Notes on Population Genetics

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Introduction

Evolution is change over time. Biological evolution is change over time in the genetic composition of populations. The genetic composition of a population is the set of genomes that the individuals in our population carry. While at first this definition of evolution seems at odds with the common textbook view of the evolution of phenotypes (such as the changing shape of the finch beaks over generations) it is genetic changes that underpin these phenotypic changes.

The genetic composition of the population can alter due to the death of individuals or the migration of individuals in or out of the population. If our individuals have different numbers of children, this also alters the genetic composition of the population in the next generation. Every new individual born into the population subtly changes the genetic composition of the population. Their genome is a unique combination of their parents' genomes, having been shuffled by segregation and recombination during meioses, and possibly changed by mutation.

Population genetics is the study of the genetic composition of natural populations. It seeks to understand how this composition has been changed over time by the forces of mutation, recombination, selection, migration, and genetic drift. To understand how these forces interact, it is helpful to develop simple theoretical models to help our intuition. In these notes we will work through these models and summarize the major areas of population genetic theory. While these models will seem naïve (and indeed they are) they are nonetheless incredibly useful and powerful. Throughout the course we will see that these simple models yield accurate predictions, such that much of our understanding of the process of evolution is built on these models. We will also see how these models are incredibly useful for understanding real patterns we see in the evolution of phenotypes and genomes, such that much of our analysis of evolution, in a range of areas from human genetics to conservation, is based on these models. Therefore, population genetics is key to understanding various applied questions from how medical genetics identifies the genes involved in disease to how we preserve small populations (such as a Florida panther) from extinction.

"Dobzhansky (1951) **?** once defined evolution as 'a change in the genetic composition of the populations' (p. 16) an epigram that should not be mistaken for the claim that everything worth saying about evolution is contained in statements about genes" **?**

pos.	con.	a	b	c	d	e	f	g	h	i	j	k	l	a	b	c	d	e	f	a	b	c	d	e	f	g	h	i	j	k	l	NS/S
781	G	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NS
789	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	S
808	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G	G	G	G	G	G	G	G	G	G	G	NS
816	G	T	T	T	T	-	-	-	-	-	-	-	T	T	T	T	T	T	T	-	-	-	-	-	-	-	-	-	-	-	-	S
834	T	-	-	-	-	-	-	-	-	-	-	-	-	C	C	-	-	-	C	-	-	-	-	-	-	-	-	-	-	-	-	S
859	C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G	G	G	G	G	G	G	G	G	G	G	NS
867	C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G	G	G	G	A	G	G	G	G	G	G	S
870	C	T	T	T	T	T	T	T	T	T	T	T	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S
950	G	-	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S
974	G	-	-	-	-	-	-	-	-	-	-	-	-	T	-	T	T	T	T	-	-	-	-	-	-	-	-	-	-	-	-	S
983	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	S
1019	C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-	-	-	S
1031	C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	S
1034	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C	C	C	-	-	C	-	C	C	S
1043	C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	A	-	-	-	-	-	-	-	S
1068	C	T	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	S
1089	C	-	-	-	-	-	-	-	-	-	-	-	-	A	A	A	A	A	A	-	-	-	-	-	-	-	-	-	-	-	-	NS
1101	G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	A	A	A	A	A	A	A	A	A	A	A	A	NS
1127	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	S
1131	C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	T	-	-	-	-	-	-	-	S
1160	T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	C	C	C	C	C	C	C	C	C	C	C	C	S

Table 1: Variable sites in the ADH gene, from exons 2 and 3 taken from **?**. The first column (pos.) gives the position in the gene, exon 2 begins at position 778 and exon 3 begins at position 942. The second column gives the consensus nucleotide (con.), i.e. the most common base at that position; individuals with nucleotides that match the consensus are marked with a dash. The first columns of sequence (a-l) are from D. melanogaster; the next columns (a-f) give sequences from D. simulans, the final coumns (a-l) from D yakuba. I've dropped the heterozygote sites from D. yakuba..

1 Allele and genotype frequencies

Population genetics emerged from early efforts to reconcile Mendelian genetics with Evolution. Thanks to Mendel and Mendelian genetics (and a lot of prior and subsequent work), we understand that the genome of an individual is formed from two gametes that fused to form a zygote. The genomes of each gamete originate from a parental genome through meiosis, in particular the segregation and recombination of the parental genome's two gametes. In this chapter we will work through how the basics of Mendelian genetics play out at the population level in sexually reproducing diploid organisms. Part of the power of population genetics comes from the fact that the rules of Mendelian genetics are nearly universal across diploids. Therefore, the simple models we build in these notes are firmly grounded in basic Mendelian principals.

Loci and alleles are the basic currency of population genetics–and indeed of genetics. Each individual's genetic makeup is defined in their genome. A *locus* (plural: *loci*) is a specific spot in the genome. A locus may be an entire gene, or a single nucleotide base pair such as A-T. At each locus, there may be multiple genetic variants segregating in the population— these different genetic variants are known as *alleles*. For example, at a particular nucleotide site in the genome, a population may segregate for A-T and G-C base pairs (note that due to the complementary nature of DNA, it will suffice to say the site segregates for A and G variants). If all individuals in the population carry the same allele, we say that the locus is *monomorphic*; at this locus there is no genetic variability in the population. If there are multiple alleles in the population at a locus, we say that this locus is *polymorphic*.

1.1   Allele frequencies

Consider a diploid autosomal locus segregating at two alleles (A_1 and A_2). We'll use these arbitrary labels for our alleles, merely to keep this general. Let N_{11} and N_{12} be the number of A_1A_1 homozygotes and A_1A_2 heterozygotes, respectively. Moreover, let N be the total number of diploid individuals in the population. We can then define the relative frequencies of A_1A_1 and A_1A_2 genotypes as $f_{11} = N_{11}/N$ and $f_{12} = N_{12}/N$, respectively. The frequency of allele A_1 in the population is then given by

$$p = \frac{2N_{11} + N_{12}}{2N} = f_{11} + \frac{1}{2}f_{12}. \tag{1}$$

Note that this follows directly from how we count alleles given individuals' genotypes, and holds independently of Hardy–Weinberg proportions and equilibrium (discussed below). The frequency of the alternate allele (A_2) is then just $q = 1 - p$.

1.2   Hardy–Weinberg proportions

Imagine a population mating at random with respect to genotypes, i.e. no inbreeding, no assortative mating, no population structure, no sex differences in allele frequencies. The frequency of allele A_1 in the population at the time of reproduction is p. An A_1A_1 genotype is made by reaching out into our population and independently drawing two A_1 allele gametes to form a zygote. Therefore, the probability that an individual is an A_1A_1 homozygote is p^2. This probability is also the expected frequency of the A_1A_1 homozygote in the population. The expected frequency of the three possible genotypes is

f_{11}	f_{12}	f_{22}
p^2	$2pq$	q^2

Note that we only need to assume random mating with respect to our alleles in order for these expected frequencies to hold, as long at p is the frequency of the A_1 allele in the population at the time when gametes fuse. See Figure 1 for a nice empirical demonstration of Hardy-Weinberg proportions.

Question 1.   You are investigating a locus with three alleles, A, B, and C, with allele frequencies p_A, p_B, and p_C. What fraction of the population is expected to be homozygotes under Hardy-Weinberg?

1.3   Allele sharing among related individuals and Identity by Descent

All of the individuals in a population are related to each other by a giant pedigree (family tree). For most pairs of individuals in a population these relationships are very distant (i.e. distant cousins), while some individuals will be more closely related (i.e. sibling/first cousins). All individuals of are related to one another by varying levels of relatedness, or
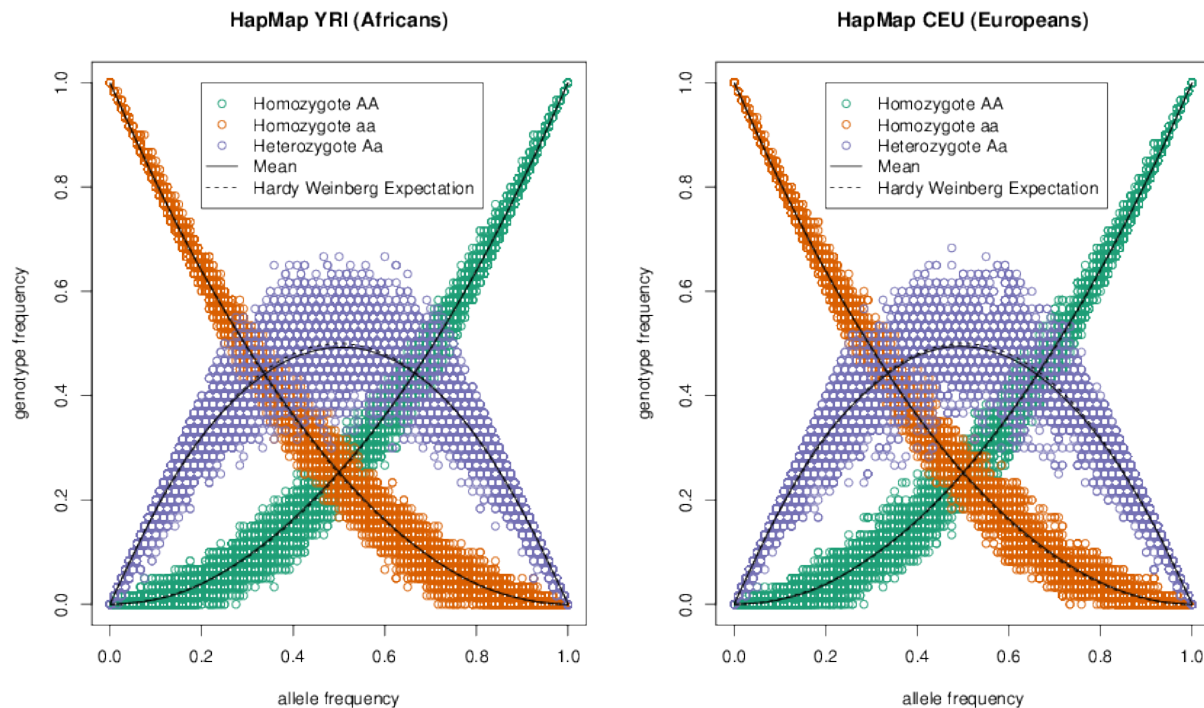
Figure 1: Demonstrating Hardy–Weinberg proportions using 10,000 SNPs from the HapMap CEU European and YRI African populations. Within each of these populations I plot the allele frequency against the frequency of the 3 genotypes. Each SNP is represented by 3 different coloured points. The solid lines show the mean genotype frequency (calculated using a loess smoothing). The dashed line shows the predicted genotype frequency from Hardy–Weinberg equilibrium. I find it really pretty that the analytical predictions work as well as they do. See http://gcbias.org/2011/10/13/population-genetics-course-resources-hardy-weinberg-eq/ here on this plot.

kinship. Related individuals can share alleles that have both descended from the shared common ancestor. To be shared, these alleles must be inherited through all meioses connecting the two individuals (e.g. surviving the 1/2 probability of segregation each meiosis). As closer relatives are separated by fewer meioses, closer relatives share more alleles. In Figure 2 we show the sharing of chromosomal regions between two cousins. As we'll see, many population and quantitative genetic concepts rely on how closely related individuals are, and thus we need some way to quantify the degree of kinship among individuals.

We will define two alleles to be identical by descent (IBD) if they are identical due to a common ancestor in the past few generations. For the moment, we ignore mutation, and we will be more precise about what we mean by 'past few generations' later on. For example, parent and child share exactly one allele identical by descent at a locus, assuming that the
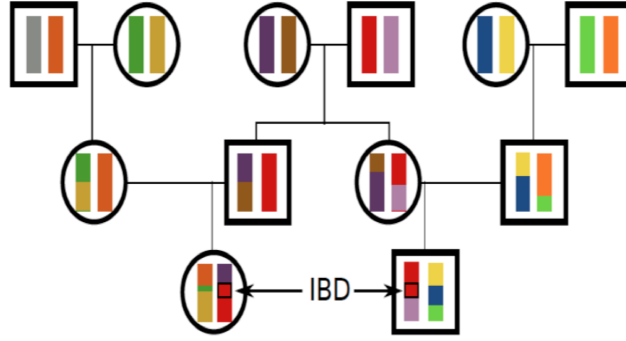
Figure 2: First cousins sharing a stretch of chromosome identical by descent. The different grandparental diploid chromosomes are coloured so we can track them and recombinations between them across the generations. Notice that the identity by descent between the cousins persists for a long stretch of chromosome due to the limited number of generations for recombination.

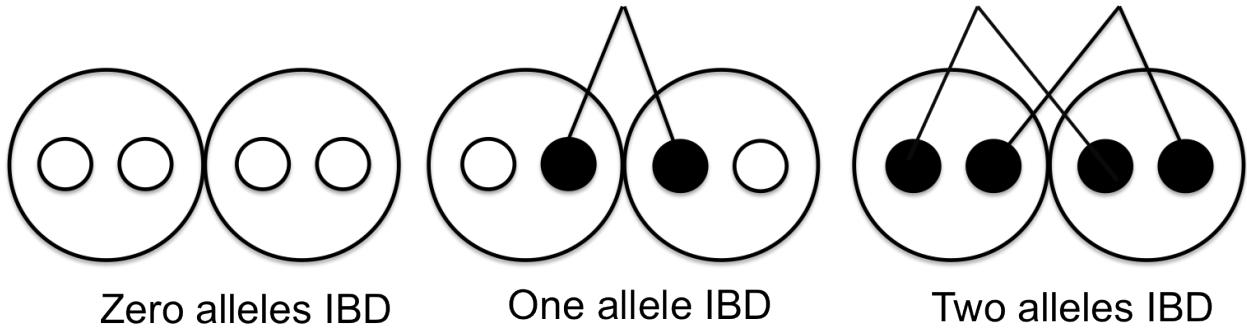Zero alleles IBD   One allele IBD   Two alleles IBD

Figure 3: Three pairs of diploid individuals sharing 0, 1, or 2 alleles IBD where lines show the sharing of alleles by descent (e.g. from a shared ancestor).

two parents of the child are randomly mated individuals from the population. In Figure 4, I show a pedigree demonstrating some configurations of IBD.

One summary of how related two individuals are is the probability that our pair of individuals share 0, 1, or 2 alleles identical by descent (see Figure 3). We denote these probabilities by r_0, r_1, and r_2 respectively. See Table 2 for some examples. We can also interpret these probabilities as genome-wide averages. For example, on average, full-sibs share zero alleles for a quarter of all of their autosomal loci.

One summary of relatedness that will be important is the probability that two alleles picked at random, one from each of the two different individuals i and j, are identical by descent. We call this quantity the *coefficient of kinship* of individuals i and j, and denote it
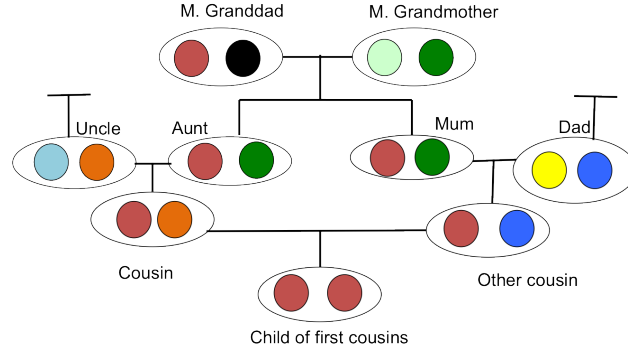
Figure 4: Alleles being transmitted through an inbred pedigree. The mum and the aunt share two alleles identical by descent (IBD). The cousins share one allele IBD. The offspring of first cousins is homozygous by descent at this locus.

Relationship (i,j)*	r_0	r_1	r_2	F_{ij}
parent–child	0	1	0	$1/4$
full siblings	$1/4$	$1/2$	$1/4$	$1/4$
identical (monzygotic) twins	0	0	1	$1/2$
1st cousins	$3/4$	$1/4$	0	$1/16$

Table 2: Probability that two individuals of a given relationship share 0, 1, or 2 alleles identical by descent on the autosomes. *Assuming this is the only relationship the pair of individuals share (above that expected from randomly sampling individuals from the population).

by F_{ij}. It is calculated as

$$F_{ij} = 0 \times r_0 + \frac{1}{4}r_1 + \frac{1}{2}r_2. \tag{2}$$

The coefficient of kinship will appear multiple times, in both our discussion of inbreeding and in the context of phenotypic resemblance between relatives.

Question 2. What are r_0, r_1, and r_2 for $1/2$ sibs? ($1/2$ sibs share one parent but not the other).

Question 3. Consider a biallelic locus where allele 1 is at frequency p, and two individuals who have IBD allele sharing probabilities r_0, r_1, r_2.
What is the overall probability that these two individuals are both homozygous for allele 1?

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f_{11}	f_{12}	f_{22}
$(1-F)p^2 + Fp$	$(1-F)2pq$	$(1-F)q^2 + Fq$

Table 3: **Generalized Hardy–Weinberg**

1.4   Inbreeding

We can define an inbred individual as an individual whose parents are more closely related to each other than two random individuals drawn from some reference population.

When two related individuals produce an offspring, that individual can receive two alleles that are identical by descent, i.e. they can be homozygous by descent (sometimes termed autozygous), due to the fact that they have two copies of an allele through different paths through the pedigree. This increased likelihood of being homozygous relative to an outbred individual is the most obvious effect of inbreeding. It is also the one that will be of most interest to us, as it underlies a lot of our ideas about inbreeding depression and population structure. For example, in Figure 4 our offspring of first cousins is homozygous by descent having received the same IBD allele via two different routes around an inbreeding loop.

As the offspring receives a random allele from each parent (i and j), the probability that those two alleles are identical by descent is equal to the kinship coefficient F_{ij} of the two parents (Eqn. 2). This follows from the fact that the genotype of the offspring is made by sampling an allele at random from each of our parents.

The only way the offspring can be heterozygous (A_1A_2) is if their two alleles at a locus are not IBD (otherwise they would necessarily be homozygous). Therefore, the probability that they are heterozygous is

$$(1-F)2pq, \tag{3}$$

where we have dropped the indices i and j for simplicity. The offspring can be homozygous for the A_1 allele in two different ways. They can have two non-IBD alleles that are not IBD but happen to be of the allelic type A_1, or their two alleles can be IBD, such that they inherited allele A_1 by two different routes from the same ancestor. Thus, the probability that an offspring is homozygous for A_1 is

$$(1-F)p^2 + Fp. \tag{4}$$

Therefore, the frequencies of the three possible genotypes can be written as given in Table 3, which provides a generalization of the Hardy–Weinberg proportions.

Note that the generalized Hardy–Weinberg proportions completely specify the genotype probabilities, as there are two parameters (p and F) and two degrees of freedom (as p and q have to sum to one). Therefore, any combination of genotype frequencies at a biallelic site

can be specified by a combination of p and F.

Question 4.   The frequency of the A_1 allele is p at a biallelic locus. Assume that our population is randomly mating and that the genotype frequencies in the population follow from HW. We select two individuals at random to mate from this population. We then mate the children from this cross. What is the probability that the child from this full sib-mating is homozygous?

1.5   Calculating inbreeding coefficients from data

If the observed heterozygosity in a population is H_O, and we assume that the generalized Hardy–Weinberg proportions hold, we can set H_O equal to f_{12}, and solve Eq. (3) for F to obtain an estimate of the inbreeding coefficient as

$$\hat{F} = 1 - \frac{f_{12}}{2pq} = \frac{2pq - f_{12}}{2pq}. \tag{5}$$

As before, p is the frequency of allele A_1 in the population. This can be rewritten in terms of the observed heterozygosity (H_O) and the heterozygosity expected in the absence of inbreeding, $H_E = 2pq$, as

$$\hat{F} = \frac{H_E - H_O}{H_E} = 1 - \frac{H_O}{H_E}. \tag{6}$$

Hence, $\hat{F}$ quantifies the deviation due to inbreeding of the observed heterozygosity from the one expected under random mating, relative to the latter. If we have multiple loci, we can replace H_O and H_E by their means over loci, $\bar{H}_O$ and $\bar{H}_E$, respectively. Note that, in principle, we could also calculate F for each individual locus first, and then take the average across loci. However, this procedure is more prone to introducing a bias if sample sizes vary across loci, which is not unlikely when we are dealing with real data.

Question 5.   Suppose the following genotype frequencies were observed for at an esterase locus in a population of *Drosophila* (A denotes the "fast" allele and B denotes the "slow" allele):

$$\begin{vmatrix} \text{AA} & \text{AB} & \text{BB} \\ 0.6 & 0.2 & 0.2 \end{vmatrix}.$$

What is the estimate of the inbreeding coefficient at the esterase locus?

1.6   Summarizing population structure

We defined inbreeding as having parents that are more closely related to each other than two individuals drawn at random from some reference population. The question that naturally arises is: Which reference population should we use? While I might not look inbred in

comparison to allele frequencies in the United Kingdom (UK), where I am from, my parents certainly are not two individuals drawn at random from the world-wide population. If we estimated my inbreeding coefficient F using allele frequencies within the UK, it would be close to zero, but would likely be larger if we used world-wide frequencies. This is because there is a somewhat lower level of expected heterozygosity within the UK than in the human population across the world as a whole.

Wright (1943, 1951) developed a set of 'F-statistics' (also called 'fixation indices') that formalize the idea of inbreeding with respect to different levels of population structure. See Figure 5 for a schematic diagram. Wright defined F_{XY} as the correlation between random gametes, drawn from the same level X, relative to level Y. We will return to why F-statistics are statements about correlations between alleles in just a moment. One commonly used F-statistic is F_{IS}, which is the inbreeding coefficient between an individual (I) and the subpopulation (S). Consider a single locus, where in a subpopulation (S) a fraction $H_I = f_{12}$ of individuals are heterozygous. In this subpopulation, let the frequency of allele A_1 be p_S, such that the expected heterozygosity under random mating is $H_S = 2p_S(1 - p_S)$. We will write F_{IS} as

$$F_{IS} = 1 - \frac{H_I}{H_S} = 1 - \frac{f_{12}}{2p_S q_S}, \tag{7}$$

a direct analog of eqn. 5. Hence, F_{IS} is the relative difference between observed and expected heterozygosity due to a deviation from random mating within the subpopulation. We could also compare the observed heterozygosity in individuals (H_I) to that expected in the total population, H_T. If the frequency of allele A_1 in the total population is p_T, then we can write F_{IT} as

$$F_{IT} = 1 - \frac{H_I}{H_T} = 1 - \frac{f_{12}}{2p_T q_T}, \tag{8}$$

which compares heterozygosity in individuals to that expected in the total population. As a simple extension of this, we could imagine comparing the expected heterozygosity in the subpopulation (H_S) to that expected in the total population H_T, via F_{ST}:

$$F_{ST} = 1 - \frac{H_S}{H_T} = 1 - \frac{2p_S q_S}{2p_T q_T}. \tag{9}$$

If the total population contains the subpopulation then $2p_S q_S \leq 2p_T q_T$, and so $F_{IS} \leq F_{IT}$ and $F_{ST} \geq 0$. We can relate the three F-statistics to each other as

$$(1 - F_{IT}) = \frac{H_I}{H_S} \frac{H_S}{H_T} = (1 - F_{IS})(1 - F_{ST}). \tag{10}$$

Hence, the reduction in heterozygosity within individuals compared to that expected in the total population can be decomposed to the reduction in heterozygosity of individuals compared to the subpopulation, and the reduction in heterozygosity from the total population to that in the subpopulation.

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Figure 5: A diagram showing the hierarchical nature of F-statistics. The two solid dots within an individual show the two alleles at a locus for an individual I. We can compare the heterozygosity on individuals (H_I), to that found by randomly drawing alleles from the sub-population ($H_S = 2p_S q_S$), to that found in the total population ($H_T = 2p_T q_T$).

If we want a summary of population structure across multiple subpopulations, we can average H_I and/or H_S across populations, and use a p_T calculated by averaging p_S across subpopulations (or our samples from sub-populations). For example, the average F_{ST} across K subpopulations (sampled with equal effort) is

$$F_{\text{ST}} = 1 - \frac{\bar{H}_S}{H_T}, \tag{11}$$

where $\bar{H}_S = 1/K \sum_{i=1}^{K} H_S^{(i)}$, and $H_S^{(i)} = 2p_i q_i$ is the expected heterozygosity in subpopulation i. Furthermore, if we have multiple sites, we can replace H_I, H_S, and H_T with their averages across loci (as above).

Interpretations of F-statistics Let us now return to Wright's definition of the F-statistics as correlations between random gametes, drawn from the same level X, relative to level Y. Without loss of generality, we may think about X as individuals and S as the subpopulation. Rewriting F_{IS} in terms of the observed homozygote frequencies (f_{11}, f_{22}) and expected homozygosities (p_S^2, q_S^2) we find

$$F_{\text{IS}} = \frac{2p_S q_S - f_{12}}{2p_S q_S} = \frac{f_{11} + f_{22} - p_S^2 - q_S^2}{2p_S q_S}, \tag{12}$$

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using the fact that $p^2 + 2pq + q^2 = 1$, and $f_{12} = 1 - f_{11} - f_{12}$. The form of eqn. (12) reveals that F_{IS} is the covariance between pairs of alleles found in an individual, divided by the expected variance under binomial sampling. Thus, F-statistics can be understood as the correlation between alleles drawn from a population (or an individual) above that expected by chance (i.e. drawing alleles sampled at random from some broader population).

We can also interpret F-statistics as proportions of variance explained by different levels of population structure. To see this, let us think about F_{ST} averaged over K subpopulations, whose frequencies are $p_1, \ldots, p_K$. The frequency in the total population is $p_T = \bar{p} = {}^1\!/\!_K \sum_{i=1}^K p_i$. Then, we can write

$$F_{\text{ST}} = \frac{2\bar{p}\bar{q} - \frac{1}{K}\sum_{i=1}^K 2p_i q_i}{2\bar{p}\bar{q}} = \frac{\left(\frac{1}{K}\sum_{i=1}^K p_i^2 + \frac{1}{K}\sum_{i=1}^K q_i^2\right) - \bar{p}^2 - \bar{q}^2}{2\bar{p}\bar{q}} = \frac{\text{Var}(p_i)}{\text{Var}(\bar{p})}, \qquad (13)$$

which shows that F_{ST} is the proportion of the variance explained by the subpopulation labels.

1.7 Other approaches to population structure

There is a broad spectrum of methods to describe patterns of population structure in population genetic datasets. We'll briefly discuss two broad-classes of methods that appear often in the literature: assignment methods and principal components analysis.

1.7.1 Assignment Methods

Here we'll describe a simple probabilistic assignment to find the probability that an individual of unknown population comes from one of K predefined populations. For example, there are three broad populations of common chimpanzee (*Pan troglodytes*) in Africa: western, central, and eastern. Imagine that we have a chimpanzee, whose population of origin is unknown (e.g. it's from an illegal private collection). If we have genotyped a set of unlinked markers from a panel of individuals representative of these populations, we can calculate the probability that our chimp comes from each of these populations.

We'll then briefly explain how to extend this idea to cluster a set of individuals into K initially unknown populations. This method is a simplified version of what Bayesian population genetics clustering algorithms such as STRUCTURE and ADMIXTURE do (Pritchard et al. Genetics 2000).

A simple assignment method We have genotype data from unlinked S biallelic loci for K populations. The allele frequency of allele A_1 at locus l in population k is denoted by $p_{k,l}$, so that the allele frequencies in population 1 are $p_{1,1}, \cdots p_{1,L}$ and population 2 are $p_{2,1}, \cdots p_{2,L}$ and so on.

You type a new individual from an unknown population at these L loci. This individual's genotype at locus l is g_l, where g_l denotes the number of copies of allele A_1 this individual carries at this locus ($g_l = 0, 1, 2$).

