

Chapter 3

Population Genetics: Difference Equation Models

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, genetic 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. It is a quantitative subject in which mathematical modeling and analysis play key roles. Population geneticists measure the genetic composition of a population by the frequencies of the various genotypes that are present. They 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. They then analyze the solutions of these equations to derive predictions that can be used to test hypotheses on mating and selection, to understand how different factors affect genotype variation, and to make inferences about genealogy and evolution.

This chapter is an introduction to elementary mathematical models of population genetics for large populations. These models are derived by imagining how genotype frequencies evolve in the limit as the population

size tends to infinity. The use of this limit is called the “infinite population assumption,” and it is imposed throughout the chapter. One of its main consequences is that genotype frequencies become deterministic functions of time, and hence infinite population models take the form of deterministic dynamical systems. However, the rules governing the dynamics of the frequencies—how they change in time—are derived by probabilistic reasoning, and, to understand the chapter, the reader should review the material in Section 2.1 on random sampling, independence, the law of large numbers, and conditional probability.

Population genetics is perhaps the most prominent field of biology for applications of probability. But this is not the only reason it is treated first in this book. It also makes an excellent introduction to probabilistic modeling in general. In reading this chapter, the student should study not just the models themselves, but also the process by which they are derived. To help in this regard, Section 3.2 presents a careful discussion of the biological and probabilistic principles of population genetics. The presentation of the models themselves in Section 3.3 follows a common strategy used in applications of mathematics to science: begin with oversimplified models and gradually derive more complex and realistic ones by relaxing different assumptions one by one. Mathematical modeling is an art that can only be learned by practice. Throughout, guided exercises in extending and developing the material are worked into the text, and the student should do them as an integral part of reading the chapter.

The models derived in Sections 3.3 and 3.4 almost all take the form of *finite difference equations*. Section 3.1 treats the essential theory of first and second order, linear difference equations needed for Section 3.3. A graphical method called cobwebbing is presented in Section 3.4 for analyzing nonlinear difference equations, in preparation for studying models with selection. Difference equations have an importance extending far beyond population genetics, since they arise as models in many applied areas.

3.1 Finite Difference Equations; Introduction

This section supplies an introduction to finite difference equations sufficient for understanding Chapter 3. The reader can begin directly with the population genetics in section 3.2 and 3.3, and refer back to this section as the need arises, but it is helpful to read at least the beginning of this section first, to learn what difference equations are about.

Difference equations are recursive equations that determine a sequence of numbers. It is common in mathematical texts to denote a generic sequence by the notation $(x_1, x_2, x_3, \dots, x_n, \dots)$. In this chapter, we shall instead denote a generic sequence by $(x(0), x(1), x(2) \dots)$, and a generic term in the

sequence by $x(t)$. We use t as the index because it will always represent some sort of time parameter, and writing $x(t)$ rather than x_t will allow us to use subscripts for other purposes. In general, our convention is that the first element of a sequence denotes a value at time $t = 0$, and that is why the first term in a sequence is taken to be $x(0)$. It will also be convenient to abbreviate the sequence $(x(0), x(1), \dots)$ by $(x(t))_{t \geq 0}$.

3.1.1 First-order difference equations

The general, *autonomous*, *first-order* difference equation for a sequence $(x(t))_{t \geq 0}$ takes the form

$$x(t+1) = \phi(x(t)), \quad t \geq 0, \quad (3.1)$$

where ϕ is a given function. We call (3.1) *autonomous* because $\phi(x)$ depends explicitly only on x . (The non-autonomous generalization of (3.1) is $x(t+1) = \phi(t, x(t))$, where $\phi(t, x)$ depends on both t and x . We shall encounter only autonomous equations, and so we restrict the discussion to this case.) We call (3.1) first-order equation because, for each t , the value of $x(t+1)$ is determined completely by the immediately preceding value $x(t)$. Second-order difference equations will be defined and discussed in the next subsection.

A specification,

$$x(0) = x_0, \quad (3.2)$$

of a value for the first term is called an *initial condition*. Given a function ϕ and an initial value x_0 , there will be a unique sequence $(x(t))_{t \geq 0}$, called the solution of (3.1)-(3.2), for which $x(0) = x_0$ and $x(t+1) = \phi(x(t))$ for all $t \geq 0$. This is easy to see by applying the difference equation for successively greater values of t , starting from $t = 0$. Thus, setting $t = 0$ in (3.1) implies $x(1) = \phi(x(0)) = \phi(x_0)$; then setting $t = 1$ implies $x(2) = \phi(x(1)) = \phi(\phi(x_0))$; and, continuing in this manner, $x(t) = \phi(\phi(\dots \phi(x_0) \dots))$, where ϕ is convolved with itself t times. By computing $x(0), x(1), x(2), \dots$ recursively in this way, one can calculate $x(t)$ numerically for any desired t , so long as each new value of $x(t)$ is in the domain of the function ϕ . If at some point, $x(t)$ is not in the domain of ϕ , the procedure must stop and the solution to the difference equation will be only a finite sequence.

Example 3.1.1. For a very simple example, consider the equation

$$x(t+1) = \frac{1}{2}x(t), \quad x(0) = x_0.$$

We have, $x(1) = x(0)/2 = x_0/2$, $x(2) = x(1)/2 = x_0/2^2$, and, dividing by two at each step, $x(t) = x_0/2^t$ for any non-negative integer t .

Example 3.1.2. Consider

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

Then $x(1) = 1/2 + 1 = 3/2$ and $x(2) = (3/2)/2 + 2/3 = 17/12 = 1.41666\dots$, and so forth. We do not know an explicit, closed form expression for the general term $x(t)$. Observe that $x = 0$ is not in the domain of $x/2 + 1/x$. Hence, if $x(0) = 0$ is the initial condition, the solution stops with this one value and cannot continue for $t \geq 1$. (Some authors would say that a solution to (3.3) does not exist for $x(0) = 0$.)

For the purposes of this chapter, we need techniques from difference equation theory to address two issues: finding, if possible, closed form solutions, and analyzing the behavior of solutions $(x(t))_{t \geq 0}$ as $t \rightarrow \infty$. The latter problem is important because knowing the exact solution is often less interesting than understanding whether or not $x(t)$ settles into some type of regular behavior as t increases. In particular, one often wants to know if $\lim_{t \rightarrow \infty} x(t)$ exists, and, if it does, what its value is. In the rest of section 3.1, we show how to resolve these questions for *linear* difference equations.

A first order difference equation is called *linear* if ϕ is linear; its general form is

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

Such equations are particularly nice because they have simple, explicit solutions whose limiting behavior can be described completely.

