Outline of Lecture 1, 9/7

1. What does a theory of evolution have to explain about the world around us – if anything?

   - *Adaptation*. Why do organisms 'fit' their environment? (Like a lock and key). This characteristic of 'good design' was a key element of the 'natural theologians' account of the 'goodness' of the Creator's universe. Example: orchid and insect with long tongue than can fertilize it. Darwin's book: *Various Contrivances by which Orchids and Fertilized by Insects,* documented that the intimate relationship between insects and the flowers that they pollinated was matched by their structural compatibility and the insect's behavior. On the strength of his observations, Darwin made bold to predict that the insect that pollinated an orchid (*Angraecum arachnites*, found in Madagascar) with nectaries that were 11 inches long would be a moth with a proboscis that long! 125 years later the moth (*Panogena lingens*) was discovered.

   - *Historical change*. Organisms change over time. (How do we know this? Question: *why* do they change over time?) Is 'evolution' to be equated with 'historical change'?

   - *Complexity*. Why isn't the universe filled with a uniform grey goo? Why do organisms have structure at all – is this an intrinsic property of organisms or an extrinsic one (or both)? Is it just because the environment is complex?

   - *Variation*. Organisms differ. Why are there so many different kinds of organisms? In detail: why do all fish have vertical fins, but all cetaceans (whales, dolphins,…) horizontal fins? (both seem to work equally well). We seem to have two amino acid differences in a certain protein, FOXP2, implicated in motor-neural development, as compared to our nearest relatives, chimpanzees (*Pan paniscus*), and it's been asserted that this difference plays a role in why we talk and chimps don't. Was there 'selection' for the gene that codes for this protein? How could we figure this out? Can we figure this out?

   - *Similarity*. The flip side of variation – organisms resemble each other, at almost any level of description you can name – from the bones in a bird's wing and a person's arm, to the individual nucleotides in their DNA. The *three taxon hypothesis* says that all life can be organized into a 'family resemblance tree' such that any two organisms will have a (least) common ancestor (LCA), and that ancestor will, in turn, be related to the third organism – the LCA and the other organism will themselves have a joint, least common ancestor. This implies evolution by descent – Darwin's theme. Is it true? How can we tell? Much of current genomic research is, of course, predicated on this assumption.

   - *Clumping*. Putting variation and similarity together: organisms seemed to be 'clumped' into groups, no matter how you want to measure them (by their morphology, gene frequencies, whatever). We may imagine drawing a (huge) space with 'notional' axes representing each possible dimension of variation, for example, the set of all genome sequences. No matter what measure we pick, the space will be very, very sparsely filled (do you believe this?).

2. We might depict *any* model for 'evolutionary' change as a *sequence* of states over time, x_1, x_2, … where there is some map, T, that carries the state x into a next state x'. In general, we say that a *discrete dynamical system* consists of a map T from a space x onto itself. (We haven't said anything much yet about constraints that characterize T or x, e.g., x could be the set of all the genes in an organism, or their frequencies in the overall population of organisms; or it could be a list of all the traits in a (set of organisms) – whatever a 'trait' is - and T could be differentiable). As is usual, we may imagine that this map can be iterated: **x, Tx, $T(T$x),...T^kx.** This sequence is called the *orbit* of **x.** It will be convenient to write the map

in the form, $x' = Tx$, or as $x'-x = Tx-x$. Equations of the second type are called *reccurrence* or *difference equations*. We give an explicit example shortly.

3. The general problem is one of constructing a state space that will be dynamically sufficient, and a set of laws of transformation in that state space that will transform all the state variables. The laws also have to be empirically sufficient. This entails an interchange between finding the laws and picking the right state variables, to predict a future state x' given a current x. The transformational laws cannot be arbitrary – usually they contain some parameters P that are not themselves a function of time or the state of the system. Second, the laws contain the elapsed time except in the case of equilibrium, and may or may not refer specifically to the absolute time t depending on whether the system carries in its present state some history of the past. Finally, most importantly, the laws of transformation must contain the present state of the system and suffice to produce the next state. Example – you can't predict the future position of a satellite from its current position alone. You need to know 3-D position, velocity, and acceleration – 9 variables in all, and that is dynamically sufficient.

