Homology Modeling

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Outline

Introduction

Protein structure modeling

- Goal: predict structure from sequence with accuracy comparable to best experimental results
- Major approaches to 3D structure prediction:
  - **Template based modeling**: template available
    - homology modeling (comparative modeling)
    - threading (fold recognition)
  - **Free modeling**: no template available
    - ab initio folding

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- Fundamental observations:
  - amino acid sequence $\rightarrow$ unique structure
  - evolution: structure changes much slower than sequence
    - similar sequences $\rightarrow$ almost identical structures
    - distantly related sequences $\rightarrow$ similar structures
    - two sequences in "safe homology modeling zone" have a similar structure

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Safe homology modeling zone

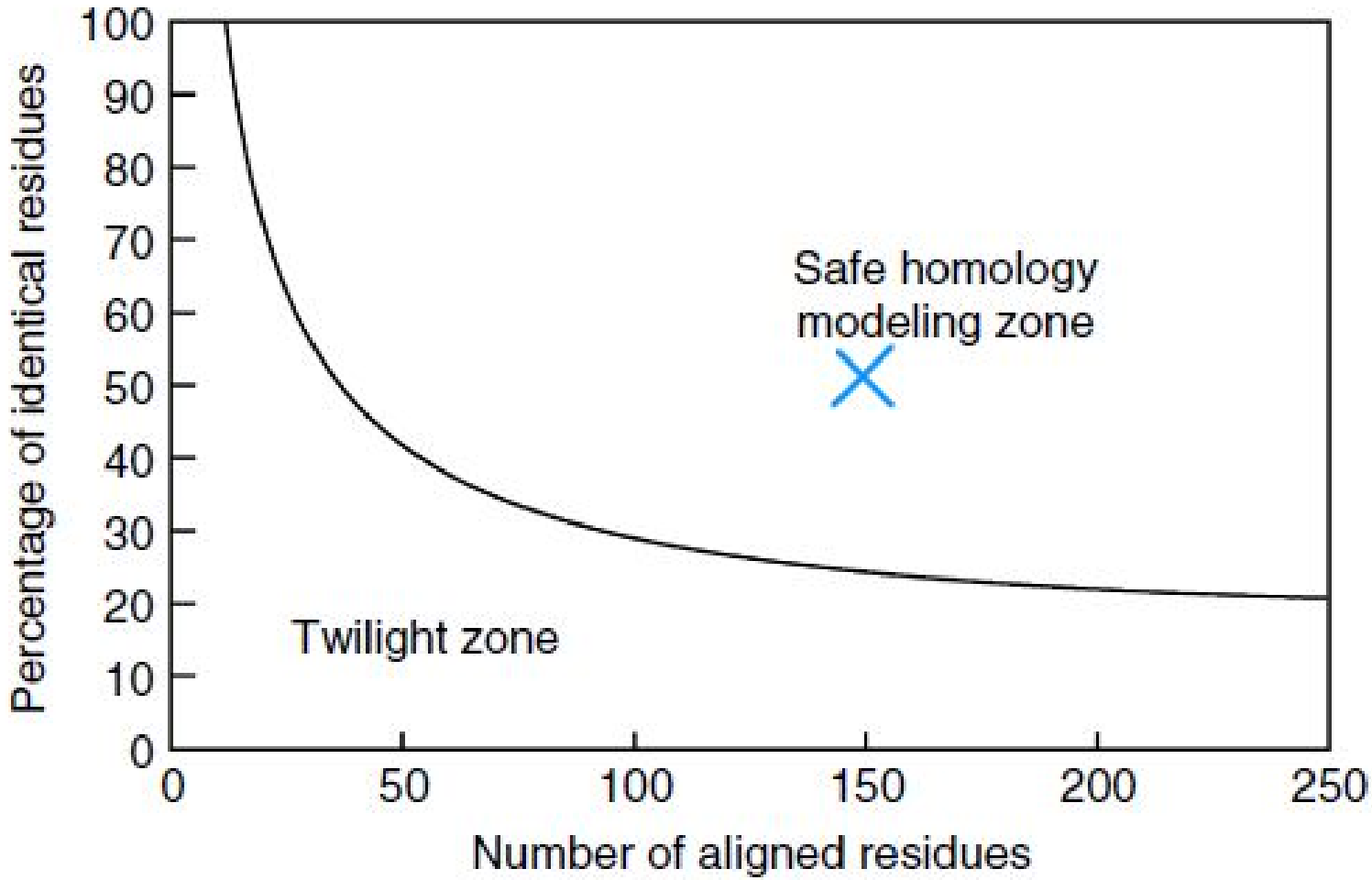

Figure: The two zones of sequence alignments. (Rost B 1999, Twilight zone of protein sequence alignments.)

