Chapter 3

Population Genetics for Large Populations

The diversity of life is a fundamental empirical fact of nature. Not only is there an astonishing variety of species; diversity also prevails *within* species. As in human populations, individuals of a species vary considerably in their outward traits—size and shape, external markings, fecundity, disease resistance, etc. This is called *phenotypic* variation, and since phenotypes are shaped by genes, it reflects an underlying genotypic diversity. The achievements of modern genetics and molecular biology described in Chapter 1 allow us to confirm and to study genotypic variability down to the molecular level.

The science of genotypic variation in interbreeding populations is called *population genetics*. Its goal is understanding how genetic variation changes under the influence of selection, mutation, and the randomness inherent in mating, as one generation succeeds another. Mathematics is a fundamental tool. Population geneticists combine what is known about heredity—how DNA carries genetic information, how chromosomes function and give rise to Mendel's laws, how mutations arise—with hypotheses about mating and selective advantage to create mathematical models for the evolution of genotype frequencies. By comparing the predictions of these models to field data, they can then test theories and make inferences about genealogy and evolution.

This chapter is an introduction to elementary population genetics models for large populations and simple genotypes. Large population models are derived by considering what happens in the limit as the population size tends to infinity. The use of this limit is called the *infinite population assumption*. Of course, actual populations are finite; the infinite population limit is meant to serve as an approximation when the population is large. There is a good modeling reason for the infinite population assumption. When it is imposed, genotype frequencies evolve deterministically, even though mating choice and survival at the individual's level are random.

Population genetics is an excellent introduction to the art of probabilistic modeling. Like any art it can only be learned by doing, and this chapter is written to encourage active participation. The student is asked to carry out many steps of the exposition and to construct extensions of models through guided exercises embedded in the text. It is important to treat these exercises as an integral part of reading the chapter.

In terms of mathematics, this chapter requires some elementary probability. The reader should understand random sampling, independence, and the law of large numbers, and be able to compute probabilities of simple sampling experiments. Most of these topics are reviewed in Section 2.1. It will also be necessary to analyze solutions to *difference equations*. A *first order difference equation* for a real-valued sequence is an equation of the form

$$x(t+1) = \phi(x(t))\,, \tag{3.1}$$

for $t = 0, 1, 2, \ldots$, where ϕ is a given function whose domain and range are subsets of the real numbers. Given an initial value $x(0)$, one can compute a numerical solution for as many values of t as one likes by recursion: $x(1) = \phi(x(0))$, $x(2) = \phi(x(1))$, etc. A *second order difference equation* takes the form

$$x(t+1) = \psi\big(x(t), x(t-1)\big)\,, \tag{3.2}$$

and it can be solved numerically by recursion starting from given initial values of $x(0)$ and $x(1)$. However, for applications and most theoretical analysis, one really would like to know what $x(t)$ is as a function of t, or barring this, how $x(t)$ behaves as t increases to infinity. The nicest situation is when there is an explicit formula for the solution. Explicit solutions are available to (3.1) when $\phi(x) = ax+b$, and to (3.2) when $\psi(x, y) = ax+by+c$. It is explained how to derive these in cases encountered in this chapter in the chapter appendix. We shall also need to understand the behavior of solutions to the first order equation when ϕ is nonlinear and techniques for doing so are explained in Section 3.4.

3.1 Modeling principles for population genetics

Mendelian genetics, as summarized in Chapter 1, is the biological framework for this chapter. In this section we address the additional biological issues and assumptions needed to formulate models. Throughout, the study of one locus with two alleles serves as a running example.

3.1.1 Some biological considerations

Sex. (And you never thought you'd see this word in a math text!) Species engaging in sexual reproduction are either **monecious** or **dioecious**. Each individual of

a monecious species houses both male and female sex organs, so individuals are themselves neither male or female. (The root meaning of "monecious" is *in one house*.) Plants with flowers that both contain an ovum and produce pollen are examples of monecious species. In contrast, individuals of dioecious (*in two houses*) species are either male or female. The distinction between monecious and dioecious species is relevant to geneology, because any individual of a monecious species can mate with any other individual. Potentially, a monecious individual can even mate with itself, which is called *self-fertilization* or *selfing*. In reality, selfing is prevented in many monecious species by various biological mechanisms, which presumably have evolved to prevent excessive inbreeding.

Autosomal vs. sex chromosomes. Genetic mechanisms of sex determination in dioecious species are diverse and complicate the analysis of inheritance. Sex is often determined by a particular chromosome, the sex chromosome, which is present in one sex, but not the other, or is present in different numbers. Chromosomes other than sex chromosomes are called **autosomal.** In diploid species, autosomal chromosomes come in homologous pairs in both male and female, so male and female genotypes for loci on autosomal chromosome have the same form. However, sex chromosomes may not be paired and there may be but one locus per individual for the genes they carry, so male and female genotypes for loci on the sex chromosome will differ in form. Genes or loci on sex chromosomes are said to be **sex-linked**.

We shall only study models for dioecious species following the human pattern of sex determination. A human female has two paired X chromosomes, but a male has only one X, which is paired instead with a Y chromosome. Genes on the X chromosome do not have loci on the Y chromosome, and so the male will carry only a single allele for these genes. A child is male only if he receives a Y from his father and an X from his mother; thus, the X chromosome in a male is always inherited from the mother.

3.1.2 Genotypes and Populations

The concepts of genotype and allele are covered in Chapter 1. Genotypes are always defined *with respect to some pre-specified set of loci*. The associated genotype of an individual is a list of all the alleles appearing at the specific loci in the chromosomes of an autosomal cell. Single letters are often used to denote alleles, and hence genotypes usually take the form of strings of letters. For example, the pea plants of Mendel discussed in Chapter 1 admit two alleles for pea color: Y, for yellow, and G, for green. The peas are diploid, and hence there are two loci for color on the chromosomes of a typical cell. The possible genotypes *with respect to the locus for pea color* are thus YY, YG, and GG. There are also two alleles, W (wrinkled) and S (smooth) for pea texture, and again two loci for texture in the chromosome. Hence the possible genotypes *with respect to the loci for color and texture* are $YYSS$, $YYWW$, $YYWS$, $YGSS$, $YGWW$, $YGWS$, $GGSS$, $GGWW$, $GGWS$.

A population is a collection of living organisms. But population geneticists are interested only in genotypes, and so they suppress the extraneous flesh and blood reality of individuals and treat a population merely as a collection of genotype letter strings, one string per individual. For example, $\{YY, YG, GG, GG, YY, YG, YG\}$ represents a population of 7 pea plants in a study of the genetics of pea color. Or, for another example, if you were to participate in a study of the genetics of eye color, you would enter the data set as letters coding your alleles for eye color. All your other distinctive features —your good looks, superior intelligence, and athletic prowess—would, sad to say, be ignored. Thinking of a population as a collection of letter strings is very helpful to a clear understanding of the models.

3.1.3 Gene and Allele Frequencies

Consider a population and one of its possible genotypes, $G_1 \cdots G_k$. The frequency $f_{G_1 \cdots G_k}$ of $G_1 \cdots G_k$ is simply:

$$f_{G_1 \cdots G_k} \stackrel{\triangle}{=} \frac{\text{number of individuals with genotype } G_1 \cdots G_k}{\text{population size}}. \tag{3.3}$$

When time is a consideration, $f_{G_1 \cdots G_k}(t)$ will denote a genotype frequency at time t.

Example 3.1.1. Consider the following population of a diploid species, in a study of a single locus that admits two alleles A and a:

$$AA,\ AA,\ AA,\ Aa,\ Aa,\ Aa,\ Aa,\ aa,\ aa,\ aa,\ aa,\ aa \tag{3.4}$$

There are 12 individuals represented in the population, three of which are AA and five are aa. Thus $f_{AA} = 3/12 = 1/4$, and $f_{aa} = 5/12$. ⋄

Allele frequencies are instead computed by counting alleles only and ignoring how they are organized into genotypes. Given a population and a locus ℓ, the *allele pool for* ℓ is the collection of all alleles from population genotypes that occur at locus ℓ. To visualize this, imagine collecting the letters for alleles at locus ℓ from all the individuals of the population and pooling them together in a box, where they are no longer identified by the individual they belong to. If A is a possible allele that can occur at ℓ, the frequency f_A of A is defined to be its frequency *relative* to the allele pool for ℓ:

$$f_A \stackrel{\triangle}{=} \frac{\text{number of } A\text{'s in the allele pool for } \ell}{\text{size of the allele pool for } \ell.} \tag{3.5}$$

If ℓ is a locus on an autosomal chromosome of a diploid species, each individual genotype contains exactly two alleles at ℓ. Therefore, if there are N individuals in the population, the size of the allele pool equals $2N$, and this will be the denominator

to use in computing f_A. Again, when time is a consideration, $f_A(t)$ will denote frequency at time t.

Example 3.1.1, continued and extended. In the single locus genotype of Example 3.2.1, the allele pool is the collection of the $24(= 2 \times 12)$ letters listed in (3.4). There are a total of 10 A's: thus $f_A = 10/24 = 5/12$.

Consider instead the population

$$AABb, AAbb, AAbb, AaBB, AaBB, Aabb, Aabb, aaBb, aaBB, aaBB, aabb, aabb,$$

where B and b denote alleles at a locus different than that of A and a. The calculation of f_A is unchanged, because the allele pool for ℓ is unchanged, the numbers of B and b alleles being irrelevant. In calculating f_A, one should not divide by the total number, 48, of letters appearing in the population, but by the total number of letters labeling alleles at the same locus as A. The reader should confirm that $f_b = 14/24$. ◇

Exercise 3.1.1. Consider a locus ℓ on the X chromosome in humans. The gene has three alleles A, a and $\bar{a}$. Consider a second locus on an autosomal chromosome admitting alleles B and b. Find f_A and f_B for a population consisting of 5 males and 7 females, where the males have genotypes ABB, ABB, aBb, $\bar{a}Bb$, and $\bar{a}bb$, and the females have genotypes $AAbb$, $aaBb$, $a\bar{a}bb$, $\bar{a}ABB$, $\bar{a}\bar{a}BB$, $aABb$, and $a\bar{a}BB$. ◇

Genotype and allele frequencies cannot be arbitrary, but must obey simple algebraic constraints. We will illustrate this for a simple case; the student should then be able to derive analogous relationships for other situations—see, for instance, Exercises 3.2.4.

Genotype and allele frequencies for the one locus/two allele case in a diploid population. Let the alleles be denoted A and a; the possible genotypes are then AA, Aa, and aa. Since each allele is either A or a, it follows that

$$f_A + f_a = 1.$$

Likewise,

$$f_{AA} + f_{Aa} + f_{aa} = 1. \tag{3.6}$$

In addition allele and genotype frequencies are related as follows:

$$f_A = f_{AA} + \frac{f_{Aa}}{2}, \qquad f_a = f_{aa} + \frac{f_{Aa}}{2}. \tag{3.7}$$

We derive the first equation of (3.7), the second being similar. Let N denote the size of the population. Since the population is diploid, the size of the allele pool for the locus at which A occurs is $2N$. Now count the number of A's in the

allele pool for ℓ in terms of the genotype frequencies. By definition of f_{AA}, there are Nf_{AA} genotypes AA in the population, and so they contribute a total of $2Nf_{AA}$ letter A's. Similarly, there are Nf_{Aa} genotypes Aa contributing a total of Nf_{Aa} letter A's. Individuals of genotype f_{aa} of course contribute no A's. Hence, using definition (3.5),

$$f_A = \frac{2Nf_{AA} + Nf_{Aa}}{2N} = f_{AA} + \frac{f_{Aa}}{2}$$

◇

In general, genotype frequencies cannot be recovered from allele frequencies, because they depend not just on numbers of alleles, but on how the alleles are distributed among individuals.

3.1.4 Random Mating

In this chapter, 'mating' is used in a special, technical sense. It refers not to the biological act, but its outcome; a 'mating' means the creation of one new individual from two parents, male and female, by sexual reproduction. Each parent to a mating carries a pool of gametes and the mating consists in uniting a gamete of one parent with the gamete of the other.

The issue at the heart of how genotype frequencies evolve is:

- *What is the probability that a mating produces an offspring with a given genotype?*

This probability will of course depend on the assumptions made about how likely it is individuals of each different genotypes mate with each other. Here we will describe the *random mating* model and deduce its consequences for genotype probabilities. The concept of random sampling, as defined and discussed in section 2.1, will play a central role. Recall that a random sample is a draw in which each individual has an equally likely chance to be chosen.

The idea of random mating is that each individual in the mating pool has the same chance of reproductive success and mate choice is totally by random.

Definition. In a **random mating**, each parent is chosen by independent random sampling from the population, and the gamete from each parent is chosen by independent random sampling from its pool of gametes.

When the species is *dioecious* the two parents are randomly sampled from the male and female sub-populations, respectively. When the species is *monecious*, male and female are sampled from the same population with replacement. Thus, in the monecious case, selfing is possible in a random mating.

As defined here, random mating might seem far removed from the real world, where selective mate choice and accidents of physical location are obviously important. A discussion of when random mating is appropriate or useful as model appears at the end of this section.

We will only work with diploid populations, and in the case of dioecious species, we will always use the human model of sex determination. In these cases, random mating leads to a simple principle for calculating offspring genotype probabilities. Let $\mathcal{S}$ denote the population from which a parent is chosen. Let $f_A^{\mathcal{S}}$ be the frequency of an allele A in population $\mathcal{S}$. If a parent is chosen from $\mathcal{S}$ in a random mating, first it is randomly selected from $\mathcal{S}$ and then a gamete is randomly selected from its gamete pool. Let $p_A^{\mathcal{S}}$ be the probability that this gamete carries allele A; that is,

$$p_A^{\mathcal{S}} = \mathbb{P}\Big(\textit{parent selected randomly from } \{\mathcal{S}\} \textit{ passes } A \textit{ to an offspring}\Big).$$

Lemma 1 *Under the assumption of random mating,*

$$p_A^{\mathcal{S}} = f_A^{\mathcal{S}}\,. \tag{3.8}$$

Observe that $f_A^{\mathcal{S}}$ is precisely the probability of selecting A in a random sample from the allele pool. Thus, Lemma 1 says, in words, that *the probability a randomly selected parent passes A to its offspring is just the probability of randomly drawing A from the allele pool.* This is key to understanding the models based on random mating.

Lemma 1 is true very generally, but we shall demonstrate why only for the specific case of two alleles at a locus. Let those alleles be denoted A and a.

