

Chapter 3

Population Genetics for Large Populations

The diversity of life is a fundamental empirical fact of nature. Casual observation alone confirms the great variety of species. But diversity also prevails *within* single species. As in human populations, the 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 genetics and molecular biology, as described in Chapter 1, have allowed us to measure and confirm the genotypic variability of populations 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. To achieve this, population geneticists combine what is known about the mechanisms of 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 propose mathematical equations for the evolution of genotype frequencies. By comparing the solutions of these equations to field data, they can then test hypotheses and make inferences about genealogy and evolution.

This chapter is an introduction to elementary, population genetics models for large populations and simple genotypes. ‘Large’ is a vague term, but here it means the limit as the population size tends to infinity. The use of this limit is called the “infinite population assumption.” When it is imposed in a model, genotype frequencies become deterministic functions of time, and evolve as deterministic dynamical systems, even though random factors influence how each generation is produced from the previous one.

The mathematics employed in this chapter are some elementary probability and *difference equations* (also called *recursion equations*). For the required probability—

random sampling, the law of large numbers, simple calculations using independence and conditioning—the student should read Section 2.1. Linear difference equations are treated briefly in section 3.1, and a graphical technique for nonlinear difference equations is described at the beginning of Section 3.4. Difference equations appear in this chapter as models for the evolution of genotype frequencies.

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.

3.1 Difference Equations; Introduction

The usual notation for a generic sequence is $(x_1, x_2, x_3, \dots, x_n, \dots)$. In this chapter, we instead use the notation $(x(0), x(1), x(2), \dots)$, and we denote a generic term in a sequence by $x(t)$. We use t as the index because it will always represent a time, and we write $x(t)$ rather than x_t so that subscripts may be used for other purposes. In general, our convention is that the first term of a sequence denotes a value at time $t = 0$, and we begin sequences with $x(0)$. Often $(x(t))_{t \geq 0}$, 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

$$x(t+1) = \alpha x(t), \quad t \geq 0 \tag{3.1}$$

$$x(t+2) = x(t+1) + x(t), \quad t \geq 0 \tag{3.2}$$

$$x(t+2) = x(t+1)x(t), \quad t \geq 0 \tag{3.3}$$

A solution to one of these difference equations is any sequence satisfying the given relationship for all integers $t \geq 0$. In each case, it is easy to see that there is a unique solution once appropriate starting values are given. Consider equation (3.1), for example. If $\{x(t)\}$ is a solution, then $x(1) = \alpha x(0)$, $x(2) = \alpha x(1) = \alpha^2 x(0)$, and $x(3) = \alpha x(2) = \alpha^3 x(0)$, for starters. Clearly, by continuing this procedure, we find that $x(t) = \alpha^t x(0)$ for all $t \geq 0$. Thus (3.1) determines a unique sequence for each initial value $x(0)$.

In the case of equation (3.2), the first equation, for $t+0$, is $x(2) = x(1) + x(0)$, which determines $x(2)$ from $x(1)$ and $x(0)$, but imposes no relationship between $x(0)$ and $x(1)$. Thus both $x(1)$ and $x(0)$ must be prescribed to get a unique solution. Consider what happens when $x(1) = x(0) = 1$. 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 3.1.3 you will derive an explicit formula for $x(t)$ as a function of t .

As a simple exercise, the reader should solve equation (3.3) 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.)

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, and higher order difference equations. We will only encounter first and second order equations. 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.

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 $t \rightarrow \infty$. 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. We shall study one technique for doing so 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, (3.1) and (3.2) above are linear difference equations, but (3.3) is non-linear. The general, autonomous, linear, first order difference equation is

$$x(t+1) = \alpha x(t) + \beta. \quad (3.4)$$

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

$$x(t+1) = \alpha x(t) + \gamma x(t-1) + \beta. \quad (3.5)$$

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 (3.1), we have already seen that the general solution to (3.4) 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 (3.4) when $\beta \neq 0$, we will take advantage of the linearity of the equation. Suppose $\{z(t)\}$ is a given solution to (3.4), and $\{x(t)\}$ is any other solution. Then

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

Thus $\{x(t) - z(t)\}$ is a solution of the linear, homogeneous version of (3.4), and so $x(t) - z(t) = A\alpha^t$ for some constant A . Therefore, given *one, particular* solution $\{z(t)\}$ of (3.4), any other solution has the form ,

$$x(t) = A\alpha^t + z(t), \quad (3.6)$$

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 (3.4). 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 (3.6) to find the general solution. The explicit form of this solution, its properties as $t \rightarrow \infty$, and what happens when $\alpha = 1$ are all summarized in the next result.

Proposition 1 (i) *If $\alpha \neq 1$, the general solution to (3.4) is*

$$x(t) = A\alpha^t + \frac{\beta}{1 - \alpha}, \quad t \geq 0, \quad \text{where } A \text{ is an arbitrary constant,} \quad (3.7)$$

and the solution to (3.4) satisfying the initial condition $x(0) = x_0$ is

$$x(t) = \left[x_0 - \frac{\beta}{1 - \alpha} \right] \alpha^t + \frac{\beta}{1 - \alpha}, \quad t \geq 0. \quad (3.8)$$

(ii) *If $|\alpha| < 1$, then, no matter what A is, $\lim_{t \rightarrow \infty} x(t) = \frac{\beta}{1 - \alpha}$, which is the unique fixed point of (3.4).*

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

(iii) *If $\alpha = 1$, the general solution to (3.4) 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 (3.7) of this proposition is a consequence of (3.6) and the fact that $z(t) = \beta/(1 - \alpha)$, $t \geq 0$ is a particular solution. To find the solution in (3.8) 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 (3.4) 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. It is enough for our purposes to outline the techniques that work for the cases we shall encounter.

To find the general solution of the homogeneous equation

$$x(t+1) = \alpha x(t) + \gamma x(t-1), \quad (3.9)$$

we look for solutions of the form $x(t) = r^t$. By substituting this in (3.9), we find that r must satisfy, $r^{t+1} = \alpha r^t + \gamma r^{t-1}$, or, dividing through by r^{t-1}

$$r^2 - \alpha r - \gamma = 0. \quad (3.10)$$

This is called the characteristic equation of (3.9). If r is a root, then r^t is indeed a solution to (3.9). 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 (3.9). That this expression does solve (3.9) is a consequence of linearity and homogeneity, as follows. Since $\{r_1^t\}$ and $\{r_2^t\}$ are both solutions,

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

and thus $\{x(t)\}$ solves (3.9).

