Schedule for MCB 446
Spring 2012

Part I: Optical spectroscopic methods: 12 lectures Gennis
(Jan 17, 19, 24, 26, 31, Feb 2, 7, 9, 14, 16, 28, March 1)

1. **Introduction to quantum mechanics and molecular orbitals**

Lecture 1: Waves and electromagnetic radiation; superposition of waves, interference and diffraction; introduction to quantum mechanics- Planck's constant and the photoelectric effect; particles and waves- the De Broglie equation.

Lecture 2: Quantum description of bound electrons as standing waves; the time-independent Schroedinger equation; eigenvectors and eigenfunctions; particle in a box and pi-electrons; the hydrogen atom, atomic orbitals and quantum numbers; electron spin; the periodic table; molecular orbitals and correlation diagrams.

2. **UV-vis absorption spectroscopy**

Lecture 3: Absorption spectroscopy and the study of biological macromolecules; the transition dipole moment; the Einstein coefficients and saturation of a transition; Beer's law and the extinction coefficient; oscillator strength; UV-vis spectra of organic molecules- n-π^* and π-π^* transitions.

Lecture 4: Absorption spectra of proteins and nucleic acids; the rates of electron vs nuclear motions; vibrational structure and the Franck-Condon factor; the shape of UV-vis absorption spectra and the mirror image rule for fluorescence spectra; solvent-induced heterogeneity, red-shifts and blue shifts; polarity vs polarizability of the medium; the protein as a "solvent"; spectral shifts in rhodopsins and vision.

Lecture 5: Excitons, energy transfer, hyperchromism; isosbestic points; spectra of peptides and secondary structure; DNA stacking and hyperchromism; energy migration in photosynthetic systems.

3. **Optical activity and CD spectroscopy**

Lecture 6: Optical activity; absorption and dispersion; principles of circular dichroism; CD of aromatic complexes; CD of nucleic acids.

4. **Fluorescence spectroscopy and FRET**

Lecture 7: CD of proteins, determining protein secondary structure;
Introduction to fluorescence spectroscopy; collisions and quenching; the distinct nature of the excited state vs the ground state; quantum yield and lifetime; intrinsic fluorescence of proteins

Lecture 8: Using tryptophan fluorescence to probe protein structure; static vs dynamic quenching; the Stern-Volmer equation; the green fluorescent protein and its applications.

Lecture 9: FRET and its applications; single-molecule FRET.

Lecture 10: Fluorescence anisotropy, rotational diffusion and the Stokes radius

In-class review February 21 (no lecture)

FIRST EXAM: Feb 23 (Covers Lectures 1-10)

5. **Radiation scattering methods and vibrational spectroscopy**

Lecture 11: Light scattering and small angle X-ray scattering: radius of gyration; Raman and resonance Raman spectroscopy

Lecture 12: The Fourier transform; FTIR spectroscopy of peptides and proteins.

Part II Magnetic Resonance: 4 lectures Nair
(March 6, 8, 13, 15)

Lecture 13: Introduction to biological NMR
Introduction to spin systems; magnetic induced alignment; Larmor frequency and forced disruption; spin relaxation and spin exchange; chemical shift and spin-spin coupling

Lecture 14: Higher dimensional NMR techniques
Spectral overlap; the nuclear Overhauser effect; two-dimensional NMR; NMR pulse sequences; COSY and NOESY; Steady state and transient NOE

Lecture 15: NMR of biological macromolecules
Resonance assignments for a peptide; TOCSY and spin systems in peptides; sequence specific assignment of peptides; strategies for sequential assignment

Lecture 16: Macromolecular secondary and tertiary structure from NMR
Conformation dependent NMR peaks; strategies for assignment for proteins; heteronuclear spectroscopy; HSQC and SAR by NMR; strategies for probing protein-ligand interactions; site specific labeling; multidimensional, multinuclear spectroscopy.

SPRING BREAK

Part III: X-ray Diffraction: **3 lectures Nair**
(March 27, 29, April 3)

Lecture 17: Introduction to macromolecular crystallography
Bragg's law and the principles of diffraction; the phase problem and overview of methods for phase determination; introduction to Miller indices; introduction to crystallographic symmetry; Bravais lattices, point groups and space groups.

Lecture 18: Crystallographic phase determination
Mathematical treatment of radiation; structure factor and electron density; assignment of symmetry; crystallographic phases; the molecular replacement method; heavy atom methods; the Patterson function; Phasing power and lack of closure.

Lecture 19: Crystallographic phase determination
Anomalous scattering; multi-wavelength anomalous diffraction; molecular replacement; the rotation function and the translation function; model bias; density modification; model building; effects of resolution; validation methods.

SECOND EXAM: April 5 (Covers Lectures 11-16)

Part IV: Time Resolved Diffraction and Electron Microscopy: 2 Lectures Nair (April 10, 12)

Lecture 20: Laue crystallography
Polychromatic methods; time resolved crystallography; Cruickshank's dilemma; ultrafast crystallography

Lecture 21: Electron Microscropy
Basics of electron microscopy; cryo-EM; three dimensional image processing and reconstruction; assessment of resolution limits; electron crystallography at near atomic resolution.

Part V: Introduction to Computational Biology: 4 Lectures Nair
(April 17, 19, 24 and 26)

Lecture 22: Model building and refinement
Energy function; stereochemical restraints and constraints; least squares refinement methods; energy minimization; simulated annealing and temperature coupling; experimentally constrained energy functions; validation methods; ProCheck and MolProbity; the Protein Data Bank

Lecture 23: *Ab initio* methods
Comparative modeling and fold recognition; secondary structure prediction; Chou and Fasman; induction methods; lattice algorithms; CASP; the Rosetta breakthrough; I sites and Hidden Markov models; Rosetta and automated fold prediction strategies

Lecture 24: Structure based drug discovery

The Docking challenge; rigid protein and rigid receptor methods; protein flexibility in ligand binding; modeling protein flexibility; Monte Carlo methods; scoring functions; conformational docking

Lecture 25: Structure based drug discovery
Ensemble docking; the induced fit approach; fragment-based approaches; functional assignments based on ligand docking; case studies (successes and many failures).

May 1 last day of class: in class review (no lecture)

FINAL EXAM