BIOCHEMISTRY (BCHM) 661: NUCLEIC ACIDS I— FALL, 2019
MWF, 9:30-10:50 A.M., BIOMOLECULAR SCIENCES BUILDING (BSB) 2118

Course Description: Biochemistry 661 and 662

Two 2-credit modules BCHM 661 and 662 concern the structure and function of nucleic acids and the mechanisms of nucleic acid transactions: a biochemical approach to molecular genetics and biological information processing. We will cover both prokaryotic and eukaryotic systems, emphasizing common logic and mechanisms, especially regarding bioenergetics and fidelity. A background including undergraduate organic chemistry, general chemistry, and molecular biology/genetics is assumed. Module I (661) is required for Biochemistry graduate students and BISI MOCB CA graduate students. Module II (662) is required for Biochemistry students and is an elective for other grad students. Module I or equivalent graduate-level nucleic acids is a pre-requisite for Module II. These courses complement CBMG modules on gene expression, bioinformatics, virology, and genetics/genomics (688F,I,K,M,P,Y). BCHM 661/662 are a combination of lectures and class discussions of required papers. Topics are as follows:

- **Module I: 8/26/2019 – 10/11/2019, Assoc. Prof. Jason D. Kahn, Dept. of Chem. & Biochem.**
    - **Chemistry and structure of DNA and RNA, from nucleotides to chromatin, chromosomes, and genomes, and methods for studying, synthesizing, sequencing and manipulating nucleic acids. Rudimentary genomics and bioinformatics.**
    - **DNA Biology: Interactions between nucleic acids and ligands such as cations, drugs, and especially proteins. Description of protein-nucleic acid complex structures and source of their binding affinity and specificity. Selected aspects of the biochemistry and regulation of DNA replication, repair, and recombination, and how these processes interact with each other.**
- **Module II: 10/14/2019 – 12/9/2019, Assoc. Prof. Jason D. Kahn, Dept. of Chem. & Biochem.**
    - **RNA Biology: Biochemistry and regulation of transcription and translation. Regulation of gene expression by DNA binding proteins and by RNA. RNA processing and decay, RNA catalysis, the origin of life. Selection-amplification methods, nucleic acid engineering including CRISPR/Cas9, and synthetic biology.**

- **Most of the remainder of this document describes Module I (661).**

Contact Information

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Contacting me:	**jdkahn@umd.edu** much preferred to 301-405-0058. Please include "BCHM661" in your subject line, and please quote any previous correspondence in your emails. Please do not drop in to my office, but I readily arrange appointments outside of office hours.
Web and email:	The course web site is available through the ELMS system (http://myelms.umd.edu). E-mail reflectors provided through Coursemail and/or ELMS will be used. It is your responsibility to make sure your e-mail address works.
Class location:	The Biomolecular Sciences Building (BSB), a.k.a. Building #296, Here it is on the official campus map, between Lot #9 and the new Clark Hall.

Assignments, Procedures, and Grading

The material for these modules is primarily lecture-based, but you may need to self-study from the literature or some of the textbooks listed below. We have not found a textbook for this class that is sufficiently useful to make you pay for it. The modules are graded independently. In 661, there will be a 75-minute mid-term exam (100 pts) and a 75-minute final exam (100 pts). Exam questions ask you to design and interpret experiments as well as discuss assigned material. In addition, 100 pts is allocated to analysis of the assigned papers: before discussion of four of the papers we will have a brief 25-point quiz. Your course grade will be based on performance relative to a curve and to my expectations. I anticipate roughly 50:50 A's:B's. The curve does not require C's and D's but I will give them without hesitation if necessary. Plus/minus final grades will be given.

