## BMB 803/805: Protein Structure, Design, and Mechanism, Spring 2021

**Classroom:** Online zoom meeting (links to be sent by instructors)

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

**BMB 803 Dates:** Jan. 11 – Mar. 19; 28 lectures by Hu & Dickson

**BMB 805 Dates:** Jan. 11 – Apr. 21; 28 lectures by Hu & Dickson + 14 lectures by Hu & Hausinger

**Instructors:**

Jian Hu, Jan. 11 – Feb. 22, and Mar. 22 – Apr. 7, 501 Biochemistry Bldg., 353-5282, hujian1@msu.edu

Alex Dickson, Feb. 24 – Mar. 19, 310C Biochemistry, 884-8985, alexrd@msu.edu

Robert Hausinger, Apr. 9 – Apr. 21, 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.

# **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).

**Examinations:** There will be three examinations in the course, the first one is a group presentation, the second is an individual presentation, and the third exam covering the materials of Drs. Hu and Hausinger in BMB805. The exams are not cumulative.

For BMB 803, the total of points is 280 (10 points per lecture). Dr. Hu’s material counts 9/14 of the course grade, 180 points total: 36 points from class attendance, 72 points from homework and 54 points from Exam 1. Dr. Dickson’s material counts 5/14 (100 points) of the course grade, 50% from assignments and 50% for the final presentation.

For BMB 805, the total of points is 420, including 280 from Drs. Hu and Dickson (BMB803) and 140 from Drs. Hu and Hausinger. Of the 140 points for the materials of Drs. Hu and Hausinger, 84 points will be from Exam 3 (given at the official final exam time – see below) and 56 points from homework.

Exam 1: Monday, Feb. 22, 9:00-10:00 am, group presentations

Exam 2: Friday, Mar. 19, 9:10-10:00 am, individual presentations

Exam 3: Tuesday, Apr. 27, 12:45pm - 2:45pm, covering lectures from Mar. 22 to Apr. 21

**Holidays and Breaks:**  Jan. 18 is Martin Luther King Day; Mar. 3 and Apr. 23 are breaks at MSU in 2021. No spring break in 2021. No class on these days.

**Topics:**

Dr. Hu (17 lectures + one group presentation, Jan. 11 – Feb. 19)

1. ***Course Introduction and Overview of Protein Functions***
2. ***Primary Structure***: amino acid properties, peptide bond, and covalent modification
3. ***Secondary Structure***: secondary structure elements and determination
4. ***Tertiary Structure***: classification and major classes of tertiary structures
5. ***Conformational Changes and Dynamics***: motion at different time scale and methods of detection
6. ***Elucidating Structure-Function Relationships of Proteins***: general strategy, approaches of structure determination (NMR, X-ray crystallography and cryo-EM) and examples
7. ***Noncovalent Forces in Intermolecular Interactions***: electrostatic, nonpolar, H-bonds, hydrophobic effect
8. ***Protein-Ligand and Protein-Protein Interactions***: biological functions, binding constants, cooperativity, binding constant measurement
9. ***General Catalytic Mechanisms of Enzymes***
10. ***Transition State Theory and Transition State Determination***:basic theory, kinetic isotope effects and transition state analog in drug design.
11. ***Enzyme Kinetics and Inhibition***: theory and enzyme inhibitors.
12. ***Membrane Proteins***: classification, structure features and biological functions
13. ***Channels***: structure, function and mechanism of channels
14. ***Carriers***:structure, function and mechanism of carriers
15. ***Protein-Membrane Interactions***: structure, function and regulation of peripheral membrane proteins
16. ***Protein Folding and Protein Stability***: folding landscape and kinetics, folding intermediate, folding transition state, molecular chaperones. general concepts and types of denaturation, structure features and approaches
17. **Intrinsically Disordered Proteins**: Structure features, functions and research approaches, phase separation
18. **Group Presentations**

Dr. Dickson (6 lectures, 3 labs + in-class presentations, Feb. 24 – Mar. 19)

1. ***Review of Non-Covalent Interactions of Amino Acids + Intro to Molecular***

***visualization with VMD***

1. ***Lab 1: Introduction to VMD (Visual Molecular Dynamics):*** loading biomolecular

coordinates and topologies; constructing representations; changing viewpoints;

rendering images

1. ***Sequence analysis:*** sequence vs. structural homology; homologs, orthologs and

paralogs; evolutionary conservation; tools for quantify sequence homology (BLAST)

1. ***Structural analysis:*** root mean squared distance; alignment and rotation matrices; TM-SCORE; alignment of heterogeneous structures
2. ***Lab 2: Advanced VMD:*** Trajectory data; rendering movies that switch between

viewpoints

1. ***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)

1. ***Homology Modeling and Structure Prediction:*** CASP competitions; PSI-BLAST;

SWISS-MODEL; multiple sequence alignments; AlphaFold

1. ***Structure and Model-Based Drug Design:*** Binding free energy; receptor-based vs

ligand-based screening; top-performing algorithms; pharmacophore screening example

1. ***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 (8 lectures, Mar. 22 – Apr. 7)

1. ***Types of Enzymatic Reactions***
2. ***Acyl transfer***:serine proteases and inhibitors
3. ***Acyl transfer (continued):*** cysteine protease, aspartic protease and metalloprotease, and their inhibitors
4. ***Phosphoryl transfer****: chemistry* of phosphoesters, catalytic mechanism of kinases
5. ***Phosphoryl transfer (continued):*** kinase inhibitors and catalytic mechanism of phosphatases
6. ***RuBisCO***: major route of CO2 fixation (carboxylation), with a primary oxygenation side reaction
7. ***Aldolases***: C-C cleavage via two classes of enzyme with stabilization by lysine imine or metallocenter
8. ***Thiamine pyrophosphate (TPP)-dependent enzymes:*** C-C cleavage (transketolase) and decarboxylation (pyruvate decarboxylase)

Dr. Hausinger (6 lectures, Apr. 9 – Apr. 21)

1. ***Introduction to pyridoxal phosphate (PLP) chemistry*:** Ornithine decarboxylase and mechanism-based inhibitors
2. ***Other PLP-dependent chemistries*:** Racemase, transaminase, -elimination/replacement
3. ***Introduction to NAD(P)-dependent hydride-transfer enzymes*:** Glyceraldehyde phosphate (GAP) dehydrogenase
4. ***Demethylation chemistry: focused on epigenetics***
5. ***Other FAD-dependent chemistries*:** Oxidases, dehydrogenases, and additional examples
6. ***Cytochrome P450 oxygenases*:** O2 activation and oxidation reactions, overview of mechanism and related heme enzymes