BIOCHEMISTRY 402 - Course Outline

(Fall, 2011)

OVERVIEW OF LECTURE TOPICS:	Number of Lectures	INSTRUCTOR

1. Structural Components of Proteins — G. Brayer

(a) Amino Acids and the Polypeptide Chain Backbone 2
- physical characteristics of side chains and nomenclature
- cis/trans peptide links and backbone geometry
- short/long range restraints on main chain folding

(b) Protein Structural Elements 4
- ranges of secondary structural elements and folding patterns
- potential helical structures and stabilization features
- types of beta sheets; structures and hydrogen bonding patterns
- beta bends and bulges, classes and roles; other non-repetitive structures

2. Protein Taxonomy and Three-Dimensional Folding — G. Brayer

(a) Classification of Proteins by Patterns of Tertiary Structure 2

(b) Major Classes of Structural Domains 2

3. Protein Chemistry — G. Mauk

(a) Electrostatics of Proteins.....3

(b) Protein Spectroscopy and Conformational Dynamics 3

(c) Chemical Analysis of Proteins.....3

(d) Chemistry of Protein Modification 4

4. Protein Structure Determination, Interpretation and Inhibitor/Drug Design — G. Brayer

(a) Protein X-ray Crystallography: An Overview 3

(b) Analysis of Three-Dimensional Structural Data 3
- structural solution techniques
- stages of electron density map interpretation
- effective resolution of diffraction data
- assessment and use of completed structures

(c) Probing Protein Structure-Function Relationships.....5
- difference electron density map applications
- interpreting variant protein structures
- elucidating the catalytic mechanisms of enzymes
- inhibitor and drug design approaches

Course Instructors and Offices

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* * * Examination Practices and Policies * * *

1. Midterm Examinations

a) There will be **two** midterm examinations in this course. Each midterm examination will be worth 20% of the final course mark of BIOC 402.

b) Problem sets with previous examination questions will be handed out by the individual lecturers.

c) Past midterm examinations will not be made available to students.

d) When marked, students will be given the opportunity to review their midterm examinations and the answer keys in scheduled viewing sessions. Marks will be posted on Vista.

e) A student without an appropriate medical excuse for missing a midterm examination will have zero recorded as their mark for that exam.

f) Students must bring appropriate identification (with photograph) to midterm examinations (e.g. drivers license).

2. Final Examination

a) Students should not book airline flights home for Christmas until the definitive final exam schedule has been posted, as preliminary schedules are often changed.

b) The final examination will cover **all** course material, with extra weight being given to lectures not covered by the previous midterm examinations.

c) This examination will be worth 60% of the final mark in BIOC 402.

d) Past final examinations will not be made available to students.

e) After the December examination period you can access your grades online at the Student Service Centre.

f) Final examinations can only be viewed if permission is obtained from the Dean of Science Office or the appropriate alternative Faculty Office for non-science students.

g) Students must bring appropriate identification (with photograph) to the final examination (e.g. drivers license).

Please Note: Students who miss the final examination because of medical, emotional or other problems must inform the Dean of Science Office as soon as possible. Only students having a justifiable reason for their absence that **is acceptable to the Dean of Science Office** will be eligible to take a deferred examination. Non-Science and Graduate students that are absent from the final examination must provide justification for their absence to their Faculty Offices and only upon receipt of official written acceptance of their reason for being absent will a deferred examination be arranged.

