Lectures for CH393L

1. *August 30*: Introduction to proteins: codons, amino acids, hydrophobicty (aromatic and aliphatic amino acids), acidic amino acid, basic amino acis, polar amino acids, proline, cysteine, three and one letter codes, amide planes, cis proline, backbone geometry, chirality, side chain structures, chiral side chains
2. *September 4*: Introduction to protein structure: Definition of backbone dihedrals: ω, ϕ, ψ , rotatable bonds and Ramachandran plot, hydrogen bonds, secondary structure, alpha helix, beta sheet (parallel and anti-parallel), turns, visual representation of proteins: sticks, ribbon, spheres, exposed surface area. Sulfide bonds. Tertiary and quaternary structures
3. *September 6:* Coordinate representation of protein structures: Cartesian representation, internal coordinates, distance matrix, torsion space, lattices, complexity of manipulation. Experimental approach for structure determination (X-ray crystallography, Neutron scattering, NMR, Energy transfer), Measures of structural flexibility.
4. *September 11:* Protein sequence classification I – Overview. The need for annotation and classification of proteins. Direct pair sequence alignment. Scoring of an alignment: identity, statistically derived substitution matrices (BLOSUM XX), deletions and insertions and gap penalties, counting alignments
5. *September 13 #:* Protein sequence classification II – Dynamics programming, global and local alignments. The significance of the raw score and the Z score.
6. *September 18:* Learning to gap: Using positive and negative examples to derive gap penalties by Mathematical Programming.
7. *September 20:* Protein sequence classification III – Approximate alignments, BLAST, multiple sequence alignments, pseudo counting, and profile matches. generation of site dependent substitution matrices, PSI-BLAST.
8. *September 25:* Predicting protein structures (and function?) from first principles, *ab-initio* folding, are we there yet? Threading - matching sequences to structures, one body and two body energy terms, construction of databases.
9. *September 27:* Learning folding and threading potential parameters: Statistical potentials, Z score optimization, and Mathematical Programming. Gap and gapless threading.
10. *October 2:* Comparing protein structures I. C_α based comparisons, RMS, URMS, Overlaps and proper rotations. RMS optimization under unitary constraints.
11. *October 4:* Comparing protein structures II. Treatment of zero eigenvalues and structural inversion. Distance matrices. Gapless threading. Why dynamics programming is difficult to apply in threading?
12. *October 9:* Positive and negative protein design. Sequence capacity. Selection temperature. Structural flips. Retention energy, and the network of sequence flow.
13. *October 11*: Structural modeling and the build up of amino acid side chains. Rotamer libraries, The Dead end elimination theorem, Mean field approaches for modeling side chains and loops.
14. *October 16*: Protein folding: Early concepts – Levinthal paradox, the framework model, hydrophobic collapse, the Go model, the Random Energy Model. The funnel picture. Implications to computer algorithms.

15. *October 18:* Mixing experiments and simulations for the determination of protein structures and folding kinetics. Electron density models. Distances from NOE. FRET and EPR distances. And "energy" functions derived from experimental structures. Low angle X-ray scattering. Hydrogen exchange.
16. *October 23*: Basic statistical mechanics of protein folding: The unfolded and the molten globule states. The impact of solvent. Ensemble averages and calculation of free energy differences. The HP model.
17. *October 25*: The standard mechanical energy model for atomically detailed models of protein structures: bonds, angles, torsion, improper torsions, Lennard Jones and electrostatic interactions.
18. *October 30:* Sampling conformations in continuous space. Microcanonical, canonical and isobaric ensembles. Metropolis Monte Carlo. Molecular Dynamics, Brownian dynamics and the Langevin equation. Choice of integrators.
19. *November 1:* Advanced sampling techniques: Umbrella sampling, meta-dynamics, and replica exchange.
20. *November 6*: Models of solvation I. TIPSX models of discrete water molecules. Long range forces and the Ewald summation.
21. *November 8*: Model of solvation II: Poisson Boltzmann equation. Solvent accessible surface. Generalized Born model. Hydrophobicity models.
22. *November 13:* Global optimization as a tool to determine protein structure. Potential smoothing protocols. The diffusion equation and Gaussian transforms. The bad derivative method. The LES approximation and other mean field approaches.
23. *November 15:* Thermodynamic based approaches to global optimization of protein structures. Simulated annealing, Entropy sampling
24. *November 20:* Thermodynamic cycle and free energy perturbation/thermodnmics integration/force biased sampling as a tool in drug design.
25. *November 27*: Elements of kinetics I. Ensemble of trajectories. Reaction pathways. Approaches to find reaction paths in large systems: LUP, NEB, String.
26. *November 29*: Elements of kinetics II. Averages over reactive trajectories. Approaches for kinetic computations. TST, TPS, Milestoning.
27. *December 4:* Some examples I: Folding of a helical peptide, Ligand diffusion in globins and the LES approximation.
28. *December 6:* Some examples II: Ion permeation through channels, Allosteric transitions.