6 Random Events in Population Genetics

The genotypes at a locus may all have the same fitness. Then the gene frequencies evolve by random genetic drift. This chapter starts by explaining why drift happens and what it means, and looks at examples of random sampling effects. We see how drift is more powerful in small than large popuations, and how in small populations it can counteract the effects of natural selection. We then see how drift can ultimately fix one allele. The Hardy–Weinberg ratios are not at an equilibrium once we allow for the effects of drift. We then add the effects of mutation, which introduces new variation: the variation observed in a population will be a balance between the drift to homozygosity and mutation that creates heterozygosity.

6.1 The frequency of alleles can change at random through time in a process called genetic drift

Imagine a population of 10 individuals, of which three have genotype *AA*, four have *Aa*, and three *aa*. There are 10 *A* genes in the population and 10 *a* genes; the gene frequencies of each gene are 0.5. We also imagine that natural selection is not operating: all genotypes have the same fitness. What will the gene frequencies be in the next generation? The most likely answer is 0.5 *A* and 0.5 *a*. However, this is only the most likely answer; it is not a certainty. The gene frequencies may by chance change a little from the previous generation. This can happen because the genes that form a new generation are a *random sample* from the parental generation. Box 6.1 looks at how genes are sampled from the parental gene pool, to produce the offspring generation's gene pool. In this chapter we look at the effect of random sampling on gene frequencies.

Genetic drift occurs because of random sampling

The easiest case in which to see the effect of random sampling is when natural selection is not acting. When the genotypes at a locus all produce the same number of offspring (they have identical fitness), the condition is called selective *neutrality*. We can write the fitnesses out in the same way as in Chapter 5, as follows:

Genotype	*AA*	*Aa*	*aa*
Fitness	1	1	1

Natural selection is not acting, and we might expect the gene frequencies to stay constant over time. Indeed, according to the Hardy–Weinberg theorem, the genotype frequencies should be constant at p^2, $2pq$, and q^2 (where p is the frequency of the gene *A* and q is the frequency of the gene *a*). But in fact random sampling can cause the gene frequencies to change. By chance, copies of the *A* gene may be luckier in reproduction, and the frequency of the *A* gene will increase. The increase is random, in the sense that the *A* gene is as likely by chance to decrease as to increase in frequency; but some gene frequency changes will occur. These random changes in gene frequencies between generations are called *genetic drift*, *random drift*, or (simply) *drift*. The word "drift" can be misleading if it is taken to imply an inbuilt bias in one direction or the other. Genetic drift is directionless drift.

Genetic drift is not confined to the case of selective neutrality. When selection is acting at a locus, random sampling also influences the change in gene frequencies between generations. The interaction between selection and drift is an important topic in evolutionary biology, as we shall see in Chapter 7. However, the theory of drift is easiest to understand when selection is not complicating the process and in this chapter we shall mainly look at the effect of drift by itself.

The power of drift depends on population size

The rate of change of gene frequency by random drift depends on the size of the population. Random sampling effects are more important in smaller populations. For example (Figure 6.1), Dobzhansky and Pavlovsky (1957), working with the fruitfly *Drosophila pseudoobscura*, made 10 populations with 4,000 initial members (large populations) and 10 with 20 initial members (small populations), and followed the change in frequency of two chromosomal variants for 18 months. The average effect was the same in small and large populations, but the variability was significantly greater among the small populations. An analogous result could be obtained by flipping 10 sets of 20,

Box 6.1
Random Sampling in Genetics

Random sampling starts at conception. In every species, each individual produces many more gametes than will ever fertilize, or be fertilized, to form new organisms. The successful gametes which do form offspring are a sample from the many gametes that the parents produce. If a parent is homozygous, the sampling makes no difference to what genes end up in the offspring; all of a homozygote's gametes contain the same gene. However, sampling does matter if the parent is a heterozygote, such as *Aa*. It will then produce a large number of gametes, of which approximately one-half will be *A* and the other half *a*. (The proportions may not be exactly one-half. Reproductive cells may die at any stage leading to gamete formation, or after they have become gametes; also, in the female, a randomly picked three-quarters of the products of meiosis are lost as polar bodies.) If that parent produces 10 offspring, it is most likely that five will inherit an *A* gene and five *a*. But because the gametes that formed the offspring were sampled from a much larger pool of gametes, it is possible that the proportions would be something else. Perhaps six inherited *A* and only four *a*, or three inherited *A* and seven *a*.

In what sense is the sampling of gametes random? We can see the exact meaning if we consider the first two offspring produced by an *Aa* parent. When it produces its first offspring, one gamete is sampled from its total gamete supply, and there is a 50% chance it will be an *A* and 50% that it will be an *a*. Suppose it happens to be an *A*. The sense in which sampling is random is that it is no more likely that the next gamete to be sampled will be an *a* gene just because the last one sampled was an *A*: the chance that the next successful gamete will be an *a* is still 50%. Coin flipping is random in the same way: if you first flip a head, the chance that the next flip will be a head is still one-half. The alternative would be some kind of "balancing" system in which, after an *A* gamete had been successful in reproduction, the next successful gamete would be an *a*. If reproduction was like that, the gene frequency contributed by a heterozygote to its offspring would always be exactly $^1/_2A$: $^1/_2a$. Random drift would then be unimportant in evolution. In fact reproduction is not like that. The successful gametes are a random sample from the gamete pool.

The sampling of gametes is only the first stage at which random sampling occurs. It continues at every stage as the adult population of a new generation grows up. Here is an imaginary example. Imagine a line of 100 pack horses are walking single file along a hazardous mountain path, but only 50 of them make it safely; the other 50 fall off the path and crash down the ravine. It could be that the 50 survivers were on average genetically surer of foot than the rest; the sampling of 50 survivers out of the original 100 would then be non-random. Natural selection would be determining which horses survived and which died. If we looked at the genotypic frequencies among the smashed horses at the bottom of the ravine they would differ from those among the survivers. Alternatively, death could be accidental: it could happen whenever a large rock bounced down the mountainside from above, and knocked one horse into the ravine. Suppose that the rocks come at unpredictable times and places and arrive so suddenly that defensive action is impossible; the horses do not vary genetically in their ability to avoid the falling rocks. The loss of genotypes would then be random in the sense defined above. If an *AA* horse had just fallen victim to a rock, that does not make it any more or less likely that the next victim will have the *AA* genotype. Now if we compared the genotype frequencies in the survivers and non-survivers, it is most likely that the two would not differ. The survivers would be a random genetic sample from the original population. They could, however, differ by chance. More *AA* horses might have been unlucky with falling rocks; more *aa* might have been lucky. Then there would be some increase in the frequency of the *a* gene in the population.

