**Table of Contents**

**Chapter 1: introduction**

* What is structural biology?
* The importance of macromolecules
* The biological roles of proteins (overview):
  + Enzymatic catalysis
  + Energy transfer
  + Solute transport
  + Cellular communication
  + Defense
  + Viral infection
  + Building cell & tissues
* Structure-function relationship in proteins
* Non-covalent interactions:
  + Electrostatic interactions (ionic, hydrogen bonds, π-π/cation, others)
  + Van der Waals interactions
  + Nonpolar interactions and the hydrophobic effect

**Chapter 2: the structure of proteins**

* Representing molecules graphically in the course
* Protein structure – and overview (hierarchy, hetero-groups)
* Primary structure:
  + Physicochemical properties of proteogenic amino acids (groups, chirality, polarity, side chains’ chemistry)
  + Non-canonical derivates of amino acids in proteins
  + The peptide bond
* Secondary structure:
  + Steric limitations on secondary structures (the Ramachandran plot).
  + The α-helix structure: geometry, stabilization, dipole and hydrogen bonds, amphipathic helices, amino acid propensities to appear in helices
  + Non-α helices (310, π, PPII)
  + The β structure: strands, sheets, and barrels
  + Why helices and sheets? – the price of desolvating the peptide bond
  + Turns and loops
* Tertiary structure:
  + General characteristics of globular proteins (hierarchy, geometry, stabilizing interactions)
  + Simple α and β motifs: EF hand, bHLH, HTH, β-hairpin, β-sandwich, β-α-β, others.
  + Complex folds and superfolds (Ig, Rossmann, P-loop, TIM barrel, globin, etc.)
  + Domains: definition, modularity, classification and databases
  + Evolutionary aspects
  + Water molecule inside protein structures
* Quaternary structure:
  + Types of quaternary structures and terminology
  + Stabilizing interactions
  + Evolutionary advantages
* Post-translational modifications:
  + Types and biological roles
  + Examples: phosphorylation, glycosylation, ADP-ribosylation
* Fibrous proteins:
  + General characteristics and biological roles
  + Structure-function relationships: α-keratin and collagen

**Chapter 3: computational methods for studying protein structure**

* Why predict protein structure?
* The physical approach:
  + The explicit (full-atom) approach: force field-based calculations of the potential energy, configurational sampling via molecular dynamics simulations
  + The mean-field approach
* The comparative approach:
  + Overview
  + Homology modeling
  + Fold recognition
* Integrative methods
* Experimentally guided computational prediction
* Evolutionary methods (correlated mutations)

**Chapter 4: the energetics and stability of protein structure**

* Overview:
  + The marginal stability of proteins
  + Thermodynamic components of the protein’s stabilization free energy
* Interactions and physical effects on protein’s stability:
  + Overview: promoting and opposing contributions to folding
  + Nonpolar and van der Waals interactions
  + Electrostatic interactions
  + Entropy changes
* Protein denaturation and adaptations to extreme environments
* Protein engineering for increased stability

**Chapter 5: the structural dynamics of proteins**

* Overview:
  + The importance of protein dynamics
  + Types of dynamic motions in proteins and their correspondence to biological processes
* Theories on protein dynamics:
  + Induced fit
  + Pre-existing equilibrium
  + Conformational selection
* Thermodynamic and kinetic effects on protein dynamics
* The biological significance of thermally induced motions
* External influence on protein dynamics:
  + Ligand binding and allostery
  + Post-translational modifications
  + Environmental changes
  + Mutations
* Protein folding:
  + Levinthal’s paradox and its solution (the energy-entropy folding funnel)
  + Folding kinetics models and the molten globule state
  + Misfolding, amyloids, and related pathologies
  + *In vivo* folding: interfering effects, molecular chaperones

**Chapter 7: membrane-bound proteins**

* Biological roles of membrane proteins
* Properties of the lipid bilayer: structure, lipid types, asymmetry, amphipathicity
* Integral membrane proteins:
  + Overall structure
  + Transmembrane segments: polarity, size, dynamics, lipid interactions
  + Membrane insertion and assembly
  + Architectural themes (example: transport proteins)
* Peripheral membrane proteins
* Effects of the membrane on proteins:
  + General effects: hydrophobic mismatch
  + Effects of specific lipids: steroids, phosphoinositides
* Structure-function relationships: G protein-coupled receptors (GPCRs)
  + Background: biological roles, medical importance, signaling, ligands and effectors
  + Classification
  + General structure and structural motifs
  + Structure-function relationship of GPCR activation and allostery: rhodopsin, β2 adrenergic receptor, M2 (muscarinic receptor)

**Chapter 8: protein-ligand interactions**

* Biological importance
* Binding affinity:
* Binding affinity of different protein-ligand complex types
* Measuring and calculating the binding affinity
* Thermodynamics of binding and enthalpy-entropy compensation
* Binding specificity:
* Theoretical models
* Binding site-ligand matching through non-covalent interactions
* Binding promiscuity
* Protein-protein binding: domains
* Protein-ligand interactions in cholinesterase inhibition by toxins and drugs:
* The biological importance of acetylcholine signaling
* Cholinesterase as a target of natural toxins: fasciculin-2
* Cholinesterase inhibition by synthetic inhibitors: organophosphate and chemical warfare, carbamates, oximes.
* Protein-ligand interactions in drug design:
* Proteins involvement in disease
* How drugs work, proteins as drug targets
* Mechanisms of protein inhibition/activation by drugs: competitive binding and molecular mimicry, non-competitive (allosteric) drug action
* Drug design: the ligand-based and receptor-based approaches, lab and virtual screening of drugs, case study (ACE inhibitors)