Course Description: The aim of this course is to walk students through the main ideas and experimental techniques in structural biology following the shortest path from the significant events in the history of the field to the recent research literature. In the first part, we will review the building blocks of proteins and DNA, discuss the physical principles determining their structures, and introduce a biochemical description of folding, binding and catalysis in terms of equilibrium constants and rate constants. Throughout, we will keep an eye on historical papers that contributed to the birth of structural biology. In the second part, selected biological problems and biophysical techniques used to address these problems will be introduced and followed by a discussion of the relevant research papers. Applications of structural biology to membrane proteins, signaling proteins, and proteins interacting with DNA will be examined. Emphasis will be given on the modern view that protein function is determined by structure as well as dynamics. Although the selection of examples is clearly not exhaustive, it is broad enough to offer a panoramic view of the field. Focusing on one or two specific proteins during the discussions is intended to prepare the students for critical scrutiny of the details in their own research.

Who can take this course: Most of the students taking the course are expected to be graduate students in the Biological Sciences and Bioengineering who are interested in Structural Biology. However, advanced undergraduate students in the Biological Sciences and Bioengineering curious about the historical and physical foundations of the field as well as the current research problems are also encouraged to take the course. In addition, the course may be attractive to engineering and natural-science students from other (non-biological) disciplines who want to get exposed to modern molecular biology. After surmounting the barrier of getting familiar with the necessary biology-related vocabulary, such students will find their existing knowledge and skills invaluable for understanding the physical principles behind the biophysical techniques that will be discussed in the course.

Evaluation:

<table>
<thead>
<tr>
<th>Part I:</th>
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<tbody>
<tr>
<td>Quizzes</td>
<td>10 %</td>
</tr>
<tr>
<td>Midterm exam</td>
<td>20 %</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Part II:</th>
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<tbody>
<tr>
<td>Homework and in-class discussion</td>
<td>15 %</td>
</tr>
<tr>
<td>Report and oral presentation</td>
<td>25 %</td>
</tr>
<tr>
<td>Comprehensive final exam</td>
<td>30 %</td>
</tr>
</tbody>
</table>

During the first part of the course, short quizzes will be given to make sure the material has been absorbed in a timely manner. The midterm exam will be a comprehensive written test of this material. In the second part, which is oriented towards following the current research literature, several research papers will be assigned for reading in addition to the relevant sections from the textbooks. The students will be expected to have read the papers carefully and critically, and to actively participate in the
discussion. To ensure closer familiarity with the structural aspects of the proteins considered in the papers, simple homework, consisting of visually examining and manipulating their three dimensional representations, will be given on a weekly basis. During the course, students are expected to choose a biological system, which they will examine from a structural perspective using the recent research literature. Towards the end of the semester, they will submit a short written report and make an in-class presentation of their findings.

**Detailed Course Content:**

<table>
<thead>
<tr>
<th>Dates</th>
<th>Topics (discussion topics in italics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep 27</td>
<td>General information about the course</td>
</tr>
<tr>
<td>Sep 28</td>
<td>Introduction: What goes on in a cell</td>
</tr>
<tr>
<td>Oct 4</td>
<td>X-ray crystallography and secondary structure: helices and pleated sheets (Pauling)</td>
</tr>
<tr>
<td>Oct 5</td>
<td>Nucleic acids and the double helix (Watson and Crick)</td>
</tr>
<tr>
<td>Oct 11</td>
<td>More X-ray crystallography and the tertiary structure of myoglobin (Kendrew)</td>
</tr>
<tr>
<td>Oct 12</td>
<td>Cooperative ligand binding and the quaternary structure of hemoglobin (Perutz)</td>
</tr>
<tr>
<td>Oct 18</td>
<td>Side chains at last: hydrophobicity, hydrophilicity and protein folding</td>
</tr>
<tr>
<td>Oct 19</td>
<td>Allosteric proteins and rearrangement of subunits (Monod)</td>
</tr>
<tr>
<td>Oct 25</td>
<td>Chemical kinetics</td>
</tr>
<tr>
<td>Oct 26</td>
<td>Catalysis: rates and structures</td>
</tr>
<tr>
<td>Nov 1</td>
<td>Lipid membranes and transport of small molecules</td>
</tr>
<tr>
<td>Nov 2</td>
<td>Ion channels and the action potential</td>
</tr>
<tr>
<td>Nov 8</td>
<td>Structure of the potassium channel KcsA</td>
</tr>
<tr>
<td>Nov 9</td>
<td>Potassium ion conduction in the selectivity filter of KcsA</td>
</tr>
<tr>
<td>Nov 12</td>
<td>Review for the exam</td>
</tr>
<tr>
<td>Nov 15</td>
<td>Kurban Bayrami</td>
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<td>Nov 16</td>
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<tr>
<td>Nov 22</td>
<td><strong>Midterm Exam</strong></td>
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<tr>
<td>Nov 26</td>
<td>Gating of potassium channels: Ligand-assisted opening of the pore (MthK)</td>
</tr>
<tr>
<td>Nov 29</td>
<td>Voltage sensors move across the membrane! (KvAP)</td>
</tr>
<tr>
<td>Nov 30</td>
<td>Do voltage sensors move across the membrane after all? (Kv1.2)</td>
</tr>
<tr>
<td>Dec 3</td>
<td>The lipid membrane and the structure of voltage-dependent channels</td>
</tr>
<tr>
<td>Dec 6-7</td>
<td>Molecular dynamics (MD) simulations</td>
</tr>
<tr>
<td>Dec 10</td>
<td>MD simulations of ion conduction and hydrophobic gating in potassium channels</td>
</tr>
<tr>
<td>Dec 13</td>
<td>Introduction to NMR</td>
</tr>
<tr>
<td>Dec 14</td>
<td>Biomolecular structure determination with NMR</td>
</tr>
<tr>
<td>Dec 17</td>
<td>Proline isomerization and the interaction of SH2 and SH3 domains in Itk kinase</td>
</tr>
<tr>
<td>Dec 20</td>
<td>Protein dynamics and conformational transitions with NMR</td>
</tr>
<tr>
<td>Dec 21</td>
<td>Population shift in the two-state signaling protein NtrC</td>
</tr>
<tr>
<td>Dec 24</td>
<td>Dissecting the conformational transition of NtrC in molecular detail</td>
</tr>
<tr>
<td>Dec 27</td>
<td>Report presentations</td>
</tr>
<tr>
<td>Jan 3</td>
<td>Intrinsic dynamics coupled to catalysis in the peptidyl-prolyl cis/trans isomerase CypA</td>
</tr>
<tr>
<td>Jan 4</td>
<td>Specific and nonspecific interactions of the Lac repressor with DNA</td>
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</tbody>
</table>