The sampling of pack horses is imaginary, but analogous sampling may happen at any time in a population, and at any life stage as juveniles develop into adults. Because there are many more eggs than adults, there is abundant opportunity for sampling as each new generation grows up. Random sampling occurs whenever a smaller number of successful individuals (or gametes) are sampled from a larger pool of potential survivers and the fitnesses of the genotypes are the same.

or 4,000, coins. On average, there would be 50% heads in both cases, but the chance of flipping 12 heads and 8 tails in the small population is higher than the chance of flipping 2,400 heads and 1,600 tails in the large.

If a population is small, it is more likely that a sample will be biased away from the average by any given percentage amount; genetic drift is therefore greater in smaller

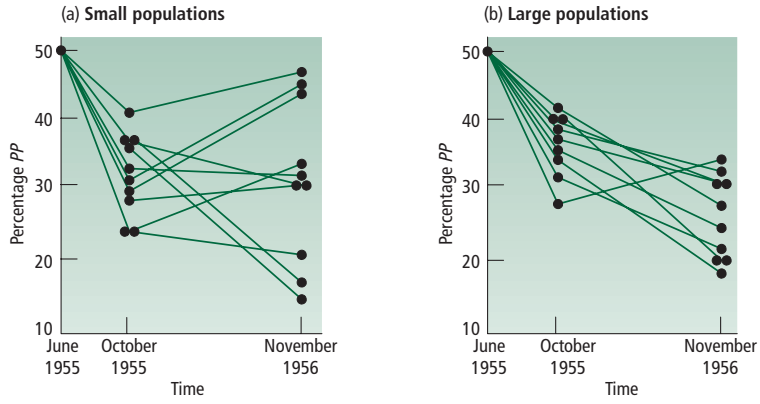

Figure 6.1
Random sampling is more effective in small populations (a) than in large (b). Ten large (4,000 founders) and 10 small (20 founders) populations of the fruitfly *Drosophila pseudoobscura* were created in June 1955 with the same frequencies (50% each) of two chromosomal inversions, *AP* and *PP*. Eighteen months later the populations with small numbers of founders show a greater variety of genotype frequencies. Redrawn, by permission of the publisher, from Dobzhansky (1970).

populations. The smaller the population, the more important are the effects of random sampling.

6.2 A small founder population may have a non-representative sample of the ancestral population's genes

A particular example of the influence of random sampling is given by what is called the *founder effect*. The founder effect was defined by Mayr (1963) as:

> the establishment of a new population by a few original founders (in an extreme case, by a single fertilized female) which carry only a small fraction of the total genetic variation of the parental population.

Population size may be reduced during founder events

We can divide the definition into two parts. The first part is the establishment of a new population by a small number of founders; we can call that a "founder event." The second part is that the founders have a limited sample of genetic variation. The full founder effect requires not only a founder event, but also that the founders are genetically unrepresentative of the original population.

Founder events undoubtedly happen. A population may be descended from a small number of ancestral individuals for either of two main reasons. A small number of individuals may colonize a place previously uninhabited by their species; the 250 or so individuals making up the modern human population on the island of Tristan da Cunha, for example, are all descended from about 20–25 immigrants in the early nineteenth century, and most are descended from the original settlers — one Scotchman and his family — who arrived in 1817. Alternatively, a population that is established in an area may fluctuate in size; the founder effect then occurs when the population passes through a "bottleneck" in which only a few individuals survive, and later expands again when more favorable times return.

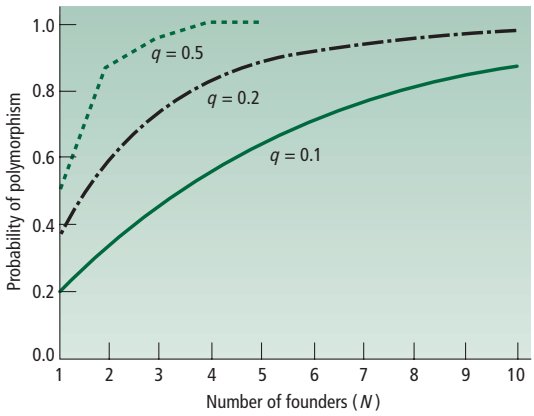

Figure 6.2
The chance that a founder population will be homozygous depends on the number of founders and the gene frequencies. If there is less variation and fewer founders, the chance of homozygosity is higher. Here the chance of homozygosity is shown for three different gene frequencies at a two-allele locus.

Founder events are unlikely to produce homozygosity

If a small sample of individuals is taken from a larger population, what is the chance that they will have reduced genetic variation? We can express the question exactly by asking what the chance is that an allele will be lost. In the special case of two alleles (*A* and *a* with proportions *p* and *q*), if one of them is not included in the founder population, the new population will be genetically monomorphic. The chance that an individual will be homozygous *AA* is simply p^2. The chance that two individuals drawn at random from the population will both be *AA* is $(p^2)^2$; in general, the chance of drawing *N* identical homozygotes is $(p^2)^N$. The founding population could be homozygous either because it is made up of *N AA* homozygotes or *N aa* homozygotes, and the total chance of homozygosity is therefore:

$$\text{Chance of homozygosity} = [(p^2)^N + (q^2)^N] \tag{6.1}$$

Figure 6.2 illustrates the relation between the number of individuals in the founder population and the chance that the founder population is genetically uniform. The interesting result is that founder events are not effective at producing a genetically monomorphic population. Even if the founder population is very small, with $N < 10$, it will usually possess both alleles. An analogous calculation could be done for a population with three alleles, in which we asked the chance that one of the three would be lost by the founder effect. The resulting population would not then be monomorphic, but would have two instead of three alleles. The general point is again the same: in general, founder events — whether by colonizations or population bottlenecks — are unlikely to reduce genetic variation unless the number of founders is tiny.