Let $f_{AA}^{\mathcal{S}}$ and $f_{Aa}^{\mathcal{S}}$ be the frequencies of AA and Aa in the population. We know from the definition of random sampling that $\mathbb{P}\Big(\textit{selected parent is } AA\Big) = f_{AA}^{\mathcal{S}}$, and $\mathbb{P}\Big(\textit{selected parent is } Aa\Big) = f_{Aa}^{\mathcal{S}}$. Now, if an AA individual is the parent, it passes A to the offspring with probability one. But if an Aa individual is chosen to mate, half of its gametes contain A and the other half do not, so the probability it passes A to an offspring is $1/2$. Therefore, by conditioning on whether the parent is AA or Aa and using (3.7),

$$\begin{aligned} p_A^{\mathcal{S}} &= \mathbb{P}\big(U\big|\text{selected parent is } AA\big)\mathbb{P}\big(\text{selected parent is } AA\big) \\ &\qquad + \frac{1}{2}\cdot\mathbb{P}\big(U\big|\text{selected parent is } Aa\big)\mathbb{P}\big(\text{selected parent is } Aa\big) \\ &= 1\cdot f_{AA}^{\mathcal{S}} + \frac{1}{2}\cdot f_{Aa}^{\mathcal{S}} = f_A^{\mathcal{S}}. \end{aligned}$$

A similar argument works for a locus on the Y chromosome in sampling from a population of male parents, because in this case the probability that a random male

passes A to the offspring is just the probability that he has an A on Y, and this is just the frequency of A in the male population. $\diamond$

This lemma contains just about everything we need to know in developing models based on random mating. We could almost take equation (3.8) as a definition of random mating. But we have tried to lead up to it in a careful way, to show how it is a consequence of the idea of completely random mate choice and of the nature of sexual reproduction.

The next example shows how to compute genotype probabilities of the offspring of a random mating in the simplest situation.

Example 3.1.2. Random mating in the one locus/two allele case in a monecious population.

Consider a locus with two alleles A and a in a monecious species. Let a random mating take place in a population with allele frequencies, f_A and f_a. The offspring of this mating will be AA only if both parents contribute allele A. Since the species is monecious, each parent is drawn by random selection from the entire population, and so, by Lemma 1, f_A is the probability it contributes A. Since the parents are chosen independently in random mating, the probability that both contribute A is f_A^2. Thus,

$$\mathbb{P}\,(\text{offspring is } AA) = f_A^2 = (f_{AA} + \frac{f_{Aa}}{2})^2. \tag{3.9}$$

Similarly,

$$\mathbb{P}\,(\text{offspring is } aa) = f_a^2 = (f_{aa} + \frac{f_{Aa}}{2})^2. \tag{3.10}$$

The event that a random mating produces an Aa is the union of the event that the first parent contributes A and the second a, which has probability $f_A f_a$ with the event that the first parent contributes a and the second A, again having probability $f_A f_a$. Hence,

$$\mathbb{P}\,(\text{offspring is } Aa) = 2f_A f_a = 2f_A(1 - f_A) = 2(f_{AA} + \frac{f_{Aa}}{2})(f_{aa} + \frac{f_{Aa}}{2}). \tag{3.11}$$

(Show that the three probabilities of (3.9)—(3.11) add up to 1!) $\diamond$

Remark. The definition of random mating stipulates that the parents are sampled independently. If the species is monecious, both samples are from the same pool of potential parents, and hence independent sampling can lead to the same individual being chosen twice, which amounts to selfing. However, when the population has size N, the probability of selfing is $1/N$ (see Exercise 3.1.4). For N of even moderate size, the selfing probability is thus small, and then the independence assumption is a good approximation even when selfing cannot occur.

Discussion.

The following remarks are meant to help the reader think more deeply about random mating as a model. They are not used in what follows, but they are interesting to consider.

1. "Random mating," as used here, has a technically precise sense. It refers not to any situation in which randomness enters mating, but to *complete* randomness, in the sense that all matings are equally likely.

2. Random mating is selectively neutral: there are no mating preferences, and the genotype of an individual or a gamete has no effect on its chances of reproductive success.

3. The definition of random mating seems removed from what happens in real populations. Offspring are not really produced one to a mating. When individuals mate they typically produce lots of offspring in one mating, many of whom do not survive long. Wouldn't one obtain a more useful definition with an approach grounded in the physical realities of mating? Unfortunately, this would require building probabilistic models for how many times an individual mates, the number of offspring per mating, etcetera, leading to models which are complex and species dependent. However, we can argue that these complications are not relevant and that the definition is essentially correct as a model for selectively neutral mating, by taking a conditional viewpoint from the perspective of the offspring. Think of a whole offspring population produced from the same parent population, and do the following experiment. Sample an offspring at random from the population and record its parents. In a selectively neutral, well-mixed parent population, each possible pair of parents should be equally likely. It is as if each child chooses its parents by two, independent random samples. Although, strictly speaking, it is nonsense to say a child chooses its parents, mathematically it is equivalent, and it leads to the definition of random mating we have given, without fussing about all kinds of other details of the mating process.

4. The definition of random mating applies to the production of one offspring. How different random matings from the same population are related probabilistically is a different matter. The simplest models assume matings are independent; for example, independence is implicit in the formulation of the infinite population assumption in the next section.

5. Is the random mating model reasonable? Surely there is an element of randomness in all mating, but, especially with mammals, fish and birds, individuals usually exercise mating preferences. Accurate models would account for sexual preference by assigning higher probabilities to some genotype pairings and lower probabilities to others. Is a model with completely random mating ever useful?

There are in fact several good reasons for this model. First, it is a baseline case, whose consequences can be fully analyzed. As such, it serves as a kind of null hypothesis, and a point of departure for more complicated models. If we want

to infer that random mating is not appropriate for a population, we need to know now in the first place how a population with random mating behave. Section 3.3 below on Wright's fixation index is a good example of the ideas of the random mating model can be used to analyze populations where mixing by mating is only partial. Secondly, there are many situations, for example, pollination of plants by wind or by insects, in which the opportunity for sexual selection is limited. Then the random mating model may indeed be a good approximation of reality. Finally, random mating may well describe gene mixing at selected loci, even if individuals themselves are not mating completely at random. For instance, consider blood type, which is inherited genetically, and human mating. If you are looking for a mate, surely you are exercising preferences about looks, personality, earning potential, whether the person in question is a mathematician or biologist, etc. But probably you are not saying to yourself, if you live outside of Transylvania,"I really go for those A blood types." Therefore, if blood types are distributed evenly across all the traits that do affect mate selection, mating will involve no preference of genotypes for blood type, and random mating is then reasonable.

3.1.5 The infinite population assumption.

Imagine a population, $\mathcal{S}$, that is created by repeated random matings in a parent population. Let $p_{G_1\cdots G_k}$ denote the probability that a random mating of parents produces a child with genotype $G_1\cdots G_k$. Let $f_{G_1\cdots G_k}$ denote the frequency of this genotype in the population, $\mathcal{S}$, of offspring. *The infinite population assumption (for $\mathcal{S}$) asserts that genotype probability and frequency are identical:*

$$f_{G_1\cdots G_k} = p_{G_1\cdots G_k}. \tag{3.12}$$

To understand why this is called the infinite population assumption, imagine creating the offspring population by successive random matings and let $f^{(N)}_{G_1\cdots G_k}$ be the genotype frequency in the first N offspring produced. For any finite N, this is a random variable. But if the outcomes of each separate random mating are independent of one another, then $\lim_{N\to\infty} f^{(N)}_{G_1\cdots G_k} = p_{G_1\cdots G_k}$ with probability one by the law of large numbers. Interpreting $\lim_{N\to\infty} f^{(N)}_{G_1\cdots G_k}$ as the frequency in an infinite population gives identity (3.12). For real populations, strict independence between different random matings may not hold. Still, it is reasonable to expect that, as N grows, the dependence between matings is limited enough for the law of large numbers to hold. In effect, the infinite population assumption asserts the law of large numbers for repeated random matings, whatever the exact degree of independence.

The infinite population assumption is justified when the population is so large that $p_{G_1\cdots G_n}$ approximates the frequency $f_{g_1\cdots G_n}$ closely with high probability. For mathematical modeling, the virtue of this approximation is that it identifies genotype frequencies, which in real populations are random, with probabilities, which

are not. As a result genotype frequencies in infinite population models evolve deterministically, as we shall see below.

3.1.6 Interaction of Generations

How individuals enter and leave the mating pool over time is an important factor in gene flow. The simplest model assumes **non-overlapping generations**. This means that the individuals of generation t mate among themselves to produce generation t+1, and once this is done, mate no more; generation t+1 mates to produce generation 2 and then mates no more, and so on. This is a good model for species with annual reproduction cycles and seasonal mating.

The extreme opposite of non-overlapping generations is a model in which births and deaths take place continually, and, as soon as an individual is born, it enters the mating pool. In such a case, distinct generations are not even well defined. Intermediate models postulate a generational structure, but allow mating pools of different generations to mix in a limited way.

3.1.7 Exercises

Exercise 3.1.2. (One gene/two alleles) Allele frequencies f_A and $f_a = 1 - f_A$ do not determine the genotype frequencies f_{AA}, f_{Aa}, and f_{aa}. Give two different sets of genotype frequencies for which $f_A = 0.5$.

Exercise 3.1.3. One locus/two allele case in a dioecious population. Consider a locus on an autosomal chromosome in a population of a dioecious species. Let A and a denote the alleles that appear at the locus. Both males and females have two copies of each locus, and so both males and females can have each of the three possible genotypes AA, Aa, and aa. Let f^m_{AA}, f^m_{Aa}, etc., denote frequencies in the male subpopulation, and f^f_{AA}, f^f_{Aa}, etc., frequencies in the female subpopulation. A random mating is formed by choosing the father by random selection from the male subpopulation and a mother by random selection from the female subpopulation.

(i) Find two expressions for $\mathbb{P}$(offspring is Aa), one in terms of allele frequencies and the other in terms of genotype frequencies of both male and female subpopulations.

(ii) Derive similar expressions for $\mathbb{P}$(offspring is AA) and $\mathbb{P}$(offspring is aa).

(iii) Let f_A be the frequency of allele A in the entire population. In general, one cannot express f_A in terms of f^m_{AA}, f^f_{AA}, etc. However, find an expression for f_A in terms of these genotype frequencies and the ratio, $\rho = N^m/N^f$, of the size of the male population to the size of the female population.

Exercise 3.1.4. Calculate the probability that selfing occurs in a random mating in a monecious population of size N.

Exercise 3.1.5. Probabilities in Mendel's experiments For this problem it may be helpful to refer to Chapter 1, Section 1. Consider the genotype for pea shape and pea color in Mendel's peas. For color, there are two alleles Y and G for yellow and green and yellow is dominant. The two alleles for shape are W for wrinkled and S for smooth and smooth is dominant.

(i) There are four possible phenotypes relative to these two traits: smooth, green peas; smooth yellow peas; yellow, smooth peas; and yellow, wrinkled peas. List the genotypes that give rise to each phenotype. You should have 9 genotypes in all.

(ii) Consider a plant with genotype $YGSW$. The genotypes of the *gametes* of this plant will have one allele for color and one for shape: they will be GS, GW, YS, YW. Assuming that the genes for color and shape assort independently, show that the gamete genotypes are equally probable.

(iii) A random cross of $YGSW$ with itself consists of of a random sample of size 2 from the gamete pool of $YGSW$, one to choose the sperm and the other the egg. The joining of their genotypes is the result of the cross. Determine the probability of each possible different phenotype that can result from the cross.

Exercise 3.1.6. This problem uses Chebyshev's inequality and the Central Limit approximation of the binomial distribution; see Chapter 2. Consider the one locus/two allele case. Let the frequency of allele A in a parent population be $f_A = 2/3$. Assume that the first generation contains N individuals produced by N independent random matings. Define f_{AA} as in Section 3.2.6. This problem shows how to get an idea the probabilities of deviation of $f_{AA}(1)$ from its mean $4/9$ for a population of size 1000.

(i) If $N = 1000$, use Chebyshev's inequality to find an upper bound on the probability that $f_{AA}(1)$ differs from $f_A^2 = 4/9$ by more than 0.05.

(ii) If $N = 1000$, use the DeMoivre-Laplace Central Limit Theorem to estimate the probability that $f_{AA}(1)$ differs from $f_A^2 = 4/9$ by more than 0.05. Note that this approximation gives a better result than the Tchebysheff inequality, which in the binomial case is not sharp.

3.2 Models with no selection

This section studies models for the evolution of genotype frequency when no selection is acting, primarily for the case of one locus with two alleles in a diploid species. We shall start with the simplest model and gradually complexify by modifying the basic assumptions.

3.2.1 Basic model

The basic model studies the case of one locus with two alleles under the following assumptions:

$$\text{random mating;} \qquad (A.1)$$
$$\text{nonoverlapping generations;} \qquad (A.2)$$
$$\text{infinite population;} \qquad (A.3)$$
$$\text{monecious species;} \qquad (A.4)$$
$$\text{no selection, mutation, or migration.} \qquad (A.5)$$

Except for the last assumption, these have been explained in the previous section. Mutation refers to a random change in an allele of a parental gamete, caused, for instance, by a copying error in the course of meiosis or by radiation damage to the sex cells. Migration adds genotypes from outside sources to a population. Selection occurs when different genotypes have different effects on survival or reproductive success. All these complications are excluded in the basic model.

Consider a locus with two alleles A and a. Assumptions (A.1)–(A.5) lead directly to a mathematical model for the evolution of the associated genotype frequencies. In this model, $f_{AA}(t)$, $f_{Aa}(t)$, $f_{aa}(t)$, $f_A(t)$, and $f_a(t)$ will denote the genotype and allele frequencies of generation t, $t \geq 0$. These are unambiguously defined, first, because assumption (A.2) means that each generation is a coherent entity, and second, because assumption (A.5) implies that the frequencies in each generation remain constant from the time of birth to the time of reproduction.

The model itself will be a set of equations that show how the genotype frequencies of generation t determine those of t+1, for every t. Consider, for example, $f_{AA}(t{+}1)$. As explained in the previous section at equation (3.12), the infinite population assumption says

$$f_{AA}(t{+}1) = P\,(\text{a random mating of generation } t \text{ parents produces } AA)\,.$$

But we saw in Example 3.1.2, equation (3.9), how to calculate this probability when (A.2), random mating, is assumed: it is $f_A^2(t)$. Also from (3.7), we know $f_A(t) = f_{AA}(t) + (1/2)f_{Aa}(t)$. Thus,

$$f_{AA}(t{+}1) = f_A^2(t) = \left(f_{AA}(t) + \frac{f_{Aa}(t)}{2}\right)^2. \qquad (3.13)$$

The same reasoning yields as well,

$$f_{Aa}(t{+}1) \;=\; 2f_A(t)f_a(t) = 2\left(f_{AA}(t) + \frac{f_{Aa}(t)}{2}\right)\left(f_{aa}(t) + \frac{f_{Aa}(t)}{2}\right) \qquad (3.14)$$

$$f_{aa}(t{+}1) \;=\; f_a^2(t) = \left(f_{aa}(t) + \frac{f_{Aa}(t)}{2}\right)^2 \qquad (3.15)$$

This system of *difference equations* prescribes exactly how genotype frequencies evolve under assumptions (A.1)-(A.5). What does it imply about the behavior over time of the genotype frequencies? The ideal answer to this question would be a solution expressing $f_{AA}(t)$, $f_{Aa}(t)$ and $f_{aa}(t)$ as explicit functions of t. Can (3.13)—(3.15) in fact be solved? Its complicated and nonlinear structure look forbidding, but magic happens if we ask instead how *allele* frequencies evolve.