**Textbooks (T) and Reference Books (R):**


Reading assignment for the period Sep 27 - Oct 26:

**Branden and Tooze:**

- Ch 1 The Building Blocks
- Ch 2 Motifs of Protein Structure
- Ch 7 DNA Structures
- Ch 18 Determination of Protein Structures (pp. 373–386)
- Ch 6 Folding and Flexibility (pp. 89–100, pp. 104–110, pp. 113–117)
- Ch 11 An Example of Enzyme Catalysis: Serine Proteinases (pp. 205–219)

**Petsko and Ringe:**

- 1-0 Overview: Protein Function and Architecture
- 1-1 Amino Acids
- 1-2 Genes and Proteins
- 1-3 The Peptide Bond
- 1-4 Bonds that Stabilize Folded Proteins
- 1-5 Importance and Determinants of Secondary Structure
- 1-6 Properties of the Alpha Helix
- 1-7 Properties of the Beta Sheet
- 1-8 Prediction of Secondary Structure
- 1-9 Folding
- 1-10 Tertiary Structure
- 1-11 Membrane Protein Structure
- 1-12 Protein Stability: Weak Interactions and Flexibility
- 1-13 Protein Stability: Post-Translational Modifications
- 1-14 The Protein Domain
- 1-15 The Universe of Protein Structures
- 1-19 Quaternary Structure: General Principles
- 1-20 Quaternary Structure: Intermolecular Interfaces
- 1-21 Quaternary Structure: Geometry
- 1-22 Protein Flexibility
2-0 Overview: The Structural Basis of Protein Function
2-1 Recognition, Complementarity and Active Sites
2-2 Flexibility and Protein Function
2-4 Nature of Binding Sites
2-6 Catalysis: Overview
2-7 Active-Site Geometry
2-9 Stabilization of Transition States and Exclusion of Water
3-4 Effector Ligands: Competitive Binding and Cooperativity
3-5 Effector Ligands: Conformational Change and Allostery

Historical papers:

Oct 4 α-helix and β-sheet


Oct 5 The double helix


Oct 11 Myoglobin


Oct 12 Hemoglobin


Oct 18 Side chains and folding


**Oct 19** Allosteric proteins


**Reading assignment for the period Nov 1 - Dec 3:**

**Nov 1, 2** Introduction to membrane proteins

Branden and Tooze, Ch 12: Membrane Proteins (pp. 223–226, 232–234, 244–247)

**Nov 8** KcsA structure


**Nov 9** Ion conduction in KcsA


**Nov 26** Opening the pore


**Nov 29** KvAP structure


Nov 30  Kv1.2 structure


Dec 3  Role of lipids


Reading assignment for the period Dec 6 - Jan 4:

Dec 6 & 7  MD simulations


Dec 10  Conduction and hydrophobic gating in K⁺ channels


Dec 13 & 14  Protein structure determination with NMR

* Branden and Tooze, Ch 18: Determination of Protein Structures (pp. 387–392)
* Petsko and Ringe, Ch 5: Structure Determination

Dec 17  Proline isomerization and the interaction of Itk SH2 and SH3 domains

**Dec 20** Protein dynamics with NMR


**Dec 21** NtrC structure and conformational states


**Dec 24** Molecular details of the NtrC conformational transition


**Jan 3** CypA dynamics and catalysis


**Jan 4** Protein-DNA interactions with NMR

* Branden and Tooze, Ch 8: DNA Recognition in Procaryotes by Helix-Turn-Helix Motifs (pp. 129–148)