However, founder events can have other interesting consequences. Although the sample of individuals forming a founder population are likely to have nearly all the ancestral population's genes, the frequencies of the genes may differ from the parental population. Isolated populations often have exceptionally high frequencies of otherwise rare alleles, and the most likely explanation is that the founding population had a disproportionate number of those rare alleles. The clearest examples all come from humans.

Consider the Afrikaner population of South Africa, who are mainly descended from one shipload of immigrants who landed in 1652, though later arrivals have added to it.

The population has increased dramatically since then to its modern level of 2,500,000. The influence of the early colonists is shown by the fact that almost 1,000,000 living Afrikaners have the names of 20 of the original settlers.

Several human populations have otherwise rare genes in high frequency

The early colonists included individuals with a number of rare genes. The ship of 1652 contained a Dutch man carrying the gene for Huntington's disease, a lethal autosomal dominant disease. Most cases of the disease in the modern Afrikaner population can be traced back to that individual. A similar story can be told for the dominant autosomal gene causing porphyria variegata. Porphyria variegata is due to a defective form of the enzyme protoporphyrinogen oxidase. Carriers of the gene suffer a severe — even lethal — reaction to barbiturate anesthetics, and the gene was therefore not strongly disadvantageous before modern medicine. The modern Afrikaner population has about 30,000 carriers of the gene, a far higher frequency than in Holland. All the carriers are descended from one couple, Gerrit Jansz and Ariaantje Jacobs, who emigrated from Holland in 1685 and 1688, respectively. Every human population has its own "private" polymorphisms, which were probably often caused by the genetic peculiarities of founder individuals.

Both of the examples we have just considered are for medical conditions. The individual carriers of the genes will have lower fitness than average, and selection will therefore act to reduce the frequency of the gene to 0. For much of the time, the porphyria variegata gene may have had a similar fitness to other alleles at the same locus. It may have been a neutral polymorphism until its "environment" came to contain (in selected cases) barbiturates.

In contrast, the gene for Huntington's disease will have been consistently selected against. Thus its present high frequency suggests that the founder population had an even higher frequency, because it will have probably been decreased by selection since then. Any particular founder sample would not be expected to have a higher than average frequency of the Huntington's disease gene, but if enough colonizing groups set out, some of them are bound to have peculiar, or even very peculiar, gene frequencies. In the case of Huntington's disease, the Afrikaner population is not the only one descended from founders with more copies of the gene than average; 432 carriers of Huntington's disease in Australia are descended from the Miss Cundick who left England with her 13 children; and a French nobleman's grandson, Pierre Dagnet d'Assigne de Bourbon, has bequeathed all the known cases of Huntington's disease on the island of Mauritius.

6.3 One gene can be substituted for another by random drift

The frequency of a gene is as likely to decrease as to increase by random drift. On average the frequencies of neutral alleles remain unchanged from one generation to the next. In practice, their frequencies drift up and down, and it is therefore possible for a gene to enjoy a run of luck and be carried up to a much higher frequency — in the extreme case, its frequency could after many generations be carried up to 1 (become fixed) by random drift.

Evolution can occur by random drift

In every generation, the frequency of a neutral allele has a chance of increasing, a chance of decreasing, and a chance of staying constant. If it increases in one generation, it again has the same chances of increasing, decreasing, or staying constant in the next generation. A neutral allele thus has a small chance of increasing for two generations in a row (equal to the square of the chance of increasing in any one generation). It has a still smaller chance of increasing though three generations, and so on. For any one allele, fixation by random drift is very improbable. The probability is finite, however, and if enough neutral alleles, at enough loci, and over enough generations, are randomly drifting in frequency, one of them will eventually be fixed. The same process can occur whatever the initial frequency of the allele. A rare allele is less likely to be carried up to fixation by random drift than is a common allele, because it would take a longer run of "good" luck. However, fixation is still possible for a rare allele. Even a unique neutral mutation has some chance of eventual fixation. Any one mutation is most likely to be lost; but if enough mutations arise, one will be bound to be fixed eventually.

Random drift, therefore, can substitute one allele for another. What is the rate at which these substitutions occur? We might expect it would be faster in smaller populations, because most random effects are more powerful in smaller populations. However, it can be shown by an elegant argument that the neutral evolution rate exactly equals the neutral mutation rate, and is independent of population size. The argument is as follows. In a population of size N there are a total of $2N$ genes at each locus. On average, each gene contributes one copy of itself to the next generation; but because of random sampling, some genes will contribute more than one copy and others will contribute none. As we look two generations ahead, those genes that contributed no copies to the first generation cannot contribute copies to the second generation, or the third, or fourth . . . once a gene fails to be copied, it is lost forever. In the next generation some more genes will likewise "drop out," and be unable to contribute to future generations. Each generation, some of the $2N$ original genes are lost in this way (Figure 6.3).

For purely neutral drift, the rate of evolution is independent of population size

If we look far enough forwards we eventually come to a time when all the $2N$ genes are descended from just one of the $2N$ genes now. This is because in every generation

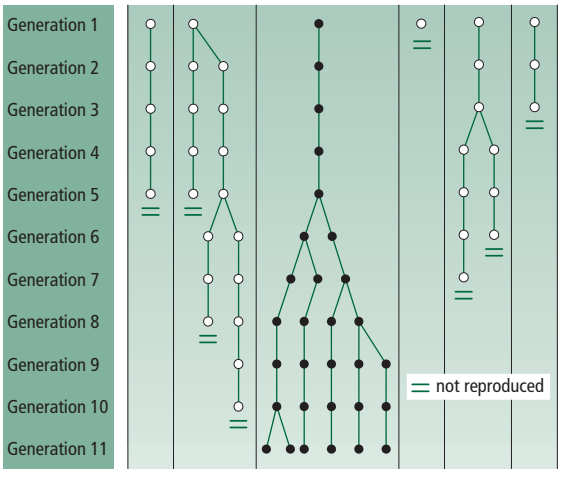

Figure 6.3
The drift to homozygosity. The figure traces the evolutionary fate of six genes; in a diploid species these would be combined each generation in three individuals. Every generation, some genes may by chance fail to reproduce and others by chance may leave more than one copy. Because once a gene has failed to reproduce its line is lost forever, over time the population must drift to become made up of descendants of only one gene in an ancestral population. In this example, the population after 11 generations is made up of descendants of gene number 3 (shaded circle) in generation 1.

some genes will fail to reproduce. We must eventually come to a time when all but one of the original genes have dropped out. That one gene will have hit a long enough run of lucky increases and will have spread through the whole population. It will have been fixed by genetic drift. Now, because the process is pure luck, each of the $2N$ genes in the original population has an equal chance of being the lucky one. Any one gene in the population, therefore, has a $1/(2N)$ chance of eventual fixation by random drift (and a $(2N-1)/(2N)$ chance of being lost by it).