4. So what about for evolutionary theory? What is the state space? What are the laws of transformation? It is important to stress that we can't go out and describe the world any way we want and demand that an explanatory and descriptive theory be built on that description – it might be dynamically insufficient. This has important consequences, because to model evolution we will necessarily build such dynamical systems – but this takes some care. What kind of 'force' is evolution? What are the state variables?

5. Much of the remainder of this course will consist in characterizing and exploring the dynamical system behavior of T and x: rate of evolution; convergence times; stability properties; measurement and inference problems – how can we tell from a current state, what has happened in the past; how can we measure the 'forces' of evolution; how various characterizations of T and x; how sensitive our these models to our assumptions.

6. We may identify two distinct 'modes' of accounting for evolutionary change, *transformational* and *variational*. Transformational theories have been the most widespread for explaining historical change. The prototypical transformational example is stellar evolution. In transformational evolution, the properties of each individual in a group change, and, as a result, the overall group compositional properties change. This explanatory mode was also common to perhaps the most popular view of biological evolutionary change in the 1700s, given the name *Lamarckism* (after Jean-Baptiste Monet, Chevalier de Lamarck), although he did not originate this approach. Like stellar evolution, on this view biological change too is transformational: all individual organisms making up a population change – each giraffe's neck gets longer reaching for the treetops – and as a result of *individual* change, the population property in question as a whole changes.

7. In contrast, Darwin seems to have been the first to introduce a completely novel account for evolution, the *variational* mode of evolutionary explanation. In a variational story, no single *individual* undergoes evolutionary change within its lifetime. Rather, *already existing* variation among individuals is *selected* (sieved) and the group population property as an ensemble changes because different individuals are selected to make up the group. Or: In the variational mode, there is variation among the individual units comprising the whole system. The system changes in time by a change in the proportions of the different kinds of units, as a consequence of differential survival and reproduction of the units. In Darwin's scheme, the group as a whole changes through time because objects with different properties leave different numbers of descendants.

8. It is important to understand that different domains of phenomena evolve by different modes. The transformational mode, which is correct for galaxies and embryos, is not correct for species.

9. The essential nature of the Darwinian revolution was not the introduction of evolution as a worldview. This is historically not the case. It is rather the replacement of a metaphysical view of variation among organisms by a materialistic view. Darwin's materialistic view replaced the Aristotelian, Platonic conception that there is a single ideal 'type' – an ideal squirrel, or whale, or E. coli – and so, and that the 'failings' of organisms in their perfection of adaptation somehow to be related to their failure attain this ideal – they are imperfect approximations to their 'true nature.' The failure of individual cases to match the ideal was a measure of the imperfection of nature. (Compare this to the Newtonian idealizations about frictionless planes, etc.) Darwin overthrew this metaphysical picture and replaced it with a materialistic one: what matters in Darwinian evolution by natural selection is the actual variation in actual individuals. This individual variation is of the essence – as we'll see many times in the course: the *rate* of evolution by natural selection is *directly proportional* to the amount of standing variation. Variation is the fuel that evolution burns. (And in addition, unlike a fire, evolution has to 'make' its own fuel.)

10. So: Darwin's explanation for the 'clumping' that we see in the biological world is the conversion of the standing variation between individuals into variation between species and groups.

11. All 'vulgar' versions of evolution at the time of Darwin thus already included variation and inheritance. Darwin added the key notion of *selection*, dubbed *natural selection* by analogy with the *artificial* selection that Darwin observed amongst pigeon, dog, horse breeders. Selection 'sieves' existing variation by letting 'pass through' individuals with certain properties, but not other properties – like panning for gold. Inheritance then transmits these individuals, with their selected properties, to the next generation. These comprise the three key components of Darwin's theory:
    a. *Variation*: Among individual members within any population, there is variation (in genes, morphology, physiology, behavior, …)
    b. *Heredity* (information transmission): Offspring resemble their parents more than they resemble individuals to which they are unrelated
    c. *Selection*: Some forms are more successful at surviving and reproducing than other forms in a given environment. (aka, the 'misnomer' "survival of the fittest")
   It is a valuable exercise to consider whether these three components are necessary and sufficient for evolution by natural selection – alternatively, whether it is possible to design some *other* system that would work to create the living world around us. At least superficially, it should be clear that without variation, evolution can do nothing – there is nothing that selection can do to separate out a group with different ensemble properties. Similarly, without some form of inheritance, a differentially selected set of individuals would not be 'passed on' to future generations. And of course, some kind of selection must be part of 'natural selection'.