The probability of this individual's genotype at locus l conditional on coming from population k (i.e. their alleles being a random HW draw from population k) is

$$P(g_l|\text{pop k}) = \mathbb{I}(g_l = 0)(1 - p_{k,l})^2 + \mathbb{I}(g_l = 1)2p_{k,l}(1 - p_{k,l}) + \mathbb{I}(g_l = 2)p_{k,l}^2 \qquad (14)$$

where $\mathbb{I}(g_l = 0)$ is an indicator function which is 1 if $g_l = 0$ and zero otherwise, and likewise for the other indicator functions. This follows simply from HWE.

Assuming that the loci are independent, the probability of individual's genotypes conditional on them coming from population k is

$$P(\text{ind.}|\text{pop k}) = \prod_{l=1}^{S} P(g_l|\text{pop k}) \qquad (15)$$

We wish to know the probability that this new individual comes from population k, i.e. $P(\text{pop k}|\text{ind.})$. We can obtain this through Bayes rule

$$P(\text{pop k}|\text{ind.}) = \frac{P(\text{ind.}|\text{pop k})P(\text{pop k})}{P(\text{ind.})} \qquad (16)$$

where

$$P(\text{ind.}) = \sum_{k=1}^{K} P(\text{ind.}|\text{pop k})P(\text{pop k}) \qquad (17)$$

is the normalizing constant. We interpret $P(\text{pop k})$ as the prior probability of the individual coming from population k, unless we have some other prior knowledge we will assume that the new individual has a equal probability of coming from each population $P(\text{pop k}) = 1/K$.

We interpret

$$P(\text{pop k}|\text{ind.}) \qquad (18)$$

as the posterior probability that our new individual comes from each of our $1, \cdots, K$ populations.

More sophisticated versions of this are now used to allow for hybrids, e.g, we can have a proportion q_k of our individual's genome come from population k and estimate the set of q_k's.

Question 6.

Returning to our chimp example, imagine that we have genotyped a set of individuals from the Western and Eastern populations at two SNPs (we'll ignore the central population to keep things simpler). The frequency of the capital allele at two SNPs (A/a and B/b) is given by

Population	locus A	locus B
Western	0.1	0.85
Eastern	0.95	0.2

A) Our individual, whose origin is unknown, has the genotype AA at the first locus and bb at the second. What is the posterior probability that our individual comes from the Western population versus Eastern chimp population?

B) Lets assume that with probability q_W our individual draws an allele from the Western population and that with probability $q_C = 1 - q_W$ they draw an allele from the Eastern population. What is the probability of our individual's genotype given q_C?

   Optional You could plot this probability as a function of q_W. How does your plot change if our individual is heterozygote at both loci?

Clustering based on assignment methods   While it is great to be able to assign our individuals to particular population, these ideas can be pushed to learn about how best to describe our genotype data in terms of discrete populations without assigning any of our individuals to populations *a priori*. We wish to cluster our individuals into K unknown populations. We begin by assigning our individuals at random to these K populations.

1. Given these assignments we estimate the allele frequencies at all of our loci in each population.

2. Given these allele frequencies we chose to reassign each individual to a population k with a probability given by eqn. (15).

We iterate steps 1 and 2 for many iterations (technically, this approach is known as *Gibbs Sampling*). If the data is sufficiently informative the assignments and allele frequencies will quickly converge on a set of likely population assignments and allele frequencies for these populations.

   To do this in a full Bayesian scheme we need to place priors on the allele frequencies (for example, one could use a beta distribution prior). Technically we are using this is the joint posterior of our allele frequencies and assignments. Programs like STRUCTURE, use this type of algorithm to cluster the individuals in an "unsupervised" manner (i.e. they work out how to assign individuals to unknown set of populations). See Figure 6 for an example of Becquet *et al* using STRUCTURE to determine the population structure of chimpanzees.

1.7.2   Principal components analysis

The use of principal component analysis (PCA) in population genetics was pioneered by Cavalli-Sforza. With large genotyping datasets PCA has made a come back. See Patterson et al 2006, PLoS Genetics and McVean, G. 2010 PLoS Genetics and for recent discussion.

   Consider a dataset consisting of N individuals at S biallelic SNPs. The ith individual's genotype data at locus ℓ takes a value $g_{i,\ell} = 0, 1,$ or 2 (corresponding to the number of copies of allele A_1 an individual carries at this SNP). We can think of this as a $N \times S$ matrix (where usually $N \ll S$).
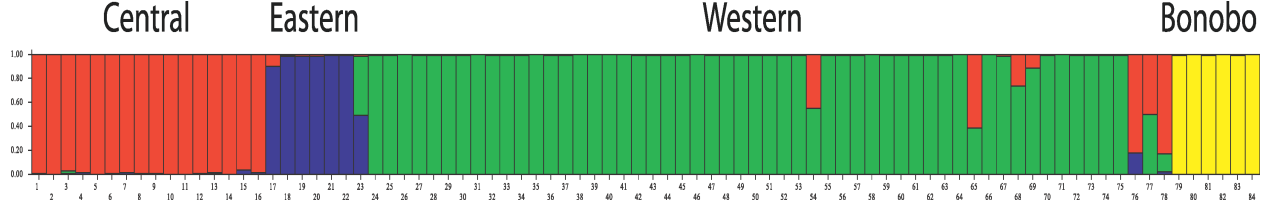
Figure 6: Becquet *et al.* (PLOS Genetics 2007) genotyped 78 common chimpanzee and 6 bonobo at over 300 polymorphic markers (in this case microsatellites, a type of multiallelic marker). They ran STRUCTURE to cluster the individuals using these data into $K = 4$ populations. In the above figure they show each individual as a vertical bar divided into four colours depicting the estimate of the fraction of ancestry that each individual draws from each of the four estimated populations. We can see that these four colours/populations correspond to: Red, central; blue, eastern; green, western; yellow, bonobo. In their caption of this figure they say: *"STRUCTURE Analysis, Blinded to Population Labels, Recapitulates the Reported Population Structure of the Chimpanzees Individuals 76-78 are reported hybrids. Only two individuals with a > 5% proportion of ancestry in more than one inferred cluster are wild born: number 54 and number 17."*

Denoting the sample mean allele frequency at SNP ℓ by p_ℓ it's common to standardize the genotype in the following way

$$\frac{g_{i,\ell} - 2p_\ell}{\sqrt{p_\ell(1 - p_\ell)}} \tag{19}$$

i.e. at each SNP we center the genotypes by subtracting the mean genotype ($2\epsilon_\ell$) and divide through by the expected variance assuming that alleles are sampled binomially from the mean frequency ($\sqrt{p_\ell(1 - p_\ell)}$). Doing this to all of our genotypes we form a data matrix (of dimension $N \times S$). We can then perform principal components analysis of this data matrix to uncover the major axes of genotype variance in our sample. We find the location of each individual on each of the principal component vectors. These PC axes reflect major axes of variation in the data, with the first PC being that which explains most, the second the second most, and so on. Figure 7 shows a PCA from Becquet *et al.* (2007) using the same chimpanzee data as in Figure 6.

It is worth taking a moment to delve further into what we are doing here. There's a number of equivalent ways to thinking about what PCA is doing, one of these is to think that when we do PCA we are building the individual by individual covariance matrix and performing eigenvalue decomposition of this matrix (with the eigenvectors giving the PC). This individual by individual covariance matrix has entries the $(i,\ j)^{th}$ entry given by

$$\sum_{\ell=1}^{S} \frac{(g_{i,\ell} - 2p_\ell)(g_{j,\ell} - 2p_\ell)}{p_\ell(1 - p_\ell)} \tag{20}$$

note that this is the covariance, is very similar to those we encountered in discussing F-statistics as correlations (equation (12)), expect now we are asking about the allelic covariance between two individuals above that expected if they were both drawn from the total

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sample at random (rather than the covariance of alleles within a single individual). So by performing PCA on the data we are learning about the major (orthogonal) axes of the kinship matrix.
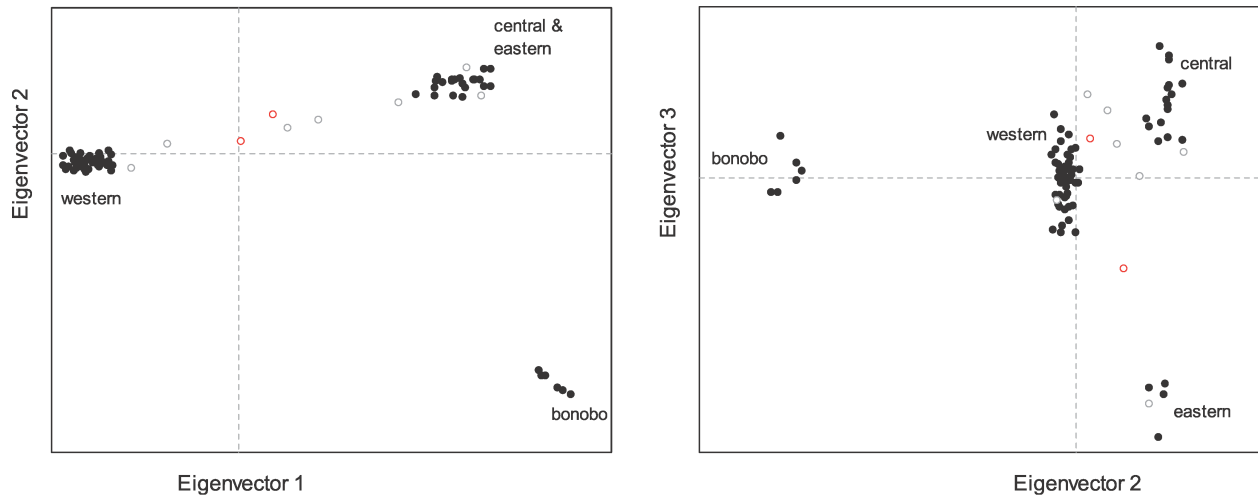
Figure 7: Principal Component Analysis by Becquet *et al.* (PLOS Genetics 2007) using the same chimpanzee data as in Figure 6. Here they plot the location of each individual on the first two principal components (called eigenvectors) in the left panel, and on the second and third principal components (eigenvectors) in the right panel. Becquet *et al.*'s caption reads: *"PCA, Without Using Population Labels, Divides the 84 Chimpanzees into Four Apparently Discontinuous Populations of Western, Central, Eastern, and Bonobo. Plots of eigenvectors 1 versus 2, and eigenvectors 2 versus 3, show clustering into populations, with the expected assignments for the 75 individuals identified as all of one ancestry by STRUCTURE (solid circles). The nine individuals identified by STRUCTURE as hybrids (open circles) are for the most part identified as hybrids by PCA as well. There are two individuals (red open circles) reported as being of a particular population but that in fact appear to be hybrids: number 23, reported as eastern but in fact a western-eastern hybrid, and number 54, a wild-born individual reported as western but in fact a western-central hybrid."*. Note that PC1 mostly separates Western chimps from the others, PC2 separates bonobos from all the three groups of common chimpanzee. While PC3 separates the Eastern chimp samples from the others. Note also how the hybrid individuals (open black and red circles) tend to fall intermediate between groups.

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1.8 Correlations between loci, linkage disequilibrium, and recombination

Up to now we have been interested in correlations between alleles at the same locus, e.g. correlations within individuals (inbreeding) or between individuals (relatedness). We have seen how relatedness between parents affects the extent to which their offspring is inbred. We now turn to correlations between alleles at different loci. To understand correlations between loci we need to understand recombination.

Recombination Let us consider a heterozygous individual, containing AB and ab haplotypes. If no recombination occurs between our two loci in this individual, then these two haplotypes will be transmitted intact to the next generation. While if a recombination (i.e. an odd number of crossing over events) occurs between the two parental haplotypes, then $1/2$ the time the child receives a Ab haplotype and $1/2$ the time the child receives a aB haplotype. Effectively, recombination breaks up the association between loci. We'll define the recombination fraction (r) to be the probability of an odd number of crossing over events between our loci. In practice we'll often be interested in relatively short regions such that recombination is relatively rare, and so we might think that $r = r_{BP}L \ll 1$, where r_{BP} is the average recombination rate per base pair (typically $\sim 10^{-8}$) and L is the number of base pairs separating our two loci.

Linkage disequilibrium The (horrible) phrase linkage disequilibrium (LD) refers to the statistical non-independence (i.e. a correlation) of alleles in a population at different loci. Our two biallelic loci, which segregate alleles A/a and B/b, have allele frequencies of p_A and p_B respectively. The frequency of the two locus haplotype is p_{AB}, and likewise for our other three combinations. If our loci were statistically independent then $p_{AB} = p_A p_B$, otherwise $p_{AB} \neq p_A p_B$ We can define a covariance between the A and B alleles at our two loci as

$$D_{AB} = p_{AB} - p_A p_B \tag{21}$$

and likewise for our other combinations at our two loci (D_{Ab}, D_{aB}, D_{ab}). Gametes with two similar case alleles (e.g. A and B, or a and b) are known as *coupling* gametes, and those with different case alleles are known as repulsion gametes (e.g. a and B, or A and b). Then, we can think of D as measuring the *excess* of coupling to repulsion gametes. These D statistics are all closely related to each other as $D_{AB} = -D_{Ab}$ and so on. Thus we only need to specify one D_{AB} to know them all, so we'll drop the subscript and just refer to D. Also a handy result is that we can rewrite our haplotype frequency p_{AB} as

$$p_{AB} = p_A p_B + D. \tag{22}$$

If $D = 0$ we'll say the two loci are in linkage equilibrium, while if $D > 0$ or $D < 0$ we'll say that the loci are in linkage disequilibrium (we'll perhaps want to test whether D is statistically different from 0 before making this choice). You should be careful to keep the concepts

of linkage and linkage disequilibrium separate in your mind. Genetic linkage refers to the linkage of multiple loci due to the fact that they are transmitted through meiosis together (most often because the loci are on the same chromosome). Linkage disequilibrium merely refers to the correlation between the alleles at different loci, this may in part be due to the genetic linkage of these loci but does not necessarily imply this (e.g. genetically unlinked loci can be in LD due to population structure).

Another common statistic for summarizing LD is r^2 which we write as

$$r^2 = \frac{D^2}{p_A(1 - p_A)p_B(1 - p_B)} \tag{23}$$

as D is a covariance, and $p_A(1 - p_A)$ is the variance of an allele drawn at random from locus A, r^2 is the squared correlation coefficient. Note that this r in r^2 is NOT the recombination fraction.

Question 7. You genotype 2 bi-allelic loci (A & B) segregating in two mouse subspecies (1 & 2) which mate randomly among themselves, but have not historically interbreed since they speciated. On the basis of previous work you estimate that the two loci are separated by a recombination fraction of 0.1. The frequencies of haplotypes in each population are:

Pop	p_{AB}	p_{Ab}	p_{aB}	p_{ab}
1	.02	.18	.08	.72
2	.72	.18	.08	.02

A) How much LD is there within populations, i.e. estimate D?

B) If we mixed the two populations together in equal proportions what value would D take before any mating has had the chance to occur?

The decay of LD due to recombination We will now examine what happens to LD over the generations if we only allow recombination to occur in a very large population (i.e. no genetic drift, i.e. the frequencies of our loci follow their expectations). To do so consider the frequency of our AB haplotype in the next generation p'_{AB}. We lose a fraction r of our AB haplotypes to recombination ripping our alleles apart but gain a fraction rp_Ap_B per generation from other haplotypes recombining together to form AB haplotypes. Thus in the next generation

$$p'_{AB} = (1 - r)p_{AB} + rp_Ap_B \tag{24}$$

this last term here is $r(p_{AB} + p_{Ab})(p_{AB} + p_{aB})$, which multiplying this out is the probability of recombination in the different diploid genotypes that could generate a p_{AB} haplotype.

We can then write the change in the frequency of the p_{AB} haplotype as

$$\Delta p_{AB} = p'_{AB} - p_{AB} = -rp_{AB} + rp_A p_B = -rD \tag{25}$$

so recombination will cause a decrease in the frequency of p_{AB} if there is an excess of AB haplotypes within the population ($D > 0$), and an increase if there is a deficit of AB haplotypes within the population ($D < 0$). Our LD in the next generation is $D' = p'_{AB}$, so we can rewrite the above eqn. in terms of the D'

$$D' = (1 - r)D \tag{26}$$

so if the level of LD in generation 0 is D_0 the level t generations later (D_t) is

$$D_t = (1 - r)^t D_0 \tag{27}$$

so recombination is acting to decrease LD, and it does so geometrically at a rate given by $(1 - r)$. If $r \ll 1$ then we can approximate this by an exponential and say that

$$D_t \approx D_0 e^{-rt} \tag{28}$$

Question 8. You find a hybrid population between the two mouse subspecies described in the question above, which appears to be comprised of equal proportions of ancestry from the two subspecies. You estimate LD between the two markers to be 0.0723. Assuming that this hybrid population is large and was formed by a single mixture event, can you estimate how long ago this population formed?

2   Genetic Drift and Neutral Diversity

Various sources of randomness are inherent in evolution. One major source of stochasticity in population genetics is genetic drift. Genetic drift occurs because more or less copies of an allele by chance can be transmitted to the next generation. This can occur because by chance the individuals carrying a particular allele can leave more or less offspring in the next generation. In a sexual population genetic drift also occurs because Mendelian transmission means that only one of the two alleles in an individual, chosen at random at a locus, is transmitted to the offspring.

Genetic drift can play a role in the dynamics of all alleles and populations, but it will play the biggest role for neutral alleles. A neutral polymorphism occurs when the segregating alleles at a polymorphic site have no discernible differences in their effect on fitness. We'll make clear what we mean by discernible later, for the moment think of this as "no effect" on fitness.

2.1   Loss of heterozygosity due to drift.

Genetic drift will, in the absence of new mutations, slowly purge our population of neutral genetic diversity as alleles slowly drift to high or low frequencies and are lost or fixed over time.

Imagine a population of a constant size N diploid individuals, and that we are examining a locus segregating for two alleles that are neutral with respect to each other. This population is randomly mating with respect to the alleles at this locus. See Figures 8 and 9 to see how genetic drift proceeds, by tracking alleles within a small population.

In generation t our current level of heterozygosity is H_t, i.e. the probability that two randomly sampled alleles in generation t are non-identical is H_t. Assuming that the mutation rate is zero (or vanishing small), what is our level of heterozygosity in generation $t+1$?

In the next generation $(t+1)$ we are looking at the alleles in the offspring of generation t. If we randomly sample two alleles in generation $t+1$ which had different parental alleles in generation t then it is just like drawing two random alleles from generation t. So the probability that these two alleles in generation $t+1$, that have different parental alleles in generation t, are non-identical is H_t.

Conversely, if our pair of alleles have the same parental allele in the proceeding generation (i.e. the alleles are identical by descent one generation back) then these two alleles must be identical (as we are not allowing for any mutation).

In a diploid population of size N individuals there are $2N$ alleles. The probability that our two alleles have the same parental allele in the proceeding generation is $1/(2N)$, the probability that they have different parental alleles is is $1 - 1/(2N)$. So by the above argument

Figure 8: Loss of heterozygosity over time, in the absence of new mutations. A diploid population of 5 individuals over the generations, with lines showing transmission. In the first generation every individual is a heterozygote.
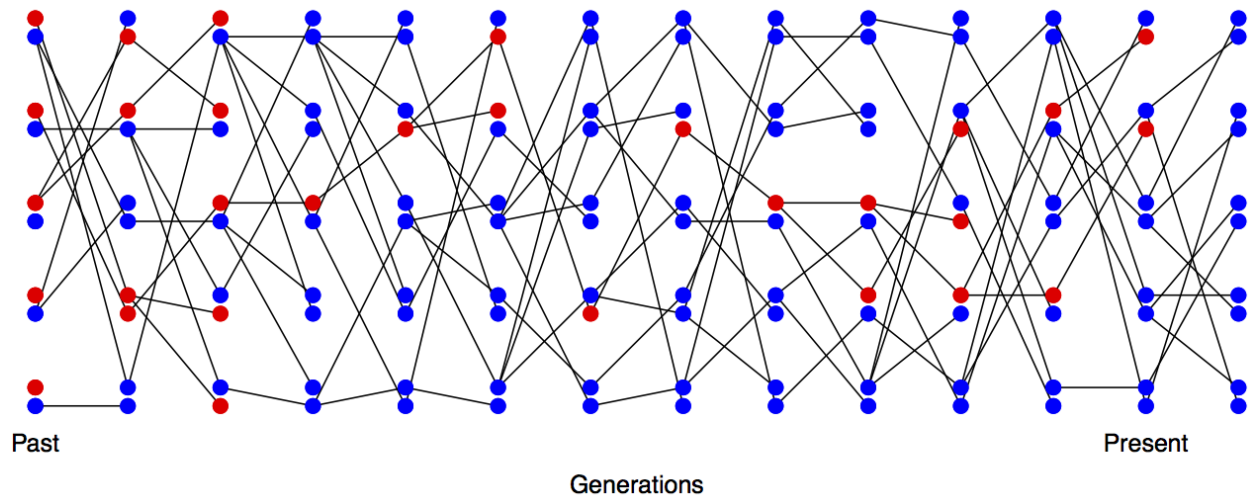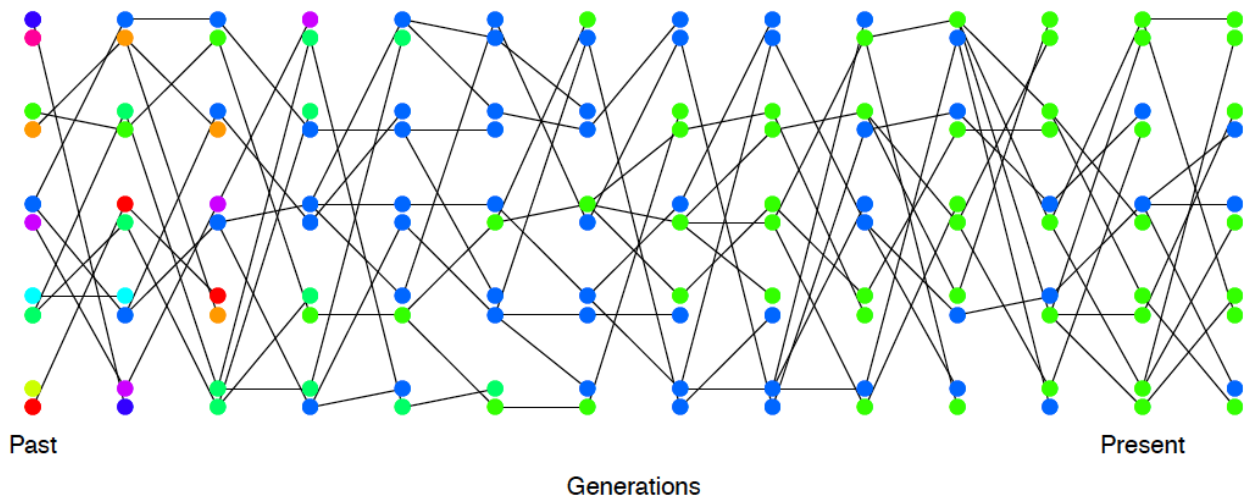

Figure 9: Loss of heterozygosity over time, in the absence of new mutations. A diploid population of 5 individuals. In the first generation I colour every allele a different colour so we can track their descendants.

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the expected heterozygosity in generation $t + 1$ is

$$H_{t+1} = \frac{1}{2N} \times 0 + \left(1 - \frac{1}{2N}\right) H_t \qquad (29)$$

By this argument if the heterozygosity in generation 0 is H_0 our expected heterozygosity in generation t is

$$H_t = \left(1 - \frac{1}{2N}\right)^t H_0 \qquad (30)$$

i.e. the expected heterozygosity with our population is decaying geometrically with each passing generation. If we assume that $1/(2N) \ll 1$ then we can approximate this geometric decay by an exponential decay (see Question 2 below), such that

$$H_t = H_0 \exp\left(-\frac{t}{2N}\right) \qquad (31)$$

i.e. heterozygosity decays exponentially at a rate $1/(2N)$.

Note how this picture of decreasing heterozygosity is in contrast to the consistency of Hardy–Weinberg equilibrium of the previous chapter. However, our Hardy-Weinberg *proportions* hold in forming each new generation. As the offspring genotypes in the next generation $(t+1)$ represent a random draw from the previous generation (t). If the parental frequency is p_t we *expect* a proportion $2p_t(1-p_t)$ of our offspring to be heterozygotes (and HW proportions for our homozygotes). However, because of population size is finite the observed genotype frequencies in the offspring will (likely) not match exactly with our expectations. As our genotype frequencies likely change slightly due to sampling, biologically this reflects random variation in family size and Mendelian segregation, the allele frequency will changed. Therefore, while each generation represents a sample from Hardy-Weinberg proportions based on the generation before, our genotype proportions is not a equilbrium (an unchanging state) as the underyling allele frequency changes over the generations. We'll develop some mathematical models for these allele frequency changes later on. For now we'll simply note that under our simple model of drift (formally the Wright Fisher model) our allele count in the $t + 1^{th}$ generation represents a binomial sample (of size $2N$) from the popuation frequency p_t in the previous generation.

Question 1. You are in charge of maintaining a population of delta smelt in the Sacramento river delta. Using a large set of microsatellites you estimate that the mean level of heterozygosity in this population is 0.005. You set yourself a goal of maintaining a level of heterozygosity of at least 0.0049 for the next two hundred years. Assuming that the smelt have a generation time of 3 years, and that only genetic drift affects these loci. What is the smallest fully outbreeding population that you would need to maintain to meet this goal? (Note that while these numbers are made up, this is similar to the calculations being carried out by conservation biologists).

Question 2. In mathematical population genetics, a commonly used approximation $(1 - x) \approx e^{-x}$ for $x << 1$ (formally this follows from the Taylor series expansion of $\exp(-x)$

ignoring second order terms of x). This is especially useful for approximating a geometric decay process by an exponential decay process, e.g. $(1-x)^t \approx e^{-xt}$. Using R, check how good of an approximation this is for three values of x, $x = 0.5, 0.1, 0.01$. Do this by plotting the geometric decay as points, and the exponential decay as a curve, using different colors for each of these three values. Note that you should have a discrete timescale for the geometric decay (e.g. using t=seq(0, 18)) and a near continuous scale for the exponential decay (e.g. using t=seq(0, 18, length.out=100). Print off your graph and hand it in.

2.2 Levels of diversity maintained by a balance between mutation and drift

Looking backwards in time from one generation to the next, we are going to say that two alleles which have the same parental allele (i.e. find their common ancestor) in the preceding generation have *coalesced*, and refer to this event as a *coalescent event*.

The probability that our pair of randomly sampled alleles have coalesced in the preceding generation is $1/(2N)$, the probability that our pair of alleles fail to coalesce is $1 - 1/(2N)$.

The probability that a mutation changes the identity of the transmitted allele is μ per generation. So the probability of no mutation occurring is $(1 - \mu)$. We'll assume that when a mutation occurs it creates some new allelic type which is not present in the population. This assumption (commonly called the infinitely-many-alleles model) makes the math slightly cleaner, and also is not too bad an assumption biologically. See Figure 10 for a depiction of mutation-drift balance in this model over the generations.

This model let's us calculate when our two alleles last shared a common ancestor and whether these alleles are identical as a result of failing to mutate since this shared ancestor. For example we can work out the probability that our two randomly sampled alleles coalesced 2 generations in the past (i.e. they fail to coalesce in generation 1 and then coalescent in generation 2), and that they are identical as

$$\left(1 - \frac{1}{2N}\right) \frac{1}{2N} (1-\mu)^4 \tag{32}$$

note the power of 4 is because our two alleles have to have failed to mutate through 2 meioses each.

