Course Syllabus

David Reich (Instructor) contact: reich@genetics.med.harvard.edu

Daniel Tabin (Teaching Fellow) contact: dtabin@g.harvard.edu

David Reich office hours: Weds. 10.15-11am (after class)

Daniel Tabin office hours: Fri. 10.15-11am (after class)

Location: Devore Conference Room, MCZ 529

Grading: Grading will be based 40% on the quality of the final original research paper on which students should expect to spend 40 hours over the course of the term, 20% on completion and understanding of the readings as assessed by participation in class meetings and presentation of the papers in class, and 40% on competition of four assignments (each worth 10%). An â€˜Aâ€™ grade will require intensive commitment to all three aspects of the course.

Prerequisites: Enrollment will be restricted to students with a background in programming. Fluency in at least one programing language is expected; we will be using R, which students are not required to know, but need to be able to quickly learn. Background in statistics and linear algebra is also very helpful.

Admission to the course: This course would be of special interest for students in Computer Science, Statistics, Organismic and Evolutionary Biology, Anthropology, Molecular and Cellular Biology, Biological and Biochemical Science, Bioinformatics and Genomics, Systems Biology, History, and Human Evolutionary Biology, but is open to all students. Prospective students should contact the instructor (reich@genetics.med.harvard.edu) and teaching fellow (dtabin@g.harvard.edu) and include their CV or transcript with a note explaining their interest in the course.

Allocation of places if course is oversubscribed: A priority will be on achieving a balance between students at the undergraduate and graduate level, and on including students from a range of disciplines from the sciences to the humanities.

Expectations and course attendance: A requirement is for students to participate in all course meetings. Additionally, students must fully read the required readings and show up to class ready and willing to discuss them. Discussion of optional readings is also encouraged, and thus students are encouraged to read or skim the optional readings. All coding must be the student's own work. Students may discuss the homework with their peers, but they must not share their code, nor use assistive generative tools to write their code. Code also may not be shared online (e.g. in a git repository) or with future students.

Assignments: Every student will be expected to:

(i) Actively participate in discussions in a way that shows they have engaged with the readings, including presentation of papers to the class.

(ii) Every three weeks, complete an assignment that involves both recreating and using common population history analysis tools.

(iii) Turn in an Original Research Paper by May 10, the last day of exam period.

Policy when written assignments are turned in late: All students have three "free late days", which they can spread among the four homework assignments and the Original Research Paper as they wish. Assignments will receive a score of "0" if they are turned in late after the free late days are used up.

Required reading before each class: It is essential that students read deeply into the assigned materials before each course meeting. All required reading can be accessed through the Canvas site: PDFs of scientific papers can be downloaded through hard links in the syllabus. Readings are restricted to the period from Jan. 24 - April 17, and the last assignment is due on April 22, so students can focus their efforts entirely on the Original Research Project in the final month of the course.

It is essential that students read deeply into the assigned materials before each course meeting. Reading these papers means not only reading the main text, but also the supplement where the detailed argumentation is often presented.

The course structure is roughly:

Jan. 22 - Feb. 23: Lectures by the instructor and guest speakers, which students should prepare for by reading the assigned scientific paper (one paper per course meeting). Reading a research paper in ancient DNA properly means not only reading the main text but also the supplement, where many of the key details can be found. Students should expect to spend 2 hours on the required reading in preparation for each class (4 hours per week over the two course meetings). The lectures will be mixed with discussion (interruptions welcome), and at the end of each lecture, a student will be responsible for giving a formal presentation of the assigned paper (15 minutes long including slides). There will also be assignments, which students should expect to spend about 3 hours per week working on (for about 9 hours total per assignment).

Feb. 26 - Apr. 19: In this period of the course we will move to two required readings per week, each of which will be formally presented by a student (15 minutes long including slides), followed by discussion led by the instructor. Students should continue to expect to spend about 2 hours on the required reading in preparation for each class (4 hours per week over the two course meetings), and about 3 hours per week working on assignments. Additionally, expect to spend a few hours per week in this period working on your Original Research Project. By the end of this period students should have fully fleshed out the details of their project with their mentor and ideally will have made a significant progress (e.g. know all of the tools they will be using and have scripts set up to run them).

Apr. 22 - May 7: On April 22 and April 24 all students will present flash talks describing their progress on their Original Research Projects. April 24 is the last day of class, and the Original Research Project is due May 7. Students should expect to spend at least 12 hours per week in this period working on their Original Research Project.