Using first (3.7) and then (3.13), (3.14), and $f_A(t) + f_a(t) = 1$, we find,

$$\begin{aligned} f_A(t+1) &= f_{AA}(t+1) + \frac{f_{Aa}}{2}(t+1) \\ &= f_A^2(t) + f_A(t)f_a(t) = f_A(t)(f_A(t) + f_a(t)) \\ &= f_A(t). \end{aligned} \tag{3.16}$$

That is, allele frequency does not change from generation to generation! Hence, for all $t \geq 0$,

$$f_A(t) = f_A(t-1) = \cdots = f_A(0)$$

and

$$\begin{aligned} f_{AA}(t) &= f_A^2(t-1) = f_A^2(0); \\ f_{Aa}(t) &= 2f_A(t-1)f_a(t-1) = 2f_A(0)\,(1 - f_A(0)) \\ f_{aa}(t) &= f_a^2(t-1) = (1 - f_A(0))^2\,. \end{aligned} \tag{3.17}$$

This solution is so important that it is given a special name, in honor of the first scientists to state it clearly.

Definition: Allele frequencies f_{AA}, f_{Aa}, and f_{aa}, with $f_{AA} + f_{Aa} + f_{aa} = 1$, are said to be in **Hardy-Weinberg** equilibrium if there exists a p, $0 \leq p \leq 1$, such that

$$f_{AA} = p^2, \qquad f_{Aa} = 2p(1-p), \qquad f_{aa} = (1-p)^2.$$

Using this definition, we can summarize the results of our analysis so far as follows.

Theorem 1 (Hardy-Weinberg Theorem) *Assume (A.1)–(A.5). Then the allele frequencies are constant, and, for all generations $t \geq 1$, the genotype frequencies for AA, Aa, and aa are in Hardy-Weinberg equilibrium with $p = f_A(0) = f_{AA}(0) + f_{Aa}(0)/2$.*

Although simple, this is an extremely important result. Biologically, it says that **in the absence of selection, random mating maintains genetic variation in the infinite population model.** And it specifies the genetic equilibrium quantitatively. In a natural population, absence of Hardy-Weinberg equilibrium indicates that one of the assumptions (A.1)–(A.5) does not hold. If the population is large

and isolated and random mating seems likely, it is then reasonable to deduce that selective pressure or mutation is acting to maintain disequilibrium.

Testing for Hardy-Weinberg equilibrium is simple, due to the following criterion, which you are asked to derive in Exercise 3.2.2.

Genotype frequencies f_{AA}, f_{Aa} and f_{aa} are in Hardy-Weinberg equilibrium if and only if

$$f_{Aa}^2 = 4f_{AA}f_{aa}. \tag{3.18}$$

Example 3.2.1. Assume (A.1)–(A.5), and let $f_{AA}(0) = 0.2$, $f_{Aa}(0) = 0.4$, and $f_{aa}(0) = 0.4$. Describe the evolution of genotype frequencies.

In generation 0, the population is not in Hardy-Weinberg equilibrium, because $(f_{Aa}/2)^2(0) = (0.2)^2 = .04$ is not equal to $f_{AA}(0)f_{aa}(0) = (0.2)(0.4) = 0.08$. The frequency of allele A is $f_A(0) = f_{AA}(0) + (f_{Aa}/2)(0) = 0.4$. The Hardy-Weinberg theorem says genotype frequencies arrive at Hardy-Weinberg equilibrium with $p = 0.4$ in one generation. Thus, for $t \geq 1$, $f_{AA}(t) = (0.4)^2 = 0.16$, $2f_{Aa}(t) = 2(0.4)(0.6) = 0.48$, and $f_{aa}(t) = 0.36$. ◇

The simplicity of Theorem 1 suggests it should have simpler derivation than we have given, and indeed it does. The genotype of each individual is produced by randomly sampling a parent from the population, randomly drawing one of its alleles, and then repeating the process, independently, for the second parent. Thus the allele pool of each successive generation is produced by repeated, independent random samples (two per mating) from the allele pool of the parent population. Lemma 1 says that the probability, $p_A(t)$ of drawing allele A in each sample from a parent of generation t is simply $f_A(t)$. If the law of large numbers applies because of the infinite population assumption, then the frequency of A in generation $t+1$ should just be $f_A(t+1) = p_A(t) = f_A(t)$, exactly as we derived above. In effect, the random matings producing each generation completely and randomly redistribute allele pools among the individuals of the next generation. This is why Hardy-Weinberg equilibrium is achieved with the first generation.

Why didn't we develop the Hardy-Weinberg theorem by this argument from the outset? First, from the purely logical standpoint, we stated the infinite population assumption not for allele frequencies but for genotype frequencies, and so it is necessary to prove $f_A(t+1) = p_A(t) = f_A(t)$ as a consequence. The derivation in (3.16) does this. Secondly, equations (3.13), (3.14), (3.15), which analyze evolution of genotypes directly, correspond more closely to what is going on biologically in mating. The student will need to understand this approach to deal with more complicated models, especially those with selection, in which genotype affects reproductive success.

3.2.2 Problems

Exercise 3.2.1. You are studying a hypothetical species of butterfly. It has one gene that controls wing color with two alleles, B and Y. Genotype BB butterflies have blue wings, genotype YY butterflies have yellow wings, and genotype BY butterflies have green wings. You sample butterflies in a population of mixed colors and find that the frequencies of blue, yellow and green butterflies are, respectively, 0.2, 0.3 and 0.5. Is the population exactly in Hardy-Weinberg equilibrium? If not, what would the Hardy-Weinberg equilibrium be given the actual allele frequencies?

Exercise 3.2.2. a) Show that genotype frequencies f_{AA}, f_{Aa} and f_{aa} are in Hardy-Weinberg equilibrium if and only if $f_{Aa}^2 = 4f_{AA}f_{aa}$. (Remember, $f_{AA} + f_{Aa} + f_{aa} = 1$.)

b) The possible values of $K = f_{AA}$ and $M = f_{aa}$ are definied by the region $K \geq 0$, $M \geq 0$, and $K + M \leq 1$. Graph this region in the (K, M) plane. Derive a relation that expresses $M = f_{aa}$ as a function of $K = f_{AA}$ when they are in Hardy-Weinberg equilibrium and graph this curve in your region.

Exercise 3.2.3. A large monecious population (size N) of AA homozygotes is brought into contact with a population of aa homozygotes of size $2N$. From that point on the populations merge at once and random mating takes place. There is no selection, mutation or migration. Assuming N is large enough that we may assume the infinite population hypothesis is valid, describe the evolution of the gene and allele frequencies in all future generations.

3.2.3 The basic model for multiple alleles of one gene

This section is in the nature of a long exercise. We continue to study the genotype for just one locus, but this time assume it admits m alleles, labeled $A_1, \ldots, A_m$, where $m \geq 3$. Therefore, the possible genotypes are the pairs A_iA_i, where i and j range between 1 and m. For notational convenience, denote the frequency of genotype A_iA_j in generation t by $f_{ij}(t)$ instead of $f_{A_iA_j}(t)$. Similarly, let $f_i(t)$ be shorthand for the allele frequency $f_{A_i}(t)$.

The exercises that follow guide you toward a statement of the Hardy-Weinberg theorem for multiple alleles. They can be solved by straightforward generalization of the two allele analysis presented in the previous section. If it helps, assume $m = 3$. This case contains all the ideas needed to understand what happens for general m.

Exercise 3.2.4. For the two allele case we know that $f_A = f_{AA} + (f_{Aa}/2)$. Work out the analogous formula for the multi-allele case. That is, for each i, express $f_i(t)$ in terms of $f_{ij}(t)$, $1 \leq j \leq m$.

Exercise 3.2.5. Apply random mating to express $f_{ij}(t+1)$ in terms of the allele frequencies $f_{A_1}(t), \ldots, f_{A_m}(t)$ in the previous generation.

Exercise 3.2.6. Generalize the Hardy-Weinberg theorem to the multi-allele case, as follows. Use the results of Exercise 3.2.5 to show that allele frequencies are constant and that the genotype frequencies reach equilibrium values in generation $t = 1$ and thereafter remain fixed. Express those equilibrium genotype frequencies in terms of the allele frequencies in the population at time $t = 0$, and define a generalization of Hardy-Weinberg equilibrium.

Rederive the Hardy-Weinberg equilibrium by arguing directly that allele frequencies are constant.

Exercise 3.2.7. (See Exercise 3.2.2a).) Show that a set of genotype frequencies f_{ij}, $1 \leq i \leq j \leq m$, is in Hardy-Weinberg equilibrium, that is, will remain constant for all future generations, if and only if for every $i \neq j$, $f_{ij}^2 = 4f_{ii}f_{jj}$.

3.2.4 One gene/two alleles for dioecious populations

In this section we analyze how the basic model changes when the species is dioecious rather than monecious, and sex is determined, as in humans, by sex chromosomes X and Y. Recall that an individual with two paired X chromosomes is female, but an individual with one X and one Y is male. This system applies to most mammals and to some insects and plants.

All the remaining assumptions (A.1), (A.2), (A.3), and (A.5) are in force. We also assume Mendel's hypothesis that different chromosomes segregate independently of one another in meiosis. This means that if, say, T_1 and T_2 are the two copies of chromosome T, and S_1 and S_2 are the two copies of chromosome S in an individual, each of the four combinations (T_1, S_1), (T_1, S_2), (T_2, S_1), (T_2, S_2) is equally likely in a randomly drawn gamete from that individuals egg or sperm.

As we saw in the monecious case, the crucial step in deriving a model was calculating the probability that an offspring of a random mating has a particular genotype. A priori, these probabilities could differ for male and female offspring. To allow for this possiblity, we shall, for instance, denote the probability that the male child of a mating has genotype AA by p_{AA}^m; the probability for a female child is similarly denoted by p_{AA}^f. Genotype and allele frequencies could also differ, and these will be denoted by f_A^m, f_A^f, f_{AA}^m, f_{AA}^f, etc.

The genotype of a locus on an autosomal chromosome is the same for both males and females, because both sexes contain two copies of an autosomal chromosome. However, if a locus is on the X chromosome, the genotype of a female will have two alleles for that locus, but the male only one. Thus, loci on autosomal chromosomes must be analyzed separately from loci on the sex chromosome.

Consider autosomal chromosomes first. Assuming with Mendel that different chromosome types segregate independently simplifies the genetics immediately, because it implies that autosomal chromosomes are inherited independently of the sex. Hence, *for genotypes of loci on autosomal chromosomes, sex and genotype are passed to progeny independently.* As a consequence, the probability that a male child

is born with a particular genotype is equal to the probability that a female child is born with the same genotype. In other words, if $G_1 \dots G_k$ denotes a genotype with respect to loci on an autosomal chromosomes.

$$p^m_{G_1 \dots G_k} = p^f_{G_1 \cdots G_k} \tag{3.19}$$

Consider now a locus on an autosomal chromosome with an allele A. The infinite population assumption, applied separately to male and female subpopulations, says that for all $t \geq 0$,

$$f^m_{AA}(t+1) = p^m_{AA}(t+1) \quad \text{and} \quad f^f_{AA}(t+1) = p^f_{AA}(t+1),$$

where $p^m_{AA}(t+1)$ and $p^f_{AA}(t+1)$ are the probabilities that a random mating of generation t parents produces AA males and females, respectively.. Thus, from (3.19), we get $f^m_{AA}(t+1) = f^f_{AA}(t+1)$ for all $t \geq 0$. This reasoning applies to any genotype of loci on autosomal chromosomes: even if they start out unequal in generation 0, **male genotype and allele frequencies will equal female genotype and allele frequencies in all later generations.**

Referring back to Exercise 3.1.2, the reader can now do the following problem to complete the analysis of a locus on an autosomal chromosome.

Exercise 3.2.8. Consider a single locus with two alleles A and a. Assume the frequencies $f^m_{AA}(0)$, $f^m_{Aa}(0)$, $f^m_{aa}(0)$ and $f^f_{AA}(0)$, $f^f_{Aa}(0)$, $f^f_{aa}(0)$ are given and that assumptions (A.1), (A.2), (A.3), (A.5), and (A.6) are in force.

a) Calculate the genotype and allele frequencies, of the first generation, in terms of the generation 0 genotype frequencies. Then calculate the allele and genotype frequencies of the second generation.

b) Show that the allele frequencies of the male and female populations are equal and constant for all generations $t \geq 1$. Show that the genotype frequencies are in Hardy-Weinberg equilibrium with

$$p = (1/2)\left(f^m_{AA}(0) + (f^m_{Aa}/2)(0) + f^f_{AA}(0) + (f^f_{Aa}/2)(0)\right)$$

in generations $2, 3, \dots$. ◇

By this exercise, the only difference between monecious loci and dioecious, autosomal loci is that it takes two generations instead of one to achieve Hardy-Weinberg equilibrium. The first random mating of the dioecious population equalizes the allele frequencies of male and female subpopulations, but does not yet produce Hardy-Weinberg equilibrium. Once the allele frequencies are equalized, Hardy-Weinberg follows immediately for all subsequent generations, because, from the point of view of frequencies, there is no longer any effective difference between males and females.

Next consider a locus ℓ carrying alleles A and a on the X chromosome. Now sex and genotype are linked. A female offspring has two X chromosomes, one from

the father and one from the mother, and hence receives one allele from each parent. But a male will have only one copy of the gene, which, because it is on the X chromosome, he receives from his mother. Thus, females have the usual genotypes AA, Aa and aa, with frequencies, $f^f_{AA}(t)$, $f^f_{Aa}(t)$, and $f^f_{aa}(t)$, but males have only the possible genotypes A and a, and their frequencies are the same as the allele frequencies, $f^m_A(t)$ and $f^m_a(t)$.

Assume again that generations do not overlap, that there is no selection, migration or mutation, and that mating is random. The next exercise guides the reader through the formulation and analysis of the model under these assumptions. It will turn out that the frequencies do not attain Hardy-Weinberg equilibrium in a finite number of steps, but do tend to Hardy-Weinberg equilibrium as time progresses.

Exercise 3.2.9. a) Show that the random mating and infinite population assumptions imply $f^m_A(1) = f^f_A(0)$, $f^f_{AA}(1) = f^m_A(0)f^f_A(0)$, $f^f_{Aa}(1) = f^m_A(0)(1-f^f_A(0)) + f^f_A(0)(1-f^m_A(0))$, $f_{aa}(1)^f = (1-f^m_A(0))(1-f^f_A(0))$. Deduce that $f^f_A(1) = (f^m_A(0) + f^f_A(0))/2$.

b) The same argument as in a) shows that for any t,

$$\begin{aligned} f^m_A(t+1) &= f^f_A(t), \qquad t \geq 0; \\ f^f_A(t+1) &= \frac{1}{2}(f^m_A(t) + f^f_A(t)) \qquad t \geq 0 \\ &= \frac{1}{2}(f^f_A(t-1) + f^f_A(t)) \qquad t \geq 1. \end{aligned}$$

Isolating the first and last expressions of the second equation, show that

$$f^f_A(t+1) = \frac{1}{2}(f^f_A(t-1) + f^f_A(t)). \tag{3.20}$$

Equation (3.20) is a *second order, homogeneous linear difference equation.*

c) The goal in this part is to solve (3.20) for given values of $f^f_A(0)$ and $f^m_A(0)$. From part a), this is equivalent to solving (3.20) given

$$f^f_A(0) \text{ and } f^f_A(1) = (f^m_A(0) + f^f_A(0))/2. \tag{3.21}$$

Step 1: Plug $x(t) = r^t$ into $x(t+1) = (x(t) + x(t-1))/2$ and factor out r^{t-1} to find two values r_1 and r_2 such that r_1^t and ${r_2}^t$ both solve (3.20). Then show that $c_1{r_1}^t + c_2{r_2}^t$ solves (3.20) for any constants c_1 and c_2. This turns out to be the general solution.

