BIO 304: Biological Function and Structure - Spring 2012

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Lectures: Th 13:40-15:30 FENS L063
Fri 9:40-10:30 FENS L067

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 revealing 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 read and discuss the work of Roderick MacKinnon (Nobel Prize in Chemistry, 2003) on the structural aspects of ion conduction and gating of potassium channels. 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.

Who can take this course: Most of the students taking the course are expected to be undergraduate students in the biological sciences who are interested in Structural Biology. However, the course may be attractive to engineering and physical science students looking for first exposure to modern molecular biology. After surmounting the barrier of getting familiar with the necessary biology-related vocabulary, such students will find their existing knowledge invaluable for understanding the physical principles behind biomolecular structure and the experimental techniques that will be discussed in the course.

Evaluation:

Homework assignments	5 %
Quizzes	10 %
In-class discussion	15 %
Midterm exam	20 %
Written report and oral presentation	25 %
Comprehensive final exam	25 %

The course will consist of lectures and in-class discussions of pre-assigned research papers, both historical and recent. Short quizzes will be given to make sure that the material in the lectures has been absorbed in a timely manner. Students will be expected to have read the assigned papers carefully and critically, and to actively participate in the discussion. To ensure closer familiarity with the structural aspects of the molecules considered in the papers, simple homework assignments, consisting of visually examining and manipulating the three dimensional molecular representations, will be given. During the semester, students will be expected to choose a biological question, which they will examine from a structural perspective using the recent research literature. In the last two weeks, they will make an in-class presentation of their findings and submit a short written report.

Detailed Course Content:

Dates	Topics (*discussion topics in italics*)
Feb 14	General information about the course
Feb 17	Introduction: Functions of biological molecules
Feb 21	Biochemical description of molecular recognition events
Feb 24	Structural chemistry and protein secondary structure
Mar 1	Nucleic acids and DNA structures
Mar 2	*Helices, pleated sheets and Pauling*
Mar 8	X-ray crystallography and biomolecular structure
Mar 9	*The double helix of Watson and Crick*
Mar 15	X-ray crystallography and biomolecular structure (cont.)
Mar 16	*Kendrew and the structure of myoglobin*
Mar 22	Cooperative ligand binding and protein quaternary structure
Mar 23	*Perutz and the two states of hemoglobin*
Mar 29	Lipid membranes and transport of small molecules
Mar 30	Membrane potential and ion channels
Apr 5 Apr 6	Semester Break
Apr 12	Introduction to molecular dynamics simulations
Apr 13	*Structure of the potassium channel KcsA*
Apr 19	*Ion conduction in the selectivity filter of KcsA*
Apr 20	*Gating of the potassium channel MthK: Ligand assisted opening of the pore*
Apr 26	**Midterm Exam**
Apr 27	Introduction to nuclear magnetic resonance (NMR) spectroscopy
May 3	Biomolecular structure determination with NMR
May 4	Enzyme thermodynamics and kinetics
May 10	*Intrinsic dynamics coupled to catalysis in the proline isomerase CypA*
May 11	*Studies of CypA minor state with X-ray crystallography and NMR*
May 17	Expression regulation and protein-DNA interactions
May 18	*NMR studies of the interaction of the lac repressor with DNA*
May 24	**Presentation of report**
May 25	*Transient Hoogsteen base pairs in double helical DNA*

Textbooks:

BT Branden and Tooze, *Introduction to Protein Structure*, 2nd edition, Garland Publishing, 1999.

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

Reference books:

Str Berg, Tymoczko and Stryer, *Biochemistry*, 7th edition, W. H. Freeman, 2011.

NC Nelson and Cox, *Lehninger Principles of Biochemistry*, 5th edition, W. H. Freeman, 2008.