In parallel to the lecture and discussion part of the course, on Fridays the Teaching Fellow (Daniel Tabin) will lead students on an eight-week bootcamp-style course on how to analyze ancient DNA data. This will be accompanied by 4 problem sets, due every 3 weeks. Students should spend an average of 3 hours every week on these assignments (~9 hours per assignment). This will end around the time when the Original Research Project will pick up.

Optional pre-course reading: Students may wish to read the Instructor's 2018 book before the course begins:

Who We Are and How We Got Here: Ancient DNA and the New Science of the Human Past (David Reich, Pantheon 2018)

Day	Events	Required Reading Prior to Class	Recommended Readings

		/ Assignments due	
Jan. 22		[Skoglund P, Mathieson I (2018)](#) Ancient genomics of modern humans: The first decade. Annual Reviews of Genomics and Human Genetics, 19, 381-404.	[DalÃ©n L, Heintzman PD, Kapp JD, Shapiro B (2023)](#) Deep-time paleogenomics and the limits of DNA survival. Science 382, 48-53. [Ãvila-Arcos MC, Raghavan M, Carina S (2023)](#) Going local with ancient DNA: A review of human histories from regional perspectives. Science 382, 53â€"58.
Jan. 24	Boot camp with TF Daniel Tabin: "Learning about history from variation in allele frequencies"		
Jan. 26	Talk by David Reich: â€œHow we got where we are today" Student presentation of paper Deadline: All students should have scheduled meetings with both the instructor and TF	[Lazaridis I et al. (2014)](#) Ancient human genomes suggest three ancestral populations for present-day Europeans. Nature 513, 409-13. ([Supplement](#))	[Haak W, Lazaridis I et al. (2015)](#) Massive migration from the steppe was a source for Indo-European languages in Europe. Nature 522, 207-11. ([Supplement](#)) [Posth, C. et al. (2023)](#). Palaeogenomics of Upper Palaeolithic to Neolithic European hunter-gatherers. *Nature* **615**, 117â€"126 (2023). ([Supplement](#))
Jan. 29	Talk by David Reich: â€œThe Genomics of inequalityâ€ Student presentation of paper Deadline: All students should have had a one-on-one meeting with both the instructor and TF	[Karmin M et al. (2015)](#) A recent bottleneck of Y chromosome diversity coincides with a global change in culture. Genome Res. 25, 459â€"466. ([Supplementary Text](#)) ([Supplementary Figures](#))	[Cox SL, Nicklisch N, Francken M, Wahl J, Meller H, Haak W, Alt KW, Rosenstock E, Mathieson I (2023)](#) Socio-cultural practices may have affected sexual dimorphism in stature in Early Neolithic Europe. ([Supplement](#)) [Arauna et al. (2022)](#) The genomic landscape of contemporary western Remote Oceanians Current Biology 32, 4565â€"4575. ([Supplement](#))
Jan. 31	Talk by Nick Patterson	[Patterson N et al. (2012)](#) Ancient admixture in human history.	[Reich D et al. (2009)](#) Reconstructing Indian population history. Nature

	(Harvard Department of Human Evolutionary Biology): â€œf-statistics: Learning about history from allele frequency correlationsâ€ **Student presentation of paper**	*Genetics* 192, 1065-93.	461, 489-95. ([Supplement]) ([Mathematical Appendix]) [Maier R, Flegontov P, Flegontova O, IÅŸÄ±ldak U, Changmai P, Reich D (2023)] On the limits of fitting complex models of population history to f-statistics. eLife, e85492. ([Supplement])
Feb. 2	**Boot camp** with TF Daniel Tabin: "Introduction to Principal Component Analysis and Fst"		
Feb. 5	**Talk** by Iain Mathieson (University of Pennsylvania): â€œLearning about natural selection from ancient DNAâ€ **Student presentation of paper**	[Irving-Pease EK et al. (2024)] The selection landscape and genetic legacy of ancient Eurasians. Nature https://doi.org/10.1038/s41586-023-06705-1 doi.org/10.1101/2022.09.22.509027. ([Supplement]) ([Online Tables])	[Mathieson I et al. (2015)] Genome-wide patterns of selection in 230 ancient Eurasians. Nature 528, 499-503. ([Supplement])
Feb. 7	**Talk** by Alissa Mittnik (Max Planck Institute for Evolutionary Anthropology, Leipzig) â€œIntegrating ancient DNA and isotope dataâ€ **Student presentation of paper**	[Reitsema LJ, Mittnik A, Kyle B et al. (2022)] The diverse genetic origins of a Classical period Greek army. ([Supplement])	[Mittnik A et al. (2019)] Kinship-based social inequality in Bronze Age Europe. Science 366, 731-4. ([Supplement]) [Fowler C et al. (2021)] A high-resolution picture of kinship practices in an Early Neolithic tomb. Nature 601, 584-7. ([Supplement]) [Ringbauer H, Novembre J and SteinrÃ¼cken M (2021)] Parental relatedness through time revealed by runs of homozygosity in ancient DNA. Nat Commun 12, 5425. ([Supplement])
Feb. 9	**Homework help:** TF Daniel Tabin	**Assignment 1 by day's end** **(PCA, Fst, allele frequencies)**	