Step 2: Write $f^f_A(t) = c_1{r_1}^t + c_2{r_2}^t$ for some constants c_1 and c_2 and then by choose c_1 and c_2 to satisfy the initial conditions, $f^f_A(0)$ and $f^f_A(1) = (f^m_A(0) + f^f_A(0))/2$, of (3.21).

(For more about solving second order linear difference equations, see the Appendix to this chapter.)

d) Express the genotype frequencies $f^f_{AA}(t+1)$, $f^f_{Aa}(t+1)$, and $f^f_{aa}(t+1)$ at any time t in terms of $f^f_A(t)$ and $f^f_A(t-1)$.

e) Find the limits $f_A^f(\infty) \stackrel{\triangle}{=} \lim_{t\to\infty} f_A^f(t)$, $f_{AA}^f(\infty) \stackrel{\triangle}{=} \lim_{t\to\infty} f_{AA}^f(t)$, etc. in terms of $f_A^f(0)$ and $f_A^m(0)$. Show that $f_{AA}^f(\infty)$, $f_{Aa}^f(\infty)$ and $f_{aa}^f(\infty)$ are in Hardy-Weinberg equilibrium.

3.2.5 Infinite population with mutation, but no selection

Consider again a single locus admitting two alleles A and a. In this section, we study what happens when mutation is allowed. Otherwise, all the other assumptions made in (A.1)—(A.5) are in force.

Mutations occur when alleles in a parental gamete become modified to new forms. They can be induced by copying errors or exposure to chemical toxins or radiation, and could produce a totally new allele, or an allele that already exists. In either case, mutations occur randomly. We will consider only the simple situation in which A and a can mutate one into the other according to the following rule:

> Independently in each gamete, A mutates to a with probability u, and a mutates to A with probability v, where $0 < u_v$. (A.7)

Frankly, the motivation for this model is more pedagogical than scientific. We want to explore, as an exercise, how the basic model might change as a result of mutation, and (A.7) is the simplest mutation mechanism one can think of. It is what is called in the trade a "toy model." The assumption $0 < u + v$ in (A.7) just assures that some mutation takes actually takes place.

In this problem it is simpler to work directly with allele frequencies, rather than analyze genotype frequencies first. We have seen in the derivation of Hardy-Weinberg equilibrium that

$$\begin{aligned} f_A(t+1) \;=\; & \text{probability an offspring} \\ & \text{acquires } A \text{ from a randomly selected parent of generation } t, \end{aligned}$$

and that this fact is an expression of the infinite population assumption. This identity will be the starting point of our derivation. We need to compute the probability on the right-hand side. According to (A.7), the offspring acquires A either if the parent contributes a gamete with genotype A and A does not mutate, or if the parent contributes a gamete with genotype a and a does mutate. The probability of the first event is $(1-u)f_A(t)$, since $f_A(t)$ is the probability a parent contributes A and $(1-u)$ is the probability it does not mutate. Similarly, the probability a parent transmits allele a, which then mutates to A, is $v(1-f_A(t))$. Therefore,

$$f_A(t+1) = (1-u)f_A(t) + v(1-f_A(t)) = v + (1-u-v)f_A(t). \tag{3.22}$$

This is a first order, linear difference equation. It is shown in the Appendix that its solution is

$$f_A(t) = (1-u-v)^t[f_A(0) - \frac{v}{u+v}] + \frac{v}{u+v}. \tag{3.23}$$

Exercise 3.2.10. a) Check by direct calculation that the right-hand side of (3.23) does indeed solve (3.22).

b) Assuming $0 < u + v < 2$, prove $\lim_{t\to\infty} f_A(t) = v/(u+v)$. Derive from this the following conclusion: if $v > 0$ and $u > 0$, alleles A and a both persist in the population forever.

What happens if $v = 0$, but $u > 0$, or $u = 0$, but $v > 0$?

Finally, determine $\lim_{t\to\infty} f_{AA}(t)$ and $\lim_{t\to\infty} f_{Aa}(t)$.

Exercise 3.2.11. Analyze the solution of (3.22) when $u = 1$ and $v = 1$ and interpret.

Exercise 3.2.12. Let $f_A(0) = 0.5$, Let $f_A^{(1)}(t)$ denote the allele frequency in generation t when $u = 1/4$ and $v = 1/2$, and let $f_A^{(2)}(t)$ be the allele frequency in generation t when $u = 1/16$ and $v = 1/8$.

(i) Show that the limiting frequency, as $t \to \infty$, is the same in both cases.

(ii) Denote the limiting frequency found in i) by $\bar{p}$. Find the smallest value T_1 such that $|f_A^{(1)}(T_1) - \bar{p}| \le 0.01$. Find the smallest value T_2 such that $|f_A^{(2)}(T_2) - \bar{p}| \le 0.01$. (Note that $f_A^{(1)}(t)$ and $f_A^{(1)}(t)$ are both increasing in t.) Compare T_1 and T_2 and explain why your result is to be expected on intuitive grounds, considering the mutation rates in both cases.

3.2.6 A model with overlapping generations

In non-overlapping generation models, each generation produces the next and then mates no more. This would be the case if reproduction occurs during regularly spaced mating season, and in each season, generation t produces the new generation $t+1$ and then dies. Suppose instead that in each mating season, the current population produces enough offspring to replace a fraction h, $0 < h < 1$, of itself by random mating, and then a fraction h of the parents are eliminated (die) by random selection. Then in each mating season, the population replaces a fraction h of itself. The population at the next mating system consists of both older individuals and new arrivals. Also assume that the new arrivals are sexually mature by the next mating season and participate on equal footing in the next cycle of reproduction. This is a simple system in which mixing occurs between the genes of individuals born at different times, and the population size is constant. In this section we derive the corresponding mathematical model when the other basic assumptions—(A.1), (A.3), (A.4), and (A.5)—are in force.

For the derivation, it is convenient to measure time so that mating seasons occur at intervals h, $2h$, $3h$, and so on. This is the proper time scale to compare models with different values of h. In a time interval of length 1, approximately $1/h$ mating seasons occur, in each of which a fraction h of the population is replaced. Thus, in one unit of time, the number of new individuals entering the population is a fraction $h(1/h) = 1$ of the size of the population, no matter what h is. Hence $t = 1$ is roughly the lifetime of one generation.

In what follows, $f_A(h), f_A(2h), \cdots$ shall denote the allele frequencies in the population at the end of each successive mating season. Thus $f_A(h)$ is the allele frequency after the first birth, death and replacement occurs, $f_A(2h)$ the frequency after second occurrence, and so on. Similarly, $f_{AA}(kh)$ will represent the genotype frequency at the end of the k^{th} mating season.

Consider genotype AA and let t and $t+h$ denote the times of two successive mating seasons. The difference $f_{AA}(t+h) - f_{AA}(t)$ will be a sum of the changes due births of new individuals minus those due to deaths in the mating season $t+h$. Now, the mating at time $t+h$ occurs in a parent population in which the frequence of allele A is, by definition, $f_A(t)$. The random mating and infinite population assumptions thus imply that the frequency of AA among the offspring is $f_A^2(t)$. The frequency of AA in the *parent* population at time $t+h$ is by definition $f_{AA}(t)$, and since death is by random selection, the frequency of AA among the individuals selected to die must be $f_{AA}(t)$ as well. Since a fraction h of the population is being replaced, it follows that

$$f_{AA}(t+h) - f_{AA}(t) = h\left[f_A^2(t) - f_{AA}(t)\right] \tag{3.24}$$

(If you are not convinced of this, imagine that the population has size N and compute the number of AA genotypes entering and leaving the population in the mating season $t+h$.)

A similar analysis applies to $f_A(t+h)$. The allele frequency among the offspring produced in the replacement event at $t+h$ is $f_A(t)$, because we know this frequency does not change in random mating. The proportion of individuals selected for elimination with genotype AA is, as we know, $f_{AA}(t)$, and the proportion selected for elimination with genotype Aa is, similarly, $f_{Aa}(t)$. As a consequence, the frequency of A among those eliminated is $f_{AA}(t) + f_{Aa}(t)/2 = f_A(t)$, also. This means that the number of A entering and leaving the population is the same in each mating season and therefore $f_A(t) = f_A(0)$ for all $t > 0$, just as in the basic model. Thus, using this result in (3.24).

$$\frac{f_{AA}(t+h) - f_{AA}(t)}{h} = -f_{AA}(t) + f_A^2(0)\,, \tag{3.25}$$

which is a first order, linear difference equation.

This equation can be used to derive a continuous time model by taking a limit as $h \downarrow 0$. When h is very small, the population is mating very frequently and replacing only a small fraction of itself each time. The limit as $h \downarrow 0$ models a population in which mating and death occur continuously and at the same rate, and in which offspring enter the mating pool immediately upon birth. This is the extreme opposite of non-overlapping generations. By letting $h \downarrow 0$ in (3.25),

$$f'_{AA}(t) = \lim_{h \downarrow 0} \frac{f_{AA}(t+h) - f_{AA}(t)}{h} = -f_{AA}(t) + f_A^2(0). \tag{3.26}$$

Exercise 3.2.13. a) Show that the solution to (3.26) is

$$f_{AA}(t) = [f_{AA}(0) - f_A^2(0)]e^{-t} + f_A^2(0)$$

b) Use Proposition 1 in the appendix to show the solution to (3.25) is

$$f_{AA}(kh) = (1-h)^k \left[f_{AA}(0) - f_A^2(0)\right] + f_A^2(0). \tag{3.27}$$

Since $0 < h < 1$,

$$f_{AA}(\infty) \stackrel{\triangle}{=} \lim_{k\to\infty} f_{AA}(kh) = f_A^2(0). \tag{3.28}$$

A similar analysis applied to the genotypes Aa and aa shows

$$f_{Aa}(\infty) \stackrel{\triangle}{=} \lim_{k\to\infty} f_{Aa}(kh) = 2f_A(0)f_a(0), \quad f_{aa}(\infty) \stackrel{\triangle}{=} \lim_{k\to\infty} f_{aa}(kh) = f_a^2(0). \tag{3.29}$$

Exercise 3.2.14. Let $f_{AA}(0) = f_{AA}$. Solve equation (3.26) in terms of f_{AA}, $f_A(0)$, and t. (Hint: consider $\tilde{f}_{AA}(t) = f_{AA}(t) - f_A^2(0)$, and find a differential equation for $\tilde{f}_{AA}(t)$.) Show that $\lim_{t\to\infty} f_{AA}(t) = f_A^2(0)$, which is the Hardy Weinberg equilibrium value.

3.2.7 Summary

In retrospect, one should expect Hardy-Weinberg equilibrium to emerge whenever random mating operates in the absence of selection and mutation, because random mating mixes the allele pool. For the models studied above that with no mutation this is true. When the population is monecious and generations do not overlap, random mating is able to completely mix the gene pool in one mating season and Hardy-Weinberg equilibrium is attained in the first generation. In the other situations, various conditions limit the mixing caused by random mating in each mating season. Thus, if the population is dioecious, an extra generation is needed to mix the male and female allele pools. If generations overlap, random mating can only achieve partial mixing, with each successive mating. But the effects accumulate and the populations in these cases do tend in the long-time limit to Hardy-Weinberg equilibrium.

3.2.8 Exercises

Exercise 3.2.15. Develop a one locus/two allele model for overlapping generations, as in Section 3.2, but with the following twist. Assume that mating seasons occur at times $h, 2h, \ldots$ and in each season a fraction h of the population is replaced. However, assume that newborns require two seasons to mature, and do not mate in the first season after they are born, but only in the second. However, newborns have the same probability as older individual to be removed, so they may not survive until

sexual maturity. Let $f_A(t)$ denote the frequency of A in that part of the population born before $t-h$, and let $g_A(t)$ be the frequency of A in that part of the population born at t. Derive a set of difference equations for $f_A(t)$ and $g_A(t)$, reduce to one equation for $f_A(t)$ and solve.

Exercise 3.2.16. Here is a model of one locus–two alleles in which mating is not fully random. Assume otherwise an infinite population, non-overlapping generations, and no selection.

Assume the population is composed of two subpopulations I and II, and let A and a denote the alleles at the locus of study. Use $p^I(t)$ and $p(t)^{II}$ to denote the frequency of allele A in each subpopulation for generation t. Now assume the next generation is produced as follows. To replace an individual in population I, determine its first allele by choosing an allele at random from population I. Determine its second allele by drawing an allele at random from population I with probability .8 and an allele at random from population II with probability .2 (Note: .8 is the probability of choosing population I, not the probability of drawing a specific allele!).

To replace an individual in population II, draw the first allele at random from population II. Determine the second allele by drawing at random from population I with probability .1 and from population II with probability .9.

a) Assuming no selection, derive equations that determine $p^I(t+1)$ and $p^{II}(t+1)$ in terms of $p(t)^I$ and $p^{II}(t)$. Your equation should reduce to a set of two linear update equations.

b) For this mating model $.5(p^I(t)+p^{II}(t)$ is the frequency of allele A in the entire population, assuming that populations I and II are equal. Show using the result of a), that $.5(p^I(t)+p_t^{II})$ is constant from one generation to the next.

c) $\lim_{t\to\infty} p^I(t)$ and $\lim_{t\to\infty} p^{II}(t)$ both exist. Guess on the basis of intuition what these limits are.

By using part b), find a single update equation for $p^I(t)$ and solve it. Verify your guess for $\lim_{t\to\infty} p^I(t)$.

Exercise 3.2.17. (Two locus model.) Let the alleles at locus ℓ_1 be A_1 and A_2. Let the alleles at locus ℓ_2 be B_1 and B_2. Suppose that ℓ_1 and ℓ_2 are on different chromosomes. By Mendel's laws, these chromosomes segregate independently. What is the evolution of the genotype frequencies $f_{A_iA_jB_kB_m}(t)$? Describe the values of these frequencies explicitly in terms of the allele frequencies of generation 0.

Exercise 3.2.18. The problem with the blending hypothesis. In so far as there was a theory of heredity in the late 1800's prior to the rediscovery of Mendel's results, it would have been a theory of blending. That is, any specific trait of an individual would be a blend half-way between the traits of its parents. Ewens, in his text, **Mathematical Population Genetics** (1979), says:

"It is easy enough to see that, with random mating, the variance in a population

for any characteristic would, under a blending theory, decrease by a factor of one-half in each generation."