More generally the probability that our alleles coalesce in generation $t+1$ and are identical due to no mutation to either allele in the subsequent generations is

$$P(\text{coal. in t+1 \& no mutations}) = \frac{1}{2N}\left(1 - \frac{1}{2N}\right)^t (1-\mu)^{2(t+1)} \tag{33}$$

to make this slightly easier on ourselves let's further assume that $t \approx t+1$ and so rewrite this as:

$$P(\text{coal. in t+1 \& no mutations}) \approx \frac{1}{2N}\left(1 - \frac{1}{2N}\right)^t (1-\mu)^{2t} \tag{34}$$

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This gives us the approximate probability that two alleles will coalesce in the $(t+1)^{\text{th}}$ generation. In general, we may not know when two alleles may coalesce: they could coalesce in generation $t = 1, t = 2, \ldots$, and so on. Thus, to calculate the probability that two alleles coalesce in *any* generation before mutating, we can write:

$$P(\text{coal. in any generation \& no mutations}) \approx P(\text{coal. in } t = 1 \text{ \& no mutations}) +$$
$$P(\text{coal. in } t = 2 \text{ \& no mutations}) + \ldots$$
$$= \sum_{t=1}^{\infty} P(\text{coal. in } t \text{ generations \& no mutation})$$

which follows from the fact that coalescing in a particular generation is mutually exclusive with coalescing in a different generation and basic probability.

While we could calculate a value for this sum given N and μ, it's difficult to get a sense of what's going on with such a complicated expression. Here, we turn to a common approximation in population genetics (and all applied mathematics), where we assume that $1/(2N) \ll 1$ and $\mu \ll 1$. This allows us to approximate the geometric decay as an exponential decay. Then, the probability two alleles coalesce in generation $t + 1$ and don't mutate can be written as:

$$P(\text{coal. in t+1 \& no mutations}) \approx \frac{1}{2N} \left(1 - \frac{1}{2N} \right)^t (1 - \mu)^{2t} \tag{35}$$

$$\approx \frac{1}{2N} e^{-t/(2N)} e^{-2\mu t} \tag{36}$$

$$= \frac{1}{2N} e^{-t(2\mu + 1/(2N))} \tag{37}$$

and then we simply approximate the summation by an integral, giving us:

$$\frac{1}{2N} \int_0^{\infty} e^{-t(2\mu + 1/(2N))} dt = \frac{1/(2N)}{1/(2N) + 2\mu} = \frac{1}{1 + 4N\mu} \tag{38}$$

Doing so gives us the probability that our two alleles coalesce at some point in time, and do not mutate on either ancestral lineage to their common ancestor. Equivalently, this can be thought about as the probability our two alleles coalesce *before* mutating.

Then, the complementary probability that our pair of alleles are non-identical (or heterozygous) is simply one minus this. This gives the equilibrium heterozygosity in a population at equilibrium between mutation and drift:

$$H = \frac{4N\mu}{1 + 4N\mu} \tag{39}$$

This compound parameter $4N\mu$, the population-scaled mutation rate, will come up a number of times so we'll give it its own name
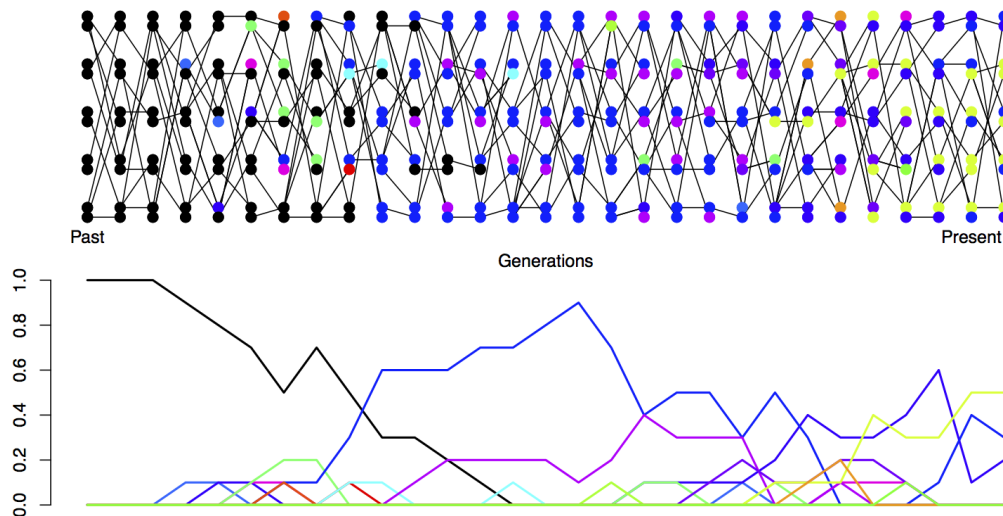
$$\theta = 4N\mu \tag{40}$$

Figure 10: Mutation-drift balance. A diploid population of 5 individuals. In the first genera-
tion everyone has the same allele (black). Each generation the transmitted allele can mutate
and we generate a new colour. In the bottom plot I trace the frequency of alleles in our
population over time.

So all else being equal, species with larger population sizes should have proportionally
higher levels of neutral polymorphism. If you've read to here please email Prof Coop a
picture of JBS Haldane in a striped suit with the title "I'm reading the chapter 2 notes".
(It's well worth googling JBS Haldane and read more about his life, he's a true character
and one of the last great polymaths.)

2.3   The effective population size

In practice populations rarely conform to our assumptions of being constant in size with
low variance in reproduction success. Real populations experience dramatic fluctuations in
size, and there is often high variance in reproductive success. Thus rates of drift in natural
populations are often a lot higher than the census population size would imply.

To cope with this population geneticists often invoke the concept of an effective popula-
tion size (N_e). In many situations (but not all), departures from model assumptions can be
captured by substituting N_e for N.

Specifically the effective population size (N_e) is the population size that would result in
the same rate of drift in an idealized constant population size as that observed in our true
population (following our modeling assumptions).

If population sizes vary rapidly in size, we can (if certain conditions are met) replace
our population size by the harmonic mean population size. Consider a diploid population

of variable size, whose size is N_t t generations into the past. The probability our pairs of alleles have not coalesced by the generation t^{th} is given by

$$\prod_{i=1}^{t} \left(1 - \frac{1}{2N_t}\right) \tag{41}$$

note that this is simply collapses to our original expression $\left(1 - \frac{1}{2N}\right)^t$ if N_i is constant. If $1/(N_i)$ is small, then we can approximate $1 - \frac{1}{2N_i}$ by $\exp(-\frac{1}{2N_i})$. Such that if N_i is never too small

$$\prod_{i=1}^{t} \left(1 - \frac{1}{2N_i}\right) \approx \prod_{i=1}^{t} \exp\left(-\frac{1}{2N_i}\right) = \exp\left(-\sum_{i=1}^{t} \frac{1}{2N_i}\right). \tag{42}$$

In our constant population size case the probability of failing to coalesce is $\exp(-t/(2N))$. So the variable population coalescent probabilities are still of the same form but the exponent has changed. Comparing the exponent in the two cases we see

$$\frac{t}{2N} = \sum_{i=1}^{t} \frac{1}{2N_i} \tag{43}$$

so that if we want a constant effective population size (N_e) that has the same coalescent probability as our variable population we need to set $N = N_e$ and rearrange this to see

$$N_e = \frac{1}{\frac{1}{t} \sum_{i=1}^{t} \frac{1}{N_i}}. \tag{44}$$

this is the harmonic mean of the varying population size. Thus our effective population size, the size of an idealized constant population which matches the rate of genetic drift, is the harmonic mean true population size over time. The harmonic mean is very strongly affected by small values, such that if our population size is one million 99% of the time but drops to a 1000 every hundred or so generations, N_e will be much closer to 1000 than a million. See Figure 11 for a depiction of a repeatedly bottlenecked population losing diversity at a fast rate.

Variance in reproductive success will also affect our effective population size. Even if our population has a large constant size of N individuals, if only small proportion of them get to reproduce then the rate of drift will reflect this much small number of reproducing individuals. See Figure 12 for a depiction of the higher rate of drift in a population where there is high variance in reproductive success.

If only N_M males get to contribute to the next generation and N_F females get to contribute to the next generation. When our two alleles pick an ancestor, 25% of the time our alleles were both in a female ancestor in which case they coalesce with probability $1/(2N_F)$, and 25% of the time they are both in a male ancestor in which case they coalesce with
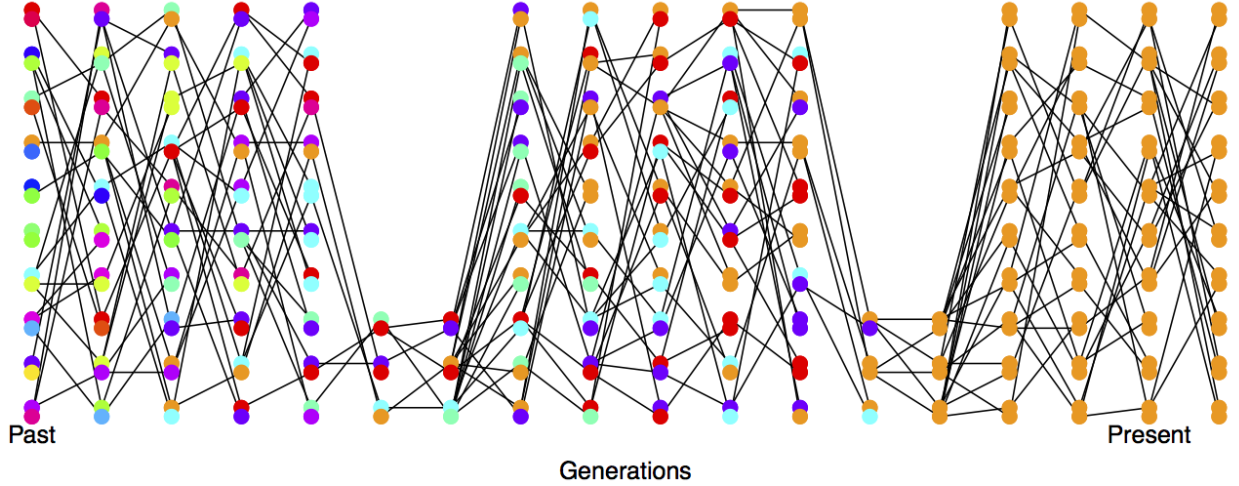
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Figure 11: Loss of heterozygosity over time in a bottlenecking population. A diploid population of 10 individuals, that bottlenecks down to three individuals repeatedly. In the first generation I colour every allele a different colour so we can track their descendants, there are no new mutations.

probability $1/(2N_M)$. The remaining 50% of the time our ancestral lineages are in two individuals are different sexes in a generation so cannot coalescence. Therefore, our probability of coalescence in the preceding generation is

$$\frac{1}{4}\frac{1}{2N_M} + \frac{1}{4}\frac{1}{2N_F} = \frac{1}{8}\frac{N_F + N_M}{N_F N_M} \tag{45}$$

i.e. the rate of coalescence is the harmonic mean of the two sexes population sizes, equating this to $\frac{1}{2N_e}$ we find

$$N_e = \frac{4N_F N_M}{N_F + N_M} \tag{46}$$

Thus if reproductive success is very skewed in one sex (e.g. $N_M \ll N/2$) our effective population size will be much reduced as a result.

2.4 The Coalescent and patterns of neutral diversity

Pairwise Coalescent time distribution and the number of pairwise differences. Thinking back to our calculations we made about the loss of neutral heterozygosity and equilibrium levels of diversity (in Sections 2.1 and 2.2), you'll note that we could first specify what generation a pair of sequences coalesce in, and then calculate some properties of heterozygosity based on that. That's because neutral mutations do not affect the probability that an individual transmits that allele, so don't affect the way in which we can trace
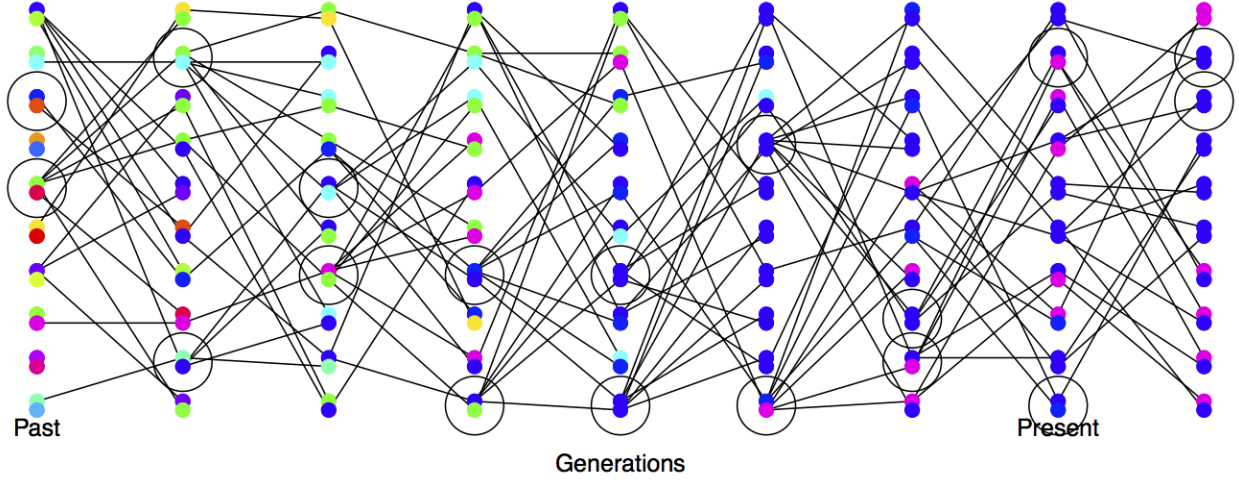
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Figure 12: High variance on reproductive success increases the rate of genetic drift. A diploid population of 10 individuals, where the circled individuals have much higher reproductive success. In the first generation I colour every allele a different colour so we can track their descendants, there are no new mutations.

ancestral lineages back.

As such it will often be helpful to consider the time to the common ancestor of a pair of sequences, and then think of the impact of that on patterns of diversity. See Figure 13 for an example of this. The probability that a pair of alleles have failed to coalesce in t generations and then coalesce in the $t+1$ generation back is

$$\frac{1}{2N}\left(1-\frac{1}{2N}\right)^t \approx \frac{1}{2N}e^{-t/(2N)} \tag{47}$$

thus the coalescent time of a pair of sequences (T_2) is approximately exponentially distributed with a rate $1/(2N)$. We'll denote that by saying that $T_2 \sim \text{Exp}\left(1/(2N)\right)$. The mean coalescent time of a pair of a pair of alleles is $2N$ generations

Conditional on a pair of alleles coalescing t generations ago there are $2t$ generations in which a mutation could occur. Thus the probability of our pair of alleles are separated by j mutations since they last shared a common ancestor is

$$P(j|T_2 = t) = \binom{2t}{j}\mu^j(1-\mu)^{2t-j} \tag{48}$$

i.e. mutations happen in j generations, and do not happen in $2t - j$ generations (with $\binom{2t}{j}$ ways this can possibly happen). Assuming that $\mu \ll 1$, and that $2t - j \approx 2t$ then we can

Generations

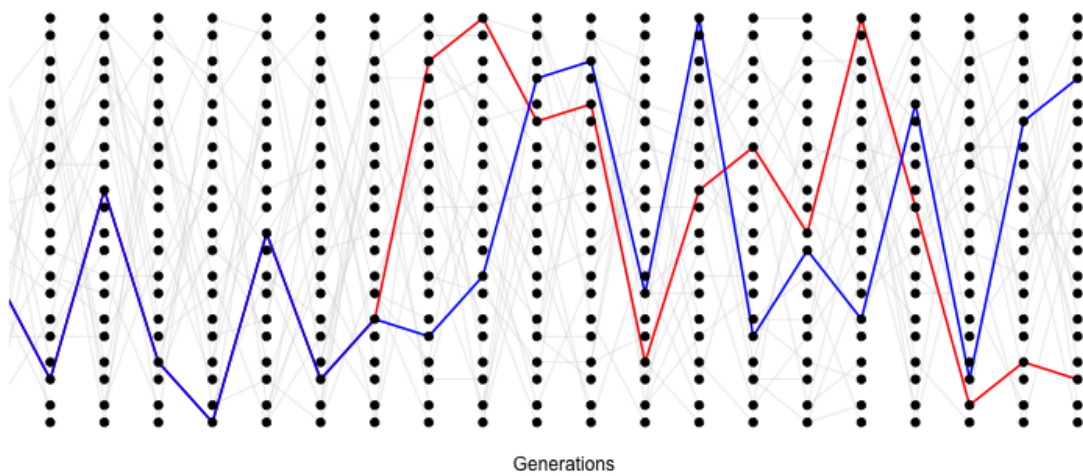Figure 13: A simple simulation of the coalescent process. The simulation consists of a diploid population of 10 individuals (20 alleles). In each generation, each individual is equally likely to be the parent of an offspring (and the allele transmitted is indicated by a light grey line). We track a pair of alleles, chosen in the present day, back 14 generations untill they find a common ancestor.

approximate the probability that we have j mutations as a Poisson distribution

$$P(j|T_2 = t) = \frac{(2\mu t)^j e^{-2\mu t}}{j!} \tag{49}$$

i.e. a Poisson with mean $2\mu t$.

As our expected coalescent time is $2N$ generations (which follows from the expected value of exponential distributions), the expected number of mutations separating two alleles drawn at random from the population is

$$\begin{aligned}\mathbb{E}(j) &= 2\mu\mathbb{E}(t) \\ &= 4N\mu \\ &= \theta\end{aligned} \tag{50}$$

We'll assume that mutations never happen at the same site twice, i.e. no multiple hits, such that we get to see all of the mutation events that separate our pair of sequences (we'll call this the infinitely-many-sites assumption, which should be fine if $N\mu_{BP} \ll 1$, where μ_{BP} is the mutation rate per base pair). Thus the number of mutations between a pair of sites is the observed number of differences between a pair of sequences.

We'll denote the observed number of pairwise differences at putatively neutral sites separating a pair of sequences as π (we usually average this over a number of pairs of sequences for a region). So we can estimate of θ from π, $\widehat{\theta}_\pi$ by setting $\widehat{\theta}_\pi = \pi$. If we have an independent estimate of μ, then from setting $\pi = \widehat{\theta}_\pi = 4N\mu$ we can obtain an estimate of the population size N that is consistent with our levels of neutral polymorphism.

Question 3. Robinson et al. (Current Biology 2016) report π for sample from populations of the California mainland gray fox and the San Nicolas Channel Island fox to be 0.0012 and 0.000014 respectively.
A) How many sites do you expect to differ between two samples sequenced over a 100kb region in each of these populations?
B) Assuming a mutation rate of 2×10^{-8} what effective population size do you estimate for these two populations?
C) Why is the effective population size of the Channel Island fox so low? [Hint: quickly google Channel island foxes to read up on their history, also to see how ridiculously cute they are.]

2.5 The coalescent process of a sample of alleles.

Usually we are not just interested pairs of alleles, or the average pairwise diversity, we are interested in the properties of diversity in samples of a number of alleles drawn from the population. To allow for this instead of just following a pair of lineages back until they coalesce, we can follow the history of a sample of alleles back through the population.
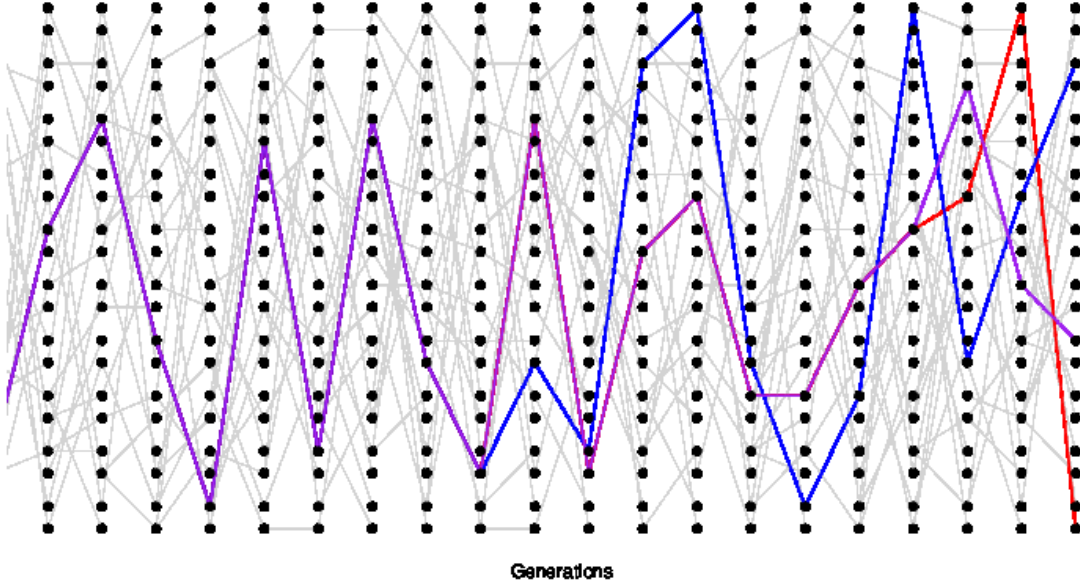
Generations

Figure 14: A simple simulation of the coalescent process for three lineages. We track the ancestry of three modern-day alleles, the first pair (blue and purple) coalesce four generations back their are then two independent lineages we are tracking, this pair then coalesces twelve generations in the past. Note that different random realizations of this process will differ from each other a lot.

Consider first sampling three alleles at random from the population. The probability that all three alleles choose exactly the same ancestral allele one generation back is $1/(2N)^2$. If N is reasonably large then this is a very small probability. As such it is very unlikely that our three alleles coalesce at once, a in a moment we'll see that it is safe to ignore such unlikely events.

The probability that a specific pair of alleles find a common ancestor in the preceding generation is still $1/(2N)$. There are three possible pairs of alleles so the probability that no pair finds a common ancestor is

$$\left(1 - \frac{1}{2N}\right)^3 \approx \left(1 - \frac{3}{2N}\right) \tag{51}$$

in making this approximation we are multiplying out the right hand-side and ignoring terms of $1/N^2$ and higher. See Figure 14 for a random realization of this process.

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More generally when we sample i alleles there are $\binom{i}{2}$ pairs, i.e. $i(i-1)/2$ pairs, thus the probability that no pair of alleles coalesces in the preceding generation is

$$\left(1 - \frac{1}{(2N)}\right)^{\binom{i}{2}} \approx \left(1 - \frac{\binom{i}{2}}{2N}\right) \tag{52}$$

while the probability of any pair coalescing is $\approx \frac{\binom{i}{2}}{2N}$.

We can ignore the possibility of more than pairs of alleles (e.g. tripletons) simultaneously coalescing at once as terms of $1/N^2$ and higher can be ignored as they are vanishingly rare. Obviously there are in reasonable sample sizes there are many more triples ($\binom{i}{3}$), and higher order combinations, than pairs ($\binom{i}{2}$) but if $i \ll N$ then we are safe to ignore these terms.

When there are i alleles the probability that we wait until the $t+1$ generation before any pair of alleles coalesce is

$$\frac{\binom{i}{2}}{2N}\left(1 - \frac{\binom{i}{2}}{2N}\right)^t \approx \frac{\binom{i}{2}}{2N}\exp\left(-\frac{\binom{i}{2}}{2N}t\right) \tag{53}$$

thus the waiting time T_i to the first coalescent event in a sample of i alleles is exponentially distributed with rate $\frac{\binom{i}{2}}{2N}$, i.e. $T_i \sim \mathrm{Exp}\left(\binom{i}{2}/2N\right)$. The mean waiting time till any of pair within our sample to coalesce is $2N/\binom{i}{2}$.

When a pair of alleles first find a common ancestral allele some number of generations back further into the past we only have to keep track of that common ancestral allele for the pair. Thus when a pair of alleles in our sample of i alleles coalesce, we then switch to having to follow $i-1$ alleles back. Then when a pair of these $i-1$ alleles coalesce, we then have to follow $i-2$ alleles back. This process continues until we coalesce back to a sample of two, and from there to a single most recent common ancestor (MRCA).

To simulate a coalescent genealogy at a locus for a sample of n alleles we therefore simply follow this algorithm

1. Set $i = n$.

2. We simulate a random variable to be the time t_i to the next coalescent event from $t_i \sim \mathrm{Exp}\left(\binom{i}{2}/2N\right)$

3. Choose a pair of alleles to coalesce at random from all possible pairs.

4. Set $i = i - 1$

5. Continue looping of steps 1-3 until $i = 1$ i.e. the most recent common ancestor of the sample is found.

by following this algorithm we are generating realizations of the genealogy of our sample.

We will first consider the time to the most recent common ancestor of the entire sample (T_{MRCA}). This is

$$T_{MRCA} = \sum_{i=n}^{2} T_i \tag{54}$$

generations back. As our coalescent times for different i are independent, the expected time to the most recent common ancestor is

$$\mathbb{E}(T_{MRCA}) = \sum_{i=n}^{2} \mathbb{E}(T_i) = \sum_{i=n}^{2} 2N / \binom{i}{2} \tag{55}$$

using the fact that $\frac{1}{i(i-1)} = \frac{1}{i-1} - \frac{1}{i}$ with a bit of rearrangement we can rewrite this is

$$\mathbb{E}(T_{MRCA}) = 4N \left(1 - \frac{1}{n} \right) \tag{56}$$

so the average T_{MRCA} scales linearly with population size. Interestingly, as we move to larger and larger samples (i.e. $n \gg 1$) the average time to the most recent common ancestor is converging on $4N$. What's happening here is that in large samples our lineages typically coalesce rapidly at the start and very soon coalesce down to a much smaller number of lineages.

The total amount of time in a genealogy   Mutations fall on lineages of the coalescent genealogy. These mutations affect all descendants of this lineage, and under the infinitely-many-sites assumption, create a new segregating site for each new mutation. The mutation process is a *Poisson process*, and the longer a particular lineage branch, the more mutations that can accumulate on it. The total number of segregating sites in the genealogy is thus a function of the *total* amount of time in the genealogy of the sample, or the sum of all the genealogy branch lengths, T_{tot}. Since our coalescent genealogies are bifurcating (only two lineages coalesce at once), our total amount of time in the genealogy is:

$$T_{tot} = \sum_{i=n}^{2} i T_i \tag{57}$$

as when there are i lineages each contributes a time T_i to the total time. Taking the expectation of the total time in the genealogy

$$\mathbb{E}(T_{tot}) = \sum_{i=n}^{2} i \frac{2N}{\binom{i}{2}} = \sum_{i=n}^{2} \frac{4N}{i-1} = \sum_{i=n-1}^{1} \frac{4N}{i} \tag{58}$$

so our expected total amount of time in the genealogy scales linearly with our population size. Our expected total amount of time is also increasing with sample size but is doing so

very slowly. To see this more carefully we can see that for large n

$$\mathbb{E}(T_{tot}) = \sum_{i=n-1}^{1} \frac{4N}{i} \approx 4N \int_{1}^{n} \frac{1}{i} di = 4N \log(n-1) \tag{59}$$

here we are approximating our sum by an integral, which will work for large n. So our expected total amount of time in the genealogy is growing with n but it is doing so very slowly. This again follows from the fact that in large samples the initial coalescence usually happens very rapidly, so that extra samples adds little to the total amount of time in the tree.

We saw above that the number of mutational differences between a pair of alleles that coalescence T_2 generations ago was Poisson with a mean of $2\mu T_2$. A mutation that occurs on any branch of our genealogy will cause a segregating polymorphism in the sample (making our infinitely-many-sites assumption). Thus if the total time in the genealogy is T_{tot} there is T_{tot} generations for mutations. So the total number of mutations segregating in our sample (S) is Poisson with mean μT_{tot}. Thus the expected number of segregating in history a sample of size n is

$$\mathbb{E}(S) = \mu \mathbb{E}(T_{tot}) = \sum_{i=n-1}^{1} \frac{4N\mu}{i} = \theta \sum_{i=n-1}^{1} \frac{1}{i} \tag{60}$$

Thus we can use this formula to derive another estimate of the population scaled mutation rate, by setting our observed number of segregating sites in a sample (S) equal to this expectation. We'll call this estimator $\widehat{\theta}_W$

$$\widehat{\theta}_W = \frac{S}{\sum_{i=n-1}^{1} \frac{1}{i}} \tag{61}$$

this estimator was devised by Watterson, hence the W.

