BIO 532: Structural Biology - Fall 2011

(September 27, 2011)

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Lectures: Tue 14:40-16:30 FENS L062
Wed 12:40-13:30 FENS L063

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. In the first part of the course, we will review the building blocks of proteins and DNA, discuss the physical principles determining their structures, and introduce a biochemical description of folding, binding and catalysis in terms of equilibrium constants and rate constants. In addition, 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 (Chemistry Nobel 1954), James Watson and Francis Crick (Physiology Nobel 1962), Max Perutz and John Kendrew (Chemistry Nobel 1962), as well as familiarize ourselves with some aspects of the work of Jacques Monod (Physiology Nobel 1965) and Christian Anfinsen (Chemistry Nobel 1972). At the end of the first part, the computational technique of molecular dynamics simulations will be introduced. In the second part of the course, we will read and discuss papers from the recent research literature. We will start by examining the structural aspects of ion conduction and gating of potassium channels, reading the articles of Roderick MacKinnon (Chemistry Nobel 2003). The discussion on ion channels will culminate with the recently (July 2011) determined structure of a voltage-gated sodium channel. Then, we will turn to nuclear magnetic resonance (NMR) spectroscopy. The many uses of NMR to structural biology will be illustrated through the Nobel lecture of Kurt Wüthrich (Chemistry Nobel 2002). Recent applications of NMR to signaling proteins, DNA, and protein-DNA interactions will be discussed. Throughout, emphasis will be given on the modern view that biomolecular function is determined by structure as well as dynamics.

Who can take this course: Most of the students taking the course are expected to be graduate students in the Biological Sciences who are interested in Structural Biology. However, advanced undergraduate students in the Biological Sciences curious about the historical and physical foundations of the field as well as the current research problems are also encouraged to take the course. In addition, the course may be attractive to engineering and natural-science students from other (non-biological) disciplines who seek 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 and skills invaluable for understanding the physical principles behind the biophysical techniques that will be discussed in the course.

Evaluation:
During the first part of the course, short quizzes will be given to make sure the material has been absorbed in a timely manner. The midterm exam will be a comprehensive written test of this material. In the second part, which is oriented towards following 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 the discussion. To ensure closer familiarity with the structural aspects of the proteins considered in the papers, simple homework assignments, consisting of visually examining and manipulating their three dimensional representations, will be given on a weekly basis. During 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.

Part I:	Quizzes	10 %
	Midterm exam	20 %
Part II:	Homework and in-class discussion	15 %
	Report and oral presentation	25 %
	Comprehensive final exam	30 %

Detailed Course Content:

Dates	Topics (*discussion topics in italics*)
Sep 27	General information about the course
Sep 28	Introduction: Functions of biological molecules
Oct 4	Structural chemistry and protein secondary structure: helices and pleated sheets (Pauling)
Oct 5	Nucleic acids and the double helix (Watson and Crick)
Oct 11	**X-ray crystallography** and the tertiary structure of myoglobin (Kendrew)
Oct 12	Cooperative ligand binding and the quaternary structure of hemoglobin (Perutz)
Oct 18	Allosteric proteins and rearrangement of subunits (Monod)
Oct 19	Side chains at last: hydrophobicity, hydrophilicity and protein folding
Oct 25	Lipid membranes and transport of small molecules
Oct 26	Introduction to **molecular dynamics (MD) simulations**
Nov 1	*Structure of the potassium channel KcsA*
Nov 2	*Ion conduction in the selectivity filter of KcsA*
Nov 8 Nov 9	Kurban Bayramı
Nov 15	*Gating of potassium channels: Ligand assisted opening of the pore (MthK)*
Nov 16	*MD simulations of ion conduction and hydrophobic gating in potassium channels*
Nov 22	**Midterm Exam**
Nov 23	*Voltage sensors move across the membrane! (KvAP)*
Nov 29	*Do voltage sensors move across the membrane after all? (Kv1.2)*
Nov 30	*The lipid membrane and the voltage sensor of ion channels*
Dec 6	*Voltage sensing in potassium and sodium channels*
Dec 7	Introduction to **nuclear magnetic resonance (NMR) spectroscopy**
Dec 13	Biomolecular structure and dynamics with NMR
Dec 14	*Proline isomerization and the interaction of SH2 and SH3 domains in Itk kinase*
Dec 20	*Population shift in the two-state signaling protein NtrC*
Dec 21	*Dissecting the conformational transition of NtrC in molecular detail*
Dec 27	*Transient Hoogsteen base pairs in DNA*
Dec 28	*Specific and nonspecific interactions of the Lac repressor with DNA*
Jan 3 **Jan 4**	**Report presentations**

Textbooks:

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

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

Reading assignment for the period Sep 27 - Oct 26:

