BMB 803/805: Protein Structure, Design, and Mechanism, Spring 2017

Classroom: 101 Biochemistry Bldg

Class Hours: 9:10 am – 10:00 am, Monday, Wednesday, & Friday

BMB 803 Dates: Jan. 9 – Mar. 22

BMB 805 Dates: Jan. 9 – Apr. 28; 28 lectures by Yan & Kuhn + 16 lectures by Hu & Hausinger

Instructors:
Honggao Yan, Jan. 9 – Feb. 20, 313A Biochemistry Bldg., 353-5282, yanh@msu.edu
Leslie Kuhn, Feb. 22 – Mar. 22, 502D Biochemistry, 353-8745, KuhnL@msu.edu
Jian Hu, Mar. 24 – Apr. 14, 501 Biochemistry, 353-8680, hujian1@msu.edu
Robert Hausinger, Apr. 17 – Apr. 28, 6193 BPS Bldg., 884-5404, hausinge@msu.edu

Office Hours: There are no defined office hours, and you are encouraged to meet with the instructors whenever useful, by arranging a time.

Required Materials: While there is no required textbook for the course, we highly recommend the book Introduction to Proteins: Structure, Function, and Motion by Kessel & Ben-Tal (ISBN: 1439810710). The following books are also recommended: How Proteins Work by Mike Williamson (ISBN: 0815344465), similar to Introduction to Proteins: Structure, Function, and Motion by Kessel & Ben-Tal); Introduction to Protein Structure by Branden & Tooze (2nd Ed, ISBN: 0815323050), an introductory text on protein structure and function, somewhat dated; Structure and Mechanism in Protein Science by Alan Fersht (3rd Ed, ISBN: 0716732688; downloadable from the author at http://www.fersht.com/Structure.html), good overall coverage but somewhat dated; Enzyme Kinetics and Mechanism by Paul F. Cook and W. W. Cleland (ISBN: 0815341407), an authoritative text on enzyme kinetics, including isotope effects; Enzymatic Reaction Mechanisms by Perry A. Frey and Adrian D. Hegeman (ISBN: 0195122585), available on line via the MSU library; and Organic Chemistry of Enzyme-Catalyzed Reactions by Richard B. Silverman (2nd Ed, ISBN: 0126437319).

Books on Reserve in Business Library: Introduction to Proteins: Structure, Function, and Motion; How Proteins Work; Introduction to Protein Structure; Structure and Mechanism in Protein Science; and Enzyme Kinetics and Mechanism.

Examinations: There will be three examinations in the course, the first one covering Dr. Yan's material, the second exam covering Dr. Kuhn's material, and the third (final) exam covering the materials of Drs. Hu and Hausinger. The exams will not be cumulative. For BMB 803, the total of points is 280 (10 points per lecture). Dr. Yan's material counts 9/14 of the course grade, 180 points total: 90 points from Exam 1, 45 points from a protein report, and 45 points from homework. Dr. Kuhn's material counts 5/14 (100 points) of the course grade, 2/3 from assignments and lab sessions and 1/3 from Exam 2. For BMB 805, the total of points is 440, including 280 from Drs. Yan and Kuhn and 160 from Drs. Hu and Hausinger. Of the 160 points for the materials of Drs. Hu and Hausinger, 120 points will be from Exam 3 (given at the official final exam time – see below) and 40 points from homework.

Exam 1: Friday, Feb. 24, 7:00-9:00 pm (students may take longer if they wish), 101 Biochemistry Bldg., covering lectures from Jan. 9 – Feb. 20

Exam 2: Thursday, Mar. 24, 7:00-9:00 pm, 101 Biochemistry Bldg., covering lectures from Feb. 22 – Mar. 22

Exam 3: Tuesday, May 2, 7:45-9:45 am, 101 Biochemistry Bldg., covering lectures from Mar. 24 to Apr. 28

Holidays and Breaks: Monday, Jan. 16 is Martin Luther King Day and Monday, Mar. 6 – Friday, Mar. 10 are spring break at MSU. There will be no class on these days.

Topics

Dr. Yan (18 lectures, Jan. 9 – Feb. 20)