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,

$$A + B = x(0) = x_0 \quad \text{and} \quad Ar_1 + Br_2 = x(1) = x_1. \quad (3.11)$$

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 3.2.3. Solve

$$x(t+1) = -3x(t) - 2x(t-1), \quad x(0) = 1, \quad x(1) = 0. \quad (3.12)$$

The characteristic equation is $r^2 + 3r + 2 = 0$, which has roots $r_1 = -1$ and $r_2 = -2$. Thus the general solution to (3.12) 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 (3.5) 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 (3.5). 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 3.2.3, continued. Solve

$$x(t+1) = -3x(t) - 2x(t-1) + 1, \quad x(0) = 1, \quad x(1) = 0. \quad (3.13)$$

We look for a constant solution of the form $x(t) = w$, $t \geq 0$. Substituting in (3.13), 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 (3.13) 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 (3.13) 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 $1/6$. $\diamond$

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

3.1.1 Problems

Exercise 3.1.1. a) Solve explicitly and determine $\lim_{t \rightarrow \infty} x(t)$ 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 3.1.2. 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 3.1.3. 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 3.1.4. 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 3.1.5. 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 3.1.6. (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 .

3.2 Modeling principles for population genetics

Mendelian genetics, reviewed in Chapter 1, is the foundation upon which the models of this chapter are built. Many other factors, such as sex, mating, and interactions between generations, also play a role. They are described in this section. Population genetics models describe how genotype and allele frequencies evolve. These frequencies are also carefully defined. Throughout, the study of one locus with two alleles serves as a running example.

3.2.1 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 are presumably adaptations preventing excessive inbreeding.

Autosomal vs. sex chromosomes. Genetic mechanisms of sex determination in dioecious species are diverse and complicate the analysis of inheritance. Sex is usually 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. He will not pass genes on the X chromosome to his male offspring, because his male offspring are precisely those that receive his Y chromosome, not his X chromosome.

3.2.2 Genotypes and Populations

Population genetics is mainly a study of genotype and allele frequencies of populations. The concepts of genotype and allele are covered in Chapter 1. Genotypes are always defined *with respect to some fixed set of loci* that we are interested in studying. However, we usually speak of *the* genotype, assuming the loci of interest are fixed beforehand. The genotype of an individual, with respect to the loci under study, is a list of all the alleles in the chromosomes of (any) one of its cells. Single letters are always used to denote alleles, and hence genotypes always 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, to the population geneticist, $\{YY, YG, GG, GG, YY, YG, YG\}$ 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 be ignored. Sorry, about that! Thinking of a population as a collection of letter strings is very helpful to a clear understanding of the models.

3.2.3 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:

$$f_{G_1 \cdots G_k} \triangleq \frac{\text{number of individuals with genotype } G_1 \cdots G_k}{\text{population size}}. \quad (3.14)$$

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

Example 3.2.1. Consider the following population of a diploid species, in a study of a single locus that admits two alleles A and a :

$$AA, AA, AA, Aa, Aa, Aa, Aa, aa, aa, aa, aa, aa \quad (3.15)$$

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 $f_{aa} = 5/12$. $\diamond$

Allele frequencies are computed by counting alleles only and ignoring how they are organized into genotypes. Let ℓ be a locus. Given a population, the *allele pool for locus ℓ* is the collection of all alleles from population genotypes that occur at locus ℓ . Recall that we think of a population as a collection of genotype letter strings. Imagine collecting the letters denoting alleles at locus ℓ from each individual and placing them all in a box, where they are no longer identified by the individual they belong to. The letters in this box form the allele pool for ℓ . Now consider a particular allele A that can occur at ℓ . The frequency f_A of A is defined to be its frequency *relative* to the allele pool corresponding to ℓ :

$$f_A \triangleq \frac{\text{number of } A\text{'s in the allele pool for } \ell}{\text{size of the allele pool for } \ell}. \quad (3.16)$$

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 an allele frequency at time t .

Example 3.2.1, continued and extended. In the single locus genotype of example 3.2.1, the allele pool is thus the collection of the $24 (= 2 \times 12)$ letters listed in (3.15). 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 appertaining to the locus of A . The reader should confirm that $f_b = 14/24$. $\diamond$

Exercise 3.2.1. 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 $a\bar{a}BB$. $\diamond$

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 3.3.4 and 3.3.5.

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,

$$f_{AA} + f_{Aa} + f_{aa} = 1. \quad (3.17)$$

In addition allele and genotype frequencies are related as follows:

$$f_A = f_{AA} + \frac{f_{Aa}}{2}, \quad f_a = f_{aa} + \frac{f_{Aa}}{2}. \quad (3.18)$$

We derive the first equation of (3.18), 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 aa of course contribute no A 's. Hence, using definition (3.16),

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

◇

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.

3.2.4 Random Mating

In this chapter, 'mating' is used in a special, technical sense. It does not refer 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 *monocious*, male and female are sampled from the same population with replacement. Thus, in the monocious case, selfing is possible in a random mating

Your first impression might be that random mating as defined here is very far from what happens in the real world. There is a discussion of when random mating is appropriate or useful as model, 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 .

Lemma 1

$$\mathbb{P}(\text{parent selected randomly from } \{\mathcal{S}\} \text{ passes } A \text{ to an offspring}) = p_A^{\mathcal{S}} = f_A^{\mathcal{S}} \quad (3.19)$$

This lemma 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 $\mathbb{P}(\text{selected parent is } AA) = f_{AA}$, and $\mathbb{P}(\text{selected parent is } Aa) = f_{Aa}$.

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 (3.18),

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

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 (3.19) 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 3.2.2. Random mating in the one locus/two allele case in a monocious population.

