BIO 532: Structural Biology - Fall 2012

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Lectures: Mon 10:40-12:30 FENS L047
Wed 12:40-13:30 FENS L065

Course Description: The aim of this course is to walk students through the main ideas and experimental techniques in structural biology following the shortest path from the significant events in the history of the field to the recent research literature. We will start by reviewing the building blocks of proteins and DNA and discussing the physical interactions responsible for their structures. Basic knowledge about X-ray crystallography as a tool for determining the three dimensional structures of biomolecules will be provided. The motivation for this general overview will come from reading some of the classic papers that contributed to the birth of structural biology. In particular, we will read the foundational papers of Linus Pauling (Nobel Prize in Chemistry, 1954), James Watson and Francis Crick (Nobel Prize in Physiology, 1962), Max Perutz and John Kendrew (Nobel Prize in Chemistry, 1962). To establish a quantitative connection between biomolecular structure and function we will look at binding—the simplest recognition event at the molecular scale—in terms of equilibrium and rate constants. Cooperative binding will be introduced to understand how hemoglobin in the red blood cells carries oxygen. In this context, we will familiarize ourselves with the relevant aspects of the work of Jacques Monod (Nobel Prize in Physiology, 1965). Coming to the present century, we turn to the question of how ion channels embedded in the cellular membrane conduct ions in a selective and controlled way. To this end, we will examine the structural aspects of ion conduction and gating of potassium channels, reading the articles of Roderick MacKinnon (Nobel Prize in Chemistry, 2003). The discussion on ion channels will culminate with the recently (July 2011) determined structure of a voltage-gated sodium channel. Motivated by the modern view that biomolecular function is determined by structure as well as dynamics, we will then turn to nuclear magnetic resonance (NMR) spectroscopy. The basic ideas of NMR as applied to structural biology will be illustrated through the Nobel lecture of Kurt Wüthrich (Nobel Prize in Chemistry, 2002). Recent applications of NMR to elucidating the role of enzyme dynamics in catalysis and the importance of DNA dynamics for protein-DNA recognition will also be examined. In addition to the experimental techniques of X-ray crystallography and NMR spectroscopy, students will be familiarized with the basic principles of molecular dynamics simulations—a powerful computational technique to study the connection between the structure and dynamics of a biomolecule and its function.

Evaluation: Throughout the course, seven short quizzes will be given to make sure the material in the lectures has been absorbed in a timely manner. During the part of the course related to the current research literature, several research papers will be assigned for reading in addition to the relevant sections from the textbooks. The students will be expected to have read the papers carefully and critically, and to actively participate in their discussion. To ensure closer familiarity with the structural aspects of the proteins considered in the papers, homework assignments, consisting of visually examining and manipulating their three dimensional representations, will be given in parallel to the assigned readings. In addition, homework assignments related to X-ray crystallography, cooperative ligand binding, MD simulations, and NMR spectroscopy will be given after the lectures on these topics. The midterm exam will be a comprehensive written test of the material covered during the first half of the course. During the second half of the course, students are expected to choose a biological system, which they will examine from a structural perspective using the recent research literature. Towards the end of the semester, they will make an in-class presentation of their findings and submit a short written report. The final exam will be a comprehensive written test of the material covered during the entire course.

Quizzes	10 %
Homework assignments	10 %
Participation in in-class discussions	10 %
Midterm exam	20 %
Report and oral presentation	20 %
Comprehensive final exam	30 %

Textbooks:

1. Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, Garland Science, 2012.

2. Branden and Tooze, *Introduction to Protein Structure*, 2^{nd} edition, Garland Science, 1999.

3. Petsko and Ringe, *Protein Structure and Function*, New Science Press, 2004.

Reference books:

1. Berg, Tymoczko and Stryer, *Biochemistry*, 6^{th} edition, W.H. Freeman, 2006.

2. Phillips, Kondev and Theriot, *Physical Biology of the Cell*, Garland Science, 2009.

3. Alberts, Johnson, Lewis, Raff, Roberts and Walter, *Molecular Biology of the Cell*, 5^{th} edition, Garland Science, 2008.

4. Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, expanded edition, Cold Spring Harbor Laboratory Press, 1996.

Detailed Course Content: (see next page)

Dates	Topics (*discussion topics in italics*)
Sep 25	General information about the course
Sep 26	Introduction: Functions of biological molecules
Oct 1	Structural chemistry and molecular interactions
Oct 3	Protein secondary structure: helices and pleated sheets (Pauling)
HW 1	Visualizing protein and DNA structures
Oct 8	Basics of **X-ray crystallography**
Oct 10	Nucleic acids and the double helix (Watson and Crick)
Oct 15	More X-ray crystallography
Oct 17	Myoglobin and protein tertiary structure (Kendrew)
Oct 19	Hydrophobicity, hydrophilicity and protein folding
HW 2	Lattice model of protein folding and the hydrophobic effect
Oct 22 Oct 24	Semester Break
Oct 29	Cumhuriyet Bayramı
Oct 31	Cooperative ligand binding and the quaternary structure of hemoglobin (Perutz)
Nov 5	Allosteric proteins and rearrangement of subunits (Monod)
Nov 7	Lipid membranes and transport of small molecules
HW 3	Pauling and MWC models of cooperative binding of oxygen to hemoglobin
HW 4	Getting familiar with the structure of the potassium channel KcsA
Nov 12	Introduction to **molecular dynamics simulations**
Nov 14	*Structure of the potassium channel KcsA*
Nov 19	*Ion conduction in the selectivity filter of KcsA*
Nov 21	*Gating of potassium channels: Ligand assisted opening of the pore (MthK)*
Nov 26	Midterm Exam
Nov 28	*Voltage sensors move across the membrane! (KvAP)*
HW 5	Numerical simulation of single-channel ion permeation
Dec 3	*Do voltage sensors move across the membrane after all? (Kv1.2)*
Dec 5	*Voltage sensing in potassium and sodium channels*
Dec 10	Introduction to **nuclear magnetic resonance (NMR) spectroscopy**
Dec 12	Biomolecular structure determination with NMR (Wüthrich)
HW 6	Simulating an NMR spectrum in the presence of chemical exchange
Dec 17	Enzyme thermodynamics and kinetics
Dec 19	*Intrinsic dynamics coupled to catalysis in the proline isomerase CypA*
Dec 24	*Studies of CypA minor state with X-ray crystallography and NMR*
Dec 26	*Specific and nonspecific interactions of the Lac repressor with DNA*
Dec 31	Report presentations
Jan 2	*Transient Hoogsteen base pairs in DNA*