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

$$x(t) = A\alpha^t + \frac{\beta}{1-\alpha}, \quad t \geq 0, \quad \text{where } A \text{ is an arbitrary constant,} \quad (3.5)$$

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

$$x(t) = \left[x_0 - \frac{\beta}{1-\alpha} \right] \alpha^t + \frac{\beta}{1-\alpha}, \quad t \geq 0. \quad (3.6)$$

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 $x(t) = x_0 + \beta t$, $t \geq 0$.

Assume $\alpha \neq 1$. In Proposition 1, the claim that $x(t) = A\alpha^t + \frac{\beta}{1-\alpha}$, $t \geq 0$, for A arbitrary, is the *general* solution to (3.4) means that: (a) for any number A , $x(t) = A\alpha^t + \frac{\beta}{1-\alpha}$, $t \geq 0$, is a solution of (3.4); and (b), conversely, any solution to (3.4) must have this form for some A . Let us

show why this must be true. To prove (a) we must demonstrate that (3.4) is true when $x(t)$ is replaced by $A\alpha^t + \frac{\beta}{1-\alpha}$; that is, we must show

$$A\alpha^{t+1} + \frac{\beta}{1-\alpha} = \alpha \left[A\alpha^t + \frac{\beta}{1-\alpha} \right] + \beta.$$

But this can be verified (do so!) by some simple algebra.

Now suppose the initial condition $x(0) = x_0$ is specified. We can find a solution of the form in (3.5) if we can find A such that

$$x_0 = x(0) = A\alpha^0 + \frac{\beta}{1-\alpha} = A + \frac{\beta}{1-\alpha}.$$

But this equation has the unique solution $A = x_0 - \beta/(1-\alpha)$ for *any* x_0 , and using this A we obtain the solution (3.6).

To prove (b), let $(z(t))_{t \geq 0}$ be any solution to (3.4). Then, from what we have just shown,

$$y(t) = \left[z(0) - \frac{\beta}{1-\alpha} \right] \alpha^t + \frac{\beta}{1-\alpha}, \quad t \geq 0,$$

is a solution with the same initial condition. Since solutions are uniquely specified once initial conditions are specified, $y(t) = z(t)$ for all t , and so $(z(t))_{t \geq 0}$ has the form $z(t) = A\alpha^t + \beta/(1-\alpha)$ with $A = z(0) - \beta/(1-\alpha)$.

The statements in Proposition 1 about the solution when $\alpha = 1$ are all demonstrated in a similar manner. \diamond

It is interesting to analyze the solutions (3.5) and (3.6) further. Again, consider the case $\alpha \neq 1$. First, notice that setting $A = 0$ in (3.5) yields a constant solution to (3.5), namely

$$x(t) = \frac{\beta}{1-\alpha}, \quad \text{for all } t = 0, 1, 2, \dots$$

This is called a *fixed point solution* of the difference equation. In fact, it is the only constant solution, and can be found directly. Indeed, let $(z(t))_{t \geq 0}$ be the constant sequence: $z(t) = \bar{x}$ for all $t \geq 0$. This will solve (3.5) if and only if

$$\bar{x} = z(t+1) = \alpha z(t) + \beta = \alpha \bar{x} + \beta. \quad (3.7)$$

This has the unique solution $\bar{x} = \beta/(1-\alpha)$, which therefore defines the unique, fixed-point solution. In the case $\alpha = 1$, if $\beta \neq 0$, $\bar{x} = \bar{x} + \beta$ admits no solution and hence $x(t+1) = x(t) + \beta$ has no fixed point.

Second, the formulas (3.5) and (3.6) reveal completely how solutions to (3.4) behave in the long time limit. If $\alpha \neq 1$ there are two different

limiting behaviors, according to whether $|\alpha| < 1$ or $|\alpha| > 1$. If $|\alpha| < 1$, then $\lim_{t \rightarrow \infty} \alpha^t = 0$, and hence

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

In other words, as t increases to ∞ , the solution $x(t)$ tends to the fixed point $\beta/(1 - \alpha)$, *no matter what the initial value is*. One describes this situation by saying that the fixed point is *globally asymptotically stable*. On the other hand, if $|\alpha| > 1$, the sequence $\{|\alpha|^t; t \geq 0\}$ goes off to ∞ as $t \rightarrow \infty$, and hence for *any* x_0 not equal to the fixed point, $|x(t)| \rightarrow \infty$. In this case, $\beta/(1 - \alpha)$ is an example of an *unstable* fixed point.

Turning to the case $\alpha = 1$, one sees immediately from (3.7) that $x(t+1) = x(t) + \beta$ admits no fixed point unless $\beta = 0$, in which case the fixed point is $\bar{x} = 0$. Because the general solution is $A + \beta t$, solutions will tend to $+\infty$ or $-\infty$, according to whether $\beta > 0$ or $\beta < 0$; when $\beta = 0$ solutions are always constant.

These limiting results, although derived for linear difference equations, illustrate concepts that generalize to the nonlinear case. A point \bar{x} is called a fixed point of the general difference equation $x(t+1) = \phi(x(t))$ if $\phi(\bar{x}) = \bar{x}$. The sequence which takes the constant value \bar{x} therefore solves the difference equation and is called a fixed-point solution. In general, a difference equation may have many different fixed points. Now suppose that ϕ is a continuous function and $(x(t))_{t \geq 0}$ is a solution to $x(t+1) = \phi(x(t))$ such that $\bar{x} = \lim_{t \rightarrow \infty} x(t)$ exists and is finite. Then, using the continuity of ϕ ,

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

Thus the limit \bar{x} must be a fixed point of the equation. This simple fact at least identifies all potential candidates for limits of solutions. If \bar{x} is a fixed point of ϕ , define the *basin of attraction of \bar{x}* to be the set of points x_0 such that the solution of $x(t+1) = \phi(x(t))$ with initial condition $x(0) = x_0$ converges to \bar{x} . For example, in the case of linear the linear difference equation (3.5) with $\alpha \neq 1$, we saw that if $|\alpha| < 1$, all solutions tend to the fixed point $\beta/(1 - \alpha)$, and therefore its basin of attraction is the set of all points in $(-\infty, \infty)$. On the other hand, if $|\alpha| > 1$, the basin of attraction consists solely of the fixed point. A fixed point is called *stable* if its basin of attraction contains an open interval about x_0 . For nonlinear equations, basins of attraction are in general difficult to calculate exactly. However, a simple criterion for stability is presented in section 3.4.

3.1.2 Second-order, linear difference equations.

A *second-order* (autonomous) difference equation takes the general form:

$$x(t+1) = \psi(x(t), x(t-1)), \quad t \geq 1. \quad (3.9)$$

Now, each term in the sequence is determined by the two previous values, and in order to start a solution off, it is necessary to specify initial values of $x(0)$ and $x(1)$:

$$x(0) = x_0, \quad x(1) = x_1. \quad (3.10)$$

Equations (3.9)–(3.10) have a unique solution which can be computed numerically by recursion: thus, $x(2) = \phi(x_1, x_0)$, $x(3) = \phi(x(2), x(1)) = \phi(\phi(x_1, x_0), x_1)$, etc., and the recursion continues so long as $(x(t), x(t-1))$ remains in the domain of ϕ .

