CS597A
Structural Bioinformatics

Thomas Funkhouser
Princeton University
Fall 2005

Outline

Overview of structural bioinformatics
- Goals
- Challenges
- Applications

Overview of course
- Goals
- Lectures
- Coursework
- Projects
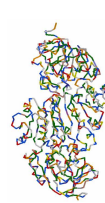

Bioinformatics

Definition:
- "The collection, archiving, organization, and interpretation of biological data." [Orengo, 2003]
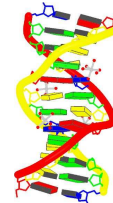
Generally speaking:
- Large biological data sets
- Computer representations and algorithms
- Storage, analysis, visualization, prediction, and design

Structural Bioinformatics

Focus on data sets with molecular structure
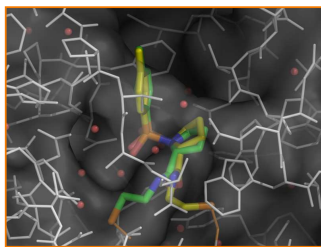

Proteins
[RCSB]

DNA
[NDB]

Small Molecules
[CCDC]

Structural Bioinformatics

Motivation 1:
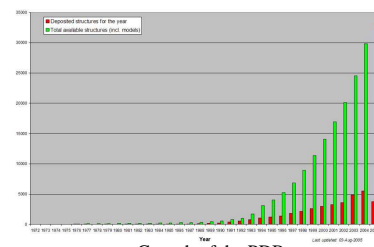- Detailed understanding of molecular interactions

[pymol.sourceforge.net]

Structural Bioinformatics

Motivation 2:
- Lots of structural data is becoming available

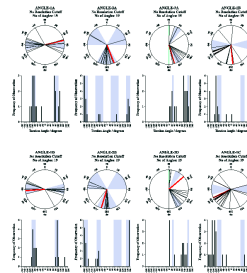Growth of the PDB
[RCSB]

Structural Bioinformatics

Goals:
- Analysis
- Visualization
- Comparison
- Prediction
- Design

Structural Bioinformatics

Goals:
- ØAnalysis
- Visualization
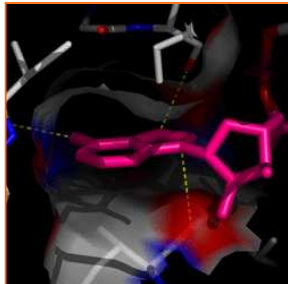- Comparison
- Prediction
- Design

Geometrical and conformational analysis of Haem Ligand (7cat)
[Karmirantzou and Thornton]

Structural Bioinformatics

Goals:
- Analysis
- ØVisualization
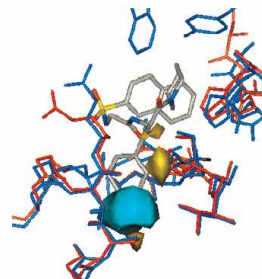- Comparison
- Prediction
- Design

Adenine ring from FAD bound to 1uxy
[Stockwell05]

Structural Bioinformatics

Goals:
- Analysis
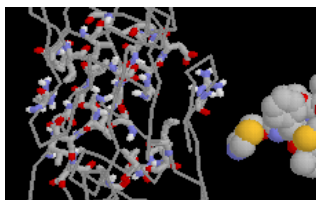- Visualization
- ØComparison
- Prediction
- Design

Comparison of S1 binding pockets of thrombin (blue) and trypsin (red).
Cyan (yellow) regions are more favorable for trypsin (thrombin) when binding NAPAP (gray).
[Katzenholtz00]

Structural Bioinformatics

Goals:
- Analysis
- Visualization
- Comparison
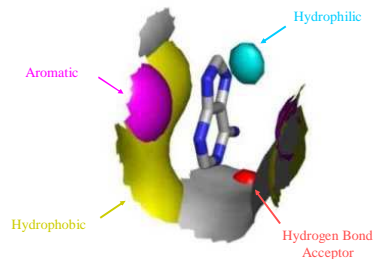- ØPrediction
- Design

Simulation of inhibitor Ritonavir binding to HIV protease
[Protein Explorer]

Structural Bioinformatics

Goals:
- Analysis
- Visualization
- Comparison
- Prediction
- ØDesign

Hydrophilic

Aromatic

Hydrophobic

Hydrogen Bond
Acceptor

Model derived from all adenine binding sites in PDB
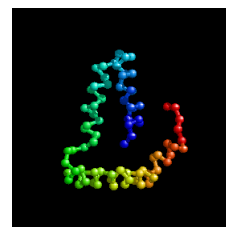[Stockwell05]

Structural Bioinformatics

Research challenges:
- Structure determination
- Binding site detection
- Binding site modeling
- Binding site matching
- Binding prediction
- Molecular design
- etc.

