Computer Aided Drug Design

——Protein structure prediction

Qin Xu
http://cbb.sjtu.edu.cn/~qinxu/CADD.htm
Course Outline

• Introduction and Case Study
• Drug Targets
  – Sequence analysis
  – Protein structure prediction
  – Molecular simulation
• Drug Design
  – Combinatorial library
  – 3D-QSAR
  – Statistical methods
• Molecular Docking
Why protein structure prediction?

By 2014/09

UniProtKB

Swiss-Prot (546,238)
- Manually annotated and reviewed.

TrEMBL (82,126,897)
- Automatically annotated and not reviewed.

Non-redundant protein sequences (nr)

Title: All non-redundant GenBank CDS translations+PDB+SwissProt+PIR+PRF excluding environmental samples from WGS projects
Molecule Type: Protein
Update date: 2014/09/23
Number of sequences: 49813357

The huge differences in known protein sequences, 3 dimensional structures and functions
Why we can do protein structure prediction?

- **Sequence**
  - From DNA/RNA sequence
  - Protein sequencing

- **Structure**
  - Secondary structure
  - Tertiary structure
  - Quaternary structure

- **Function**
  - Activity, specificity
  - Binding
  - Regulation

Anfinsen's dogma: the native structure of a globular proteins is determined only by the protein's amino acid sequence
Protein structure prediction

• Secondary structure prediction
  – Distribution of amino acids
  – Featured sequence ➔ Featured domain

• Tertiary structure prediction
  – The 3D structure of target proteins
  – Structure of active site, binding site, possible conformational changes
  – Molecular docking, molecular dynamics simulations
Protein 3D structure prediction

1. Protein sequence
2. Database similarity search
3. Does sequence align with protein of known 3D structure?
   - Yes: 3D comparative modeling
   - No: Protein family, domain, cluster analysis
4. Relationship to known structure?
   - Yes: Predicted three dimensional structure
   - No: Structural analysis
5. Is there a predicted structure?
   - Yes: 3D analysis in laboratory
   - No: Structural analysis
Protein 3D structure prediction

• Homology Modeling
  – Homolog template
  – Similar sequence $\rightarrow$ similar secondary structure $\rightarrow$ similar featured domain $\rightarrow$ similar backbone $\rightarrow$ similar 3D structure with optimized side chains

• Threading method
  – Fold recognition method
  – Long distance homology protein

• Ab initio prediction
  – Sequence $\rightarrow$ Structure
  – Conformer search
  – Energy minimization
Basic steps in homology modeling

BLAST, FASTA, PSI-BLAST,...
http://www.ebi.ac.uk/Tools/ss/fasta/

CLUSTAL,...
http://www.ebi.ac.uk/Tools/msa/clustalw2/

MODELLER, SWISS-MODEL
http://salilab.org/modeller/, swissmodel.expasy.org/

PROCHECK, VERIFY3D,...
http://www.ebi.ac.uk/thornton-srv/software/PROCHECK/
http://nihserver.mbi.ucla.edu/Verify_3D/
Welcome to SWISS-MODEL

SWISS-MODEL is a fully automated protein structure homology-modelling server, accessible via the ExPASy web server, or from the program DeepView (Swiss Pdb-Viewer). The purpose of this server is to make Protein Modelling accessible to all biochemists and molecular biologists worldwide.

Start Modelling

"SWISS-MODEL: modelling protein tertiary and quaternary structure using evolutionary information" has been accepted in Nucleic Acids Research web server issue. You can download the abstract, full text or PDF.

Protein Structure Bioinformatics Group
c/o Prof. Torsten Schwede
Swiss Institute of Bioinformatics
Biozentrum, University of Basel
Klingelbergstrasse 50/70
CH-4056 Basel / Switzerland
help-swissmodel@unibas.ch
Homology Modeling with SWISS-MODEL
Search for Templates

Start a New Modelling Project

Target Sequence:
(Paste your target sequence here)

Supported Inputs:
- Sequence
- Uniprot AC
- Target-Template Alignment
- Upload Template
- Deepview Project

Project Title:
Untitled Project

Email:
Optional

Search For Templates
Build Model

By using the SWISS-MODEL server, you agree to comply with the following terms of use and to cite the corresponding articles.
# Homology Modeling with SWISS-MODEL

## Untitled Project

Created: today at 13:11

**Summary**

**Templates** 50  **Models** 0

### Template Results

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<th>Identity</th>
<th>Method</th>
<th>Oligo State</th>
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<td>hetero-oligomer</td>
<td>2 x ZN²⁺, 1 x Ca²⁺</td>
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<td>2 x ZN²⁺, 4 x Ca²⁺</td>
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### Oink

Your browser does not support WebGL. You might want to try Chrome, Firefox, IE 11, or newer versions of Safari.

If you are using a recent version of Safari, your graphic card might be blocked. Check the browser documentation for details.