We shall encounter population genetics models which are second-order, *linear* difference equations, that is, are of the form:

$$x(t+1) = \alpha x(t) + \gamma x(t-1) + \beta. \quad (3.11)$$

This equation can be solved by a method reminiscent of the theory of second-order, linear *differential* equations. Consider first the case in which $\beta = 0$:

$$x(t+1) = \alpha x(t) + \gamma x(t-1), \quad (3.12)$$

(where $\gamma \neq 0$, so that the equation is truly second-order). This is called the *homogeneous* case.

The virtue of the homogeneous equation is that solutions to it obey a superposition principle: if $(z(t))_{t \geq 0}$ and $(y(t))_{t \geq 0}$ both solve (3.12), then so does the linear combination $(x(t) = Az(t) + By(t))$, for any constants A and B . Indeed, if $z(t+1) = \alpha z(t) + \gamma z(t-1)$ and $y(t+1) = \alpha y(t) + \gamma y(t-1)$, then

$$\begin{aligned} x(t+1) &= Az(t+1) + By(t+1) = A[\alpha z(t) + \gamma z(t-1)] + B[y(t) + \gamma y(t-1)] \\ &= \alpha [Az(t) + By(t)] + \gamma [Az(t-1) + By(t-1)] \\ &= \alpha x(t) + \gamma x(t-1), \end{aligned}$$

and thus $(x(t))_{t \geq 0}$ solves (3.12) as well. This superposition principle is the key to the solution method. It turns out that if $(z(t))_{t \geq 0}$ and $(y(t))_{t \geq 0}$ are *independent* solutions of (3.12), in the sense that $(y(t))_{t \geq 0}$ is not a constant multiple of $(z(t))_{t \geq 0}$, then $Az(t) + By(t)$, $t \geq 0$, is the *general* solution of (3.12); that is, *all* solutions of (3.12) have this form. Suppose we now want to solve (3.12), subject to the initial conditions $x(1) = x_1$ and $x(0) = x_0$. We know it must be $x(t) = Az(t) + By(t)$ for some A and B , and to find A and B , we need only to solve the equations for A and B required by the initial conditions:

$$Az(0) + By(0) = x_0 \quad \text{and} \quad Az(1) + By(1) = x_1. \quad (3.13)$$

To complete the project of solving (3.12) it therefore remains to find two independent solutions $(z(t))_{t \geq 0}$ and $(y(t))_{t \geq 0}$. This is done by looking for solutions of the form $z(t) = r^t$. By substituting $z(t)$ for $x(t)$ in (3.12), we find that r must satisfy, $r^{t+1} = \alpha r^t + \beta r^{t-1}$, or, dividing through by r^{t-1}

$$r^2 - \alpha r - \beta = 0. \quad (3.14)$$

This is called the characteristic equation of the (3.12). If r is a root, then r^t is indeed a solution to (3.12). 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 , then we obtain two distinct solutions r_1^t and r_2^t . Hence, by the superposition principle, $x(t) = Ar_1^t + Br_2^t$ is the general solution to (3.12).

Example 3.2.3. Solve

$$x(t+1) = -3x(t) - 2x(t-1), \quad x(0) = 1, \quad x(1) = 0. \quad (3.15)$$

The characteristic equation is $r^2 + 3r + 2 = 0$, which has roots $r_1 = -1$ and $r_2 = -2$. Thus the general solution to (3.15) 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 $r = \alpha/2$. In this case, we obtain immediately only the solution $(\alpha/2)^t$. However, it can be checked that in this case $t(\alpha/2)^t$ is again a solution; this is left as an exercise. Then, the general solution has the form $x(t) = Ar^t + Bt(\alpha/2)^t$.

We turn now to the inhomogeneous equation, namely (3.11) with $\beta \neq 0$. (This will not be needed later, but we include it for completeness.) There is a variant of the superposition principle for the inhomogeneous equation: if $x_p(t)$ is any particular solution to (3.11), then the general solution to (3.11) can be written in the form

$$x(t) = Az(t) + By(t) + x_p(t), \quad t \geq 0,$$

where $z(t)$ and $y(t)$ are independent solutions to the homogeneous equation (3.12), and A and B are arbitrary constants. This principle is again a consequence of the linearity of the difference equation. To prove it, let $(x_p(t))$ be a fixed particular solution to the inhomogeneous equation, and let $(x(t))$ be any other solution. We want to show $x(t) = Az(t) + By(t) + x_p(t)$. But

$$\begin{aligned} x(t+1) - x_p(t+1) &= [\alpha x(t) + \gamma x(t-1) + \beta] - [\alpha x_p(t) + \gamma x_p(t-1) + \beta] \\ &= \alpha (x(t) - x_p(t)) + \gamma (x(t-1) - x_p(t-1)), \end{aligned}$$

since the β terms cancel out. This says that $x(t) - x_p(t)$ solves the homogeneous equation; hence, $x(t) - x_p(t) = Az(t) + By(t)$, and so $x(t) = Az(t) + By(t) + x_p(t)$, as we wanted to show.

Therefore, to solve inhomogeneous equations we only need to come up with some solution of the inhomogeneous equation. The easiest method is to guess simple forms. For example the constant sequence, $x(t) = \bar{x}$ for all $t \geq 0$ solves (3.11) if $\bar{x} = \alpha\bar{x} + \gamma\bar{x} + \beta$. As long as $\alpha + \gamma \neq 1$ this has the unique solution $\bar{x} = \beta/(1 - \alpha - \gamma)$, which therefore provides a particular solution. The problem of finding particular solutions when $\alpha + \gamma = 1$ is left to the exercises.

Example 3.2.3, continued. Solve

$$x(t+1) = -3x(t) - 2x(t-1) + 1, \quad x(0) = 1, \quad x(1) = 0. \quad (3.16)$$

We look for a constant solution of the form $x(t) = w$, $t \geq 0$. Substituting in (3.16), 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 (3.16) 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 (3.9) 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 methods developed in this section can be extended to linear difference equations of any order.

3.1.3 Problems

Exercise 3.1.1. a) Calculate and plot the values $x(0), x(1), x(2), x(3)$ for the solution to

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

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

(iii) $x(t+1) = (2/3)x(t) + (1/x^2(t)), x(0) = 3.$

b) For case (i) of part a), identify the fixed point γ and observe that it is stable. Determine how large n must be in order that $|x(n) - \gamma| \leq 0.01$.

c) What is the fixed point of (iii) in part a)? 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 $Ar^t + Btr^t$ solves the equation.