2.6 The fixation of neutral alleles

It is very unlikely that a rare neutral allele accidentally drifts up to fixation; more likely, such an allele will be eventually lost from the population. However, populations experience a large and constant influx of rare alleles due to mutation, so even if it is very unlikely that an individual allele fixes within the population, some neutral alleles will fix.

Probability of the eventual fixation of a neutral allele   An allele which reaches fixation within a population is an ancestor to the entire population. In a particular generation there can be only single allele that all other alleles at the locus in later generation can claim as an ancestor. A neutral locus, the actual allele does not affect the number of descendents that the allele has (this follows from the definition of neutrality: neutral alleles don't leave more or less descendents on average). An equivalent way to state this is that the allele labels

Past   Present
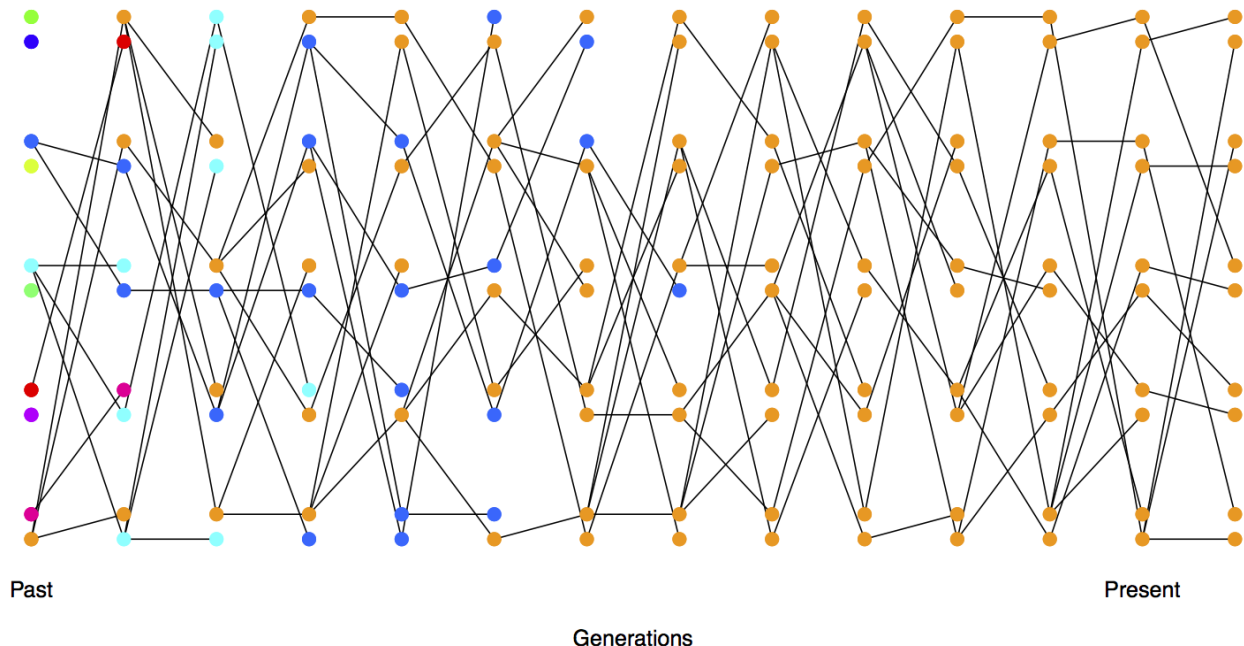
Generations

Figure 15: Each allele initially present in a small diploid population is given a different colour so we can track their descendants over time. By the 9th generation all of the alleles present in the population can trace their ancestry back to the orange allele.

don't affect anything; thus the alleles are *exchangeable*. As a consequence of this, any allele is equally likely to be the ancestor of the entire population. In a diploid population size of size N, there are $2N$ alleles all of which are equally likely to be the ancestor of the entire population at some later time point. So if our allele is present in a single copy, the chance that it is the ancestor to the entire population in some future generation is $1/(2N)$, i.e. the chance our neutral allele is eventually fixed is $1/(2N)$. See Figure 15, our orange allele in the first generation is one of 10 differently coloured alleles, and so has a 1/10 chance of being the ancestor of the entire population at some later time point (as it is by the 9th generation).

More generally if our neutral allele is present in i copies in the population, of $2N$ alleles, the probability that this allele is fixed is $i/(2N)$, i.e. the probability that a neutral allele is eventually fixed is simply given by its frequency (p) in the population. We can also derive this result by letting $Ns \to 0$ in eqn. (182).

An allele newly arisen mutation only becomes a fixed difference if it is lucky enough to be the ancestor of the entire population. As we saw above this occurs with probability $1/(2N)$. How long does is take on average for such an allele to fix within our population? Well in developing equation (56) we've seen that it takes $4N$ generations for a large sample of alleles to all trace their ancestry back to a single most recent common ancestor. Thus it must take roughly $4N$ generations for a neutral allele present in a single copy within the population to

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the ancestor of all alleles within our population. This argument can be made more precise, but in general we would still find that it takes $\approx 4N$ generations for a neutral allele to go from its introduction to fixation with the population.

Rate of substitution of neutral alleles   A substitution between populations that do not exchange gene flow is simply a fixation event within one population. The rate of substitution is therefore the rate at which new alleles fix in the population, so that the long-term substitution rate is the rate at which mutations arise that will eventually become fixed within our population.

Assume that there are two classes of mutational changes that can occur with a region, highly deleterious mutations and neutral mutations. A fraction C of all mutational changes are highly deleterious, and can not possibly contribute to substitution nor polymorphism (i.e. $Ns \gg 1$). The other $1 - C$ fraction of mutations are neutral. If our mutation rate is μ per transmitted allele per generation, then a total of $2N\mu(1-C)$ neutral mutations enter our population each generation.

Each of these neutral mutations has a $1/(2N)$ probability chance of eventually becoming fixed in the population. Therefore, the rate at which neutral mutations arise that eventually become fixed within our population is

$$2N\mu(1-C)\frac{1}{2N} = \mu(1-C) \tag{62}$$

thus the rate of substitution under a model where newly arising alleles are either highly deleterious or neutral, is simply given by the mutation rate towards neutral alleles, i.e. $\mu(1-C)$.

Consider a pair of species have diverged for T generations, i.e. orthologous sequences shared between the species last shared a common ancestor T generations ago. If they have maintained a constant μ over that time, will have accumulated an average of

$$2\mu(1-C)T \tag{63}$$

neutral substitutions. This assumes that T is a lot longer than the time it takes to fix a neutral allele, such that the total number of alleles introduced into the population that will eventually fix is the total number of substitutions. We'll see below that a neutral allele takes on average $4N$ generations to fix from its introduction into the population.

This is a really pretty result as the population size has completely canceled out of the neutral substitution rate. However, there is another way to see this in a more straight forward way. If I look at a sequence in me compared to say a particular chimp, I'm looking at the mutations that have occurred in both of our germlines since they parted ways T generations ago. Since neutral alleles do not alter the probability of their transmission to

the next generation, we are simply looking at the mutations that have occurred in $2T$ generations worth of transmissions. Thus the average number of neutral mutational differences separating our pair of species is simply $2\mu(1-C)T$.

Question 4. For this, and the next question, assume that humans and chimp diverged around 5.5×10^6 years, a generation time 20 years, that the speciation occurred instantaneously in allopatry with no subsequent gene flow, and the ancestral effective population size of the human and chimp common ancestor population was 10,000 individuals.
Nachman and Crowell sequenced 12 pseudogenes in human and chimp found substitutions at 1.3% of sites.
A) What can you say about the mutation rate per site per generation at these genes, and how does it compare to other estimates of human mutation rate?
B) All of the pseudogenes they sequenced are on the autosomes. What would you prediction be for pseudogenes on the X and Y chromosomes, given that there are fewer rounds of replication in the female germline than in the male germline.

2.7   Neutral diversity and population structure

Up to now we have assumed that our alleles that we have modelled in the coalescent setting are drawn from a randomly mating population such that any pair of lineages is equally likely to coalesce with each other. However, when there is population structure this assumption is violated.

We have previously written the measure of population structure F_{ST} as

$$F_{\text{ST}} = \frac{H_T - H_S}{H_T} \tag{64}$$

where H_S is the probability that two alleles sampled at random from a subpopulation differ, and H_T is the probability that two alleles sampled at random from the total population differ.

A simple population split model   Imagine a population of constant size of N_e diploid individuals that τ generations in the past split into two daughter populations (sub-populations) each of size N_e individuals, who do not subsequently exchange migrants. In the current day we sample an equal number of alleles from both subpopulations.
Consider a pair of alleles sampled within one of our sub-populations, they have experienced a population of size N_e and so the probability that they differ is $H_S = \theta/(1+\theta)$ (where $\theta = 4N_e\mu$). The heterozygosity in our total population is a little more tricky to calculate. Assuming that we equally sample both sub-populations, when we draw two alleles from our total sample, 50% of the time they are drawn from the same subpopulation and 50% of the time they are drawn from different subpopulations. Therefore, our total heterozygosity is
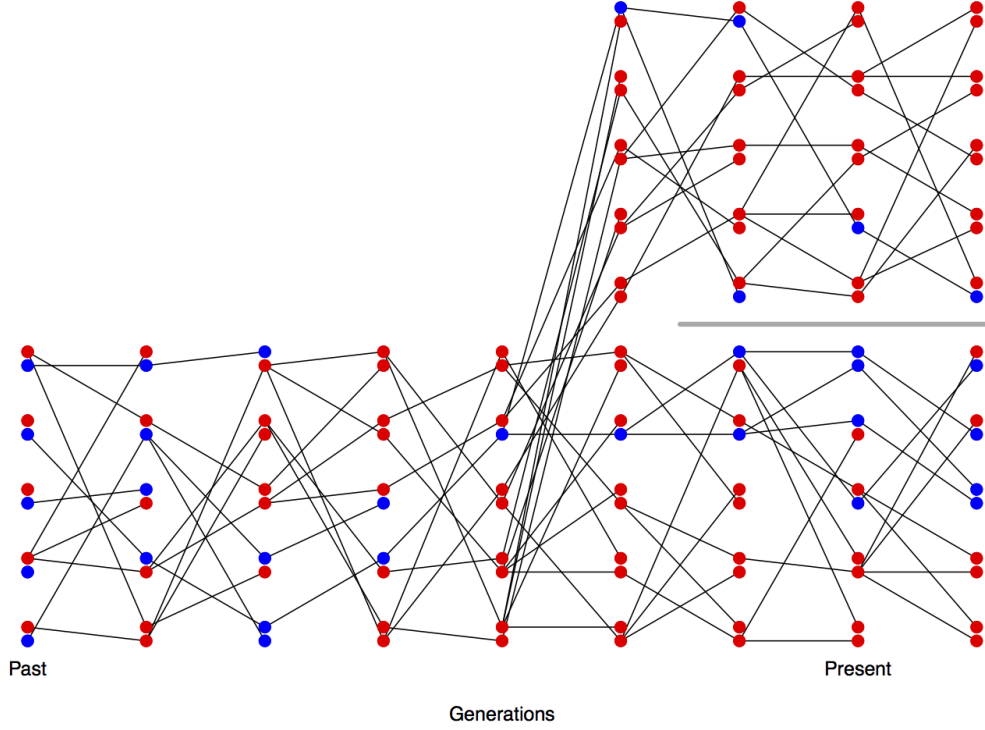
Figure 16: Change in allele frequencies following a population split.

given by

$$H_T = \tfrac{1}{2}H_S + \tfrac{1}{2}H_B \tag{65}$$

where H_B is the probability that a pair of alleles drawn from our two different sub-populations differ from each other. Our pair of alleles can not find a common ancestor with each other for at least τ generations into he past as they are in distinct populations (not connected by migration). The probability that one or other of them mutates in this time is $1 - (1 - \mu)^{2T}$. With probability $(1 - \mu)^{2T}$ neither of our alleles mutate in the T generations back in time before they find themselves back in the combined ancestral population. Conditional on failing to mutate before the combined ancestral population, the probability that they do manage to mutate before coalescing in that population of size N_e is $\theta/(\theta + 1)$. Putting these components together

$$H_B = \left(1 - (1 - \mu)^{2T}\right) + (1 - \mu)^{2T}\frac{\theta}{\theta + 1} \tag{66}$$

We can plug this into our expression for H_T, and then that in turn into F_{ST}.

To understand this better we can make a simple approximation based on our mutation rate being very low, such that $N_e\mu \ll 1$ so $H_S \approx 4N_e\mu$, and that $\mu \ll 1$ and $\mu T \ll 1$. Assuming this, then

$$H_B \approx 2\mu T + 4N_e\mu. \tag{67}$$

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So that

$$F_{\mathrm{ST}} \approx \frac{\mu T}{\mu T + 4 N_e \mu} \tag{68}$$

note that μ cancels out of this. In this simple toy model F_{ST} is increasing because the amount of between population diversity increases with the divergence time of the two populations (initially linearly with T). It does so at a rate give by $T/(4N_e)$ so that differentiation will be higher between populations separated by long divergence times or with small effective population sizes.

Question 5. The gorilla lineage split from the human-chimp lineage $\sim$7 million years ago. Lets assume that this speciation event occurred instantaneously in allopatry with no subsequent gene flow.
A) What is the probability of that gorilla is not an outgroup to human and chimp at a single locus?
B) It has been estimated that the gorilla lineage is not an outgroup at around 30% of autosomal loci. What effective population size would you need to assume to explain this observation? Is that only plausible explanation?
C) The gorilla lineage is an outgroup for large portions of the X chromosome, what is a plausible explanation for this finding?

A simple model of migration between an island and the mainland. We can also use the coalescent to think about patterns of differentiation under a simple model of migration drift equilibrium. Lets consider a small island population that is relatively isolated from a large mainland population, and that both of these populations are constant in size. We'll assume that the expected heterozygosity for a pair of alleles sampled on the mainland is H_M.

Our island has a population size N_I that is very small compared to our mainland population. Each generation some low fraction m of our individuals on the island have migrant parents from the mainland the generation before. Our island may also send migrants back to the mainland, but these are a drop in the ocean compared to the large population size on the mainland and their effect can be ignored.

If we sample an allele on the island back and trace its ancestral lineage backward in time, each generation our ancestral allele have a low probability m of being descended from the mainland in the proceeding generation (if we go far enough the allele eventually has to be descended from an allele on the mainland). The probability that a pair of alleles sampled on the island are descended from a shared recent common ancestral allele on the island, is the probability that our pair of alleles coalesce before either lineage migrates. For example, the probability that our pair of alleles coalesce $t+1$ generations back is

$$\frac{1}{2N_I}(1-m)^{2(t+1)}\left(1 - \frac{1}{2N_I}\right)^t \approx \frac{1}{2N_I}\exp\left(-t\left(\frac{1}{2N_I} + 2m\right)\right), \tag{69}$$

with the approximation following from assuming that $m \ll 1$ & $\frac{1}{(2N_I)} \ll 1$ (note that this is very similar to our derivation of heterozygosity above). The probability that our alleles

coalescence before either one of them migrates off the island, irrespective of the time, is

$$\int_0^\infty \frac{1}{2N_I} \exp\left(-t\left(\frac{1}{2N_I} + 2m\right)\right) dt = \frac{1/(2N_I)}{1/(2N_I) + 2m}. \tag{70}$$

Lets assume that the mutation rate is very low such as it is very unlikely that the pair of alleles mutate before they coalesce on the island. Therefore, the only way that the alleles can be different from each other is if one or other of them migrates to the mainland, which happens with probability

$$1 - \frac{1/(2N_I)}{1/(2N_I) + 2m} \tag{71}$$

Conditional on one or other of our alleles migrating to the mainland, both of our alleles represent independent draws from the mainland and so differ from each other with probability H_M. Therefore, the level of heterozygosity on the island is given by

$$H_I = \left(1 - \frac{1/(2N_I)}{1/(2N_I) + 2m}\right) H_M \tag{72}$$

So the reduction of heterozygosity on the island compared to the mainland is

$$F_{IM} = 1 - \frac{H_I}{H_M} = \frac{1/(2N_I)}{1/(2N_I) + 2m} = \frac{1}{1 + 4N_I m}. \tag{73}$$

The level of inbreeding on the island compared to the mainland will be high in the migration rate is low and the effective population size of the island is low, as allele frequencies on the island are drifting and diversity is not being replenished on the island by migration. The key parameter here is the number individuals on the island replaced by immigrants from the mainland each generation ($N_I m$).

We have framed this as being about the reduction in genetic diversity on the island compared to the mainland. However, if we consider collecting individuals on the island and mainland in proportion to population sizes the total level of heterozygosity would be $H_T = H_M$, as samples from our mainland would greatly outnumber those from our island. Therefore, considering our island our sub-population we have derived another simple model of F_{ST}.

Question 6. You are investigating a small river population of sticklebacks, which receives infrequent migrants from a very large marine population. At a set of (putatively neutral biallelic markers the freshwater population has frequencies:
0.2, 0.7, 0.8
at the same markers the marine population has frequencies:
0.4, 0.5 and 0.7.
From studying patterns of heterozygosity at a large collection of markers, you have estimated the long term effective size of your freshwater population is 2000 individuals.
What is your estimate of the migration rate from the marine populations into the river?

3   The phenotypic resemblance between relatives

We can use our understanding of the sharing of alleles between relatives to understand the phenotypic resemblance between relatives in quantitative phenotypes. We can then use this to understand the evolutionary change in quantitative phenotypes in response to selection.

3.1   A simple additive model of a trait

Let's imagine that the genetic component of the variation in our trait is controlled by L autosomal loci that act in an additive manner. The frequency of allele 1 at locus l is p_l, with each copy of allele 1 at this locus increasing your trait value by a_l above the population mean. The phenotype of an individual, let's call her i, is X_i. Her genotype at SNP l, is $G_{i,l}$. Here $G_{i,l} = 0,\ 1,$ or 2 represents the number of copies of allele 1 she has at this SNP. Her expected phenotype, given her genotype, is then

$$\mathbb{E}(X_i | G_{i,1}, \cdots, G_{i,L}) = \mu + X_{A,i} = \mu + \sum_{l=1}^{L} G_{i,l} a_l \tag{74}$$

where μ is the mean phenotype in our population, and $X_{A,i}$ is the deviation away from the mean phenotype due to her genotype. Now in reality the genetic phenotype is a function of the expression of those alleles in a particular environment. Therefore, we can think of this expected phenotype as being an average across a set of environments that occur in the population.

When we measure our individual's observed phenotype we see

$$X_i = \mu + X_{A,i} + X_{E,i} \tag{75}$$

where X_E is the deviation from the mean phenotype due to the environment. This X_E included the systematic effects of the environment our individual finds herself in and all of the noise during development, growth, and the various random insults that life throws at our individual. If a reasonable number of loci contribute to variation in our trait then we can approximate the distribution of $X_{A,i}$ by a normal distribution due to the central limit theorem (see Figure 17). Thus if we can approximate the distribution of the effect of environmental variation on our trait ($X_{E,i}$) also by a normal distribution, which is reasonable as there are many small environmental effects, then the distribution of phenotypes within the population (X_i) will be normally distributed (see Figure 17).

Note that as this is an additive model we can decompose eqn. 75 into the effects of the two alleles at each locus, in particular we can rewrite it as

$$X_i = \mu + X_{iM} + X_{iP} + X_{iE} \tag{76}$$
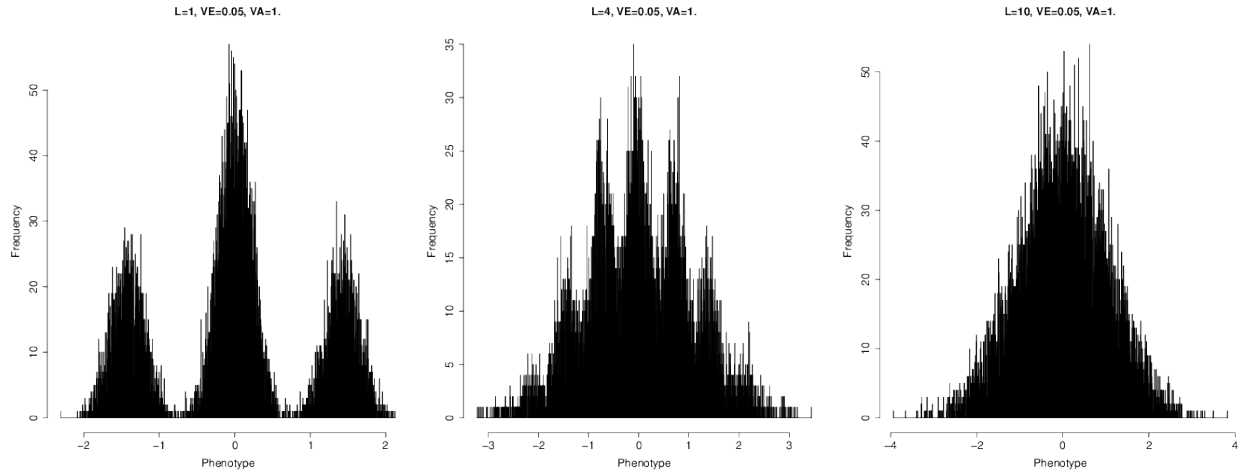
Figure 17: The convergence of the phenotypic distribution to a normal distribution. Each of the three histograms shows the distribution of the phenotype in a large sample, for increasing large numbers of loci (L). I have simulated each individual's phenotype following equation 74 and 75. Specifically I simulate each individuals biallelic genotype at L loci, assuming Hardy-Weinberg proportions and that the allele is at 50% frequency. I assume that all of the alleles have equal effects and combine them additively together. I then add an environmental contribution, which is normally distributed with variance 0.05. Note that in the left two pictures you can see peaks corresponding to different genotypes.

where X_{iM} and X_{iP} are the contribution to the phenotype of the allele that our individual received from her mother (maternal alleles) and father (paternal alleles) respectively. This will come in handy in just a moment when we start thinking about the phenotype covariance of relatives.

Now obviously this model seems silly at first sight as alleles don't only act in an additive manner, as they interact with alleles at the same loci (dominance) and at different loci (epistasis). Later we'll relax this assumption, however, we'll find that if we are interested in evolutionary change over short time-scales it is actually only the "additive component" of genetic variation that will (usually) concern us. We will define this more formally later on, but for the moment we can offer the intuition that parents only get to pass on a single allele at each locus on to the next generation. As such, it is the effect of these transmitted alleles, averaged over possible matings, that is an individual's average contribution to the next generation (i.e. the additive effect of the alleles that their genotype consists of).

3.2 Additive genetic variance and heritability

As we are talking about an additive genetic model we'll talk about the additive genetic variance (V_A), the variance due to the additive effects of segregating genetic variation. This is a subset of the total genetic variance if we allow for non-additive effects.

The variance of our phenotype across individuals (V) can write this as

$$V = Var(X_A) + Var(X_E) = V_A + V_E \tag{77}$$

in writing this we are assuming that there is no covariance between $X_{G,i}$ and $X_{E,i}$ i.e. there is no covariance between genotype and environment.

Our additive genetic variance can be written as

$$V_A = \sum_{l=1}^{L} Var(G_{i,l} a_l) \tag{78}$$

where $Var(G_{i,l} a_l)$ is the contribution to the additive variance among individuals of the l locus. Assuming random mating we can write our additive genetic variance as

$$V_A = \sum_{l=1}^{L} a_l^2 2p_l(1 - p_l) \tag{79}$$

where the $2p_l(1 - p_l)$ term follows the binomial sampling of two alleles per individual at each locus.

The narrow sense heritability We would like a way to think about what proportion of the variation in our phenotype across individuals is due to genetic differences as opposed to environmental differences. Such a quantity will be key in helping us think about the evolution of phenotypes. For example, if variation in our phenotype had no genetic basis then no matter how much selection changes the mean phenotype within a generation the trait will not change over generations.

We'll call the proportion of the variance that is genetic the heritability, and denote it by h^2. We can then write this as

$$h^2 = \frac{Var(X_A)}{V} = \frac{V_A}{V} \tag{80}$$

remember that we thinking about a trait where all of the alleles act in a perfectly additive manner. In this case our heritability h^2 is referred to as the narrow sense heritability, the proportion of the variance explained by the additive effect of our loci. When we allow dominance and epistasis into our model we'll also have to define the broad sense heritability (the total proportion of the phenotypic variance attributable to genetic variation).

The narrow sense heritability of a trait is a useful quantity, indeed we'll see shortly that it is exactly what we need to understand the evolutionary response to selection on a quantitative phenotype. We can calculate the narrow sense heritability by using the resemblance between relatives. For example, if our phenotype was totally environmental we should not expect relatives to resemble each other any more than random individuals drawn from the population. Now the obvious caveat here is that relatives also share an environment, so may resemble each other due to shared environmental effects.

3.3   The covariance between relatives

So we'll go ahead and calculate the covariance in phenotype between two individuals (1 and 2) who have a phenotype X_1 and X_2 respectively.

$$Cov(X_1, X_2) = Cov\left((X_{1M} + X_{1P} + X_{1E}), ((X_{2M} + X_{2P} + X_{2E}))\right) \tag{81}$$

We can expand this out in terms of the covariance between the various components in these sums.

To make our task easier we (and most analyses) will assume two things

1. that we can ignore the covariance of the environments between individuals (i.e. $Cov(X_{1E}, X_{2E}) = 0$)

2. that we can ignore the covariance between the environment variation experience by an individual and the genetic variation in another individual (i.e. $Cov(X_{1E}, (X_{2M} + X_{2P})) = 0$).

The failure of these assumptions to hold can severely undermine our estimates of heritability, but we'll return to that later. Moving forward with these assumptions, we can write our phenotypic covariance between our pair of individuals as

$$Cov(X_1, X_2) = Cov((X_{1M}, X_{2M}) + Cov(X_{1M}, X_{2P}) + Cov(X_{1P}, X_{2M}) + Cov(X_{1P}, X_{2P}) \quad (82)$$

This is saying that under our simple additive model we can see the covariance in phenotypes between individuals as the covariance between the allelic effects in our individuals. We can use our results about the sharing of alleles between relatives to obtain these terms. But before we write down the general case lets quickly work through some examples.

The covariance between Identical Twins   Lets first consider the case of a pair of identical twins from two unrelated parents. Our pair of twins share their maternal and paternal allele identical by descent ($X_{1M} = X_{2M}$ and $X_{1P} = X_{2P}$). As their maternal and paternal alleles are not correlated draws from the population, i.e. have no probability of being IBD as we've said the parents are unrelated, the covariance between their effects on the phenotype is zero (i.e. $Cov(X_{1P}, X_{2M}) = Cov(X_{1M}, X_{2P}) = 0$). In that case eqn. 82 is

$$Cov(X_1, X_2) = Cov((X_{1M}, X_{2M}) + Cov(X_{1P}, X_{2P}) = 2Var(X_{1M}) = V_A \quad (83)$$

Now in general identical twins are not going to be super helpful for us in estimating h^2 as under models with non-additive effects identical twins have higher covariance than we'd expect as they resemble each other also because of the dominance effects as they don't just share alleles they share their entire genotype.

The covariance in phenotype between mother and child   . If the mother and father are unrelated individuals (i.e. are two random draws from the population) then the mother and a child share one allele IBD at each locus (i.e. $r_1 = 1$ and $r_0 = r_2 = 0$). Half the time our mother transmits her paternal allele to the child, in which case $X_{P1} = X_{M2}$ and so $Cov(X_{P1}, X_{M2}) = Var(X_{P1})$ and all the other covariances in eqn. 82 zero, and half the time she transmits her maternal allele to the child $Cov(X_{M1}, X_{M2}) = Var(X_{M1})$ and all the other terms zero. By this argument $Cov(X_1, X_2) = \frac{1}{2}Var(X_{M1}) + \frac{1}{2}Var(X_{P1}) = \frac{1}{2}V_A$.

