BIO 532: Structural Biology - Fall 2010

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Lectures: Mon 15:40-17:30 FENS L027
Tue 15:40-16:30 FENS L067

Office Hours: Thr 15:40-17:30 FENS G021

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, 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. Throughout, we will keep an eye on historical papers that contributed to the birth of structural biology. In the second part, selected biological problems and biophysical techniques used to address these problems will be introduced and followed by a discussion of the relevant research papers. Applications of structural biology to membrane proteins, signaling proteins, and proteins interacting with DNA will be examined. Emphasis will be given on the modern view that protein function is determined by structure as well as dynamics. Although the selection of examples is clearly not exhaustive, it is broad enough to offer a panoramic view of the field. Focusing on one or two specific proteins during the discussions is intended to prepare the students for critical scrutiny of the details in their own research.

Who can take this course: Most of the students taking the course are expected to be graduate students in the Biological Sciences and Bioengineering who are interested in Structural Biology. However, advanced undergraduate students in the Biological Sciences and Bioengineering 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 want to get exposed 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:

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

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, 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 submit a short written report and make an in-class presentation of their findings.

Detailed Course Content:

Dates	Topics (*discussion topics in italics*)
Sep 27	General information about the course
Sep 28	Introduction: What goes on in a cell
Oct 4	X-ray crystallography and secondary structure: helices and pleated sheets (Pauling)
Oct 5	Nucleic acids and the double helix (Watson and Crick)
Oct 11	More X-ray crystallography and the tertiary structure of myoglobin (Kendrew)
Oct 12	Cooperative ligand binding and the quaternary structure of hemoglobin (Perutz)
Oct 18	Side chains at last: hydrophobicity, hydrophilicity and protein folding
Oct 19	Allosteric proteins and rearrangement of subunits (Monod)
Oct 25	Chemical kinetics
Oct 26	Catalysis: rates and structures
Nov 1	Lipid membranes and transport of small molecules
Nov 2	Ion channels and the action potential
Nov 8	*Structure of the potassium channel KcsA*
Nov 9	*Potassium ion conduction in the selectivity filter of KcsA*
Nov 12	Review for the exam
Nov 15 Nov 16	Kurban Bayramı
Nov 22	**Midterm Exam**
Nov 26	*Gating of potassium channels: Ligand-assited opening of the pore (MthK)*
Nov 29	*Voltage sensors move across the membrane! (KvAP)*
Nov 30	*Do voltage sensors move across the membrane after all? (Kv1.2)*
Dec 3	*The lipid membrane and the structure of voltage-dependent channels*
Dec 6-7	Molecular dynamics (MD) simulations
Dec 10	*MD simulations of ion conduction and hydrophobic gating in potassium channels*
Dec 13	Introduction to NMR
Dec 14	Biomolecular structure determination with NMR
Dec 17	*Proline isomerization and the interaction of SH2 and SH3 domains in Itk kinase*
Dec 20	Protein dynamics and conformational transitions with NMR
Dec 21	*Population shift in the two-state signaling protein NtrC*
Dec 24	*Dissecting the conformational transition of NtrC in molecular detail*
Dec 27 **Dec 28**	**Report presentations**
Jan 3	*Intrinsic dynamics coupled to catalysis in the peptidyl-prolyl cis/trans isomerase CypA*
Jan 4	*Specific and nonspecific interactions of the Lac repressor with DNA*

Textbooks (T) and Reference Books (R):

T1. Branden and Tooze, *Introduction to Protein Structure*, 2nd edition, Garland Publishing, 1999.

T2. Petsko and Ringe, *Protein Structure and Function*, New Science Press, 2004.

R1. Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, expanded edition, Cold Spring Harbor Laboratory Press, 1996.

R2. Berg, Tymoczko and Stryer, *Biochemistry*, 6th edition, W.H. Freeman, 2006.

R3. Alberts, Johnson, Lewis, Raff, Roberts and Walter, *Molecular Biology of the Cell*, 5th edition, Garland Science, 2008.

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 11 An Example of Enzyme Catalysis: Serine Proteinases (pp. 205–219)

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
2-6 Catalysis: Overview
2-7 Active-Site Geometry
2-9 Stabilization of Transition States and Exclusion of Water
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).

Oct 18 Side chains and folding

- 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 19 Allosteric proteins

- 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).
- Jacque Monod, Jean-Pierre Changeux and François Jacob, Allosteric Proteins and Cellular Control Systems, *J. Mol. Biol.*, **6**, 306–329 (1963).

Reading assignment for the period Nov 1 - Dec 3:

Nov 1, 2 Introduction to membrane proteins

Branden and Tooze, Ch 12: Membrane Proteins (pp. 223–226, 232–234, 244–247)

Nov 8 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 9 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 26 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 29 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 30 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).

Dec 3 Role of lipids

1. Lee, S.Y., Lee, A., Chen, J., Mackinnon, R., Structure of the KvAP voltage-dependent K^+ channel and its dependence on the lipid membrane, *PNAS*, **102**, 15441–15446 (2005).
2. Stephen B. Long, Xiao Tao, Ernest B. Campbell, Roderick MacKinnon, Atomic structure of a voltage-dependent K^+ channel in a lipid membrane-like environment, *Nature*, **450**, 376–382 (2007).

Reading assignment for the period Dec 6 - Jan 4:

Dec 6 & 7 MD simulations

* Karplus and Petsko, Molecular dynamics Simulations in Biology, *Nature*, **347**, 631–9 (1990).

Dec 10 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).

Dec 13 & 14 Protein structure determination with NMR

* Branden and Tooze, Ch 18: Determination of Protein Structures (pp. 387–392)
* Petsko and Ringe, Ch 5: Structure Determination
* Kurt Wüthrich, NMR Studies of Structure and Function of Biological Macromolecules (Nobel Lecture), *J. Biomolec. NMR*, **27**, 13–39 (2003).

Dec 17 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).

Dec 20 Protein dynamics with NMR

* Anthony Mittermaier and Lewis E. Kay, New Tools Provide New Insights in NMR Studies of Protein Dynamics, *Science*, **312**, 224–8 (2006).

Dec 21 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 24 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).

Jan 3 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).
3. 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).

Jan 4 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).