Consider a locus with two alleles A and a in a monocious 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 monocious, 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,

$$\mathbb{P}(\text{offspring is } AA) = f_A^2 = (f_{AA} + \frac{f_{Aa}}{2})^2. \quad (3.20)$$

Similarly,

$$\mathbb{P}(\text{offspring is } aa) = f_a^2 = (f_{aa} + \frac{f_{Aa}}{2})^2. \quad (3.21)$$

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,

$$\mathbb{P}(\text{offspring is } Aa) = 2f_A f_a = 2f_A(1 - f_A) = 2(f_{AA} + \frac{f_{Aa}}{2})(f_{aa} + \frac{f_{Aa}}{2}). \quad (3.22)$$

(Show that the three probabilities of (3.20)—(3.22) add up to 1!) $\diamond$

Remark. The definition of random mating stipulates that the parents are sampled independently. If the species is monocious, 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 3.2.4). 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. 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 an 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 (didn’t we all, when teenagers, wished we could have done this?), it is a mathematically equivalent way to look at the situation, 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. We did not impose assumptions about how different random matings from the same population are related probabilistically, for example, whether they are independent or not. We return to this question later.

5. What good is the random mating model? 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 several responses to this criticism. First, 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. Second, 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.” At least I hope not. 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. Finally, random mating is not proposed as a universal model. It is a baseline case whose virtue is simplicity. When modeling, one should start with the simplest assumptions and explore what they imply, before adding on further layers of complexity. Models with random mating are simple and they can be analyzed very completely. We can gain insight into more complicated models by comparing them to the random mating model, and we can infer when random mating is not occurring in nature by comparing data to the predictions of random mating models.

3.2.5 The infinite population assumption.

The models in this chapter are derived by considering what happens in the limit as population size tends to infinity. This is called the *infinite population assumption*, and the idea is that it should yield accurate models for large populations. In mathematical practice, it means the following. Consider an offspring population built by random mating from a given parent population. Let $f_{G_1 \dots G_k}$ denote the frequency of a genotype in the offspring population, and let $p_{G_1 \dots G_k}$ denote the probability that genotype is produced in a single random mating. The infinite population assumption consists in imposing for every genotype the identity

$$f_{G_1 \dots G_k} = p_{G_1 \dots G_k}. \quad (3.23)$$

To understand what this has to do with large populations, imagine creating the offspring population by successive random matings and let $f_{G_1 \dots G_k}^{(N)}$ be the genotype frequency in the first N offspring produced. If the random matings were independent of each other, then the law of large numbers would imply that $\lim_{N \rightarrow \infty} f_{G_1 \dots G_k}^{(N)} = p_{G_1 \dots G_k}$ with probability one. The definition of random mating did not actually

impose conditions on the correlation of different random matings. 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. Thus, identity (3.23) represents what should happen in the limit as population size tends to infinity. In practice, the infinite population assumption really says the population under study is so large that (3.23) is an excellent approximation. This approximation has the virtue of identifying genotype frequencies, which in real populations are random, with the deterministic quantities $p_{G_1 \dots G_k}$. As a result genotype frequencies in infinite population models evolve deterministically.

3.2.6 Interaction of Generations

How individuals enter and leave the mating pool over time is an important factor in gene flow. The simplest model assumes **nonoverlapping 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 $t+2$ 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 nonoverlapping 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.

3.2.7 Problems

Exercise 3.2.2. (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 3.2.3. *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_{AA}^m , f_{Aa}^m , etc., denote frequencies in the male subpopulation, and f_{AA}^f , f_{Aa}^f , 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 $\mathbb{P}(\text{offspring is } Aa)$, 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 $\mathbb{P}(\text{offspring is } AA)$ and $\mathbb{P}(\text{offspring is } aa)$.

- (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_{AA}^m , f_{AA}^f , 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 3.2.4. Calculate the probability that selfing occurs in a random mating in a monocious population of size N .

Exercise 3.2.5. 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 3.2.6. This problem uses Chebyshev's inequality and the Central Limit approximation of the binomial distribution; see Chapter 2, Sections 2.3.6 and 2.3.7. 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.

3.3 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.

3.3.1 Basic model

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

Random mating. (A.1)

Nonoverlapping generations. (A.2)

Infinite population. (A.3)

Monecious species. (A.4)

No selection, mutation, or migration. (A.5)

The meaning of these assumptions, except for the last one, was explained in the previous section. Mutation refers to a random change in an allele of a parental gamete due to physical changes in coding DNA, caused for instance by copying error in meiosis or by radiation damage. Mutation alters the basic rule stated in Lemma 2.1 for the probability of transmission of an allele. Migration adds genotypes from outside sources to a population. Selection occurs when different genotypes have different effects on survival or reproductive success. Thus, when selection acts, the genotype frequencies within one generation can change over time, as that generation matures and the less fit individuals die off, or random mating will no longer be valid, since there will be individual differences in mating success. These processes are all 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 consist of first order difference equations for the genotype frequencies, and the derivation is simple using the work of the previous section. Consider, for example, $f_{AA}(t+1)$, for any $t \geq 0$. As explained in the previous section at equation (3.23), 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 3.2.2, equation (3.20), how to calculate this probability when (A.2), random mating, is assumed: it is $f_A^2(t)$. Also from (3.18), we know $f_A(t) = f_{AA}(t) + (1/2)f_{Aa}(t)$. Thus,

$$f_{AA}(t+1) = f_A^2(t) = \left(f_{AA}(t) + \frac{f_{Aa}(t)}{2} \right)^2. \quad (3.24)$$

The same reasoning yields as well,

$$f_{Aa}(t+1) = 2f_A(t)f_a(t) = 2 \left(f_{AA}(t) + \frac{f_{Aa}(t)}{2} \right) \left(f_{aa}(t) + \frac{f_{Aa}(t)}{2} \right) \quad (3.25)$$

$$f_{aa}(t+1) = f_a^2(t) = \left(f_{aa}(t) + \frac{f_{Aa}(t)}{2} \right)^2 \quad (3.26)$$

These three difference equations, (3.24), (3.25), and (3.26), constitute the basic model.