Exercise 3.1.3. The homogeneous, linear second order 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 $x(t)$, for any $t \geq 0$.

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 3.1.7. Verify that the linear difference equation in Example 3.1.2 is Newton's method for finding the root of $x^2 - 2$. Calculate the next term $x(3)$ of the solution with initial condition $x(0) = 1$ and observe how close it is to $\sqrt{2}$. In fact $\sqrt{2}$ is a stable fixed point for the difference equation and $x(0) = 1$ is in its basin of attraction.

Exercise 3.1.7. (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

$$x(t) = A\alpha^t + \sum_{s=0}^t \alpha^{t-s} g(s) \text{ is a solution for any constant } A.$$

(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

In this section we develop the essential concepts required for building population genetics models. We discuss sex, genotype and generational structure, define genotype and allele frequencies and their relationship to each other, and present the basic mathematics of random mating. 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 genealogy, 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 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 female genotypes including a locus 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 before hand and understood. The genotype of an individual is a list of all the alleles it carries at the loci of interest 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 eye color alleles, and all your other distinctive features—your good looks, superior intelligence, and athletic prowess—would be ignored. Sorry. 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:

$$f_{G_1 \cdots G_k} \triangleq \frac{\text{number of individuals with genotype } G_1 \cdots G_k}{\text{population size}}. \quad (3.17)$$

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 :

$$AA, AA, AA, Aa, Aa, Aa, Aa, aa, aa, aa, aa$$

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 in a box. That box then contains 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 :

$$f_A \triangleq \frac{\text{number of } A\text{'s in the allele pool for } \ell}{\text{size of the allele pool for } \ell} \quad (3.18)$$

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 genotypes of example 3.2.1, all letters denote alleles at the locus containing A . The allele pool is thus the collection of the $24 (= 2 \times 12)$ letters comprising these genotypes. There are 24 letters total of which 10 are 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. 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 , $\bar{a}Bb$, 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,

$$f_{AA} + f_{Aa} + f_{aa} = 1. \quad (3.19)$$

In addition allele and genotype frequencies are related as follows:

$$f_A = f_{AA} + \frac{f_{Aa}}{2}, \quad f_a = f_{aa} + \frac{f_{Aa}}{2}. \quad (3.20)$$

We derive the first equation of (3.20), the second being similar. Let N denote the size of the population. Since the population is diploid, the size of the allele pool for the locus at which A occurs is $2N$. Now count the number of A 's in the allele pool for ℓ in terms of the genotype frequencies. By definition of f_{AA} , there are Nf_{AA} genotypes AA in the population, and so they contribute a total of $2Nf_{AA}$ letter A 's. Similarly, there are Nf_{Aa} genotypes Aa contributing a total of Nf_{Aa} letter A 's. Individuals of genotype f_{aa} of course contribute no A 's. Hence, using definition (3.18),

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

\diamond

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

The issue at the heart of modeling the evolution of genotype frequencies is:

- For each genotype G , what is the probability that an offspring of a mating has genotype G ?

The purpose of this section is to define a particular model called *random mating* and deduce from it principles for calculating offspring genotype probabilities. The concept of random sampling, as defined and discussed in section 2.1, will play a central role. Recall that to “sample a population at random” means to select an individual from it randomly so that each individual has an equally likely chance of being chosen.

The idea of the **random mating** model is that each individual in the mating pool has the same chance of reproductive success and that mate choice is totally by random. Suppose this is true, and do the following experiment. Sample an individual at random from the population of all offspring of the mating pool and record its parents. Then each possible pair of parents should be equally likely as an outcome. But from section 2.1, we know that this result is probabilistically the same as sampling the parent population at random. Thus we can imagine that each individual is created by mating randomly sampled parents. Informally, we say that the child chooses its parents by random sampling, although, strictly speaking, this is nonsensical! Once the parents are chosen, a mating takes place through the union of two gametes, one egg and one sperm, from the respective parents. Now, each parent contains a pool of gametes produced by meiosis, as described in Chapter 1. We will assume further that the gamete from each parent is chosen by random sampling. Because the gametes of a single individual may carry different alleles, this assumption expresses a biological hypothesis, namely, that gamete genotype does not confer any selective advantage. Let us formalize this discussion by stating a precise definition.

Definition. A **random mating** is the creation of a new individual by uniting the gametes (one egg and one sperm) of two parents chosen by *independent* random samplings from the mating pool. Furthermore, the gamete a chosen parent contributes is selected by a random sample of its gametes.

The models we shall study all assume diploidy, and, in the case of dioecious species, the human model of sex determination. In these cases, random mating leads to a simple principle for calculating offspring genotype probabilities. Let A be an allele and consider a random mating. For convenience, let p_A^1 denote the probability the first parent chosen in a random mating passes allele A to the child and let f_A^1 be the frequency of A in the pool from which this parent is drawn. Similarly define p_A^2 and f_A^2 for the second parent. Of course when the organism is monocious and both parents are drawn from the same pool, then $f_A^1 = f_A^2$.

Lemma 1 *In a random mating, the allele a child gets from each parent at locus ℓ is a random sample from that parent's allele pool for locus ℓ . Therefore,*

$$p_A^i = f_A^i \quad i=1, 2. \quad (3.21)$$

Proof: Fix a diploid locus ℓ . If the genotype of an individual at locus ℓ is A_1A_2 ($A_1 = A_2$ being possible), half its gametes contain a copy of A_1 and the other half copies of A_2 . Hence, if it participates in a random mating, A_1 and A_2 have the same probability ($1/2$) of being passed to its offspring when it mates.

Consider now a random mating, choosing parent i from a population i . Each individual of population i has an equal chance of being drawn, and, as we have just seen, each of its alleles at locus ℓ has an equal chance of being passed to the child. Therefore, in a random mating each allele in the allele pool for locus ℓ of parent i has an equal chance of being passed to the child. But this is equivalent to choosing the allele from the allele pool of parent i by random sampling, which is what the lemma claims. Now we know from (2.5) in Chapter 2 that, in a random sampling, the probability of drawing type A is just the frequency of type A , and hence (3.21) follows.

A similar argument works for a locus on the Y chromosome. \diamond

This lemma contains just about everything we need to know in developing models based on random mating. We could almost take equation (3.21) 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 offspring of 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 population of genotypes AA , Aa , and aa in a monocious population. Then both parents are drawn from a common population and so $f_A^1 = f_A^2 = f_A$ and $f_a^1 = f_a^2 = f_a$. The probability that the offspring of a random mating is AA is the probability that it gets allele A from each parent, and since parents are chosen independently,

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

Similarly,

$$\mathbb{P}(\text{offspring is } aa) = f_a^2 = (f_{aa} + \frac{f_{Aa}}{2})^2. \quad (3.23)$$

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,

$$\mathbb{P}(\text{offspring is } Aa) = 2f_A f_a = 2\left(f_{AA} + \frac{f_{Aa}}{2}\right)\left(f_{aa} + \frac{f_{Aa}}{2}\right) (= 2f_A(1 - f_A)) \quad (3.24)$$

(Show that these three probabilities 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 technical definition of random mating is abstract and far removed from what mating means biologically in real populations. The following remarks are meant to help the reader think more deeply about the modeling issues arising here. The reader may pass over them for now if he or she wishes, since they are not used in the sequel. However, we encourage reading them eventually.