12. But what *sort* of variation, heredity, and selection? Consider heredity. There are interesting constraints on the kind of 'information transmission' systems that can (easily) lead to evolution by natural selection. One of these constraints was first driven home in perhaps the most devastating review of *Origin of Species* – at least the one that troubled Darwin the most - by the Scottish engineer Fleeming Jenkin. This EECS pioneer almost sunk Darwin's theory. Jenkin's point had to do with the nature of inheritance. In Darwin's time, the most widely accepted notion of 'inheritance' was essentially that of *blending inheritance* - 'mixing by

blood' – like blending paint (a very old idea). But blending inheritance runs afoul of natural selection's demand for variation. It is easy to see that if in fact inheritance worked by blending, then any variation would be quickly swamped within a few generations – in fact it is halved at ever generation – and so turned into a kind of uniform brown mud. We wind up with nothing for natural selection to 'select'.   Darwin himself was unable to refute this argument, and wound up embracing Lamarck's inheritance of acquired characteristics, along with a theory of 'hyper mutation' that would pump in enough variation to keep selection going (if ½ of all variation is lost each generation, then ½ the variation we see in the current generation must be due to mutations introduced by the immediately preceding generation).

13. The problem was resolved by Mendel's discovery that inheritance is quantal, or particulate in nature, and not blending (the particles of course ultimately turned out to be genes). R.A. Fisher (1911, 1930) demonstrated exactly how blending inheritance would halve variance at each generation: Let x denote the deviation of one parent from the mean of any trait (e.g., height, or "Paul Newman blue eyes"), and y denote the deviation from the mean of that trait for the other parent. The variance of the trait is the expected (mean) value of the square of deviations from the mean, or $E[x^2]$. On the model of perfect blending inheritance, then the deviation of the offspring would be $\frac{1}{2}(x+y)$ – exactly half-way in between. We can now calculate the expected value of the square of this deviation: $E[\{\frac{1}{2}(x+y)\}^2]=E[\frac{1}{4}(x^2+2xy+y^2)]$. The quantity $E(xy)$ must be zero, since the expected value of deviations from the mean is always 0. The expected value of x^2 = the expected value of y^2, so we have, $E[\frac{1}{4}(x^2+2xy+y^2)]=$ $E[\frac{1}{4}(2x^2)]=E[\frac{1}{2}(x^2)]=\frac{1}{2}E[x^2]$ – that is, exactly half the original variance. Thus under blending inheritance variance declines exponentially with each generation. We also must show how 'particulate' inheritance removes this problem. Intuitively, if inheritance works via 'quanta' that we call genes, and these genes are not blended – neither created nor destroyed – during reproduction, then the variance remains constant (all other things like mutation being equal) – we can juggle a handful of different colored jelly beans around, and mix them, but the individual numbers of different colored jelly beans will remain the same. This can be demonstrated more precisely via the so-called "Hardy-Weinberg laws", which we turn to below. Sadly, though Mendel's work was published during Darwin's lifetime – Darwin even had a copy of Mendel's publications – it seems that he never read about them, and the articles were found uncut (unopened) in Darwin's library at the time of his death. Mendel's algebraic system evidently did not appeal to Darwin, who claimed in his autobiography to be all in a muddle about mathematics.

14. We next pursue an elaboration of the notion of a dynamical system mapping as our model of evolutionary change. We describe any (array of) organisms via two key descriptive spaces: <u>Genotype space</u> and <u>Phenotype space</u>. By "genotype" we mean the full array of genes in an organism or set of organisms (for now, think of it as a very long vector, say, 20,000 elements in the case of humans.) For now we don't say what the 'axes' are in this space. Genes occur in variants, called *alleles*. The variants within a species, over all genes, specify distinct *genotypes*. For example, we saw that there is a particular gene that specifies normal human hemoglobin in red blood cells, and another, which differs in exactly one DNA 'letter' (the nucleotide adenine, A, is replaced by a thymine, T), whose corresponding protein has a valine instead of a glutamic acid, which in turn yields a hemoglobin that forms 'bent' crystals and causes red blood cells to become crooked and 'sickle' shaped instead normally elliptical. These are two *alleles* of the gene for hemoglobin (more precisely, the beta-chain of one part of hemoglobin), or two 'genotypes'. By "phenotype" we mean the 'form that shows' – i.e., the actual biological form that an organism presents to the world (and so casually interacts with it in the sense of affecting the outcome of selection). In our example, the two distinct hemoglobins (and consequently distinct red blood cell shapes) are two different 'phenotypes'. Of course, genotypes can also differ between species as well as between individuals. A genotype, then, is simple the string of nucleic acids, the 'genetic code' that make up the DNA