At first glance, the equations (3.24), (3.25), (3.26) look too complicated to solve explicitly, since they consist of three coupled, nonlinear difference equations. But they hide an underlying simplicity that reveals itself if we ask how the *allele* frequencies evolve. Using first (3.18) and then (3.24), (3.25), and $f_A(t) + f_a(t) = 1$, we find,

$$\begin{aligned} f_A(t+1) &= f_{AA}(t+1) + \frac{f_{Aa}(t+1)}{2} \\ &= f_A^2(t) + f_A(t)f_a(t) = f_A(t)(f_A(t) + f_a(t)) \\ &= f_A(t). \end{aligned} \quad (3.27)$$

Thus, the model reduces to the trivially simple equation

$$f_A(t+1) = f_A(t).$$

Its solutions are constant in time: $f_A(t) = f_A(t-1) = \dots = f_A(0)$ for all $t \geq 0$. Under the basic model, allele frequencies do not change from generation to generation! And since allele frequencies determine genotype frequencies by equation (3.18), we obtain the complete solution to (3.24), (3.25), and (3.26): for all $t \geq 1$ the genotype frequencies take on the constant values

$$\begin{aligned} f_A(t) &= f_A(0) = f_{AA}(0) + (1/2)f_{Aa}(0), & f_a(t) &= 1 - f_A(t) = 1 - f_A(0) \\ f_{AA}(t) &= f_A^2(t-1) = f_A^2(0); \\ f_{Aa}(t) &= 2f_A(t-1)f_a(t-1) = 2f_A(0)(1 - f_A(0)) \\ f_{aa}(t) &= f_a^2(t-1) = (1 - f_A(0))^2. \end{aligned} \quad (3.28)$$

This solution is so important that it is given a special name, in honor of the first researchers 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

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

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 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 3.3.2.

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

$$f_{Aa}^2 = 4f_{AA}f_{aa}. \quad (3.29)$$

Example 3.3.1. 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 $f_{aa}(t) = 0.36$. $\diamond$

The simplicity of Theorem 1 suggests it should have much simpler explanation than we have given, and indeed it does. Recall Lemma 1, which was a crucial. It says $p_A(t)$, the probability that a parent of generation t passes allele A to its offspring in random mating is $p_A(t) = f_A(t)$. But $f_A(t)$ equals the probability a gamete of type A is chosen in a random sample of the gamete pool. Since the contribution of each parent is independent, each member of generation $t+1$ is effectively produced by two, independent random samples from the allele pool. Thus the the allele pool of generation $t+1$ for the locus of A is built by repeated random samplings (two *independent* samples per mating) of the allele pool of generation t . From the infinite population assumption, which is essentially a law of large numbers, we should therefore expect $f_A(t+1) = p_A(t) = f_A(t)$, which is exactly the Hardy-Weinberg result. 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 simple method in the first place, other than our natural, professorial desire to confuse students?! 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 (3.27) does this. Secondly, equations (3.24), (3.25), (3.26), 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.

3.3.2 Problems

Exercise 3.3.1. 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 3.3.2. 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 defined 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 3.3.3. A large monocious 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.

3.3.3 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 we assume that it admits m alleles, labeled $A_1, \dots, A_m$, where $m \geq 3$. Therefore, the possible genotypes are the pairs $A_i A_j$, where i and j range between 1 and m . For notational convenience, denote the frequency of genotype $A_i A_j$ in generation t by $f_{ij}(t)$ instead of $f_{A_i A_j}(t)$. 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 3.3.4. 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 3.3.5. Apply random mating to express $f_{ij}(t+1)$ in terms of the allele frequencies $f_{A_1}(t), \dots, f_{A_m}(t)$ in the previous generation.

Exercise 3.3.6. Generalize the Hardy-Weinberg theorem to the multi-allele case, as follows. Use the results of Exercise 3.3.5 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 3.3.7. (See Exercise 3.3.2a.) 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 $i \neq j$, $f_{ij}^2 = 4f_{ii}f_{jj}$.

3.3.4 One gene/two alleles for dioecious populations

In this section we analyze how the basic model changes when the species is dioecious rather than monocious. All the remaining assumptions (A.1), (A.2), (A.3), and (A.5) are in force.

For dioecious species, loci on autosomal chromosomes must be analyzed separately from loci on the sex chromosome, because males only have one copy of genes located on the X chromosome. Consider autosomal chromosomes first. Assume Mendel's hypothesis that different chromosomes segregate independently of one another in meiosis—see Chapter 1. This means autosomal chromosomes are inherited independently of the sex chromosome, and hence, for the genotypes of loci on autosomal chromosomes,

$$\text{sex and genotype are passed to progeny independently.} \quad (\text{A.6})$$

This principle will be adopted as another assumption in deriving the dioecious model. It has the following consequence. Let $a_1 \cdots a_k$ denote any genotype with respect to loci on an autosomal chromosome. Let $p_{a_1 \cdots a_k}^m(t+1)$ denote the probability that a *male* offspring of a random mating of parents of generation t produces the genotype $a_1 \cdots a_k$, and let the $p_{a_1 \cdots a_k}^f(t+1)$ denote the probability of the same event

for a female offspring. Then

$$p_{a_1 \dots a_k}^m(t+1) = p_{a_1 \dots a_k}^f(t+1) \quad (3.30)$$

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 $t \geq 0$,

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

where $p_{AA}^m(t+1)$ and $p_{AA}^f(t+1)$ are the probabilities that a random mating of generation t parents produces AA males and females, respectively. Thus, from (3.30), we get $f_{AA}^m(t+1) = f_{AA}^f(t+1)$ for all $t \geq 0$. This reasoning applies to any genotype. Hence for the dioecious model and genotypes on autosomal chromosomes, **male genotype and allele frequencies are equal to female genotype and allele frequencies in every generation t , starting with $t = 1$** . Referring back to Exercise 3.2.2, do the following problem to complete the analysis of the dioecious case.

Exercise 3.3.8. Consider a single locus with two alleles A and a . Assume the frequencies $f_{AA}^m(0)$, $f_{Aa}^m(0)$, $f_{aa}^m(0)$ and $f_{AA}^f(0)$, $f_{Aa}^f(0)$, $f_{aa}^f(0)$ 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

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

in generations $2, 3, \dots$. ◇

Exercise 3.3.8 shows that autosomal gene frequencies for dioecious species differ in a minor way from the monocious case. The fact that there are separate sexes means only that it takes two generations instead of one for random mating to mix alleles so that Hardy-Weinberg equilibrium is attained.

