OUTLINE OF INTRODUCTION SECTION

Lecture 1: Introduction

- Course Outline
- Cell structure; nucleus endoplasmic reticulum, Golgi apparatus, mitochondria, lysosomes, membranes, etc.
- Protein structure/assemblies
- Lipids
- Membranes; membrane protein classes
- Protein-nucleic acid assemblies; chromatin, ribosomes, viruses
- “Double Helix;” BBC film of Crick, Watson, Wilkins, Franklin, etc. and structure of DNA

OUTLINE OF PROTEINS SECTION

Lecture 2: Protein Folding Motifs and Quaternary Assembly

- Introduction to general aspects of protein assembly
- Aims of this section of course
- Structural hierarchy, secondary structure, loops, motifs and domains
- Folding hierarchy, super-secondary motifs, $\alpha\alpha$, $\beta\alpha\beta$, $\beta\beta$ motifs
- Tertiary motifs
- Alpha structures, helix packing, helix dipole, helix-turn-helix motif, amphipathic helices, packing geometry, helix bundles and globin fold
- Beta structures, parallel vs. anti-parallel sheet, crossovers, loops, sheet topology diagrams, the Greek key
- Beta-alpha-beta structures, helical crossovers
- Folding domains, sequence characteristics, repeated sequence domains
- Domain vs. quaternary assembly
- Fold classification, the CATH database

Lecture 3: Hemoglobin

- Myoglobin structure
- Hemoglobin quaternary assembly, symmetry of packing, cooperativity
- Hemoglobin/myoglobin sequence and secondary structure differences
- Subunit contacts and interactions
- Quaternary structure changes on oxygen binding
- Oxy vs. deoxy tertiary structure changes on oxygen binding
- Salt bridge interactions, role of penultimate Tyrosine, oxygen binding to iron
- Sequential tertiary structure changes, quaternary changes and cooperativity
Lecture 4: Clathrin

- Overview of the endocytic pathway, receptors, fuzzy coat, coated pits and vesicles
- Structure of fuzzy coat, transition to pits and vesicle, symmetry of vesicle formation, 5 vs. 6 fold packing symmetry, Euler’s theorem
- Negative stain EM of vesicle and cage structure
- Clathrin molecule, triskelion, domain organization
- Clathrin packing and assembly in vesicles
- Cryo-EM of cages and coats, location of clathrin domains, adaptor proteins, receptor interactions
- Clathrin molecular structure from x-ray crystallography, proximal leg and N-terminal domain

Lecture 5: Spectrin

- Proteins of the erythrocyte membrane, cytoskeletal components
- Spectrin, Ankyrin, 4.1/4.2, Actin general features and interactions
- Assembly of Spectrin, repeated sequence domains, head-to-head vs. head-to-tail assembly
- Building the cytoskeleton, interactions
- Spectrin molecular details from x-ray structures, comparison with Actinin, structure of repeated unit
- Spectrin flexibility and conformational changes

Lecture 6: Actin, Myosin and Tubulin

- Review of striated muscle, supramolecular structure, sliding filament model
- Symmetry of sarcomere and filaments
- Assembly of myosin, repeating motifs of tail region, coiled-coil structures
- Myosin ATPase domain, molecular details from x-ray crystallography, domain structure, helix tail, ATP binding
- Assembly of Actin
- Molecular details from crystallography, domain structure
- Filament assembly, subunit interactions
- Actin-Myosin interactions

- Overview of cilia and organization of axoneme, protein of the axoneme
- Supramolecular structure of microtubules, helix geometry
- Tubulin dimmers, GTP/GDP binding
- Molecular structure, EM of tubulin sheets, subunit interfaces
- Molecular details, EM-crystallography, domain structure, nucleotide binding, subunit interfaces
OUTLINE OF LIPIDS SECTION

Lecture 7: Introduction

- Definitions and chemical classification of lipids
- Overview of lipid functions in cell and organisms
- Lipids – molecules with dual physical properties. HLB
  (hydrophilic lipophilic balance); water and hydrocarbon (oil) solubility