- **View**
  - 1ck7.1A
  - 1gxd.1A
Homology Modeling with SWISS-MODEL

UniProt AC

Start a New Modelling Project

Uniprot AC: Q6GZX4

Target Sequence:
- Target: HAFSAEDVLKEYDRRRMEAMLLSLLYYPNDRLKLLDDKEWSPPRQVCPEPAPVEWNNPSESERKLIVGCHFPSGIYK
- Target: GSKAQASEVDVVKNCWSEKFMRMQQGITCKIPGVSVALKIAKYNLTVGVEEFNVYDSTVQHVAAS
- Target: LRELHRSKQVENYGLHILTLDRVDOQHLRLDVKDFKALVESEAHRMRQGHMINVYILQLYKHKHGPFDGD
- Target: ILTVKTSKGVLIDDSFRKITYTDLGWKFPT

Supported Inputs:
- Sequence
- Target-Template Alignment
- Upload Template
- Deepview Project

Project Title: 001R.FR3G Q6GZX4 Putative transcription factor 001R

Email: Optional

Search For Templates Build Model
Homology Modeling with SWISS-MODEL

UniProt AC

UniProtKB consists of two sections:

- **Reviewed (Swiss-Prot)** - Manually annotated
  Records with information extracted from literature and curator-evaluated computational analysis.

- **Unreviewed (TrEMBL)** - Computationally analyzed
  Records that await full manual annotation.

The UniProt Knowledgebase (UniProtKB) is the central hub for the collection of functional information on proteins, with accurate, consistent and rich annotation. In addition to capturing the core data mandatory for each UniProtKB entry (mainly, the amino acid sequence, protein name or description, taxonomic data and citation information), as much annotation information as possible is added.

Results

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<th>Gene names</th>
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Homology Modeling with SWISS-MODEL

Known template

---

Start a New Modelling Project

- Target: KSCCPRTAARNQYNICRLPGTPFPVCAALSGCKIISGTGCPPGYRH
  1crn.1.A: TCCPSIVARSNFTVCRPLGPTCAACATYTGCIIIPEAGACPGYAN

Supported Inputs

- Sequence
- Uniprot AC
- Target-Template Alignment
- Upload Template
- Deepview Project

Build Model

Sequence Identity: 50.00

Upload Target-Template Alignment File...

Project Title: Template Alignment: 1crn.1

Email: Optional

---

By using the SWISS-MODEL server, you agree to comply with the following terms of use and to cite the corresponding articles.
Homology Modeling with SWISS-MODEL Results
Homology Modeling with MOE

• MOE
  – Molecular Operating Environment
  – http://www.chemcomp.com/
  – Current release: MOE2013.08

• SAMM
  – Shanghai Molecular Modeling
Forcefield setup

MMFF94x (default): small molecules and compounds
Amber99, CHARMM27, OPLS-AA: macromolecules, proteins

MOE|Window|Potential Setup…Load
• Target 69 of CASP4
Searching templates
Alignment

SE|Homology|Align
Sequence identity is a key factor for the accuracy of protein structure prediction.

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Sequence identity and Model precision

% structure overlap
the fraction of equivalent residues
(Cα atoms within 3.5Å each other).
Sequence identity and Model accuracy

Table: Best results with CASP3 targets*

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<th>% identity</th>
<th>C$\alpha$ r.m.s. deviation (Å)</th>
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r.m.s deviation = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\vec{R}_i^{\text{expt}} - \vec{R}_i^{\text{pred}})^2}

Sequence identity and applications

- Comparable to medium resolution NMR.
- Fine specificity.
- Docking of small ligands, proteins.

- Molecular replacement in crystallography.
- Engineering of proteins.
- Support site-directed mutagenesis experiments.

- NMR structure refinement.
- Finding binding/active sites by 3D motif searching.
- Functional annotation by fold assignment.
Homology modeling
# Models in database

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<td>0.3737</td>
<td>-92.4200</td>
<td>2.2006</td>
<td>-2333.</td>
<td>-3005.</td>
<td>-606.</td>
<td>1818</td>
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<td>0.2551</td>
<td>-94.9756</td>
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</table>
Secondary structures of Models
3D Structures of Models
backbones variations at a loop

Database Viewer (right click on models)
Copy selected to MOE
3D Structures of Models
detailed variations at a loop

SE|Selection|Residues|With Selected Atoms
Model Evaluation

Ramachandran Plot (Phi-Psi Plot)  Dihedrals
MOE|Compute|Biopolymer|Protein Geometry
Report on outliers

Phi/Psi Plot Values

Cutoff-Value: 0.0005

<table>
<thead>
<tr>
<th>Chain</th>
<th>Residue</th>
<th>Psi</th>
<th>Phi</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>[t69]</td>
<td>GLN 128</td>
<td>2.7</td>
<td>74.0</td>
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<td>LYS 64</td>
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<td>3</td>
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<td>PRO 129</td>
<td>49.2</td>
<td>-142.3</td>
</tr>
</tbody>
</table>

95.36% of the residues are in the core region of the Ramachandran Map.
Core: Score > 0.02  Allowed: 0.0005 <= Score <= 0.02  Outlier: Score < 0.0005

Backbone Dihedral Values

Z-Score Threshold: 4.0

<table>
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<tr>
<th>Chain</th>
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<th>Angle</th>
<th>Z-Score</th>
<th>Torsion</th>
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</table>
Select and View outliers
Binding site

MOE|Compute|Site finder

MOE|Compute|Surface and Maps
Course Outline

• Introduction and Case Study

• Drug Targets
  – Sequence analysis
  – Protein structure prediction
  – Molecular simulation

• Drug Design
  – Combinatorial library
  – 3D-QSAR
  – Statistical methods

• Molecular Docking