Next, consider a locus ℓ carrying alleles A and a on the X chromosome of a human population. In this case (A.6) is no longer true. A female offspring has two X chromosomes, one from the father and one from the mother, and hence receives one allele from each parent. A male offspring receives a Y chromosome from the father, which does not carry a locus for the gene. Males only obtain an allele for ℓ from their mother. Hence sex and alleles are not inherited independently.

Since each male carries only one X chromosome its genome will carry only one allele for ℓ , and so the male genotypes are the single letters A or a . In this case there are no frequencies $f_{AA}^m(t), f_{Aa}^m(t), f_{aa}^m(t)$ to contend with, only $f_A^m(t)$ and $f_a^m(t) = 1 - f_A^m(t)$. The females have the usual genotypes AA, Aa and aa , whose frequencies are indicated as usual with a superscript f . 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. The reader will need to solve a second-order linear difference equation to complete this problem and should refer to Section 3.1 to learn how to do this.

Exercise 3.3.9. a) Show that the random mating and infinite population assumptions imply $f_A^m(1) = f_A^f(0), f_{AA}^f(1) = f_A^m(0)f_A^f(0), f_{Aa}^f(1) = f_A^m(0)(1 - f_A^f(0)) + f_A^f(0)(1 - f_A^m(0)), f_{aa}^f(1) = (1 - f_A^m(0))(1 - f_A^f(0))$. Deduce that $f_A^f(1) = (f_A^m(0) + f_A^f(0))/2$.

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

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

Isolating the first and last expressions of the second equation,

$$f_A^f(t+1) = \frac{1}{2}(f_A^f(t-1) + f_A^f(t)). \quad (3.31)$$

This is a *second order, homogeneous linear difference equation*. By solving it—see section 3.1.2—find a formula for $f_A^f(t)$ in terms of $t, f_A^f(0)$, and $f_A^m(0)$.

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

d) Find the limits $f_A^f(\infty) \triangleq \lim_{t \rightarrow \infty} f_A^f(t), f_{AA}^f(\infty) \triangleq \lim_{t \rightarrow \infty} f_{AA}^f(t)$, 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.

3.3.5 Infinite population with mutation, but no selection

In this section we study again a single locus admitting two alleles A and a . We shall impose the assumptions (A.1)-(A.4) and also exclude migration and selection. However, we want to allow mutation. Mutation occurs when an allele in a parental gamete becomes modified in the course of mating. Mutations, which can be induced by copying errors or exposure to chemical toxins or radiation, cannot be predicted

and so are considered to be random. One simple model supposes that A can mutate into a and vice-versa according to the following rule:

In each random mating and for each parent independently, allele A mutates to a with probability u , and allele a mutates to A with probability v , in passing from parent to child. Moreover, $0 < u + v$. (A.7)

Frankly, the motivation for this model is not really scientific. Rather, 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 technical assumption, $0 < u + v$, excludes the case in which $u = v = 0$ and no mutation occurs.

It is simpler in this problem to work directly with allele frequencies, rather than analyze genotype frequencies first. We generalize the infinite population assumption so that it includes also the statement:

$f_A(t+1)$ = probability an offspring
acquires A from a randomly selected parent.

We have seen in the derivation of Hardy-Weinberg equilibrium that this is consistent with the infinite population assumption, (3.23), stated for genotypes. 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 parent transmits allele a which then mutates is $v(1 - f_A(t))$. Therefore,

$$f_A(t+1) = (1 - u)f_A(t) + v(1 - f_A(t)) = v + (1 - u - v)f_A(t). \quad (3.32)$$

This is a first order, linear difference equation. According to formula (3.7) developed in section 3.2.1, its solution is

$$f_A(t) = (1 - u - v)^t \left[f_A(0) - \frac{v}{u + v} \right] + \frac{v}{u + v}. \quad (3.33)$$

The next exercise asks the reader to show how this solution behaves in the long-time limit.

Exercise 3.3.10. Verify this solution using (3.7). Assuming $0 < u + v < 2$, prove $\lim_{t \rightarrow \infty} f_A(t) = v/(u + v)$. Derive from this the following conclusions: if $v > 0$ and $u > 0$, variation between A and a alleles is maintained. What happens if $v = 0$, but $u > 0$, or $u = 0$, but $v > 0$?

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

Exercise 3.3.11. Analyze the solution of (3.32) when $u = 1$ and $v = 1$ and interpret.

Exercise 3.3.12. 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 $t \rightarrow \infty$, 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 $|f_A^{(1)}(T_1) - \bar{p}| \leq 0.01$. Find the smallest value T_2 such that $|f_A^{(2)}(T_2) - \bar{p}| \leq 0.01$. (Note that $f_A^{(1)}(t)$ and $f_A^{(2)}(t)$ 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.

3.3.6 A model with overlapping generations

In non-overlapping generation models, each generation produces the next and then mates no more. One concrete way to picture this is to imagine that mating takes place only during regularly spaced mating seasons, and in each season, the parent population mates to produce a new generation, and then dies. Suppose instead that the population replaces only a fraction h of itself in each mating season, as follows. The entire population first mates randomly to produce enough offspring to replace a fraction h of itself. Once this is done, a fraction h of the parent population (not the newborns) dies by random selection and is replaced by the newborns. By the next mating season, the new arrivals are assumed to be sexually mature and to participate on an equal footing in random mating. This is a simple system in which mixing occurs between the genes of individuals born at different times. It is the purpose of this section to derive the corresponding mathematical model when the other assumptions of the basic model—(A.1), (A.3), (A.4), and (A.5)—are in force.

For the derivation, if h is the fraction of the population replaced, it is convenient to measure time so that the mating seasons occur at times $h, 2h, 3h$, 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, independently of the value of h , the total number of new individuals entering the population in one unit of time is equal to the size of the population.

In what follows $f_A(h), f_A(2h), \dots$ 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 frequency 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

$$f_{AA}(t + h) - f_{AA}(t) = h [f_A^2(t) - f_{AA}(t)] \quad (3.34)$$

(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 the allele frequencies remains constant over time, just as in the basic model.