of an individual organism. Selection acts on phenotypes (note that we have been a bit vague as to whether a phenotype might include the notion of a genotype or DNA sequence – doesn't this casually interact with the world? More later.) In the case of normal vs. sickle-shaped red blood cells, we know that the latter are extremely debilitating and lead to early death – the sickle-cell phenotype is 'selected against'. We stress that a full evolutionary theory must pass back and forth between these spaces by means of (as yet) unspecified, and current unknown, mappings. Here is a picture:
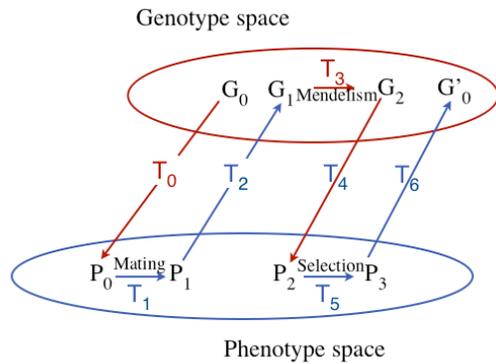
15.

If we start off in genotype space, in some state G_0, then we must pass back and forth between genotype space and phenotype space several times in order to reach the next possible genotype state G_0': first, the genotype must be realized as a phenotype P_0; (the actual organisms) – this via a set of 'developmental laws' T_0 that turn genotypes into organisms; then these organisms must meet and mate, again via some set of laws T_1; then the mated pairs produce the 'raw' DNA, the *gametes* (e.g., egg and sperm), which brings us back to genotype space via another mapping T_2 specifying how gametes get produced from mated organisms; the genes then reassort and combine via the rules commonly known as Mendelism, T_3; then the fertilized egg(s) (a *zygote*) develops into offspring, via developmental transformations T_4; natural selection then acts on the offspring, winnowing them, T_5; then finally these surviving offspring produce an array of genotypes (via their games, i.e., sperm and eggs) which become the new G_0' to start the process all over again. Whew. It almost goes without saying that except in extremely limited cases we have no knowledge whatsoever about these T's, or how to compute them. We can say, however, that our theory will have to be both dynamically and empirically sufficient. As it stands, to do this would result in a theory concerning a vastly more complex domain than any yet dealt with by physics or molecular biology.

(Aside 1: We should remark that even under naïve assumptions the size of these spaces might be enormous – for example, suppose we take genotype space to be 'discrete' and consist of the set of possible gene sequences for an organism. If there are 10,000 genes in an organism's gene sequence – not far off - with 3 gene types or 'alleles' each, that amounts to $3^{10,000}$ possible genotypes or 'points' in this space.) (Aside 2: as correctly pointed out, we really ought to included *another* space in this analysis, namely, the external environment or context in which G and P reside.)

16. If we have no knowledge of these *T* mappings then how can evolutionary biology proceed? In fact, there are two moves that are made, the obvious ones. We can either 'assume away' P, and do our modeling only in genotype space; or we can assume away G, and do our modeling only in phenotype space. Both strategies are adopted. We can collapse G=P, and work entirely in Phenotype space. This is the province of biometrics – we put this to one side for now. Or, we can collapse G and P, and work entirely in genotype space. This is the strategy of most of evolutionary population genetics: to study the origin and dynamics of genetic variation within populations.

17. While this is a much more modest goal that all of evolutionary theory, it is an essential ingredient. If we adopt this subgoal, we are in effect equating evolution as "change in gene frequencies", as is common in this approach. However, while population genetics has much to say about changes or the stability of the frequencies of genes in populations and about the rate of divergences in gene frequencies in populations, it has contributed little to our understanding of speciation and nothing to our understanding of extinction.