BIOC 402 Proteins: Structure and Function

Lecture Schedule (Fall 2011)

G. Brayer	Wednesday, September	7	
	Friday, September	9	
	Monday, September	12	
	Wednesday, September	14	
	Friday, September	16	
	Monday, September	19	
	Wednesday, September	21	
	Friday, September	23	
	Monday, September	26	
	Wednesday, September	28	
	Friday, September	**30**	**Midterm examination #1**
G. Mauk	Monday, October	3	
	Wednesday, October	5	
	Friday, October	7	
	Monday, October	10	Thanksgiving Day University Closed
	Wednesday, October	12	
	Friday, October	14	
	Monday, October	17	
	Wednesday, October	19	
	Friday, October	21	
	Monday, October	24	
	Wednesday, October	26	
	Friday, October	28	
	Monday, October	31	
	Wednesday, November	2	
	Friday, November	**4**	**Midterm examination #2**
G. Brayer.....	Monday, November	7	
	Wednesday, November	9	
	Friday, November	11	Remembrance Day University Closed
	Monday, November	14	
	Wednesday, November	16	
	Friday, November	18	
	Monday, November	21	
	Wednesday, November	23	
	Friday, November	25	
	Monday, November	28	
	Wednesday, November	30	
	Friday, December	2	

BIOC 402: Detailed Description of Material in Individual Lectures

(Subject to change as necessary)

Parts 1+2: Lectures by Dr. G. Brayer

Structural Components of Proteins; Protein Folding and Taxonomy

Lecture	Topics Covered
1	Course scope, lecture topics and expectations. Methods of visualizing protein structure. Obtaining molecular graphics software and completing structural analysis exercises. Review of the scope of protein roles in biochemistry. Defining the factors that contribute to protein versatility - potential combinations, flexibility, prosthetic groups, energy changes.
2	Physical and structural characteristics of the amino acids. Amino acid groups and abbreviations. Nomenclature rules for amino acid atoms. Residue identification and naming exercise.
3	Amino acid side chain rotatable bond designations. Structural characteristics and dimensions of the peptide bond. Short and long range planar restraints on main chain conformations. Trans and cis peptide bonds - occurrence and steric implications.
4	Cis-proline example and structural role - molecular graphics exercise. The conformation of the cis-proline reverse open turn. Steric hinderance plots - construction and implications. Role of side chains in restricting main chain rotational space. Potential energy plots (and variables) as a refinement of steric hinderance plots.
5	Basic types of secondary folding patterns. The range of potential helical structures (advantages/disadvantages) and nomenclature. Placement of helical structures in steric hinderance plots; stabilizing factors in the formation of an alpha-helix.
6	Structural placement of side chains in alpha-helical structures. The role of prolines in helical structures. Beta-sheet structures, hydrogen bonding patterns and structural examples - parallel, anti-parallel and mixed. Exercise in secondary structure identification and analysis.
7	Beta-bulge types and roles - example structure. Types I and II beta-turns - structural and functional roles in proteins. The non-repetitive structure of coil. Incorporation of multiple secondary structures into proteins folds.
8	Methods for the topological analysis of beta-sheet structures; connection types between beta-strands. Preparation of beta-sheet topology diagrams. Generalized results from topology studies - fold types, frequency patterns, handedness, absence of knots.
9	Beta-barrel classes - parallel and anti-parallel. Topological analysis of barrel structures. Structural domain definition and observed inter-domain relationships. Introduction to protein taxonomy and the classification of proteins by tertiary structure.
10	Key characteristics considered in identifying major classes of structural domains - secondary structural elements, connection topologies, layers of backbone. Organizing protein structures into major categories and subgroups. Illustrative examples of proteins falling into all of the key folding groups. Exercise in domain folding analysis and category identification.