1. The term “random mating” as used here has a technically precise sense. It refers not to any situation in which there is some random factors in mating, but to the specific model in which mating is *completely* random, in the sense that there are no mating preferences and no differences between individuals in their chances of passing genes to offspring.

2. While the random mating model may look simple in hindsight, the strategy used to derive it is subtle. A naive approach would attempt to base a model directly on the actual physical process of mating. But 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. By taking a conditional viewpoint, looking at the parents of a random individual, and just applying the idea that all potential parents have equal chances, one is able to bypass the ultimately irrelevant details of direct models.

3. 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.

4. 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 in general exercise mating preferences. Accurate models would account for sexual preference by assigning higher probabilities to some pairings and lower probabilities to others. Is a model with completely random mating ever useful?

There are several responses to this question. First, there are many situations, for example, pollination of plants by wind or insect, 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. In modeling one wants to start with the simplest assumptions and explore what they imply before adding on further layers of complexity, and models with random mating 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 in nature when random mating is not occurring 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*

$$f_{G_1 \dots G_k} = p_{G_1 \dots G_k}. \quad (3.25)$$

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; it is the same as the *empirical frequency* of $G_1 \cdots G_k$ in the first N matings, and it is a random variable. If the random matings were independent of each other, then the law of large numbers would imply that $\lim_{N \rightarrow \infty} f_{G_1 \cdots G_k}^{(N)} = p_{G_1 \cdots G_k}$ 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 declines fast enough that the law of large numbers holds. Thus, identity (3.25) represents what should happen, at least heuristically, in the limit as population size tends to infinity. In practice, the infinite population assumption means supposing the population under study is so large that (3.25), which really ought to be an approximation, may be treated as an exact identity. (A mathematically rigorous treatment would derive a law of large numbers from models with specified correlations between matings. However, in all elementary treatments, $f_{G_1 \cdots G_k} = p_{G_1 \cdots G_k}$ is just assumed as reasonable.)

The great, simplifying virtue of the infinite population assumption is that it identifies genotype frequencies, which in real, finite populations are random, with the deterministic quantities $p_{G_1 \cdots G_k}$. Hence, in infinite population models, genotype frequencies 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 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 green 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 Tchebysheff'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 Tchebysheff'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 a set of first order difference equations for the genotype frequencies, derived as a logical consequence of the assumptions. The derivation is in fact simple using the work we have already done in the previous section. Consider, for example, $f_{AA}(t+1)$, for any $t \geq 0$. According to (A.2), generation $t+1$ is produced by random matings of parents in generation t , and $f_{AA}(t+1)$ equals the frequency of AA in the offspring born to generation t parents. Therefore, by the infinite population assumption, (3.25),

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

But we saw in Example 3.2.2, equation (3.22), how to calculate this probability: it is $f_A^2(t)$. Also from (3.20), we know $f_A(t) = f_{AA}(t) + (1/2)f_{Aa}(t)$. Thus,

$$f_{AA}(t+1) = f_A^2(t) = \left(f_{AA}(t) + \frac{f_{Aa}(t)}{2} \right)^2. \quad (3.26)$$

The same reasoning yields as well,

$$f_{Aa}(t+1) = 2f_A(t)f_a(t) = 2 \left(f_{AA}(t) + \frac{f_{Aa}(t)}{2} \right) \left(f_{aa}(t) + \frac{f_{Aa}(t)}{2} \right) \quad (3.27)$$

$$f_{aa}(t+1) = f_a^2(t) = \left(f_{aa}(t) + \frac{f_{Aa}(t)}{2} \right)^2 \quad (3.28)$$

These three difference equations, (3.26), (3.27), and (3.28), constitute the basic model.

At first glance, the equations (3.26), (3.27), (3.28) 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 (3.20) and then (3.26), (3.27), and $f_A(t) + f_a(t) = 1$, we find,

$$\begin{aligned} f_A(t+1) &= f_{AA}(t+1) + \frac{f_{Aa}(t+1)}{2} \\ &= f_A^2(t) + f_A(t)f_a(t) = f_A(t)(f_A(t) + f_a(t)) \\ &= f_A(t). \end{aligned} \quad (3.29)$$

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 (3.20), we obtain the complete solution to (3.26), (3.27), and (3.28): for all $t \geq 1$ the genotype frequencies take on the constant values

$$\begin{aligned} f_A(t) &= f_A(0) = f_{AA}(0) + (1/2)f_{Aa}(0), & f_a(t) &= 1 - f_A(t) = 1 - f_A(0) \\ f_{AA}(t) &= f_A(t+1)^2 = f_A^2(0); \\ f_{Aa}(t) &= 2f_A(t+1)f_a(t+1) = 2f_A(0)(1 - f_A(0)) \\ f_{aa}(t) &= f_a^2(t+1) = (1 - f_A(0))^2. \end{aligned} \tag{3.30}$$

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

$$f_{Aa}^2 = 4f_{AA}f_{aa}. \quad (3.31)$$

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 derivation than we have given, and indeed it does. Recall Lemma 1, which was a crucial element in deriving the model (3.26), (3.27), (3.28). It says that the probability $p_A(t)$ that a parent of generation t passes allele A to its offspring in random mating is $p_A(t) = f_A(t)$. In effect, 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 expect $f_A(t+1) = p_A(t)$. But then it follows that $f_A(t+1) = p_A(t) = f_A(t)$, and we are done. 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 developed the infinite population assumption not for allele frequencies but for genotype frequencies. The derivation in (3.29) that allele frequencies are constant amounts to a proof that $f_A(t+1) = p_A(t)$ from the infinite population assumption as stated in (3.25). Also, equations (3.26), (3.27), (3.28), while complicated, follow more directly from viewing mating as a process producing new individuals rather than new allele pools. Finally, the student will need to understand the analysis at the genotype level for dealing 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.

c) For any valid set of frequencies f_{AA} , f_{Aa} and f_{aa} , show that $|f_{Aa}^2 - 4f_{AA}f_{aa}|$ is bounded by 1. This shows that the difference is never too large, so what may look like a small difference, may correspond to a situation far from Hardy-Weinberg equilibrium.

