BIO 304 / BIO 532 Spring 2018

Biological Function and Structure / Structural Biology

(May 11, 2018)

Instructor: Deniz Sezer
E-mail: dsezer@sabanciuniv.edu
Office: FENS G021

Lectures: Thu 11:40-13:30 FENS L035
Fri 09:40-10:30 FENS G025

Extra time: Fri 09:00-09:30 FENS G025

Teaching Assistant: Sofia Piepoli

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 discuss 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 address structural changes upon protein phosphorylation and examine the role of protein dynamics in catalysis.
In the homework assignments and the take-home exam, **programming skills on the level of CS 201 are taken for granted**. An extra weekly lecture will be offered to introduce as much **Python** as will be necessary to complete the assignments.

Evaluation: The course will consist of lectures and in-class discussions of pre-assigned papers, both historical and recent. Students will be expected to have read the assigned papers carefully and critically, and to actively participate in the discussion. Homework assignments will be given to make sure that the material in the lectures has been absorbed in a timely manner. Towards the end 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.

In-class paper discussion	6 %
Homework assignments	18 %
Midterm exam (in-class): Apr 12	26 %
Presentation and written report	20 %
Final exam (in-class): June 1	30 %

Supporting reading material:

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, Garland Science, 2012.
- Branden and Tooze, *Introduction to Protein Structure*, 2$^{\text{nd}}$ edition, Garland Science, 1999.
- Petsko and Ringe, *Protein Structure and Function*, New Science Press Ltd, 2004.
- Milo, Phillips, Orme, *Cell Biology by the Numbers*, Garland Science, 2016.
(Available at `http://book.bionumbers.org`.)

Detailed Course Content:
(See next page.)

week	date	Lecture topic, Extra time, Homework assignment, *Discussion topic*
1	Feb 8	General information about the course. What is "biological function"?
	Feb 9	Python: Generating scientific plots.
	Feb 9	What is in a cell: Proteomes and metabolomes of *E. coli* and yeast.
		HW0: I can plot with Python.
2	Feb 15	Binding. Oxygen binding to myoglobin and hemoglobin (multiplicity).
	Feb 16	Python: Reading data from a file and exposure to the `numpy` module.
	Feb 16	Pauling model of oxygen binding to hemoglobin (direct interaction).
		HW1: Pauling's model of oxygen binding to hemoglobin.
3	Feb 22	Hill, Pauling and cooperativity.
	Feb 23	Python: Fitting to experimental data.
	Feb 23	Cooperativity from indirect (allosteric) interaction: MWC model of binding.
		HW2: MWC analysis of oxygen binding to hemoglobin.
4	Mar 1	Basics of structural chemistry.
	Mar 2	VMD: Visualizing molecular structures with VMD.
	Mar 2	Interactions between molecules.
		HW3: Hydrogen bond. Visualization of an α-helix with VMD.
5	Mar 8	Partial charges and dipole moments. *D1: Helices, pleated sheets and Pauling.*
	Mar 9	Python: Writing to a file. Creating a pdb "movie" file.
	Mar 9	Introduction to X-ray crystallography.
		HW4: A- and B-from double helices.
6	Mar 15	Nucleic acid helices. Waves and interference.
	Mar 16	Double-slit interference.
	Mar 16	*D2: The double helix of Watson and Crick.*
		HW5: Morphing of B-DNA to A-DNA.
7	Mar 22	The phase problem.
	Mar 23	Fourier synthesis.
	Mar 23	*D3: Kendrew and structure of myoglobin.*
		HW6: Fourier transform in 2D with Python.
8	Mar 29	Amino acids. Ionizable groups and pK_a. Solubility.
	Mar 30	Multiple isomorphous replacement.
	Mar 30	*D4: Perutz and structure of hemoglobin.*
	Apr 5-6	Spring break
9	Apr 12	**Exam 1** (in-class)
	Apr 13	Protein folding.
		HW7: KcsA structures.
10	Apr 19	The hydrophobic effect. Lipid membranes.
	Apr 20	*D5: Structure of the potassium channel KcsA.*
	Apr 20	*D5: Structure of the potassium channel KcsA.*
		HW8: Lattice model of protein folding.
11	Apr 26	Introduction to NMR.
	Apr 27	*D6: Ion conduction by KcsA.*
	Apr 27	*D6: Ion conduction by KcsA.*
		HW9: Structural changes in the receiver domain of the protein NTRC.
12	May 3	Structural determination with NMR.
	May 4	*D7: Structural changes upon phosphorylation: NTRC.*
	May 4	*D7: Structural changes upon phosphorylation: NTRC.*
13	May 10	Chemical kinetics. Enzyme kinetics (Michaelis-Menten equation).
	May 11	Probing kinetics with NMR
	May 11	*D8: Enzyme dynamics during catalysis: CypA.*
14	May 17	**Presentations.**
	May 18	**Presentations.**
	June 1	**Final Exam** (in-class)