Now apply the fact that allele frequency remains constant (so, $f_A(t) = f_A(0)$ for all t) to (3.34). The result is the following difference equation for $f_{AA}(t)$:

$$f_{AA}(t + h) = [1 - h]f_{AA}(t) + hf_A^2(0) \quad (3.35)$$

Except for the fact that the sequence $f_{AA}(0), f_{AA}(h), f_{AA}(2h), \dots$ is indexed by multiples of h rather than by integers, this is a linear difference equation of first order. By Proposition 1, its solution is

$$f_{AA}(kh) = (1 - h)^k [f_{AA}(0) - f_A^2(0)] + f_A^2(0). \quad (3.36)$$

Since $0 < h < 1$,

$$f_{AA}(\infty) \triangleq \lim_{k \rightarrow \infty} f_{AA}(kh) = f_A^2(0). \quad (3.37)$$

A similar analysis applied to the genotypes Aa and aa shows

$$f_{Aa}(\infty) \triangleq \lim_{k \rightarrow \infty} f_{Aa}(kh) = 2f_A(0)f_a(0), \quad f_{aa}(\infty) \triangleq \lim_{k \rightarrow \infty} f_{aa}(kh) = f_a^2(0). \quad (3.38)$$

Exercise 3.3.13. Verify (3.36)–(3.38) in detail, and show that the limiting genotype frequencies are in Hardy-Weinberg equilibrium.

The equation (3.34) 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. Thus the limit as $h \downarrow 0$ corresponds to a situation 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. To obtain the continuous time model, divide both sides of equation (3.34) by h and let $h \downarrow 0$. The result is

$$f'_{AA}(t) = \lim_{h \downarrow 0} \frac{f_{AA}(t+h) - f_{AA}(t)}{h} = -f_{AA}(t) + f_A^2(0). \quad (3.39)$$

Exercise 3.3.14. Let $f_{AA}(0) = f_{AA}$. Solve equation (3.39) 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 $\lim_{t \rightarrow \infty} f_{AA}(t) = f_A^2(0)$, which is the Hardy Weinberg equilibrium value.

3.3.7 Conclusion

Hardy-Weinberg equilibrium emerges over and over in the models we have derived. Indeed, one should expect it to occur, at least in the limit, in any infinite population when random mating occurs and selection and mutation do not operate, because random mating mixes the allele pool of each locus by random selection. When the population is monocious 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. The other models of the chapter mainly deal with conditions that limit the mixing random mating can do 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. But additional mixing occurs with each mating season, and the population tends in the limit to Hardy-Weinberg equilibrium. The close relationship between random mating and Hardy-Weinberg equilibrium is the main lesson of this section.

3.3.8 Exercises

Exercise 3.3.15. Develop a one locus/two allele model for overlapping generations, as in Section 3.3, but with the following twist. Assume that mating seasons occur at times $h, 2h, \dots$ 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. For modeling one needs at the start to keep track of the frequencies in the mating and non-mating portions of the population. To initialize the system, imagine at time zero that the entire is a population ready to mate in the first season and let $f_{AA}(0)$, $f_{Aa}(0)$, $f_{aa}(0)$ $f_A(0)$ denote the frequencies in this generation. If possible, find a solution to your model.

Exercise 3.3.16. 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 $p^{II}(t)$ 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 $p^I(t)$ 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 $.5(p^I(t) + p^{II}(t))$ is constant from one generation to the next.

c) $\lim_{t \rightarrow \infty} p^I(t)$ and $\lim_{t \rightarrow \infty} p^{II}(t)$ 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 $\lim_{t \rightarrow \infty} p^I(t)$.

Exercise 3.3.17. (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 $f_{A_i A_j B_k B_m}(t)$? Describe the values of these frequencies explicitly in terms of the allele frequencies of generation 0.

Exercise 3.3.18. *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 an 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.

3.4 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. Therefore we will need techniques to analyze nonlinear equations; we discuss these 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,

$$x(t+1) = \phi(x(t)), \quad (3.40)$$

when ϕ is a nonlinear function. However there is an exceptional case. A point $\bar{x}$ is called a fixed point of (3.40), or of ϕ , if $\phi(\bar{x}) = \bar{x}$. The solution of (3.40) 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 (3.40).

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 (3.40), it is often more interesting to know whether $\lim_{t \rightarrow \infty} x(t)$ 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 $y = \lim_{t \rightarrow \infty} x(t)$, then because ϕ is continuous, $\lim_{t \rightarrow \infty} \phi(x(t)) = \phi(\lim_{t \rightarrow \infty} x(t)) = \phi(y)$. But, if $x(t)$ solves $x(t+1) = \phi(x(t))$, then

$$y = \lim_{t \rightarrow \infty} x(t+1) = \lim_{t \rightarrow \infty} \phi(x(t)) = \phi\left(\lim_{t \rightarrow \infty} x(t)\right) = \phi(y)$$

showing y is a fixed point of ϕ ! Thus, to narrow down the possible limits of solutions to (3.40), 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 that helps 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 $\bar{x}$.

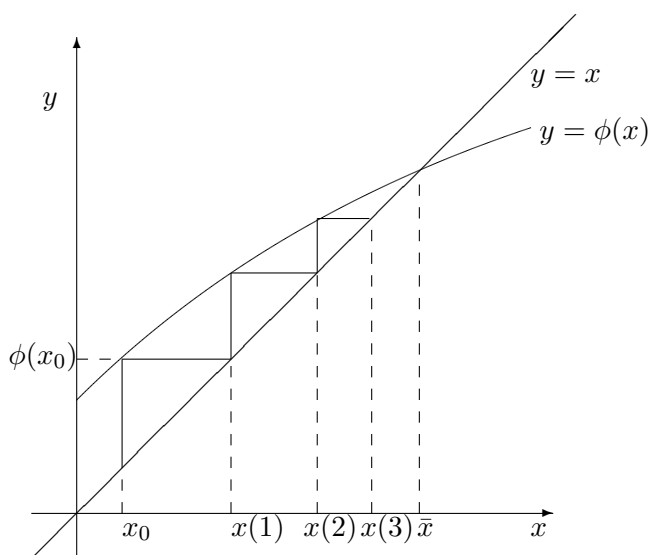


Figure 1.