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 gene, but this time we assume that it admits m alleles, labelled A_1, \dots, A_m , where $m \geq 3$. Therefore, the possible genotypes are the pairs A_iA_j , where i and j range between 1 and m . For notational convenience, denote the frequency of genotype A_iA_j in generation t by $f_{ij}(t)$ instead of $f_{A_iA_j}(t)$. Similarly, let $f_i(t)$ be shorthand for the allele frequency $f_{A_i}(t)$.

The exercises that follow guide you toward a statement of the Hardy-Weinberg theorem for multiple alleles. They can be solved by straightforward generalization of the two allele analysis presented in the previous section. If it helps, do them for the more concrete case $m = 3$ rather than general m . This case contains all the ideas and shows why the general case works.

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 what happens to the basic model when it is assumed 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 these cases differ in how sex and genotype are jointly inherited. Consider autosomal chromosomes first. Recall from Chapter 1 Mendel's hypothesis that different chromosomes segregate independently of one another in meiosis. This means autosomal chromosomes are inherited independently of the sex chromosome, and hence, for genotypes with respect to loci on autosomal chromosomes,

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

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 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

$$p_{a_1 \cdots a_k}^m(t+1) = p_{a_1 \cdots a_k}^f(t+1) \quad (3.32)$$

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 as defined in the previous paragraph. It immediately follows from (3.32) that $f_{AA}^m(t+1) = f_{AA}^f(t+1)$ for all $t \geq 0$. This reasoning applies to any genotype. Hence for the dioecious model, **the male genotype and allele frequencies are equal to the corresponding 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, ◇

Exercise 3.3.8 shows that autosomal gene frequencies for dioecious species differ in only a minor way from the monocious case. The fact that there are separate sexes only means that it takes two generations instead of one for random mating to mix alleles sufficiently 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 $f_A^m(1) = f_A^f(0)$, $f_{AA}(1)^f = f_A^m(0)f_A^f(0)$, $f_{Aa}(1)^f = f_A^m(0)(1 - f_A^f(0)) + f_A^f(0)(1 - f_A^m(0))$, $f_{aa}(1)^f = (1 - f_A^m(0))(1 - f_A^f(0))$. 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,

$$f_A^f(t+1) = \frac{1}{2}(f_A^f(t-1) + f_A^f(t)). \quad (3.33)$$

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 $f_{AA}^f(t)$, $f_{Aa}^f(t)$, and $f_{aa}^f(t)$ 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 shall 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:

(A.7); In each random mating and for each parent independently, an allele A being transmitted to the offspring mutates to a with probability u , and an allele a being transmitted to the offspring mutates to A with probability v . Moreover, $0 < u + v$.

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.

In deriving the basic model we worked first with genotype frequencies and derived equations (3.26), (3.27), (3.28). But then (page 24) we gave a simpler analysis using just allele frequencies. We adopt the latter approach for the mutation problem. The infinite population assumption says that

$$f_A(t+1) = \text{probability an offspring} \\ \text{acquires } A \text{ from a randomly selected parent}$$

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 we know from Lemma 1 that the probability a randomly selected parent of generation t contributes a gamete with genotype A is $f_A(t)$ and the probability that A does not mutate is $1 - u$. Similarly, the probability of the second event is $v(1 - f_A(t))$. Therefore,

$$f_A(t+1) = (1 - u)f_A(t) + v(1 - f_A(t)) = v + (1 - u - v)f_A(t). \quad (3.34)$$

This is a first order, linear difference equation. According to formula (3.5) developed in section 3.2.1, its solution is

$$f_A(t) = (1 - u - v)^t \left[f_A(0) - \frac{v}{u + v} \right] + \frac{v}{u + v}. \quad (3.35)$$

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 (3.5). 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; if $v = 0$, while $u > 0$, allele A disappears in the long-time limit, while if $u = 0$ and $v > 0$, allele a disappears.

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 (3.34) 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 in the case in which $u = 1/4$ and $v = 1/2$. Let $f_A^{(2)}(t)$ be the allele frequency in generation t in the case that $u = 1/16$ 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, in each of which the entire population mates to produce offspring and then dies, thereby entirely replacing itself. 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) is eliminated by random selection and 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

$$f_{AA}(t+h) - f_{AA}(t) = h \left[f_A^2(t) - f_{AA}(t) \right] \quad (3.36)$$

(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 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 (3.36). The result is the following difference equation for $f_{AA}(t)$:

$$f_{AA}(t+h) = [1-h]f_{AA}(t) + hf_A^2(0) \quad (3.37)$$

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 using Proposition 1, one can show that its solution is

$$f_{AA}(kh) = (1-h)^k \left[f_{AA}(0) - f_A^2(0) \right] + f_A^2(0) \quad (3.38)$$

and that

$$f_{AA}(\infty) \triangleq \lim_{k \rightarrow \infty} f_{AA}(kh) = f_A^2(0). \quad (3.39)$$

A similar analysis applied to the genotypes Aa and aa shows

$$f_{Aa}(\infty) \triangleq \lim_{k \rightarrow \infty} f_{Aa}(kh) = 2f_A(0)f_a(0), \quad f_{aa}(\infty) \triangleq \lim_{k \rightarrow \infty} f_{aa}(kh) = f_a^2(0). \quad (3.40)$$

Exercise 3.2.13. Verify (3.38)–(3.40) in detail, and show that the limiting genotype frequencies are in Hardy-Weinberg equilibrium.

The equation (3.36) 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 (3.36) by h and let $h \downarrow 0$. The result is

$$f'_{AA}(t) = \lim_{h \downarrow 0} \frac{f_{AA}(t+h) - f_{AA}(t)}{h} = -f_{AA}(t) + f_A^2(0). \quad (3.41)$$

Exercise 3.3.14. Let $f_{AA}(0) = f_{AA}$. Solve equation (3.41) 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. Thus, 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 if in a model, extra mixing can occur with each mating season, the population should tend to Hardy-Weinberg equilibrium. The close relationship between random mating and Hardy-Weinberg equilibrium is the takehome 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) Show using the result of a), that $(p^I(t)/2) + p^{II}(t)$ 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

We shall study a standard infinite population model with random mating *and* selection. In this case, the difference equations determining the evolution of allele frequency are non-linear. In general, non-linear difference equations do not have closed-form solutions. However there are some simple tools for analyzing the qualitative behavior of solutions that will allow us to understand the selection models. These tools are described first.

3.4.1 Nonlinear, first-order difference equations

There is a simple graphical technique, called cobwebbing, that allows one to visualize solutions of first order difference equations of the form:

$$x(t+1) = \phi(x(t)) \tag{3.42}$$

It will always be assumed that the function ϕ is continuous. By itself, cobwebbing is not a rigorous mathematical method. But it helps in guessing

the long term asymptotic behavior of solutions and in interpreting rigorous, analytic techniques. In particular, cobwebbing makes clear heuristically how solutions behave near fixed points. Recall from section 3.1 that \bar{x} is a fixed point of (3.42) if $\phi(\bar{x}) = \bar{x}$. Then, the constant sequence, $x(t) = \bar{x}$ for all $t \geq 0$, is a solution of (3.42). Fixed points are important, because, as we argued in section 3.1, limiting values of solutions are fixed points.

