BMB 803/805: Protein Structure, Design, and Mechanism, Spring 2023

Classroom: 101 Biochemistry Bldg. (both courses will meet together in the same room)

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

BMB 803 Dates: Jan. 9 – Mar. 22; 28 lectures/labs by Hu & Dickson

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

Instructors:
Jian Hu, Jan. 9 – Feb. 20, and Mar. 24 – Apr. 14, 501 Biochemistry Bldg., 353-8680, hujian1@msu.edu
Alex Dickson, Feb. 22 – Mar. 22, 310C Biochemistry, 884-8985, alexrd@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 students are encouraged to meet with the instructors whenever necessary by arranging a meeting time.

Recommend Materials: Introduction to Proteins: Structure, Function, and Motion by Amit Kessel and Nir Ben-Tal (2nd Edition, ISBN: 1498747175) for BMB803 (electronic version and a hard copy available at the MSU library). Enzymatic Reaction Mechanisms by Perry A. Frey and Adrian D. Hegeman (ISBN: 0195122585) for BMB805 (electronic version is available at the MSU library).

Grading:
For BMB 803, the total of points is 280 (10 points per lecture). Dr. Hu's materials count 18/28, 180 points in total: 50% points from homework assignment and 50% points from the final group presentation. Dr. Dickson's materials count 10/28 (100 points) of the course grade, 50% from assignments and 50% for the final presentation.
For BMB 805, the total of points is 440, including 280 from Drs. Hu and Dickson (BMB803) and 160 from Drs. Hu and Hausinger. Of the 160 points for the materials of Drs. Hu and Hausinger, 60% will be from Exam 3 (given at the official final exam time – see below) and 40% points from homework.
There will be three examinations in the course: the first is a group presentation based on given topics; the second is an individual presentation based on the materials provided by Dr. Dickson in BMB803; and the third exam covers the materials provided by Drs. Hu and Hausinger in BMB805. The exams are not cumulative.

Exam 1: Monday, Feb. 20, 9:10-10:00 am, group presentations
Exam 2: Wednesday, Mar. 23, 9:10-10:00 am, individual presentations
Exam 3: Tuesday, May. 2 12:45pm - 2:45pm, open book exam, 101 Biochemistry Bldg.

Holidays and Breaks: Jan. 16 is Martin Luther King Day; Spring break Mar. 6-10. No class on these days.

Topics:
Dr. Hu (18 lectures, Jan. 9 – Feb. 20)
1. ***Course Introduction and Overview of Protein Functions***

2. ***Primary, Secondary, and Tertiary Structure***: properties and covalent modifications of amino acids, types of secondary structure and intrinsically disordered proteins/regions, super-secondary structures, and tertiary structures
3. ***Primary, Secondary, and Tertiary Structure (Continued)***
4. ***Proteins Structure Determination***: general strategy, approaches of structure determination (NMR, X-ray crystallography and cryo-EM)
5. ***Noncovalent Forces in Protein Structure***: electrostatic, nonpolar, hydrogen bonds, hydrophobic effects
6. ***Conformational Changes and Dynamics***: motion at different time scales and methods of detection
7. ***Protein-Ligand and Protein-Protein Interactions***: biological functions, binding constants, cooperativity, binding constant measurement
8. ***Protein Folding and Protein Stability***: folding landscape and kinetics, folding models, folding intermediate, molecular chaperones
9. ***Membrane Proteins***: classification, protein-membrane interactions, structure features, and biological functions
10. ***Membrane Mimetic Systems in Membrane Protein Study***
11. ***Channels***: structure, function, and mechanism
12. ***Carriers***: structure, function, and mechanism
13. ***Receptors***: structure, function, and mechanism
14. ***General Catalytic Mechanisms of Enzymes***
15. ***Transition State Theory and Transition State Determination***: basic theory, kinetic isotope effects and transition state analog in drug design
16. ***Enzyme Kinetics and Inhibition***: theory and enzyme inhibitors
17. ***Directed Evolution***: theory, approaches, and examples
18. ***Group Presentations***

<u>Dr. Dickson</u> (6 lectures, 3 labs + in-class presentations, Feb. 22 – Mar. 22)

19. ***Online Resources for Protein Modeling and Analysis + Intro to Molecular visualization with VMD***
20. ***Lab 1: Introduction to VMD (Visual Molecular Dynamics):*** loading biomolecular coordinates and topologies; constructing representations; changing viewpoints; rendering images
21. ***Sequence analysis:*** sequence vs. structural homology; homologs, orthologs and paralogs; evolutionary conservation; tools for quantify sequence homology (BLAST)
22. ***Structural analysis:*** root mean squared distance; alignment and rotation matrices; TM-SCORE; alignment of heterogeneous structures
23. ***Lab 2: Advanced VMD:*** Trajectory data; rendering movies that switch between viewpoints
24. ***Homology Modeling and Structure Prediction:*** CASP competitions; PSI-BLAST; SWISS-MODEL; multiple sequence alignments; AlphaFold
25. ***Molecular Modeling and Molecular Dynamics:*** Online tools; forcefields; energy barriers and timescales; CHARMM-GUI
26. ***Structure and Model-Based Drug Design:*** Binding free energy; receptor-based vs ligand-based screening; top-performing algorithms; pharmacophore screening example
27. ***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. 24 – Apr. 14)

28. ***Types of Enzymatic Reactions***
29. ***Acyl transfer***: serine proteases and inhibitors
30. ***Acyl transfer (continued):*** cysteine protease, aspartic protease and metalloprotease, and their inhibitors
31. ***Phosphoryl transfer****: chemistry* of phosphoesters, catalytic mechanism of kinases
32. ***Phosphoryl transfer (continued):*** kinase inhibitors and catalytic mechanism of phosphatases
33. ***Aldolases***: C-C cleavage via two classes of enzyme with stabilization by lysine imine or metallocenter
34. ***Thiamine pyrophosphate (TPP)-dependent enzymes:*** C-C cleavage (transketolase) and decarboxylation (pyruvate decarboxylase)
35. ***RuBisCO***: major route of CO_2 fixation (carboxylation), with a primary oxygenation side reaction
36. ***Biotin-dependent enzymes***: a variety of carboxylases
37. ***Biotin synthase***: radical SAM enzymes and Fe-S clusters

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

38. ***Introduction to pyridoxal phosphate (PLP) chemistry*****:** Ornithine decarboxylase and mechanism-based inhibitors
39. ***Other PLP-dependent chemistries*****:** Racemase, transaminase, β-elimination/replacement
40. ***Introduction to NAD(P)-dependent hydride-transfer enzymes*****:** Glyceraldehyde phosphate (GAP) dehydrogenase
41. ***Demethylation chemistry: focused on epigenetics***
42. ***Other FAD-dependent chemistries*****:** Oxidases, dehydrogenases, and additional examples
43. ***Cytochrome P450 oxygenases*****:** O_2 activation and oxidation reactions, overview of mechanism and related heme enzymes