

Syllabus of BIOINF 528 (2017 Fall, Bioinformatics Program)

Course Name:

Structural Bioinformatics

Course Description:

This course introduces fundamental concepts and methods for structural bioinformatics and the advanced applications. Topics covered include sequence, structure and function databases of DNA and protein molecules, advanced sequence and structure alignment methods, methods of protein folding and protein structure prediction (homologous modeling, threading and *ab initio* folding), basics of molecular dynamics and Monte Carlo simulation, principle and application of machine learning, and techniques of protein structure determination (X-ray crystallography, NMR and cryo-EM). Emphasis is on the understanding of the concepts taught and the practical utilization, with the objective to help students to use the cutting-edge bioinformatics tools/methods to solve problems in their own research. For this term, four world's top experts are invited to give lectures on mass spectrometry and proteomics (Prof. Philip Andrews), NMR spectroscopy (Prof. Tomek Cierpicki), Cryo-electron microscopy (Prof. Melanie Ohi), and X-ray crystallography (Prof. Mark Saper).

Instructor:

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Schedule and location:

9:00 am - 12:00 noon, Friday; #2036 Palmer Commons

Textbook:

No textbook is required for this course. All teaching materials will be posted on the website of the class.

Presentation, homework, & grades:

There will be homework assignments, including code writing and literature reading and presentation. Final grade consists of literature presentation (20%), homework (30%), and exam (50%).

Table of content

1. Bioinformatics databases

- 1.1. Introduction
 - 1.1.1. Motivation
 - 1.1.2. Central dogma of life
 - 1.1.3. Type of bioinformatics databases
- 1.2. Nucleotide sequence databases
 - 1.2.1. EMBL
 - 1.2.2. GeneBank
 - 1.2.3. DDBJ
- 1.3. Protein amino acid sequence databases
 - 1.3.1. How protein sequences are determined
 - 1.3.1.1. DNA/mRNA coding
 - 1.3.1.2. Edman degradation reaction
 - 1.3.1.3. Mass spectrometry
 - 1.3.2. SwissProt/TrEMBL
 - 1.3.3. PIR
 - 1.3.4. UniProt
 - 1.3.4.1. UniProtKB/Swiss-Prot and UniProtKB/TrEMBL
 - 1.3.4.2. UniParc
 - 1.3.4.3. UniRef
- 1.4. Protein structure databases
 - 1.4.1. History of structural biology
 - 1.4.2. Protein Data Bank
 - 1.4.3. SCOP
 - 1.4.4. CATH
- 1.5. Protein function databases
 - 1.5.1. Pfam-protein family database
 - 1.5.2. GO-gene ontology
 - 1.5.3. PROSITE-protein function pattern and profile
 - 1.5.4. ENZYME-Enzyme commission
 - 1.5.5. BioLiP-ligand protein binding interaction

2. Pair-wise sequence alignments and database search

- 2.1. Biological motivation-why sequence alignment?
- 2.2. What is a sequence alignment?
 - 2.2.1. Scoring matrix
 - 2.2.1.1. PAM
 - 2.2.1.2. BLOSUM
 - 2.2.2. Gap penalty
- 2.3. Dynamics programming
 - 2.3.1. Needleman-Wunsch: global alignment algorithm
 - 2.3.2. Smith-Waterman: local alignment algorithm
 - 2.3.3. Gotoh algorithm

- 2.4. Heuristic methods
 - 2.4.1. FASTA
 - 2.4.2. BLAST
- 2.5. Statistics of sequence alignment score
 - 2.5.1. E-Value
 - 2.5.2. P-Value
- 3. Phylogenetic tree & multiple sequence alignments**
 - 3.1. Neighbor-joining method and phylogenetic tree
 - 3.2. How to construct multiple sequence alignments?
 - 3.2.1. ClustalW
 - 3.2.2. PSI-BLAST
 - 3.2.2.1. PSI-Blast pipeline
 - 3.2.2.2. Profile pseudocount
 - 3.2.2.3. PSSM-position specific scoring matrix
 - 3.2.2.4. Installing and running PSI-Blast programs
 - 3.2.2.5. Interpret PSI-Blast out
 - 3.2.3. Hidden Markov Models
 - 3.2.3.1. Viterbi algorithm
 - 3.2.3.2. HMM based multiple-sequence alignment
 - 3.2.3.2.1. Creating HMM by iteration
 - 3.2.3.2.2. HMMER
 - 3.2.3.2.3. SAM
 - 3.3. Sequence profile & profile based alignments
 - 3.3.1. What is sequence profile?
 - 3.3.2. Henikoff weighting scheme
 - 3.3.3. Profile-to-sequence alignment
 - 3.3.4. Profile-to-profile alignment
- 4. Protein structure alignments**
 - 4.1. Structure superposition versus structural alignment
 - 4.2. Structure superposition methods
 - 4.2.1. RMSD
 - 4.2.2. TM-score
 - 4.3. Structure alignment methods
 - 4.3.1. DALI
 - 4.3.2. CE
 - 4.3.3. TM-align
 - 4.4. How to define the fold of proteins?
 - 4.5. Number of protein folds in the PDB
- 5. Protein secondary structure predictions**
 - 5.1. What is protein secondary structure?
 - 5.2. Hydrogen bond
 - 5.3. How to define a secondary structure element?
 - 5.4. Basics of machine learning and neural network methods
 - 5.5. Methods for predicting secondary structure
 - 5.5.1. Chou and Fasman method

