BIO 304 Spring 2015

Biological Function and Structure

(January 23, 2015)

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Lectures: Mon 14:40-15:30 FENS L027
Tue 10:40-11:30 FENS G029

TA: Tuğçe Oruç

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). 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 in potassium channels. Then we will examine how sodium channels sense the voltage across the cell membrane. 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.

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:

In-class discussion	10 %
Quizzes and homework assignments	15 %
Midterm exam	25 %
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. Homework assignments and 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. In the second half of 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 week, they will make an in-class presentation of their findings and submit a short written report.

Detailed Course Content: (See next page.)

	Lecture topic (*Discussion topic*)
Feb 2	General information about the course
Feb 3	Overview of biological molecules and their functions
Feb 9	Structural chemistry
Feb 10	Interactions between molecules
Feb 16	*Helices, pleated sheets and Pauling*
Feb 17	Introduction to X-ray crystallography
Feb 23	*The double helix of Watson and Crick*
Feb 24	The phase problem of X-ray crystallography
Mar 2	*Perutz, Kendrew and protein structure*
Mar 3	Protein folding and the hydrophobic effect
Mar 9	Introduction to molecular dynamics simulations
Mar 10	Lipid membranes and permeation of small molecules
Mar 16	Molecular recognition: binding
Mar 17	Membrane potential and ion channels
Mar 23	*Structure of the potassium channel KcsA*
Mar 24	*Ion conduction in the selectivity filter of KcsA*
Mar 30	Review
Mar 31	**Midterm Exam**
Apr 6 Apr 7	Semester Break
Apr 13	*Structures of voltage sensitive sodium channels*
Apr 14	Introduction to NMR spectroscopy
Apr 20	Biomolecular structure determination with NMR
Apr 21	Biomolecular dynamics with NMR
Apr 27	*Interaction of the lac repressor with DNA*
Apr 28	Enzyme thermodynamics and kinetics
May 4	*Intrinsic dynamics coupled to catalysis in CypA*
May 5	*CypA minor state with X-ray crystallography and NMR*
May 11	**Presentations**
May 12	**Presentations**
May ??	**Final Exam**

Textbooks:

Kuriyan	Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, Garland Science, 2012.
Petsko	Petsko and Ringe, *Protein Structure and Function*, New Science Press, 2004.
Branden & Tooze	Branden and Tooze, *Introduction to Protein Structure*, 2nd edition, Garland Science, 1999.

Primary sources:

Feb 16 α-helix and β-sheet

1. Linus Pauling, Robert B. Corey, and H. R. Branson, The structure of proteins: two hydrogen-bonded helical configurations of the polypeptide chain, *PNAS*, **37**, 205–211 (1951).
2. Linus Pauling and Robert B. Corey, Configurations of polypeptide chains with favored orientations around single bonds: two newpleated sheets, *PNAS*, **37**, 729–740 (1951).

Feb 23 The double helix

1. Linus Pauling and Robert B. Corey, A proposed structure for the nucleic acids, *PNAS*, **39**, 84–97 (1953).
2. J. D. Watson and F. H. C. Crick, Molecular Structure of Nucleic Acids, *Nature*, **171**, 737–738 (1953).
3. J. D. Watson and F. H. C. Crick, Genetical Implications of the Structure of Deoxyribonucleic Acid, *Nature*, **171**, 964–967 (1953).

Mar 2 Myoglobin and Hemoglobin

1. J. C. Kenrew, G. Bodo, H. M. Dintzis, R. G. Parrish, H. Wyckoff, and D. C. Phillips, A three-dimensional model of the myoglobin molecule obtained by X-ray analysis, *Nature*, **181**, 662–666 (1958).
2. M. F. Perutz, M. G. Rossmann, Ann F. Cullis, Hilary Muirhead, Georg Will, and A. C. T. North, Structure of Haemoglobin: A Three-Dimensional Fourier Synthesis at 5.5-Å Resolution, Obtained by X-Ray Analysis, *Nature*, **185**, 416–422 (1960).
3. J. C. Kendrew, R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Pillips, and V. C. Shore, Structure of Myoglobin: A Three-Dimensional Fourier Synthesis at 2 Å Resolution, *Nature*, **185**, 422–427 (1960).

Mar 23 KcsA structure

* Clay Armstrong, The Vision of the Pore (Research Commentaries), *Science*, **280**, 56–57 (1998).

1. Declan A. Doyle, João Morais Cabral, Richard A. Pfuetzner, Anling Kuo, Jacqueline M. Gulbis, Steven L. Cohen, Brian T. Chait, and Roderick MacKinnon, The Structure of the Potassium Channel: Molecular Basis of K^+ Conduction and Selectivity, *Science*, **280**, 69–77 (1998).
2. Yufeng Zhou, João H. Morais-Cabral, Amelia Kaufman and Roderick MacKinnon, Chemistry of ion coordination and hydration revealed by a K^+ channel-Fab complex at 2.0 Å resolution, *Nature*, **414**, 43–48 (2001).

Mar 24 Ion conduction in KcsA

* Christopher Miller, See potassium run (news and views), *Nature*, **414**, 23–24 (2001).

1. João H. Morais-Cabral, Yufeng Zhou and Roderick MacKinnon, Energetic optimization of ion conduction rate by the K^+ selectivity filter, *Nature*, **414**, 37–42 (2001).
2. Simon Bernèche and Benoît Roux, Energetics of ion conduction through the K^+ channel, *Nature*, **414**, 73–77 (2001).

Apr 13 Sensing voltage

* Richard Horn, Peering into the spark of life (news and views), *Nature*, **475**, 305–306 (2011).

1. Jian Payandeh, Todd Scheuer, Ning Zheng, William A. Catterall, The crystal structure of a voltage-gated sodium channel, *Nature*, **475**, 353–558 (2011).
2. Xu Zhang, Wenlin Ren, Paul DeCaen, Chuangye Yan, Xiao Tao, Lin Tang, Jingjing Wang, Kazuya Hasegawa, Takashi Kumasaka, Jianhua He, JiaweiWang, David E. Clapham, Nieng Yan, Crystal structure of an orthologue of the NaChBac voltage-gated sodium channel, *Nature*, **486**, 130–134 (2012).

Apr 27 Lac repressor-DNA interactions with NMR

1. Charalampos G. Kalodimos, Nikolaos Biris, Alexandre M. J. J. Bonvin, Marc M. Levandoski, Marc Guennuegues, Rolf Boelens, and Robert Kaptein, Structure and Flexibility Adaptation in Nonspecific and Specific Protein-DNA Complexes, *Science*, **462**, 386–9 (2004).

May 4 CypA dynamics and catalysis

1. Elan Zohar Eisenmesser, Daryl A. Bosco, Mikael Akke, and Dorothee Kern, Enzyme Dynamics During Catalysis, *Science*, **295**, 1520–3 (2002).
2. Elan Z. Eisenmesser, Oscar Millet, Wladimir Labeikovsky, Dmitry M. Korzhnev, Magnus Wolf-Watz, Daryl A. Bosco, Jack J. Skalicky, Lewis E. Kay, Dorothee Kern, Intrinsic dynamics of an enzyme underlies catalysis, *Nature*, **438**, 117–21 (2005).

May 5 X-ray evidence for minor state of CypA

1. James S. Fraser, Michael W. Clarkson, Sheena C. Degnan, Renske Erion, Dorothee Kern, Tom Alber, Hidden alternative structures of proline isomerase essential for catalysis, *Nature*, **462**, 669–73 (2009).