Feb. 12	Talk by Eadaoin Harney (23andMe and Harvard Department of Human Evolutionary Biology): â€œApproaches for isolating DNA from ancient skeletal remains" Student presentation of paper Deadline: All students should have made meaningful progress toward identifying an Original Research Project and a mentor	Orlando et al. (2021) Ancient DNA analysis. Nature Reviews Methods Primers, 1, 14.	Prendergast ME, Sawchuk E (2018) Boots on the ground in Africa's ancient DNA â€˜revolutionâ€™: archaeological perspectives on ethics and best practices. 92, 803-15. Harney E et al. (2021) A Minimally Destructive Protocol for DNA Extraction from Ancient Teeth. Genome Research 31, 472-83. (Supplement)
Feb. 14	Talk by Jakob Sedig: "Ethics in Ancient DNAâ€ Student presentation of paper	Alpaslan-Roodenberg S et al. (2021) Ethics of DNA research on human remains: five globally applicable guidelines. Nature 599, 41-6.	Wagner JK et al. (2020) Fostering Responsible Research on Ancient DNA. American Society of Human Genetics 107, 183â€“195 Bedford et al. (2018) Archaeology in Oceania, Ancient DNA and its contribution to understanding the human history of the Pacific. Archaeology in Oceania 53, 205â€“219. Wolinsky H (2019) Ancient DNA and contemporary politics. EMBO Rep. 20, e49507.
Feb. 16	Boot camp with TF Daniel Tabin: "Introduction to f-statistics"		
Feb. 19	NO CLASS President's Day		
Feb.	Boot camp with		

21	TF Daniel Tabin: "Advanced f-statistics"		
Feb. 23	Talk by David Reich: â€œCritical analysis of ancient DNA claims: How to identify errorsâ€	[Mondal et al. (2016)](#) Genomic analysis of Andamanese provides insights into ancient human migration into Asia and adaptation. Nat Genet. 48, 1066-70. ([Supplement](#)) [Technical comment by Skoglund P et al. (2018)](#) No evidence for unknown archaic ancestry in South Asia. Nat. Genet. 50, 632-63. [Authors' reply](#)	[Gallego Llorente M et al. (2015)](#) Ancient Ethiopian genome reveals extensive Eurasian admixture throughout the African continent. ([Supplement](#)) ([Erratum](#)) [Technical comment by Skoglund P, Reich D (2015)](#) Comment on â€œAncient Ethiopian genome reveals extensive Eurasian admixture throughout the African continentâ€ (unpublished as authors accepted the critique and rewrote their paper in response). [Goldberg A. et al. (2017)](#) Ancient X chromosomes reveal contrasting sex bias in Neolithic and Bronze Age Eurasian migrations. 114, 2657-2662. ([Supplement](#)) [Technical comment by Lazaridis I, Reich D (2017)](#) Failure to replicate a genetic signal for sex bias in the steppe migration into central Europe. Proc. Natl. Acad. Sci 114, E3873-4. [Authors' reply](#)
Feb. 26	The standard model of archaic-modern human relationships (part 1) Student presentation of papers	[PrÃ¼fer K et al. (2014)](#) The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505, 43-9. ([Supplement](#)) [Skov L et al. (2022)](#) Genetic insights into the social organization of Neanderthals. Nature 610, 519â€"525. (Supplement)	
Feb. 28	The standard model of archaic-modern human	[Hadjinjak et al. (2018)](#) Reconstructing the genetic history of late Neanderthals. Nature 555, 652â€"656. ([Supplement](#))	[Meyer et al. (2016)](#) Nuclear DNA sequences from the Middle Pleistocene Sima de los Huesos hominins. 531, 504â€"507.

