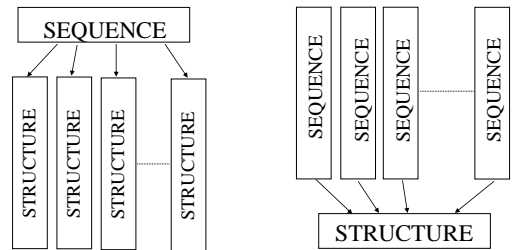
Knowledge-based methods

Finding patterns in known structures

Deriving rules (usually in the form of PMF)

Applying the rules

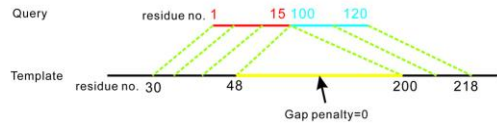
Threading



Sequence-structure compatibility (fold recognition)

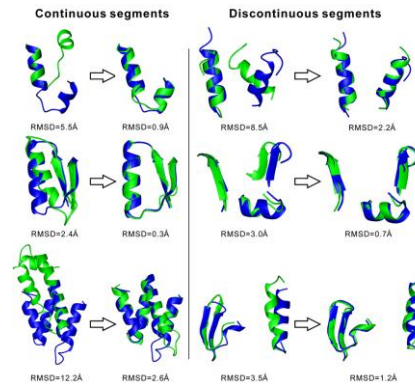
Structure-sequence compatibility (inverse folding)

Segmental Threading



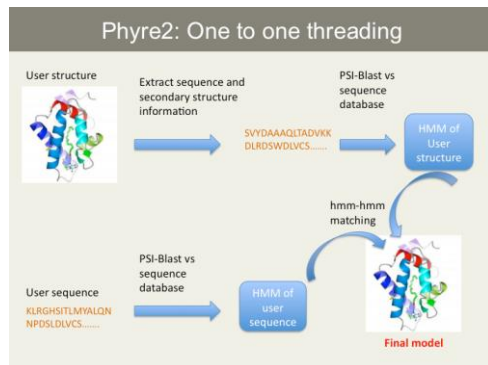
Wu and Zhang, 2010

Segmental Threading



Wu and Zhang, 2010

One to one threading



<http://www.sbg.bio.ic.ac.uk/phyre2>

Threading

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

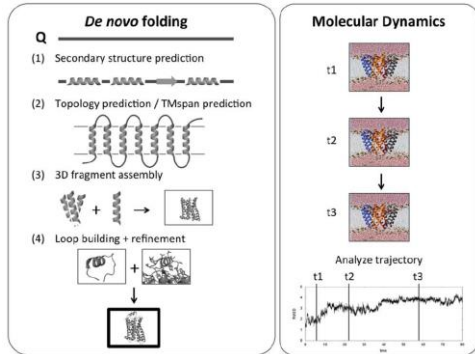
Homology Modeling

- 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)

Swiss-Model

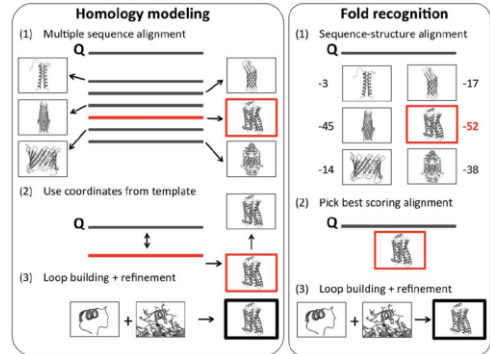
- **Method:** Knowledge-based approach.
- **Requirements:** At least one known 3D-structure of a related protein. Good quality sequence alignments.
- **Procedures:** Superposition of related 3D-structures. Generation of a multiple alignment. Generation of a framework for the new sequence. Rebuild lacking 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.

Protein modeling techniques



J. Koehler Leman et al., 2014

Protein modeling techniques



J. Koehler Leman et al., 2014