Population size features in the workings . . .

Because the same argument applies to any gene in the population, it also applies to a new, unique, neutral mutation. When the new mutation arises, it will be one gene in a population of $2N$ genes at its locus (that is, its frequency will be $1/(2/N)$). The new mutation has the same $1/(2N)$ chance of eventual fixation as does every other gene in the population. The most likely fate of the new mutation is to be lost (probability of being lost $= (2N-1)/(2N) \approx 1$ if N is large); but it does have a small $(1/(2N))$ chance of success. That completes the first stage of the argument: the probability that a neutral mutation will eventually be fixed is $1/(2N)$.

The rate of evolution equals the probability that a mutation is fixed, multiplied by the rate at which mutations appear. We define the rate at which neutral mutations arise as u per gene per generation. (u is the rate at which new selectively neutral mutations arise, not the total mutation rate. The total mutation rate includes selectively favorable and unfavorable mutations as well as neutral mutations. We are here considering only the fraction of all mutations that are neutral.) At each locus, there are $2N$ genes in the population: the total number of neutral mutations arising in the population will be $2Nu$ per generation. The rate of neutral evolution is then $1/(2N) \times 2Nu = u$. The population size cancels out and the rate of neutral evolution is equal to the neutral mutation rate.

. . . and cancels out

Figure 6.3 also illustrates another important concept in the modern theory of genetic drift, the concept of coalescence (Box 6.2).

Box 6.2
The Coalescent

If we look forward far enough in time from any one generation, we must come to a time when all the genes at a locus are descended from one of the $2N$ copies of that gene in the current population (see Figure 6.3). The same argument works backwards. If we look far enough back from any one generation, we must come to a time when all the copies of the genes at one locus trace back to a single copy of that gene in the past. Thus, if we trace back from all the copies of a human gene, such as a globin gene, we must eventually come to a time in the past when only one gene gave rise to all the modern copies of the gene. (In Figure 6.3, look at generation 11 at the end. All copies of the gene trace back to a single gene in generation 5. Notice that the existence of a single ancestral gene for all the modern genes at a locus does not mean that only one gene existed at that time. Generation 5 has as many genes as every other generation.) The way all copies of a gene trace back to a single ancestral gene is called *coalescence*, and that single lucky ancestral gene is called *the coalescent*. Genetic coalescence is a consequence of the normal operation of genetic drift in natural populations. Every gene in the human species, and every gene in every species, traces back to a coalescent. The time when the coalescent existed for each gene probably differs between genes, but they all have a coalescent ancestor at some time. Population geneticists study how far back the coalescent exists for a gene, depending on population size, demography, and selection. A knowledge of the time back to the coalescent can be useful for dating events in the past using "gene trees," which we meet in Chapter 15.

Further reading: Fu & Li (1999), Kingman (2000).

6.4 Hardy–Weinberg "equilibrium" assumes the absence of genetic drift

Random drift has consequences for the Hardy–Weinberg theorem

Let us stay with the case of a single locus, with two selectively neutral alleles *A* and *a*. If genetic drift is not happening — if the population is large — the gene frequencies will stay constant from generation to generation and the genotype frequencies will also be constant, in Hardy–Weinberg proportions (Section 5.3, p. 98). But in a smaller population the gene frequencies can drift around. The average gene frequencies in one generation will be the same as in the previous generation, and it might be thought that the long-term average gene and genotype frequencies will simply be those of the Hardy–Weinberg equilibrium, but with a bit of "noise" around them. That is not so, however. The long-term result of genetic drift is that one of the alleles will be fixed. The polymorphic Hardy–Weinberg equilibrium is unstable once we allow for genetic drift.

Suppose that a population is made up of five individuals, containing five *A* alleles and five *a* alleles (that is obviously a tiny population, but the same point would apply if there were 500 copies of each allele). The genes are randomly sampled to produce the next generation. Maybe six *A* alleles are sampled and four *a* alleles. This is now the starting point to produce the next generation; the most likely ratio in the next generation is six *A* and four *a*: there is no "compensating" process to push it back toward five and five. Maybe in the next generation six *A* and four *a* are drawn again. The fourth generation might be seven *A* and three *a*, the fifth, six *A* and four *a*, the sixth, seven *A* and three *a*, then seven *A* and three *a*, eight *A* and two *a*, eight *A* and two *a*, nine *A* and one *a*, and then 10 *A*. The same process could have gone off in the other direction, or started by favoring A and then reversed to fix *a* — random drift is directionless. However, when one of the genes is fixed, the population is homozygous and will stay homozygous (Figures 6.3 and 6.4).

The Hardy–Weinberg equilibrium is a good approximation, and retains its importance in evolutionary biology. But it is also true that, once we allow for random drift, the Hardy–Weinberg ratios are not at an equilibrium. The Hardy–Weinberg ratios are for neutral alleles at a locus and the Hardy–Weinberg result suggests that the genotype (and gene) ratios are stable over time. However, random events cause gene frequencies to drift about, and one of the genes will eventually be fixed. Only then will the system be stable. The true equilibrium, incorporating genetic drift, is at homozygosity.