This problem is about understanding Ewen's statement. We need a model. Suppose we have a characteristic whose strength can be described by a continuum of values, x, say height. Let the random variable X denote the height of an individual drawn at random from the population. Let us interpret the "variance in a population for the height characteristic" as simply the variance of X. Denote this variance as σ^2. Now what happens in random mating? We draw and individual from the population at random and let X_1 denote its height. We draw a second individual from the population independently of the first and denote its height as X_2. The random variable X_1 and X_2 are independent and have variance σ^2. We mate the two individuals to produce an offspring with height $(1/2)(X_1 + X_2)$; this is the blending. Now finish the reasoning!

Comment: Notice that under blending the variance of any characteristic over a population must disappear. (Why?) This is in total opposition to the Hardy-Weinberg result, which shows that for inheritance of discrete traits, variation is maintained. The blending theory is not consistent with real populations, which do maintain variation.

3.3 Wright's Fixation Index

This section may be skipped; it is not used subsequently.

Hardy-Weinberg equilibrium is an important tool of genetic analysis, and one of its important applications is *Wright's fixation index.* Real populations of a species are often spread out over a large geographic area that does not offer uniformly good habitat. As a result, distinct subpopulations develop, and, although there is definitely mating, and hence gene flow, between members of different subpopulations, most mating takes place within subpopulations. Therefore the random mating assumption does not apply to the larger population, and differences in gene frequencies can develop between subpopulations, due, for example to inbreeding effects or to different selective pressures on different subpopulations.

The American geneticist, Sewall Wright, whom we will meet again in the next chapter, was interested in quantifying the effect of population structure on the frequency of heterozygotes. We will explain his idea for the usual case of one locus and two alleles, A and a.

The frequency f_{Aa} of heterozygotes in a population is called its *heterozygosity*, and it is the same as the probability that a random selected individual is a heterozygote. If the population is in Hardy-Weinberg equilibrium, then we know its heterozygosity is $2f_A(1 - f_A)$, and the relation of the actual heterozygosity to this number measures how well the population is mixed.

Now consider a large population that is subdivided into K populations $\mathcal{S}_1, \ldots, \mathcal{S}_K$. For each index i, let c_i denote the fraction of the total population in subpopulation

i. Let $f_{A,i}$ be the frequency of allele A in $\mathcal{S}_i$. The frequency of A in the total population is then the average

$$f_A = \sum_{i=1}^{K} c_i f_{A,i}.$$

To define Wright's fixation index we will need two quantities, H_T and H_S. The quantity H_T (T is for *total*) is just what the heterozygosity of the total population would be if it were in Hardy-Weinberg equilibrium. Thus $H_T = 2f_A(1 - f_A)$. The quantity H_S (S stands for *subpopulation*) is the average of the subpopulation heterozygosities assuming each subpopulation is in Hardy-Weinberg equilibrium, where each subpopulation is weighted by its proportion in the total:

$$H_S = \sum_{i=1}^{K} c_i 2f_{A,i}\big(1 - f_{A,i}\big).$$

This is the same as the average heterozygosity in the total population assuming each subpopulation is in Hardy-Weinberg equilibrium, because, if we were to select an individual at random from the total population, the probability it would be in subpopulation $\mathcal{S}_i$ is c_i, and given that it is in $\mathcal{S}_i$, the probability it would be heterozygous is $2f_{A,i}\big(1 - f_{A,i}\big)2f_{A,i}\big(1 - f_{A,i}\big)$. Wright's fixation index of the subpopulations relative to the total population is

$$F_{ST} := \frac{H_T - H_S}{H_T}.$$

As we shall see, $H_T \geq H_S \geq 0$. The numerator thus measures how much the variation in heterozygosity among the subpopulations reduces the heterozygosity we would expect if there were no subpopulation structure and random mating applied to the total population. Wright's index thus measures the relative size of this reduction; it always takes a value between 0 and 1.

From the definition of F_{ST} and H_T and a little bit of algebra,

$$H_S = H_T\big(1 - F_{ST}\big) = 2f_A(1 - f_A) \cdot \big(1 - F_{ST}\big).$$

Since $2f_A(1 - f_A)$ is the heterozygosity we would expect if the entire population were in Hardy-Weinberg equilibrium, and H_S is the actual heterozygosity (assuming subpopulations are in Hardy-Weinberg equilibrium), we see that $1 - F_{ST}$ is the multiplicative factor by which the stratification by subpopulations reduces heterozygosity.

There is another way to look at heterozygosity and Wright's index which is also informative. It is based on the following formula from probability. If X and Y are two random variables, then

$$\mathrm{Var}(X) = \mathrm{Var}\Big(E[X|Y]\Big) + E\Big[\mathrm{Var}(X|Y)\Big] \tag{3.30}$$

This is often used to simplify the computation of the variance of X when it has a simple dependence on an auxiliary random variable Y. Note that both terms on the right-hand side are positive. You can think of the first term as a measure of how much of the variance of X is due to the fluctuation of its conditional mean with respect to Y. Formula (3.30) is disussed and derived on pages 41–42 of Chapter 2.

To apply this formula to Wright's index, imagine sampling the allele pool of the total population at random. We shall be interested in what the sampled allele is and where it came from. So let $X = 1$ if this allele is A and 0 if it is not. Let $Y = i$ if it comes from subpopulation i. Now consider the various terms in (3.30). Clearly X is a Bernoulli random variable with $P(X = 1) = f_A$. Hence, $\mathrm{Var}(X) = f_A(1-f_A)$, which is precisely one-half of H_T. On the other hand, suppose we know that $Y=i$. Conditioned on this information, the allele we sample is equally likely to be any member of the allele pool of subpopulation i, hence, conditioned $P(X=1\big|Y=i) = f_{A,i}$. It then follows that $\mathrm{Var}(X|Y=i) = f_{A,i}(1-f_{A,i})$, and hence,

$$E\Big[\mathrm{Var}(X|Y)\Big] = \sum_{i=1}^{K} c_i \mathrm{Var}\big((X\big|Y=i\big)\big) = \sum_{i=1}^{K} c_i f_{A,i}\big(1-f_{A,i}\big) = (1/2)H_S.$$

This equation gives us a nice probabilistic interpretation of H_S, and it implies that $(H_T - H_S)/2 = \mathrm{Var}(X) - E\Big[\mathrm{Var}(X|Y)\Big] = \mathrm{Var}\Big(E[X\big|Y]\Big)$. As a consequence,

$$F_{ST} = \frac{H_T - H_S}{H_T} = \frac{(H_T/2) - H_S/2)}{H_T/2} = \frac{\mathrm{Var}\Big(E[X\big|Y]\Big)}{f_A(1-f_A)}\,.$$

This formula makes it clear immediately that $F_{ST} \geq 0$, since a variance is always non-negative. Moreover, the numerator has a nice interpretation. It is the variance of the random variable which takes value $E[X\big|Y=i]$ if $Y=i$. But if $Y=i$, X is a Bernoulli random variable with mean $f_{A,i}$ and so $E[X\big|Y=i] = f_{A,i}$. Thus $E[X\big|Y]$ is the random variable obtained by choosing a subpopulation at random according to the probabilities $c_1, \ldots, c_K$ and recording its allele frequency, that is, it's the allele frequency of a randomly chosen subpopulation. Hence the numerator in the last expression for F_{ST} is the variance of allele frequency over subpopulations.

This discussion has been theoretical. In reality, one knows neither the subpopulation allele frequency nor the over-all frequency, exactly. The data only give empirical frequencies of samples, and there are interesting statistical questions on how to estimate F_{ST}.

Wright's fixation index and its variants is one of the most widely used tools to study the structure of populations. This is partly because one can translate models about how the subpopulations may have diverged or how long they have been diverging into expected values for F_{ST}. Observed values can then be used to draw inferences about genealogical history. A nice review of the index and references to some of its main applications may be found in

Holdinger, K.E. and Weir, B.S., Genetics in geographically structured populations: defining, estimating and interpreting F_{ST}, *Nature Reviews, Genetics*, **10** (2009), 639-650.

3.4 An Infinite Population Model with Selection

So far, all our models have been selectively neutral, in the sense that genotype does not influence reproductive fitness. In this section, we will describe a standard method to introduce selection. It again leads to a difference equation model, but this time one that is nonlinear. Its analysis requires new techniques, which we discuss first in the next section.

3.4.1 Nonlinear, first-order difference equations

In general, it is not possible to find closed form solutions to the difference equation,

$$x(t+1) = \phi(x(t)), \tag{3.31}$$

when ϕ is a nonlinear function. However there is an exceptional case. A point $\bar{x}$ is a called a fixed point of (3.31), or of ϕ, if $\phi(\bar{x}) = \bar{x}$. The solution of (3.31) that starts off with $x(0) = \bar{x}$, is just the constant sequence, $x(t) = \bar{x}$, for all $t \geq 0$; indeed, if $x(0) = \bar{x}$, then $x(1) = \phi(x(0)) = \phi(\bar{x}) = \bar{x}$, and thus, $x(2) = \phi(x(1)) = \phi(\bar{x}) = \bar{x}$, and so on. This constant solution is called an *equilibrium solution* or *steady state* of the difference equation (3.31).

Equilibrium solutions turn out to be important in the analysis of solutions starting at other initial values. For example, given a solution $\{x(t)\}$ to (3.31), it is often more interesting to know whether $\lim_{t\to\infty} x(t)$ exists or not, and what the value of this limit is, than to know $x(t)$ as a function of t. When ϕ is continuous, *this limit must be a fixed point* of ϕ, by the following argument. If $y = \lim_{t\to\infty} x(t)$, then because ϕ is continuous, $\lim_{t\to\infty} \phi(x(t)) = \phi\big(\lim_{t\to\infty} x(t)\big) = \phi(y)$. But, if $x(t)$ solves $x(t+1) = \phi(x(t))$, then

$$y = \lim_{t\to\infty} x(t+1) = \lim_{t\to\infty} \phi(x(t)) = \phi\Big(\lim_{t\to\infty} x(t)\Big) = \phi(y)$$

showing y is a fixed point of ϕ. Thus, to narrow down the possible limits of solutions to (3.31), it is only necessary to identify the fixed points of ϕ, which is a relatively simple task.

Just knowing the fixed points does not tell us which other solutions have a limit, and which fixed point that limit is. Fortunately, there is a simple graphical technique called cobwebbing for visualizing solutions to help answer these questions. By itself, cobwebbing is not a rigorous mathematical method. But it helps in guessing correct answers, and in interpreting rigorous, analytic techniques. In particular, cobwebbing makes clear heuristically how solutions behave near fixed points.

Cobwebbing is carried out in the Cartesian plane. Start by graphing the diagonal line $y = x$ and, superimposed on that, the graph, $y = \phi(x)$. The fixed points of ϕ are then easy to read off, since they are just the x-coordinates of the points in the plane at which the graphs of $y = \phi(x)$ and $y = x$ intersect. The unique fixed point in Figure 1 is labeled $\bar{x}$.

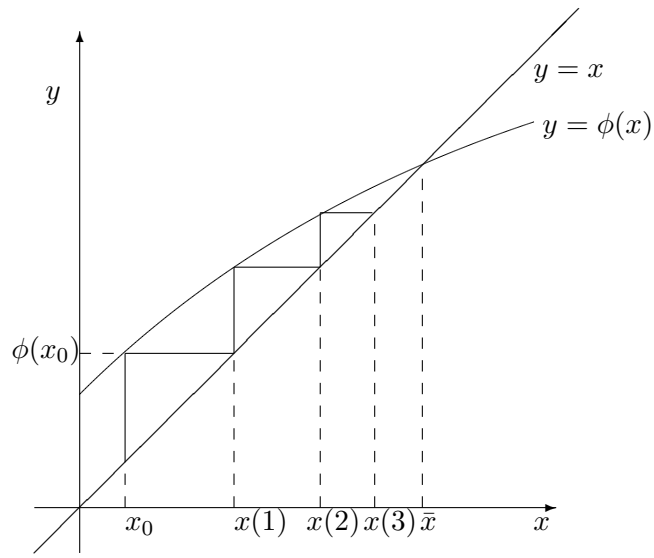

Figure 1.

The object of cobwebbing is to plot successive values of the solution to (3.31), starting at any given initial condition, $x(0) = x_0$, on the x-axis. The fundamental operation is a stepping procedure that, starting from any point (x, x) on the diagonal, leads to the point $(\phi(x), \phi(x))$. Figure 1 shows how the method works. Plot the initial point $x(0) = x_0$ on the x-axis. First draw a vertical line segment from the point (x_0, x_0) to the curve $y = \phi(x)$, and then draw a horizontal line from the curve back to $y = x$. The result looks like a step. Since the vertical line intersects the graph of $y = \phi(x)$ at the ordinate $y = \phi(x_0)$, the horizontal line is drawn at the level $y = \phi(x_0)$ and will intersect the line $y = x$ at $(\phi(x_0), \phi(x_0))$. So the first graphical step leads from (x_0, x_0) to $(\phi(x_0), \phi(x_0)) = (x(1), x(1))$. Iteration of the stepping procedure starting from $(x(1), x(1))$ then produces the point $(\phi(x(1), \phi(x(1)) = (x(2), x(2))$; a third repetition leads to $(x(3), x(3))$, and so on. Thus, the x-coordinates of the successive points on $y = x$ hit by the stepping procedure plot out the solution to equation (3.31). Figure 1 carries out the first few iterations.

Cobwebbing helps determine how solutions to a difference equation behave, starting from different initial values x_0. For example, it is clear from Figure 1, that the successive values of the plotted solution $x(t)$ will increase and will converge to the fixed point $\bar{x}$, as $t \to \infty$. It is also clear that the same limiting behavior will obtain for any initial values x_0 close to but less than $\bar{x}$. If x_0 is close to $\bar{x}$ but larger than $\bar{x}$, cobwebbing will show that the solution decreases toward $\bar{x}$; you should check this. This graphical analysis suggests, but does not prove, that $\lim_{t\to\infty} x(t) = \bar{x}$ for all starting values x_0 sufficiently close to $\bar{x}$. In the terminology of dynamical systems, $\bar{x}$ is an example of a *stable* fixed point. A definition of this important concept follows.

Definition 1 *Let x^* be the fixed point of a difference equation. The set of all points x such that $\lim_{t\to\infty} x(t) = x^*$, when $(x(t))_{t\geq 0}$ is the solution of $x(t+1) = \phi(x(t))$ starting at $x(0) = x$, is called the* basin of attraction *of x^*. The fixed point x^* is called* stable *if its basin of attraction includes an open interval about x^*.*

Figure 2 illustrates a quite different situation. The cobwebbing is not shown, and you should supply it yourself. You will see that when the initial point, $x(0)$ is close to the fixed point, x^*, the successive points $x(1), x(2), \ldots$ of the solution will spiral away from x^*. The picture this time really will look like a cobweb, and x^* is not stable.

Although the cobwebbing analyses used in Figures 1 and 2 do not provide a mathematical proof of stability or non-stability, the insights they provide can be turned into a theorem. The key point is to identify a feature of ϕ that discriminates between the two cases.