Part 3: Lectures by Dr. A. G. Mauk

Chemical Characterization of Proteins

Lecture	Topics Covered
1	Overview of major topics for this month. Introduction to protein structural dynamics and natively disordered proteins. Introduction to electrostatic properties of proteins; amino acids side chains as H-bond acceptors and donors.
2	Roles of H-bonding, factors controlling pK_as of titratable groups. Titration properties of proteins. Solvent-accessible surfaces of proteins.
3	Isoionic and isoelectric pH. Interpretation of protein titration curves. Defining "conformational change." Overview of spectroscopic methods to detect conformational changes.
4	UV spectroscopy of amino acids and proteins. Introduction to fluorescence spectroscopy of proteins (steady-state and lifetime measurements).
5	Fluorescence spectroscopy of proteins (conclusion). Circular dichroism and determination of protein secondary structure.
6	Chemical methods of monitoring conformational change.
7	Overview of protein mass spectrometry (electrospray and MALDI-TOF MS). Proteomics: goals and chemical strategy.
8	Chemical cleavage of proteins. Mechanism of CNBr reaction. Enzymatic cleavage of proteins. Peptide mapping.
9	Amino acid composition analysis. Ninhydrin and fluorescent methods for detecting amino acids.
10	Protein sequence analysis. Amino-terminal residue analysis. Mechanism of Edman degradation.
11	Limitations of Edman degradation. N-terminal blocking groups. Introduction to chemical modification of proteins and introduction to thiol-specific reagents.
12	Redox chemistry of Cys. Cleavage of disulfide bonds. Assays for thiol groups. Reagents for chemical modification of thiol groups. Redox chemistry of Met. Reagents for chemical modification of His, Tyr, Arg, Lys
13	Overview of post-translational modification of proteins, reversible and irreversible. Protein phosphorylation and acetylation, crosslinking, hydrolysis, glycosylation, cofactors. Age-related changes.

Part 4: Lectures by Dr. G. Brayer

Protein Structure Determination, Interpretation and Inhibitor/Drug Design

Lecture	Topics Covered
1	**Introduction to Protein Crystallography.** Historical perspective. Protein data bank and exercise. Range of biological systems studied by X-ray crystallography - small organic compounds of biological relevance, biological macromolecules, substrates/ inhibitors bound to proteins. Analysis of genetically modified proteins. The crystallographic approach: advantages and disadvantages.

2	**Protein Crystallization Methodology.** The overall strategy used to promote protein crystallization. Methods of attaining supersaturation - specific example: vapour diffusion from hanging drops. Crystallizing agents: salts, organic solvents, polyethylene glycols (PEG's).
3	**Protein Crystals and Diffraction.** The composition of macromolecular crystals. The basic principles of diffraction. The light microscope and diffraction theory. The three special needs for protein crystals.
4	**Diffraction Arrays and Data Collection.** Diffraction patterns from molecular arrays. Practical aspects of collecting diffraction data - crystal mounting, basics of area detector operation, rotating anodes and synchrotrons.
5	**Phasing and the Electron Density Map.** The phase problem. Phase determination solutions - MIR/ MR/ MAD. The electron density map equation and implications.
6	**Visualization and Refinement of a Protein Structure.** Constructing the first electron density map. Fitting the amino acid sequence. Refinement of a preliminary structural fit.
7	**Structure Determination Considerations.** The refinement R-factor. The concept of resolution. Assessing the validity of refinement statistics. Exercise in electron density map fitting. Exercise in understanding disorder and phasing concepts.
8	**The Structure Determination of Type II Citrate Synthase.** Biochemical background for *E. coli* citrate synthase. Project goals and approach to solution of wild-type structure - crystallization and data collection, key data measurement statistics, phase determination strategy. The concepts of space group/asymmetric unit. Examination of citrate synthase structural characteristics - secondary elements/ electrostatic surface, hexamer formation and bound water. The atomic motion parameter.
9	**Solving the F383A Variant Structure of Citrate Synthase.** Potential mechanistic roles for F383. Experimental requirements for the difference map approach. Calculation and interpretation of the variant difference map. Structural insight into F383 functionality.
10	**Drug Development for Human Alpha-Amylase.** Overview of Difference Map Approach - advantages, experimental flow chart. Human alpha-amylase background. Project goals and wild-type structure solution. Unique structural features of human alpha-amylase.
11	**Human Alpha-Amylase/ Isoacarbose Complexation.** Data collection and statistics. Difference map calculation and isoacarbose fitting. Refinement of the isoacarbose complex structure. Structural and mechanistic insights from isoacarbose inhibition. Moving promising inhibitors towards potential therapeutics.