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Homology modeling

- Terms
  - **Target**: the protein whose structure is to be modeled
  - **Template**: a homologue protein with known structure
- Length and % sequence identity of the alignment between the two must fall into the ”safe” region

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- The steps of homology modeling:
  1. Template selection and original alignment
  2. Alignment correction
  3. Backbone generation
  4. Loop modeling
  5. Side-chain modeling
  6. Model optimization
  7. Model validation
- Steps 3-6: model building

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Homology modeling steps

1. Template selection and original alignment

- Use sequence homology search and alignment tool, e.g. BLAST, with:
  - query sequence: target
  - database: PDB
- Obtained list of hits - the templates and alignments

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2. Alignment correction

- Region of low sequence identity $\rightarrow$ use MSA with other sequences

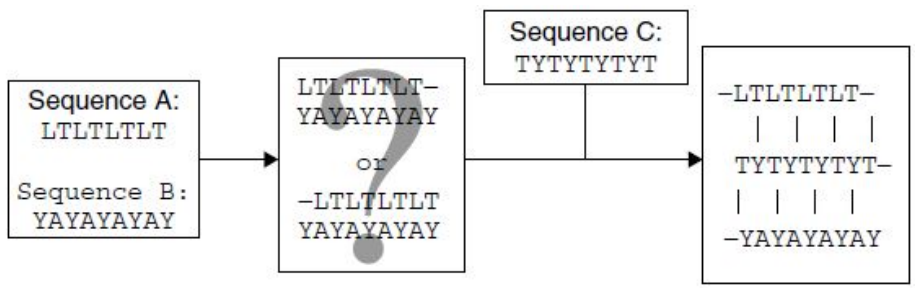


Figure: A third sequence C enables to align sequences A and B
(Krieger et al., Homology Modeling)

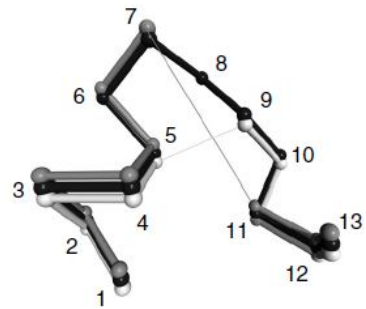
Homology modeling steps

2. Alignment correction

- MSA helps to place deletions or insertions

		1	2	3	4	5	6	7	8	9	10	11	12	13
Template		PHE	ASP	ILE	CYS	ARG	LEU	PRO	GLY	SER	ALA	GLU	ALA	VAL
Model(bad)	1	PHE	ASN	VAL	CYS	ARG	ALA	PRO	---	---	---	GLU	ALA	ILE
Model(good)	2	PHE	ASN	VAL	CYS	ARG	---	---	---	ALA	PRO	GLU	ALA	ILE

(a)



(b)

Figure: (a) The 3-residue deletion appears to be modeled better in the first alignment (aligned proline). (b) Structural alignment with template (C_α-trace: black). While the alignment with the higher score (dark gray) leads to a big gap of 7.5Å, the second alignment has only a tiny gap of 1.3Å. (Krieger et al., Homology Modeling)

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3. Backbone generation

- Copy coordinates of aligned residues from the template
  - if different residues $\rightarrow$ only copy the backbone coordinates (N, C_α, C and O)
  - if identical residues $\rightarrow$ side chain can also be included
- Multiple template modeling: if two templates align (well) to different regions $\rightarrow$ combine the good regions of both templates into one model

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- Treatment of gaps:
  - in the model (deletions) $\rightarrow$ omit residues from the template
  - in the template (insertions) $\rightarrow$ cut the template backbone, insert the missing residues
- $\rightarrow$ conformational change in backbone
  - cannot happen in secondary structure elements $\rightarrow$ in loops and turns
  - difficult to predict!
  - often different also in aligned loops!