The object of cobwebbing is to plot successive values of the solution to (3.40), 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 (3.40). 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 $t \rightarrow \infty$. 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. Although the argument is not rigorous, it is clear that $\lim_{t \rightarrow \infty} x(t) = \bar{x}$ for all starting values x_0 sufficiently close to $\bar{x}$. We say that $\bar{x}$ is a *stable* fixed point. When x^* is a fixed point, the set of x such that $\lim_{t \rightarrow \infty} x(t) = x^*$, 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^* . In general, 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 $x(1), x(2), \dots$ of the solution will spiral away from x^* . The picture this time really will look like a cobweb, and x^* is not stable.

There are nice sufficient conditions that a fixed point be either stable or unstable. Assume that ϕ is differentiable at a fixed point x^* . The tangent line to the graph of ϕ at x^* is defined by $y = \phi(x^*) + \phi'(x^*)(x - x^*) = x^* + \phi'(x^*)(x - x^*)$, and, for values of x close to x^* , approximates the graph of $y = \phi(x)$ nicely. Indeed, let $e(x) = \phi(x) - [x^* + \phi'(x^*)(x - x^*)]$ denote the error made in approximating $\phi(x)$ by $x^* + \phi'(x^*)(x - x^*)$. Then, as a direct consequence of the definition of derivative,

$$\lim_{x \rightarrow x^*} e(x)/(x - x^*) = 0;$$

in words, the error is vanishingly small compared to $|x - x^*|$ as x approaches x^* . With this observation in mind, write the difference equation $x(t+1) = \phi(x(t))$ of (3.40) in the form

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

The equation obtained by dropping the error term is

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

This is called the *linearization* of (3.40); it is a linear difference equation with a fixed point at x^* and it should be a good approximation to (3.40), as long as $x(t)$ is

close to x^* . In fact, when $|\phi'(x^*)| < 1$, the results of section 3.1 imply that x^* is a stable fixed point of the linearized equation, and, using this, it can be shown x^* is a stable point for (3.40) as well. Likewise, when $|\phi'(x^*)| > 1$, x^* is unstable for the linear system, and hence also for (3.40). The rigorous proof shall not be given here. We content ourselves with stating the result as the next theorem.

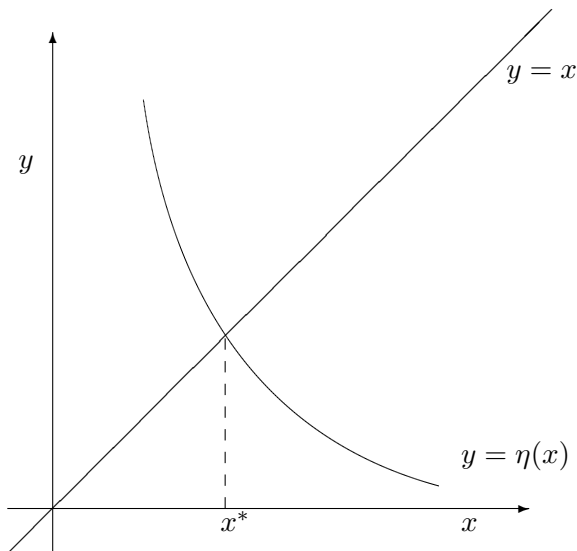


Figure 2.

Theorem 2 *Let z be a fixed point of a continuously differentiable function ϕ . If*

If $|\phi'(z)| < 1$, then z is a stable fixed point.

If $|\phi'(z)| > 1$, then z is not stable.

We have given one plausibility argument for this theorem. The reader should supply another by drawing a number of examples, some satisfying $|\phi'(z)| > 1$, others satisfying $|\phi'(z)| < 1$, and graphing solutions by cobwebbing.

If $|\phi'(x^*)| = 1$, the fixed point x^* can be either stable or not stable; analysis of the linearized equation cannot distinguish between the two cases.

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 $\lim_{s \rightarrow \infty} x(2s+1) = z$ and $\lim_{s \rightarrow \infty} x(2s) = w$. 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 monocious, 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 means these frequencies change over the lifetime of the generation. Our convention will be that $f_A(t)$, $f_{AA}(t)$, etc., denote the frequencies in generation t at the time of its birth. On the other hand, $p_A(t)$, $p_{AA}(t)$, etc., will denote the frequencies in generation t at the time of reproductive maturity, when it is giving birth to the next generation by random mating. 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 step 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,

$$\begin{aligned} f_A(t+1) &= p_A(t), & f_{AA}(t+1) &= p_A^2(t), \\ f_{Aa}(t+1) &= 2p_A(t)(1 - p_A(t)), & f_{aa}(t+1) &= (1 - p_A(t))^2, \end{aligned} \quad (3.41)$$

for all $t \geq 0$.

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 denominator, 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,

$$p_{AA}(t) = \frac{w_{AA}f_{AA}(t)}{w_{AA}f_{AA}(t) + w_{Aa}f_{Aa}(t) + w_{aa}f_{aa}(t)}. \quad (3.42)$$

Likewise,

$$p_{Aa}(t) = \frac{w_{Aa}f_{Aa}(t)}{w_{AA}f_{AA}(t) + w_{Aa}f_{Aa}(t) + w_{aa}f_{aa}(t)}, \quad (3.43)$$

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

If $t \geq 1$, the equations of (3.41), applied with $t-1$ replacing t , imply generation t in infancy is in Hardy-Weinberg equilibrium with $p = p_A(t-1) = f_A(t)$; hence

$$p_{AA}(t) = \frac{w_{AA}f_A^2(t)}{w_{AA}f_A^2(t) + w_{Aa}2f_A(t)(1 - f_A(t)) + w_{aa}(1 - f_A(t))^2}. \quad (3.44)$$

The same reasoning shows that

$$p_{Aa}(t) = \frac{w_{Aa}2f_A(t)(1 - f_A(t))}{w_{AA}f_A^2(t) + w_{Aa}2f_A(t)(1 - f_A(t)) + w_{aa}(1 - f_A(t))^2}. \quad (3.45)$$

The final step of the derivation is simply to combine the results obtained in equations (3.41), (3.44), and (3.45). From (3.41), $f_A(t+1) = p_A(t) = p_{AA}(t) + p_{Aa}(t)/2$. Hence, adding (3.44) and one-half of (3.45), we find that for $t \geq 1$.