Structural Bioinformatics

Research challenges:
- Ø Structure determination
- Binding site detection
- Binding site modeling
- Binding site matching
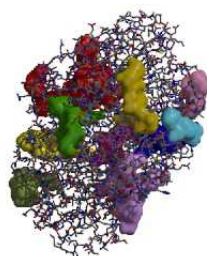- Binding prediction
- Molecular design
- etc.

Protein Folding Simulation
[David Jones]

Structural Bioinformatics

Research challenges:
- Structure determination
- Ø Binding site detection
- Binding site modeling
- Binding site matching
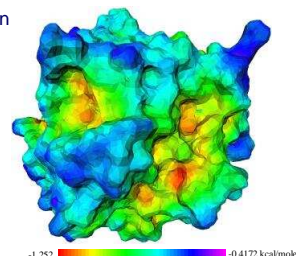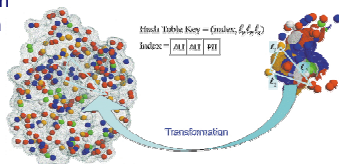- Binding prediction
- Molecular design
- etc.

Surface Clefts detected in 1b14
[Surfnet]

Structural Bioinformatics

Research challenges:
- Structure determination
- Binding site detection
- Ø Binding site modeling
- Binding site matching
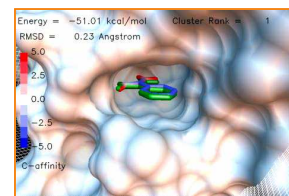- Binding prediction
- Molecular design
- etc.

-1.252   -0.4172 kcal/mole/e

Surface potential for the Carboxypeptidase A
[Continuum Dynamics]

Structural Bioinformatics

Research challenges:
- Structure determination
- Binding site detection
- Binding site modeling
- Ø Binding site matching
- Binding prediction
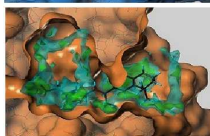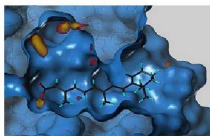- Molecular design
- etc.

Hash Table Key – (radius; $\ell_p \ell_q \ell_r$)
Index – | ALT | ALT | VAL |

Transformation

[Shulman-Peleg04]

Structural Bioinformatics

Research challenges:
- Structure determination
- Binding site detection
- Binding site modeling
- Binding site matching
- Ø Binding prediction
- Molecular design
- etc.

Energy = −51.01 kcal/mol   Cluster Rank = 1
RMSD = 0.23 Angstrom

Benzamidine binding to beta-Trypsin (3ptb)
[AutoDock]

Structural Bioinformatics

Research challenges:
- Structure determination
- Binding site detection
- Binding site modeling
- Binding site matching
- Binding prediction
- ØMolecular design
- etc.

SuperStar HDS maps for the binding site of the protein-ligand complex 1CBX. The ligand is coloured gold. Blue binding site shows map for carbonyl oxygen probe. Amber binding site shows map for aromatic CH carbon probe.
[CCDC]

Structural Bioinformatics

Applications:
- Biology
- Medicine
- Agriculture
- Industry
- etc.

Outline

Overview of structural bioinformatics
- Goals
- Challenges
- Applications

Overview of course ←
- Goals
- Lectures
- Coursework
- Projects

CS597A

Goals
- Survey current methods in structural bioinformatics
- Investigate specific research problems in depth
- Build shared infrastructure for research
- Build links across disciplines

Lectures

Class meetings:
- One topic per meeting
- 50% lecture
- 50% discussion

Speakers:
- Professors
- Guests
- Students

Lectures

Student presentations:
- Choose topic from schedule
- Submit list of relevant papers/resources
- 15-20 minute presentation
- Lead discussion afterwards

Readings

Book
- P.E. Bourne, H. Weissig, "Structural Bioinformatics," Wiley-Liss, 2003.

Papers
- Read ~1 paper for each lecture
- Be prepared for class discussion

Course Projects

Description
- Investigate research problem
- Any problem(s) related to course
- Multi-disciplinary teams (if possible)

Dates
- Proposal (Oct 19)
- Presentation I (Nov 16)
- Presentation II (Dec 14)
- Presentation III (~Jan 15)
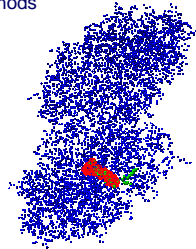- Written report (~Jan 15)

Course Projects

Example projects
- Develop new method
- Evaluate/compare existing methods
- Combine methods in system
- Apply method

Key elements
- Investigation
- Evaluation

Wrap Up

Students' to do list:
- Hand in survey questionaire
- Send me a picture of yourself by email
- Sign up for in-class presentations
- Start thinking about project topics