The covariance between general pairs of relatives under an additive model   The two examples make clear that to understand the covariance between phenotypes of relatives we simply need to think about the alleles they share IBD. Consider a pair of relatives (1 and 1) with a probability r_0, r_1, and r_2 of sharing zero, one, or two alleles IBD respectively. When they share zero alleles $Cov((X_{1M} + X_{1P}), (X_{2M} + X_{2P})) = 0$, when they share one allele $Cov((X_{1M} + X_{1P}), (X_{2M} + X_{2P})) = Var(X_{1M}) = \frac{1}{2}V_A$, and when they share two alleles

$Cov((X_{1M} + X_{1P}), (X_{2M} + X_{2P})) = V_A$. Therefore, the general covariance between two relatives is

$$Cov(X_1, X_2) = r_0 \times 0 + r_1 \frac{1}{2} V_A + r_2 V_A = 2F_{1,2} V_A \tag{84}$$

So under a simple additive model of the genetic basis of a phenotype to measure the narrow sense heritability we need to measure the covariance between a set of pairs of relatives (assuming that we can remove the effect of shared environmental noise). From the covariance between relatives we can calculate V_A, we can then divide this by the total phenotypic variance to get h^2.

Question 1. **A)** In polygynous blackbird populations (i.e. males mate with several females), paternal half-sibs can be identified. Suppose that the covariance of tarsus lengths among half-sibs is 0.25 cm^2 and that the total phenotypic variance is 4 cm^2. Use these data to estimate h^2 for tarsus length in this population.

B) Why might paternal half-sibs be preferable for measuring heritability than maternal half-sibs?

Another way that we can estimate the narrow sense heritability is through the regression of child's phenotype on the parental mid-point phenotype. The parental mid-point phenotype is simple the average of the mum and dad's phenotype. Denoting the child's phenotype by X_{kid} and mid-point phenotype by X_{mid} so that if we take the regression $X_{kid} \sim X_{mid}$ this regression has slope $\beta = Cov(X_{kid}, X_{mid})/Var(X_{mid})$. The covariance of $Cov(X_{kid}, X_{mid}) = \frac{1}{2} V_A$, and $Var(X_{mid}) = \frac{1}{2} V$ as by taking the average of the parents we have halved the variance, such that the slope of the regression is

$$\beta_{mid,kid} = \frac{Cov(X_{kid}, X_{mid})}{Var(X_{mid})} = \frac{V_A}{V} = h^2 \tag{85}$$

i.e. the regression of the child's phenotype on the parental midpoint phenotype is an estimate of the narrow sense heritability. This is a common way to estimate heritability, although it doesn't bypass the need to control for environmental correlations between relatives.

Our regression allows us to attempt to predict the phenotype of the child given the phenotypes of the parents; how well we can do this depends on the slope. If the slope is close to zero then the parental phenotypes hold no information about the phenotype of the child, while if the slope is close to one then the parental mid-point is a good guess at the child's phenotype.

More formally the expected phenotype of the child given the parental phenotypes is

$$\mathbb{E}(X_{kid}|X_{mum}, X_{dad}) = \mu + \beta_{mid,kid}(X_{mid} - \mu) = \mu + h^2(X_{mid} - \mu) \tag{86}$$
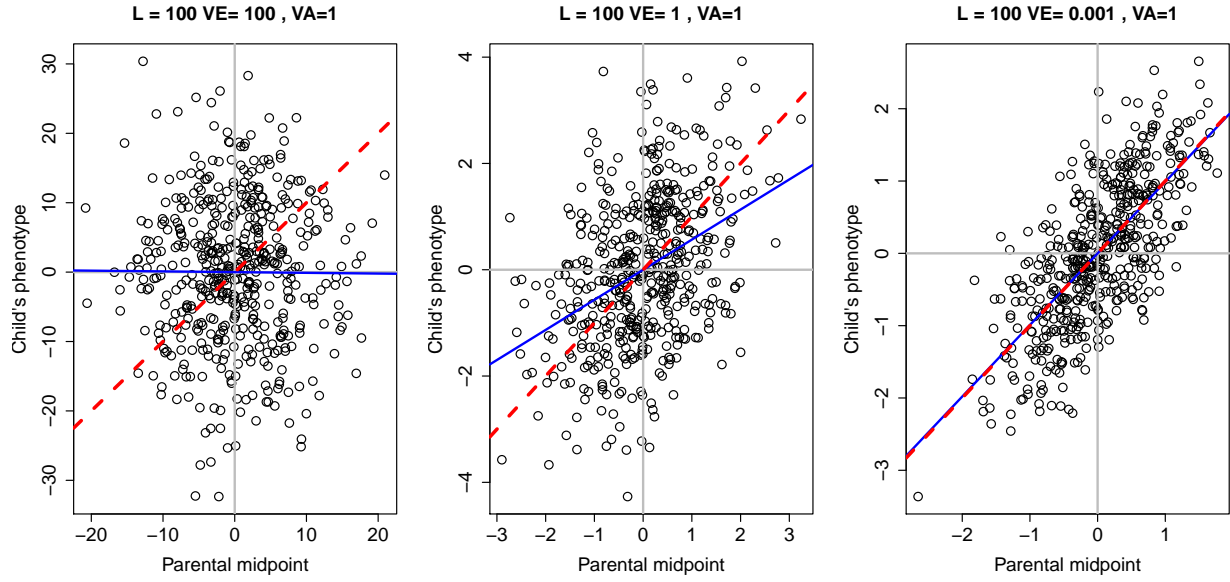
Figure 18: Regression of parental mid-point phenotype on child's phenotype. The three panels show decreasing levels of environmental variance (V_E) holding the additive genetic variance constant ($V_A = 1$). In these figures I simulate 100 loci, as described in the caption of Figure 17. I simulate the genotypes and phenotypes of the two parents, and then simulate the child's genotype following mendelian transmission. The blue line shows $x = y$ the red line shows the best fitting linear regression line.

this follows from the definition of linear regression. So to find the child's predicted phenotype we simply take the mean phenotype and add on the difference between our parental mid-point multiplied by our narrow sense heritability.

Question 2.   Briefly explain Galtons observation of the regression towards mediocrity in light of Mendelian inheritance.

Estimating additive genetic variance across a variety of different relationships. In many natural populations we may have access to individuals of a range of different relationships to each other (through monitoring of the paternity of individuals), but relatively few individuals of a given relationship (e.g. sibs). We can try and use this information as fully as possible in a mixed model framework. Considering equation 75 we can write an individual's phenotype X_i as

$$X_i = \mu + X_{A,i} + e_i \tag{87}$$

where $e_i \sim N(0, V_E)$ and $X_{A,i}$ is normally distributed across individuals with covariance matrix $V_A A$ where the the entries for a pair of individuals i and j are $A_{ij} = 2F_{i,j}$ and $A_{ii} = 1$. Given the matrix A we can estimate V_A. We can also add fixed effects into this model to account for generation effects, additional mixed effects could also be included to account for shared environments between particular individuals (e.g. a shared nest). This is sometimes called the "animal model", and also goes by the name of variance components analysis.

3.4   The response to selection

Evolution by natural selection requires:

1. Variation in a phenotype

2. That survival is non-random with respect to this phenotypic variation.

3. That this variation is heritable.

Points 1 and 2 encapsulate our idea of Natural Selection, but evolution by natural selection will only occur if the 3rd condition is met. It is the heritable nature of variation that couples change within a generation due to natural selection, to change across generations (evolutionary change).

Lets start by thinking about the change within a generation due to directional selection, where selection acts to change the mean phenotype within a generation. For example, a decrease in mean height within a generation, due to taller organisms having a lower chance of surviving to reproduction than shorter organisms. Specifically, we'll denote our mean phenotype at reproduction by μ_S, i.e. after selection has acted, and our mean phenotype before selection acts by μ_{BS}. This second quantity may be hard to measure, as obviously selection acts throughout the life-cycle, so it might be easier to think of this as the mean

phenotype if selection hadn't acted. So the mean phenotype changes within a generation is $\mu_S - \mu_{BS} = S$.

We are interested in predicting the distribution of phenotypes in next generation, in particular we are interested in the mean phenotype in the next generation to understand how directional selection has contributed to evolutionary change. We'll denote the mean phenotype in offspring, i.e. the mean phenotype in the next generation before selection acts, as μ_{NG}. The change across generations we'll call the response to selection R and put this equal to $\mu_{NG} - \mu_{BS}$.

The mean phenotype in the next generation is

$$\mu_{NG} = \mathbb{E}\left(\mathbb{E}(X_{kid}|X_{mum}, X_{dad})\right) \tag{88}$$

where the outer expectation is over the randomly mating of individuals who survive to reproduce. We can use eqn. 86 to obtain an expression for this

$$\mu_{NG} = \mu_{BS} + \beta_{mid,kid}(\mathbb{E}(X_{mid}) - \mu_{BS}) \tag{89}$$

so to obtain μ_{NG} we need to compute $\mathbb{E}(X_{mid})$ the expected mid-point phenotype of pairs of individuals who survive to reproduce. Well this is just the expected phenotype in the individuals who survived to reproduce (μ_S), so

$$\mu_{NG} = \mu_{BS} + h^2(\mu_S - \mu_{BS}) \tag{90}$$

So we can write our response to selection as

$$R = \mu_{NG} - \mu_{BS} = h^2(\mu_S - \mu_{BS}) = h^2 S \tag{91}$$

So our response to selection is proportional to our selection differential, and the constant of proportionality is the narrow sense heritability. This equation is sometimes termed the Breeders equation. It is a statement that the evolutionary change across generations (R) is proportional to the change caused by directional selection within a generation, and the strength of this relationship is determined by the narrow sense heritability.

Using the fact that $h^2 = V_A/V$ we can rewrite this in a different form as

$$R = V_A \frac{S}{V} \tag{92}$$

i.e. our response to selection is the additive genetic variance of our trait (V_A) multiplied by the change within a generation as a fraction of the total phenotypic variance (S/V, sometimes called the the selection gradient β).

If our selection pressure is sustained over many generations we can use our breeders equation to predict the response. If we are willing to assume that our heritability does not

Phenotype distribution before selection, Mean=0, VA=1, VE=1, Taking top 10%

Phenotype distribution after selection, parental mean= 2.474

Phenotype distribution in the children Mean in children = 1.208
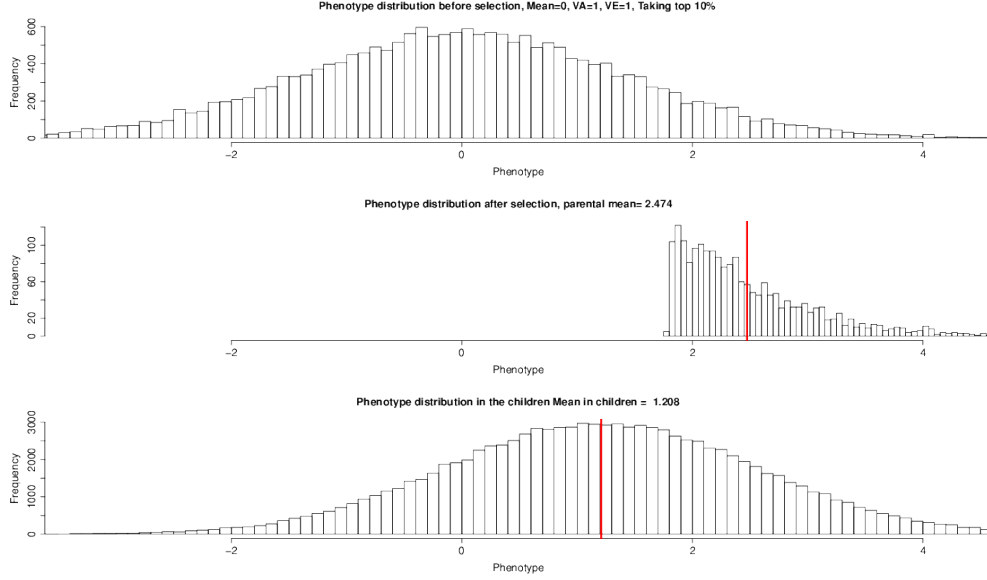
change and we maintain a constant selection gradient, then after n generations our phenotype mean will have shifted

$$nh^2 S \tag{93}$$

i.e. our population will keep up a linear response to selection.

A change in mean phenotype within a generation occurs because of the differential fitness of our organisms. To think more carefully about this change within a generation lets think about a simple fitness model where our phenotype affects the viability of our organisms (i.e. the probability they survive to reproduce). The probability that an individual has a phenotype X before selection is $p(X)$, so that the mean phenotype before selection is

$$\mu_{BS} = \mathbb{E}[X] = \int_{-\infty}^{\infty} xp(x)dx \tag{94}$$

The probability that an organism with a phenotype X survives to reproduce is $w(X)$, and we'll think about this as the fitness of our organism. The probability distribution of phenotypes in those who do survive to reproduce is

$$\mathbb{P}(X|\text{survive}) = \frac{p(x)w(x)}{\int_{-\infty}^{\infty} p(x)w(x)dx}. \tag{95}$$

where the denominator is a normalization constant which ensures that our phenotypic distribution integrates to one. The denominator also has the interpretation of being the mean fitness of the population, which we'll call $\overline{w}$, i.e.

$$\overline{w} = \int_{-\infty}^{\infty} p(x)w(x)dx. \tag{96}$$

Therefore, we can write the mean phenotype in those who survive to reproduce as

$$\mu_S = \frac{1}{\bar{w}} \int_{-\infty}^{\infty} xp(x)w(x)dx \tag{97}$$

If we mean center our population, i.e. set the phenotype before selection to zero, then

$$S = \frac{1}{\bar{w}} \int_{-\infty}^{\infty} xp(x)w(x)dx \tag{98}$$

if $\mu_S = 0$. Inspecting this more closely we can see that S has the form of a covariance between our phenotype X and our fitness $w(X)$ $(Cov(X, w(X)))$. Thus our change in mean phenotype is directly a measure of the covariance of our phenotype and our fitness. Rewriting our breeder's equation using this observation we see

$$R = \frac{V_A}{V}Cov(X, w(X)) \tag{99}$$

we see that the response to selection is due to the fact that our fitness (viability) of our organisms/parents covaries with our phenotype, and that our child's phenotype is correlated with the parent phenotype.

Question 3. A student has been studying barnacle populations and has found the mean height (before selection) to be 10 mm and the variance in height to be 4 mm2. After a stormy season (one generation), the mean of the population in the next generation before selection has increased to 12 mm. In a breeding experiment, the student found the slope of the regression between parental midpoint and child to be 0.2. Assuming the observed change was caused by selection, what was the mean height of the parents that survived the stormy season?

Question 4. A population of red deer were trapped on Jersey (an island off of England) during the last inter-glacial period. From the fossil record we can see that the population rapidly adapted to their new surroundings, presumably due to reduced predation and limited food. Within 6,000 years they evolved from an estimated mean weight of the population of 200kg to an estimated mean weight of 36kg (a 6 fold reduction! True story see: Lister, A.M. Nature 1989). Using a current day population on the mainland you estimate that the generation time of red deer is 5 years and that the narrow sense heritability of the phenotype is 0.5. (Assuming discrete generations).
A) Estimate the mean change per generation in the mean body weight.

B) Estimate the change in mean body weight caused by selection within a generation.

C) What do you have to assume to perform the calculations in B. Assuming we only have fossils from the founding population and the population after 6000 years, should we assume that the calculations accurately reflect what actually occurred within our population?

3.5 Multiple traits.

Traits often covary with each other, due to both environmentally induced effects (e.g. due to the effects of diet on multiple traits) and due to the expression of underlying genetic covariance between traits. In turn this genetic covariance can reflect pleiotropy, a mechanistic effect of an allele on multiple traits (e.g. variants that effect skin pigmentation often effect hair color) or the genetic linkage of loci independently affecting multiple traits. If we are interested in evolution over short time-scales we can (often) ignore the genetic basis of this correlation.

Consider two traits $X_{1,i}$ and $X_{2,i}$ in an indivdual i, these could be say the individual's leg length and nose length. As before we can write these as

$$
\begin{aligned}
X_{1,i} &= \mu_1 + X_{1,A,i} + X_{1,E,i} \\
X_{2,i} &= \mu_2 + X_{2,A,i} + X_{2,E,i}
\end{aligned}
$$

$$(100)$$

As before we can talk about the total phenotypic variance (V_1, V_2), environmental variance $(V_{1,E}$ and $V_{2,E})$, and the additive genetic variance in trait one and two $(V_{1,A}, V_{2,A})$. But now we also have to consider the total covariance $V_{1,2} = Cov(X_1, X_2)$, the environmentally induced covariance between the traits $(V_{E,1,2} = Cov(X_{1,E}, X_{2,E}))$ and the additive genetic covariance $(V_{A,1,2} = Cov(X_{1,A}, X_{2,A}))$ between trait one and two.

We can store these values in a matrices

$$
\mathbf{V} = \left(\begin{array}{cc} V_1 & V_{1,2} \\ V_{1,2} & V_2 \end{array} \right)
$$

$$(101)$$

and

$$
\mathbf{G} = \left(\begin{array}{cc} V_{1,A} & V_{A,1,2} \\ V_{A,1,2} & V_{2,A} \end{array} \right)
$$

$$(102)$$

we can generalize this to an abitrary number of traits.

We can estimate these quantities, in a similar way to before, by studying the covariance in different traits between relatives:

$$
Cov(X_{1,i}, X_{2,j}) = 2F_{i,j} V_{A,1,2}
$$

$$(103)$$

The response of multiple traits to selection, the multivariate breeder's equation. We can generalize these results for multiple traits, to ask how selection on multiple phenotypes plays out over short time intervals. We'll write our change in the mean our multiple phenotypes within a generation as the vector $\mathbf{S}$ and our response across multiple generations as the vector $\mathbf{R}$. These two quantities are related by

$$
\mathbf{R} = \mathbf{G}\mathbf{V}^{-1}\mathbf{S} = \mathbf{G}\beta
$$

$$(104)$$

where $\mathbf{V}$ and $\mathbf{G}$ are our matrices of the variance-covariance of phenotypes and additive genetic values (eqn. (102) (101)) and β is a vector of selection gradients (i.e. the change

within a generation as a fraction of the total phenotypic variance). To make this a bit more intuitive, consider two traits we are writing

$$
\begin{aligned}
R_1 &= V_{A,1}\beta_1 + V_{A,1,2}\beta_2 \\
R_2 &= V_{A,2}\beta_2 + V_{A,1,2}\beta_1
\end{aligned}
$$

$$(105)$$

where the 1 and 2 index our two different traits. This is a statement that our response in any one phenotype is modified by selection on other traits that covary with that trait. This offers a good way to think about how genetic trade offs play out over evolution over short time-scales.

3.6 Non-additive variation.

Up to now we've assumed that our alleles contribute to our phenotype in an additive fashion. However, that does not have to be the case as there may be non-additivity among the alleles present at a locus (dominance) or among alleles at different loci (epistasis). We can accommodate these complications into our models. We do this by partitioning our total genetic variance into independent variance components.

Consider autosomal biallelic locus ℓ, with frequency p for allele 1, and genotypes 0, 1, and 2 corresponding to how many copies of allele 1 individuals carry. We'll denote the mean phenotype of an individual with genotype 0, 1, and 2 are $\overline{X}_{\ell,0}$, $\overline{X}_{\ell,1}$, $\overline{X}_{\ell,2}$ respectively. Here this mean is taken over all the environments and genetic backgrounds the alleles are present on. We'll mean center (MC) these phenotypic values setting $\overline{X}'_{\ell,0} = \overline{X}_{\ell,0} - \mu$, and likewise for the other genotypes.

To illustrate the approach we'll plot two different cases of dominance relationship in Figure 3.6. In the first row of Figure 3.6 we show the relationship between genotype and MC phenotype under an additive model, and in the second row under a model where the allele 1 is dominant, such that the phenotype of the genotype of the heterozyote is the same as the 11 homozygote. The area of each circle is proportion to the fraction of the population in each genotypic class (p^2, $2pq$, and q^2).

The first variance component is the variance due to the additive contribution of each allele (V_A). We can think about the average (marginal) MC phenotype for an allele 1 as the average of the MC phenotype for heterozgotes and 11 homozygotes weighted by the probability that an allele 1 in present in these genotypes. These marginal MC phenotypes for allele 1 and 2 are given by

$$a_{\ell,1} = p\overline{X}'_{\ell,2} + q\overline{X}'_{\ell,1}, \quad a_{\ell,2} = p\overline{X}'_{\ell,1} + q\overline{X}'_{\ell,0} \tag{106}$$

the marginal value for allele 1, $a_{\ell,1}$, follows from the fact that (assuming HW) an allele 1 will be paired with another allele 1 with probability p, resulting in a genotype 11 (with phenotypic deviation $\overline{X}'_{\ell,2}$) and will be paired with an allele 2 with probability q in a heterozygote (with phenotypic deviation $\overline{X}'_{\ell,1}$). A similar argument can be made for $a_{\ell,2}$.

The additive MC genetic values (breeding values) of genotype 0, 1, and 2 are then

genotype: 0,   1,   2.
additive genetic value: $a_{\ell,2} + a_{\ell,2}$, $a_{\ell,1} + a_{\ell,2}$, $a_{\ell,1} + a_{\ell,1}$

Here we are simply adding up the additive contributions of the alleles present in each genotype. These are the genotypic values of the trait that would result taking only the additive component of the genotype. They also have the interpretation as being the mean phenotype of each genotypes' offspring averaged over across all possible matings to other individuals in the population (assuming individuals mate at random).

The additive genetic values of the genotypes are shown as red dots in Figure 3.6. Note that the additive values of the genotypes line up with the observed MC phenotypic means in
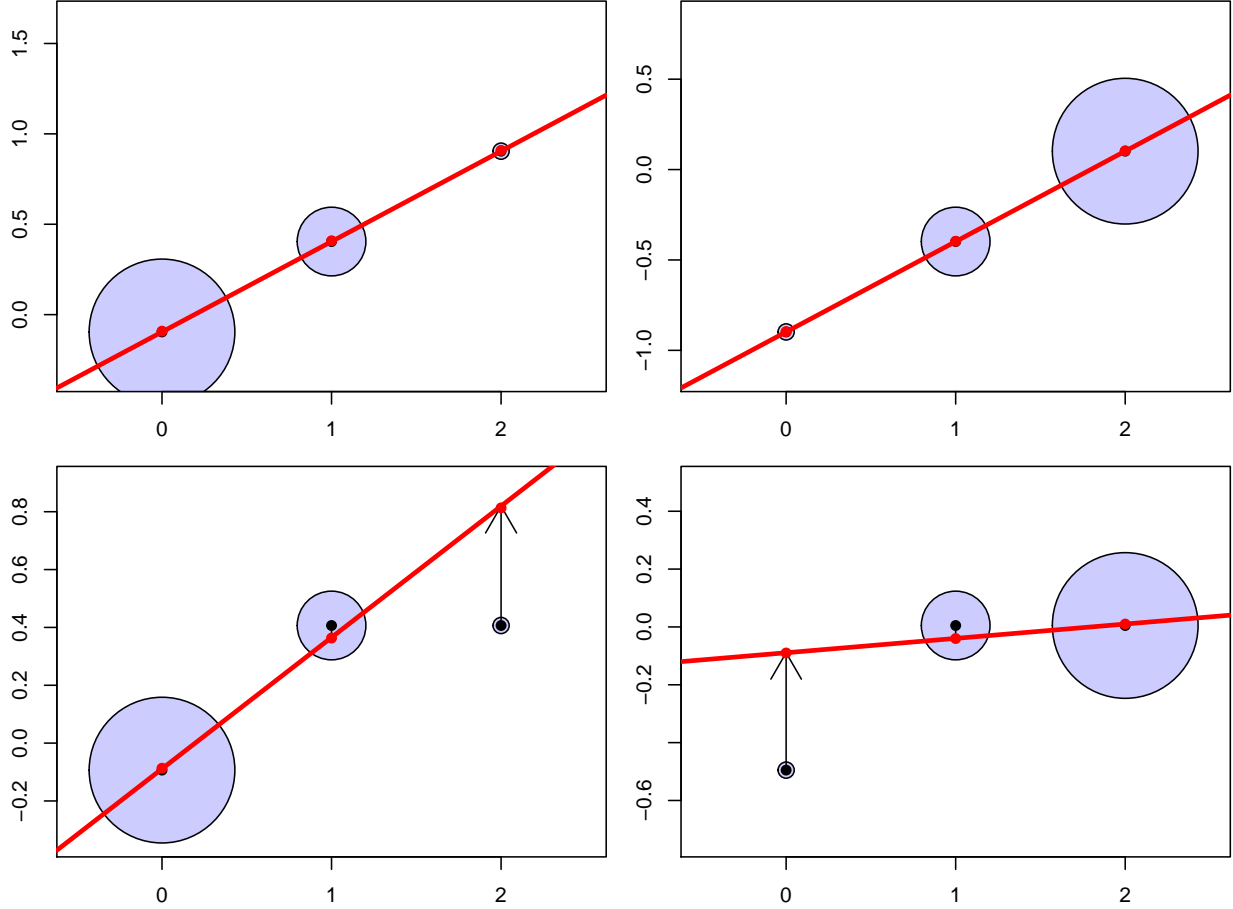
Figure 19: The average mean-centered (MC) phenotypes of each genotype. **Top Row:** Additive relationship between genotype and phenotype. **Bottom Row:** Allele 1 is dominant over allele 2, such that the heterozygote has the same phenotype as the 22 genotype (2). The area of each circle is proportion to the fraction of the population in each genotypic class (p^2, $2pq$, and q^2). One the left column $p = 0.1$ and the right column is $p = 0.9$. The additive genetic values of the genotypes are shown as red dots. The regression between phenotype and additive genotype is shown as a red line. The black vertical arrows show the difference between the average MC phenotype and additive genetic value for each genotype.

the top row when our alleles interact in a completely additive manner. Our additive genetic values always fall along a linear line (the red line in our figure). The additive values are falling best fitting line of linear regression for our population, when phenotype is regressed against the additive genotype (0, 1, 2 copies of allele 1) across all individuals in our population. Note in the dominant case the additive genetic values differ from the observed phenotypic means, and are closer to the observed values for the genotypes that are common in the population.

The difference in the additive effect of the two alleles $a_{\ell,2} - a_{\ell,1}$ can be interpreted as a average effect of swapping an allele 1 for an allele 2, we'll call this difference $\alpha_\ell = a_{\ell,2} - a_{\ell,1}$. Our α_ℓ is also the slope of the regression of genotype against phenotype (the red line in Figure 3.6). Note that the slope of our regression of genotype on phenotype (α_ℓ) does not depend on allele frequency for our completely additive locus (top row of 3.6). In contrast, when there is dominance, our the slope between genotype on phenotype (α_ℓ) is a function of allele frequency (bottom row of 3.6). When a dominant allele (1) is rare there is a strong slope of genotype on phenotype, bottom left Figure 3.6. This strong slope is because replacing a single copy of the 2 allele with a 1 allele in an individual has a big effect on average phenotype, as it will most likely move an individual from being a 22 homozygote to being a 12 heterozygote. However, when the dominant allele (1) is common in the population, replacing a 2 allele by a 1 allele in an individual on average has little phenotypic effect. This small effect is because as we are mainly turning heterozygotes into homozygotes (11), who have the same mean phenotype.