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- repeat until convergence
- Strongly depends on energy function

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  1. % sequence identity between template and target
     - >90% → accuracy compared to crystallographically determined structures
     - 50%-90% → RMSD error 1.5Å (larger local errors)
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   - input: amino acid sequence of the target
   - optionally: up to 5 template structures
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   - input: user-defined target-template alignment
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- Four general steps:
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  2. target template alignment
  3. model building
  4. evaluation
- SWISS-MODEL approach: **rigid fragment assembly**
- The procedure steps can be iteratively repeated

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  - Splitting of PDB files into protein chains
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- If found templates cover separate regions of the target $\rightarrow$ modeling separate batches independently

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- Joining of rigid fragments
  $\rightarrow$ deviations in target structure geometry
  $\rightarrow$ regulation by **steepest descent energy minimization**

SWISS-MODEL

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- Several tools to evaluate reliability of the model:
  - **C-score** estimates variability of the template structure at each position (IN/DELs: C-score=99)
  - **Force field energy for the overall structure/each residue** identifies regions with conformational or electrostatic problems
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   Full-atomic model built by REMO from C_α-traces
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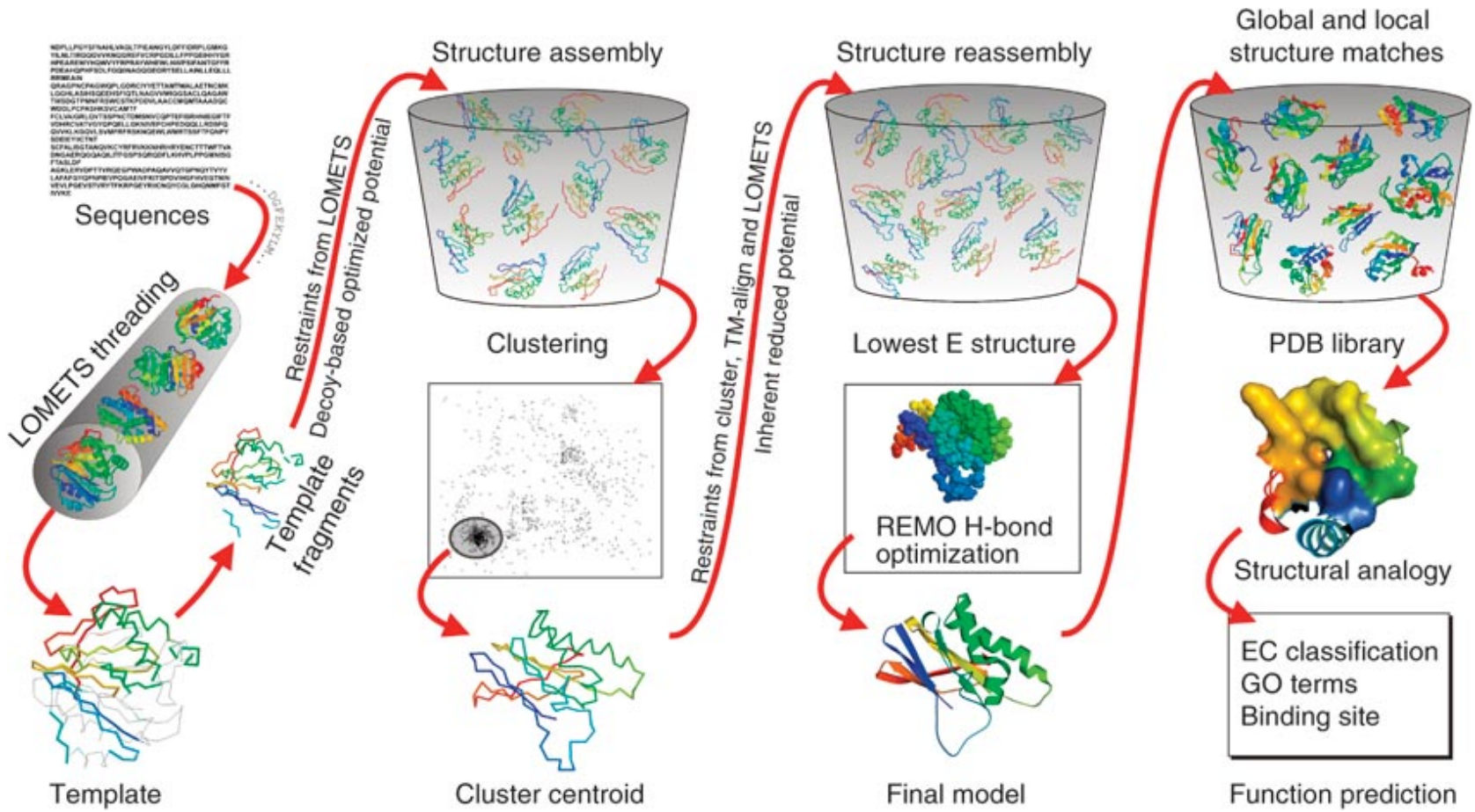
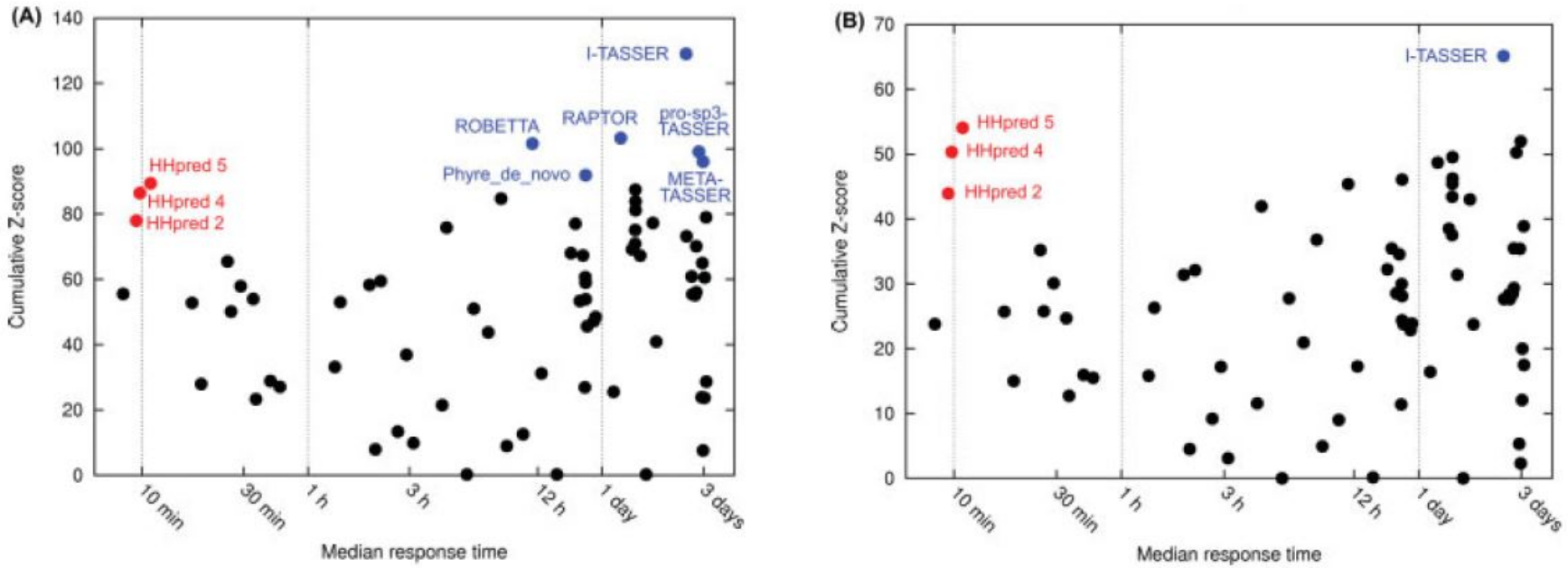


Figure: I-TASSER pipeline. (Roy, Kucukural, Yang 2010, I-TASSER: a unified platform for automated protein structure and function prediction.)

CASP8 results



(a) (b)

Figure: Model accuracy versus response time for the 72 servers in CASP8 (a) on the 164 target domains and (b) on the 85 single-domain targets. (Soeding et al. 2009, Fast and accurate automatic structure prediction with HHpred.)

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