1. ***Introduction***
2. ***Primary Structure***: nature of peptide bond, geometrical and chemical properties of amino acids, pK_a and pK_a determination by NMR, disulfide bond
3. ***Secondary Structure***: α-helix, β-sheet, turns and loops, motifs, domains, secondary structure determination
4. ***Tertiary Structure***: classification and major classes of tertiary structures, tertiary structure determination by X-ray crystallography and NMR
5. ***Conformational Changes and Dynamics***: overall motion, side-chain motions, domain movements, methods of detection
6. ***Noncovalent Forces***: electrostatic, nonpolar, H-bonds, hydrophobic effect
7. ***Ligand Binding***: binding models, macroscopic/microscopic binding constants, cooperativity, binding constant measurement
8. ***Steady-State Enzyme Kinetics***: one-substrate system (Michaelis-Menten equation and its meaning, Haldane relationship, determination of kinetic constants, derivation of kinetic equations, activation and inhibition), multi-substrate system (kinetic mechanisms and equations, determination of kinetic constants)
9. ***Transient-State Enzyme Kinetics***: elementary chemical kinetics, general methods and strategies, data analysis (computer simulation and fitting)
10. ***Transition State Theory and Its Applications***: basic theory, enzymatic catalysis, inhibitor design
11. ***Elucidating Structure-Function Relationships of Proteins***: general procedure, examples
12. ***Protein Stability***: general concepts (degradation vs. denaturation, reversible vs. irreversible denaturation, two-state vs. multi-state denaturation, local vs. global denaturation), thermal denaturation, chemical denaturation, structure of denatured state, stability measurement
13. ***Protein Folding***: folding landscape and kinetics, folding intermediate, folding transition state, molecular chaperones

Dr. Kuhn (10 lectures plus one 2-hour laboratory, Feb. 22 – Mar. 22) Draft of topics

14. ***Use of PyMOL molecular graphics software for biomolecular visualization***
15. ***Relationships between protein sequence and tertiary structure***: alignment of protein sequences, scoring of alignments, insights from alignments and constraints placed on sequence evolution, strengths and weaknesses of structural information provided by X-ray crystallography and NMR
16. ***Three-dimensional structural modeling***: homology modeling (when applicable, how done); validating structures by assessing stereochemistry; fold recognition

17. ***Structural plasticity and determinacy in short protein sequences, and how transmembrane protein structure and prediction differ from soluble protein prediction***: applications for modeling the structure of intracellular targeting motifs; secondary structure prediction; transmembrane sequence prediction
18. ***Protein recognition – Solvation***: why water is essential to life; how protein-associated water is defined by biophysical techniques; overview of the role of water in structure, ligand binding, selectivity, and catalysis
19. ***Protein recognition - Protein:protein complexes***: interactions that result in recognition and binding, enthalpic versus entropic contributions, ligand polyspecificity and regulation of affinity, statistical features of interfaces (buried surface area, interfacial hydrogen bonds, hydrophobic patches)
20. ***Protein recognition – Case studies***: how zinc fingers read specific DNA sequences; dissecting the determinants of protein-ligand recognition by analyzing crystallographic complexes and sequence evolution data for PDZ domains; domain swapping and protein misfolding/aggregation diseases
21. ***Protein Recognition – Structure-based drug design***: how protein structures are used to guide the discovery of new protein inhibitors by screening or redesign of known inhibitors and substrates; developing an inhibitor into a safe pharmaceutical
22. ***Special session***: Afternoon or evening two-hour team-based laboratory session, with students building 3-dimensional protein structures using physical models (Counts as one of the homework assignments)

Dr. Hu (10 lectures, Mar. 24 – Apr. 14)

23. ***Overview comments on enzyme mechanisms***: resonance, electron pushing, general types of reactions, useful isotopes
24. ***Overview continued***
25. ***Transition state determination of enzymatic reactions***
26. ***Acyl transfer***: catalytic mechanisms and inhibition of serine and aspartic proteases
27. ***Acyl transfer continued***
28. ***Phosphoryl transfer****: chemistry* of phosphoesters, catalytic mechanisms of kinases and phosphatases
29. ***Phosphoryl transfer continued***
30. ***RuBisCO***: major route of CO_2 fixation (carboxylation), with side reactions that include oxygenation, epimerase, isomerase, and lyase chemistries
31. ***Aldolases***: C-C cleavage via two classes of enzyme with stabilization by lysine imine or metallocenter
32. ***Thiamine pyrophosphate (TPP)-dependent enzymes:*** C-C cleavage (transketolase) and decarboxylation (pyruvate decarboxylase)

Dr. Hausinger (6 lectures, Apr. 17 – Apr. 28)

33. ***Ornithine decarboxylase***: example of a pyridoxal phosphate (PLP)-dependent decarboxylase, mechanism-based inactivation
34. ***Other PLP-dependent chemistries***: racemase, transaminase, β-elimination/replacement
35. ***Glyceraldehyde (GAP) dehydrogenase***: example of an nicotinamide adenine dinucleotide (NAD)-dependent hydride-transfer enzyme
36. ***Methyl-histone demethylase***: example of a flavin adenine dinucleotide (FAD)-dependent demethylase relevant to epigenetics
37. ***General FAD-dependent reactions***: other oxidases, dehydrogenases, and additional examples
38. ***Cytochrome P450 oxygenases***: O_2 activation and oxidation reactions, overview of mechanism and related heme enzymes