18. Still, the sufficient set of state variables for describing an evolutionary process within a population must include some information about the statistical distribution of gene frequencies. It is for this reason that the empirical and mathematical study of population genetics has always begun with and centered on the characterization of the genetic variation in populations.

19. We begin then by adopting the "evolution as change in gene frequencies" view, and describing the simplest dynamical system modeling this. We want to know what theory says about the reproduction of genotypes in a population. This results in the derivation of the so-called *Hardy-Weinberg proportions.* We imagine a population reproducing without any natural selection or any interference by any other forces such as mutation or migration. The Hardy-Weinberg result serves as a kind of "Newton's First Law" for the genetics of evolving populations, because it says that under such conditions gene frequencies (and their variance) will "remain at rest" – that is, gene frequency proportions will *remain in equilibrium* as long as there is no other force to disturb them. We use this as a 'baseline' model and then introduce selection, migration, etc. as 'forces' that displace a population from its equilibrium. H-W is the second half of the demonstration that Mendelism actually goes hand-in-hand with Darwin's theory – it is virtually a necessary part of Darwinism, since it serves to maintain variation unless there is some other force to disturb it. It would be an interesting exercise to see whether one could develop an alternative that could replace Mendelism, and still get the conditions for the evolution of complex life.

20. The Hardy-Weinberg "law" is based on following assumptions:
    - A single random mating population
    - Infinitely many individuals (Why do we need this assumption? Follow it out in the analysis below)
    - No mutation
    - No selection (no differential fertility, viability)
    - No immigration or emigration
    - Non-overlapping generations

21. Suppose we have one gene that comes in two variants, or alleles, denoted A and a. If we have <u>genotypes</u> with current genotype frequencies P, Q, and R of genotypes AA, Aa, and aa, they have a fraction $p = P + 1/2\ Q$ of their genes being A rather than a. The value p is the <u>gene frequency</u> (note the difference between gene frequency and a genotype frequency, e.g., P). The gene frequency of the a allele is, for the same reasons, $q = 1/2\ Q+R$. These can also be computed by counting the fractions of A and a among the individuals.

22. Random mating is equivalent to random union of gametes. Imagine making a pot of female gametes, a pot of male gametes, and drawing a pair, one from each. The equivalence comes because a random member of the offspring generation is descended from a random female and a random male, and Mendelian inheritance ensures that the gametes each contributes contain a random one of the two copies (at this locus) in that individual. Drawing a random parent, and then having it choose one of the two copies by Mendelian segregation, is equivalent to drawing one of the copies from the population at random. [Indeed, the *variance*

of this draw, in the case of just two alleles in fractions p and $(1-p)$ is $\frac{1}{2}\,p(1-p)$ as per standard sampling theory from a binomial distribution, a result we shall draw on below – or refer to appendix A in your Sean Rice textbook.

23. The probability that the offspring gets an A from the female parent is p, and the probability that it gets an A from the male parent is also p. Because these are independent as a result of random mating, the probability that the individual is AA is then p^2.

24. The result is that AA, Aa, and aa have expected genotype frequencies p^2, $2pq$ and q^2.

25. The gene frequency in this offspring population is again p, since in that generation P is p^2 and Q is $2pq$, so that $p = P + 1/2\ Q = p^2 + 1/2\ (2pq) = p$.

26. If we again mate these individuals randomly, the gene frequencies in the second generation are again p and q.

27. Thus the genotype frequencies become these "Hardy-Weinberg" proportions, and stay that way forever. The gene frequencies remain forever p. If we are talking about just *one* gene 'location' (= "locus") then the frequencies for two alleles are forever p and $(1-p)$.

28. Mendelian genetic systems thus do not tend to lose genetic variability just because of random mating. Blending inheritance would lose it. The fundamental reason is that segregation in a heterozygote yields gametes that are $1/2\ A$ and $1/2\ a$, whereas in blending inheritance it is as if they were all medium-sized A's. [Q: what would happen in a non-Mendelian world? Variation lost? No evolution of complex life?]

29. When we relax the assumption of no differential viability and no differential fertility, we now have natural selection going on. We can count genes to *define* the notion of absolute fitness. More about this next time.