Theorem 2 *Let ϕ be continuously differentiable and let z be a fixed point of the difference equation $x(t+1) = \phi(x(t))$. ϕ. If*

$$\begin{array}{l} \textit{If} \quad \mid \phi'(z) \mid < 1, \quad \textit{then} \quad z \quad \textit{is a stable fixed point.} \\ \textit{If} \quad \mid \phi'(z) \mid > 1, \quad \textit{then} \quad z \quad \textit{is not stable.} \end{array}$$

If $|\phi'(x^*)| = 1$, the fixed point x^* can be either stable or not stable.

Figures 1 and 2 provide clear illustrations of this theorem. The tangent line to ϕ at $\bar{x}$ in Figure 1 has a positive slope less than that of the line $y = x$, which has slope 1. Hence Theorem 2 confirms that $\bar{x}$ is stable. While it is less immediately clear, a sketch of the tangent to η at x^* in Figure 2 shows that its slope is strictly less than -1, and hence that this fixed point is not stable.

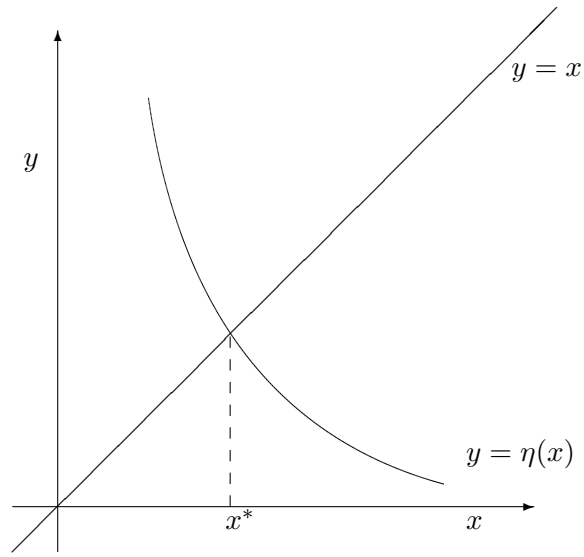

Figure 2.

We omit the proof of Theorem 2, but to see why it works we suggest drawing for yourself a number of examples, some satisfying $|\phi'(z)| > 1$, others satisfying $|\phi'(z)| < 1$, and graphing solutions by cobwebbing.

Here is another plausibility argument, which is actually the basis of a rigorous proof. Assume that ϕ is differentiable at a fixed point x^*. The tangent line to the graph of ϕ at x^* is given by the equation $y = \phi(x^*)+\phi'(x^*)(x-x^*) = x^*+\phi'(x^*)(x-x^*)$, and, for values of x close to x^*, approximates the graph of $y = \phi(x)$ to first order. Therefore, if $\{x(t)\}_{t\geq 0}$ satisfies the difference equation, $x(t+1) = \phi(x(t))$ and $x(t)$ is close to x^*,

$$x(t+1) \approx x^* + \phi'(x^*)(x(t) - x^*).$$

That is, near x^*, $\{x(t)\}_{t\geq 0}$ is approximately a solution to the linear difference equation

$$z(t+1) = x^* + \phi'(x^*)(z(t) - x^*).$$

It is shown in the appendix to this chapter that the solution $\{z(t)\}$ will converge to x^* if $|\phi'(x^*)| < 1$, but that $|z(t)|$ will go off to infinity if $|\phi'(x^*)| > 1$. It can be proved that the stability properties of the approximate linear equation transfer to those of the original nonlinear equation, at least for starting values close to x^*.

3.4.2 Exercises

Exercise 3.4.1. Show that $\sqrt{2}$ is a stable fixed point of

$$x(t+1) = \frac{x(t)}{2} + \frac{1}{x(t)}.$$

(This difference equation is actually Newton's method for finding roots of $x^2 - 2$. Note in this example how close already $x(2)$ is to $\sqrt{2}$ when $x(0) = 1$.)

Exercise 3.4.2. Graph $\phi(x) = (x^3 - 4x)/8$ carefully. Explore the solutions starting from $x(0) = 1$, $x(0) = 2/\sqrt{3}$ and $x(0) = 3$. From cobwebbing, guess the basin of attraction of the fixed point $x^* = 0$. Show that your guess is correct by a rigorous argument. (For this problem use a graphing calculator or a mathematical package such as MAPLE or MATHEMATICA.)

Exercise 3.4.3. Consider the difference equation

$$x(t+1) = f(x(t)),$$

where $f(x) = 4x(1-x)$. Graph this function on the unit interval $[0, 1]$ and notice that f maps the unit interval into itself. A solution of period 2 to the difference equation is a sequence of the form $(z, w, z, w, \dots)$; that is, $w = f(z)$ and $z = f(w)$, so the solution alternates between these two values. Argue by cobwebbing that it is plausible $x(t+1) = 4x(t)(1 - x(t))$ has a solution of period 2. Then find a solution of period 2 analytically; determine exact values of z and w.

A period 2 solution is stable if for all $x(0)$ close to z, the solution converges to the period 2 solution, in the sense that $\lim_{s\to\infty} x(2s+1) = z$ and $\lim_{s\to\infty} x(2s) = w$. Show that the periodic solution you found is not stable.

3.4.3 A Model with Selection

For our model with selection, we keep assumptions (A.1)—(A.4); the population is monecious, generations do not overlap, and mating is random. We assume also there is no migration or mutation. For added clarity, let us assume that mating occurs seasonally. Thus, generation t produces generation $t+1$ all at one time and then generation $t+1$ matures over an interval of time until the next mating season.

Here, *selection* will mean that an individual's genotype affects the probability it survives to reproductive maturity. The survival probabilities, which are also called *selection coefficients*, will be denoted by w_{AA}, w_{Aa} and w_{aa}. Thus, for example, w_{AA} denotes the probability that an individual of genotype AA survives from birth to reproductive maturity. We assume the selection coefficients are the same from generation to generation and individuals survive or don't survive independently from one another. If, for example, $w_{AA} = 1/3$ and the population is large, roughly only $1/3$ of those individuals born as AA in any generation will survive to reproduce.

It is necessary to be careful in defining the genotype and allele frequencies in a generation t, because selection causes them to change over the lifetime of the generation. We will be interested in the frequencies only at the beginning of each generation, when it is produced by random mating, and at the time of reproductive maturity, after selection has taken place and when mating takes place to produce the next generation. We will use $f_A(t)$, $f_{AA}(t)$, etc., to denote the frequencies in generation t at the time of its birth, and on the other hand, $p_A(t)$, $p_{AA}(t)$, etc., to denote them for generation t at the time of reproduction. Because the population is infinite and individuals survive independently of one another, the law of large numbers implies $p_{AA}(t)$ equals *the conditional probability that an individual has genotype AA given that it has survived*, and similarly for $p_{Aa}(t)$ and $p_{aa}(t)$.

The derivation of the model proceeds in two steps. The first relates frequencies between generations, the second within generations. The first step is easy given what we know. The probability that a randomly chosen parent of generation t passes allele A to an offspring is $p_A(t) = p_{AA}(t) + p_{Aa}(t)/2$. Hence by random mating and the infinite population assumption,

$$\begin{aligned} f_A(t+1) &= p_A(t), && (3.32)\\ f_{AA}(t+1) &= p_A^2(t) = f_A^2(t+1), && (3.33)\\ f_{Aa}(t+1) &= 2p_A(t)(1-p_A(t)) = 2f_A(t+1)(1-f_A(t+1)), && (3.34)\\ f_{aa}(t+1) &= 1-p_A(t))^2 = (1-f_A(t+1))^2, && (3.35) \end{aligned}$$

for all $t \geq 0$. As a result $f_{AA}(t)$, $f_{Aa}(t)$ and $f_{aa}(t)$ are in Hardy-Weinberg equilibrium, for any $t \geq 1$.

The second step expresses the probabilities, $(p_{AA}(t), p_{Aa}(t), p_{aa}(t))$, in terms of $(f_{AA}(t), f_{Aa}(t), f_{aa}(t))$ and the selection coefficients. Remember that $p_{AA}(t)$ is the conditional probability an individual has genotype AA *given* it has survived: in mathematical notation

$$p_{AA}(t) = \frac{P(U_{AA} \cap S)}{P(S)} = \frac{P(S|U_{AA})P(U_{AA})}{P(S)}$$

where S is the event a randomly chosen individual born in generation t survives and U_{AA} is the event a randomly chosen individual is AA. By definition, $P(U_{AA}) = f_{AA}(t)$ and $P(S|U_{AA}) = w_{AA}$, and so the numerator of $p_{AA}(t)$ is $w_{AA}f_{AA}(t)$. As for the numerator, let U_{Aa} and U_{aa} denote the event an individual born in generation t is Aa and, respectively aa. By the law of total probabilities (see Chapter 2, Section 2.1.4),

$$\begin{aligned} P(S) &= P(S|U_{AA})P(U_{AA}) + P(S|U_{Aa})P(U_{Aa}) + P(S|U_{aa})P(U_{aa})\\ &= w_{AA}f_{AA}(t) + w_{Aa}f_{Aa}(t) + w_{aa}f_{aa}(t). \end{aligned}$$

Thus,

$$p_{AA}(t) = \frac{w_{AA}f_{AA}(t)}{w_{AA}f_{AA}(t) + w_{Aa}f_{Aa}(t) + w_{aa}f_{aa}(t)}, \quad \text{and} \tag{3.36}$$

$$p_{Aa}(t) = \frac{w_{Aa}f_{Aa}(t)}{w_{AA}f_{AA}(t) + w_{Aa}f_{Aa}(t) + w_{aa}f_{aa}(t)}. \tag{3.37}$$

There is a similar equation for $p_{aa}(t)$.

But equations (3.32)—(3.35) applied with $t-1$ replacing t, imply $f_{AA}(t) = f_A^2(t)$ and $f_{Aa}(t) = 2f_A(t)(1 - f_A(t))$, as long as $t \geq 1$. Hence

$$p_{AA}(t) = \frac{w_{AA}f_A^2(t)}{w_{AA}f_A^2(t) + w_{Aa}2f_A(t)(1 - f_A(t)) + w_{aa}(1 - f_A(t))^2}, \tag{3.38}$$

$$p_{Aa}(t) = \frac{w_{Aa}2f_A(t)(1 - f_A(t))}{w_{AA}f_A^2(t) + w_{Aa}2f_A(t)(1 - f_A(t)) + w_{aa}(1 - f_A(t))^2}. \tag{3.39}$$

The final step of the derivation is simply to combine the results obtained in equations (3.32), (3.38), and (3.39). From (3.32), $f_A(t+1) = p_A(t) = p_{AA}(t) + p_{Aa}(t)/2$. Hence, adding (3.38) and one-half of (3.39), we find that for $t \geq 1$.

$$f_A(t+1) = \frac{w_{AA}f_A^2(t) + w_{aA}f_A(t)(1 - f_A(t))}{w_{AA}f_A^2(t) + w_{Aa}2f_A(t)(1 - f_A(t)) + w_{aa}(1 - f_A(t))^2}. \tag{3.40}$$

This equation will also be valid for $t = 0$, if we assume generation 0 at inception is also in Hardy-Weinberg equilibrium, because (3.38) and (3.39) are then valid for $t = 0$ also. From now on, let us impose this assumption. It simplifies the model and does not affect the analysis of the limiting behavior of $f_A(t)$.

Equation (3.40), for all $t \geq 0$, is the the final model. It looks a little scary, so, to beautify it, define the so-called *fitness function*,

$$W(p) = p^2 w_{AA} + 2p(1 - p)w_{Aa} + (1 - p)^2 w_{aa}, \qquad 0 \leq p \leq 1.$$

Then the numerator in (3.40) is $W(f_A(t))$, and we can write the model as

$$f_A(t+1) = \frac{w_{AA}f_A^2(t) + w_{aA}f_A(t)(1 - f_A(t))}{W(f_A(t))}, \quad t \geq 0. \tag{3.41}$$

This is a cosmetic change only, but turns out to be helpful.

Remarks.

1. Assume $w_{Aa} \neq 0$. By factoring it out of numerator and denominator in (3.40)

$$f_A(t+1) = \frac{(w_{AA}/w_{Aa})f_A^2(t) + f_A(t)(1 - f_A(t))}{(w_{AA}/w_{Aa})f_A^2(t) + 2f_A(t)(1 - f_A(t)) + (w_{aa}/w_{Aa})(1 - f_A(t))^2}. \tag{3.42}$$

Thus, the selection model really depends only the two ratios w_{AA}/w_{Aa} and w_{aa}/w_{Aa}), which can take on any non-negative values. Similarly, when $w_{Aa} = 0$—which implies that the genotype Aa is lethal—the model depends only on w_{AA}/w_{Aa}.

2. So far we assumed selection occurs only because different genotypes have different survival rates. But other genetic factors also contribute to selection; for instance, genotypes might affect reproductive success even of individuals surviving to reproductive maturity. Fortunately, it is possible to reinterpret the selection coefficients to cover all these possibilities with the same model. The only assumption needed is that the parents of a randomly chosen offspring of generation t are chosen independently. Instead of interpreting $p_{AA}(t)$, $p_{Aa}(t)$, and $p_{aa}(t)$ as frequencies at the time of reproduction, we just think of them as the probability that a randomly selected parent is AA, Aa, or aa, respectively. Then we impose as an assumption that $p_{AA}(t)$, $p_{Aa}(t)$, and $p_{aa}(t)$ are related to $f_{AA}(t)$, $f_{Aa}(t)$, and $f_{aa}(t)$ as in equations (3.38) and (3.39), where w_{AA}, w_{Aa}, and w_{aa} are non-negative coefficients. In this broader view, it is not necessary to interpret these selection coefficients as survival probabilities; they are just nonnegative weights which quantify how the ratios of genotype probabilities in mating differ from the genotype frequencies of the infant population. As we saw above, the final model, (3.41), depends only on the ratios w_{AA}/w_{Aa} and w_{aa}/w_{Aa}, at least when $w_{Aa} \neq 0$. It is common in the literature to parameterize these ratios using two numbers r and s, by taking $w_{Aa} = 1$, $w_{AA} = 1-r$ and $w_{aa} = 1-s$.

3.4.4 Analysis of the selection model

In this section, we use cobwebbing to analyze the selection model (3.41). We assume the selection coefficients w_{AA}, w_{Aa} and w_{aa} are all strictly positive, so that $W(p) > 0$ for all p in $[0, 1]$. For notational convenience, $f(t)$ will be used to denote $f_A(t)$, and $\phi(p)$ will denote the function

$$\phi(p) = \frac{p^2 w_{AA} + p(1-p)w_{Aa}}{W(p)}.$$

Then, the difference equation (3.41) takes the form:

$$f(t+1) = \phi(f(t)). \tag{3.43}$$

For any, strictly positive choice of the fitness coefficients, ϕ has fixed points at 0 and 1: this is easy to check by direct calculation. These fixed points make sense. For example, $p = 0$ corresponds to the complete absence of allele A, and if it is absent in one generation it cannot appear in future generations because there is no mutation. Likewise, $p = 1$ corresponds to the complete absence of allele a.

The graph of $y = \phi(p)$ will have one of four possible general shapes, each corresponding to a different range of values of the selection coefficients. These shapes

are illustrated in Figures 3—7. The graphs are plotted over the interval $0 \leq p \leq 1$, which is the only region of interest—being a frequency, $f_A(t)$ must remain in the interval $[0, 1]$ for all t. We shall explain each graph, and its consequence for the behavior of solutions to (3.43), on a case by case basis. The explanations require the following facts about ϕ. We omit the proofs, which require only routine, if somewhat messy, calculations.