Course readings:

Feb 22 Hemoglobin evolution and physiology

- Ron Milo, Jennifer H. Hou, Michael Springer, Michael P. Brenner, and Marc W. Kirschner, The relationship between evolutionary and physiological variation in hemoglobin, *Proceedings of the National Academy of Sciences*, **104**, 16998–17003 (2007).

Feb 23 Binding and allostery in Hemoglobin

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 12.A**, 531–548.
- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 14.B**, 645–655.

Mar 2 Conformation of protein backbone and molecular interactions

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 4.B**, 137–150.
- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 1.A**, 6–15.

Mar 9 Introduction to nucleic acids

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 1.B** (first half), 15–25.

Mar 16 Protein structure and X-ray crystallography

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 1.B** (second half), 25–34.
- Branden and Tooze, *Introduction to Protein Structure*, **Ch. 18** (first half), 373–386.

Mar 22 Protein structure

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 4.A**, 131–137.
- Petsko and Ringe, *Protein Structure and Function*, **Ch. 1** (first half), 1–17.

Mar 29 Protonation/deprotonation of amino acid side chains

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 10.C**, 428–438.

Apr 19 Protein folding and the hydrophobic effect

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 10.D**, 438–446.

Apr 20 Potassium ion channels

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Secs. 11.20-23**, 489–493.

Apr 26 NMR in service of structural biology

- Kurt Wütrich, *NMR Studies of Structure and Functions of Biological Macromolecules*, Nobel Lecture 2002.

May 3 Determination of biomolecular structure

- Branden and Tooze, *Introduction to Protein Structure*, **Ch. 18** (second half), 387–392.
- Petsko and Ringe, *Protein Structure and Function*, **Ch. 5**, 167–173.

May 10 Enzyme kinetics

- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Secs. 15.1-12** and **15.18**, 673–691 and 699–700.
- Kuriyan, Konforti, and Wemmer, *The Molecules of Life*, **Sec. 16.A**, 721–735.

Discussion papers:

Mar 8 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).

Mar 16 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 23 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 30 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).

Apr 20 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).

Apr 27 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).

May 4 Structural changes upon phosphorylation revealed with NMR

1. Brian F. Volkman, Michael J. Nohaile, Nancy K. Amy, Sydney Kustu, and David E. Wemmer, Three-dimensional solution structure of the N-terminal receiver domain of NTRC, *Biochemistry*, **34**, 1413–1424 (1995).

2. Dorothee Kern, Brian F. Volkman, Peter Luginbühl, Michael J. Nohaile, Sydney Kustu, and David E. Wemmer, Structure of a transiently phosphorylated switch in bacterial signal transduction, *Nature*, **402**, 894–898 (1999).

May 11 Enzyme dynamics during catalysis studied with NMR

1. Elan Zohar Eisenmesser, Daryl A. Bosco, Mikael Akke, and Dorothee Kern, Enzyme Dynamics During Catalysis, *Science*, **295**, 1520–1523 (2002).
2. Elan Z. Eisenmesser, Oscar Millet, Wladimir Labeikovsky, Dmitry M. Korzhnev, Magnus Wolf-Watz, Daryl A. Bosco, Jack J. Skalicky, Lewis E. Kay, and Dorothee Kern, Intrinsic dynamics of an enzyme underlies catalysis, *Nature*, **438**, 117–121 (2005).