Lecture 8: The Free Energy of Transfer from Water to Hydrocarbons

- Lipid distribution (partition) between water and hydrocarbon
- The partition coefficient, \( K_{w/o} \)
- Data obtained from varying the number of \(-CH_2-\) in a chain
- The free energy of transport from water to oil
  \[ \Delta G_{t_{w\rightarrow o}} = RT \ln K_{w/o} \]
- \( \Delta G_{r_{w\rightarrow o}} \) for methylene groups, \((-CH_2-)\) methyls
  \((-CH_3)\), double bonds \((-CH = CH-)\) and hydrophilic groups

Lecture 9: Surface Behavior of Lipids

- Surface tensions and energy of cohesion
- Insoluble lipids – spreading and non spreading
- The spreading pressure
- Stable monolayers – Pockels – Langmuir balance
- Surface pressure/molecular area isotherms
- Unstable monolayers of soluble lipids
- Micelle formation and solubilization of hydrocarbons

Lecture 10: Structure of Lipids

- Classification of lipids based on interaction with \( H_2O \)
- Structure and packing of aliphatic chains in lipids
- Phase transitions in lipids; aliphatic chain transitions
- Effects of polar substitution on phase transitions
- The non ideal liquid state of lipids; the concept of fluidity

Lecture 11: The Mesomorphic State, a 4th State of Matter. Liquid Crystals

- Discontinuous changes in specific heat and volume between the solid crystalline state and the liquid state
- Definition of liquid crystals
- Structure of liquid crystals
- Classification of liquid crystals and ordered fluids
- Molecular motions, translations and translocation of lipids
OUTLINE OF LIPOPROTEINS SECTION

Lecture 12: The Lipids of Lipoproteins

- Introductions and historical prospective
- The classes of lipoproteins: chylomicrons (CM), VLDL, LDL, HDL, albumin
- The lipids of lipoproteins – classification and physical properties – phosphatidyl choline (PC), triacylglycerol (TG), cholesterol (C), cholesterol esters (CE)
- The interaction of lipids in lipoproteins

Lecture 13: Phase Behavior of the Lipoprotein Lipids

- The phase rule
- The PC- H₂O system
- The PC-C-H₂O, PC-CE-H₂O, PC-TG-H₂O system
- The lipoprotein lipid phase diagram
- Location of phases within a lipoprotein

Lecture 14: The Apoproteins

- The major apoproteins AI, AII, AIV, B, C, CI, CII, CIII and E
- Exchangeable and non exchangeable apoproteins
- Secondary and tertiary structure of apolipoproteins, amphipathic alpha helices (AAH) and amphipathic B strands (ABS)
- Interaction of apoproteins with lipids

Lecture 15: Lipoprotein Assembly, Plasma Conversions and Uptake – Physical Considerations

- Synthesis and secretion of apoB containing lipoproteins CM, VLDL
- Plasma conversions of VLDL to LDL – LDL uptake
- Formation of HDL

OUTLINE OF MEMBRANES SECTION

Lecture 16: Cell Membranes

- Review of overall membrane organization
- Cell membranes; plasma membrane, organelle membranes
- Membrane functions
- Membrane structure; average structure, localized structural domains
- Membrane composition; lipids, proteins
- Membrane lipids; organization, bilayers, distribution, dynamics
- Membrane proteins; organization, dynamics, functional classes
• Structural motifs of membrane proteins?

Lecture 17: Bacteriorhodopsin

• Halobacteria, H. Halobium, energetics, purple membrane
• Bacteriorhodopsin, light activated proton pump
• Early studies; isolation, chemical characterization
• Electron microscopy, x-ray diffraction, hexagonal arrangement
• Electron crystallography; Henderson/Unwin, 2D and 3D, transmembrane alpha helical bundles
• Labeling, neutron diffraction
• Retinal location, orientation
• Helix connectivity
• High resolution studies; electron and x-ray crystallography
• Proton channel, photocycle and pump mechanism

Lecture 18: Photosynthetic Reaction Center

• Plants, bacteria, energy transduction, photosynthesis
• Structure of R. viridis reaction center; L, M, H and cytochrome subunits
• Arrangement of prosthetic groups; heme, bacteriochlorophyll, bacteriopheophytin, carotenoid, quinine
• Electron flow
• Structure of bacterial light-harvesting complex; protein and pigment organization
• Structure of mitochondrial cytochrome bc1 complex; protein subunit structure

