

BSCI 274 : Proteins
Fall 2006
MWF 9:10-10:00 AM
SC 2212 (+MRBIII U5202)

- Instructor: Brandt Eichman, Ph.D. (U5221 MRBIII, 6-5233, brandt.eichman@vanderbilt.edu)
- Office Hours: Mon 3-5 PM; other times possible by appointment only
- Text:
1. *Proteins: Structure and Function* – D. Whitford (Wiley, 2005).
 2. Journal articles from the primary literature
- Other text:
3. *Introduction to Protein Structure, 2nd edition* – Branden and Tooze (1999)
 4. *Proteins: Structures and Molecular Properties, 2nd edition* – T.E. Creighton (1993)
 5. *Principles of Physical Biochemistry, 2nd edition* – van Holde, Johnson, Ho (2006)
- Web page: <http://www.vanderbilt.edu/oak/> - point to "2006.08.FALL.AS.BSCI.274.01 Proteins". The website contains syllabus, lectures, articles, and other course information.
- Evaluation: 50% 2 in-class exams, emphasizing material from lectures and student presentations
25% Research paper, due on day of Final Exam
25% Presentations of research articles and participation in class discussions.
- Presentations: The class will be a mixture of lecture and group discussions. We will read and discuss recent original research articles highlighting concepts covered in class. Students will be paired up into teams, and each team will take turns presenting these articles in PowerPoint format. One of the main functions of the presenting team will be to lead a discussion on that topic. Every student, not just the presenting team, will be expected to read the paper ahead of time and take part in a discussion during the presentation. The articles will be available on the course website. Several exam questions will be taken directly from these articles, and will focus on 1) the scientific questions being addressed, 2) the experimental procedures used, and 3) the main conclusions from the paper.
- Paper: A 10-page (double-spaced) paper on a particular protein or group of proteins. The paper must 1) relate how the protein is linked to a specific human disease, and 2) emphasize the physical/structural basis for the protein's biological function. **Undergraduate** students will write the paper in the style of a review article, and **graduate** students will write an original research grant proposal.
- Content: This course is designed to provide the students with an in-depth understanding of how the chemical and physical nature of proteins relate to their biological functions. This is an advanced course that builds upon fundamental concepts introduced in BSCI 220 (Biochemistry I). A select group of special topics will be covered in detail that will highlight various experimental methods to probe protein structure in solution. These topics include, but are not limited to: 1) membrane proteins/channels; 2) motor proteins, 3) fibrous proteins; 4) protein evolution and *de novo* design; 5) intermolecular interactions between proteins and small ligands, DNA, and other proteins; 6) structure-based drug design; 7) supramolecular assemblies and multiprotein machines; and 8) protein folding and dynamics.

*** Excused absences from exams (participation in University-sponsored sports events or debates) must be arranged at the beginning of the semester, by Friday, Sept 1. Other make-up exams will not be given, except in the case of a true, documented emergency.

*** The Vanderbilt Honor Code governs the exams, including any make-up exams, on which no assistance may be given or received. Uncertainty concerning application of the honor code does not excuse a violation.

Lecture Topics

Part I: Chemical and physical properties of proteins

- Introduction to protein chemistry; structure and properties of amino acids; peptide bonds
- Review of secondary structure; Ramachandran plots
- Tertiary and quaternary structure; protein motifs; topology
- Forces that stabilize protein structure: hydrophobicity, electrostatics, polar and dipolar, entropy
- Protein folding and dynamics
- Protein separation and purification
- Structure prediction, homology modeling, sequence alignments and evolution

Part II: Methods to probe protein structure and behavior

- Covalent modifications: active-site labeling, covalent cross-linking, introduction of chromophores
- Optical and vibrational spectroscopy; absorption, circular dichroism, fluorescence, NMR, EPR
- X-ray crystallography, light scattering, electron microscopy
- Analytical ultracentrifugation
- Single molecule measurements

Part III: Intermolecular interactions

- Interactions with small ligands and DNA
- Enzyme catalysis; inhibition
- Structure-based drug design
- Symmetry within proteins, multisubunit proteins; protein-protein interactions
- Membrane proteins and channels
- Supramolecular assemblies; multiprotein machines
- Fibrous proteins
- Molecular motors