First, ϕ has a third fixed point, found by looking for a solution $p \neq 1$ to $W(p) = pw_{AA} + (1-p)w_{Aa}$, whenever $2w_{Aa} - w_{AA} - w_{aa} \neq 0$. It is

$$\bar{p} = \frac{w_{Aa} - w_{aa}}{2w_{Aa} - w_{AA} - w_{aa}}. \tag{3.44}$$

This fixed point will satisfy $0 < \bar{p} < 1$ if either $w_{Aa} > w_{AA}$ and $w_{Aa} > w_{aa}$, or $w_{Aa} < w_{AA}$ and $w_{Aa} < w_{aa}$, and in no other cases.

Second, the derivative of ϕ is

$$\phi'(p) = \frac{p^2 w_{AA} w_{Aa} + 2p(1-p)w_{AA}w_{aa} + (1-p)^2 w_{Aa}w_{aa}}{W^2(p)}. \tag{3.45}$$

This is always positive in the interval $0 \leq p \leq 1$, and hence ϕ is always strictly increasing in this interval.

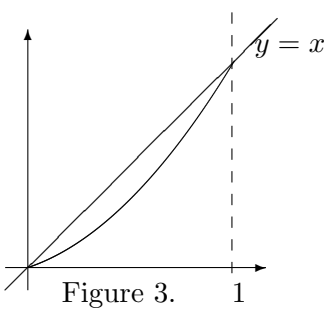

Figure 3.

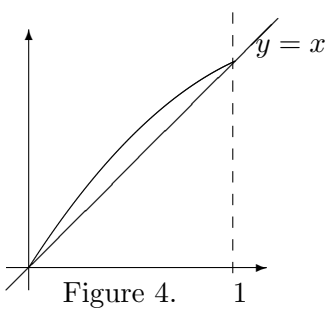

Figure 4.

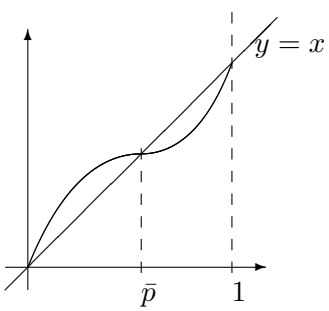

Figure 5.

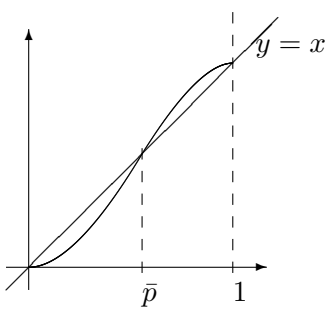

Figure 6.

Case I. Allele a is favored by selection: $w_{AA} < w_{Aa} < w_{aa}$.

In this case, the graph of ϕ will have the shape shown in Figure 3. Cobwebbing will show that if $0 \leq f(0) < 1$, then

$$\lim_{t\to\infty} f(t) = 0. \tag{3.46}$$

This makes sense. It says that allele A will disappear from the population if allele a has a selective advantage.

To see why Figure 3 is the correct graph, first use the fact, stated above, that when $w_{AA} < w_{Aa} < w_{aa}$, the fixed point $\bar{p}$ does not lie in $[0, 1]$. Hence the only fixed points of ϕ in $0 \leq p \leq 1$ are $p = 0$ and $p = 1$, and the graph of ϕ must lie either entirely above or entirely below the diagonal on the interval $0 < p < 1$. However, the slope of the tangent line to $y = \phi(p)$ at $p = 0$ is, by equation (3.45), $\phi'(0) = w_{Aa}/w_{aa}$. Since $0 < w_{Aa} < w_{aa}$, $\phi'(0) < 1$, which implies the graph of ϕ must lie below the diagonal. Thus $\phi(p) < p$ for all $0 < p < 1$.

Now pick a point $f(0)$ between 0 and 1, but strictly less than 1 and start cobwebbing. In every iteration, $f(t+1) = \phi(f(t)) < f(t)$. Therefore successive values of $f(t)$ decrease and can only tend to 0. This proves (3.46).

Case II. Allele A is favored by selection: $w_{aa} < w_{Aa} < w_{AA}$.

In this case, if $0 < f(0) \leq 1$,

$$\lim_{t\to\infty} f(t) = 1.$$

This is really Case I with the roles of A and a reversed. The graph of ϕ is shown in Figure 4. This time it lies strictly above the line $y = p$, and you can convince yourself by cobwebbing that all solutions, except the solution which starts and stays at $p = 0$, converge to 1.

Case III. Heterozygote dominance. $w_{aA} > w_{AA}$ and $w_{aA} > w_{aa}$.

In this case, if $0 < f(0) < 1$,

$$\lim_{t\to\infty} f(t) = \bar{p},$$

where $\bar{p}$ is the frequency defined above in (3.44).

The graph of ϕ for this case is shown in Figure 5. From the remark after equation (3.44), we know the fixed point $\bar{p}$ is strictly inside the interval $[0, 1]$. Since $\phi'(0) = w_{aA}/w_{aa} > 1$, the graph of ϕ will be above the graph of $y = p$ for $0 < p < \bar{p}$. It will pass through $y = p$ at $p = \bar{p}$ and be below $y = p$ for $\bar{p} < p < 1$. The graph of $y = \phi(p)$ is always increasing. Thus, at $\bar{p}$, $0 < \phi'(\bar{p}) < 1$, and $\bar{p}$ is a stable fixed point. By cobwebbing you can see that whether $f(0)$ is above or below $\bar{p}$, $\lim_{t\to\infty} f(t) = \bar{p}$.

This result is also very intuitive. It says that if heterozygotes are favored by selection, both A and a alleles will be maintained in the population. The fixed point $\bar{p}$ provided by the model quantifies the ultimate balance between the alleles.

Case IV. Homozygote dominance $w_{aA} < w_{AA}$ and $w_{aA} < w_{aa}$.

In this case,

$$\text{if } 0 < f(0) < \bar{p}, \text{ then } \lim_{t\to\infty} f(t) = 0, \text{ and if } \bar{p} < f(0) < 1, \lim_{t\to\infty} f(t) = 1. \qquad (3.47)$$

The graph of $y = \phi(p)$ in this case is shown in Figure 6. The fixed point $\bar{p}$ is again inside $[0, 1]$, but this time, the graph of $y = \phi(p)$ is below $y = p$ for $0 < p < \bar{p}$ and above for $\bar{p} < p < 1$. Thus, the slope $\phi'(\bar{p})$ of ϕ at $\bar{p}$ is strictly greater that 1, which implies that $\bar{p}$ is not stable. The student can check the validity of the limits stated in (3.47) by cobwebbing.

The interpretation of this case is also clear. If both homozygotes are favored by selection over heterozygote, the population will eliminate heterozygosity by eliminating either allele A ($f(t) \to 0$) or allele a ($f(t) \to 1$). But which allele wins depends on the initial frequency of A's versus a's and the exact values of the selection coefficients. The the formula, (3.44) for $\bar{p}$ is a quantitative expression for the boundary between the region in which a wins and that in which A wins.

The analysis of this section shows that, despite the complex nonlinearity of the selection model, it is not too difficult to analyze. The conclusions of the analysis are all what one would expect intuitively. This could be grounds for criticism. What use is all the work of modeling if the end result only confirms what we know intuitively must be true? However, the model also give quantitative information. In the case of heterozygote dominance it tells us exactly what the limiting allele frequency must be, and in the case of homozygote dominance, the boundary between the intervals where A takes over or a takes over.

3.4.5 Mean Fitness Increases

This section presents another perspective on how solutions to the selection model (3.43) evolve. It is sometimes called the *Fundamental Theorem of Natural Selection.* Recall that we have called W the fitness function. In the interpretation of the selection coefficients as survival probabilities, it was shown that $W(f_A(t))$ is the probability that a randomly selected individual from the infant population of generation t survives. This justifies interpreting $W(f_A(t))$ as the mean fitness of generation t.

Theorem 3 *For the one locus/two allele selection model (3.41), mean fitness always increases from generation to generation. That is, for any t*

$$W(f(t+1)) > W(f(t)) \qquad \text{if } f(t) \text{ is not a fixed point.}$$

Comment: The mean fitness W provides what is called a Lyapunov function for the difference equation (3.43). Lyapunov functions for a dynamical system are functions which are either increasing or decreasing along solutions, and they are very useful

in analyzing the solution behavior. In the case of the selection model, as $t \to \infty$, the solution $x(t)$ approaches a value p in $[0,1]$ at which the fitness function achieves a local maximum, unless the solution is at a fixed point.

To prove Theorem 3 it is only necessary to show $W(\phi(p)) > W(p)$, whenever p is a point in $(0,1)$ and p is not a fixed point. If this is true, then $W(f(t+1)) = W(\phi(f(t)) > W(f(t))$, so long as $f(t)$ is not a fixed point, and thus fitness increases.

The proof is just a computation. Plug $\phi(p)$ into W and calculate. The result, after some messy computation, is

$$W(\phi(p)) - W(p) = \frac{(\phi(p)-p)^2}{p(1-p)}\left[W(p) + pw_{AA} + (1-p)w_{aa}\right]. \tag{3.48}$$

This is strictly positive for every p in the interval $(0,1)$ such that $\phi(p) \neq p$.

3.4.6 Exercises

Exercise 3.4.4. Consider the study of a locus with two alleles A and a. Assume that the selection coefficients have been determined to be $w_{AA} = 0.5$, $w_{aa} = 0.6$ and $w_{Aa} = 0.4$. If at time $t = 0$, the genotype frequencies are $f_{AA}(0) = 0.4$, $f_{Aa}(0) = 0.2$ and $f_{aa}(0) = 0.4$, determine the limiting frequencies of allele A in generation t as t tends to ∞.

Exercise 3.4.5. Imagine an isolated population that has had a chance to evolve over a long period of time. Suppose that observations over many generations show that it in every generation the probability of being born AA is 0.16, of being born Aa is 0.48, and of being born aa is 0.36. It is known that selection acts and that the survival probabilities of AA and aa are $w_{AA} = 0.1$ and $w_{aa} = 0.2$. What is the selection coefficient w_{Aa} for the heterozygote genotype? (Hint: Assume that the stable genotype frequencies represent the limit of a model with selection.)

Exercise 3.4.6. Suppose it is known that $w_{AA} = w_{Aa} = w$ and that $w > w_{aa}$. This case was not actually covered in the text. Determine $\lim_{t\to\infty} p_A(t)$ by analyzing the shape of ϕ and invoking cobwebbing.

(Hint: By calculating $\bar{p}$ show that the only fixed points of ϕ in $[0,1]$ are 0 and 1. Calculate the value of $\phi'(0)$—see chapter 2, page 38, and use this and knowledge about the fixed points to graph the general shape of ϕ.)

Exercise 3.4.7. Derive the formula for the fixed point $\bar{p}$ in (3.44). Derive the formula given in the text for $\phi'(p)$.

Exercise 3.4.8. Derive formula (3.48) in the proof that mean fitness increases.

Exercise 3.4.9. Assume that selection coefficients w_{AA}, w_{aa}, and w_{Aa} are given and interpret them as survival probabilities, as in the text. Assume in addition that in the process of reproduction, A mutates to a with probability u and a mutates to A

with probability v. Let $f_A(t)$ and $p_A(t)$ be defined as in Section 3.4.3. Argue first that

$$f_A(t+1) = (1-u-v)p_A(t) + v.$$

Now use the expression found in the text for $p_A(t)$ in terms of $f_A(t)$ and the selection coefficients, to find a nonlinear difference equation

$$f_A(t+1) = \psi(f_A(t))$$

for $f_A(t)$. (Find the explicit form of ψ.)

3.5 Notes and References

1. *Finite difference equation.* The **first order difference** of a sequence $\{x(t)\}$ is the sequence $\{x(t+1) - x(t)\}$. The term *first order difference equation* is most properly applied to equations of the form

$$x(t+1) - x(t) = \psi(x(t)).$$

But, as is standard, we have used the term to refer to any equation of the sort $x(t+1) = \phi(x(t))$; of course this equation can be written in the form $x(t+1) - x(t) = \phi(x(t)) - x(t)$ so that it truly contains a first oreder difference $\{x(t)\}$, but this is rather artificial. Difference equations, as we have defined them, are really examples of *discrete-time dynamical systems.*

Finite difference equations occur throughout mathematics, often as the expression of an algorithm. For example, Newton's method for finding a root of the function f is $x(t+1) - x(t) = f(x(t))/f'(x(t))$. Euler's method for approximating the solution of the first order differential equation $x' = g(x)$ is $x(t+h) - x(t) = hg(x(t))$. The popular autoregressive moving average processes for the analysis of time series are finite difference equation models.

A source for traditional theory of difference equations is Kenneth S. Miller, *An Introduction to the Calculus of Finite Differences and Difference Equations,* Dover Publications, New York, 1966.

Mathematical ecologists and epidemiologists model many biological phenomena— predator-prey models, population growth, etc.— with difference equations. In fact, it was the mathematical ecologist Robert May who first studied how solutions to the discrete logistic equation,

$$x(t+1) = \lambda x(t)\,(1 - x(t))\,,$$

depend upon the parameter λ. He published his first work on this equation in the journal **Nature**, volume 261, pages 459-467, 1976. In this study he discovered the phenomenon of *chaos*, that is, sensitive dependence on initial conditions, for certain ranges of values of λ. May's work was an important inspiration to the development

of the popularly known theory of chaos in dynamical systems. The behavior of solutions to even very simple families of difference equations can be very rich. The textbook, K.T. Alligood, T.D. Sauer, J.A. Yorke, *Chaos*, Springer-Verlag, New York, 1996, is one among several introductory-level books on the subject.

2. The population genetics models presented here are all standard. I have been guided in my treatment by the following sources

- W.J. Ewens, *Population Genetics*, Methuen & Co., Ltd., London, 1969.
- J.C. Kingman, *Mathematics of Genetic Diversity,* CBMS-NSF regional conference series in applied math **34**, SIAM, Philadelphia, 1980.
- S. Tavaré, *Ancestral Inference in Population Genetics*, in Lectures on Probability Theory and Statistics; editor, J. Picard, Lecture Notes in Mathematics **1837**, Springer-Verag, Berlin, 2004.
- D.L. Hartl and A.G. Clark, *Principles of Population Genetics,* second edition, Sinauer Associates, Sunderland, MA, 1989.

The first three sources are at a mathematical level higher than this text. The third book is a standard population genetics text covering the scientific issues and presenting data, as well as the math.

3.6 Appendix: A Brief Introduction to Difference Equations

The usual notation for a generic sequence is $(x_1, x_2, x_3, \dots, x_n, \dots)$. In conformity with the notation of this chapter, we instead use $(x(0), x(1), x(2) \dots)$, and denote a generic term of the sequence by $x(t)$. The use of t reminds us that we can often think of t as will a time parameter. Often $\big(x(t)\big)_{t\geq 0}$, or simply $\{x(t)\}$, is used to abbreviate $(x(0), x(1), \dots)$.