The variance in the population phenotype due to these additive breeding values at locus ℓ assuming HW proportions is

$$
\begin{aligned}
V_{A,\ell} &= p^2(2a_{\ell,2})^2 + 2pq(a_{\ell,1} + a_{\ell,1})^2 + q^2(2a_{\ell,0})^2 \\
&= 2(pa_{\ell,1}^2 + qa_{\ell,2}^2) \\
&= 2pq\alpha_\ell^2
\end{aligned}
\tag{107}
$$

The total additive effect can be found by summing this additive genetic variance across loci

$$
V_A = \sum_{\ell=1}^{L} V_{A,\ell} = \sum_{\ell=1}^{L} 2p_\ell q_\ell \alpha_\ell^2.
\tag{108}
$$

Having assigned the additive genetic variance to be the variance explained by the additive contribution of the alleles at a locus, we define the dominance variance as the population variance among genotypes at a locus due to their deviation from additivity. We can calculate how much each genotypic mean deviates away from its additive prediction at locus ℓ (the length of the arrows in Figure), for example the heterozygote deviates

$$
d_{\ell,1} = \overline{X}'_{\ell,1} - (a_{\ell,1} + a_{\ell,2})
\tag{109}
$$

away from its additive genetic value, with similar expressions for each of the homozygotes

Relationship (i,j)*	$Cov(X_i, X_j)$
parent–child	$^1/_2 V_A$
full siblings	$^1/_2 V_A + ^1/_4 V_D$
identical (monzygotic) twins	$V_A + V_D$
1st cousins	$^1/_8 V_A$

Table 4: Phenotypic covariance between some pairs of relatives, include the dominance variation. *Assuming this is the only relationship the pair of individuals share (above that expected from randomly sampling individuals from the population).

($d_{\ell,0}$ and $d_{\ell,2}$). We can then write the dominance variance at our locus as the genotype-frequency weighted sum of our squared dominance deviations

$$V_{D,\ell} = p^2 d_{\ell,0}^2 + 2pq d_{\ell,1}^2 + q^2 d_{\ell,2}^2. \tag{110}$$

Writing our total dominance variance as the sum across loci

$$V_D = \sum_{\ell=1}^{L} V_{D,\ell}. \tag{111}$$

Having now partitioned all of the genetic variance into additive and dominant terms, we can write our total genetic variance as

$$V_G = V_A + V_D. \tag{112}$$

We can do this because by construction the covariance between our additive and dominant deviations for the genotypes is zero. We can define the narrow sense heritability as before $h^2 = V_A/V_P = V_A/(V_G + V_E)$, which is the proportion of phenotypic variance due to additive genetic variance. We can also define the total proportion of the phenotype variance due to genetic differences among individuals, as the broad-sense heritability $H^2 = V_G/(V_G + V_E)$.

When dominance is present in the loci influencing our trait ($V_D > 0$), we need to modify our phenotype covariance among relatives to account for this non-additivity. Specifically our equation for the covariance among a general pair of relatives (eqn. 84 for additive variation) becomes

$$Cov(X_1, X_2) = 2F_{1,2} V_A + r_2 V_D \tag{113}$$

where r_2 is the probability that the pair of individuals share 2 alleles identical by descent, making the same assumptions (other than additivity) that we made in deriving eqn. 84. In table 4 we show the phenotypic covariance for some common pairs of relatives. The regression of offspring phenotype on parental midpoint still has a slope V_A/V_P.

Full sibs and parent-offspring have the same covariance if there is no dominance variance (as they have the same kinship coefficient $F_{1,2}$). However, when dominance is present

($V_D > 0$), full-sibs resemble each other more than parent-offspring pairs. That's because parents and offspring share precisely one allele, while full-sibs can share both alleles (i.e. the full genotype at a locus) identical by descent. We can attempt to estimate V_D by comparing different sets of relationships. For example non-identical twins (full sibs born at same time) should have $1/2$ the phenotypic covariance of identical twins if $V_D = 0$. Therefore, we can attempt to estimate V_D by looking at whether identical twins have more than twice the phenotypic covariance than non-identical twins.

The most important aspect of this discussion for thinking about evolutionary genetics is that the parent-offspring covariance is still only a function of V_A. This is because our parent (e.g. the mother) transmits only a single allele, at each locus, to its offspring. The other allele the offspring receives is random (assuming random mating), as it comes from the other unrelated parent (the father). Therefore, the average effect on the offspring phenotype of the allele the offspring receives from the mother, is averaged over the random allele the child receives from the father. Thus we only care about the additive effect of the allele, as parents transmit only alleles not genotypes to their offspring. This means that the short-term response to selection, as described by the breeder equation, depends only on V_A and the additive effect of alleles. Therefore, if we can estimate the narrow-sense heritability we can predict the short-term response. However, if alleles display dominance our value of V_A will change as our loci change frequency, e.g. as dominant alleles become common in the population their contribution to V_A decreases. Therefore, our value of V_A will not be a constant across generations.

Up to this point we have only considered dominance and not epistasis. However, we include epistasis in a similar manner (for example among pairs of loci). This gets a little tricky to think about so we will only briefly explain it. We can first estimate the additive effect of the alleles by considering the effect of the alleles averaging over the other alleles they are paired with, just as before. We can then calculate the additive genetic variance from this. We can estimate the dominance variance, by calculating the residual variance among genotypes at a locus unexplained by the additive effect of the loci. We can then estimate the epistatic variance by estimating the residual variance left unexplained among the two locus genotypes from the additive and dominant deviations calculated from each locus separately. In practice these high variance components are hard to estimate, and usually small as much of our variance is assigned to the additive effect. Again we would find that we mostly care about V_A for predicting short-term evolution, but that the contribution of loci to the additive genetic variance will depend on the epstatic relationships among loci.

Question 5.   You collect observations of red deer within a generation; recording an individuals number of offspring and phenotypes, which are known to have additive genetic variation, and construct the plots shown in Figure 20 (standardizing the phenotypes). Answer the following questions. For each question choose one of the bold options. Briefly justify each of your answers with reference to the breeder's equation and multi-trait breeder's equation. No calculations are required.

A) Looking at just at figure 20 A, in what direction do you expect male antler size to evolve?
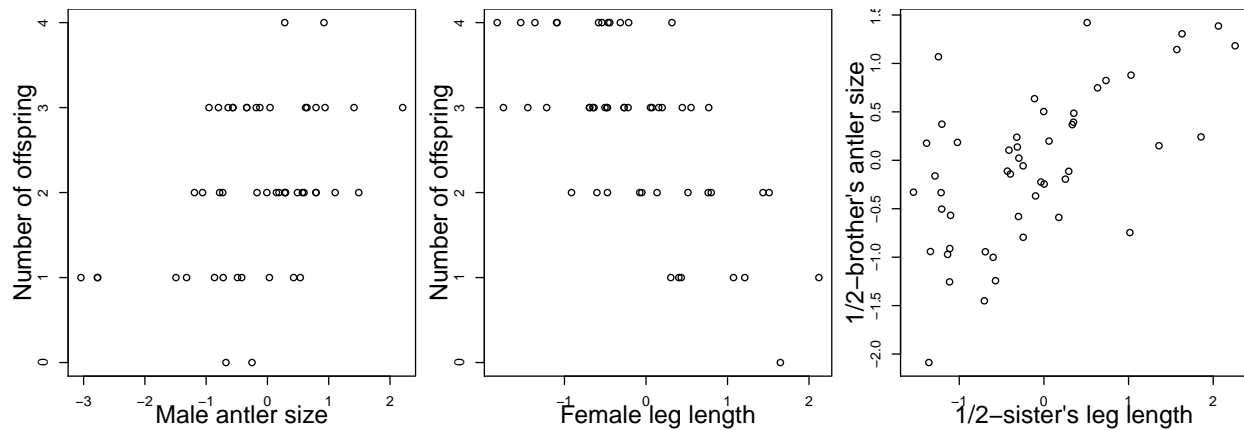
Figure 20: Observations of red deer within a generation; recording an individuals number of offspring and phenotypes, which are known to have additive genetic variation. The figures left to right are A-C.

Insufficient information, increase, decrease.

B) Looking just at figures 20 B and C, in what direction do you expect male antler size to evolve?
Insufficient information, increase, decrease.

C) (3 Points) Looking at figures 20 A, B, and C in what direction do you expect male antler size to evolve?
Insufficient information, increase, decrease.

Question 6. How could you use $1/2$ sibs vs full-sibs to estimate V_D? Why might this be difficult in practice? Why are identical vs non-identical twins better suited for this?

Question 7. Can you construct a case where $V_A = 0$ and $V_D > 0$? You need just describe it qualitatively, you don't need to work out the math. (tricker question).

4 One-locus models of selection

4.1 Fitness

As we have seen, natural selection occurs when there are differences between individuals in fitness. We may define fitness in various ways. Most commonly, it is defined with respect to the contribution of a phenotype or genotype to the next generation. Differences in fitness can arise at any point during the life cycle. For instance, different genotypes or phenotypes may have different survival probabilities from one stage in their life to the stage of reproduction (viability), or they may differ in the number of offspring produced (fertility), or both. Here, we define the absolute fitness of a genotype as the expected number of offspring of an individual of that genotype.

4.2 Haploid selection model

We start out by modelling selection in a haploid model, as this is mathematically relatively simple. Let the number of individuals carrying alleles A_1 and A_2 in generation t be P_t and Q_t. Then, the relative frequencies at time t of alleles A_1 and A_2 are $p_t = P_t/(P_t + Q_t)$ and $q_t = Q_t/(P_t + Q_t) = 1 - p_t$. Further, assume that individuals of type A_1 and A_2 on average produce W_1 and W_2 offspring individuals, respectively. We call W_i the absolute fitness.

Therefore, in the next generation, the absolute number of carriers of A_1 and A_2 are $P_{t+1} = W_1 P_t$ and $Q_{t+1} = W_2 Q_t$, respectively. The mean absolute fitness of the population at time t is

$$\overline{W}_t = W_1 \frac{P_t}{P_t + Q_t} + W_2 \frac{Q_t}{P_t + Q_t} = W_1 p_t + W_2 q_t, \tag{114}$$

i.e. the sum of the fitness of the two types weighted by their relative frequencies. Note that the mean fitness depends on time, as it is a function of the allele frequencies, which are themselves time dependent.

The frequency of allele A_1 in the next generation is then given by

$$p_{t+1} = \frac{P_{t+1}}{P_{t+1} + Q_{t+1}} = \frac{W_1 P_t}{W_1 P_t + W_2 Q_t} = \frac{W_1 p_t}{W_1 p_t + W_2 q_t} = \frac{W_1}{\overline{W}_t} p_t. \tag{115}$$

Importantly, eqn. (115) tells us that the change in p only depends on a ratio of fitnesses. Therefore, we need to specify fitness only up to an arbitrary constant. As long as we multiply all fitnesses by the same value, that constant will cancel out and eqn. (115) will hold. Based on this argument, it is very common to scale absolute fitnesses by the absolute fitness of one of the genotypes, e.g. the most or the least fit genotype, to obtain relative fitnesses. Here, we will use w_i for the relative fitness of genotype i. If we choose to scale by the absolute fitness of genotype A_1, we obtain the relative fitnesses $w_1 = W_1/W_1 = 1$ and $w_2 = W_2/W_1$.

Without loss of generality, we can therefore rewrite eqn. (115) as

$$p_{t+1} = \frac{w_1}{\overline{w}} p_t, \tag{116}$$

dropping the dependence of the mean fitness on time in our notation, but remembering it. The change in frequency from one generation to the next is then given by

$$\Delta p_t = p_{t+1} - p_t = \frac{w_1 p_t}{\overline{w}} - p_t = \frac{w_1 p_t - \overline{w} p_t}{\overline{w}} = \frac{w_1 p_t - (w_1 p_t + w_2 q_t) p_t}{\overline{w}} = \frac{w_1 - w_2}{\overline{w}} p_t q_t, \tag{117}$$

recalling that $q_t = 1 - p_t$.

Assuming that the fitnesses of the two alleles are constant over time, the number of the two allelic types τ generations after time t are $P_{t+\tau} = (W_1)^\tau P_t$ and $Q_{t+\tau} = (W_2)^\tau Q_t$, respectively. Therefore, the relative frequency of allele A_1 after τ generations past t is

$$p_{t+\tau} = \frac{(W_1)^\tau P_t}{(W_1)^\tau P_t + (W_2)^\tau Q_t} = \frac{(w_1)^\tau P_t}{(w_1)^\tau P_t + (w_2)^\tau Q_t} = \frac{p_t}{p_t + (w_2/w_1)^\tau q_t}, \tag{118}$$

where the last step includes dividing the whole term by $(w_1)^\tau$ and switching from absolute to relative allele frequencies.

Rearranging eqn. (118) and setting $t = 0$, we can work out the time τ for the frequency of A_1 to change from p_0 to p_τ. First, we write

$$p_\tau = \frac{p_0}{p_0 + (w_2/w_1)^\tau q_0} \tag{119}$$

and rearrange this to obtain

$$\frac{p_\tau}{q_\tau} = \frac{p_0}{q_0} \left(\frac{w_1}{w_2}\right)^\tau. \tag{120}$$

Solving this for τ yields

$$\tau = \log\left(\frac{p_\tau q_0}{q_\tau p_0}\right) / \log\left(\frac{w_1}{w_2}\right). \tag{121}$$

In practice, it is often helpful to parametrize the relative fitnesses w_i in a specific way. For example, we may set $w_1 = 1$ and $w_2 = 1 - s$, where s is called the selection coefficient. Using this parametrization, s is simply the difference in relative fitnesses between the two alleles. Equation (118) becomes

$$p_{t+\tau} = \frac{p_t}{p_t + q_t(1 - s)^\tau}, \tag{122}$$

as $w_2/w_1 = 1 - s$. Then, if $s \ll 1$, we can approximate $(1 - s)^\tau$ in the denominator by $\exp(-s\tau)$ to obtain

$$p_{t+\tau} \approx \frac{p_t}{p_t + q_t e^{-s\tau}}. \tag{123}$$

This equation takes the form of a logistic function. That is because we are looking at the relative frequencies of two 'populations' (of alleles A_1 and A_2) that are growing (or declining) exponentially, under the constraint that p and q always sum to 1.

Moreover, eqn. (120) for the time τ it takes for a certain change in frequency to occur becomes

$$\tau = -\log\left(\frac{p_\tau q_0}{q_\tau p_0}\right) / \log\left(1 - s\right).$$

(124)

Assuming again that $s \ll 1$, this simplifies to

$$\tau \approx \frac{1}{s} \log\left(\frac{p_\tau q_0}{q_\tau p_0}\right).$$

(125)

One particular case of interest is the time it takes to go from an absolute frequency of 1 to near fixation in a population of size N. In this case, we have $p_0 = 1/N$, and we may set $p_\tau = 1 - 1/N$, which is very close to fixation. Then, plugging these values into eqn. (125), we obtain

$$
\begin{aligned}
tau &= \frac{1}{s} \log\left(\frac{1 - 2/N + 1/N^2}{1/N^2}\right) \\
&\approx \frac{1}{s}(\log(N) + \log(N - 2)) \\
&\approx \frac{2}{s} \log(N)
\end{aligned}
$$

(126)

where we make the approximations $N^2 - 2N + 1 \approx N^2 - 2N$ and later $N - 2 \approx N$.

> **Question 1.** You are studying the frequency of antibiotic-resistant bacteria in a patient. Before administering the antibiotic the frequency of the resistance allele is $1/1000$. You adminster the antibiotic, alarming just 8 days later you find the frequency of the resistance allele to be 99%. Assume a generation time of $1/4$ a day for these bacteria.
> What is the selection coefficient associated with the resistance to antibiotics?

Haploid model with fluctuating selection We can now consider the case where the fitnesses depend on time, and say that $w_{1,t}$ and $w_{2,t}$ are the fitnesses of the two types in generation t. The frequency of allele A_1 in generation $t + 1$ is

$$p_{t+1} = \frac{w_{1,t}}{\overline{w}_t} p_t,$$

(127)

which simply follows from eqn. (116). The ratio of the frequency of allele A_1 to that of allele A_2 in generation $t + 1$ is

$$\frac{p_{t+1}}{q_{t+1}} = \frac{w_{1,t}}{w_{2,t}} \frac{p_t}{q_t}.$$

(128)

Therefore, if we think of the two alleles starting in generation t at frequencies p_t and q_t, then τ generations later,

$$\frac{p_{t+\tau}}{q_{t+\tau}} = \left(\prod_{i=t}^{\tau-1} \frac{w_{1,i}}{w_{2,i}}\right) \frac{p_t}{q_t}. \tag{129}$$

The question of which allele is increasing or decreasing in frequency comes down to whether $\left(\prod_{i=t}^{\tau-1} \frac{w_{1,i}}{w_{2,i}}\right)$ is > 1 or < 1. As it is a little hard to think about this ratio, we can instead take the τth root of it and consider

$$\sqrt[\tau]{\left(\prod_{i=t}^{\tau-1} \frac{w_{1,i}}{w_{2,i}}\right)} = \frac{\sqrt[\tau]{\prod_{i=t}^{\tau-1} w_{1,i}}}{\sqrt[\tau]{\prod_{i=t}^{\tau-1} w_{2,i}}}. \tag{130}$$

The term $\sqrt[\tau]{\prod_{i=t}^{\tau-1} w_{1,i}}$ is the geometric mean fitness of allele A_1 over the τ generations past generation t. Therefore, allele A_1 will only increase in frequency if it has a higher geometric mean fitness than allele A_2 (at least in our simple deterministic model).

4.3   Diploid model

We will now move on to a diploid model of a single locus with two segregating alleles. We will assume that the difference in fitness between the three genotypes comes from differences in viability, i.e. differential survival of individuals from the formation of zygotes to reproduction. We denote the absolute fitnesses of genotypes A_1A_1, A_1A_2, and A_2A_2 by W_{11}, W_{12}, and W_{22}. Specifically, W_{ij} is the probability that a zygote of genotype A_iA_j survives to reproduction. Assuming that individuals mate at random, the number of zygotes that are of the three genotypes and form generation t are

$$N p_t^2, \quad N 2 p_t q_t, \quad N q_t^2. \tag{131}$$

The mean fitness of the population of zygotes is then

$$\overline{W}_t = W_{11} p_t^2 + W_{12} 2 p_t q_t + W_{22} q_t^2. \tag{132}$$

Again, this is simply the weighted mean of the genotypic fitnesses.

How many zygotes of each of the three genotypes survive to reproduce? An individual of genotype A_1A_1 has a probability of W_{11} of surviving to reproduce, and similarly for other genotypes. Therefore, the expected number of A_1A_1, A_1A_2, and A_2A_2 individuals who survive to reproduce is

$$N W_{11} p_t^2, \quad N W_{12} 2 p_t q_t, \quad N W_{22} q_t^2. \tag{133}$$

	$A_1 A_1$	$A_1 A_2$	$A_2 A_2$
Absolute no. at birth	Np_t^2	$N2p_tq_t$	Nq_t^2
Fitnesses	W_{11}	W_{12}	W_{22}
Absolute no. at reproduction	$NW_{11}p_t^2$	$NW_{12}2p_tq_t$	$NW_{22}q_t^2$
Relative freq. at reproduction	$\frac{NW_{11}p_t^2}{N\overline{W}} = \frac{W_{11}}{\overline{W}}p_t^2$	$\frac{NW_{12}2p_tq_t}{N\overline{W}} = \frac{W_{12}}{\overline{W}}2p_tq_t$	$\frac{NW_{22}q_t^2}{N\overline{W}} = \frac{W_{22}}{\overline{W}}q_t^2$

Table 5: Relative genotype frequencies after one episode of viability selection.

It then follows that the total number of individuals who survive to reproduce is

$$N \left(W_{11}p_t^2 + W_{12}2p_tq_t + W_{22}q_t^2 \right). \tag{134}$$

This is simply the mean fitness of the population multiplied by the population size (i.e. $N\overline{w}$).

The relative frequency of $A_1 A_1$ individuals at reproduction is simply the number of $A_1 A_1$ genotype individuals at reproduction ($NW_{11}p_t^2$) divided by the total number of individuals who survive to reproduce ($N\overline{W}$), and likewise for the other two genotypes. Therefore, the relative frequency of individuals with the three different genotypes at reproduction is

$$\frac{NW_{11}p_t^2}{N\overline{W}}, \quad \frac{NW_{12}2p_tq_t}{N\overline{W}}, \quad \frac{NW_{22}q_t^2}{N\overline{W}} \tag{135}$$

(see Table 5).

As there is no difference in the fecundity of the three genotypes, the allele frequencies in the zygotes forming the next generation are simply the allele frequency among the reproducing individuals of the previous generation. Hence, the frequency of A_1 in generation $t+1$ is

$$p_{t+1} = \frac{W_{11}p_t^2 + W_{12}p_tq_t}{\overline{W}}. \tag{136}$$

Note that, again, the absolute value of the fitnesses is irrelevant to the frequency of the allele. Therefore, we can just as easily replace the absolute fitnesses with the relative fitnesses. That is, we may replace W_{ij} by $w_{ij} = W_{ij}/W_{11}$, for instance.

Question 2. You have been studying an annual wildflower for many generations with two color morphs orange and white. You have discovered that a single bi-allelic locus controls flower color, with the white allele being recessive. The pollinator of these plants is an almost blind bat, so individuals are pollinated at random with respect to flower color. Your population census of 200 individuals showed that the population consisted of 168 orange-flowered individuals, and 32 white-flowered individuals.

Heavy February rainfall creates optimal growing conditions for an exotic herbivorous beetle with a preference for orange-flowered individuals. This year it arrives at your study site with a ravenous appetite. Only 50% of orange-flowered individuals survive its wrath, while 90% of white-flowered individuals survive until the end of the growing season.

A What is the initial frequency of the white allele, and what do you have to assume to obtain this?

B What is the frequency of the white allele in the seeds forming the next generation?

The change in frequency from generation t to $t+1$ is

$$\Delta p_t = p_{t+1} - p_t = \frac{w_{11}p_t^2 + w_{12}p_t q_t}{\overline{w}} - p_t. \tag{137}$$

To simplify this equation, we will first define two variables $\overline{w}_1$ and $\overline{w}_2$ as

$$\overline{w}_1 = w_{11}p_t + w_{12}q_t, \tag{138}$$
$$\overline{w}_2 = w_{12}p_t + w_{22}q_t. \tag{139}$$

These are called the marginal fitnesses of allele A_1 and A_2, respectively. They are so called as $\overline{w}_1$ is the average fitness of an allele A_1, i.e. the fitness of A_1 in a homozygote weighted by the probability it is in a homozygote (p_t) plus the fitness of A_1 in a heterozygote weighted by the probability it is in a heterozygote (q_t). We further note that the mean relative fitness can be expressed in terms of the marginal fitnesses as

$$\overline{w} = \overline{w}_1 p_t + \overline{w}_2 q_t, \tag{140}$$

where, for notational simplicity, we have omitted the dependence of mean and marginal fitnesses on time.

We can then rewrite eqn. (137) using $\overline{w}_1$ and $\overline{w}_2$ as

$$\Delta p_t = \frac{(\overline{w}_1 - \overline{w}_2)}{\overline{w}} p_t q_t. \tag{141}$$

The sign of Δp_t, i.e. whether allele A_1 increases of decreases in frequency, depends only on the sign of $(\overline{w}_1 - \overline{w}_2)$. The frequency of A_1 will keep increasing over the generations so long

as its marginal fitness is higher than that of A_2, i.e. $\overline{w}_1 > \overline{w}_2$, while if $\overline{w}_1 < \overline{w}_2$, the frequency of A_1 will decrease. Note the similarity between eqn. (141) and the respective expression for the haploid model in eqn. (117). (We will return to the special case where $\overline{w}_1 = \overline{w}_2$ shortly).

We can also rewrite (137) as

$$\Delta p_t = \frac{1}{2} \frac{p_t q_t}{\overline{w}} \frac{d\overline{w}}{dp}, \tag{142}$$

the demonstration of this we leave to the reader. This form shows that the frequency of A_1 will increase ($\Delta p_t > 0$) if the mean fitness is an increasing function of the frequency of A_1 (i.e. if $\frac{d\overline{w}}{dp} > 0$). On the other hand, the frequency of A_1 will decrease ($\Delta p_t < 0$) if the mean fitness is a decreasing function of the frequency of A_1 (i.e. if $\frac{d\overline{w}}{dp} < 0$). Thus, although selection acts on individuals, under this simple model, selection is acting to increase the mean fitness of the population. The rate of this increase is proportional to the variance in allele frequencies within the population ($p_t q_t$).

Question 3. Show that eqns. (142) and (141) are equivalent. (Trickier question.)

So far, our treatment of the diploid model of selection has been in terms of generic fitnesses w_{ij}. In the following, we will use particular parametrizations to gain insight about two specific modes of selection: directional selection and heterozygote advantage.

4.3.1 Diploid directional selection

Directional selection means that one of the two alleles always has higher marginal fitness than the other one. Let us assume that A_1 is the fitter allele, so that $w_{11} \geq w_{12} \geq w_{22}$, and hence $\overline{w}_1 > \overline{w}_2$. As we are interested in changes in allele frequencies, we may use relative fitnesses. We parameterize the reduction in relative fitness in terms of a selection coefficient, similar to the one we met in the haploid selection section, as follows:

genotype	$A_1 A_1$	$A_1 A_2$	$A_2 A_2$
absolute fitness	W_{11}	$\geq W_{12} \geq$	W_{22}
relative fitness (generic)	$w_{11} = W_{11}/W_{11}$	$w_{12} = W_{12}/W_{11}$	$w_{22} = W_{22}/W_{11}$
relative fitness (specific)	1	$1 - sh$	$1 - s$.

Here, the selection coefficient s is the difference in relative fitness between the two homozygotes, and h is the dominance coefficient. For selection to be directional, we require that $0 \leq h \leq 1$ holds. The dominance coefficient allows us to move between two extremes. One is when $h = 0$, such that allele A_1 is fully dominant and A_2 fully recessive. In this case, the heterozygote $A_1 A_2$ is as fit as the $A_1 A_1$ homozgyote genotype. The inverse holds when $h = 1$, such that allele A_1 is fully recessive and A_2 fully dominant.

We can then rewrite eqn. (141) as

$$\Delta p_t = \frac{p_t hs + q_t s(1-h)}{\overline{w}} p_t q_t, \tag{143}$$

where

$$\overline{w}_t = 1 - 2p_t q_t sh - q_t^2 s. \tag{144}$$

Question 4. Comparing the red ($h = 0$) and black ($h = 0.5$) trajectories in Figure 21, provide an explanation for why A_1 increases faster initially if $h = 0$, but then approaches fixation more slowly compared to the case of $h = 0.5$.

A special case is when $h = 0.5$. This case is the case of no dominance, as the interaction among alleles with respect to fitness is strictly additive. Then, eqn. (143) simplifies to

$$\Delta p_t = \frac{1}{2} \frac{s}{\overline{w}} p_t q_t. \tag{145}$$

If selection is very weak, i.e. $s \ll 1$, the denominator ($\overline{w}$) is close to 1 and we have

$$\Delta p_t = \frac{1}{2} s p_t q_t. \tag{146}$$

It is instructive to compare eqn. (146) to the respective expression under the haploid model. To this purpose, start from the generic term for Δp_t under the haploid model in eqn. (117) and set $w_1 = 1$ and $w_2 = 1 - s$. Again, assume that s is small, so that eqn. (117) becomes $\Delta p_t = s p_t q_t$. Hence, if s is small, the diploid model of directional selection without dominance is identical to the haploid model, up to a factor of $1/2$. That factor is due to the choice of the parametrisation; we could have set $w_{11} = 1$, $w_{12} = 1 - s$, and $w_{22} = 1 - 2s$ in diploid model instead, in which case the agreement with the haploid model would be perfect.