6.5 Neutral drift over time produces a march to homozygosity

Over the long term, pure random drift causes the population to "march" to homozygosity at a locus. The process by which this happens has already been considered (Section 6.4) and illustrated (Figure 6.3). All loci at which there are several selectively neutral alleles will tend to become fixed for only one gene. It is not difficult to derive an expression for the rate at which the population becomes homozygous. First we define the degree of homozygosity. Individuals in the population are either homozygotes or

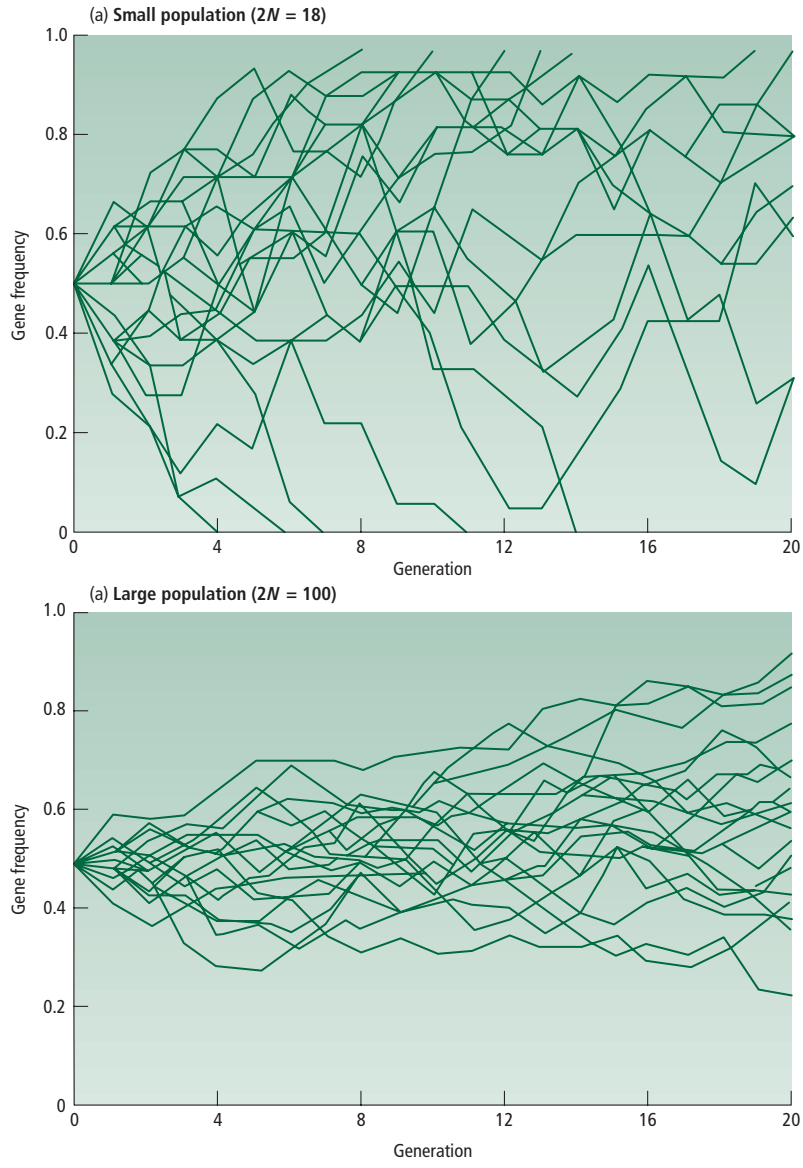

Figure 6.4
Twenty repeat simulations of genetic drift for a two-allele locus with initial gene frequency 0.5 in: (a) a small population ($2N = 18$), and (b) a larger population ($2N = 100$). Eventually one of the alleles drifts to a frequency of 1. The other alleles are then lost. The drift to homozygosity is more rapid in a smaller population, but in any small population without mutation homozygosity is the final result.

heterozygotes. Let f be the proportion of homozygotes, and $H = 1 - f$ is the proportion of heterozygotes (f comes from "fixation"). Homozygotes here includes all types of homozygote at a locus; if, for example, there are three alleles A_1, A_2, and A_3 then f is the number of A_1A_1, A_2A_2, and A_3A_3 individuals divided by the population size; H likewise is the sum of all heterozygote types. N will again stand for population size.

How will f change over time? We shall derive the result in terms of a special case: a species of hermaphrodite in which an individual can fertilize itself. Individuals in the population discharge their gametes into the water and each gamete has a chance of combining with any other gamete. New individuals are formed by sampling two

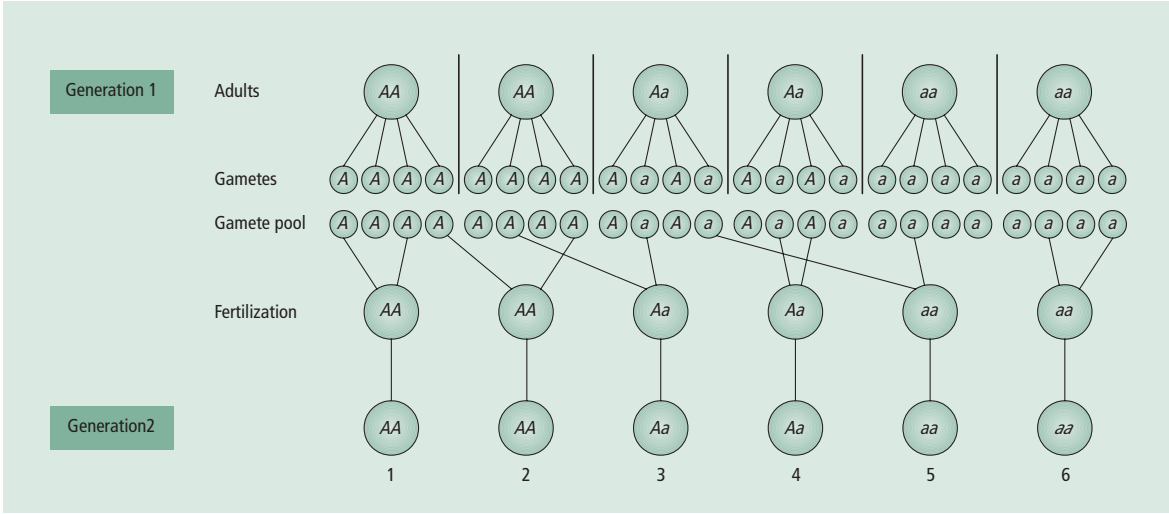

Figure 6.5
Inbreeding in a small population produces homozygosity. A homozygote can be produced either by combining copies of the same gene from different individuals, or by combining two copies of the same physical gene. Here we imagine that the population contains six adults, which are potentially self-fertilizing hermaphrodites, and each produces four gametes. Homozygotes can then be produced by the kind of cross-mating assumed in the Hardy–Weinberg theorem (e.g., offspring number 2) or by self-fertilization (e.g., offspring number 1). Self-fertilization only necessarily produces a homozygote if its parent is homozygous (compare offspring 1 and 4).

gametes from the gamete pool. The gamete pool contains $2N$ gamete types, where "gamete types" should be understood as follows. There are $2N$ genes in a population made up of N diploid individuals. A gamete type consists of all the gametes containing a copy of any one of these genes. Thus, if an individual with two genes produces 200,000 gametes, there will be on average 100,000 copies of each gamete type in the gamete pool.

