Biological Function and Structure/Structural Biology

(January 21, 2016)

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Lectures: Wed 11:40-13:30 FASS G048
Thr 12:40-13:30 FENS L027

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. In this context, 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. 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). Subsequently, we will examine recent NMR studies that have revealed the role of protein dynamics in the binding of transcription factors to DNA.

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.

Reference textbooks:

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

Detailed Course Content: (See next page.)

	Lecture topic (*Discussion topic*)	
Feb 3	General information about the course	
Feb 4	Biological molecules and their functions	
Feb 10	Basics of structural chemistry	Interactions between molecules
Feb 11	Introduction to X-ray crystallography (waves)	
	HW 1: Hydrogen bond strength	(due Feb 17)
Feb 17	Interference of waves	The phase problem
Feb 18	*Helices, pleated sheets and Pauling*	
	HW 2: Visualizing molecular structures	(due Feb 24)
Feb 24	Finding phases for small molecules	Multiple isomorphous replacement
Feb 25	*The double helix of Watson and Crick*	
	HW 3: Getting used to the Fourier transform	(due Mar 2)
Mar 2	Oxygen binding to myoglobin	Protein folding: energy and multiplicity
Mar 3	*Kendrew and structure of myoglobin*	
Mar 9	Protein folding and the hydrophobic effect	Oxygen binding to hemoglobin (Pauling)
Mar 10	*Perutz and structure of hemoglobin*	
	HW 4: Lattice model of protein folding	(due Mar 16)
Mar 16	Cooperative oxygen binding (MWC)	Lipid membrane and permeation
Mar 17	Membrane potential and ion channels	
	HW 5: Analysis of Pauling's and MWC models	(due Mar 23)
Mar 23	*Structure of the potassium channel KcsA*	
Mar 24	*Ion conduction by KcsA*	
Mar 30 Mar 31	Semester Break	
Apr 6	**Midterm Exam**	
Apr 7	Solution of exam questions	
Apr 13	Introduction to NMR spectroscopy	
Apr 14	Biomolecular structure determination with NMR	
Apr 20	Biomolecular dynamics with NMR	Control of transcription
Apr 21	*Interaction of the lac repressor with DNA*	
	HW 6: Calculation of NMR exchange spectra	(due Apr 28)
Apr 27	*Allostery without structural change: CAP*	
Apr 28	A model of dynamic allostery	
May 4	Population shift model of allostery	
May 5	*Dynamic allostery in a PDZ domain*	
May 11	**Presentations**	
May 12	**Presentations**	
May ??	**Final Exam**	

Primary sources:

Feb 18 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, *Proceedings of the National Academy of Sciences*, **37**, 205–211 (1951).
2. Linus Pauling and Robert B. Corey, Configurations of polypeptide chains with favored orientations around single bonds: two new pleated sheets, *Proceedings of the National Academy of Sciences*, **37**, 729–740 (1951).

Feb 25 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 3 Myoglobin

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. 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 10 Hemoglobin

1. 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).
2. Hilary Muirhead and M. F. Perutz, Structure of haemoglobin: A three-dimensional Fourier synthesis of reduced human haemoglobin at 5.5 Å resolution, *Nature*, **199**, 633–638 (1963).

Mar 23 KcsA structure

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

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).

Apr 21 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).

Apr 27 Dynamic allostery of the activator CAP

1. Natalia Popovych, Shangjin Sun, Richard H. Ebright, and Charalampos G. Kalodimos, Dynamically driven protein allostery, *Nature Structural and Molecular Biology*, **13**, 831–838 (2006).
2. Shiou-Ru Tzeng and Charalampos G. Kalodimos, Dynamic activation of an allosteric regulatory protein, *Nature*, **462**, 368–372 (2009).

May 5 Dynamic allostery in a PDZ domain

1. Chad M. Petit, Jun Zhang, Paul J. Sapienza, Ernesto J. Fuentes, and Andrew L. Lee, Hidden dynamic allostery in a PDZ domain, *Proceedings of the National Academy of Sciences*, **106**, 18249–18254 (2009).