Lecture 19: Porins

• Porins in Gram-negative bacterial and mitochondria
• E. coli porins; PhoE, OmpF and OmpC
• Early structural studies; electron microscopy of OmpF and PhoE, trimers
• Transmembrane beta-barrel structures
• X-ray structures of OmpF, PhoE an Dr. capsulatus porins; 16-strand barrels, channel structure
• X-ray structure of OmpA; 8-strand barrel
• X-ray structure of FepA, 22-strand barrel, and Ompla (12 strand barrel
• Structure of maltoporins; 18-strand barrel, role of loops, structure of pore, sugar transport

Lecture 20: Bacterial Toxins

• S. aureus alpha hemolysin; cell lysis, oligomerization
• Structure of alpha hemolysin; monomer structure, heptamer structure
• Pore structure; 14-strand beta-barrel
• Anthrax toxin; subunit structure, mechanism of action
• Structure of protective antigen; domain structure of monomer, heptameric assembly, 14-strand beta-barrel?
• Structure of cholera toxin

Lecture 21: **Influenza Virus Hemagglutinin**

• Influenza virus; structure and mode of action
• Influenza virus hemagglutinin; receptor binding and membrane fusion activities
• Influenza virus hemagglutinin structure; bromelain treatment, trimeric assembly, coiled-coil domain, HA1 and HA2, receptor binding site, glycosylation sites, fusion activation site
• Influenza epidemics and pandemics; antigenic drift and shift, relation to structure
• Low pH structure of influenza virus hemagglutinin; conformational changes, fusion model

Lecture 22: **Potassium Channel**

- Membrane ion channels, Na\(^+\), K\(^+\), Ca\(^{2+}\)
- Potassium channels; voltage-gated and ligand-gated
- Structure of KcsA K\(^+\) channel pore; selectivity filter, ion conduction
- Structure of calcium-gated MthK K\(^+\) channel; gating model
- Structure of chloride channels

**OUTLINE OF PROTEIN-NUCLEIC ACID INTERACTIONS SECTION**

Lecture 23: **Chromatin**

• Procaryotic and eukaryotic chromatin
• DNA structure; review double helix structure, higher order folding
• Eucaryotic chromatin; DNA/histone complexes
• Histones; sequence, structure, evolution, assembly
• Nucleosomes; “beads on a string,” nucleosome core particle, histone octamer
• Nucleosome/core particle structure; electron microscopy, x-ray diffraction
• Nucleosome core particle; x-ray crystallography (Klug/Richmond), DNA-histone interactions, DNA superhelix, histone octamer

Lecture 24: **Ribosomes**

• Ribosomes and protein synthesis
• Procaryotic and eukaryotic ribosomes; subunits, ribosomal RNA and ribosomal proteins, disassembly/reassembly (Nomura)
• E coli ribosome structure; cross lining, electron microscopy, immunoelectron microscopy
• E coli 30S and 50S subunits; neutron scattering, distance measurements, triangulation
• E coli ribosome structure; cryoelectron microscopy, 3D crystals
• High resolution x-ray structures of 50S and 30S subunits; structure of complete ribosome
• Mechanism of protein synthesis

Lecture 25: Viruses

• Introduction; examples of DNA/RNA ss/ds viruses, overall structure, nucleic acid, protein capsid, membrane envelope
• Virus shape; spherical, rod-shaped, complex
• Virus structure; core-shell model, symmetric protein shells (Crick/Watson)
• Tobacco mosaic virus; rod-shaped RNA virus, electron microscopy, helical structure, RNA and protein helices
• TMV protein; disks, cylinders, helix, TMV protein disk structure
• TMV structure; x-ray fiber diffraction, RNA helix, disk-helix transition, RNA-protein interactions
• TMV assembly; initiation sequence, disk-helix transition

Lecture 26: Spherical Viruses

• Spherical viruses; cubic symmetry, polyhedra, icosahedral symmetry
• Examples; adenovirus, herpes virus, polyoma virus, etc.
• Icosahedral symmetry; simple (T=1) and complex (T-3) icosahedra, Caspar/Klug quasi-equivalence
• Satellite tobacco necrosis virus (STNV); T=1 capsid structure, symmetry
• Tomato bushy stunt virus (TBSV); T=3 capsid structure, symmetry, quasi-equivalence