	relationships (part 2) Student presentation of papers	Browning et al. (2018) Analysis of Human Sequence Data Reveals Two Pulses of Archaic Denisovan Admixture. Cell 173, 53â€"61. (Supplement)	(Supplement)
Mar. 1	Homework help: TF Daniel Tabin	**Assignment 2 by day's end** **(f-statistics)**	
Mar. 4	Early modern human introgression into Neanderthals Student presentation of papers	Petr M et al. (2020) The evolutionary history of Neanderthal and Denisovan Y chromosomes. Science 369, 1653â€"1656. (Supplement) Harris et al. (2023) Diverse African genomes reveal selection on ancient modern human introgressions in Neanderthals. Current Biology 33, 1â€"12	Posth C et al. (2017) Deeply divergent archaic mitochondrial genome provides lower time boundary for African gene flow into Neanderthals. Nature Communications 8, 16046. (Supplement)
Mar. 6	Archaic - modern human admixture everywhere Student presentation of papers	Slon et al. (2018) The genome of the offspring of a Neanderthal mother and a Denisovan father. 561, 113â€"116. (Supplement) Hadjinjak et al. (2021) Initial Upper Palaeolithic humans in Europe had recent Neanderthal ancestry. Nature 592, 253-257. (Supplement)	Peter BM (2020) 100,000 years of gene flow between Neandertals and Denisovans in the Altai mountains. bioRxiv doi.org/10.1101/2020.03.13.990523. (Supplement)
Mar. 8	Boot camp with TF Daniel Tabin: "Introduction to clustering		

	algorithms"		
Mar. 11	NO CLASS Spring break		
Mar. 13	NO CLASS Spring break		
Mar. 15	NO CLASS Spring break		
Mar. 18	Natural selection and its interaction with interbreeding Student presentation of papers	Sankararaman S et al. (2014) The genomic landscape of Neanderthal ancestry in present-day humans. Nature 507, 354-7. (Supplement) Harris K and Nielsen R (2016) The genetic cost of Neanderthal introgression. Genetics 203, 881-891.	Racimo, F. et al. (2015) Evidence for archaic adaptive introgression in humans. *Nat Rev Genet* **16**, 359â€"371. Huerta-SÃ¡nchez E et al. (2014) Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. Nature 512, 194â€"197. (Supplement)
Mar. 20	The standard model of Native American population history Student presentation of papers	Skoglund P et al. (2015) Genetic evidence for two founding populations of the Americas. Nature 525, 104-8. (Supplement) Rasmussen M et al. (2014) The genome of a Late Pleistocene human from a Clovis burial site in western Montana. Nature 506, 225-229. (Supplement)	Moreno-Mayar JV et al. (2018) Terminal Pleistocene Alaskan genome reveals first founding population of Native Americans. Nature 553, 203-207. (Supplement)
Mar. 22	Boot camp with TF Daniel Tabin: "Expectation maximization		

	algorithms"		
Mar. 25	Complications in the standard model of Native American population history Student presentation of papers	[Posth C, Nakatsuka N et al. (2018)](#) Reconstructing the Deep Population History of Central and South America. Cell 175, 1185-1197. ([Supplement](#)) [Moreno-Mayar V et al. (2018)](#) Early human dispersals within the Americas. Science 362, eaav2621. ([Supplement](#))	[Sikora et al. (2019)](#) The population history of northeastern Siberia since the Pleistocene. Nature 570, 182â€"188. ([Supplement](#)) [Yu et al. (2020)](#) Paleolithic to Bronze Age Siberians reveal connections with First Americans and across Eurasia. Cell 181, 1232-1245. ([Supplement](#))
Mar. 27	The population history of East Asia (part 1) Student presentation of papers	[Wang et al. (2021)](#) Human population history at the crossroads of East and Southeast Asia since 11,000 years ago. Cell 184, 3829-3841. ([Supplement](#)) [Yang M et al. (2020)](#) Ancient DNA indicates human population shifts and admixture in northern and southern China. Science 369, 282-288. ([Supplement](#))	[Ning C et al. (2020)](#) Ancient genomes from northern China suggest links between subsistence changes and human migration. Nat Commun. 11, 2700. ([Supplement](#)) [Mao et al. (2021)](#) The deep population history of northern East Asia from the Late Pleistocene to the Holocene. Cell 184, 3256-2366. ([Supplement](#))
Mar. 29	Homework help: TF Daniel Tabin	**Assignment 3 by day's end** **(EM algorithm, ADMIXTURE)**	
Apr. 1	The deep population history of East Asia (part 2) Student presentation of papers	[Jeong et al. (2019)](#) The genetic history of admixture across inner Eurasia. Nat. Ecol. Evol. 3, 966-976. ([Supplement](#)) [Cooke et al. (2021)](#) Ancient genomics reveals tripartite origins of Japanese populations. Science Advance 7, eabh2419. ([Supplement](#))	[Kumar et al. (2022)](#) Bronze and Iron Age population movements underlie Xinjiang population history. Science 376, 62â€"69 (2022). ([Supplement](#)) ([Online Tables](#)) [Zeng TC, Vyazov L, Kim A et al. (2023)](#) Postglacial genomes from foragers across Northern Eurasia reveal prehistoric mobility associated with the spread of the Uralic and Yeniseian languages. bioRxiv doi.org/10.1101/2023.10.01.560332. ([Supplement](#))
Apr. 3	The deep population history of East Asia (part 3) Student presentation of papers	[McColl et al. (2021)](#) The prehistoric peopling of Southeast Asia. Science 361, 88-92. ([Supplement](#)) [Lipson M et al. (2020)](#) Three Phases of Ancient Migration Shaped the Ancestry of Human Populations in Vanuatu, Current Biology, 30, 4846-4856. ([Supplement](#))	[Choin et al. (2021)](#) Genomic insights into population history and biological adaptation in Oceania. Nature 592, 583â€"589. ([Supplement](#)) [Carlhoff S et al. (2021)](#) Genome of a middle Holocene hunter-gatherer from Wallacea. Nature 596, 543â€"547. ([Supplement](#)) https://doi.org/10.1038/s41586-021-