Academic Integrity and Other Policies

The University of Maryland, College Park has a nationally recognized Code of Academic Integrity, administered by the Student Honor Council. This Code sets standards for all undergraduate and graduate students. You are responsible for upholding these standards for this course. It is very important for you to be aware of the consequences of cheating, fabrication, facilitation, and plagiarism. For more information on the Code of Academic Integrity or the Student Honor Council, consult the Course Related Policies page at http://www.ugst.umd.edu/courserelatedpolicies.html; it is directed to undergraduate courses but the spirit is the same, and I have not found a corresponding resource for graduate courses. To exhibit your commitment to academic integrity, you will be expected to sign the Honor Pledge on all examinations: "I pledge on my honor that I have not given or received any unauthorized assistance on this examination."

The hour exam and the final are "Major Graded Events." If you miss the hour exam, you must present a valid University excuse (please secure a note from the Health Services if possible). Quizzes are also graded but you can self-excuse *once* if absolutely necessary. You will then be assigned a grade based on the remaining work for the class. Do not miss the final.

Textbooks, Literature, and Software

Required: Please download and install Pymol from https://pymol.org/edu/?q=educational/

All supplementary materials will be on reserve at the STEM Library in Engineering.

Supplementary textbooks (both modules): Any recent undergraduate biochemistry text may also be useful

Bates, A. D. and Maxwell, A. (2005). *DNA Topology*. 2^{nd} ed. Oxford University Press. Excellent monograph on this difficult topic.

Bloomfield, V.A., Crothers, D.M., and Tinoco, I., Jr. (2000). *Nucleic Acids: Structure, Properties and Functions.* University Science Books, Sausalito CA. Biophysical chemistry.

Cox, M.M., Doudna, J.A., and O'Donnell, M. (2015) *Molecular Biology: Principles and Practice.* 2^{nd} ed. W.H. Freeman. Basically the third half of an undergrad biochemistry text, expanded.

Atkins, J.F., Gesteland, R.F., Cech, T.R., and (2006), *RNA Worlds: From Life's Origins to Diversity in Gene Regulation*. Cold Spring Harbor Laboratory Press. Actually the 4^{th} ed. of a classic.

Ptashne, M. and Gann, A. (2002). *Genes & Signals*. Cold Spring Harbor Laboratory Press. Heuristics of gene regulation.

Weaver, R. F. (2011). *Molecular Biology.* 5th ed. McGraw-Hill, Boston. Undergrad bio text with experiments.

Discussion Papers

We will discuss several papers (1-8), a balance between classic papers and current research. Papers will be posted to ELMS. You are responsible for doing whatever background reading you need to in order to understand the essence of the assigned papers. We will have written quizzes in which you may be expected e.g. to answer how the experiment in Figure 3 worked (with the paper in front of you). Bring a paper copy of the assigned paper, marked up however you wish, to the quiz/discussion.

1. Genschel, J., Kadyrova, L.Y., Iyer, R.R., Dahal, B.K., Kadyrov, F.A. and Modrich, P. (2017) Interaction of proliferating cell nuclear antigen with PMS2 is required for MutLα activation and function in mismatch repair. *Proc. Natl. Acad. Sci. USA*, **114**, 4930–4935.
2. Lieberman-Aiden, E., van Berkum, N.L., Williams, L., Imakaev, M., Ragoczy, T., Telling, A., Amit, I., Lajoie, B.R., Sabo, P.J., Dorschner, M.O., *et al.* (2009) Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science*, **326**, 289–293.
3. Pandey, M., Syed, S., Donmez, I., Patel, G., Ha, T. and Patel, S.S. (2009) Coordinating DNA replication by means of priming loop and differential synthesis rate. *Nature*, **462**, 940–943.
4. Puglisi, J.D., Chen, L., Blanchard, S. and Frankel, A.D. (1995) Solution structure of a bovine immunodeficiency virus Tat-TAR peptide-RNA complex. *Science*, **270**, 1200–1203.
5. Watson, J.D. and Crick, F.H.C. (1953) Genetical implications of the structure of deoxyribonucleic acid. *Nature*, **171**, 964–967.
6. Watson, J.D. and Crick, F.H.C. (1953) Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature*, **171**, 737–738.
7. Weeks, K.M. and Crothers, D.M. (1991) RNA recognition by Tat-derived peptides: interaction in the major groove? *Cell*, **66**, 577–588.
8. Dekker, J., Rippe, K., Dekker, M. and Kleckner, N. (2002) Capturing chromosome conformation. *Science*, **295**, 1306–1311.