Cobwebbing is carried out in the Cartesian plane. Start by graphing the diagonal line $y = x$ and, superimposed on that, the graph, $y = \phi(x)$, of the function ϕ appearing in (3.42). The fixed points of ϕ are then easy to read off, since they are just the x -coordinates of the the points in the plane where the graphs of $y = \phi(x)$ and $y = x$ intersect. Figure 1 shows an example; the unique fixed point in Figure 1 is labeled \bar{x} . The object of cobwebbing is to plot successive values of the solution to (3.42), starting at any given initial condition $x(0) = x_0$, on the x -axis. The fundamental operation of cobwebbing 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 indeed 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 (3.42). Figure 1 carries out the first few iterations.

Cobwebbing can help one see easily 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

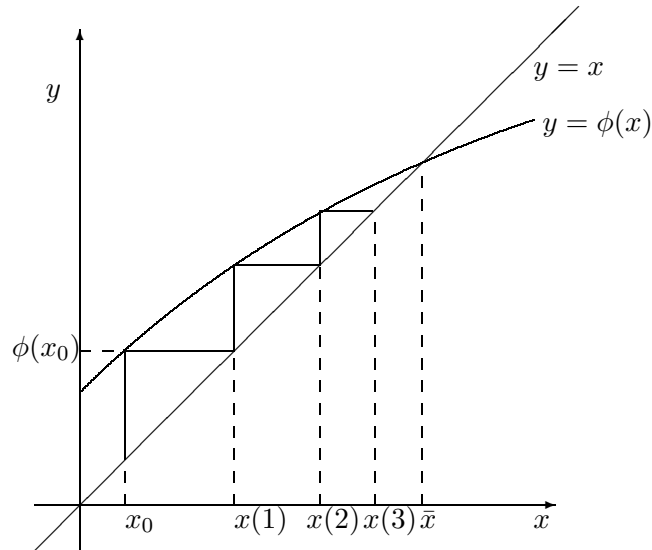


Figure 1.

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} . In the case of Figure 1, \bar{x} is an example of a *stable* fixed point. In general, if x^* is a fixed point, the set of x such that $\lim_{t \rightarrow \infty} x(t) = x^*$, where $(x(t))_{t \geq 0}$ is the solution of $x(t+1) = \phi(x(t))$ starting at $x(0) = x$, is called the *basin of attraction* of x^* . Then, x^* is called *stable* if its basin of attraction includes an open interval about x^* .

Figure 2 illustrates a quite different situation for a different function η around its fixed point x^* . The cobwebbing is not shown, and you should supply it yourself. You will see that when the initial point is close to x^* , the successive points $x(1), x(2), \dots$ of the solution to $x(t+1) = \eta(x(t))$ 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 (3.42) 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 (3.42)*; it is a linear difference equation with a fixed point at x^* and it should be a good approximation to (3.42), 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 (3.42) as well. Likewise, when $|\phi'(x^*)| > 1$, x^* is unstable for the linear system, and hence also for (3.42). The rigorous proof shall not be given here. We content ourselves with stating the result formally in the following theorem.

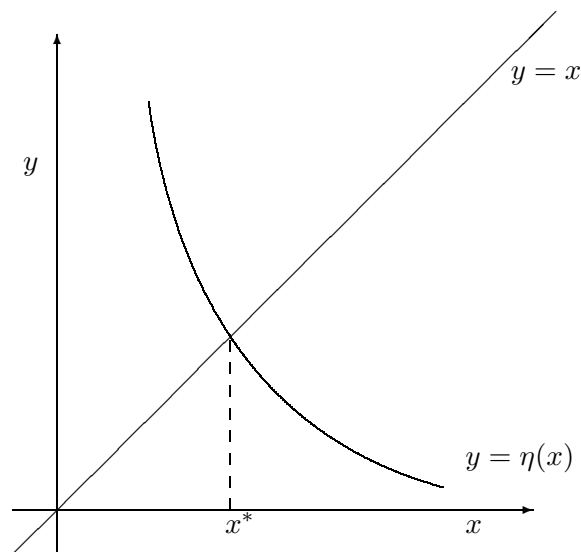


Figure 2.

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

$$\begin{aligned} \text{If } |\phi'(z)| < 1, \text{ then } z \text{ is a stable fixed point.} \\ \text{If } |\phi'(z)| > 1, \text{ then } z \text{ is not stable.} \end{aligned}$$

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 equation appeared in Example 3.1.2. Note in this example how close already $x(2)$ is to $\sqrt{2}$ when $x(0) = 1$. This difference equation is actually Newton's method for finding roots of $x^2 - 2$.)

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

In this section, we keep assumptions (A.1)—(A.4) of the basic model: we study an infinite, monocious population with non-overlapping generations and random mating. In addition, for concreteness, we assume that mating occurs seasonally; 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. Also, migration and mutation are not allowed. However, we now assume that selection occurs because genotype affects the probability of survival to reproductive maturity. The survival probabilities, which are also called *selection coefficients*, will be denoted by w_{AA} , w_{Aa} and w_{aa} , where, for example, w_{AA} denotes the probability that an individual of genotype AA survives from birth to reproductive maturity. We suppose these survival probabilities are the same from generation to generation and individuals survive or don't survive independently from one another. Survival is therefore equivalent probabilistically to the following experiment. Endow each individual at birth with a coin appropriate to its genotype; an individual with genotype AA gets a coin for which the probability of heads is w_{AA} , an Aa individual gets a coin for which the probability of heads is w_{Aa} , and so on. Each individual flips its coin independently and survives to reproductive maturity only if it flips heads.

The first goal is to derive a model from our assumptions for the usual case of one locus with two alleles. For this it is necessary to define two sets of genotype and allele frequencies per generation. The old notation, $f_A(t)$, $f_{AA}(t)$, etc., will denote the frequencies in generation t at the time of its birth. The notation $p_A(t)$, $p_{AA}(t)$, etc., will denote the frequencies in generation t at the time of reproductive maturity when it is giving birth to the next generation. 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 survives*, and similarly for $p_{Aa}(t)$ and $p_{aa}(t)$.