			03823-6
Apr. 5	Boot camp with TF Daniel Tabin: "Using f-statistics for model testing; qpAdm day 1"		
Apr. 8	Herbivores Student presentation of papers	Librado et al. (2021) The origins and spread of domestic horses from the Western Eurasian steppes. Nature 598, 634–640. (Supplement) Verdugo et al. (2019) Ancient cattle genomics, origins, and rapid turnover in the Fertile Crescent. Science 365, 173-176. (Supplement)	Gaunitz et al. (2018) Ancient genomes revisit the ancestry of domestic and Przewalski's horses. 360, 111-114. (Supplement)
Apr. 10	Carnivores Student presentation of papers	Bergström, A. et al. (2022) Grey wolf genomic history reveals a dual ancestry of dogs. Nature 607, 313–320. (Supplement) Bergstrom et al. (2020) Origins and genetic legacy of prehistoric dogs. Science 370, 557-564. (Supplement)	Ottoni C et al. (2017) The palaeogenetics of cat dispersal in the ancient world. Nat Ecol Evol 1, 0139. (Supplement)
Apr. 12	Boot camp with TF Daniel Tabin: "qpAdm day 2"		
Apr. 15	Ancient epigenetics Student presentation of papers	Gokhman D et al. (2019) Reconstructing Denisovan anatomy using DNA methylation maps. Cell 179, 180-192. Gokhman D et al. (2020) Differential DNA methylation of vocal and facial anatomy genes in modern humans. Nature Communications 11, 1189. (Supplement)	Gokhman D et al. (2017) Gene ORGANizer: linking genes to the organs they affect. Nucleic Acids Research 45, doi: 10.1093/nar/gkx302.
Apr. 17	Genealogical trees and population history Student presentation of papers	Speidel L, Forest M, Shi S, Myers SR (2019) A method for genome-wide genealogy estimation for thousands of samples. Nature Genetics 51, 1321-1329 (Supplement). Speidel L et al. (2021) Inferring population histories for ancient genomes using genome-wide	Hubisz MJ, Williams AL, Siepel A (2020) Mapping gene flow between ancient hominins through demography-aware inference of the ancestral recombination graph. PLoS Genet 16(8): e1008895. (Supplement)

		genealogies. Molecular Biology and Evolution, 38, 3497â€"3511. ([Supplement](#))	
Apr. 19	Homework help: TF Daniel Tabin	**Assignment 4 by day's end (qpAdm)**	
Apr. 22	Flash talks of original research projects progress for all students		
Apr. 24	Flash talks of original research projects progress for all students		
May 7	NO CLASS	**RESEARCH PAPER DUE**	

Online resources for research

[Course](#) by Shop Mallick (Bioinformatics Director in our lab)
[Course](#) on computational biology tools by Stephan Schiffel (Group Leader at Max Planck Institute)
[Software](#) published by our laboratory (please also explore the extensive software written by other groups)
[Compendium](#) of the world's published ancient DNA data