Bio 113/244 Fundamentals of Molecular Evolution

Professor: Dmitri Petrov (dpetrov@stanford.edu, 650 736 1169).
Office: Herrin Labs, room 352B

Lectures: MW 2:15 – 3:30 PM, Room 380-380Y

Discussion sections: Once a week. Mandatory.

Office Hours: Tuesday 3:30-5 PM in Herrin 352B.

Web page: http://www.stanford.edu/class/biosci113/

Prerequisites: The BioCore OR graduate standing OR permission of the instructor.

Teaching Asistants:

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Exams: All exams are take home. There is one midterm (take home on Wed., February 8, back by 10AM on Mon, February 13) and the final exam (take home on Wed., March 15, back by 5PM on Wed, March 22). You are free to use lecture notes and any books you choose. Do not consult with one another. **Late exams will not be accepted.**

Paper: One 5-7 page paper. The paper is obligatory for graduate students (Bio244) and optional for undergraduates (Bio113). Undergraduates get extra credit for a good paper. The topic has to be approved by February 8, a draft of the paper is due on Feb. 22 by the end of the lecture, and the final draft of the paper is due on March 15. **Late drafts or late final papers will not be accepted**.

Grading:

Participation in sections	10%
Quizzes in sections	10%
Midterm	30%

Final exam 50%

Texts:

- Fundamentals of Molecular Evolution by Dan Graur, Wen-Hsiung Li **(FME)**
  Sinauer Assoc; ISBN: 0878932666; 2nd edition (January 2000)
- Population Genetics: A Concise Guide by John H. Gillespie **(PG)**
  Publisher: Johns Hopkins Univ Pr; ISBN**:** 0801880092; 2nd edition (July 2004)

Syllabus

Wed, Jan 11	Introduction. The very brief history of evolutionary biology. What is molecular evolution? What do you need to know to succeed in this class? Logistics.
Mon, Jan 16	**Martin Luther King Day. No class.**
Wed, Jan 18	Molecular evolutionary data. Polymorphism, divergence, and mutation. Mutation vs substitution. Importance of understanding population processes in order to understand the evolutionary process. Inference of the individual evolutionary events from the final outcomes. DNA sequence as repeated trials. The concept of a "rate" of molecular evolution. Homology assignment and the problem of multiple hits. Jukes-Cantor (JC) correction. reading: FME 67-79
Mon, Jan 23	JC correction revisited. Saturation. Mutation. Types and chemical basis of mutation. Transitions and transversions. Deletions and insertions. Gene duplications. Kimura's 2-parameter correction. Analysis of substitutions in protein sequences. Replacement and synonymous substitutions. Data. Observation that the rate of replacement substitutions in general is lower than that of synonymous substitutions. reading: FME 5-38, 79-85,
Wed, Jan 25	Continuing with the multiple hit corrections in the protein coding sequences. Non-randomness imposed by selection and genetic code structure. Less variation in the rate of synonymous than non-

	synonymous evolution among different proteins. Multiple hit correction in protein sequences. The problem of choosing among different paths. The idea of deleterious, advantageous, and neutral mutations. The observation of the molecular clock. The first appearance of the neutral theory. reading: FME 99-108
Mon, Jan 30	The process of evolution -- population genetics. Allele (gene) and genotype frequencies. Evolution as "mutation + change in gene frequency". Random mating and Hardy-Weinberg (HW) equilibrium. Heterozygosity. Relationship between gene frequency and heterozygosity. Extension of the concept to multiple alleles, non-HW equilibrium and even to non-diploid organisms. reading: PG 1-19
Wed, Feb 1	Random genetic drift (RGD) and binomial sampling. Probability of fixation of neutral alleles. Rate of neutral substitution. Loss of heterozygosity through RGD. Infinite allele model. Derivation of the rate of loss of heterozygosity. Time scales of drift and mutation. Theta as the measure comparing rates of mutation and the speed of mutation. Theta and the effective population size. reading: PG 21-31; 47-49
Mon, Feb 6	DNA sequence data. Infinite sites model. Pairwise divergence as the measurement of theta. Coalescence. Measuring theta through the number of segregating sites. Natural selection. Basic viability selection model and heterozygous effect. reading: PG 40-47; 59-76
Wed, Feb 8	Continuing thinking about natural selection. Importance of heterozygosity to selection. Strong selection and mutation-selection balance. "Reasonable" values of selection coefficients and heterozygous effects. **PAPER TOPIC IS DUE.** **MIDTERM IS HANDED OUT.** reading: PG 59-85
Mon, Feb 13	**EXAM IS DUE BEFORE 10AM AT DMITRI'S OFFICE (HERRIN 352B). LATE EXAMS WILL NOT BE ACCEPTED.** Interaction between drift and natural selection. Diffusion

	approximation. Probability of fixation of mutations with weak selective effects. Rare alleles -- interaction between drift and selection. Asymmetry between purifying and positive selection. reading: PG 91-95; 203-206
Wed, Feb 15	Neutral theory. Constraint and neutral mutation rate. Molecular clock. Reading of the Kimura/Ohta paper. Puzzle over the constancy of the rate in absolute time, rather in the number of generations. Nearly-neutral theory and the effectively neutral mutation rate. reading: FME 139-154, PG 36-40; 95-98 Kimura & Ohta, Protein polymorphism as a phase of molecular evolution. Nature, 1971, v. 229, pp. 467-69
Mon, Feb 20	**PRESIDENT'S DAY. NO CLASS.**
Wed, Feb 22	Testing neutral theory. Review of basic statistics summarizing polymorphism. Tajima's D tests. Connecting polymorphism and divergence. Macdonald-Kreitman test. Examples from literature. reading: FME 63-64 McDonald & Kreitman, 1991. Adaptive evolution at the Adh locus in Drosophila. Nature, v. 351, 652-654. **DRAFT PAPER IS DUE by the end of the lecture (without this draft, the final paper will not be accepted).**
Mon, Feb 27	Positive selection and adaptive evolution. Ka/Ks measurements. Evolution of lysozyme in langur monkeys. Contribution of neutral, slightly deleterious and advantageous mutations to evolution. reading: FME 119-124 Messier & Stewart. 1997. Episodic adaptive evolution of primate lysozymes. Nature, v. 385, 151-154. Smith & Eyre-Walker. 2002. Adaptive protein evolution in Drosophila. Nature, v. 415, 1022-1024.
Wed, Mar 1	Joint effects of genetic linkage and selection. Muller's ratchet, selective sweeps, and background selection. Testing predictions of background selection and selective sweeps. reading: PG 174-179 Begun & Aquadro. 1992. Levels of naturally occurring polymorphism correlate with recombination rates in *D. melanogaster*. Nature, v. 356,

	519-520.
Mon, Mar 6	Codon bias and selection at synonymous sites. Evolution through mutational bias. Using variation in recombination rate across the genome as a proxy for the variation in the effective population size. reading: FME 132-139
Wed, Mar 8	Evolution of gene duplications. Paralogy and orthology. Dating gene duplications. Probability of nonfunctionalization and subfunctionalization. reading: FME 250-255, 271-283 Force et al. 1999. Preservation of duplicate genes by complementary, degenerative mutations. Genetics, v. 151, 1531-1545.
Mon, Mar 13	Genome evolution. GC content and genome size evolution. Evolution by transposition. reading: FME 367-390
Wed, Mar 15	Final review. **The Final Exam is given out. FINAL PAPER IS DUE.**
Wed, Mar 22	**The Final exam is due in Herrin 352B by 5PM. Late exams will not be accepted.**