A difference equation is a recursive equation that determines a sequence of numbers. Some simple examples are

$$x(t+1) = \alpha x(t), \quad t \geq 0 \tag{3.49}$$

$$x(t+2) = x(t+1) + x(t), \quad t \geq 0 \tag{3.50}$$

$$x(t+2) = x(t+1)x(t), \quad t \geq 0 \tag{3.51}$$

Difference equations of the sort $x(t+1) = \phi(t, x(t))$, $t \geq 0$, where ϕ is some given function of (t, x), are called first-order difference equations. Equations of the sort $x(t+2) = \psi(t, x(t+1), x(t))$, where ψ is function of (t, x, y), are called second-order difference equations. In the same way, one can define third, fourth, When $x(t+1) = \phi(x(t))$, or $x(t+2) = \psi(x(t+1), x(t))$, that is, when the right-hand side

does not depend on t explicitly, the difference equation is said to be *autonomous*. We will deal exclusively with autonomous equations of first and second order. Equation (3.49) is an example of an autonomous, first order equation, and equations (3.50) and (3.51) are examples of autonomous equations.

Given a given a value (the initial value), $x(0) = a$, for the first term, it is clear that a first order difference equation defines a unique sequence: $x(1) = \phi(x(0)) = \phi(a)$, $x(1) = \phi(x(1)) = \phi(\phi(a))$, etc. The term $x(t+1)$ following $x(t)$ is well-defined so long as $x(t)$ is in the domain of ϕ. This sequence is called the *solution* of the difference equation for the given initial condition.

Likewise, given initial values for $x(0)$ and $x(1)$, a second order difference will have a unique solution. For example, consider (3.50) given $x(1) = x(0) = 1$. Then $x(2) = 1 + 1 = 2$, $x(3) = x(2) + x(1) = 2 + 1 = 3$, $x(4) = x(3) + x(2) = 5$, etcetera. This is just the definition of the famous Fibonacci sequence, in which each term is the sum of the previous two. In Exercise 3.6.3 you will derive an explicit formula for $x(t)$ as a function of t.

As a simple exercise, the reader should solve equation (3.51) with initial conditions $x(0) = x(1) = 1$. This solution is very simple! A slightly more challenging problem is to solve the equation when $x(0) = 1$ and $x(1) = 2$. (Hint: express the answer in terms of the Fibonacci sequence.)

Two major goals in the study of any difference equation are: to find a solution in closed form, i.e., a formula expressing the solution $x(t)$ as an explicit function of t; and to analyze the limiting behavior of $x(t)$ as $t \to \infty$. Of course, if you can solve the first problem, the solution to the second usually follows as an easy consequence. Now, except for special cases, finding an explicit solution is usually hopeless. However, it is often possible to deduce the long-time, limiting behavior, even when a closed form solution is not known. One technique for doing so is explained in Section 3.4.

One class of difference equations that do admit explicit solutions is *linear difference equations*. A difference equation is said to be linear if it is linear in all the variables $x(t)$, $x(t+1)$, $x(t+2)$, etc., that appear in it. For example, (3.49) and (3.50) above are linear difference equations, but (3.51) is non-linear. The general, autonomous, linear, first order difference equation is

$$x(t+1) = \alpha x(t) + \beta. \tag{3.52}$$

The general, autonomous, linear, second order difference equation is

$$x(t+1) = \alpha x(t) + \gamma x(t-1) + \beta. \tag{3.53}$$

If $\beta = 0$, these equations are said, in addition, to be *homogeneous*, and when $\beta \neq 0$, they are called *inhomogeneous*. These equations are important in elementary population genetics, and we will devote the rest of this section to formulas and methods for their solution.

Consider first-order, linear equations. By solving equation (3.49), we have already seen that the general solution to (3.52) with $\beta = 0$, is $x(t) = A\alpha^t$. Here, we use A in place of $x(0)$, to indicate it can be any constant.

To solve (3.52) when $\beta \neq 0$, we will take advantage of the linearity of the equation. Suppose $\{z(t)\}$ is a given solution to (3.52), and $\{x(t)\}$ is any other solution. Then

$$x(t+1) - z(t+1) = \alpha x(t) + \beta - \big[\alpha z(t) + \beta\big] = \alpha[x(t) - z(t)].$$

Thus $\{x(t) - z(t)\}$ is a solution of the linear, homogeneous version of (3.52), and so $x(t) - z(t) = A\alpha^t$ for some constant A. Therefore, given *one, particular* solution $\{z(t)\}$ of (3.52), any other solution has the form ,

$$x(t) = A\alpha^t + z(t), \tag{3.54}$$

which means the right-hand side is a *general* solution.

The trick is now to guess a particular solution $\{z(t)\}$. Suppose we can find a fixed point of the equation (3.52). This is a value b such that $b = \alpha b + \beta$. Then the constant sequence, $z(t) = b$ for all t is a particular solution, because

$$z(t+1) = b = \alpha b + \beta = \alpha z(t) + \beta.$$

But, as long as $\alpha \neq 1$, $b = \alpha b + \beta$ has the unique solution $b = \beta/(1-\alpha)$, and we find a constant particular solution, which can be inserted in (3.54) to find the general solution. The explicit form of this solution, its properties as $t \to \infty$, and what happens when $\alpha = 1$ are all summarized in the next result.

Proposition 1 *(i) If $\alpha \neq 1$, the* general solution *to (3.52) is*

$$x(t) = A\alpha^t + \frac{\beta}{1-\alpha}, \quad t \geq 0, \quad \textit{where } A \textit{ is an arbitrary constant,} \tag{3.55}$$

and the solution to (3.52) satisfying the initial condition $x(0) = x_0$ is

$$x(t) = \left[x_0 - \frac{\beta}{1-\alpha}\right]\alpha^t + \frac{\beta}{1-\alpha}, \qquad t \geq 0. \tag{3.56}$$

(ii) If $|\alpha| < 1$, then, no matter what A is, $\lim_{t\to\infty} x(t) = \dfrac{\beta}{1-\alpha}$, which is the unique fixed point of (3.52).

If $|\alpha| > 1$, then $\lim_{t\to\infty} |x(t)| = \infty$ unless $x(0) = \frac{\beta}{1-\alpha}$.

(iii) If $\alpha = 1$, the general solution to (3.52) is $x(t) = A + \beta t$, $t \geq 0$, and the solution with initial condition $x(0) = x_0$ is $x(t) = x_0 + \beta t$, $t \geq 0$. There is no fixed point, unless $\beta = 0$, in which case all points are fixed points and all solutions are constant.

The statement in equation (3.55) of this proposition is a consequence of (3.54) and the fact that $z(t) = \beta/(1-\alpha)$, $t \geq 0$ is a particular solution. To find the solution in (3.56) with $x(0) = x_0$, set $A + \beta/(1-\alpha) = x(0) = x_0$ and solve for A.

The limiting behavior described in part (ii) of the proposition follows directly from the closed form solution in part (i).

Part (iii) can be checked directly by substituting the proposed solution into both sides of (3.52) when $\alpha = 1$ and showing that there is equality. $\diamond$

We turn now to second-order, linear equations. The procedure will be similar. First, find the general solution to the homogeneous equation, and then represent the general solution to the inhomogeneous solution as a particular solution plus the general solution to the homogeneous equation. It is possible to give a complete theory for the second-order equation, as we did in Proposition 1 for first-order equations. We shall not do so here, but only treat cases needed in Chapter 3.

To find the general solution of the homogeneous equation

$$x(t+1) = \alpha x(t) + \gamma x(t-1), \tag{3.57}$$

we look for solutions of the form $x(t) = r^t$. By substituting this in (3.57), we find that r must satisfy, $r^{t+1} = \alpha r^t + \gamma r^{t-1}$, or, dividing through by r^{t-1}

$$r^2 - \alpha r - \gamma = 0. \tag{3.58}$$

This is called the characteristic equation of (3.57). If r is a root, then r^t is indeed a solution to (3.57). There are two cases to consider, according to whether the characteristic equation has two distinct roots or only one root.

Case (i): If there are two distinct roots r_1 and r_2, we obtain two solutions r_1^t and r_2^t, which are independent from one another in the sense that one is not a scalar multiple of the other. We claim then that $x(t) = Ar_1^t + Br_2^t$ is the general solution to (3.57). That this expression does solve (3.57) is a consequence of linearity and homogeneity, as follows. Since $\{r_1^t\}$ and $\{r_2^t\}$ are both solutions,

$$\begin{aligned} x(t+2) &= Ar_1^{t+2} + Br_2^{t+2} + A\big[\alpha r_1^{t+1} + \gamma r_1^t\big] + B\big[\alpha r_2^{t+1} + \gamma r_2^t\big] \\ &= \alpha\big[Ar_1^{t+1} + Br_2^{t+1}\big] + \gamma\big[Ar_1^t + Br_2^t\big] = \alpha x(t+1) + \gamma x(t), \end{aligned}$$

and thus $\{x(t)\}$ solves (3.57).

To show that $x(t) = Ar_1^t + Br_2^t$ is the general solution, it is necessary to show that A and B can be chosen to match arbitrary initial conditions, $x(0) = x_0$ and $x(1) = x_1$. But this just requires,

$$A + B = x(0) = x_0 \quad \text{and} \quad Ar_1 + Br_2 = x(1) = x_1. \tag{3.59}$$

Indeed, there is a solution for A and B no matter what x_0 and x_1 are, because $r_1 \neq r_2$ by assumption.

Example 3.6.1. Solve

$$x(t+1) = -3x(t) - 2x(t-1), \qquad x(0) = 1,\ x(1) = 0. \tag{3.60}$$

The characteristic equation is $r^2+3r+2 = 0$, which has roots $r_1 = -1$ and $r_2 = -2$. Thus the general solution to (3.60) is $x(t) = A(-1)^t+B(-2)^t$. The initial conditions require $1 = x(0) = A + B$ and $0 = x(1) = -A - 2B$; these are easily solved to find $A = 2$, $B = -1$. Hence $x(t) = 2(-1)^t - (-2)^t$.

Case (ii): Suppose the characteristic equation has a single root r. This occurs when $\beta = -\alpha^2/4$, and then the root is $r = \alpha/2$, and we obtain the solutions $x(t) = A(\alpha/2)^t$. An independent solution is needed to get the general solution. The reader can check that, in this case, $t(\alpha/2)^t$ is a second solution. Thus, the general solution has the form, $x(t) = Ar^t + Bt(\alpha/2)^t$.

Consider, finally equation (3.53) with $\beta \neq 0$. (This will not be needed later, but we include it for completeness.) Again, if $\{z(t)\}$ is any particular solution of this equation, the general solution is $\{y(t)+z(t)\}$, where $\{y(t)\}$ is the general solution of the homogeneous version of (3.53). The reader should check that this is true using an argument like the one we gave for first-order equations. As before, we can try finding a constant particular solution. This will not be possible if $\alpha + \gamma = 1$, but when $\alpha + \gamma \neq 1$, $b = \beta/(1 - \alpha - \gamma)$ will be a constant, particular solution. We illustrate with an example and go no further with the theory.

Example 3.6.1, continued. Solve

$$x(t+1) = -3x(t) - 2x(t-1) + 1, \qquad x(0) = 1,\ x(1) = 0. \tag{3.61}$$

We look for a constant solution of the form $x(t) = w$, $t \geq 0$. Substituting in (3.61), requires $w = -3w - 2w + 1$, or $w = 1/6$. We found previously that the general solution to the homogeneous equation $x(t+1) = -3x(t) - 2x(t-1)$ is $x(t) = A(-1)^t + B(-2)^t$. Therefore the general solution to (3.61) is $x(t) = A(-1)^t + B(-2)^t + 1/6$. The initial conditions require $1 = x(0) = A + B + 1/6$ and $0 = x(1) = -A - 2B + 1/6$, and solving gives $A = 3/2$, $B = -2/3$. Thus, the solution to (3.61) is $x(t) = (3/2)(-1)^t - (2/3)(-2)^t + 1/6$. Some algebra shows that $x(t) = (-1)^t(1/6)[9 - 2^{t+2}] + 1/6$, and for $t \geq 2$ this will oscillate between positive and negative values with ever increasing amplitude, as t increases. Hence, the solution will not converge to the constant solution $1/6$. ◇

The techniques developed in this section can be developed into a theory that completely describes the solutions to linear difference equations of any order.

3.6.1 Problems

Exercise 3.6.1. a) Solve explicitly and determine $\lim_{t\to\infty} x(t)$ or show it does not exist:

(i) $x(t+1) = (1/2)x(t) + 2$, $x(0) = 2$.

(ii) $x(t+1) = 2x(t) + 2$, $x(0) = 2$.

b) Find and plot the first 4 terms in the solution of $x(t+1) = (2/3)x(t) + (1/x^2(t))$, $x(0) = 3$.

c) What is the fixed point of the equation of part b)? Does the solution appear to be converging to the fixed point?

Exercise 3.6.2. Consider $x(t+1) = \alpha x(t) + \beta x(t-1)$, where $4\beta = -\alpha^2$, so that the characteristic equation has only one root $r = \alpha/2$. Show that $Ar^t + Btr^t$ is the general solution to the difference equation.

Exercise 3.6.3. The difference equation, $x(t+1) = x(t) + x(t-1)$, with initial conditions $x(0) = 1$ and $x(1) = 1$, defines the Fibonacci sequence. Solve the equation to find a formula for $x(t)$ as a function of t.

Exercise 3.6.4. a) The object of this part is to find a particular solution to $x(t+1) = \alpha x(t) + \beta x(t-1) + \gamma$, when $\gamma \neq 0$, and $\alpha + \beta = 1$. It does not have a constant particular solution.

However, show that if, in addition, $\alpha \neq 2$, there is a constant A such that $x(t) = At$ is a particular solution.

b) Show that if $\alpha = 2$ and $\beta = -1$ there is a particular solution of the form Bt^2.

c) Solve $x(t+1) = (1/3)x(t) + (2/3)x(t-1) + 1$, $x(0) = 1$, $x(1) = 0$.

Exercise 3.6.5. Find the solution of $x(t+1) = -(5/6)x(t) - (1/6)x(t-1) + 1$, $x(0) = 0$, $x(1) = 0$. Show that the solution tends to the constant solution.

Exercise 3.6.6. (a) Consider the equation $x(t+1) = \alpha x(t) + g(t+1)$, where $(g(t))_{t\geq 1}$ is a given sequence. For convenience, define $g(0) = 0$. Show that $x(t) = A\alpha^t + \sum_{s=0}^{t} \alpha^{t-s} g(s)$ is a solution for any constant A.

(b) Consider $x(t+1) = h(t+1)x(t) + g(t+1)$, the fully time-inhomogeneous, first-order, linear difference equation . As before, set $g(0) = 0$. For $0 \leq s < t$, define $T(s,t) = h(s+1)h(s+2)\cdots h(t)$; for all $t \geq 0$, define $T(t,t) = 1$. Show that

$$x(t) = AT(0,t) + \sum_{s=0}^{t} T(s,t)g(s)$$

is a solution for any constant A.