The derivation 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 an offspring is $p_A(t) = p_{AA}(t) + p_{Aa}(t)/2$. Hence by random mating and the infinite population assumption, for all $t \geq 0$,

$$\begin{aligned} f_A(t+1) &= p_A(t), & f_{AA}(t+1) &= p_A^2(t), & (3.43) \\ f_{Aa}(t+1) &= 2p_A(t)(1 - p_A(t)), & f_{aa}(t+1) &= (1 - p_A(t))^2 \end{aligned}$$

The second step is to express 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. For example, $p_{AA}(t)$ is the conditional probability that an individual has genotype AA

given that it survives: 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,

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

If $t \geq 1$, the equations of (3.43), 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 (3.43), (3.44), and (3.45). From (3.43), $f_A(t+1) = p_A(t) = p_{AA}(t) + p_{Aa}(t)/2$. 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 thus the final model. It looks a little scary, so, to simplify writing it, define the so-called *fitness function*

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

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

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

Our derivation of this equation assumed that selection occurs because different genotypes have different survival rates. But selection also can occur because different genotypes have different probabilities of reproductive success, or because of a combination differential survival rates and reproductive fitness. Fortunately, it is possible to reinterpret the selection coefficients, to cover all these possibilities with the same model. The only assumption we need is that the parents of a randomly chosen offspring of generation t are chosen independently. We defined $p_{AA}(t)$ above as the frequency of AA in generation t at the time of mating. However because random mating was assumed, $p_{AA}(t)$ equals the probability that parent i has genotype AA , for both parent $i = 1$ and parent $i = 2$, and this was really the only interpretation we ultimately used in the derivation of the final equation for $f_A(t)$. Thus, for a more general model, in which we don't worry exactly how selection occurs, let us interpret $p_{AA}(t)$, and similarly $p_{Aa}(t)$ and $p_{aa}(t)$, just as genotype probabilities of parents in a mating. Then it will still be true, as in equation (3.43), that $f_A(t+1) = p_A(t) = p_{AA}(t) + (p_{Aa}(t)/2)$. Next, assuming $w_{Aa} \neq 0$, divide the expressions in equations 3.44) and (3.45); the result is

$$\frac{p_{AA}(t)}{p_{Aa}(t)} = \frac{w_{AA} f_{AA}(t)}{w_{Aa} f_{Aa}(t)}. \quad (3.48)$$

A similar argument implies

$$\frac{p_{aa}(t)}{p_{Aa}(t)} = \frac{w_{aa} f_{aa}(t)}{w_{Aa} f_{Aa}(t)}. \quad (3.49)$$

It turns out that these two equations, when employed in conjunction with $f_A(t+1) = p_A(t) = p_{AA}(t) + (p_{Aa}(t)/2)$ and with $p_{AA}(t) + p_{Aa}(t) + p_{aa}(t) = 1$, also lead to equation (3.47) for $(f_A(t))_{t \geq 0}$. Thus, we can recover the same selection model by imposing (3.48) and (3.49) as *assumptions* that define the selection coefficients. In this view, the selection coefficients are nonnegative weights which quantify how the ratios of genotype probabilities in mating differ from the genotype frequencies of the infant population. This approach reveals that the model (3.47) depends only on the ratios of the selection coefficients to each other. Therefore there are really only two free parameters

among w_{AA} , w_{Aa} , and w_{aa} in determining the model numerically. It is common in the literature to parameterize the selection coefficient ratios using two numbers r and s , by taking $w_{Aa} = 1$, $w_{AA} = 1-r$ and $w_{aa} = 1-s$. When this parameterization is used, selection coefficients cannot be interpreted as survival probabilities. Of course, this whole discussion assumed $w_{Aa} > 0$. However, the equation (3.47) makes sense even when $w_{Aa} = 0$, and it can be interpreted in the same general manner if one takes $w_{Aa} = 0$ to mean that $p_{Aa} = 0$.

3.4.4 Analysis of the selection model

In this section, we use cobwebbing to analyse the selection model (3.47). It shall be assumed that 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 the form:

$$f(t+1) = \phi(f(t)). \quad (3.50)$$

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; $p = 0$ 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 (3.50) on a case by case basis. The explanations require the following facts about ϕ which are stated without proofs, which require only routine, if somewhat messy, calculation.

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

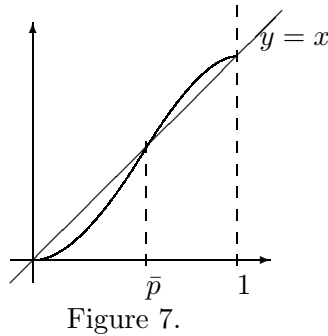
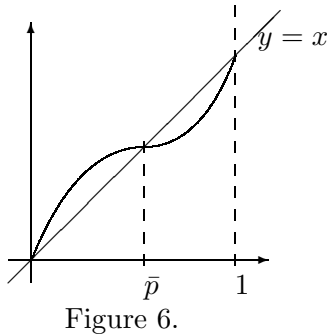
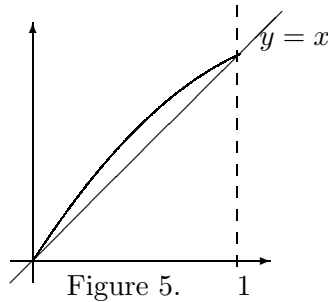
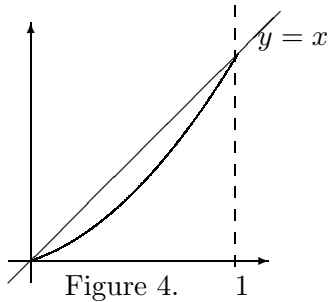
$$\bar{p} = \frac{w_{Aa} - w_{aa}}{2w_{Aa} - w_{AA} - w_{aa}}. \quad (3.51)$$

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

$$\phi'(p) = \frac{p^2 w_{AA} w_{Aa} + 2p(1-p)w_{AA}w_{aa} + (1-p)^2 w_{Aa}w_{aa}}{W^2(p)}. \quad (3.52)$$

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

$$\lim_{t \rightarrow \infty} f(t) = 0. \quad (3.53)$$

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 (3.52), $\phi'(0) = w_{Aa}/w_{aa}$. 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 (3.53).

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 (3.51).

The graph of ϕ for this case is shown in Figure 6. From the remark after equation (3.51), 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,

$$\text{if } 0 < f(0) < \bar{p}, \text{ then } \lim_{t \rightarrow \infty} f(t) = 0, \text{ and if } \bar{p} < f(0) < 1, \lim_{t \rightarrow \infty} f(t) = 1. \quad (3.54)$$

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 (3.54) 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 gives 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 (3.50) 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 (3.50). 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

$$W(\phi(p)) - W(p) = \frac{(\phi(p) - p)^2}{p(1-p)} [W(p) + pw_{AA} + (1-p)w_{aa}]. \quad (3.55)$$

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 equation (3.52)—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 (3.51). Derive the formula given in the text for $\phi'(p)$.

Exercise 3.4.8. Derive formula (3.55) 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-Verag, Berlin, 2004.
- D.L. Hartl and A.G. Clark, *Principles of Population Genetics*, second edition, Sinauer Associates, Sunderland, MA, 1989.

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