Lecture Outline for 661, Module I

I. Nucleic Acid Sequence, Structure, Chemistry, Recognition, and Methods (10 lectures)

1. Introduction and nucleic acid building blocks — M 8/26/19

   Introduction, central dogma, nucleotide structure, primary structure, chemical stability, nomenclature, base pairing and hydrogen bonding

2. Structures of double helices and other structural elements — W 8/28/19

   A, B, and Z form helices. Tertiary structure and tRNA

3. DNA and RNA hybridization and thermodynamics — F 8/30/19

   DNA melting, hybridization, base-pair stability rules, prediction of RNA secondary structure, microarrays

   Discussion of Watson and Crick, 1953, both papers. No quiz.

→ Labor Day, no class ← — M 9/2/19

4. Biochemical methods for studying protein-nucleic acid complexes — W 9/4/19

   Binding curves, gel mobility shift, footprinting/interference, crosslinking, filter binding, ChIP

5. Principles of protein-nucleic acid recognition and examples — F 9/6/19

   Structural motifs, direct and indirect readout, structures.

6. Genetic engineering and enzymatic manipulation of nucleic acids — M 9/9/19
   Basic genetic engineering, restriction enzymes, radiolabeling, polymerases
7. DNA sequencing and bioinformatics — W 9/11/19
   PCR, DNA sequencing, genomics, BLAST
   Discussion of Weeks and Crothers 1991, Puglisi et al. 1995. Quiz.
8. DNA bending, flexibility, and cyclization — F 9/13/19
   Bending and twisting flexibility, sequence-directed bending, methods for detection and quantitation

<u>→ EXAM I ← Covers through Lecture 7</u> **M 9/16/19**

9. Topology, topoisomerases and catch-up — W 9/18/19
   Linking number, superhelix structure, topoisomerase reaction mechanisms
10. Chromosome structure — F 9/20/19
    Nucleosomes, chromatin, higher-order structure, telomeres, 3C→*n*C

<u>II. DNA Biology (8 lectures)</u>

11. Catch-up and review — M 9/23/19
    Discussion of Dekker at al. 2002, Lieberman-Aiden et al. 2009. Quiz.
12. DNA replication I: Fundamental mechanisms, genome replication — W 9/25/19
    Polymerization mechanisms, fidelity, structure
13. DNA Replication II: — F 9/27/19
    Origin recognition and polymerase holoenzymes in *E. coli*; the cell cycle
    Discussion of Pandey at al. 2009. Quiz.
14. DNA Damage and Repair I — M 9/30/19
    Direct reversal, BER, NER, mismatch repair, transcription-coupled repair
15. DNA Damage and Repair II — W 10/2/19
16. Recombination I — F 10/4/19
    Homologous recombination and Holliday junctions, recombinational repair of replication forks
    Discussion of Genschel et al., 2017. Quiz.
17. Recombination II — M 10/7/19
18. Connections among replication, repair, and recombination, overall review — W 10/9/19

<u>→ FINAL EXAM, MODULE I ← Covers DNA Biology</u> **In class, Friday 10/11/19**

Learning Outcomes:

The purpose of this class is to help you learn the fundamental concepts and the analytical methods needed to understand the research literature concerning nucleic acids and molecular biology. At the end, you should be able to interpret and design experiments relevant to your own research in biochemistry and molecular biology. The purpose of classwork in graduate education is to launch you into thinking as a professional.

Syllabus Date and version: August 25, 2019, v. 1.00