From this analogy, we can borrow some insight we gained for the haploid model. Specifically, the trajectory of the frequency of allele A_1 in the diploid model without dominance follows a logistic growth curve similar to (123). Similarly, eqn. 126 for the haploid model suggests that in the diploid model without dominance it takes

$$\tau \approx \frac{4}{s} \log(2N) \tag{147}$$

generations for the favourable allele (A_1) to transit from its entry into the population ($p_0 = 1/(2N)$) to close to fixation ($p_\tau = 1 - 1/(2N)$). Note again the difference by a factor of 2 due to the choice of parametrization. Also, the total number of alleles is $2N$ in the diploid model, rather than N, which explains another factor of 2 in the argument of the logarithm. More generally we can use this correspondance of the trajectory additive diploid model to the haploid model to understand how quickly allele frequencies should change given a selection coefficient between arbitrary frequencies.
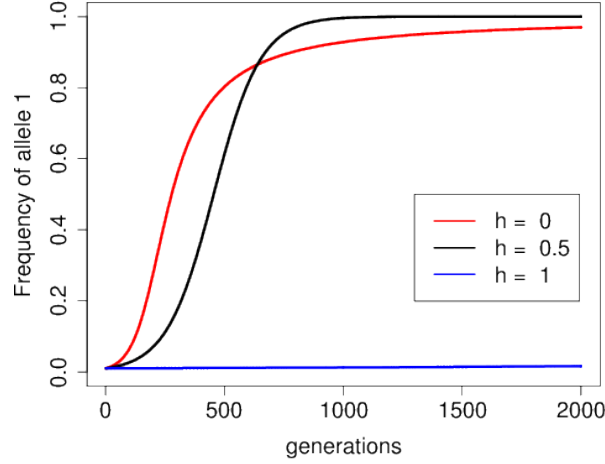
Figure 21: The trajectory of the frequency of allele A_1, starting from $p_0 = 0.01$, for a selection coefficient $s = 0.01$ and three different dominance coefficients.

4.3.2 Heterozygote advantage

What if the heterozygotes are fitter than either of the homozygotes? In this case, it is useful to parameterize the relative fitnesses as follows:

genotype	A_1A_1	A_1A_2	A_2A_2
absolute fitness	w_{11}	$< w_{12} >$	w_{22}
relative fitness (generic)	$w_{11} = W_{11}/W_{12}$	$w_{12} = W_{12}/W_{12}$	$w_{22} = W_{22}/W_{12}$
relative fitness (specific)	$1 - s_1$	1	$1 - s_2$

Here, s_1 and s_2 are the differences between the relative fitnesses of the two homozygotes and the heterozygote. Note that to obtain relative fitnesses we have divided absolute fitness by the heterozygote fitness. We could use the same parameterization as in the model of directional selection, but the reparameterization we have chosen here makes the math prettier.

In this case, when allele A_1 is rare, it is often found in a heterozygous state and so it increases in frequency. However, when allele A_1 is common, it is often found in the homozygote state, while the allele A_2 is often found in the heterozygote state; it is now A_2 that increases in frequency at the expense of allele 1. Thus, at least in the deterministic model, neither allele can reach fixation and both alleles will be maintained as a balanced polymorphism in the population at an equilibrium frequency.

We can solve for this equilibrium frequency by setting $\Delta p_t = 0$ in eqn. (141), i.e. $p_t q_t (\overline{w}_1 - \overline{w}_2) = 0$. Doing so, we find that there are three equilibria, all of which are stable. Two of them

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are not very interesting ($p = 0$ or $q = 0$), but the third one is the polymorphic equilibrium, where $\overline{w}_1 - \overline{w}_2$ holds. Using the parametrization above, we see that the marginal fitnesses of the two alleles are formally equivalent. Insertion of the selection coefficients s_1 and s_2 yields

$$p_e = \frac{s_2}{s_1 + s_2} \tag{148}$$

for the equilibrium frequency of interest. This is also the frequency of A_1 at which the mean fitness of the population is maximised.

Underdominance. Another case that is of potential interest is the case of fitness underdominance, where the heterozygote is less fit than either of the homozygotes. This can be parametrized as follows:

genotype	A_1A_1	A_1A_2	A_2A_2
absolute fitness	w_{11}	$< w_{12} >$	w_{22}
relative fitness (generic)	$w_{11} = W_{11}/W_{12}$	$w_{12} = W_{12}/W_{12}$	$w_{22} = W_{22}/W_{12}$
relative fitness (specific)	$1 + s_1$	1	$1 + s_2$

This case also permits three equilibria, $p = 0$, $p = 1$, and a polymorphic equilibrium $p = p_U$. However, now only the first two equilibria are stable, while the polymorphic equilibrium is unstable. If $p < p_U$ then Δp_t is negative and allele A_1 will be lost, while if $p > p_U$, allele A_1 will become fixed.

While such alleles might not spread within populations (if $p_U \gg 0$ and selection is reasonably strong), they are of interest in the study of speciation and hybrid zones. That is because alleles A_1 and A_2 may have arisen in a stepwise fashion, i.e. not by a single mutation, in separate subpopulations. Now, heterozygote disadvantage will play a potential role in species maintenance, if isolation of the subpopulations is not complete.

Question 5. You are studying the polymorphism that affects flight speed in butterflies. The polymorphism does not appear to affect fecundity. Homozygotes for the B allele are slow in flight and so only 40% of them survive to have offspring. Heterozygotes for the polymorphism (Bb) fly quickly and have a 70% probability of surviving to reproduce. The homozygotes for the alternative allele (bb) fly very quickly indeed, but often die of exhaustion, with only 10% of them making it to reproduction.
A) What is the equilibrium frequency of the B allele?
B) Calculate the marginal fitnesses of the B and the b allele at the equilbrium frequency.

Diploid fluctuating fitness We would like to think about the case where the diploid absolute fitnesses are time-dependent. The three genotypes then have fitnesses $w_{11,t}$, $w_{12,t}$, and $w_{22,t}$ in generation t. However, this case is much less tractable than the haploid case, as segregation makes it tricky to keep track of the genotype frequencies. We can make some progress and gain some intuition by thinking about how the frequency of allele A_1 changes when it is rare.

When A_1 is rare, i.e. $p_t \ll 1$, its frequency in the next generation (136) can be approximated as

$$p_{t+1} \approx \frac{w_{12}}{\overline{w}} p_t. \tag{149}$$

To obtain this, we have ignored the p_t^2 term and assumed that $q_t \approx 1$ in the numerator. Following a similar argument to approximate q_{t+1}, we can write

$$\frac{p_{t+1}}{q_{t+1}} = \frac{w_{12,t}}{w_{22,t}} \frac{p_t}{q_t}. \tag{150}$$

Then, starting from out from p_0 and q_0 in generation 0, $t + 1$ generations later, we have

$$\frac{p_{t+1}}{q_{t+1}} = \left(\prod_{i=0}^{t-1} \frac{w_{12,i}}{w_{22,i}} \right) \frac{p_0}{q_0}. \tag{151}$$

From this, we can see, following our haploid argument from above, that the frequency of allele A_1 will increase when rare only if

$$\frac{\sqrt[t]{\prod_{i=0}^{t-1} w_{12,i}}}{\sqrt[t]{\prod_{i=0}^{t-1} w_{22,i}}} > 1, \tag{152}$$

i.e. if the heterozygote has higher geometric mean fitness than the A_2A_2 homozygote.

The question now is, whether allele A_1 will approach fixation in the population, or whether there are cases in which we can obtain a balanced polymorphism. To investigate that, we can simply repeat our analysis for $q \ll 1$, and see that in that case

$$\frac{p_{t+1}}{q_{t+1}} = \left(\prod_{i=0}^{t-1} \frac{w_{11,i}}{w_{12,i}} \right) \frac{p_0}{q_0}. \tag{153}$$

Now, for allele A_1 to carry on increasing in frequency and to approach fixation, the A_1A_1 genotype has to be out-competing the heterozygotes. For allele A_1 to approach fixation, we need the geometric mean of $w_{11,i}$ to be greater than the geometric mean fitness of heterozygotes ($w_{12,i}$). At the same time, if heterozygotes have higher geometric mean fitness than the A_1A_1 homozygotes, then the A_2 allele will increase in frequency when it is rare. Therefore, a balanced polymorphism can result when the heterozygote has higher geometric fitness than

either of the homozygotes.

Intriguingly, we can have a balanced polymorphism even if the heterozygote is never the fittest genotype in any generation, if the heterozygotes has a higher geometric mean fitness than either of the homozygotes. In this case, the polymorphism will remain balanced in the population, despite the fact that the heterozygote is never the fitest genotype.

Question 6. Consider a plant population found in one of two different environments each generation. These occur randomly, $1/3$ of time the population experiences the dry environment and with probability $2/3$ it experiences the wet environment Y. The Absolute Fitnesses are as follows:

Environment	AA	Aa	aa
Wet.	6.25	5.0	3.75
Dry	3.85	5.0	6.15

A) Show whether the equilibrium frequency of A will be 0, 1, or in between.
B) If the probabilities of wet and dry environments were equal, i.e., 0.5 how would your conclusion change?
(HINT: Lets write $w_{AA,\text{dry}}$ and $w_{AA,\text{wet}}$ for the fitnesses of the AA homozygote in the two environments. Then if the two environments are equally common $\prod_{i=0}^{t} w_{AA,i} \approx w_{AA,\text{dry}}^{t/2} w_{AA,\text{wet}}^{t/2}$ for large values of t.)

Question 7. OPTIONAL trickier question.
Imagine a randomly-mating population of hermaphrodites. In this population a derived allele (D) segregates that distorts transmission in its favour over the ancestral allele (d) in the production of all the gametes of heterozygotes. The drive leads to a fraction r of the gametes of heterozygotes (D/d) to carry the D allele ($r > 0.5$). The D allele causes viability problems in the homozygote state such that the relative fitnesses are $w_{dd} = 1$, $w_{Dd} = 1$, $w_{DD} = 1 - e$. The allele is currently at frequency p in the population at birth. Assuming that the population is very large and no mutation occurs:
A) What is the frequency of the D allele in the next generation, before selection has had a chance to act?
B) What conditions do you need for a polymorphic equilibrium to be maintained? At what is the equilibrium frequency of this balanced polymorphism?
C) Imagine the cost of the driver were additive $w_{dd} = 1$, $w_{Dd} = 1 - e$, $w_{DD} = 1 - 2e$. Under what conditions can the driver invade the population? Can a polymorphic equilibrium be maintained?

4.4 Mutation–selection balance

Mutation is constantly introducing new alleles into the population. Therefore, variation can be maintained within a population not only if selection is balancing (e.g. through heterozygote advantage or fluctuating selection over time, as we have seen in the previous section), but also due to a balance between mutation and selection. A case of particular interest is when mutation introduces deleterious alleles and selection acts against these alleles. To study this balance, we return to the model of directional selection, where allele A_1 is advantageous, i.e.

genotype	$A_1 A_1$	$A_1 A_2$	$A_2 A_2$
absolute fitness	W_{11}	$\geq W_{12} \geq$	W_{22}
relative fitness	$w_{11} = 1$	$w_{12} = 1 - sh$	$w_{22} = 1 - s.$

For a start, we consider the case where allele A_2 is not completely recessive ($h > 0$), so that the heterozygotes suffer at least some disadvantage. We denote by $\mu = \mu_{1 \to 2}$ the mutation rate per generation from A_1 to the deleterious allele A_2, and assume that there is no reverse mutation ($\mu_{2 \to 1} = 0$). Let us assume that selection against A_2 is relatively strong compared to the mutation rate, so that it is justified to assume that A_2 is always rare, i.e. $q_t = 1 - p_t \ll 1$. Compared to previous sections, for mathematical clarity, we also switch from following the frequency p_t of A_1 to following the frequency q_t of A_2. Of course, this is without loss of generality. The change in frequency of A_2 due to selection can be written as

$$\Delta_S q_t = \frac{\overline{w}_2 - \overline{w}_1}{\overline{w}} p_t q_t \approx -hs q_t. \tag{154}$$

This approximation can be found by assuming that $q^2 \approx 0$, $p \approx 1$, and that $\overline{w} \approx w_1$. All of these assumptions make sense if $q \ll 1$. From eqn. (154) we see that selection acts to reduce the frequency of A_2 (as both h and s are positive), and it does so geometrically across the generations. That is, if the initial frequency of A_2 is q_0, then its frequency at time t is approximately

$$q_t = q_0 (1 - hs)^t. \tag{155}$$

We will now consider the change in frequency induced by mutation. Recalling that μ is the mutation rate from A_1 to A_2 per generation, the frequency of A_2 after mutation

$$q' = \mu p_t + q_t = \mu(1 - q_t) + q_t. \tag{156}$$

Assuming that $\mu \ll 1$ and that $q \ll 1$, the change in the frequency of allele A_2 due to mutation ($\Delta_M q_t$) can be approximated by

$$\Delta_M q_t = q' - q_t = \mu. \tag{157}$$

Hence, when A_2 is rare and the mutation rate is low, mutation acts to linearly increase the frequency of the deleterious allele A_2.

If selection is to balance deleterious mutation, their combined effect over one generation has to be zero. Therefore, to find the mutation–selection equilibrium, we set

$$\Delta_M q_t + \Delta_S q_t = 0, \tag{158}$$

insert eqns. (154) and (157), and solve for q to obtain

$$q_e = q_t = \frac{\mu}{hs}. \tag{159}$$

We see that the frequency of the deleterious allele A_2 is balanced at the mutation rate (μ) divided by the reduction in relative fitness in the heterozygote (hs).

It is worth pointing out that the fitness of the A_2A_2 homozygote has not entered this calculation, as A_2 is so rare that it is hardly ever found in the homozygous state. Therefore, if A_2 has any deleterious effect in a heterozygous state (i.e. if $h > 0$) it is this effect that determines the frequency at which A_2 is maintained in the population. Also, note that by writing the total change in allele frequency as $\Delta_M q_t + \Delta_S q_t$ we have implicitly assumed that we can ignore terms of order $\mu \times s$. That is, we have assumed that there is no interaction between mutation and selection. We can do so as we assumed that both μ and s are small.

What effect do such deleterious mutations at mutation–selection balance have on the population? It is common to express this effect in terms of a reduction of the mean relative fitness of the population. For a single site at which a deleterious mutation is segregating at $q_e = \mu/(hs)$, the mean relative fitness is reduced to

$$\overline{w} = 1 - 2p_e q_e hs - q_e^2 s \approx 1 - 2\mu. \tag{160}$$

Somewhat remarkably, the drop in mean fitness due to a site segregating at mutation–selection balance is independent of the selection coefficient against the heterozygote; it depends only the mutation rate. Note that this applies only if the mutation is not totally recessive, i.e. if $h > 0$.

A reduction of $1 - 2\mu$ is very small, given that the mutation rate of a gene is likely $< 10^{-5}$. However, if there are many loci segregating at mutation–selection balance, this can accumulate to a substantial so-called genetic load, and a major cause of variation in fitness-related traits among individuals.

As an aside, if an allele was truly recessive (although few likely are), we have $h = 0$, and so eqn. (159) is not valid. However, we can make an argument similar to the one above to show that, for truly recessive alleles,

$$q_e = \sqrt{\frac{\mu}{s}}. \tag{161}$$

> **Question 8.** You are studying an outbred population of mice living in a farmers field. Mutations occur at a gene called nurseryrhyme that cause a totally recessive form of blindness. These blind mice do not survive to reproduce as the farmers wife cuts off their tail (and other bits) with a carving knife. Surveying the field for baby mice you find that 3 in ten thousand mice are blind.
> **A** Assuming that the population mates at random, what is the mutation rate of blindness causing alleles?
> **B** Following more careful study you now find that there is actually a 20% reduction in the viability of heterozygotes for these mutations. What would you now estimate as the mutation rate for this gene? **C)** Explain how and why your answers differ?

4.4.1   Inbreeding depression

All else being equal, eqn. (159) suggests that mutations that have a smaller effect in the heterozygote can segregate at higher frequency under mutation–selection balance. As a consequence, alleles that have strongly deleterious effects in the homozygous state can segregate at low frequencies in the population, as long as they do not have a strong effect in heterozygotes. Thus, outbred populations may have many alleles with recessive deleterious effects segregating within them.

One consequence of this is that inbred individuals from usually outbred populations may have dramatically lower fitnesses than outbred individuals. This is a consequence of being homozygous at many loci for alleles with recessive deleterious effects. Indeed, this seems to be a common observation, dating back to systematic surveys by Darwin. In typically outbred populations, the mean fitness of individuals decreases with the inbreeding coefficient, i.e. this so-called inbreeding depression is a common observation.

Purging the inbreeding load. Populations that regularly inbreed over sustained periods of time are expected to partially purge this load of deleterious alleles. This is because such populations have exposed many of these alleles in a homozygous state, and so selection can more readily remove these alleles from the population.

4.5 Migration–selection balance

Another reason for the persistence of deleterious alleles in a population is that there is a constant influx of maladaptive alleles from other populations where these alleles are locally adapted. This seems unlikely to be as broad an explanation for the persistence of deleterious alleles genome-wide as mutation-selection balance. However, a brief discussion of such alleles is worthwhile as it helps to inform our ideas about local adaptation.

As a first pass at this lets consider a haploid two allele model with two different populations, where the relative fitnesses of our alleles are as follows

allele	1	2
population 1	1	1-s
population 2	1-s	1

As a simple model of migration lets suppose within a population a fraction of m individuals are migrants from the other population, and $1 - m$ individuals are from the same deme.

To quickly sketch a solution to this, we'll set up a situation analogous to our mutation-selection balance model. To do this let's assume that selection is strong compared to migration ($s \gg m$) then allele 1 will be almost fixed in population 1 and allele 2 will be almost fixed in population 2. If that is the case, migration changes the frequency of allele 2 in population 1 (q_1) by

$$\Delta_{Mig.} q_1 \approx m \tag{162}$$

while as noted above $\Delta_S q_1 = -s q_1$, so that migration and selection are at an equilibrium when $0 = \Delta_S q_1 + \Delta_{Mig.} q_1$, i.e. an equilibrium frequency of allele 2 in population 1 of

$$q_{e,1} = \frac{m}{s} \tag{163}$$

so that migration is playing the role of mutation and so migration-selection balance (at least under strong selection) is analogous to mutation selection balance.

We can use this same model by analogy for the case of migration-selection balance in a diploid model, in that case we replace our haploid s by the cost to heterozygotes hs.

Question 9. You are investigating a small river population of sticklebacks, which receives infrequent migrants from a very large marine population. At a set of (putatively) neutral biallelic markers the freshwater population has frequencies:
0.2, 0.7, 0.8
at the same markers the marine population has frequencies:
0.4, 0.5 and 0.7.
From studying patterns of heterozygosity at a large collection of markers, you have estimated the long term effective size of your freshwater population is 2000 individuals.
A) What is F_{ST} across these neutral markers in the freshwater population, with respect to the large marine population (i.e. treat the marine population as the total)?
B) You are also studying an unlinked locus involved in the regulation of salt uptake. In the marine population the ancestral allele is at close to fixation, but in your river population the derived allele is at 0.99 frequency. Estimate the selective disadvantage of the ancestral allele in your river population. [Hint how can you use neutral differentiation to estimate the migration rate?]

4.5.1 Some theory of the spatial distribution of allele frequencies under deterministic models of selection

Imagine a continuous haploid population spread out along a line. Individuals disperse a random distance Δx from its birthplace to the location where it reproduces, where Δx is drawn from the probability density $g(\ )$. To make life simple we will assume that $g(\Delta x)$ is normally distributed with mean zero and standard deviation σ, i.e. migration is unbiased an individuals migrate an average distance of σ.

Our frequency of allele 2 at time t in the population at spatial location x is $q(x,t)$. Assuming that only dispersal occurs, how does our allele frequency change in the next generation? Our allele frequency in the next generation at location x reflects the migration from different locations in the proceeding generation. Our population at location x receives a contribution $g(\Delta x)q(x + \Delta x, t)$ of allele 2 from the population at location $x + \Delta x$, such that the frequency of our allele at x in the next generation is

$$q(x, t+1) = \int_{-\infty}^{\infty} g(\Delta x)q(x + \Delta x, t)d\Delta x. \tag{164}$$

To obtain $q(x + \Delta x, t)$, lets take a Taylor series expansion of $q(x,t)$

$$q(x + \Delta x, t) = q(x, t) + \Delta x \frac{dq(x,t)}{dx} + \tfrac{1}{2}(\Delta x)^2 \frac{d^2q(x,t)}{dx^2} + \cdots \tag{165}$$

then

$$q(x,t+1) = q(x,t) + \left(\int_{-\infty}^{\infty} \Delta x g(\Delta x) d\Delta x \right) \frac{dq(x,t)}{dx} + \frac{1}{2} \left(\int_{-\infty}^{\infty} (\Delta x)^2 g(\Delta x) d\Delta x \right) \frac{d^2 q(x,t)}{dx^2} + \cdots$$

$$(166)$$

$g(\ )$ has a mean of zero so $\int_{-\infty}^{\infty} \Delta x g(\Delta x) d\Delta x = 0$ and has variance σ^2 so $\int_{-\infty}^{\infty} (\Delta x)^2 g(\Delta x) d\Delta x = \sigma^2$ and all higher terms are zero (as all high moments of the normal are zero). Looking at the change in frequency $\Delta q(x,t) = q(x,t+1) - q(x,t)$ then

$$\Delta q(x,t) = \frac{\sigma^2}{2} \frac{d^2 q(x,t)}{dx^2} \tag{167}$$

This is a diffusion equation, so that migration is acting to smooth out allele frequency differences with a diffusion constant of $\frac{\sigma^2}{2}$. This is exactly analogous to the equation describing how a gas diffuses out to equal density, as both particles in a gas and our individuals of type 2 are performing Brownian motion (blurring our eyes and seeing time as continuous).

We will now introduce fitness differences into our model and set the relative fitnesses of allele 1 and 2 at location x to be 1 and $1 + s\gamma(x)$. To make progress in this model we'll have to assume that selection isn't too strong i.e. $s\gamma(x) \ll 1$ for all x. The change in frequency of allele 2 obtained within a generation due to selection is

$$q'(x,t) - q(x,t) \approx s\gamma(x)q(x,t)\big(1 - q(x,t)\big) \tag{168}$$

i.e. logistic growth of our favoured allele at location x. Putting our selection and migration terms together we find

$$q(x,t+1) - q(x,t) = s\gamma(x)q(x,t)\big(1 - q(x,t)\big) + \frac{\sigma^2}{2} \frac{d^2 q(x,t)}{dx^2} \tag{169}$$

in deriving this we have essentially assumed that migration acted upon our original frequencies before selection and in doing so have ignored terms of the order of σs.

The cline in allele frequency associated with a sharp environmental transition. To make progress lets consider a simple model of location adaptation where the environment abruptly changes. Specifically we assume that $\gamma(x) = 1$ for $x < 0$ and $\gamma(x) = -1$ for $x \geq 0$, i.e. our allele 2 has a selective advantage at locations to the left of zero, while this allele is at a disadvantage to the right of zero. In this case we can get an equilibrium distribution of our two alleles were to the left of *zero* our allele 2 is at higher frequency, while to the right of zero allele 1 predominates. As we cross from the left to the right side of our range the frequency of our allele 2 decreases in a smooth cline.

Our equilibrium spatial distribution of allele frequencies can be found by setting the LHS of eqn. (169) to zero to arrive at

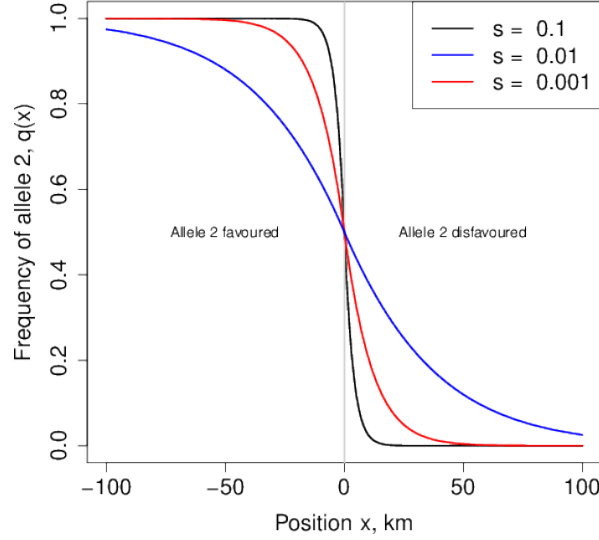$$s\gamma(x)q(x)\left(1 - q(x)\right) = -\frac{\sigma^2}{2} \frac{d^2 q(x)}{dx^2} \tag{170}$$

Figure 22: An equilibrium cline in allele frequency. Our individuals dispersal an average distance of $\sigma = 1$km per generation, and our allele 2 has a relative fitness of $1 + s$ and $1 - s$ on either side of the environmental change at $x = 0$.

We then could solve this differential equation with appropriate boundary conditions ($q(-\infty) = 1$ and $q(\infty) = 0$) to arrive at the appropriate functional form to our cline. While we won't go into the solution of this equation here, we can note that by dividing our distance x by $\ell = \sigma/\sqrt{s}$ we can remove the effect of our parameters from the above equation. This compound parameter ℓ is the characteristic length of our cline, and it is this parameter which determines over what geographic scale we change from allele 2 predominating to allele 1 predominating as we move across our environmental shift.

The width of our cline, i.e. over what distance do we make this shift from allele 2 predominating to allele 1, can be defined in a number of different ways. One simple way to define the cline width, which is easy to define but perhaps hard to measure accurately, is the slope (i.e. the tangent) of $q(x)$ at $x = 0$. Under this definition the cline width is approximately $0.6\sigma/\sqrt{s}$.

The rate of spatial spread of a beneficial allele. Consider a beneficial mutation that has arisen in a specific spatial location and has begun to spread geographically.

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5 Stochasticity and Genetic Drift in allele frequencies

5.1 Stochastic loss of strongly selected alleles

Even strongly selected alleles can be lost from the population when they are sufficiently rare. This is because the number of offspring left by individuals to the next generation is fundamentally stochastic. A selection coefficient of s=1% is a strong selection coefficient, which can drive an allele through the population in a few hundred generations once the allele is established. However, if individuals have on average a small number of offspring per generation the first individual to carry our allele who has on average 1% more children could easily have zero offspring, leading to the loss of our allele before it ever get a chance to spread.

To take a first stab at this problem lets think of a very large haploid population, and in order for this population to stay constant in size we'll assume that individuals without the selected mutation have on average one offspring per generation. While individuals with our selected allele have on average $1 + s$ offspring per generation. We'll assume that the distribution of offspring number of an individual is Poisson distributed with this mean, i.e. the probability that an individual with the selected allele has i children is

$$P_i = \frac{(1+s)^i e^{-(1+s)}}{i!} \tag{171}$$

Consider starting from a single individual with the selected allele, and ask about the probability of eventual loss of our selected allele starting from this single copy (p_L). To derive this we'll make use of a simple argument (derived from branching processes). Our selected allele will be eventually lost from the population if every individual with the allele fails to leave descendants.

1. In our first generation with probability P_0 our individual leaves no copies of itself to the next generation, in which case our allele is lost (Figure 23A).

2. Alternatively it could leave one copy of itself to the next generation (with probability P_1), in which case with probability p_L this copy eventually goes extinct (Figure 23B).

3. It could leave two copies of itself to the next generation (with probability P_2), in which case with probability p_L^2 both of these copies eventually goes extinct (Figure 23C).