Branden and Tooze:

Ch 1 The Building Blocks
Ch 2 Motifs of Protein Structure
Ch 7 DNA Structures
Ch 18 Determination of Protein Structures (pp. 373–386)
Ch 6 Folding and Flexibility (pp. 89–100, pp. 104–110, pp. 113–117)
Ch 12 Membrane Proteins (pp. 223–226, 232–234, 244–247)

Petsko and Ringe:

1-0 Overview: Protein Function and Architecture
1-1 Amino Acids
1-2 Genes and Proteins
1-3 The Peptide Bond
1-4 Bonds that Stabilize Folded Proteins
1-5 Importance and Determinants of Secondary Structure
1-6 Properties of the Alpha Helix
1-7 Properties of the Beta Sheet
1-8 Prediction of Secondary Structure
1-9 Folding
1-10 Tertiary Structure
1-11 Membrane Protein Structure
1-12 Protein Stability: Weak Interactions and Flexibility
1-13 Protein Stability: Post-Translational Modifications
1-14 The Protein Domain
1-15 The Universe of Protein Structures
1-19 Quaternary Structure: General Principles
1-20 Quaternary Structure: Intermolecular Interfaces
1-21 Quaternary Structure: Geometry
1-22 Protein Flexibility
2-0 Overview: The Structural Basis of Protein Function
2-1 Recognition, Complementarity and Active Sites

2-2 Flexibility and Protein Function

2-4 Nature of Binding Sites

3-4 Effector Ligands: Competitive Binding and Cooperativity

3-5 Effector Ligands: Conformational Change and Allostery

Historical papers:

Oct 4 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).

Oct 5 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).

Oct 11 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).

Oct 12 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).

Oct 18 Allosteric proteins

- Jacque Monod, Jean-Pierre Changeux and François Jacob, Allosteric Proteins and Cellular Control Systems, *J. Mol. Biol.*, **6**, 306–329 (1963).
- Jacque Monod, Jeffries Wyman and Jean-Pierre Changeux, On the Nature of Allosteric Transitions: A Plausible Model, *J. Mol. Biol.*, **12**, 88–118 (1965).

Oct 19 Side chains and folding

1. J. C. Kendrew, H. C. Watson, B. E. Strandberg, R. E. Dickerson, D. C. Pillips, and V. C. Shore, A Partial Determination by X-ray Methods, and Correlation with Chemical Data, *Nature*, **190**, 666–670 (1961).

* Christian B. Anfinsen, Principles that Govern the Folding of Protein Chains (Nobel Lecture), *Science*, **181**, 223–230 (1973).

Oct 26 MD simulations

* Martin Karplus and Gregory A. Petsko, Molecular dynamics simulations in biology, *Nature*, **347**, 631–9 (1990).
* J. Andrew McCammon, Bruce R. Gelin, and Martin Karplus, Dynamics of folded proteins, *Nature*, **267**, 585–90 (1977).

Reading assignment for the period Nov 1 - Dec 28:

Nov 1 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).

Nov 2 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).

Nov 15 Opening the pore

* Maria Schumacher and John P. Adelman, Ion channels: An open and shut case (news and views), *Nature*, **417**, 501–502 (2002).

1. Youxing Jiang, Alice Lee, Jiayun Chen, Martine Cadene, Brian T. Chait, Roderick MacKinnon, Crystal structure and mechanism of a calcium-gated potassium channel, *Nature*, **417**, 515–522 (2002).
2. Youxing Jiang, Alice Lee, Jiayun Chen, Martine Cadene, Brian T. Chait, Roderick MacKinnon, The open pore conformation of potassium channels, *Nature*, **417**, 523–526 (2002).

Nov 16 Conduction and hydrophobic gating in K^+ channels

1. Morten O. Jensen, David W. Borhani, Kresten Lindorff-Larsen, Paul Maragakis, Vishwanath Jogini, Michael P. Eastwood, Ron O. Dror, and David E. Shaw, Principles of conduction and hydrophobic gating in K^+ channels, *PNAS*, **107**, 5833–8 (2010). [Look at the figures and the movies in the Supporting Information of the paper.]

Nov 23 KvAP structure

* Fred J. Sigworth, Structural biology: Life's transistors (news and views), *Nature*, **423**, 21-22 (2003).

1. Youxing Jiang, Alice Lee, Jiayun Chen, Vanessa Ruta, Martine Cadene, Brian T. Chait and Roderick MacKinnon, X-ray structure of a voltage-dependent K^+ channel, *Nature*, **423**, 33–41 (2003).
2. Youxing Jiang, Vanessa Ruta, Jiayun Chen, Alice Lee and Roderick MacKinnon, The principle of gating charge movement in a voltage-dependent K^+ channel, *Nature*, **423**, 42–48 (2003).

