

## **BIOLOGICAL STRUCTURE I (BIOCHEMISTRY 585)**

- Semester:** Spring, 2008
- Meetings:** BSW 208: M 2:00-2:50pm; BSW 219: T, Th 2:00-3:15pm. NOTE TWO ROOMS!
- Units:** 4. 2-4 hrs of lecture per week plus 0-2 hours of computer lab.
- Texts:** *Structural Biology: Practical NMR Applications*, by Quincy Teng (Springer).  
*Outline of Crystallography for Biologists*, by David Blow (Oxford).  
  
In addition, original scientific articles, reviews and handouts will often be used to illustrate points. Some texts will be recommended as supplementary or background material.
- Instructors:** Matt Cordes, BSW 436, cordes@email.arizona.edu  
  
Bill Montfort, BSW 533, montfort@email.arizona.edu
- T.A.** None
- Office Hrs:** immediately after class or by appointment. Materials relevant to course but not downloadable from website, such as class handouts, will be made available for temporary checkout and copying.
- Website:** <http://www.biochem.arizona.edu/classes/bioc585/>
- Questions:** You are strongly encouraged to ask questions at any time during lecture, and the instructor will stay to answer questions after lecture as long as students wish. Also, feel free to use email to ask questions of the instructors, who will do their best to answer promptly.
- Exams:** The mid-term exam will be take-home and will consist of the following: questions and problems based on the content of lectures and assigned reading; a critical review of one or several publications related to the content of the course; problems based on the viewing of molecular structures or on analysis of data. The first exam will be handed out at about the time of Spring Break. The final exam will be written in class during the scheduled hours for the examination: **Tuesday, May 13, 2-4 pm.**
- Problem Sets:** May be handed out periodically for work at home.
- Grading:** Problem sets are 33% of the grade, and the mid-term and final count 33% each.
- Background:** We assume that students have completed undergraduate courses in mathematics through integral calculus, physical chemistry, organic chemistry, and general biochemistry. We recommend that students without background in physical chemistry not take this course. We also assume a general understanding of protein structure at the level taught in BIOC 565 (Proteins and Enzymes).
- Computing:** The student will be expected to become familiar with the use of some software programs. Students will also be given problems that involve visiting and using websites relevant to

biological structure. For these purposes, each student will have a user account for the biochemistry computer lab in BSW 243. Students are welcome to use their own personal computers for this work as well, but if problems arise which are specific to their own setup, the course instructor may not be able (or willing) to help fix them.

### **GENERAL DESCRIPTION OF COURSE:**

#### ***What this course is not:***

- A basic introduction to biological structure. We will not spend any time, for instance, on the basics of protein structure/folding. Most of this material is covered in Biochem 462 (Biochemistry) or Biochem 565 (Proteins and Enzymes) and not much class time will be devoted to it here. As background material, I suggest two texts:

*Introduction to Protein Architecture*, by A.M. Lesk

*Introduction to Protein Structure*, by Branden and Tooze

- An exhaustive theoretical treatment of major methods for structural investigation, such as X-ray crystallography or NMR. An entire course could be taught on either one of these subjects alone.
- A course covering every topic and method used in biological structure—the field is too broad and varied to do this. For instance, very little time will be devoted to low-resolution methods for structural investigation.

#### ***What this course is:***

- A graduate level course in **selected modern experimental methods as applied to the investigation of biological structure**. The goal is that the student will be equipped to recognize, comprehend and evaluate major techniques used in modern structural biology journal articles. Accordingly, the course is largely devoted to the two most common techniques for high-resolution macromolecular structure determination, **NMR** and **X-ray crystallography**. These techniques will be discussed primarily as they apply to soluble, globular proteins. However, some attention will also be paid to membrane protein and nucleic acid structure.
- An exploration of **issues and topics of current interest in biological structure**, as taught through specific examples.

The subject matter may be quantitative, requiring that the student be comfortable with mathematical descriptions. Emphasis will be placed on the physical picture behind the math, which should be accessible to students. We recognize that students differ in their level of familiarity with physical chemistry and the associated mathematics. We do not expect every student can understand all that is taught.

## **OVERVIEW OF COURSE SECTIONS AND TOPICS**

### **Part I. Biomolecular NMR Spectroscopy (7.5 weeks)**

*Matt Cordes*

The objectives of this section are 1) to obtain a basic understanding of how NMR works as applied to biological molecules 2) to be able to critically evaluate original research articles that incorporate NMR techniques 3) to gain hands-on experience in examining and analyzing NMR spectra and NMR-generated structures. We will use *Structural Biology: Practical NMR Applications*, by Quincy Teng as a primary text, though we will not rely too heavily on it or cover it in any comprehensive way. The student may also find the following texts useful as supplementary material: *Modern NMR Techniques for Chemistry Research*, by Andrew Derome (Pergamon Press), *NMR of Proteins and Nucleic Acids*, by Kurt Wuthrich (Wiley Interscience), *Biomolecular NMR Spectroscopy* by Jeremy N.S. Evans (Oxford) and *Protein NMR Spectroscopy*, by Cavanagh *et al.* (Academic Press). Readings will also include many handouts and original research/review articles from the literature. In particular, we will critically examine several research articles dealing with NMR studies of the protein calmodulin, as an exemplary illustration of the utility of NMR in probing protein structure and dynamics. Discussion of calmodulin will continue in Dr. Montfort's X-ray crystallography portion, allowing us to compare and contrast the strengths and limitations of the two techniques. Approximately 3 hours of class time per week will be lectures. Approximately 1 hour a week will be spent in the computer lab analyzing NMR data and examining structures generated from NMR data. To facilitate these analyses, we will become familiar with NMR data analysis and structure determination software programs such as Sparky and MOLMOL. Below is a list of selected topics which are likely to be discussed in this section.

basics of high-field pulse NMR

chemical shift, relaxation, dipolar coupling, nuclear Overhauser effect, J coupling

how multidimensional NMR works

methods for spin-system and sequential resonance assignment

structural information from NMR

dihedral angle restraints

distance restraints

long-range info from residual dipolar couplings

hydrogen bond restraints

other types of info

programs/algorithms for structure determination

dynamic information from NMR

exchange spectroscopy

amide hydrogen exchange

lineshape analysis

relaxation rates and NOEs

relaxation dispersion

NMR methods for large systems

## **Part II. Macromolecular Crystallography (~7.5 weeks)**

*Bill Montfort*

The objectives for this section are (1) to obtain a rough understanding of how macromolecular crystallography works, (2) to learn how to critically assess a crystallographic structure report, (3) to obtain practical knowledge in crystallizing proteins and examining electron density maps.

We will cover the following topics (not necessarily in this order):

1. Diffraction theory
2. 'Phase' determination
3. Calculating and interpreting electron density maps
4. Model building and refinement
5. Structure assessment
6. Crystallization of macromolecules
7. Dynamic crystallography (if time permits)

I will introduce molecular modeling to you using the program suite CCP4i and the molecular modeling program COOT, both available in our computer lab. With this free software, you will learn to display PDB files and calculate and display electron density maps. 1 session per week will be spent in the computer lab. We will use a variety of journal articles, reviews and textbooks in this part of the course, particularly the textbook '*Outline of Crystallography for Biologists*' by David Blow (Oxford University Press). We will also compare and contrast X-ray and NMR methods using the protein calmodulin.

### **Optional Course: Bioc 585b Practical Macromolecular Crystallography (4 weeks, beginning after spring break).**

*Andrzej Weichsel*

This course will provide hands-on crystallization and diffraction measurement. Details will be forthcoming.