BMB 803/805: Protein Structure, Design, and Mechanism, Spring 2020

Classroom: N103 BCC, Business College

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

BMB 803 Dates: Jan. 6 – Mar. 18

BMB 805 Dates: Jan. 6 – Apr. 24; 28 lectures by Yan & Dickson + 16 lectures by Hu & Hausinger

Instructors:
Honggao Yan, Jan. 6 – Feb. 17, 311 Biochemistry Bldg., 353-5282, yanh@msu.edu
Alex Dickson, Feb. 19 – Mar. 18, 310C Biochemistry, 884-8985, alexrd@msu.edu
Jian Hu, Mar. 20 – Apr. 10, 501 Biochemistry, 353-8680, hujian1@msu.edu
Robert Hausinger, Apr. 13 – Apr. 24, 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 (2nd Edition, ISBN: 1498747175). 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. Dickson'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. Dickson'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 Dickson and 160 from Drs. Hu and Hausinger. Of the 160 points for the materials of Drs. Hu and Hausinger, 96 points will be from Exam 3 (given at the official final exam time – see below) and 64 points from homework.

Exam 1: Thursday, Feb. 20, 7:00-9:00 pm (students may take longer if they wish), 101 Biochemistry Bldg., covering lectures from Jan. 6 – Feb. 17

Exam 2: Friday, Mar. 20, 7:00-9:00 pm, 101 Biochemistry Bldg., covering lectures from Feb. 19 – Mar. 18

Exam 3: Tuesday, April 28, 12:45 pm – 2:45 pm, N103 BCC (Business College), covering lectures from Mar. 20 to Apr. 24

Report: A protein report is due on Feb. 22 as an open part of the exam for Dr. Yan's lectures

Holidays and Breaks: Monday, Jan. 20 is Martin Luther King Day and Monday, Mar. 2 – Friday, Mar. 6 are spring break at MSU. There will be no class on these days.

Topics

<u>Dr. Yan</u> (18 lectures, Jan. 6 – Feb. 17)

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

<u>Dr. Dickson</u> (6 lectures, 3 labs + in-class presentations, Feb. 20 – Mar. 18)

14. ***Review of Non-Covalent Interactions of Amino Acids + Intro to Molecular visualization with VMD***
15. ***Lab 1: Introduction to VMD (Visual Molecular Dynamics):*** loading biomolecular coordinates and topologies; constructing representations; changing viewpoints; rendering images

16. ***Sequence analysis***: sequence vs. structural homology; homologs, orthologs and paralogs; evolutionary conservation; tools for quantify sequence homology (BLAST)
17. ***Structural analysis***: root mean squared distance; alignment and rotation matrices; TM-SCORE; alignment of heterogeneous structures
18. ***Lab 2***: ***Advanced VMD:*** Trajectory data; rendering movies that switch between viewpoints
19. ***Navigating Online Databases***: protein domains and superfamilies (CATH/Pfam); protein sequence heterogeneity (OMIM/BioMuta/DisGeNET); drugs and ligands (Drugbank/ChEMBL); protein-protein complexes and interactions (IntAct/BioGRID); protein function (GO/reactome); protein structure (RCSB/PDBsum)
20. ***Homology Modeling and Structure Prediction***: CASP competitions; PSI-BLAST; SWISS-MODEL; multiple sequence alignments; AlphaFold
21. ***Structure and Model-Based Drug Design:*** Binding free energy; receptor-based vs ligand-based screening; top-performing algorithms; pharmacophore screening example
22. ***Molecular visualization project:*** Independent projects where students make a one-minute visualization capturing the relationship between structure and function. This course module runs through the duration of this section and contains the following assessments:
    - *Homework 1: Molecular system overview and proposal*
    - *Homework 2: Storyboard and script*
    - *Final video (content)*
    - *Final video (in-class presentation)*

Dr. Hu (10 lectures, Mar. 20 – Apr. 10)

23. ***Overview comments on enzyme mechanisms***: resonance, electron pushing, general types of reactions
24. ***Overview continued:*** general catalytic mechanisms
25. ***Transition state determination of enzymatic reactions:*** transition state, KIE and transition state analog in drug design
26. ***Acyl transfer***: serine proteases and inhibitors
27. ***Acyl transfer continued:*** cysteine protease, aspartic protease and metalloprotease, and their inhibitors
28. ***Phosphoryl transfer****: chemistry* of phosphoesters, catalytic mechanism of kinases
29. ***Phosphoryl transfer continued:*** kinase inhibitors and catalytic mechanism of phosphatases
30. ***RuBisCO***: major route of CO_2 fixation (carboxylation), with a primary oxygenation side reaction
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. 13 – Apr. 24)

33. ***Introduction to pyridoxal phosphate (PLP) chemistry*****:** Ornithine decarboxylase and mechanism-based inhibitors
34. ***Other PLP-dependent chemistries*****:** Racemase, transaminase, β-elimination/replacement
35. ***Introduction to NAD(P)-dependent hydride-transfer enzymes*****:** Glyceraldehyde phosphate (GAP) dehydrogenase
36. ***Introduction to FAD-dependent chemistry***: Demethylases relevant to epigenetics

37. ***Other FAD-dependent chemistries*:** Oxidases, dehydrogenases, and additional examples
38. ***Cytochrome P450 oxygenases*:** O_2 activation and oxidation reactions, overview of mechanism and related heme enzymes