Nov 29 Kv1.2 structure

* Robert F. Service, A New Portrait Puts Potassium Pore in a Fresh Light (news focus), *Science*, **309**, 867 (2005).

1. Stephen B. Long, Ernest B. Campbell and Roderick MacKinnon, Crystal Structure of a Mammalian Voltage-Dependent *Shaker* Family K^+ Channel, *Science*, **309**, 897–903 (2005).
2. Stephen B. Long, Ernest B. Campbell and Roderick MacKinnon, Voltage Sensor of Kv1.2: Structural Basis of Electromechanical Coupling, *Science*, **309**, 903–908 (2005).

Nov 30 Lipids and the voltage sensor

1. Stephen B. Long, Xiao Tao, Ernest B. Campbell, and Roderick MacKinnon, Atomic structure of a voltage-dependent K^+ channel in a lipid membrane-like environment, *Nature*, **450**, 376–82 (2007).
2. Seok-Yong Lee, Anirban Banerjee, and Roderick MacKinnon, Two separate interfaces between the voltage sensor and pore are required for the function of voltage-dependent K^+ channels, *PLOS Biology*, **7**, e1000047 (2009).

Dec 6 Voltage sensing in potassium and sodium channels

1. Xiao Tao, Alice Lee, Walrati Limapichat, Dennis A. Dougherty, and Roderick MacKinnon, A Gating Charge Transfer Center in Voltage Sensors, *Science*, **328**, 67–73 (2010).
2. Jian Payandeh, Todd Scheuer, Ning Zheng, and William A. Catterall, The crystal structure of a voltage-gated sodium channel, *Nature*, **475**, 353–58 (2011).

Dec 7 Introduction to biomolecular NMR

* Branden and Tooze, Ch 18: Determination of Protein Structures (pp. 387–392)

* Petsko and Ringe, Ch 5: Structure Determination

Dec 13 Structure and dynamics with NMR

* Kurt Wüthrich, NMR Studies of Structure and Function of Biological Macromolecules (Nobel Lecture), *J. Biomolec. NMR*, **27**, 13–39 (2003).
* Anthony Mittermaier and Lewis E. Kay, New Tools Provide New Insights in NMR Studies of Protein Dynamics, *Science*, **312**, 224–8 (2006).

Dec 14 Proline isomerization and the interaction of Itk SH2 and SH3 domains

* Branden and Tooze, Ch 13: Signal Transduction: pp. 270–278.

1. Robert J. Mallis, Kristine N. Brazin, D. Bruce Fulton, Amy H. Andreotti, Structural characterization of a proline-driven conformational switch within the Itk SH2 domain, *Nature Struct. Biol.*, **9**, 900–5 (2002).
2. Andrew Severin, Raji E. Joseph, Scott Boyken, D. Bruce Fulton and Amy H. Andreotti, Proline Isomerization Preorganizes the Itk SH2 Domain for Binding to the Itk SH3 Domain *J. Mol. Biol.*, **387**, 726–743 (2009).

Dec 20 NtrC structure and conformational states

1. Dorothee Kern, Brian F. Volkman, Peter Luginbhl, Michael J. Nohaile, Sydney Kustu, David E. Wemmer, Structure of a transiently phosphorylated switch in bacterial signal transduction, *Nature*, **402**, 894–8 (1999).
2. Brian F. Volkman, Doron Lipson, David E. Wemmer, and Dorothee Kern, Two-State Allosteric Behavior in a Single-Domain Signaling Protein, *Science*, **291**, 2429–33 (2001).

Dec 21 Molecular details of the NtrC conformational transition

1. Alexandra K. Gardino, Janice Villali, Aleksandr Kivenson, Ming Lei, Ce Feng Liu, Phillip Steindel, Elan Z. Eisenmesser, Wladimir Labeikovsky, Magnus Wolf-Watz, Michael W. Clarkson, and Dorothee Kern, Transient Non-native Hydrogen Bonds Promote Activation of a Signaling Protein, *Cell*, **139**, 1109–18 (2009).

Dec 27 Transient conformational transitions in DNA

* Barry Honig and Remo Rohs, Biophysics: Flipping Watson and Crick (news and views), *Nature*, **470**, 472–3 (2011).

1. Evgenia N. Nikolova, Eunae Kim, Abigail A. Wise, Patrick J. OBrien, Ioan Andricioaei, and Hashim M. Al-Hashimi, Transient Hoogsteen base pairs in canonical duplex DNA, *Nature*, **470**, 498-502 (2011).

Dec 28 Protein-DNA interactions with NMR

* Branden and Tooze, Ch 8: DNA Recognition in Procaryotes by Helix-Turn-Helix Motifs (pp. 129–148)

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).