Syllabus: Bchm 104b

About the course:
The course will provide an introduction to the physico-chemical principles that govern the structure, dynamics and function of biological macromolecules. We will then use those principles to look at and understand the structures and physical properties of proteins and nucleic acids. In addition, the course will introduce the fundamentals of macro-molecular X-ray crystallography.

Biochem 104b deals with a topic that is a very active area of research. Many of the fundamental driving forces that shape macromolecules are only partially understood. In addition, biological macromolecules are very large and complex systems and so might evade rigorous quantitative analysis even if the basic principles were known.

Therefore, the course will make extensive use of simple models and will compare the behavior predicted from those models with experimental observations of real macromolecular systems. The overall goal is to provide students with a solid and quantitatively-reasoned intuition of why proteins and nucleic acids behave the way they do.

Literature:
There is no official textbook for this course. Instead the course material is drawn from a series of different books and the primary research literature. Students who want to extend their reading are pointed to the list of books on the course website.

Outline of course

First Section: Molecular Driving Forces

- A quick review of required skills and concepts.
- A molecular picture of entropy:
  - polynomial distributions
  - microscopic vs. macroscopic states
  - Boltzmann Equation
  - deriving the Maxwell-Boltzmann distribution law from the Boltzmann equation.
- Molecular forces:
  - electrostatics1: Coulomb’s law, dielectric constant, Bjerum Length
  - electrostatics2: Born solvation energies, burying ionizable charges
  - induced dipoles, Van der Waals Forces, Lennard Jones potential
  - hydrogen bonding
Second Section: Protein Structure and Dynamics
- A first look at protein structure: Oil and water don’t mix. Potential hydrogen bonds are almost always satisfied. Charged and flexible amino-acids are usually solvent exposed.
- Why do proteins fold while randomly polymerized amino acids do not? Low energy of folding -> “it all add up to zero”, Levinthal paradox
- Charge and steric properties of the peptide backbone shape protein secondary structure. Alpha helix, beta-sheet, turns.
- The 20 side chains and their physical properties, predicting secondary structure propensities from molecular geometry -> beta-branched a.a. do not like helices, a demonstration of entropic effects on protein structure.
- Protein folds: how the shape of secondary structure elements and side chains determines the geometry of simple folds. Four helix bundle, leucine zipper
- Evolutionary restrictions on protein structure
- Lysozyme as a molecular laboratory.
- Helical propensity in the context of a folded protein.
- The effect of single side-chain mutations, deletions and insertions
- Double mutant cycles
- A critical evaluation of our ability to predict the effect of mutations.
- New concepts:
  - Hot spots: in large macromolecular interfaces a small number of amino acids provides the majority of binding energy (J. Wells work).
  - Evolutionarily conserved networks: Statistical analysis of related sequences reveal sparse a.a. networks that communicate information and determine protein stability (R. Ranganthan work)
- Protein dynamics / Conformational changes:
  - The time scale of protein motions spans from fs to minutes.
  - Protein energy landscapes, folding funnels
  - Dynamic transition, temperature dependence of protein function
  - Concerted structural changes

Third section: X-ray diffraction and crystallography
- Overview from crystal to atomic structure
- Adding waves
- How the diffraction pattern gets its spots. Diffraction from a duck
- Duck plus goose diffraction. Laue condition.
- Fourier Transforms. The phase problem and how to solve it.
- Examples and new advances.

Fourth section: Nucleic acid structure
- What holds the duplex DNA together? DNA melting.
- More about what holds DNA together. DNA vs. RNA
- Secondary structure. Energetics. RNA folding
- DNA as an entropic spring. DNA topology.

**Fifth section: Ligand binding, conformational equilibria, and coupling:**
- Langmuir isotherms.
- Simple linkage mechanisms.
- Q-method. Receptor with multiple sites for the same ligand.
- Allostery. Perfect cooperativity
- Wyman plot. Thermodynamic box.
- Example: binding of transcription factors to DNA.
- Example: force effects on conformational equilibria.