We construct a model of how homozygosity changes under drift

To calculate how f, the degree of homozygosity, changes through time, we derive an expression for the number of homozygotes in one generation in terms of the number of homozygotes in the generation before. We must first distinguish between *a* gene-bearing gametes in the gamete pool that are copies of the same parental *a* gene, and those that are derived from different parents. There are then two ways to produce a homozygote, when two *a* genes from the same gametic type meet or when two *a* genes from different gametic types meet (Figure 6.5); the frequency of homozygotes in the next generation will be the sum of these two.

The first way of making a homozygote is by "self-fertilization." There are $2N$ gamete types but, because each individual produces many more than two gametes, there is a chance $1/(2N)$ that a gamete will combine with another gamete of the same gamete type as itself: if it does, the offspring will be homozygous. (If, as above, each individual makes 200,000 gametes, there would be $200{,}000N$ gametes in the gamete pool. We first sample one gamete from it. Of the remaining gametes, practically 100,000 of them (99,999 in fact) are copies of the same gene. The proportion of gametes left in the pool

that contain copies of the same gene as the gamete we sampled is 99,999/200,000N, or 1/(2N).)

The second way to produce a homozygote is by combining two identical genes that were not copied from the same gene in the parental generation. If the gamete does not combine with another copy of the same gamete type (chance $1 - (1/(2N))$) it will still form a homozygote if it combines with a copy made from the same gene but from another parent. For a gamete with an *a* gene, if the frequency of *a* in the population is p, the chance that two *a* genes meet is simply p^2. p^2 is the frequency of *aa* homozygotes in the parental generation. If there are two type of homozygote, *AA* and *aa*, the chance of forming a homozygote will be $p^2 + q^2 = f$. In general, the chance that two independent genes will combine to form a homozygote is equal to the frequency of homozygotes in the previous generation. The total chance of forming a homozygote by this second method is the chance that a gamete does not combine with another copy of the same parental gene, $1 - (1/(2N))$, multiplied by the chance that two independent genes combine to form a homozygote (f). That is, $f(1 - (1/(2N)))$.

Homozygosity can arise from crosses between different individuals

Now we can write the frequency of homozygotes in the next generation in terms of the frequency of homozygotes in the parental generation. It is the sum of the two ways of forming a homozygote. Following the normal notation for f' and f (f' is the frequency of homozygotes one generation later),

$$f' = \frac{1}{2N} + \left(1 - \frac{1}{2N}\right)f \tag{6.2}$$

Heterozygosity is a measure of genetic variation

We can follow the same march to increasing homozygosity in terms of the decreasing heterozygosity in the population. A population's "heterozygosity" is a measure of its genetic variation. In formal terms, *heterozygosity* is defined as the chance that two genes at a locus, drawn at random from the population, are different. For example, a genetically uniform population (in which everyone is *AA*) has a heterozygosity of zero. The chance of drawing two different genes is zero. If half the individuals in the population are *AA* and half are *aa*, the chance of drawing two different genes is half, and heterozygosity equals one-half. Box 6.3 describes the calculation of heterozygosity. (Heterozygosity is symbolized by H.)

Heterozygosity can be shown, by rearrangement of equation 6.2, to decrease at the following rate (the rearrangement involves substituting $H = 1 - f$ in equation 6.2):

$$H' = \left(1 - \frac{1}{2N}\right)H \tag{6.3}$$

That is, heterozygosity decreases at a rate of 1/(2N) per generation until it is zero. The population size N is again important in governing the influence of genetic drift. If N is small, the march to homozygosity is rapid. At the other extreme, we re-encounter the Hardy–Weinberg result. If N is infinitely large, the degree of heterozygosity is stable: there is then no march to homozygosity.

Although it might seem that this derivation is for a particular, hermaphroditic breeding system, the result is in fact general (a small correction is needed for the case of two sexes). The march to homozygosity in a small population proceeds because two

Box 6.3
Heterozygosity (H) and Nucleotide Diversity (π)

"Heterozygosity" is a general measure of the genetic variation per locus in a population. Imagine a locus at which two alleles (*A* and *a*) are present in the population. The frequency of *A* is *p*, the frequency of *a* is *q*. Heterozygosity is defined as the chance of drawing two different alleles if two random genes are sampled from the population (for one locus). The chance of drawing two copies of *A* is p^2, and the chance of drawing two copies of *a* is q^2. The total chance of drawing two identical genes is $p^2 + q^2$. The chance of drawing two different genes is 1 minus the chance of drawing two identical genes. Therefore, in this case $H = 1 - (p^2 + q^2)$.

In general, a population may contain any number of alleles at a locus. The different alleles can be distinguished by number subscripts. For instance, if a population has three alleles, their frequencies can be written p_1, p_2, and p_3. If a population has four alleles, their frequencies can be written p_1, p_2, p_3, and p_4, and so on for any number of alleles. We can symbolize the frequency of the *i*th allele by p_i (where *i* has as many values as there are alleles in the population). Now:

$$H = 1 - \sum p_i^2$$

The summation (symbolized by $\sum$) is over all values of *i*: that is, for all the alleles in the population at that locus. The term $\sum p_i^2$ equals the chance of picking two identical genes; $1 - t$ is the chance of picking two different genes.

If the population is in Hardy–Weinberg equilibrium, the heterozygosity equals the proportion of heterozygous individuals. But *H* is a more general definition of genetic diversity than the proportion of heterozygotes. The chance that two random genes differ measures genetic variation in all populations, whether or not they are in Hardy–Weinberg equilibrium. For example, $H = 50\%$ in a population consisting of half *AA* and half *aa* individuals (with no heterozygotes).

The term "heterozygosity" is meaningful for a diploid population. However, the same measure of genetic diversity can be used for non-diploid genes, such as the genes in mitochondria and chloroplasts. It can also be used for bacterial populations. The word "heterozygosity'" can sound rather odd for non-diploid gene loci, and population geneticists often call *H* "gene diversity."

