Biochemistry 104b Physical Chemistry of Macromolecules, 2

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Meeting time: T, F 9:30-10:50
Text: J. Kuryan et al., *The Molecules of Life: Physical and Chemical Principles* Garland, 2013

What is this course about?

Understanding biological phenomena ultimately comes down to understanding macromolecules - their structures and how they interact with each other and with small molecules. Genes are switched on and off by the specific interactions of transcription factor proteins with DNA; cells sense and respond to their environment by producing receptors that can bind to specific target molecules; binding triggers conformational changes in the receptors that in turn evoke the cellular response; the correct reactions of metabolism occur only because protein and RNA catalysts form structures with functional groups placed with sub-Ångstrom precision in the positions needed for catalysis.

A difficulty encountered in understanding macromolecular structures and interactions is that any given macromolecule is incredibly complex. Even a small protein has billions of possible molecular configurations. Two individual molecules in a complex somehow choose a few specific non-covalent interactions out of millions of possible ones. A macromolecule must perform its function while contacting and interacting with thousands of water molecules; these contacts are the most important factor in determining the macromolecule's structure. Detailed enumeration and analysis of these possible structures and interactions at the level of individual atoms and bonds ranges from difficult to impossible.

Fortunately, such enumeration is not necessary. This course will cover a relatively small number of principles and techniques that have been highly successful at revealing and interpreting macromolecular structures and interactions. The ideas we will discuss will help you understand why proteins, nucleic acids, and membranes *in general* behave the way they do. When you are doing research and are confronted with a *specific* question, the same ideas will help to formulate and test hypotheses about the structures and interactions of the particular macromolecule you are studying. The power of these concepts is that they are all based on **simple physical models** of the molecules and the forces that act on them. A consequence of this simplicity is that, in most cases, you can get the correct answer (or at least a good approximation to it) very quickly and using only rudimentary tools (e.g., a pencil, a piece of paper, maybe a computer, and a brain).

Rules for the Course

I welcome questions, queries, and confusions from students. I want to help you understand the quantitative material presented in the course, and I am aware that my lectures will not at all times be crystal-clear. I do not keep office hours, but rather am always available in my lab to be interrupted for help. Since I'm sometimes away, you should phone before coming to see me. In spite of the soft-and-cuddly words above, I am hard-nosed and unyielding about assigned work, so here are the rules now.

1. **Homework**. Along with readings, about 3 hours worth of problems per week will be assigned. These problems are essential for understanding the material covered in class; they are at least as important as the lectures. I do not collect these, but instead post solutions towards the end of the relevant section. It will be essential to master the problems because they give you real-life experience in the concepts I'm trying to get across in the lectures. In addition, the problems give you practice in doing "word problems" using high-school algebra and first-year calculus, minimal elements of mathematical literacy with which you must be comfortable in this course (and for the rest of your lives). Make sure that you do these problems throughout the span of lectures - don't put them off until just before the solution are posted!

2. **Exams**. There will be two exams - a midterm and a final. The final exam will refer to issues treated throughout the course. I may also give a 20-minute pop-quiz when the mood strikes me.

3. **Missed work and makeups**. Students are expected to perform all the work, period! There will be no makeups for missed exams, which will without exception receive a failing grade. In unusual circumstances in which an hour exam is missed for documentable reasons -- e.g., death of the student -- a makeup oral exam will be given to the corpse.

4. **Grades**. Final grades will be calculated as an impressionistic mix of exam grades, class participation, and outright bribes. All grading will be done by me, not by the TA.

5. **Discussion sections.** Each week, a discussion session will be held by Lev, the graduate teaching assistant. These sessions are for clarifying confusions, going over problems, and correcting my mistakes. *Skip them at your peril!*

6. **Background expectations.** This is a second-semester course in physical chemistry at a graduate-education level. I expect that everyone will have familiarity with basic thermodynamics, especially equilibrium constants, Gibbs free energy, and entropy. You must be able to differentiate and integrate with ease, and have facility with simple mathematical functions -- polynomials, exponentials, logarithms, and be proficient at setting up and solving "word problems." You should also be able to make rough numerical estimates without calculators.

7. **PYMOL molecular graphics.** We'll be using PYMOL frequently to visually examine macromolecules. This excellent program has a steep initial learning-curve, but it is worth learning to become comfortable with the basic maneuvers. A cheatsheet is posted on LATTE. **Make sure that you download a free "educational" copy of PYMOL to use in class - and practice!**

CLASS SCHEDULE

Section 1: Thermodynamic background, molecular forces (2½ weeks)

Jan 12 Introduction & thermodynamics review on K_{eq}, ΔG^o, and standard states
16 More thermo review - entropy, heat capacity and PYMOL - bring laptops!
19 Electrostatics 1 - Force, energy, potential. Coulomb & Born
23 Electrostatics 2 - Ionic screening, H-bonding, vdw forces. Reading - Russell & Fersht
26 Hydrophobicity - the force that isn't. Micelles and membranes

Section 2: Macromolecular structures (4 weeks)

Jan 30 Protein basics: polypeptide properties and configurational entropy
Feb 2 Secondary structures and model-building ***Bring molecular models to class***
6 Thermodynamics of protein folding - theory and practice. Readings: Ericson, Blaber
9 Lysozyme as a protein-folding laboratory
13 More protein folding analysis Reading: Agashe
16 Membrane proteins

Spring (?) break

27 Nucleic acids 1 - what holds the double helix together? Watson-Crick equilibrium
Mar 2 Nucleic acids 2 - polyelectrolytes and protein interactions

March 4-5 MIDTERM EXAM

Section 3: Multiple equilibrium and linkage (3 weeks)

Mar 6 Langmuir functions. Simple linkage examples
Mar 9 More elaborate linkage systems - ZIF, comp inhib Thermodynamic box
13 **** no class *****
16 The Q-method - Multi-site linkage, statistical factors
20 Cooperativity, Hill, Adair, Monod
23 Wyman linkage relations
27 Linkage examples in modern biochemistry, ITC etc

Another break

Section 4: Membrane transport proteins (2½ weeks)

Apr 10 Transmembrane equilibria, electrical language. Katchalsky machine, entropy of dilution
13 Nernst potential, Ion channels and K^+ selectivity Reading: MacKinnon
17 Coupled symport: Glutamate transporters Reading: Mindell&Newstead
20 CFTR: and energy-driven ion channel
24 Membrane protein folding
25 Final reckoning