4. More generally it could leave could leave k copies ($k > 0$) of itself to the next generation (with probability P_k), in which case with probability p_L^k all of these copies eventually go extinct (e.g. Figure 23D).

summing over these probabilities we see that

$$
\begin{aligned}
p_L \quad &= \textstyle\sum_{k=0}^{\infty} P_k p_L^k \\
&= \textstyle\sum_{k=0}^{\infty} \frac{(1+s)^k e^{-(1+s)}}{k!} p_L^k \\
&= e^{-(1+s)} \left(\textstyle\sum_{k=0}^{\infty} \frac{(p_L(1+s))^k}{k!} \right)
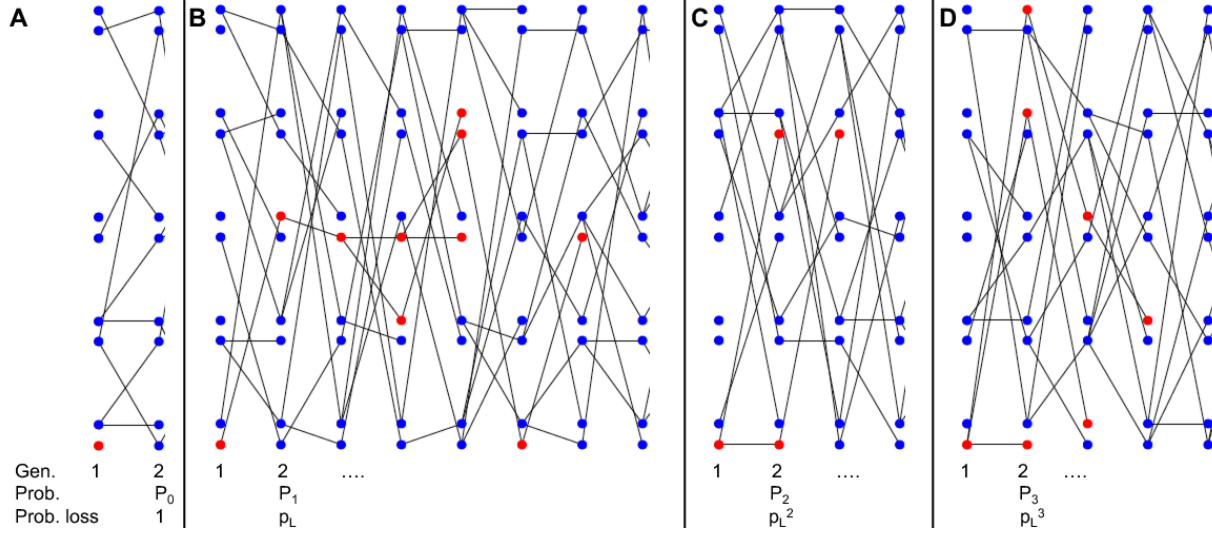\end{aligned} \tag{172}
$$

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Figure 23:

well the term in the brackets is itself an exponential expansion, so we can rewrite this as

$$p_L = e^{(1+s)(p_L-1)} \tag{173}$$

solving this would give us our probability of loss for any selection coefficient. Lets rewrite this in terms of the the probability of escaping loss $p_F = 1 - p_L$. We can rewrite eqn (173) as

$$1 - p_F = e^{-p_F(1+s)} \tag{174}$$

to gain an approximation to this lets consider a small selection coefficient $s \ll 1$ such that $p_F \ll 1$ and then expanded out the exponential on the right hand side (ignoring terms of higher order than s^2 and p_F^2) then

$$1 - p_F \approx 1 - p_F(1+s) + p_F^2(1+s)^2/2 \tag{175}$$

solving this we find that

$$p_F = 2s. \tag{176}$$

Thus even an allele with a 1% selection coefficient has a 98% probability of being lost when it is first introduced into the population by mutation.

We can also adapt this result to a diploid setting. Assuming that heterozygotes for the 1 allele have $1 + (1-h)s$ children, the probability of allele 1 is not lost, starting from a single copy in the population, is

$$p_F = 2(1-h)s \tag{177}$$

for $h > 0$. Note this is a slightly different parameterization from our diploid model above.

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> **Question 1.** Melanic squirrels suffer a higher rate of predation (due to hawks) than normally pigmented squirrels. Melanism is due to a dominant, autosomal mutation. The frequency of melanic squirrels at birth is 4×10^{-5}.
>
> **A)** If the mutation rate to new melanic alleles is 10^{-6}, assuming the melanic allele is at mutation-selection equilibrium, what is the reduction in fitness of the heterozygote? Suddenly levels of pollution increase dramatically in our population, and predation by hawks now offers an equal (and opposite) advantage to the dark individuals as it once offered to the normally pigmented individuals.
> **B)** What is the probability that a single copy of this allele (present just once in the population) is lost?
> **C)** If the population size of our squirrels is a million individuals, and is at mutation selection-balance, what is the probability that the population adapts from anyone of these standing pool of melanic alleles?

5.2 The interaction between genetic drift and weak selection.

For strongly selected alleles, once the allele has escaped initial loss at low frequencies, their path will be determined deterministically by their selection coefficients. However, if selection is weak the stochasticity of reproduction can play a role in the trajectory an allele takes even when it is common in the population.

To see this lets think of our simple Wright-Fisher model (see R exercise). Each generation we allow a deterministic change in our allele frequency, and then binomially sample two alleles for each of our offspring to construct our next generation.

So the expected change in our allele frequency within a generation is given just by our deterministic formula. To make things easy on our self lets assume an additive model, i.e. $h = 1/2$, and that $s \ll 1$ so that $\overline{w} \approx 1$. This gives us

$$\mathbb{E}(\Delta p) = \frac{s}{2}p(1-p) \tag{178}$$

our variance in our allele frequency change is given by

$$Var(p' - p) = Var(p') = \frac{p'(1-p')}{2N} \tag{179}$$

this variance in our allele frequency follows from the fact that we are binomially sampling $2N$ new alleles in the next generation from a frequency p'. Denoting our count of allele 1 by i our

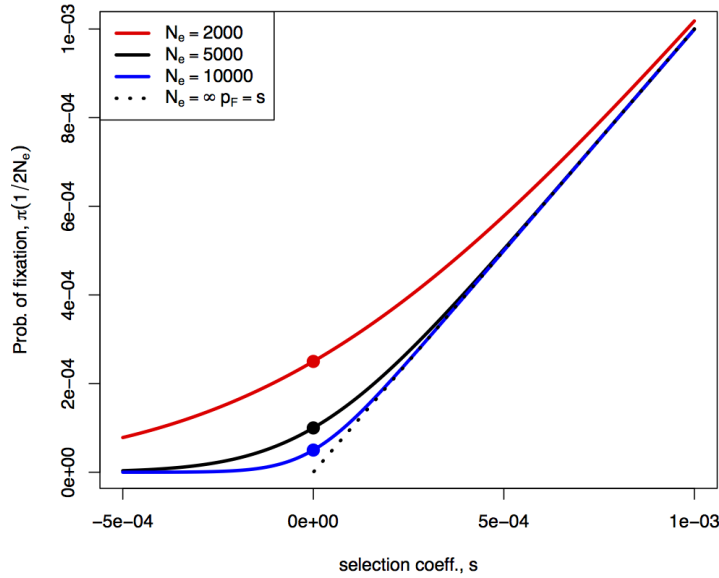$$Var(p' - p) = Var(\frac{i}{2N} - p) = Var(\frac{i}{2N}) = \frac{Var(i)}{(2N)^2} \tag{180}$$

Figure 24: The probability of the fixation of a new mutation with selection coefficient s ($h = 1/2$) in a diploid population of effective size N_e. The dashed line gives the infinite population solution. The dots give the solution for $s \to 0$, i.e. $1/(2N_e)$

and from binomial sampling $Var(i) = 2Np'(1-p')$ and so we arrive at our answer. Assuming that $s \ll 1$, $p' \approx p$, then in practice we can use

$$Var(\Delta p) = Var(p' - p) \approx \frac{p(1-p)}{2N}.$$
(181)

To get our first look at the relative effects of selection vs drift we can simply look at when our change in allele frequency caused selection within a generate is reasonably faithfully passed across the generations. In particular if our expected change in frequency is much great than the variance around this change, genetic drift will play little role in the fate of our selected allele (once the allele is not too rare within the population). When does selected dominant genetic drift? This will happen if $\mathbb{E}(\Delta p) \gg Var(\Delta p)$ when $Ns \gg 1$. Conversely any hope of our selected allele following its deterministic path will be quickly undone if our change in allele frequencies due to selection is much less than the variance induced by drift. So if $Ns \ll 1$ then drift will dominate the fate of our allele.

To make further progress on understanding the fate of alleles with selection coefficients of the order $1/N$ requires more careful modeling. However, we can obtain the probability that under our diploid model, with an additive selection coefficient s, the probability of allele 1

fixing within the population starting from a frequency p is given by

$$\pi(p) = \frac{1 - e^{-2Nsp}}{1 - e^{-2Ns}} \tag{182}$$

the proof of this is sketched out below (see Section 5.2.2). A new allele will arrive in the population at frequency $p = 1/(2N)$, then its probability of reaching fixation is

$$\pi\left(\frac{1}{2N}\right) = \frac{1 - e^{-s}}{1 - e^{-2Ns}} \tag{183}$$

if $s \ll 1$ but $Ns \gg 1$ then $\pi(\frac{1}{2N}) \approx s$, which nicely gives us back our result that we obtained above (eqn. (177)). Our probability of fixation (eqn. (183)) is plotted as a function of s and N in Figure 24. To recover our neutral result we can take the limit $s \to 0$ to obtain our neutral fixation probability $1/(2N)$.

In the case where Ns close to 1 then

$$\pi\left(\frac{1}{2N}\right) \approx \frac{s}{1 - e^{-2Ns}} \tag{184}$$

this is greater than our result $p_F = s$ from the branching process argument (using our additive model of $h = 1/2$), increasingly so for smaller N. Why is this? The reason why is that p_F is really the probability of never being lost in an infinitely large population. So to persist indefinitely the allele has to escape loss permanently, by never being absorbed by the zero state. When the population size is finite, to fix we only need to reach a size 2N individuals. Weakly beneficial mutations (Ns 1) are slightly more likely to fix than the s probability, as they only have to reach 2N to never be lost.

5.2.1 The fixation of slightly deleterious alleles.

From Figure 24 we can see that weakly deleterious alleles can fix, especially in small populations. To understand how likely it is that deleterious alleles accidently reach fixation by genetic drift, lets assume a diploid model with additive selection (with a selection coefficient of $-s$ against our allele 2). If $Ns \gg 1$ then our deleterious allele (allele 2) can not possibly reach fixation. However, if Ns is not large then

$$\pi\left(\frac{1}{2N}\right) \approx \frac{s}{e^{2Ns} - 1} \tag{185}$$

for our deleterious allele. So deleterious alleles can fix within populations (albeit at a low rate) if Ns is not too large. As above this is because while deleterious mutations will never escape loss in infinite population, but they can become fixed in finite population by reach 2N copies. This is captured by the denominator of the fixation probability under the diffusion model, which that this increases the fixation prob. of alleles with —Ns— 1. The absorption

of alleles at 2N copies can also be modeled in finite individual models (i.e. not the diffusion limit), but we will not go into that here.

Question 2. 'Haldane's sieve is the name for the idea that the mutations that contribute to adaptation are likely to be dominant or at least co-dominant.
A) Briefly explain this argument with a verbal model relating to the results weve developed in the last two chapters.
B) Haldanes sieve is thought to be less important for adaptation from previously deleterious standing variation, than adaptation from new mutation. Can you explain the intuition behind of this idea?
C) Haldanes sieve is likely to be less important in inbred, e.g. selfing, populations. Why is this?

5.2.2 A Sketch Proof of the probability of fixation of weakly selected alleles

We'll let $P(\Delta p)$ be the probability that our allele frequency shifts by Δp in the next generation. Using this we can write our probability $\pi(p)$ in terms of the probability of achieving fixation averaged over the frequency in the next generation

$$\pi(p) = \int \pi(p + \Delta p) P(\Delta p) d(\Delta p) \tag{186}$$

This is very similar to the technique that we used deriving our probability of escaping loss in a very large population above.

So we need an expression for $\pi(p + \Delta p)$. To obtain this we'll do a Taylor series expansion of $\pi(p)$ assuming that Δp is small

$$\pi(p + \Delta p) \approx \pi(p) + \Delta p \frac{d\pi(p)}{dp} + (\Delta p)^2 \frac{d^2\pi(p)}{dp^2}(p) \tag{187}$$

ignoring higher order terms.

Taking the expectation over Δp on both sides, as in eqn. 186, we obtain

$$\pi(p) = \pi(p) + \mathbb{E}(\Delta p)\frac{d\pi(p)}{dp} + \mathbb{E}((\Delta p)^2)\frac{d^2\pi(p)}{dp^2} \tag{188}$$

Well $\mathbb{E}(\Delta p) = \frac{s}{2}p(1-p)$ and $Var(\Delta p) = \mathbb{E}((\Delta p)^2) - \mathbb{E}^2(\Delta p)$, so if $s \ll 1$ then $\mathbb{E}^2(\Delta p) \approx 0$, and $\mathbb{E}(\Delta p)^2 = \frac{p(1-p)}{2N}$. This leaves us with

$$0 = \frac{s}{2}p(1-p)\frac{d\pi(p)}{dp} + \frac{p(1-p)}{2N}\frac{d^2\pi(p)}{dp^2} \tag{189}$$

and we can specify the boundary conditions to be $\pi(1) = 1$ and $\pi(0) = 0$. Solving this differential equation is somewhat involved process but in doing so we find that

$$\pi(p) = \frac{1 - e^{-2Nsp}}{1 - e^{-2Ns}} \tag{190}$$

This proof can be extended to alleles with arbitrary dominance, however, this does not lead to a analytically tractable expression so we do not pursue this here.

6 The effect of linked selection on patterns of neutral diversity

A newly derived allele with an additive selection coefficient s will take a time $\tau \approx 4\log(2N)/s$ generations to reach to fixation within our population (see eqn. (147)). This short time window offers very little time for recombination between the selected site and linked neutral sites.

First lets imagine examining variation at a locus fully linked to our selected locus, just after our sweep reached fixation. A pair of neutral alleles sampled at this locus must both trace their ancestral lineages back through to the neutral allele on whose background the selected allele initially arose. As that neutral allele, which existed τ generations ago is the ancestor of the entire population at this locus. Our individuals who carry the beneficial allele are, from the perspective of these two alleles, exactly like a rapidly expanding population. Therefore, our pair of neutral alleles sampled at our locus will be forced to coalesce $\approx \tau$ generations ago. This is a very short-time scale compared to the average neutral coalescent tie of $2N$ generations of a pair of alleles.

If we now allow recombination into our model we can think about a pair of alleles sampled at a neutral locus a recombination distance r away from our selected site. Our pair of alleles will be forced to coalesce $\approx \tau$ generations if neither of them reside on haplotypes that the selected allele recombined onto during the sweep. This is equivalent to saying that neither of our neutral alleles recombine off of the beneficial allele's background moving backward in time.

The probability that our lineage fail recombines off our beneficial allele's background and onto the ancestral background in the jth generation back is

$$r(1 - X(j)) \tag{191}$$

so the probability (p_{NR}) that our lineage fails to recombine off in the τ generations it takes our selected allele to move through the population is

$$p_{NR} = \prod_{j=1}^{\tau} \left(1 - r(1 - X(j))\right) \tag{192}$$

assuming that r is small then $(1 - r(1 - X(j))) \approx e^{-r(1-X(j))}$, such that

$$p_{NR} = \prod_{j=1}^{\tau} (1 - r(1 - X(j))) \approx \exp\left(-r\sum_{j=1}^{\tau} 1 - X(j)\right) = \exp\left(-r\tau(1 - \widehat{X})\right) \tag{193}$$

where $\widehat{X}$ is the average frequency of the derived allele across the trajectory $\widehat{X} = \frac{1}{\tau}\sum_{j=1}^{\tau} X(j)$. As our allele is additive its trajectory for frequencies < 0.5 is the mirror image of its trajectory for frequency > 0.5, therefore it average frequency $\widehat{X} = 0.5$. So

$$p_{NR} = e^{-r\tau/2}. \tag{194}$$

The probability that both of our lineages fail to recombine off the sweep and hence are forced to coalesce is p_{NR}^2, assuming that they coalesce at a time close to τ so that they recombine independently of each other for times $< \tau$.

If one or other of our lineages recombine off the sweep it will take them on average $\approx 2N$ generations to find a common ancestor as we are back our neutral coalescent. Thus the expected time till our pair of lineages find a common ancestor is

$$\mathbb{E}(T_2) = \tau \times p_{NR}^2 + (1 - p_{NR}^2)(\tau + 2N) \approx \left(1 - p_{NR}^2\right) 2N \tag{195}$$

where this last approximation assumes that $\tau \ll 2N$. So the expected pairwise diversity for neutral alleles at a recombination distance r away from the selected sweep (π_r) is

$$\mathbb{E}(\pi_r) = 2\mu\mathbb{E}(T_2) \approx \theta\left(1 - e^{-r\tau}\right) \tag{196}$$

so diversity increases as we move away from the selected site, slowly exponentially plauteuing to its neutral expectation $\theta = 4N\mu$.

To get a sense of the physical scale over which diversity is reduced consider a region where recombination occurs at a rate r_{BP} per base pair per generation, and our locus is ℓ base pairs away from the selected site $r = r_{BP}\ell$ (where $r_{BP}\ell \ll 1$ so we don't need to worry about more than one recombination event occurring per generation). Typical recombination rates are on the order of $r_{BP} = 10^{-8}$, in Figure 25 we show the reduction in diversity, given by eqn. (196), for two different selection coefficients.

For our expected diversity levels to recover to 50% of its neutral expectation $\mathbb{E}(\pi_r)/\theta = 0.5$, requires a physical distance ℓ^* such that $\log(0.5) = -r_{BP}\ell^*\tau$ as using our expression for τ then $\ell^* = \frac{-\log(0.5)}{r_{BP}\tau}$. As τ depends inversely on the selection s (eqn. (147)), the width of our trough of reduced diversity depends on s/r_{BP}. All else being equal we expect stronger sweeps or sweeps in regions of low recombination to have a larger hitchhiking effect. So that a selection coefficient of $s = 0.1\%$ would reduce diversity over 10's of kb, while a sweep of $s = 1\%$ would affect $\sim$100kb.

Question 1. A recently published study has identified the genetic basis of melanism in the pepper moth. This allele swept to fixation in northern parts of the UK; a classic case of adaptation to industrial pollution (made famous by the work of Kettlewell). The genetic basis of melanism is a transposable element (TE) inserted into a pigmentation gene. The investigators found that diversity is suppressed in a broad region around the TE. Specifically, on the background of the TE, it takes roughly 200 kb in either direction for diversity levels to recover to 50% of genome-wide levels.

Random facts: In all moths and butterflies only males recombine; chromosomes are transmitted without recombination in female. The recombination rate in males is 2.9 cM/Mb.
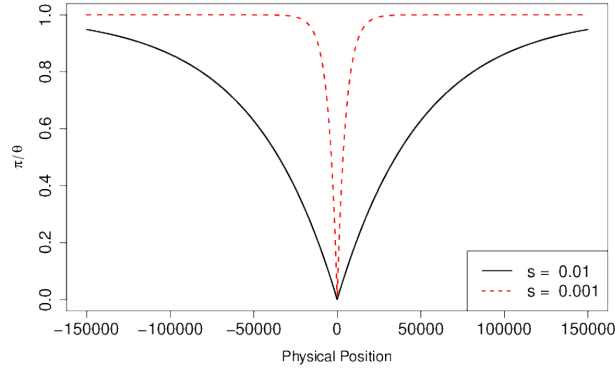
Figure 25: Reduction in diversity compared to its neutral expectation as a function of the distance away from a site where a selected allele has just gone to fixation. The recombination rate is $r_{BP} = 1 \times 10^{-8}$.

Peppered moths have an effective population size of roughly a hundred thousand individuals. Kettlewell used to eat moths when out collecting them in the field (personal communication, Art. Shapiro).
A) Briefly explain how this pattern offers further evidence that the melanic allele was favoured by selection.
B) Using this information what is your estimate as to the age of the allele?
C) What is your estimate of the selection coefficient favouring this melanic?

6.1   A simple recurrent model of selective sweeps

We sample a pair of neutral alleles at a locus a genetic distance r away from a locus where sweeps are initiated within the population at some very low rate ν per generation. The waiting time between sweeps at our locus is exponential $\sim Exp(\nu)$. Each sweep rapidly transits through the population in τ generations, such that each sweep is finished long before the next sweep ($\tau \ll 1/\nu$).

As before our chance that our neutral lineage fails to recombine off the sweep is p_{NR}, such that the probability that our pair of lineages are forced to coalesce by a sweep $e^{-r\tau}$. Our lineages therefore have a very low probability

$$\nu e^{-r\tau} \tag{197}$$

of being forced to coalesce by a sweep per generation. In addition of lineages can coalesce at a neutral rate of $1/(2N)$. Thus the average waiting time till a coalescent event between

90

our neutral pair of lineages due to either a sweep or a neutral coalescent event is

$$\mathbb{E}(T_2) = \frac{1}{\nu e^{-r\tau} + 1/(2N)} \tag{198}$$

Now imagine that the sweeps don't occur at a fixed location with respect to our locus of interest, but now occur uniformly at random across our sequence. The sweeps are initiated at a very low rate of ν_{BP} per basepair per generation. The rate of coalescent due to sweeps at a locus ℓ basepairs away from our neutral loci is $\nu_{BP}e^{-r_{BP}\ell\tau}$. If our neutral locus is in the middle of a chromosome that stretches L basepairs in either direction the total rate of sweeps per generation that force our pair of lineages to coalesce is

$$2\int_0^L \nu_{BP}e^{-r_{BP}\ell\tau}d\ell = \frac{2\nu_{BP}}{r_{BP}\tau}\left(1 - e^{-r_{BP}\tau L}\right) \tag{199}$$

so that if L is very large ($r_{BP}\tau L \gg 1$) the rate of coalesce per generation due to sweeps is $\frac{2\nu_{BP}}{r_{BP}\tau}$. The total rate of coalescence for a pair of lineages per generation is then

$$\frac{2\nu_{BP}}{r_{BP}\tau} + \frac{1}{2N} \tag{200}$$

So our average time till a pair of lineages coalesce is

$$\mathbb{E}(T_2) = \frac{1}{\frac{2\nu_{BP}}{r_{BP}\tau} + \frac{1}{2N}} = \frac{r_{BP}2N}{\frac{4N\nu_{BP}}{\tau} + r_{BP}} \tag{201}$$

such that our expected pairwise diversity ($\pi = 2\mu\mathbb{E}(T_2)$) in a region of recombination rate r_{BP} that experiences sweeps at rate ν_{BP} is

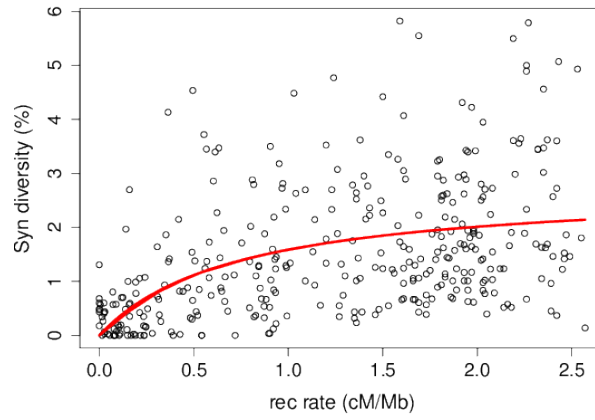$$\mathbb{E}(\pi) = \theta\frac{r_{BP}}{\frac{4N\nu_{BP}}{\tau} + r_{BP}} \tag{202}$$

Figure 26: The relationship between (sex-averaged) recombination rate and synonymous site pairwise diversity (π) in *Drosophila melanogaster* using the data of Shapiro et al. 07 (kindly provided by Peter Andolfatto, see Sella et al. 09 for details). The curve is the predicted relationship between π and recombination rate obtained by fitting equation (202) to this data using non-linear least squares via the `nls()` function in `R`.

6.2 Interaction of multiple selected loci.

Consider two biallelic loci segregating for A/a and B/b. There are four haplotypes AB, Ab, aB, ab, which for simplicity we label 1-4. The frequency of our four haplotypes are x_1, x_2, x_3, and x_4. Each individual has a genotype consisting of two haplotypes, we label w_{ij} the fitness of an individual with the genotype made up of haplotype i and j (we assume that $w_{ij} = w_{ji}$, i.e. there are no parent of origin effects). Assuming that these fitnesses reflect differences due to viability selection, and that individuals mate at random, we can write the following table of our genotype proportions after selection:

	AB	Ab	aB	ab
AB	$w_{11}x_1^2$	$w_{12}2x_1x_2$	$w_{13}2x_1x_3$	$w_{14}2x_1x_4$
Ab	$\bullet$	$w_{22}x_2^2$	$w_{23}2x_2x_3$	$w_{24}2x_2x_4$
aB	$\bullet$	$\bullet$	$w_{33}x_3^2$	$w_{34}2x_3x_4$
ab	$\bullet$	$\bullet$	$\bullet$	$w_{44}x_4^2$

This follows from assume that our haplotypes are brought together at random (HWE) then discounted by their fitnesses. Our mean fitness $\bar{w}$ is the sum of all the entries in the table, which normalized the complete table to sum to one. The frequency of AB haplotype (1) in the next generation of gametes is

$$x_1' = \frac{\left(w_{11}x_1^2 + \frac{1}{2}w_{12}2x_1x_2 + \frac{1}{2}w_{13}2x_1x_3 + \frac{1}{2}(1-r)w_{14}2x_1x_4 + \frac{1}{2}rw_{23}2x_2x_3\right)}{\bar{w}} \tag{203}$$

Here each of the HWE genotype frequencies (e.g. $2x_1x_2$) is weighted by their fitness relative to the mean fitness ($w_{ij}/\bar{w}$), and by their probability of transmitting the AB haplotype to the next generation, for example AB/Ab individuals (1/2) transmit the AB haplotype only half the time. The final two terms include the recombination fraction (r). The first term involving recombination refers to the AB/ab genotype (1/4), who with probability $(1-r)/2$ transmit a non-recombinant AB haplotype to the gamete. Similarly the second term refers to a Ab/aB genotype, a proportion $r/2$ of their gametes carry the recombinant AB haplotype.

In the single locus case we defined the marginal fitness of an allele, here it will help us to define the mariginal fitness of the ith haplotype

$$\bar{w}_i = \sum_{j=1}^{4} w_{ij}x_j \tag{204}$$

this is the fitness of the ith haplotype averaged over all of the genotypes it could occur in, weighted by their probability under random mating. Using this notation, and with some rearrangement of equation (203), we obtain

$$x_1' = \frac{x_1\bar{w}_1 - w_{14}rD}{\bar{w}} \tag{205}$$

here we have assumed that $w_{23} = w_{14}$, i.e. that the fitness of AB/ab individuals is the same as Ab/aB individuals (i.e. that fitness depends only on the alleles carried by an individual,

and not on which chromosome they are carried, this assumption is sometimes called no *cis*-epistasis).

We can then write the change in the frequency of our 1 haplotype as

$$\Delta x_1 = \frac{x_1(\bar{w}_1 - \bar{w}) - r w_{14} D}{\bar{w}} \tag{206}$$

Generalizing from this we write the change in our set of four haplotypes as

$$\Delta x_i = \frac{x_1(\bar{w}_i - \bar{w}) \pm r w_{14} D}{\bar{w}} \tag{207}$$

where the coupling haplotypes 1 and 4 use $+D$ and repulsion haplotypes 2 and 3 use $-D$. Note that the sum of these four Δx_i is zero, as our allele frequencies sum to one.

So the change in the frequency of a haplotype (eg AB, haplotype 1) is determined by the interplay of two factors. First the extent to which the marginal fitness of our haplotype is higher (or lower) than the mean fitness of the population (the magnitude and sign of $(\bar{w}_1 - \bar{w})/\bar{w}$). Second whether there is a deficit or any excess of our haplotype compared to linkage equilibrium (the magnitude and sign of D) modified by the strength of recombination.