Biomolecular Structure and Mechanics

SV Master - Spring Semester 2011
Instructor: Matteo Dal Peraro

Objective. Introducing the principles of structural biology along with the principal experimental and computational techniques used to investigate the structure, dynamics and function of biological systems. The main focus is on the description of molecular interactions and how they can be quantitatively modeled using theoretical and computational tools to investigate relevant problems in the domain of biophysics and biochemistry.

Content. The course is structured in three main parts: the first two focus on the theoretical foundation of experimental and computational techniques used in structural biology, with the stress on the interplay between the two approaches. A journal club on recent literature topics closes these two parts. The final lectures will address some of the most challenging problems in structural biology.
1.Structure: intermolecular interactions and structure of biomolecules, experimental methods in structural biology, homology-based structure prediction.
2.Dynamics: elements of statistical mechanics, classical molecular mechanics, molecular dynamics and Monte Carlo methods, free energy calculations.
3.Selected topics: de novo protein structure prediction and design; protein folding, assembly, and misfolding; structure-based drug discovery, multiscale molecular simulation techniques.
Computational projects will run in parallel to theoretical lectures during the first half of the semester for the student to have a first hand experience on basic molecular modeling tools applied to problems such as protein structure prediction; protein, nucleic acids and membrane dynamics; structure-based drug design. During the second half of the semester projects are offered where students can apply these tools to specific open problems. Here are some titles from previous years:
- *Study of the human defensin 5 antimicrobial peptide and its mechanism of action*
- *Study of LOV domain conformational changes under light activation*
- *Study of O-GlcNAcase enzyme and development of new inhibitors*

Grading. The final grade is based on computational lab assignments and journal club for a 60%; the final project counts for the remaining 40%. Written reports are due for the final project and intermediate assignments (*, **). No final written exam is scheduled.

References. Various books, papers and other material will be used and suggested for reading; slides handout and supporting material for lectures and computational projects will be distributed in class and/or posted on moodle.epfl.ch.
Main reference textbooks:
- *Molecular modelling: principles and applications*, A.R. Leach, Pearson
- *Molecular modeling and simulations: and interdisciplinary guide*, T. Schlick, Springer

Practical info: theory lectures are held in room ELD 220 on Wednesdays at 10am, and computational labs in room BC 07/08 or AAB 011-013 on Thursdays at 11am.

Office hours: all Fridays during the semester from 10am in AAB 017, phone: 31861, email: matteo.dalperaro@epfl.ch.

Course timetable

<table>
<tr><th>date</th><th>theory</th><th>computational lab</th></tr>
<tr><td>1st week</td><td>• structure of biomolecules
• intermolecular interactions</td><td>• Linux primer
• 3D visualization and analysis</td></tr>
<tr><td>2nd week</td><td>• X-ray crystallography, NMR, EM
• structure classification and prediction</td><td>• structure analysis: X-ray lattice, H-bond network, pK_a</td></tr>
<tr><td>3rd week</td><td>• molecular mechanics force fields
• energy minimization methods</td><td>• homology modeling *</td></tr>
<tr><td>4th week</td><td>• elements of statistical mechanics
• molecular dynamics I</td><td rowspan="2">• force field parameterization and molecular dynamics *</td></tr>
<tr><td>5th week</td><td>• molecular dynamics II
• other simulation techniques</td></tr>
<tr><td>6th week</td><td>• Monte Carlo method
• simulation-experiment interplay</td><td>• time evolution analysis *</td></tr>
<tr><td>7th week</td><td>• free energy calculations
• electrostatics and solvation</td><td>• free energy calculations *</td></tr>
<tr><td>8th week</td><td>• journal club on selected papers *</td><td rowspan="6">project proposal and assignment **

possible general topics:
• molecular simulation theory
• biophysics of membranes
• membrane proteins
• molecular docking
• Monte Carlo simulations
• protein design
• coarse-grained simulations
• ….</td></tr>
<tr><td>9th week</td><td>• structure-based drug discovery
• de novo drug design</td></tr>
<tr><td>10th week</td><td>• multiscale molecular modeling
• enzymatic catalysis</td></tr>
<tr><td>11th week</td><td>• coarse-grained force fields
• coarse-grained models and beyond</td></tr>
<tr><td>12th week</td><td>• ab initio protein folding
• aggregation and misfolding</td></tr>
<tr><td>13th week</td><td>• biomolecular design and engineering
• structure-based systems biology</td></tr>
<tr><td>14th week</td><td colspan="2">project presentations and discussion **</td></tr>
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* Individual computational project with report due in 2 weeks from class.
** Final computational project (in groups of 2-3 students) with presentation during the last week of course and report due after a week from presentation.