$$f_A(t+1) = \frac{w_{AA}f_A^2(t) + w_{Aa}f_A(t)(1 - f_A(t))}{w_{AA}f_A^2(t) + w_{Aa}2f_A(t)(1 - f_A(t)) + w_{aa}(1 - f_A(t))^2}. \quad (3.46)$$

This equation will also be valid for $t = 0$, if we assume generation 0 in its infancy is in Hardy-Weinberg equilibrium (that is, $f_{AA}(0) = f_A^2(0)$, $f_{Aa}(0) = 2f_A(0)(1 - f_A(0))$, and $f_{aa}(0) = (1 - f_A(0))^2$), because (3.44) and (3.45) 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 (3.46), 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*

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

Then the numerator in (3.46) is $W(f_A(t))$, and we can write the model as

$$f_A(t+1) = \frac{w_{AA}f_A^2(t) + w_{Aa}f_A(t)(1 - f_A(t))}{W(f_A(t))}, \quad t \geq 0. \quad (3.47)$$

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 (3.46)

$$f_A(t+1) = \frac{(w_{AA}/w_{Aa})f_A^2(t) + f_A(t)(1 - f_A(t))}{(w_{AA}/w_{Aa})f_A^2(t) + 2f_A(t)(1 - f_A(t)) + (w_{aa}/w_{Aa})(1 - f_A(t))^2}. \quad (3.48)$$

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 (3.44) and (3.45), 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, (3.47), 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 (3.47). 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 (3.47) takes the form:

$$f(t+1) = \phi(f(t)). \quad (3.49)$$

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 4, 5, 6 and 7. The graphs are plotted over the interval $0 \leq p \leq 1$, which is the only region of interest—being a frequency, the $f_A(t)$ must remain in the interval $[0, 1]$ for all t . We shall explain each graph, and its consequence for the behavior of solutions to (3.49), 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

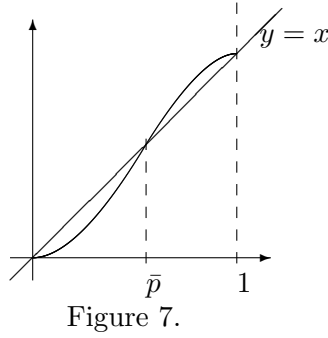
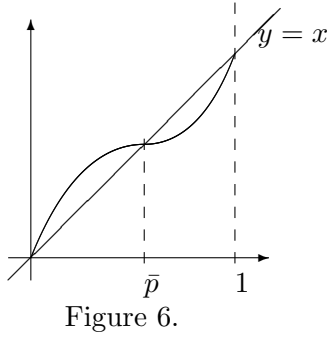
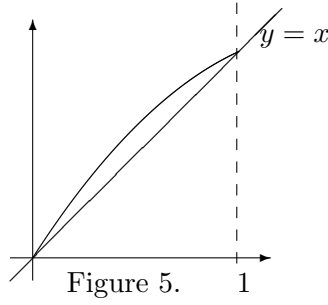
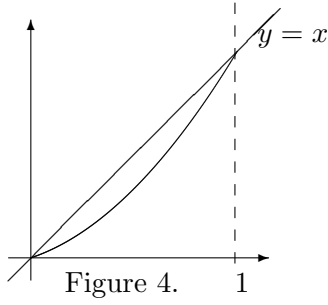
$$\bar{p} = \frac{w_{Aa} - w_{aa}}{2w_{Aa} - w_{AA} - w_{aa}}. \quad (3.50)$$

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

$$\phi'(p) = \frac{p^2 w_{AA} w_{Aa} + 2p(1-p)w_{AA} w_{aa} + (1-p)^2 w_{Aa} w_{aa}}{W^2(p)}. \quad (3.51)$$

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



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 4. Cobwebbing will show that if $0 \leq f(0) < 1$, then

$$\lim_{t \rightarrow \infty} f(t) = 0. \quad (3.52)$$

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

To see why Figure 4 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 (3.51), $\phi'(0) = w_{Aa}/w_{aa}$. 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 (3.52).

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

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

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

This is really Case I with the roles of A and a reversed. The graph of ϕ is shown in Figure 5. 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 $0 < f(0) < 1$,

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

where $\bar{p}$ is the frequency defined above in (3.50).

The graph of ϕ for this case is shown in Figure 6. From the remark after equation (3.50), 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 $\bar{p}$, $\lim_{t \rightarrow \infty} f(t) = \bar{p}$.

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,

$$\text{if } 0 < f(0) < \bar{p}, \text{ then } \lim_{t \rightarrow \infty} f(t) = 0, \text{ and if } \bar{p} < f(0) < 1, \lim_{t \rightarrow \infty} f(t) = 1. \quad (3.53)$$

The graph of $y = \phi(p)$ in this case is shown in Figure 7. 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 than 1, which implies that $\bar{p}$ is not stable. The student can check the validity of the limits stated in (3.53) 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 ($f(t) \rightarrow 0$) or allele a ($f(t) \rightarrow 1$). But which allele wins depends on the initial frequency of A 's versus a 's and the exact values of the selection coefficients. The value $\bar{p}$ 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, where the dividing line between the regions where A takes over and a takes over lies.

3.4.5 Mean Fitness Increases

This section presents another perspective on how solutions to equation (3.49) for the allele frequency $f(t)$ 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 (3.47), mean fitness always increases from generation to generation. That is, for any t*

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

Comment: The mean fitness W provides what is called a Lyapunov function for the difference equation (3.49). 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 $t \rightarrow \infty$, 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 this shows mean fitness increases.

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

$$W(\phi(p)) - W(p) = \frac{(\phi(p) - p)^2}{p(1 - p)} [W(p) + pw_{AA} + (1 - p)w_{aa}]. \quad (3.54)$$

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

3.4.6 Problems

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 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 $\lim_{t \rightarrow \infty} p_A(t)$ 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 (3.50). Derive the formula given in the text for $\phi'(p)$.

Exercise 3.4.8. Derive formula (3.54) in the proof that mean fitness increases.

Exercise 3.4.9. Suppose that in addition to selection, allele A mutates to a with probability u and a to A with probability v in the course of mating. Derive a difference equation for $f_A(t)$.

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 order 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-Verlag, 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.