Proteins and Nucleic Acids - Fall 2002

Instructor:	George Rose
TA:	To be announced
Lectures:	MTW 9:00 - 9:50
Textbook:	Principles of Protein Structure, Karplus & Rose (in aspiration); *Nucleic Acids*; Bloomfield, Crothers, Tinoco; University Science Books; Sausalito, CA (2002).
Office Hours:	Contact (grose@jhu.edu) or TA
Organization:	Classes will be divided between lecture and discussion. Reading material will be distributed in advance of the formal lectures. Problem sets will be computer-based, using Python, an almost universally-available scripting language. A formal introduction to UNIX and Python will be given during the first week.
Grades:	There will be periodic quizzes and problem sets; grades will depend on both. Problem sets are not group exercises; they are to be completed independently. There will be no mid-term or final exam.

WEEK 1 (Sept. 9): Introduction:
Proteins, nature's molecular robots, and DNA/RNA, the genetic material. Goals of this course. Brief historical introduction. Universality – from the genetic code to the structure of proteins. Open questions in the post-genomic era. Experimental approaches to understanding macromolecules. Models and model-making. Computer simulations. Visualizing three-dimensional structures (Rasmol, Molscript, *etc.*).

WEEK 1 (Sept. 10, 11): Python and UNIX (Rose & García-Moreno): Introduction to programming, programming languages, programming environments, formula translation, parsing pdb files, etc.

WEEK 2 (Sept. 16, 17, 18): The building blocks L-α-amino acids: dimensions, diversity, structure, pKa's, isomerization, hydrogen-bonding, hydrophobicity and conformational properties. Torsion angles. The Ramachandran plot and steric considerations. Sidechain rotamers.

WEEK 3 (Sept. 23, 24, 25): Folded conformations of proteins Hierarchy of structure. Secondary structure: α-helix, β-sheet, P_{II}, tight turns, Ω-loops. Supersecondary structure: αα, ββ, βαβ. Water.

WEEK 4 (Sept. 30): Folded conformations of proteins Domains and subdomains. Tertiary structure. Quaternary structure. The coiled-coil.

WEEK 4 (Oct. 1, 2): Protein stability Thermodynamic foundations: enthalpic factors - bond lengths and angles, torsion angles, van der Waals interactions, electrostatics, hydrogen bonding, packing. Two-state behavior.

WEEK 5 (Oct. 7, 8, 9): Protein stability Thermodynamic foundations: entropic factors - chain entropy, solvent entropy. Estimating protein stability. Denaturation: by temperature, by pH, by solvents. The denatured state. The puzzle of extremophiles.

WEEK 6 (Oct. 15, 16): Membrane Proteins Structure. The bilayer. Thermodynamics and separability of folding, insertion, association. Free energies of transfer. The hydrophobicity profile. Glycophorin as a model.

WEEK 7 (Oct. 21, 22, 23): Nucleic acids Polynucleotides - covalent structure, basics of conformations (sugar pucker, glycosyl bond, phosphodiester bonds). Helices: Watson-Crick pairing, base stacking, A- & B-form helices, triple helices. Optical properties: CD and UV absorbance of bases and their use in following stacking-unstacking reactions. Thermodynamics of helix formation: short helices (two-state); long helices; enthalpy of base stacking.

WEEK 8 (Oct. 28): Nucleic acids The polyelectrolyte effect: preferential interaction coefficients of M^+ and Cl^- in presence of polynucleotides; power law dependence of DNA Tm on salt as example of apparently stoichiometric binding of M^+.

WEEK 8 (Oct. 29, 30): RNA folding Structural versatility of RNA: internal loops, hairpin loops, tertiary interactions (e.g., tetraloop-receptor from P4-P6). Secondary structure: prediction from thermodynamics (Turner's rules) and phylogentics. RNA tertiary folding energetics: the role of Mg^{2+}; special cases of monovalent ion binding sites.

WEEK 9 (Nov. 4): Protein-Nucleic acid interactions Biological roles, energetics, topology, structural motifs.

WEEK 9 (Nov. 5, 6): Protein dynamics The illusion of static structure. Free energy landscape. Timescales. Evidence from X-ray crystallography and NMR. HX. Importance for function.

Week 10(Nov. 11) Protein dynamics Molecular dynamics. Probing conformational change: calmodulin.

WEEK 10 (Nov. 12, 13): Protein folding The Anfinsen experiments. Apparent exceptions. Levinthal paradox. Persistence of local structure. Fragment complementation. Disulfide trapping. Kinetic traps. Molten globules. Intermediates.

Week 11(Nov. 18) Protein folding The transition state and ϕ-analysis. HX. Mutagenesis.

WEEK 11 (Nov. 19, 20): Polymer theory and the unfolded state Random walks, radius of gyration, end-to-end distance. The random coil; the statistical coil. Persistence length. Characteristic ratio. Phase transitions. Helix-coil theory. Denaturation in water, urea, GuCl. SAXS. Evidence for conformational bias in the unfolded state. Models of the unfolded state. Revisiting Levinthal.

WEEK 12 (Nov. 25, 26, 27): Sequence/structure relationships and evolution What is evolution? Genetic mechanism in evolution: indels, fissions, fusions, shuffling, duplications. Proteins as clocks. Divergent evolution vs. convergent evolution. How did protein domains arise? How do we know whether a protein domain is ancient or modern? Sequence conservation. Blosum matrices. Needleman-Wunsch. Dynamic programming. Sequence searches: Blast, PSI-Blast, Fasta.

WEEK 13 (Dec. 2, 3, 4): Models of protein folding The folding funnel. Secondary structure < tertiary structure vs. tertiary structure < secondary structure. Nucleation condensation. Hierarchic condensation. E-gap. LINUS. Contact order.