The classic population genetic theory of diversity has been worked out in terms of heterozygosity at one locus. When talking about the theory, we usually refer to heterozygosity (*H*). However, most modern measurements of genetic diversity are at the DNA level. At this level, much the same index of diversity is referred to as "nucleotide diversity" and is symbolized by π.

Intuitively, the meaning of nucleotide diversity is as follows. Imagine picking out a stretch of DNA from two DNA molecules drawn at random from a population. Count the number of nucleotide differences between the two DNA stretches. Then divide by the length of the stretch. The result is π. π is the average number of nucleotide differences per site between a pair of DNA sequences drawn at random from a population. Here is a concrete example. Suppose a simple population has four DNA molecules. A comparable region of those four has the following set of sequences: (1) TTTTAGCC, (2) TTTTAACC, (3) TTTAAGC, and (4) TTTAGGC. We first count the number of differences between all possible pairs. Pair 1–2 has 1 difference, 1–3 has 2, 1–4 has 1, 2–3 has 1, 2–4 has 2, and 3–4 has 1. The average number of differences for all six pairwise comparisons is $(1 + 2 + 1 + 1 + 2 + 1)/6 = 1.33$. π is calculated per site, so we divide the average number of differences by the total sequence length (8). $\pi = 1.33/8 = 0.0166$. More formally,

$$\pi = \Sigma p_i p_j \pi_{ij}$$

where p_i and p_j are the frequencies of the *i*th and *j*th DNA sequence, and π_{ij} is the number of pairwise differences per site between sequences *i* and *j*. Some figures for *H* and π in real populations are given in Section 7.2 (p. 164).

The increase in homozygosity under drift is due to inbreeding

copies of the same gene may combine in a single individual. In the hermaphrodite, it happens obviously with self-fertilization. But if there are two sexes, a gene in the grandparental generation can appear as a homozygote, in two copies, in the grandchild generation. The process, by which a gene in a single copy in one individual combines in two copies in an offspring, is *inbreeding*. Inbreeding can happen in any breeding system with a small population, and becomes more likely the smaller the population. However, the general point in this section can be expressed without referring to inbreeding. With random sampling, two copies of the same gene may make it into an offspring in a

future generation. Random sampling has then produced a homozygote. Genetic drift tends to increase homozygosity, and the rate of this increase can be exactly expressed by equations 6.2 and 6.3.

6.6 A calculable amount of polymorphism will exist in a population because of neutral mutation

Genetic variation for neutral genes is determined by a balance between drift and mutation

So far, it might appear that the theory of neutral drift predicts that populations should be completely homozygous. However, new variation will be contributed by mutation and the equilibrial level of polymorphism (or heterozygosity) will actually be a balance between its elimination by drift and its creation by mutation. We can now work out what that equilibrium is. The *neutral* mutation rate is equal to u per gene per generation. (u, as before, is the rate at which selectively neutral mutations arise, not the total mutation rate.) To find out the equilibrial heterozygosity under drift and mutation, we have to modify equation 6.2 to account for mutation. If an individual was born a homozygote, and if neither gene has mutated, it stays a homozygote and all its gametes will have the same gene. (We ignore the possibility that mutation produces a homozygote, for example by a heterozygote *Aa* mutating to a homozygous *AA*. We are assuming that mutations produce new genes.) In order for a homozygote to produce all its gametes with the same gene, neither of its genes must have mutated. If either of them has mutated, the frequency of homozygotes will decrease. The chance that a gene has not mutated equals $(1 - u)$ and the chance that neither of an individual's genes has mutated equals $(1 - u)^2$.

Now we can simply modify the recurrence relation derived above. The frequency of homozygotes will be as before, but multiplied by the probability that they have not mutated to heterozygotes:

$$f' = \left[\frac{1}{2N} + \left(1 - \frac{1}{2N}\right)f\right](1 - u)^2 \tag{6.4}$$

Homozygosity (f) will now not increase to one. It will converge to an equilibrial value. The equilibrium is between the increase in homozygosity due to drift, and its decrease by mutation. We can find the equilibrium value of f from $f^\star = f = f'$. $f^\star$ indicates a value of f that is stable in successive generations ($f' = f$). Substituting $f^\star = f' = f$ in the equation gives (after a minor manipulation):

$$f^\star = \frac{(1 - u)^2}{2N - (2N - 1)(1 - u)^2} \tag{6.5}$$

The equation simplifies if we ignore terms in u^2, which will be relatively unimportant because the neutral mutation rate is low. Then

$$f^\star = \frac{1}{4Nu + 1} \tag{6.6}$$

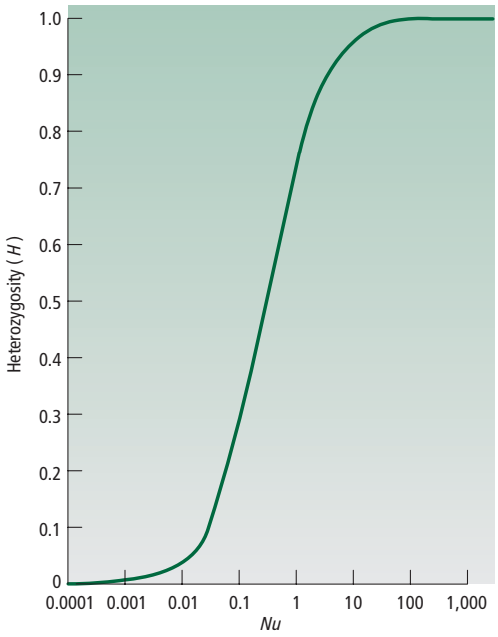

Figure 6.6
The theoretical relationship between the degree of heterozygosity and the parameter Nu (the product of the population size and neutral mutation rate).

The equilibrial heterozygosity ($H^* = 1 - f^*$) is:

$$H^* = \frac{4Nu}{4Nu + 1} \tag{6.7}$$

This is an important result. It gives the degree of heterozygosity that should exist for a balance between the drift to homozygosity and new neutral mutation. The expected heterozygosity depends on the neutral mutation rate and the population size (Figure 6.6). As the march to homozygosity is more rapid if the population size is smaller, it makes sense that the expected heterozygosity is lower if N is smaller. Heterozygosity is also lower if the mutation rate is lower, as we would expect. In sum, the population will be less genetically variable for neutral alleles when population sizes are smaller and the mutation rates lower.