- 5.5.2. PHD
- 5.5.3. PSIPRED
- 5.5.4. PSSpred

6. Introduction to Monte Carlo Simulation

- 6.1. Introduction: why Monte Carlo simulation?
- 6.2. Monte Carlo Sampling of Probabilities
 - 6.2.1. Random number generator
 - 6.2.1.1. How to test a random number generator?
 - 6.2.2. Sampling of rectangular distributions
 - 6.2.3. Sampling of probability distribution
 - 6.2.3.1. Reverse transform method
 - 6.2.3.2. Rejection sampling method
- 6.3. Boltzmann distribution
- 6.4. Metropolis method
- 6.5. Advanced Metropolis methods
 - 6.5.1. Replica exchange simulation
 - 6.5.2. Simulated annealing

7. Protein folding and protein structure modeling

- 7.1. Basic concepts
- 7.2. Ab initio modeling
 - 7.2.1. Anfinsen thermodynamic hypothesis
 - 7.2.2. Molecular dynamics simulation
 - 7.2.2.1. CHARMM
 - 7.2.2.2. AMBER
 - 7.2.3. Knowledge-based free modeling
 - 7.2.3.1. Bowie-Eisenberg approach
 - 7.2.3.2. ROSETTA
 - 7.2.3.3. QUARK
 - 7.2.3.4. Why is beta-protein so difficult to fold?
- 7.3. Comparative modeling (homology modeling)
 - 7.3.1. Principle of homology modeling
 - 7.3.2. PSI-BLAST
 - 7.3.3. Modeller
- 7.4. Threading and fold-recognition
 - 7.4.1. What is threading?
 - 7.4.2. Threading programs
 - 7.4.2.1. Bowie-Luthy-Eisenberg
 - 7.4.2.2. HHpred
 - 7.4.2.3. MUSTER
 - 7.4.3. Meta-server threading
 - 7.4.3.1. 3D-jury
 - 7.4.3.2. LOMETS
- 7.5. Combined modeling approaches
 - 7.5.1. TASSER/I-TASSER
 - 7.5.1.1. Force field design
 - 7.5.1.2. Search engine: replica-exchange Monte Carlo simulation

- 7.5.1.3. Major issues and recent development
- 7.6. CASP: A blind test on protein structure predictions

8. Protein function and structure-based function annotation

- 8.1. Gene ontology
- 8.2. Enzyme classification
- 8.3. Ligand-protein interaction
- 8.4. Structure-based function prediction
 - 8.4.1. Concavity
 - 8.4.2. FindSite
 - 8.4.3. COFACTOR
 - 8.4.4. COACH

9. Principle of X-ray Crystallography & Molecular Replacement

- 9.1. What is X-ray Crystallography
- 9.2. Why can a wave be represented by $\exp(i\alpha)$?
- 9.3. How to calculate scattering on two electrons?
- 9.4. What is Laue condition?
- 9.5. What is Bragg's law?
- 9.6. How to calculate electron density of crystal?
- 9.7. What is Patterson function?
- 9.8. How to calculate electron density of crystal?
- 9.9. What is the idea of Molecular Replacement?
- 9.10. How to judge quality of MR?
- 9.11. What are often-used software for MR?

10. Introduction to nuclear magnetic resonance (NMR)

- 10.1. Basic magnetic property of nuclei
 - 10.1.1. Magnetic moment
 - 10.1.2. Nuclei in external magnetic field
 - 10.1.3. Nuclear shielding of magnetic field
- 10.2. Chemical shift
- 10.3. NMR spectrum
 - 10.3.1. Correlation spectroscopy (COSY)
 - 10.3.2. Heteronuclear single-quantum correlation spectroscopy (HSQC)
 - 10.3.3. Nuclear Overhauser effect spectroscopy (NOESY)
- 10.4. From NOE to 3D structure model

PART III: Selected Topics (by invited speakers)

Prof. Philip Andrews:

Introduction to mass spectrometry and proteomics

Prof. Tomek Cierpicki:

NMR spectroscopy for protein structure determination

Prof. Melanie Ohi:

Cryo-electron microscopy for protein structure determination

Prof. Mark Saper:

X-ray crystallography for protein structure determination