<u>Class</u>	<u>Date</u>	<u>Subjects</u>	<u>References</u>
1	W Aug 23	Intro to protein chemistry; course overview	Ch.1
2	F Aug 25	Amino acids and polypeptides	Ch.2; Creighton Ch.1
3	M Aug 28	Peptide bonds; 2° structure	Ch.3 (pp 39-50); Creighton Ch.5
4*	W Aug 30	3° structure; protein motifs and topology	Ch.3 (pp 50-62); Creighton 6.2
5	F Sep 1	4° structure; protein symmetry	Ch.3 (pp 62-83)
6	M Sep 4	Forces stabilizing protein structures	Creighton Ch.4
7	W Sep 6	Protein separation / purification	Ch.9; van Holde Ch.5
8	F Sep 8	Optical and vibrational spectroscopy	Ch.10 (pp 379-390); Creighton 5.4, 7.1
9	M Sep 11	X-ray crystallography	Ch.10 (pp 349-360)
10	W Sep 13	X-ray crystallography	Ch.10 (pp 349-360)
11	F Sep 15	NMR Spectroscopy (guest: W. Chazin)	Ch.10 (pp 360-375)
12	M Sep 18	NMR Spectroscopy (guest: W. Chazin)	Ch.10 (pp 360-375)
13	W Sep 20	EPR and spin labeling (guest: H. Mchaourab)	Ch.10 (pp 390-393); Hubbell paper
14	F Sep 22	Discussion #1: Spectroscopy	Science 308 , 1023-1028 (2005)
15	M Sep 25	Protein Evolution and Design	Ch 6; Branden Ch.17
16	W Sep 27	De Novo Protein Design (guest: J. Meiler)	Ch 6; Branden Ch.17
17	F Sep 29	Discussion #2: Protein Evolution and Design	Science 302 , 1364-1368 (2000)
18	M Oct 2	Folding and Dynamics, H/D exchange	Ch.11, Creighton Ch.7
19	W Oct 4	Folding and Disease	Ch.11
20	F Oct 6	Discussion #3: Folding and Dynamics	PNAS 98 , 4349-4354 (2001)
21	M Oct 9	Exam 1	25%
22	W Oct 11	Protein-Ligand interactions	Ch.3 (pp 66-81); Creighton Ch.8
23	F Oct 13	Enzymes and Catalysis	Ch.7
	M Oct 16	No class (October Break)	
24	W Oct 18	Structure-Based Drug Design	Ch.12
25	F Oct 20	Discussion #4: Structure-Based Drug Design	PNAS 97 , 1008-1013 (2000)
26	M Oct 23	Membrane Proteins (guest: C. Sanders)	Ch.5
27	W Oct 25	Membrane Proteins (guest: C. Sanders)	Ch.5
28	F Oct 27	Discussion #5: Membrane Proteins	Nature 417 , 515-522 (2002)
29	M Oct 30	Protein-DNA interactions	Creighton 8.3.2; Branden Ch.8-10
30	W Nov 1	Protein-DNA interactions	Creighton 8.3.2; Branden Ch.8-10
31	F Nov 3	Discussion #6: Protein-DNA interactions	Nature 442 , 270-275 (2006)
32	M Nov 6	Motors and Pumps	
33	W Nov 8	Motor Proteins; Single Molecule Techniques	van Holde Ch.16
34	F Nov 10	Discussion #7: Motor Proteins	Molecular Cell 17 , 745-750 (2005)
35	M Nov 13	Protein Modification/Turnover	Ch.8; Creighton 2.4; Sauer paper
36	W Nov 15	Protein Modification/Turnover	Ch.8; Creighton 2.4; Sauer paper
37	F Nov 17	Discussion #8: Protein Modification/Turnover	Cell 103 , 633-643 (2000)
	Nov 18-26	Thanksgiving Holidays	
38	M Nov 27	Supramolecular Assemblies; Cryo-EM; scattering	Ch.10 (pp 375-379); van Holde Ch.7
39	W Nov 29	Discussion #9: Supramolecular Assemblies	Molecular Cell 22 , 511-519 (2006)
40	F Dec 1	Fibrous Proteins	Ch.4
41	M Dec 4	Discussion #10: Fibrous Proteins	PNAS 102 , 17342-17347 (2005)
42	W Dec 6	Exam 2	25%
FINAL	Tu Dec 12	Papers Due (9:00 AM)	25%

Selected reading / discussion topics

1. Structural basis of energy transduction in the transport cycle of MsbA
Dong *et al* (2005) *Science* **308**, 1023-1028 (plus supplement)
2. Design of a novel globular protein fold with atomic-level accuracy
Kuhlman *et al* (2000) *Science* **302**, 1364-1368
3. Protein folding from a highly denatured state: The folding of chymotrypsin inhibitor 2 at atomic res.
Kazmirski *et al* (2001) *PNAS* **98**, 4349-4354
4. Rational discovery of novel nuclear hormone receptor antagonists
Schapira *et al* (2000) *PNAS* **97**, 1008-1013
5. Crystal structure and mechanism of a calcium-gated potassium channel
Jiang *et al* (2002) *Nature* **417**, 515-522
6. Mechanism of DNA translocation in a replicative hexameric helicase
Enemark *et al* (2006) *Nature* **442**, 270-275
7. Direct visualization of RecBCD movement reveals cotranslocation of the RecD motor...
Handa *et al* (2005) *Mol Cell* **17**, 745-750
8. Crystal and solution structures of an HslUV protease-chaperone complex
Sousa *et al* (2000) *Cell* **103**, 633-643
9. Three-dimensional structure of the human DNA-PKcs/Ku70/Ku80 complex...
Spagnolo *et al* (2006) *Mol Cell* **22**, 511-519
10. 3D structure of Alzheimer's amyloid- β (1-42) fibrils
Luhrs *et al* (2005) *PNAS* **102**, 17342-17347

Additional background reading

Site directed spin labeling :

Watching proteins move using site-directed spin labeling
Hubbell *et al* (1996) *Structure* **4**, 779-783

Proteasome :

Sculpting the Proteome with AAA+ Proteases and Disassembly Machines
Sauer *et al* (2004) *Cell* **119**, 9-18