6.7 Population size and effective population size

What is "population size"? We have seen that N determines the effect of genetic drift on gene frequencies. But what exactly is N? In an ecological sense, N can be measured by counting, such as the number of adults in a locality. However, for the theory of population genetics with small populations, the estimate obtained by ecological counting is only a crude approximation of the "population size," N, implied by the equations. What matters is the chance that two copies of a gene will be sampled as the next generation is produced, and this is affected by the breeding structure of the population. A

population of size N contains $2N$ genes at a locus. The correct interpretation of N for the theoretical equations is that N has been correctly measured when the chance of drawing two copies of the same gene is $1/(2N)$.

Effective population size can differ from observed population size

If we draw two genes from a population at a locality, we may be more likely for various reasons to get two copies of the same gene than would be implied by the naive ecological measure of population size. Population geneticists therefore often write N_e (for "effective" population size) in the equations, rather than N. In practice, effective population sizes are usually lower than ecologically observed population sizes. The relation between N_e, the effective population size implied by the equations, and the observed population size N can be complex. A number of factors are known to influence effective population size.

1. *Sex ratio*. If one sex is rarer, the population size of the rarer sex will dominate the changes in gene frequencies. It is much more likely that identical genes will be drawn from the rarer sex, because fewer individuals are contributing genes to the next generation. Sewall Wright proved in 1932 that in this case:

$$N_e = \frac{4N_m \cdot N_f}{N_m + N_f} \tag{6.8}$$

   Where N_m = number of males, and N_f = number of females in the population.
2. *Population fluctuations*. If population size fluctuates, homozygosity will increase more rapidly while the population goes through a "bottleneck" of small size. N_e is disproportionately influenced by N during the bottleneck, and a formula can be derived for N_e in terms of the harmonic mean of N.
3. *Small breeding groups*. If most breeding takes place within small groups, then the effective population size will differ from the total population size (made up of all the small breeding groups put together). N_e can be smaller or larger than N, depending on whether we look at the effective size of the local populations, or of all the local populations together. It also depends on the extinction rates of goups, and the migration rates between groups. Several models of population subdivision have been used to derive exact expressions for N_e.
4. *Variable fertility*. If the number of successful gametes varies between individuals (as it often does among males when sexual selection is operating, see Chapter 12), the more fertile individuals will accelerate the march to homozygosity. Again, the chance that copies of the same gene will combine in the same individual in the production of the next generation is increased and the effective population size is decreased relative to the total number of adults. Wright showed that if k is the average number of gametes produced by a member of the population and σ_k^2 is the variance of k (see Box 9.1, p. 233, for the definition of variance), then:

$$N_e = \frac{4N - 2}{\sigma_k^2 + 2} \tag{6.9}$$

   For $N_e < N$, the variance of k has to be greater than random. If k varies randomly, as a Poisson process, $\sigma_k^2 = k = 2$ and $N_e \approx N$.

These are all quite technical points. The N_e in the equations for neutral evolution is an exactly defined quantity, but it is difficult to measure in practice. It is usually less than the observed number of adults, N. $N_e = N$ when the population mates randomly, is constant in size, has an equal sex ratio, and has approximately Poisson variance in fertility. Natural deviations from these conditions produce $N_e < N$. How much smaller N_e is than N is difficult to measure, though it is possible to make estimates by the formulae we have seen. Other things being equal, species with more subdivided and inbred population structures have a lower N_e than more panmictic species.

Summary

1 In a small population, random sampling of gametes to produce the next generation can change the gene frequency. These random changes are called genetic drift.

2 Genetic drift has a larger effect on gene frequencies if the population size is small than if it is large.

3 If a small population colonizes a new area, it is likely to carry all the ancestral population's genes; but the gene frequencies may be unrepresentative.

4 One gene can be substituted for another by random drift. The rate of neutral substitution is equal to the rate at which neutral mutations arise.

5 In a small population, in the absence of mutation, one allele will eventually be fixed at a locus. The population will eventually become homozygous. The Hardy–Weinberg equilibrium does not apply to small populations. The effect of drift is to reduce the amount of variability in the population.

6 The amount of neutral genetic variability in a population will be a balance between its loss by drift and its creation by new mutation.

7 The "effective" size of a population, which is the population size assumed in the theory of population genetics for small populations, should be distinguished from the size of a population that an ecologist might measure in nature. Effective population sizes are usually smaller than observed population sizes.

Further reading

Population genetics texts, such as those of Crow (1986), Hartl & Clark (1997), Gillespie (1998), or Hedrick (2000), and molecular evolution texts such as Page & Holmes (1998), Graur & Li (2000), and Li (1997), explain the theory of population genetics for small populations. Crow & Kimura (1970) is a classic account of the mathematical theory. Lewontin (1974) and Kimura (1983) also explain much of the material. Wright (1968) is more advanced. Beatty (1992) explains the history of ideas, including Wright's, about random drift. Kimura (1983) also contains a clear account of the parts of the theory most relevant to his neutral theory and discusses the meaning of effective population size. For the medical examples of founder events in humans, see Dean (1972) and Hayden (1981).

Study and review questions

1 A population of 100 individuals contains 100 *A* genes and 100 *a* genes. If there is no mutation and the three genotypes are selectively neutral, what would you expect the genotype and gene frequencies to be a long time, say 10,000 generations, in the future?

2 Review: (a) the meaning of "random" in random sampling, and the reason why drift is more powerful in smaller populations, and (b) the argument why all the genes at any locus (such as the insulin locus) in the human population are now descended from one gene in an ancestral population some time in the past.

3 What is the heterozygosity (H) of the following populations:

Population	Genotypes			H
	AA	*Aa*	*aa*	
1	25	50	25	
2	50	0	50	
3	0	50	50	
4	0	0	100	

4 If the neutral mutation rate is 10^{-8} at a locus, what is the rate of neutral evolution at that locus if the population size is: (a) 100 individuals, or (b) 1,000 individuals?

5 What is the probability in a population of size N that a gene will combine (a) with another copy of itself to produce a new individual, and (b) with a copy of another gene?

6 Try to manipulate equation 6.2 into 6.3 and equation 6.6 into 6.7.